Vulnerability to the Rapid (“Telescoped”) Development of Alcohol Dependence in Individuals with Anxiety Disorder*

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ABSTRACT. Objective: The frequent co-occurrence of alcohol dependence and anxiety disorder is a long-standing clinical conundrum. An underdeveloped perspective on this issue concerns the impact of a co-occurring anxiety disorder on the sequence and developmental course of alcohol-related milestones. Extrapolating from the body of basic science indicating overlap in the neurobiological processes associated with both anxiety disorder and alcohol dependence—particularly those involving the hypothalamic–pituitary–adrenal axis and elements of the amygdala—we hypothesized that anxiety-disordered individuals are vulnerable to the rapid development of alcohol dependence. Specifically, we predicted that the time from pre-dependence alcohol milestones (e.g., age at which regular drinking began) to post-dependence alcohol milestones would be briefer (“telescoped”) among those with an anxiety disorder. **Method:** Seventy-eight individuals with alcohol dependence who had recently

begun a chemical dependency treatment program underwent a diagnostic interview to determine the presence of current anxiety disorders and to establish the age at which several alcohol use and dependence milestones were first achieved. **Results:** We found that, compared with others in the sample, anxiety-disordered individuals transitioned significantly more quickly from the time they first began drinking regularly and first began getting drunk regularly to the onset of alcohol dependence, as well as from most pre-dependence alcohol milestones to the point at which their alcohol dependence was most severe. **Conclusions:** Individuals with anxiety disorders transition from regular drinking to alcohol dependence more rapidly than do individuals without anxiety disorders. These findings contribute to an improved understanding of the etiology of comorbidity and suggest novel directions for future research. (*J. Stud. Alcohol Drugs*, 72, 1019–1027, 2011)

THE POSITIVE CORRELATION BETWEEN anxiety disorder and alcohol dependence (“comorbidity”) has been established across multiple epidemiological surveys that include tens of thousands of individuals selected and weighted to be representative of the general U.S. population (Hasin et al., 2007; Kessler et al., 1997; Regier et al., 1990). These studies suggest that the odds of being diagnosed with alcohol dependence are two to four times greater among those with versus those without an anxiety disorder. Similarly, the rate of anxiety disorders among those being treated for alcohol and other substance use disorders greatly exceeds chance (e.g., Kushner et al., 2005, 50%; Ross et al., 1988, 45.4%; Schneider et al., 2001, 42.3%). A variety of theories have been put forward to account for this association, but, to date, the mechanisms and processes responsible for the high rate at which anxiety and alcohol use disorders co-occur remain uncertain. A promising but little used approach to better understanding this association concerns the impact of anxiety disorder on the course and temporal sequencing of alcohol-related milestones.

Epidemiological evidence suggests that various risk factors related to alcohol use are “stage specific,” with some affecting nonpathological milestones of alcohol use and

others affecting vulnerability to alcohol dependence directly (Heiman et al., 2008). Several lines of evidence suggest that anxiety disorder may increase one’s vulnerability to the development of alcohol dependence. Schneider et al. (2001) reported that an anxiety disorder in the presence of alcohol dependence predicts an earlier age at onset of withdrawal symptoms. Sartor and colleagues (2007) reported that having generalized anxiety disorder predicted a faster progression from age at first drink to the onset of alcohol dependence. Other studies show that anxiety problems are not related to an overall increase in alcohol consumption (e.g., Buckner et al., 2006; Gilles et al., 2006; Ham et al., 2007; Lewis et al., 2008; Menary et al., 2011) but are related to drinking to relieve negative affect and increased problems related to drinking (e.g., Cooper et al., 1995; Geisner et al., 2004; Kassel et al., 2000). These data suggest that anxiety disorder may relate more directly to drinking motives and the risk of transitioning to an alcohol disorder than to the actual intensity of alcohol use.

Consistent with this view, neurobiological theories of the development of alcohol dependence provide a framework for understanding how anxiety disorders might enhance susceptibility to transitioning from regular use of alcohol to the development of alcohol dependence. For example, Koob and Le Moal (2008), building on the pioneering work of Solomon and Corbit (1974), articulated a neurobiologically based opponent process theory of alcohol dependence. In this model, activation of the brain’s reward system (e.g., dopamine release in the nucleus accumbens) is the predominant response to alcohol use initially (“a-process”). However, with

Received: March 31, 2011. Revision: July 20, 2011.

*This research was supported by National Institute on Alcohol Abuse and Alcoholism Grants RO1 AA0105069 and KO2 AA0017886 (to Matt G. Kushner).

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chronic exposure to alcohol, the reward system is ultimately down-regulated, with a compensatory up-regulation of the brain's stress/anti-reward system (e.g., increased hypothalamic–pituitary–adrenal [HPA] and amygdalar activation; “b-process”). According to this view, the motivation for and psychological reaction to alcohol use tracks along with these neurobiological adaptations, where a-process drinking is driven by increasing pleasurable feelings and b-process drinking is driven by relieving aversive feelings.

Alcohol dependence, in this model, is understood to be a function of the hedonic homeostatic dysregulation associated with the transition from a-process to b-process drinking (e.g., Koob, 2003). However, because the brain's stress/anti-reward systems are understood to be up-regulated for those with an anxiety disorder even before alcohol exposure (Holsboer, 1989; LeDoux, 2007; Pervanidou, 2008; Van den Bergh et al., 2008), less exposure to alcohol may be required for these individuals to develop b-process–dominant drinking and, ultimately, alcohol dependence. Here we are suggesting that those individuals with an anxiety disorder may have a “head start” in achieving the neurobiological and motivational status that prefigures alcohol dependence in several neurobiological models of alcohol dependence, including that of Koob and Le Moal (2008; also see Koob, 2003), as well as Schepis and colleagues (2011).

Placed within the context of the “telescoping” paradigm (i.e., an accelerated transition from a nonpathological to a pathological state in a defined group; e.g., Lisansky, 1957), the material reviewed led us to hypothesize that the time from the initiation of pre-dependence alcohol use milestones (e.g., drinking regularly) to the onset and progression of alcohol dependence should be briefer for those with versus without an anxiety disorder. Specifically, we examined the time from several pre-dependence alcohol use milestones (e.g., age at the initiation of regular drinking) to the age at alcohol dependence onset and the point at which alcohol dependence severity was at its worst among individuals with versus without an anxiety disorder. Telescoping would be indicated by shorter intervals between the pre-dependence milestones and the alcohol dependence milestones among those with anxiety disorders. Confirmation of alcohol dependence telescoping among those with anxiety disorders would be consistent with the hypothesized neurobiological vulnerability to alcohol dependence in this group and would add to our understanding of etiological processes underlying the observed association between anxiety disorder and alcohol dependence.

Method

Participants

The data used in this study were originally collected as a part of a prospective treatment follow-up study reported

by Kushner et al. (2005). These participants were recruited from an adult (i.e., 18 years and older) inpatient chemical dependency treatment program. Participants were required to have a current diagnosis of alcohol dependence and to report that they were seeking treatment primarily for alcohol problems (vs. other drugs). Participants were excluded if they reported having a psychotic episode or manic episode in the 4 months before treatment. For the present study, participants who completed the baseline assessment were included ($N = 78$), with 26 (33.3%) who were female. Mean age at the time of the study was approximately 40 years. Additional recruitment information, including rates of participation and reasons for nonparticipation, can be found in Kushner et al. (2005). Participants were provided with a complete description of the study and informed consent was obtained.

Structured Clinical Interview for DSM-IV: Diagnoses and alcohol milestones

Diagnoses. All study diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID-IV I/P, Version 2.0; First et al., 1989). The SCID is a semi-structured diagnostic interview that determines the presence of specific psychiatric diagnoses during pre-specified timeframes according to DSM-IV criteria (American Psychiatric Association, 1994). The SCID was administered by senior honors undergraduate students who were trained and supervised by doctorate-level psychologists. The SCID was used to document the presence or absence of disorder during the 4 months preceding the interview (“current”). (This timeframe was used for reasons pertaining to the initial data collection reported by Kushner et al., 2005.) The specific anxiety disorders included in the present study were panic disorder (with or without agoraphobia), agoraphobia without panic, social phobia, obsessive–compulsive disorder, and generalized anxiety disorder. Post-traumatic stress disorder (PTSD) and major depression diagnoses were also assessed. Three individuals with PTSD but no other anxiety disorder were excluded from the analyses; however, individuals with PTSD and any other included anxiety disorder ($n = 9$) were retained in the sample. All individuals with major depression were retained in the sample as long as an anxiety disorder was also present.

Alcohol milestones and the creation of change scores. In the alcohol dependence module of the SCID, we added questions to determine the age at which various alcohol use milestones were first reached. Pre-dependence alcohol milestones included first drink, first regular drinking, first episode of drunkenness, and first regularly getting drunk. Alcohol dependence milestones included age at first meeting SCID criteria for alcohol dependence and age at most severe alcohol dependence. An example of one of the questions used to obtain these milestones is: “At what age did you first begin drinking alcohol regularly?”

For data analyses, we used change scores (in years) from each pre-dependence alcohol use milestone to each alcohol dependence milestone. These change scores were typically positive but could be coded as zero in cases in which the onset of a pre-dependence milestone and one of the two dependence milestones were reported as having occurred in the same year. (Keep in mind that this does not necessarily mean the two problems started at the same time but, rather, that they started within the same year.) Additionally, a small percentage of the change scores (~5%) were negative, indicating that one of the pre-dependence alcohol milestones was reported as having occurred after one of the alcohol dependence milestones. The vast majority of such cases involved the age at which the participant began getting drunk regularly being reported as later than the age at onset of alcohol dependence. However, there were also a few cases in which a participant reported dependence as having begun before the onset of regular drinking. Randall and colleagues (1999) encountered this same issue in their study of telescoping in women, and they chose to include negative numbers in their change score averages. However, we chose to exclude negative change scores from analyses. This decision reflected our concern that there was a greater likelihood of misunderstanding or otherwise inaccurate reporting in these instances. This issue also highlights our decision to include regular intoxication as a pre-dependence alcohol use milestone rather than as a pathological outcome along with the dependence milestones. The rationale for this decision is theoretically based and is also taken up in detail in the Discussion section.

Substance-induced anxiety disorder. Two criteria based on DSM-IV and adopted in this study must both be met to unambiguously establish substance-induced anxiety: (a) Alcohol disorder must have begun before anxiety disorder, and (b) anxiety symptoms must resolve following periods of abstinence lasting 1 month or more. In the present sample, two cases—one otherwise meeting the criteria for agoraphobia without panic and one meeting the criteria for panic disorder—were coded as not having an anxiety disorder because they met both of these substance-induced anxiety disorder criteria.

Data analysis

Chi-square tests and *t* tests were conducted to assess the statistical significance of differences in demographic characteristics between the anxiety and no-anxiety groups. Chi-square tests were applied to categorical variables such as sex, race, and employment status. Continuous variables, including age and number of drinks in 30 days before treatment (log-transformed) were contrasted between the groups using *t* tests. For the analyses of mean age at each drinking milestone and time between milestones, univariate analysis of variance (ANOVA) was used to look at two main fac-

tors: sex (male vs. female) and anxiety disorder diagnosis (no anxiety disorder vs. anxiety disorder). For the analysis of covariance (ANCOVA) analysis of time between pre-dependence and dependence milestones, anxiety diagnosis (present vs. absent) was the main effect, and gender was the covariate. We chose not to test for interaction effects between gender and anxiety status because our main goal was to examine the effect of anxiety disorder on ages at and time between various milestones while controlling for the effects of sex. Furthermore, small cell sizes would leave tests of interaction terms grossly underpowered. Statistical analysis of data was conducted using SPSS Version 19.0 software (SPSS Inc., Chicago, IL).

Results

Demographics by anxiety disorder status

Table 1 shows demographic and clinical variables for those with versus without an anxiety disorder. The rate of anxiety disorder in the sample was 54% ($n = 42$). There was a greater percentage of women in the anxiety disorder group than in the non-anxiety-disordered group, $\chi^2(1, N = 78) = 6.77, p < .01$. Table 1 shows that participants with an anxiety disorder had fewer drinks in the month preceding treatment than did participants without an anxiety disorder. However, an independent samples *t* test revealed that this was not a significant difference, $t(76) = 1.60, p < .10$. There were no significant differences between the anxiety group and the no-anxiety group in race, employment status, selective serotonin reuptake inhibitor use, other antidepressant use, anti-anxiety medication use, and atypical antipsychotic use. (Because benzodiazepines were not permitted on the inpatient substance treatment unit from which we recruited, they were not a part of our analysis.) Finally, although depression was common in both groups, a significantly greater proportion of the anxiety disorder group met criteria for this diagnosis, $\chi^2(1, N = 78) = 6.99, p < .01$. (Because depression had no significant effect on the overall results and because it was highly prevalent in both groups, we did not include it as a covariate in the final analyses shown.)

Anxiety disorder characteristics

Table 2 shows the rate of various anxiety disorders, age at onset of anxiety disorder, and order of onset information for anxiety disorders and alcohol dependence. As can be seen, panic disorder was the most common anxiety disorder in the sample, followed closely by social phobia and generalized anxiety disorder. Obsessive-compulsive disorder and agoraphobia without panic were relatively rare in the sample. Slightly more than one fifth of the sample met criteria for PTSD. As noted in the Method section, however, all of these cases also had to have at least one other anxiety disorder to

TABLE 1. Baseline demographics and clinical characteristics for those with and without an anxiety diagnosis

Variable	No anxiety diagnosis (<i>n</i> = 36; 46%) <i>M</i> (<i>SD</i>) or %	Anxiety diagnosis (<i>n</i> = 42; 54%) <i>M</i> (<i>SD</i>) or %
Age at treatment, in years [‡]	41.95 (10.16)	37.95 (10.48)
Sex, % female**	19.4%	45.2%
Race, % White	80.6%	76.2%
Employment		
Employed	61.3%	51.7%
Not employed	32.3%	48.3%
Student, not employed	6.5%	0%
Medication use		
Selective serotonin reuptake inhibitor	36.1%	47.6%
Other antidepressant	36.1%	31.0%
Other anti-anxiety medication	13.9%	11.9%
Atypical antipsychotic	0%	4.8%
Number of drinks in 30 days before treatment, (log transformed) [‡]	5.93 (1.32)	5.55 (0.68)
Major depression**	50%	78.6%

Note: Number of drinks was log transformed because of the significantly skewed distribution of this variable.

[‡]*p* < .10; ***p* < .01.

be included in the sample. In fact, nearly half of all cases had more than one anxiety disorder. Finally, Table 2 shows that, in nearly two thirds of cases, the onset of anxiety disorder occurred before that of alcohol dependence. (Where criteria for multiple anxiety disorders were met, we based the order of onset on the disorder with earliest onset.) In approximately 10% of cases, the onset of both the anxiety disorder and alcohol dependence occurred within the same year.

Mean ages at alcohol use milestones

Using ANOVA, we determined that significant differences between men and women were present for only one of the

six drinking milestones: age at first drink (Table 3). The mean age at which women reported taking their first drink was about 2 years younger than the mean age at which men reported achieving this milestone. ANOVA tests also revealed that the only significant difference between the anxiety disorder group and the non-anxiety-disordered group in the mean age at which the drinking milestones were reached was the age at which alcohol dependence severity was rated to be at its worst (Table 3). As shown, the mean age at which participants with an anxiety disorder reported their alcohol dependence was at its worst was about 6 years younger than those without an anxiety disorder. Table 3 also shows that group differences in the same direction were reported for age at dependence onset and age at first drink; however, these differences only approached statistical significance. The anxiety disorder group was about 3.5 years younger, on average, when they reported alcohol dependence onset compared with the non-anxiety-disordered group. Those with an anxiety disorder also were about 1.5 years younger than the non-anxiety-disordered group when they took their first drink.

Time from pre-dependence drinking milestones to dependence milestones

Gender effects. As shown in Table 4, men reported a significantly shorter transition time than women between the regular drunkenness and worst dependence milestones. No other statistically significant differences were found between men and women on times between the pre-dependence alcohol milestones and the dependence alcohol milestones. However, sex differences for time from first drink and first

TABLE 2. Anxiety disorder characteristics in anxiety-disordered participants

Variable	<i>n</i>	%
Panic disorder	19	46.4
Agoraphobia (no panic)	1	2.4
Social phobia	16	39.0
Generalized anxiety disorder	15	36.6
Obsessive-compulsive disorder	3	7.3
Posttraumatic stress disorder	9	22.0
Multiple anxiety disorders present	18	43.9
Age at anxiety disorder onset, ^a in years, <i>M</i> (<i>SD</i>)	18.8 (13.4)	
Anxiety disorder onset before alcohol dependence onset	26	63.4
Alcohol dependence before anxiety disorder onset	11	26.8
Anxiety disorder and alcohol dependence onset at same time	4	9.8

^aWhere multiple anxiety disorders were present, we used the disorder with the earliest onset to calculate this mean.

TABLE 3. Mean ages, in years, at drinking milestones, by sex and anxiety disorder

	Overall Sample (<i>N</i> = 78) <i>M</i> (<i>SD</i>)	Gender		Statistic <i>F</i> (<i>df</i>)	Effect size η^2	Anxiety disorder			
		Male (<i>n</i> = 52) <i>M</i> (<i>SD</i>)	Female (<i>n</i> = 26) <i>M</i> (<i>SD</i>)			No (<i>n</i> = 36) <i>M</i> (<i>SD</i>)	Yes (<i>n</i> = 42) <i>M</i> (<i>SD</i>)	Statistic <i>F</i> (<i>df</i>)	Effect size η^2
Alcohol use milestones									
Age at first drink	13.00 (4.23)	13.73 (3.58)	11.50 (5.05)	5.09* (1, 76)	.06	13.86 (3.81)	12.24 (4.46)	2.93 [‡] (1, 76)	.04
Age at first episode of drunkenness	14.14 (3.06)	14.25 (3.04)	13.92 (3.15)	0.20 (1, 76)	.00	14.42 (3.22)	13.90 (2.94)	0.54 (1, 76)	.01
Age at first regular drinking	18.00 (5.60)	18.46 (5.88)	17.08 (4.96)	1.06 (1, 76)	.01	18.42 (5.86)	17.64 (5.41)	0.37 (1, 76)	.00
Age at first regular drunkenness	21.11 (8.76)	21.51 (8.70)	20.31 (8.98)	0.32 (1, 76)	.00	22.65 (9.83)	19.79 (7.59)	2.11 (1, 76)	.03
Age at alcohol dep. Onset	22.95 (9.74)	22.71 (9.79)	23.42 (9.82)	0.09 (1, 75)	.00	25.17 (11.36)	21.00 (7.68)	3.63 [‡] (1, 75)	.05
Age at worst alcohol dep.	34.46 (11.81)	33.37 (12.32)	34.46 (11.81)	1.32 (1, 74)	.02	37.86 (11.91)	31.40 (10.99)	6.05* (1, 74)	.08

Notes: Dep. = dependence.

[‡]*p* < .10; **p* < .05.

regular drinking to the age at worst dependence severity approached statistical significance. In each case, the transition time was shorter for men than for women.

Anxiety disorder group effects. ANCOVAs were conducted to determine differences in the amount of time between pre-dependence alcohol use milestones and dependence milestones by anxiety disorder status while controlling for sex. Results largely conformed to study predictions. We found that the amount of time elapsed between various pre-dependence drinking milestones and alcohol dependence milestones was less for individuals with an anxiety disorder than for those without an anxiety disorder. As shown in Table 4, individuals with an anxiety disorder transitioned from regular drinking and from their first episode of drunkenness to age at alcohol dependence onset significantly faster than did those without an anxiety disorder. Additionally, we found that anxiety-disordered individuals transitioned significantly faster from first drink, first episode of drunkenness, and first regular drinking to the age at worst alcohol dependence severity. Furthermore, there was a strong statistical trend in the predicted direction for time from first regular intoxication to age at worst alcohol dependence. In other words, individuals with an anxiety disorder moved more quickly from every pre-dependence drinking milestone to the point at which they judged their alcohol dependence to be most severe. Last, we found that anxiety-disordered individuals did not transition significantly faster from first drink and first regular drunkenness to onset of alcohol dependence (although the differences were in the predicted direction).

Discussion

Past studies have consistently shown that alcohol disorders and anxiety disorders co-occur more frequently than can be explained by chance alone (Boyd et al., 1984; Grant

et al., 2004). However, the mechanisms linking these disorders are not well understood. In this regard, there has been little attention paid to the influence of anxiety disorders on the rate of transition through various drinking milestones, including the developmental course of alcohol dependence. Noting that the brain processes understood to characterize anxiety disorder overlap with the neuro-dysregulations leading to alcohol dependence, we hypothesized that having an anxiety disorder sets the neurobiological stage (i.e., prepares the brain) for the rapid development of alcohol dependence leading to a speeding up (“telescoping”) of the transition from pre- to post-dependence alcohol use milestones. This hypothesis was supported by our finding that the mean times between several pre-dependence alcohol use milestones and alcohol dependence milestones were significantly shorter for those with an anxiety disorder (Table 4).

The idea that a constitutionally (vs. alcohol-induced) dysregulated brain stress/anxiety response system could place individuals at high risk for developing dependence was anticipated by researchers conducting the earlier basic scientific work on which our hypotheses were based. For example, Koob (2003) notes that dysregulations in the brain’s hedonic response systems that produce a vulnerability to dependence can result either from the chronic use of drugs/alcohol or from “. . . constitutive elements (genetics or developmental history) . . .” (p. 238). Schepis and colleagues (2011) also clearly include psychiatric illness in general, and internalizing disorders in particular, as potential precursors to the type of HPA axis dysregulation they associate with susceptibility to the development of alcohol dependence. Our specific contribution in the present work is to translate these neurobiologically based findings and models to a specific hypothesis about how and why the vulnerability to alcohol dependence among those with anxiety disorders manifests and to cast predictions based on this hypothesis in a telescoping framework.

TABLE 4. Time between pre-dependence alcohol use milestones and alcohol dependence

	Overall <i>M Δ</i> (<i>SD</i>)	Gender		Statistic <i>F (df)</i>	Effect size η^2	Anxiety disorder ^a		Statistic <i>F (df)</i>	Effect size η^2
		Male <i>M Δ</i> (<i>SD</i>)	Female <i>M Δ</i> (<i>SD</i>)			No <i>M Δ</i> (<i>SD</i>)	Yes <i>M Δ</i> (<i>SD</i>)		
Alcohol milestones									
From age at first drink									
To age at dependence onset	10.00 (9.27)	9.02 (9.40)	11.92 (8.74)	1.71 (1, 75)	.02	11.31 (10.30)	8.85 (8.22)	2.615 (1, 74)	.03
Range	0.00– 42.00	0.00– 42.00	0.00– 34.00			0.00– 42.00	0.00– 37.00		
To age at worst dependence	21.50 (11.87)	19.69 (12.14)	25.20 (10.56)	3.75 [‡] (1, 74)	.05	24.00 (10.99)	19.25 (12.31)	6.11* (1, 73)	.08
Range	3.00– 50.00	3.00– 50.00	6.00– 44.00			6.00– 50.00	3.00– 43.00		
From age at first episode of drunkenness									
To age at dependence onset	8.83 (8.89)	8.49 (8.98)	9.50 (8.86)	0.22 (1, 75)	.003	10.75 (10.24)	7.15 (7.24)	4.08* (1, 74)	.05
Range	0.00– 40.00	0.00– 40.00	0.00– 34.00			0.00– 40.00	0.00– 30.00		
To age at worst dependence	20.32 (11.28)	19.16 (11.82)	22.68 (9.88)	1.65 (1, 74)	.02	23.44 (10.95)	17.50 (10.94)	8.36** (1, 73)	.10
Range	2.00– 48.00	2.00– 48.00	6.00– 44.00			6.00– 48.00	2.00– 38.00		
From age at first regular drinking									
To age at dependence onset	6.40 (6.83)	5.89 (6.43)	7.39 (7.58)	0.73 (1, 65)	.01	8.41 (7.98)	4.57 (5.01)	7.36** (1, 64)	.10
Range	0.00– 26.00	0.00– 25.00	0.00– 26.00			0.00– 26.00	0.00– 16.00		
To age at worst dependence	16.46 (10.54)	14.96 (10.67)	19.52 (9.75)	3.23 [‡] (1, 74)	.04	19.44 (9.70)	13.78 (10.65)	9.93** (1, 73)	.12
Range	1.00– 38.00	1.00– 38.00	4.00– 35.00			1.00– 34.00	1.00– 38.00		
From age at first regular drunkenness									
To age at dependence onset	4.17 (5.49)	3.81 (5.20)	4.71 (6.05)	0.36 (1, 55)	.01	4.94 (6.67)	3.29 (4.15)	1.93 (1, 55)	.03
Range	0.00– 25.00	0.00– 25.00	0.00– 24.00			0.00– 25.00	0.00– 15.00		
To age at worst dependence	13.84 (9.89)	12.25 (9.85)	17.17 (9.31)	4.18* (1, 72)	.06	15.21 (8.85)	12.55 (10.75)	3.34 [‡] (1, 71)	.05
Range	0.00– 38.00	0.00– 38.00	0.00– 35.00			0.00– 33.00	0.00– 38.00		

Notes: Milestones are in years. Zero in the range means that the two events happened in the same year (i.e., at the same age). Also see Method section regarding our handling of a small number of cases in which the initiating event was reported to have occurred before the outcome event (e.g., as in a report that an individual met criteria for alcohol dependence before the age at which he or she reported beginning to get drunk regularly). Δ = Change.

^a*F* tests for anxiety status reflect analysis of variance co-varying for gender; means are unadjusted.

[‡]*p* < .10; **p* < .05; ***p* < .01.

As alluded to in the Introduction, Koob's neurobiologically based opponent process model holds that pre-dependence alcohol use is characterized by activation of the reward system (i.e., "a-process") that is driven by increases in dopamine activity in the nucleus accumbens, opioid peptides in the ventral tegmental area, and gamma-aminobutyric acid (GABA) in the amygdala. However, with chronic exposure to alcohol, drinking becomes characterized by activation of the stress/anti-reward system (i.e., the "b-process") entailing increasing corticotropin-releasing factor (CRF) activity and corresponding amygdala and HPA axis activation. Because such dysregulations in the stress/anti-reward system are present even before experience with alcohol among those with anxiety disorder, b-process-dominant drinking may

characterize even very early drinking experiences for these individuals. With that said, b-process drinking is not synonymous with alcohol dependence but is rather a dynamic stage in the development of alcohol dependence. For example, Koob (2003) characterizes dependence as "... a continuous process of hedonic homeostatic dysregulation" (p. 232). It was from this perspective that we hypothesized that those with anxiety disorder start further along this continuum of dysregulation from the beginning of their involvement with alcohol.

Although the present work was inspired by these neurobiological models of alcohol dependence, our data were based exclusively on data gathered by clinical interview. Future research inspired by the current work could seek to study

directly the role of increased CRF activity and decreased neurotransmitter activity (e.g., neuropeptide Y) in the extended amygdala as it relates to alcohol dependence/withdrawal in individuals with anxiety disorders. Along these lines, it has been shown in animal models that antagonism of CRF1 in the amygdala blocks anxiety responses associated with withdrawal (Heinrichs et al., 1995; Rassnick et al., 1993). Similarly, Heilig and Koob (2007) describe studies indicating that CRF1 antagonism blocks stress- but not alcohol-cue-induced relapse in animal models. Furthermore, Gilpin and colleagues (2011) recently found that neuropeptide Y opposes GABA in the amygdala and inhibits the transition to alcohol dependence in an animal model. Notably, Coric and colleagues (2010) failed to find an anxiolytic effect for a CRF1 antagonist relative to placebo in human subjects with generalized anxiety disorder. However, Sinha et al. (2011) recently reported an association of high adrenal sensitivity, anxiety symptoms, and stress-induced alcohol craving with relapse following treatment for alcohol dependence. Additionally, future work could translate hypotheses such as those considered here to psychiatric disorders other than anxiety disorders. An early example of this approach was published in a detailed review by Markou and colleagues (1998) highlighting the neurobiological similarities between depression and drug dependence.

When considering the impact of anxiety on the course and sequencing of alcohol milestones, a potentially important issue is the age at onset of anxiety disorder relative to that of drinking milestones. For example, if a manifest anxiety disorder were required for the telescoping effect, then we would have to conclude that our model does not apply to the minority for whom anxiety disorder begins only after alcohol dependence is present. We attempted to examine this issue in post-hoc comparisons within the anxiety disorder group and found that the order of onset had no significant effect on the observed telescoping of alcohol disorder (analyses not shown). Notwithstanding the small *n* involved (only 11 individuals reported anxiety disorder onset after that of alcohol dependence), this may suggest that amygdala and HPA axis dysregulation, or at least a high vulnerability for such dysregulations, exists as a neurobiological risk factor for alcohol dependence among those with the anxiety disorder endophenotype even before the development of manifest anxiety disorder. Importantly, however, the statistical uncertainties noted just above make it clear that additional research will be necessary to articulate the role of comorbid disorder onset in alcohol-related telescoping.

That our work was conducted in a clinical sample in which every participant had alcohol dependence precluded the testing of some logical extensions of our hypotheses; specifically, those related to individuals who have not progressed to alcohol dependence at the time assessed. For example, our conceptual hypothesis—that individuals with anxiety disorders have a lower threshold for the development

of alcohol dependence—suggests that equivalent quantity of and time of exposure to alcohol should produce higher rates of alcohol dependence in an anxiety-disordered group compared with a non-anxiety-disordered group. Prospective samples beginning with individuals early in the window of risk for the onset of anxiety and alcohol disorders would be ideal for testing such hypotheses.

Also, given the logic of the model and the design of this study, it would be ideal if we could have confirmed that the total amount of alcohol consumed between the various milestones measured was roughly equivalent between those with and without an anxiety disorder. Determining this would be necessary to conclude definitively that anxiety disorder is associated with a lowered threshold for the development of alcohol dependence versus an increase in the drinking quantity and/or frequency leading to earlier development of alcohol dependence. With that said, the data we do have show that drinking amounts in the month before the study were similar between those with and without anxiety disorder, with the anxiety disorder group showing a statistical trend ($p < .10$) toward less drinking (Table 1). Nonetheless, designs and samples that would allow for a reasonable estimate of lifetime exposure to alcohol would be ideally suited to testing our study hypotheses.

Our decision to include regular intoxication as a “pre-dependence” alcohol use milestone reflected our understanding of Koob’s model in which the neuro-adaptations leading to alcohol dependence result from repeated bouts of intoxication with increasing withdrawal (see Heilig and Koob, 2007). A consequence of this design decision, however, was the emergence of a few (about 5%) seemingly paradoxical (or even nonsensical) instances of negative transition times (i.e., individuals reporting the initial emergence of a “pre-dependence” alcohol milestone [e.g., age at first regular intoxication] as occurring only after the initial onset of alcohol dependence). Showing that our decision to exclude these negative transition times did not have a meaningful effect on study results, post-hoc examination demonstrated that all of the same effects were significant when these transition times were included. Nonetheless, the emergence of even a small number of negative transition times serves as an alert for future researchers to attend closely to how alcohol milestones are measured and conceptualized on the developmental course between alcohol use and disorder.

In the course of testing the study predictions, some unrelated but interesting findings emerged. First, contrary to several earlier studies (e.g., Hernandez-Avila et al., 2004; Lisansky, 1957; Piazza et al., 1989; Randall et al., 1999; Schuckit et al., 1998), we did not find telescoping for women compared with men. In fact the trend (and one significant effect) was for men to have shorter transition times than women. Notably, at least two recent reports also failed to find telescoping in women (Hölscher et al., 2010; Keyes et al., 2010). Keyes and colleagues (2010) also found that a subset

of men transitioned more rapidly to alcohol dependence than did women. Clearly, the question of gender-related telescoping remains ambiguous.

We also found that the age at which one of the four pre-dependence milestones (i.e., first drink) was experienced was significantly earlier for women than for men. This is in contrast to other studies that find men typically initiate alcohol use at an earlier age than women (Hernandez-Avila et al., 2004; Piazza et al., 1989; Randall et al., 1999; Schuckit et al., 1998). In reviewing these past studies, however, we noted that the gender differences are generally small and not statistically significant. Furthermore, there are at least some reports (e.g., Hölscher et al., 2010) that also found women to have earlier substance involvement than men. As noted, these findings were not related to study predictions, but we do suggest that future studies in this area consider gender as a potentially important moderator. Although men tend to have more alcohol-related problems than women, women tend to have more anxiety-related problems than men (e.g., Kushner and Sher, 1993). Therefore, samples chosen for the presence of both anxiety and alcohol problems should be expected to have a different gender distribution than those chosen for either of these disorders alone.

In conclusion, this study articulates and begins to extrapolate and test predictions based on the influence of overlapping neurobiology of anxiety disorder and alcohol dependence. We suggested that those with anxiety disorder might be especially vulnerable to what Koob and Le Moal (2008) termed the “the dark side of addiction” (p. 38), in which drinking is motivated to compensate for a hypersensitive stress/anti-reward system. One pathway leading to the hypersensitivity described by Koob and others is neuroadaptations in response to chronic alcohol use itself. In this work, we developed the idea that having an anxiety disorder (or perhaps even being biologically vulnerable to developing an anxiety disorder) creates an alternative pathway to a hypersensitive stress/anti-reward state, setting the stage for the rapid development of alcohol dependence. In other words, we built on the work of Koob and others by proposing and beginning to test the idea that anxiety disorder constitutes an individual difference associated with a neurobiological vulnerability to the rapid transition from nonpathological to pathological alcohol use.

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