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Comorbid Alcohol Dependence and Anxiety Disorders: A National Survey

Lauren R. Pacek, B.S.^{1,*}, Carla L. Storr, ScD^{1,2}, Ramin Mojtabai, MD, PhD^{1,3}, Kerry M. Green, PhD⁴, Lareina N. La Flair, PhD, MPH¹, Anika A. H. Alvanzo, MD⁵, Bernadette A. Cullen, BCh, BAO³, and Rosa M. Crum, MD, MHS^{1,3,6}

¹Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health

²Department of Family & Community Health, University of Maryland Baltimore School of Nursing

³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine

⁴Department of Behavioral and Community Health, University of Maryland School of Public Health

⁵Division of General Internal Medicine, Johns Hopkins University School of Medicine

⁶Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health

Abstract

Objective—The goal of this study was to describe onset of comorbid anxiety disorders and alcohol dependence based on a large national survey of the US adult population, and to explore and describe these patterns by gender.

Methods—Using Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data, we compared age of onset and temporal ordering of onset of comorbid alcohol dependence and anxiety disorders. Analyses were stratified by gender. Mean ages of onset were calculated, and Wald F-tests were used to assess differences in ages of onset, accounting for the complex survey design of the NESARC. Weighted estimates were used, adjusted to be representative of the US population on various sociodemographic variables based on the 2000 Decennial Census.

Results—Differences in temporal ordering were observed, but varied by disorder combination. The majority (65%) had a primary (earliest onset) anxiety disorder, while the remaining 35% had a primary alcohol dependence diagnosis. Age of onset for some individuals with an anxiety disorder comorbid with alcohol dependence was earlier than for those with an anxiety disorder alone. Among individuals with comorbid social phobia and alcohol dependence, and comorbid specific phobia and alcohol dependence, it was more common to experience anxiety disorder as the primary diagnosis. Conversely, among individuals with comorbid panic disorder and alcohol dependence, and generalized anxiety disorder and alcohol dependence, it was more common to experience alcohol dependence as the primary diagnosis. Women were more likely to report having multiple comorbid anxiety disorders. No gender differences were found in terms of age of onset or temporal ordering of onset of comorbid disorders.

*Corresponding author: Lauren R. Pacek; 624 N. Broadway Hampton House Suite 811 Baltimore, MD 21205. Phone: 410-502-4845, Fax: 410-955-9088, lropelew@jhsph.edu.

DISCLOSURES

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Conclusions—Subsets of individuals with comorbid disorders exist, some whose primary diagnosis is alcohol dependence, and a majority of individuals whose primary diagnosis is an anxiety disorder with significant variability in age and temporal ordering of onset and few gender differences. Improved understanding of patterns of comorbidity and lag time between the onsets of specific disorders may enable us to identify potential groups for early intervention.

Keywords

alcohol dependence; anxiety disorders; comorbidity; age of onset; panic disorder; social phobia; generalized anxiety disorder; specific phobia

Alcohol dependence and anxiety disorders are some of the most commonly diagnosed mental health conditions in the United States (Kessler et al., 2005) and are often comorbid (Merickangas et al., 1998; Kushner et al., 1990; Shuckit & Hesselbrock, 1994; Grant et al., 2004; Grant et al., 2005). Studies estimate that 35–54% of individuals with anxiety disorders also have a lifetime diagnosis of an alcohol use disorder (Kaufman & Charney, 2000). Several possible explanations exist for this comorbidity: 1) alcohol use may trigger psychopathology via neuroadaptation in brain reward pathways that can lead to subsequent development of psychiatric disorders (i.e., the precipitation model; McEwan, 2000; Brady and Sinha, 2005); 2) psychiatric disorders may cause an increase in alcohol use due to the possible alleviation of mental health symptoms (i.e., the self-medication hypothesis; Quitkin et al., 1972; Lader, 1972; Markou et al., 1998) and; 3) a third factor or underlying vulnerability may influence the risk for developing both alcohol use/use disorder and psychiatric disorders, and may explain the observed association (i.e., genetic vulnerability). Anxiety disorders are also highly comorbid with one another; 50% of individuals with an anxiety disorder meet criteria for another anxiety disorder (Goldenberg et al., 1995; Dick et al., 1994a; Dick et al., 1994b; Wittchen et al., 1994; Kessler et al., 1995).

Delineating the temporal order in which comorbid disorders occur may aid in understanding their etiology, and lead to improved treatment and prevention efforts. Goldenberg and colleagues (1995) described the temporality of onset of anxiety and substance use disorders in a study of adults from treatment facilities with primary anxiety disorders (i.e., anxiety disorder with onset prior to substance use disorder) and secondary anxiety disorders (i.e., anxiety disorder with onset subsequent to substance use disorder). Sixty-two percent of the sample had a primary anxiety disorder, and 38% had a secondary anxiety disorder (Goldenberg et al., 1995). Thus, in that prior treatment sample, it seems that anxiety disorders were more likely to occur prior to the comorbid substance use disorder(s). Similar findings have been seen in prospective studies utilizing adolescent samples: the onset of anxiety disorders tends to precede the onset of alcohol use disorders (Fergusson et al., (2011); Behrendt et al., (2011); Zimmerman et al., (2003).

When examining anxiety disorders collectively, the median age of onset is approximately 11 years, which leads to the impression of earlier onset than what is typically found for alcohol dependence (median age of onset: 23 years) (Kessler et al., 2005). Considerable variation, though, is observed when examining individual anxiety disorders. The median ages of onset for specific phobia and social phobia were 7 and 13, respectively, suggesting that onset tends to occur during childhood/adolescence (Kessler et al., 2005). Conversely, the median ages of onset for panic disorder and generalized anxiety disorder were 24 and 31, respectively, suggesting that onset tends to occur more often during adulthood (Kessler et al., 2005).

Research shows that women have a higher prevalence of anxiety disorders than men (Bruce et al., 2005; Regier et al., 1990; Kessler et al., 1994; McLean et al., 2011; Beekman et al.,

1998). Less is known about how gender affects other parameters, like age of onset and patterns of comorbidity. Despite not finding gender differences in terms of age of onset and chronicity of illness, McLean and colleagues (2011) noted that women with an anxiety disorder were more likely than men to have another comorbid anxiety disorder, and to report a greater illness burden associated with their diagnoses. Some evidence has suggested that women are also more likely than men to have comorbid internalizing and substance use disorders (Compton et al., 2000; Kessler et al., 1997), though others have not observed this (Brook et al., 1998). Additional studies, conducted by Sonne and colleagues (2003) and Kessler and colleagues (1997), found that temporality of onset of some comorbid disorders differed by gender. Findings indicated that, among a sample of outpatient treatment-seeking individuals with comorbid alcohol dependence and post-traumatic stress disorder (PTSD), PTSD more often preceded alcohol dependence in women than in men (Sonne et al., 2003). Similarly, among individuals with alcohol use disorders comorbid with another disorder, higher proportions of women reported that their alcohol dependence was temporally secondary to their comorbid diagnosis (Kessler et al., 1997).

In an attempt to improve our understanding of temporal ordering among those with comorbidity, we examined temporal ordering of onset of specific anxiety disorders and alcohol dependence in a large sample of the US general population. We assessed alcohol dependence rather than both abuse and dependence combined (i.e., alcohol use disorders) due to known stronger positive associations found for alcohol dependence and comorbid disorders, as compared to between alcohol abuse and comorbid disorders (Grant et al., 2004; Pacek et al., 2012), as well as recommendations to assess the conditions separately (Babor & Caetano, 2008). Given the inconsistent findings between abuse and comorbid disorders, we thought it prudent to focus on dependence alone. Temporal ordering of onset of each type of disorder was examined overall and stratified by gender. We hypothesized that individuals with comorbid disorders would report different ages of onset than those without comorbid alcohol dependence and anxiety. Based on past research indicating gender differences in terms of comorbidity, we further hypothesized that men and women would report different ages of onset in terms of temporal ordering of disorders.

METHODS

Study Sample

Data came from Wave 1 (2001–2002) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative survey initiated by the National Institute on Alcohol Abuse and Alcoholism and conducted within the United States (Grant et al., 2004). Details of the study have been described elsewhere (Grant et al., 2003; Grant et al., 2004). Briefly, using multi-stage probability sampling, 43,093 non-institutionalized adults, age 18 and older, were interviewed. The overall response for the survey was 81% (Grant et al., 2003). The research protocol received ethical review and approval from the US Census Bureau and the US Office of Management and Budget in accordance with the Declaration of Helsinki. The Johns Hopkins School of Public Health Institutional Review Board waived human subject status of the de-identified dataset used in this secondary data analysis.

Four non-mutually exclusive subgroups were utilized for the present analyses. The following describes the composition of each of the subgroups: 1) individuals with lifetime alcohol dependence (with or without alcohol abuse) comorbid with a lifetime diagnosis of any of the following anxiety disorders: panic disorder without agoraphobia, social phobia, specific phobia(s), or generalized anxiety disorder ($N=1,502$); 2) individuals with lifetime alcohol dependence without comorbid anxiety disorders ($N=3,279$) and individuals with lifetime anxiety disorders without comorbid alcohol dependence ($N=5,667$; combined

subgroup sample size $N=8,946$); 3) individuals with lifetime alcohol dependence comorbid with a single anxiety disorder, exclusive of other anxiety disorders ($N=995$) and; 4) of the latter sample, individuals not reporting identical ages of onset for lifetime alcohol dependence and their comorbid anxiety disorder ($N=947$).

Measures

Lifetime alcohol dependence and several anxiety disorders (panic, social and specific phobias, and generalized anxiety disorder) were assessed using the Alcohol Use Disorders and Associated Disabilities Interview Schedule-DSM IV Version (AUDADIS-IV), administered via structured computer-assisted personal interview (CAPI) (Grant et al., 2001). The AUDADIS is a fully structured diagnostic interview designed for use by lay interviewers. It assesses alcohol and drug consumption, and selected Axis I and II psychiatric disorders. Anxiety disorders due to general medical conditions or substance use were excluded. Age of onset of alcohol dependence was assessed via the following question: “About how old were you the FIRST time SOME of these experiences [alcohol dependence criteria] BEGAN to happen around the same time?” Age of onset of anxiety disorders was assessed by asking the following question for panic disorder, social phobia, specific phobia, and generalized anxiety disorder, respectively: “About how old were you the FIRST TIME you BEGAN to” 1) have panic attacks along with some of the other experiences you told me about; 2) experience a strong fear or avoidance of any social situation; 3) experience a strong fear or avoidance of any of these objects or situations; 4) feel tense, nervous or worried for at least 6 months and also had some of the other experiences you mentioned.

Determination of Primary Diagnosis

Primary diagnosis was determined by comparing participants’ ages of onset for alcohol dependence and their respective anxiety disorder. The disorder with the earlier age of onset was labeled “primary.” Individuals reporting identical ages of onset (e.g., individual reporting onset of alcohol dependence at 24 years and also reporting onset of generalized anxiety disorder at 24 years) for alcohol dependence and their anxiety disorder precluded a determination of primary diagnosis, and were excluded from analyses concerning the primary diagnosis.

Statistical Analyses

We examined the weighted mean ages of onset, comparing individuals with comorbid disorders to those with single disorders across disorders (e.g., comparing individuals with lifetime comorbid alcohol dependence and panic disorder (Subgroup 1) with individuals with lifetime panic disorder without alcohol dependence (Subgroup 2). Next, analyses were conducted among individuals with lifetime comorbid alcohol dependence and a single anxiety disorder, exclusive of other anxiety disorders (Subgroup 3). Among these individuals, we compared the weighted mean ages of onset of alcohol dependence and their respective anxiety disorder (i.e., among individuals with lifetime comorbid alcohol dependence and panic disorder, exclusive of other anxiety disorders, we compared the ages of onset of alcohol dependence and panic disorder). Then, we made comparisons among individuals who did not report identical ages of onset for alcohol dependence and their respective anxiety disorder among the aforementioned subgroup (i.e., individuals with lifetime comorbid alcohol dependence and a single anxiety disorder, exclusive of other anxiety disorders; Subgroup 4). We compared the difference in weighted mean ages of onset between alcohol dependence and each anxiety disorder separately among individuals with primary alcohol dependence and individuals with a primary anxiety disorder.

All analyses were completed using STATA 12 ‘svy’ commands (Statacorp, 2011). These commands are capable of taking into account the weighted design of the NESARC. The

NESARC sample is weighted to adjust for the probabilities of selection of a sample housing unit or housing unit equivalent from the group quarters' sampling frame, non-response at the household and person levels, the selection of one person per household, and the oversampling of young adults. Once weighted, the data were adjusted to be representative of the US population on various sociodemographic variables, including age, sex, race/ethnicity, and region, based on the 2000 Decennial Census. Prior to conducting any analyses, the following code was used to declare that the dataset used a complex survey design: "svyset psu [pweight=weight], strata(stratum) vce(linearized) singleunit(centered)". The "vce(linearized)" portion of this code estimates the correct variance using Taylor series linearization. The "singleunit(centered)" portion of this code specifies that strata with one sampling unit are centered at the grand mean instead of the stratum mean. F-statistic approximations to the Rao-Scott statistic (i.e., svy: tab command; used in lieu of chi-square tests when analyzing complex survey data in STATA) took into account the complex survey design. Mean age of onset of disorders were calculated using the "svy: mean" command and comparisons were made using an adjusted Wald F-test (i.e., "test" command; with a null hypothesis that the difference between two mean values is not significantly different from 0), which approximates a t-test when using 'svy' commands. Significance levels were set at 0.05. The "subpop()" command in STATA was used for all subgroup analyses.

RESULTS

Mean Age of Onset - Individuals with Comorbid versus Single Conditions

In this study, 8,946 individuals (3,749 men; 5,197 women) had a single condition (i.e., alcohol dependence or anxiety disorder, not comorbid with one another). Additionally 1,502 individuals (739 men; 763 women) had lifetime alcohol dependence with at least one comorbid anxiety disorder. All estimates presented below are weighted and adjusted to be representative of the US adult population on various sociodemographic variables, including age, sex, race/ethnicity, and region, based on the 2000 Decennial Census, not the actual sample of respondents themselves.

Full study sample—As shown in Table 1A, the mean age of onset of alcohol dependence was nearly identical for individuals with lifetime comorbid alcohol dependence and anxiety disorder(s) as compared to individuals with lifetime alcohol dependence only (24.04 and 24.08 years, respectively; $p=0.965$). However, individuals with comorbid panic disorder and alcohol dependence reported an earlier age of panic disorder onset than those without comorbid alcohol dependence (29.23 versus 32.72 years, $p<0.001$). The age of onset of social phobia was similar for both groups ($p=0.054$) regardless of whether alcohol dependence was present or not, but individuals with comorbid alcohol dependence reported onset of specific phobia and generalized anxiety disorder at significantly younger mean ages than those without comorbid alcohol dependence (specific phobia: 13.42 versus 14.73 years, $p=0.005$; generalized anxiety disorder: 29.06 versus 34.02, $p<0.001$).

Gender-stratified analyses—Table 1B presents information regarding differences in mean ages of onset for disorders among men with comorbid disorders versus non-comorbid disorders, while Table 1C presents this information for women. For both genders, no significant differences for mean age of onset of alcohol dependence were observed between individuals with lifetime comorbid alcohol dependence and anxiety disorder(s) as compared to individuals with lifetime alcohol dependence alone ($p=0.577$ for men; $p=0.245$ for women). No significant differences were observed for reported mean age of alcohol dependence or social phobia when comparing men or women with comorbid versus non-comorbid disorders ($p=0.083$ for men; $p=0.357$ for women). Among men, ages of onset for specific phobia plus comorbid alcohol dependence and specific phobia alone were similar

($p=0.134$). However, differences in mean age of onset of panic disorder and generalized anxiety disorder were noted among men with comorbid versus single conditions (panic: 29.22 versus 32.91 years, $p=0.008$; generalized anxiety disorder: 29.63 versus 33.79, $p=0.004$). For women, differences were observed on the basis of reported mean age of panic disorder, specific phobia, and generalized anxiety disorder for those with and without comorbid alcohol dependence (panic: 29.24 versus 32.66 years, $p=0.002$; specific phobia: 13.50 versus 14.82, $p=0.023$; generalized anxiety disorder: 28.50 versus 34.11 years, $p<0.001$).

When comparing men and women (results not shown), no significant differences were observed in terms of both the mean ages of onset of any of the disorders, as well as in terms of the mean difference in ages of onset between comorbid and single conditions for any of the disorders.

Mean Age of Onset - Specific Alcohol/Anxiety Disorder Comorbid Combinations

Of the individuals with comorbid alcohol dependence and anxiety disorders, 995 (536 men; 459 women)—approximately 66% of the comorbid subgroup—had alcohol dependence comorbid with only a single anxiety disorder. Only 27 men and 21 women reported identical ages of onset for alcohol dependence and their respective anxiety disorder, precluding a determination of primary diagnosis. Among the 947 individuals for whom a primary disorder could be determined, a primary alcohol dependence diagnosis occurred for 35% (328 individuals) of those with a single anxiety disorder comorbid with alcohol dependence; an anxiety disorder was the primary diagnosis for the remaining 65% (619) of individuals. Approximately one-third (34%) of the study sample reported multiple anxiety disorders. Women were significantly more likely than men to report multiple comorbid anxiety disorders (40.40% versus 27.08%); $F(1, 62) = 17.78$, $p<0.001$.

Full study sample—Mean age comparisons based on the 995 individuals with alcohol dependence and only one comorbid anxiety disorder are shown in Table 2. As shown in Table 2A, the age of onset of alcohol dependence among individuals with panic disorder and generalized anxiety disorder was earlier than their age of onset for their anxiety disorder (panic disorder: 24.41 versus 29.45 years, $p<0.001$; generalized anxiety disorder: 25.37 versus 30.42 years, $p=0.050$). Individuals with alcohol dependence and comorbid social phobia and comorbid specific phobia, however, tended to develop their respective anxiety disorder at a younger age than they were to develop alcohol dependence (social phobia: 15.07 versus 24.48 years, $p<0.001$; specific phobia: 13.11 versus 23.96 years, $p<0.001$).

Gender-stratified analyses—Similar patterns to those found for the full study sample were observed when examining men and women separately. Shown in Table 2B, men with alcohol dependence and comorbid panic disorder and generalized anxiety disorder tended to develop alcohol dependence prior to their respective anxiety disorder diagnosis (panic disorder: 24.39 versus 30.04 years, $p<0.001$; generalized anxiety disorder: 24.41 versus 30.49 years, $p<0.001$). Additionally, men with alcohol dependence and comorbid social phobia and specific phobia seemed to develop their anxiety disorder diagnosis at a significantly younger age than developing alcohol dependence (social phobia: 14.64 versus 24.38 years, $p<0.001$; specific phobia: 13.12 versus 24.12 years, $p<0.001$).

Based on women with alcohol dependence and one comorbid anxiety diagnosis, similar patterns emerged, as shown in Table 2C. Women with alcohol dependence and comorbid panic disorder and generalized anxiety disorder developed alcohol dependence at an earlier age than onset of their comorbid anxiety disorder (panic disorder: 24.43 versus 28.71 years, $p<0.001$; generalized anxiety disorder: 26.94 versus 30.29 years, $p=0.048$). Women with

alcohol dependence and comorbid social phobia and specific phobia developed their anxiety disorder at an earlier age than they did alcohol dependence (social phobia: 15.94 versus 24.68 years, $p=0.002$; specific phobia: 13.10 versus 23.76 years, $p<0.001$). Significant differences between men and women in terms of mean ages of onset, as well as differences in ages of onset of alcohol dependence and anxiety disorders were not observed for any specific comorbid disorder pair.

Specific Alcohol/Anxiety Disorder Comorbid Combinations – Temporal Ordering of Alcohol Dependence versus Anxiety Disorder Diagnosis

Alcohol dependence as the primary diagnosis—As shown in Table 3A, based on individuals with panic disorder or specific phobia comorbid with alcohol dependence, the mean age of onset of alcohol dependence was significantly earlier than the onset of the corresponding anxiety disorder (panic disorder: 22.93 versus 33.46 years, $p<0.001$; specific phobia: 20.88 versus 28.81 years, $p<0.001$). The temporal ordering for the disorders could not be established for individuals with alcohol dependence comorbid with social phobia or generalized anxiety disorder as no statistical differences in ages were detected. Individuals with a primary diagnosis of alcohol dependence reported an age of onset for alcohol dependence that was on average 10.19 years younger than the age of onset reported for their comorbid anxiety disorder diagnosis.

Anxiety disorder as the primary diagnosis—Table 3B provides age of onset information based on those with an anxiety disorder as their primary diagnosis. Among individuals with alcohol dependence and comorbid panic disorder, social phobia, or specific phobia, the average age of onset of the respective anxiety disorders was significantly earlier than the average age of onset of alcohol dependence (panic disorder: 21.90 versus 29.33 years, $p<0.001$; social phobia: 11.85 versus 24.63 years, $p<0.001$; specific phobia: 10.07 versus 24.62 years, $p<0.001$). The temporal ordering for the disorders could not be established for individuals with alcohol dependence comorbid with generalized anxiety disorder as no statistical difference in ages was detected. On average, individuals with a primary diagnosis of anxiety reported the age of onset of their respective anxiety disorder as being approximately 10.14 years before the age of onset reported for alcohol dependence.

Gender-stratified analyses—Gender-stratified analyses revealed the same pattern of findings as those presented for the full group (results not shown). There were no significant differences between men and women for any of the specific comorbid disorder pairs, both in terms of mean ages of onset as well as differences in mean ages of onset between disorders, regardless of whether alcohol dependence or the anxiety disorder was the primary diagnosis. Furthermore, there was no difference between men and women in terms of the proportion of individuals who had a primary anxiety disorder and primary alcohol dependence diagnosis; $F(1, 57) = 0.69$, $p=0.906$.

DISCUSSION

Congruent with prior findings showing that anxiety disorders are often comorbid with one another (Kaufman & Charney, 2000), approximately 34% of individuals with alcohol dependence in this study had multiple comorbid anxiety disorders. Additionally, among the remaining 66% of individuals with comorbid alcohol dependence and a single anxiety disorder, approximately 35% of had a primary alcohol dependence diagnosis, while 65% of individuals had a primary anxiety disorder diagnosis. This suggests some amount of heterogeneity among individuals with comorbid alcohol dependence and anxiety disorders. Furthermore, among those with a primary anxiety disorder, the anxiety disorder emerged on average 10 years before the development of alcohol dependence. These findings are quite

similar to those from the study by Goldenberg and colleagues (1995), who also found that among slightly more than 60% of comorbid cases, alcohol and substance use disorders emerged on average 10 or more years after the onset of the primary anxiety disorder.

We observed variation in terms of age of onset when considering specific anxiety disorder-alcohol dependence comorbid pairs. For instance, it was more common for individuals with comorbid social phobia and alcohol dependence or comorbid specific phobia and alcohol dependence to have their respective anxiety disorder be the primary condition. As a result, these findings are potentially indicative of the self-medication hypothesis, as discussed previously (Quitkin et al., 1972; Lader, 1972; Markou et al., 1998). However, when considering panic disorder and generalized anxiety disorder, the majority of individuals with either of these conditions comorbid with alcohol dependence were likely to experience alcohol dependence as their primary condition. Findings for these specific comorbid disorder pairs may provide support for the precipitation model, whereby use of alcohol may trigger the development of psychopathology (McEwan, 2000; Brady and Sinha, 2005). Variability also emerged when examining the mean difference in years between development of alcohol dependence and an anxiety disorder when considering specific anxiety disorders. The mean difference in development of the two disorders varied from 7.93 to 12.02 years when alcohol dependence was the primary disorder, and from 5.80 to 14.55 years when anxiety was the primary disorder.

In the NESARC sample, women were more likely than men to report having multiple comorbid anxiety disorders, which is consistent with previous research (Kaufman & Charney, 2000; Goldenberg et al., 1995; Dick et al., 1994a; Dick et al., 1994b; Wittchen et al., 1994; Kessler et al., 1995). Beyond this, gender differences failed to emerge in each set of analyses when considering the age of onset and the ordering and temporal ordering of conditions, which is inconsistent with prior findings regarding gender differences in temporal ordering of onset of comorbid conditions (Kessler et al., 1997; Sonne et al., 2003) and is incongruent with our original hypotheses.

The present study has several limitations. All information was collected via self-report, which is subject to social desirability bias and may underestimate the prevalence of mental health or substance use conditions. Retrospective recall bias may also be an issue, particularly related to reporting age of onset. An additional concern is how well an individual can distinguish and recall symptoms (potentially overlapping ones) for multiple conditions. Special probes may need to be developed to help adults recall their experiences with more accuracy (Kessler et al., 1998). Furthermore, our analyses did not examine primary conditions among individuals with multiple anxiety disorders and did not examine additional comorbid conditions such as other substance use disorders or depression. Given that females in the study sample were significantly more likely to report having multiple comorbid anxiety disorders, it is possible that our decision to exclude individuals with multiple comorbid anxiety disorders for certain analyses may have had an effect on the results of the gender-stratified analyses. Our comparisons did not account for other potential factors that might influence the findings. Additionally, we did not examine other anxiety disorders such as PTSD or obsessive-compulsive disorder (OCD), as information on these disorders was not collected during Wave 1 of the NESARC. It is also important to note that disorder prevalence and comorbidity in this study were assessed as lifetime measures, not accounting for persistence of disorders.

Notwithstanding these limitations, this study has a number of strengths. Findings are from a large, nationally representative survey, whereas many prior studies of alcohol use disorders and anxiety disorders were often limited to treatment-seeking samples (Gerlach et al., 2006; Randall et al., 2001; Terra et al., 2006). Also, we assessed anxiety disorders separately,

rather than collapsing them into a single "anxiety disorder" category. This allowed us to compare and contrast patterns for specific anxiety conditions and identify significant differences that were not apparent when collapsed into a single anxiety disorder category. All disorders were assessed using DSM-IV-TR criteria (APA, 1994), which has the advantage of conferring a diagnostic label.

Implications for Future Research

Our findings have implications for treatment and future research concerning comorbid alcohol dependence and anxiety disorders. One implication concerns the importance of assessing alcohol dependence and anxiety disorders in patients who present with one primary set of alcohol dependence-related or anxiety disorder complaints. It is possible that the patient may be experiencing symptomatology from one or more comorbid diagnostic conditions. Comorbidity among psychiatric disorders has implications for the treatment and management of such conditions. For instance, research shows that individuals who use alcohol as a means to alleviate their mood or anxiety symptoms (i.e., the self-medication hypothesis) may have an elevated risk for the development and persistence of alcohol dependence (Crum et al., 2013a; Crum et al., 2013b). In light of this, it is important for physicians and other healthcare professionals to continue to be aware of the comorbid nature of anxiety disorders and alcohol dependence, and to have the resources at hand to implement interventions that may prevent the development or halt the escalation of alcohol dependence in these individuals.

A better understanding of the more common pattern(s) of comorbidity and of the lag time between the onsets of specific disorders, can improve our ability to identify individuals who should be targeted for early intervention. In addition to individuals presenting with one set of symptoms potentially experiencing concurrent comorbid symptomatology, in light of our findings showing that in comorbid disorder pairs, one condition tends to have an onset some years following the onset of the other condition, some individuals may warrant inclusion in interventions to prevent or mitigate the onset of additional conditions. Furthermore, as highlighted by Caron and Rutter (1991) and Kaufman and Charney (2000), it is possible that comorbid patterns of disorders constitute meaningful subgroups of patients; thus, it is possible that the differing patterns of comorbidity observed in this study—individuals with primary alcohol dependence versus individuals with primary anxiety disorders—represent such meaningful subgroups. In the future, in addition to examining other anxiety disorders not included in the present study (e.g., PTSD, OCD, etc.), researchers should consider examining the comorbid nature of mood and anxiety disorders with other substance use disorders, and subsequently explore temporal order and associated ages of onset. Future research may also want to examine other specific subgroups of the population that have shown distinct comorbid patterns, such as subgroups by race/ethnicity (Alvanzo et al., 2011), in addition to gender. Additionally, in the future, investigators could consider running adjusted regression models, examining the age of onset of various conditions, while controlling for a variety of potential confounding variables. An additional alternate strategy may be to include individuals from Wave 2 of the NESARC survey experiencing new onset of these conditions. In the present analysis, we felt that we had adequate sample size and power, and thus opted not to employ this strategy. Furthermore, there is a need for longitudinal research, with data collection beginning in youth in order to minimize reliance on recall and to disentangle premorbid pathways that lead to alcohol dependence and other psychiatric disorders.

In summary, this study described the mean ages of onset of various anxiety disorders and alcohol dependence among a population-based sample of adults with comorbidity, and explored the temporal ordering of onset of each type of disorder, with descriptions presented for the full study sample and stratified by gender. Results contribute to a body of prior

research showing that alcohol dependence and a variety of anxiety disorders are prevalent among the general adult population, both as singular disorders as well as in comorbid states. Subsets of individuals with comorbid disorders exist, some whose primary diagnosis is alcohol dependence, and a majority of individuals whose primary diagnosis is an anxiety disorder. Among these individuals, the mean difference in years between the onset of alcohol dependence and their respective anxiety disorder varies by the type of anxiety disorder. Examinations of specific alcohol dependence/anxiety disorder pairs reveals that some anxiety disorders are more likely than others to occur prior to a diagnosis of alcohol dependence, and that some are more likely to occur subsequently. Among the specific disorder combinations, there is substantial variation in the lag time between developing alcohol dependence and a subsequent anxiety disorder, and vice versa. An additional novel finding of the present study suggests a lack of gender differences in the temporal ordering of comorbid alcohol dependence and anxiety disorders.

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Table 1

Weighted Mean Age of Onset of Disorder among Individuals with Lifetime Comorbid Alcohol Dependence and Anxiety Disorder(s) at Baseline as Compared to Individuals without Comorbid Disorders

A. Mean Age of Onset – Full Study Sample							
Condition	Comorbid Conditions ^a			Single Conditions ^b			p-value
	n	Mean	95% CI	n	Mean	95% CI	
Alcohol dependence	1,502	24.04	[23.51–24.58]	3,279	24.08	[23.64–24.48]	0.965
Panic disorder	409	29.23	[27.98–30.48]	1,244	32.72	[31.72–33.72]	<0.001
Social phobia	487	14.28	[13.20–15.37]	1,496	15.46	[14.73–16.18]	0.054
Specific phobia	839	13.42	[12.73–14.11]	3,191	14.73	[14.14–15.32]	0.005
GAD	445	29.06	[27.69–30.43]	1,312	34.02	[32.95–35.09]	<0.001

B. Mean Age of Onset – Men							
Condition	Comorbid Conditions ^a			Single Conditions ^b			p-value
	n	Mean	95% CI	n	Mean	95% CI	
Alcohol dependence	739	24.07	[23.36–24.77]	2,235	23.84	[23.37–24.30]	0.577
Panic disorder	182	29.22	[27.28–31.16]	297	32.91	[30.97–34.86]	0.008
Social phobia	237	13.98	[12.56–15.40]	499	15.35	[14.22–16.48]	0.083
Specific phobia	380	13.45	[12.31–14.38]	754	14.47	[13.41–15.53]	0.134
GAD	197	29.63	[27.54–31.71]	305	33.79	[31.71–35.87]	0.004

C. Mean Age of Onset – Women							
Condition	Comorbid Conditions ^a			Single Conditions ^b			p-value
	n	Mean	95% CI	n	Mean	95% CI	
Alcohol dependence	763	24.01	[23.28–24.74]	1,044	24.63	[24.31–25.97]	0.245
Panic disorder	227	29.24	[27.48–31.00]	947	32.66	[31.48–33.84]	0.002
Social phobia	250	14.64	[12.96–16.32]	997	15.51	[14.63–16.40]	0.357
Specific phobia	459	13.50	[12.50–14.50]	2,437	14.82	[14.18–15.46]	0.023
GAD	248	28.50	[26.74–30.27]	1,312	34.11	[32.91–35.32]	<0.001

Note. Based on NESARC 2001–02 (Wave 1) for the full target sample ($n=1502$) relative to those without comorbidity ($n=8946$), and separately for males ($n=739$) relative to males without comorbidity ($n=3749$), and females ($n=763$) relative to females without comorbidity ($n=5197$). GAD = Generalized Anxiety Disorder.

^a Alcohol dependence comorbid with one or more anxiety disorder

^b Alcohol dependence without a comorbid anxiety disorder, or an anxiety disorder without comorbid alcohol dependence

Weighted Mean Age of Onset for Specific Comorbid Disorder Combinations, Exclusive of Other Comorbid Anxiety Disorders

Table 2

A. Mean Age of Onset for Specific Comorbid Disorder Combinations – Full Study Sample						
Disorder Combination ^a	Alcohol Dependence			Anxiety Disorder		
	<i>n</i>	Mean	95% CI	Mean	95% CI	<i>p</i> -value
Alcohol dependence + Panic disorder	214	24.41	[23.18–25.63]	29.45	[27.81–31.09]	–5.04 <0.001
Alcohol dependence + Social phobia	182	24.48	[22.81–26.51]	15.07	[13.17–16.96]	9.41 <0.001
Alcohol dependence + Specific phobia	451	23.96	[22.95–24.96]	13.11	[12.04–14.17]	10.85 <0.001
Alcohol dependence + GAD	148	25.37	[23.57–27.17]	30.42	[28.17–32.67]	–5.05 0.050
B. Mean Age of Onset for Specific Comorbid Disorder Combinations – Men						
Disorder Combination ^a	Alcohol Dependence			Anxiety Disorder		
	<i>n</i>	Mean	95% CI	Mean	95% CI	<i>p</i> -value
Alcohol dependence + Panic disorder	112	24.39	[22.58–26.21]	30.04	[27.77–32.30]	–5.65 <0.001
Alcohol dependence + Social phobia	110	24.38	[22.43–26.34]	14.64	[12.30–16.99]	9.74 <0.001
Alcohol dependence + Specific phobia	231	24.12	[22.84–25.39]	13.12	[11.63–14.61]	11.0 <0.001
Alcohol dependence + GAD	83	24.41	[22.07–26.74]	30.49	[27.15–33.84]	–6.08 <0.001
C. Mean Age of Onset for Specific Comorbid Disorder Combinations – Women						
Disorder Combination ^a	Alcohol Dependence			Anxiety Disorder		
	<i>n</i>	Mean	95% CI	Mean	95% CI	<i>p</i> -value
Alcohol dependence + Panic disorder	102	24.43	[22.69–26.16]	28.71	[26.04–31.39]	–4.28 <0.001
Alcohol dependence + Social phobia	72	24.68	[21.89–27.48]	15.94	[12.49–19.39]	8.74 <0.002
Alcohol dependence + Specific phobia	220	23.76	[22.19–25.32]	13.10	[11.61–14.58]	10.66 <0.001
Alcohol dependence + GAD	65	26.94	[24.10–29.79]	30.29	[27.32–33.26]	–3.35 0.048

Note: Based on NESARC, 2001–02 (Wave 1), among the full target sample ($n=995^b$), and separately for males ($n=536^c$) and females ($n=459^d$). GAD = Generalized Anxiety Disorder

^a Among those with a single anxiety disorder

^b Includes 48 individuals who reported identical ages of onset for both alcohol dependence and anxiety disorder

^c Includes 27 males who reported identical ages of onset for both alcohol dependence and anxiety disorder

^d Includes 21 females who reported identical ages of onset for both alcohol dependence and anxiety disorder

Weighted Mean Age of Onset for Specific Temporal Comorbid Disorder Combinations, Exclusive of Other Comorbid Anxiety Disorders

Table 3

A. Mean Age of Onset when Alcohol Dependence is Primary Diagnosis ^a (n = 328 ^b)						
Disorder Combination ^c	Alcohol Dependence			Anxiety Disorder		
	n	Mean	95% CI	Mean	95% CI	Difference p-value
Alcohol dependence + Panic disorder	140	22.93	[21.58–24.27]	33.46	[31.54–35.38]	–10.53 <0.001
Alcohol dependence + Social phobia	30	24.61	[20.02–29.19]	34.91	[25.80–44.02]	–10.30 0.058
Alcohol dependence + Specific phobia	76	20.88	[19.08–22.68]	28.81	[26.16–31.46]	–7.93 <0.001
Alcohol dependence + GAD	82	21.50	[19.58–23.42]	33.52	[29.79–37.26]	–12.02 0.077

B. Mean Age of Onset when Anxiety Disorder is Primary Diagnosis ^a (n = 619 ^b)						
Disorder Combination ^c	Alcohol Dependence			Anxiety Disorder		
	n	Mean	95% CI	Mean	95% CI	Difference p-value
Panic disorder + Alcohol dependence	59	29.33	[25.98–32.68]	21.90	[18.87–24.93]	7.43 <0.001
Social phobia + Alcohol dependence	144	24.63	[22.75–26.51]	11.85	[10.94–12.76]	12.78 <0.001
Specific phobia + Alcohol dependence	369	24.62	[23.46–25.78]	10.07	[9.32–10.82]	14.55 <0.001
GAD + Alcohol dependence	47	31.26	[27.43–35.09]	25.46	[21.94–28.99]	5.80 0.115

Note: Based on NESARC, 2001–02 (Wave 1). GAD = Generalized Anxiety Disorder

^aPrimary diagnosis = diagnosis occurring first

^bExcludes individuals reporting identical ages of onset for both alcohol dependence and the comorbid anxiety disorder

^cExclusive of all other anxiety disorders