Effects of Early Internalizing Symptoms on Speed of Transition through Stages of Alcohol Involvement

by

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ABSTRACT

Alcohol use disorders and internalizing disorders are highly comorbid in adults, but how this comorbidity unfolds over development is not well understood. Previous retrospective studies in adults have shown that internalizing problems are associated with a rapid transition from first drink and first regular drinking to the onset of alcohol dependence. Some results also suggest that internalizing is a stronger predictor of rapid transitions through later stages of alcohol involvement, but these stage-specific effects have not been explicitly tested. The present study utilized a prospective dataset to investigate effects of adolescent internalizing symptoms on speed of transition through multiple stages of alcohol involvement. Specifically, it was hypothesized that greater early internalizing symptoms would predict a later age of first drink, a slower transition from first drink to first binge, and a faster transition from first binge to first dependence symptom. The moderating effects of gender were also examined. Data were from a longitudinal study of children of alcoholics and matched controls (n = 454) followed from late childhood to mid-life. Linear regression and Cox regression were the primary analytic strategies. Covariates were externalizing symptoms, family history of alcohol use disorders, and gender. Analyses also controlled for age at which the participant entered each interval. Generally, stage-specific hypotheses concerning the effects of internalizing were not supported. Internalizing symptoms marginally predicted an earlier age of first drink and a faster transition from first binge to first dependence symptom, and significantly predicted a faster transition through the overall interval from first drink to first dependence symptom. Internalizing was a stronger predictor of rapid transitions for women, and the effects of internalizing were not specific to early or later stages of

alcohol involvement among women. These results suggest that early internalizing problems are a general risk factor for a rapid transition through all stages of alcohol involvement, and this risk may be stronger for women than for men. These results have important implications for our theoretical understanding of the relationship between internalizing problems and alcohol use disorders as well as prevention and intervention efforts targeting these problems.

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INTRODUCTION

It is well-established that alcohol use disorders are highly comorbid with internalizing disorders (depression and anxiety disorders) in adults. This has been shown both in population-level studies (Hasin et al., 2007; Kessler et al., 1997) and in clinical samples (Kushner et al., 2005; Schneider et al., 2001). Multiple etiologic models exist that speak to this association, including the self-medication model (Khantzian, 1997) and the stress-response dampening model (Sher, 1987). Etiologic models such as these have been studied extensively in adults (e.g., Carrigan & Randall, 2003; Levenson et al., 1980; Swendsen et al., 2000) and to a lesser extent in adolescents (e.g., Colder, 2001), but few studies have attempted to understand how these co-occurring problems evolve over the course of human development and over the course of various stages of involvement with alcohol.

Broadly speaking, there are three possible ways in which this comorbidity might develop. The first possibility is that internalizing problems lead to the onset of alcohol problems. Alternatively, it might be that alcohol problems lead to the onset of internalizing problems. In contrast to these competing causal models, the other possibility is that a third variable causes both alcohol problems and internalizing problems (see Kushner et al., 2000 for a discussion of these three possibilities). Although there is some evidence to support each of these models, this study will focus on the first. Because internalizing problems likely onset for many individuals before the onset of alcohol use, it is important to understand how early internalizing symptoms impact the course of alcohol use and the progression to alcohol use disorders. Much of the research

on this model has used the standard prospective methodology of predicting rates of alcohol use and problems or incidence of alcohol use disorders from childhood and adolescent internalizing symptoms. These investigations have returned mixed results.

With respect to positive findings, prior research has demonstrated that internalizing problems in childhood and early adolescence prospectively predict alcohol use (Costello et al., 1999; Henry et al., 1993), regular and hazardous use of alcohol (Sihvola et al., 2008; Zimmerman et al., 2003), and the prospective development of an alcohol use disorder (Buckner et al., 2008; Guo et al., 2001; Sartor et al., 2007). However, some studies have found that internalizing problems in childhood and adolescence do not predict drinking outcomes (Englund et al., 2008; Steele et al., 1995), while other studies have found mixed effects (Kaplow et al., 2001; King et al., 2004; Maggs et al., 2008; Pitkänen et al., 2008). For example, King et al. (2004) found that neither separation anxiety nor overanxious disorder at age 11 predicted subsequent alcohol use or regular alcohol use, but depression at age 11 predicted both outcomes. Given these conflicting findings, it is clear that internalizing problems cannot simply be classified as a prospective risk factor for alcohol use and alcohol use disorders. More careful consideration of the relationship between these two variables over the course of development is needed.

In a recent review of the literature, Hussong and colleagues (2011) articulated a novel conceptual approach to the comorbidity question that is grounded in developmental psychology. They argue that a developmentally-focused approach could help make sense of some of the conflicting findings in the literature while also laying the groundwork for

new, more nuanced investigations into the "internalizing pathway" to alcohol use disorders. A key component of their argument is that the development of alcohol use disorders is a multi-staged, dynamic process that differs across individuals. Consequently, alcohol use disorders cannot be considered a unitary categorical outcome of interest. This idea is certainly not without precedent, as many researchers have proposed different typologies of alcohol use disorders, such as Cloninger's (1987) Type I and Type II alcoholics. However, the issue with static typologies of alcohol use disorders is that they do not allow for the conceptualization of a dynamic interplay between risk factors and alcohol use behavior at different stages of involvement with alcohol.

Recently, researchers have begun to identify subtypes of problematic alcohol use that are characterized by differing levels of involvement with alcohol over the course of development (e.g., early-onset alcohol dependence that persists into adulthood versus early-onset alcohol dependence that remits in adulthood). Interestingly, it has been shown that levels of adolescent negative affectivity as well as family history of internalizing disorders differ across these developmental subtypes (Chassin et al., 2002; Meier et al., 2013). Such evidence suggests that comorbid internalizing problems may in fact influence the course and trajectory of alcohol use disorders, but the precise nature of the relationship remains unclear.

As alluded to above, conceptualizing alcohol use disorders in such a way that developmental context is taken into account allows for the possibility that the same variable (such as internalizing problems) could serve to both reduce and/or exacerbate alcohol use and problems at different stages of involvement with alcohol and at different

stages of development. For example, Hussong and colleagues (2011) point out that separation anxiety has been shown to delay the onset of alcohol use (Kaplow et al., 2001), which upon first impression would seem to be protective against the development of alcohol use disorders. However, the authors point out that this delay in onset of use could theoretically be due to social withdrawal, which itself could act as a risk factor for alcohol use disorders if solitary drinking is initiated. This is a conceptual rather than an empirical example, but it illustrates one way in which internalizing symptoms could have varying effects on alcohol use behaviors at different points in development and at different stages of involvement with alcohol.

A developmentally-focused research approach has the potential to elucidate the relationship between internalizing problems and alcohol use disorders, but testing nuanced hypotheses concerning multiple stages of alcohol involvement is a challenge. One approach that might be particularly useful (and which has yielded interesting results in preliminary studies) is examining the influence of internalizing psychopathology on the speed of transition between different alcohol use milestones (e.g., initiation of use, initiation of binge drinking, onset of alcohol use disorders). If internalizing problems do have a dynamic impact on the course of alcohol use and eventual development of alcohol use disorders, this would be evidenced by results showing that internalizing problems accelerate (or slow down) the transition through specific stages of involvement with alcohol on the way to development of alcohol use disorders. Data with this degree of temporal resolution would allow for the construction of a more detailed picture of the way in which internalizing problems influence the development of alcohol use disorders.

Two recent studies illustrate the potential of this method to lead to new insights. In a 2007 study, Sartor and colleagues found that the presence of childhood or adolescent generalized anxiety disorder (assessed retrospectively in adulthood) predicted a faster transition from first drink to the onset of alcohol dependence. In other words, those with childhood or adolescent generalized anxiety disorder reported less time between taking their first drink and developing alcohol dependence. This was in contrast to lifetime oppositional defiant disorder and conduct disorder, both of which predicted an earlier onset of alcohol use but not a faster transition to alcohol dependence. These results, while limited due to their retrospective nature, illustrate the potential utility of studying alcohol use disorders in a developmental context. Knowing that internalizing problems predict a greater likelihood of onset of alcohol use disorders is informative, but the results of this study go a step further by suggesting the manner in which the process unfolds (possible delayed onset coupled with a rapid transition to disorder once use has begun).

In another example of this kind of retrospective analysis, Kushner et al. (2011) examined the transition between various alcohol use milestones and the onset of alcohol use disorders in an inpatient sample of alcohol-dependent adults. The authors found that the presence of a current anxiety disorder (in adulthood) retrospectively predicted a faster transition from both onset of regular drinking and onset of regular intoxication to the onset of alcohol dependence. However, current anxiety disorder did not predict a faster transition from first drink to the onset of dependence. These findings suggest that later stages of alcohol involvement may be the critical stages at which internalizing problems exert their influence (in this case, after the onset of regular or heavy drinking). Although

the authors did not analyze group differences in terms of the transition from first drink to regular drinking, given that the overall time from first drink to the onset of dependence did not differ by anxiety status, it appears that presence of an anxiety disorder may have predicted a slower transition through the first stages of alcohol use (from first drink to regular drinking and from first drink to regular intoxication) in this study. The use of adult internalizing diagnoses in this study is obviously not as compelling as childhood or adolescent diagnoses, but current disorder at least serves as a marker of vulnerability to internalizing problems and suggests that individuals who are predisposed to such problems may differ in their course of development of alcohol use disorders.

The results of the above studies suggest that internalizing problems may predict a delayed onset of alcohol use as well as a slower transition through early stages of alcohol involvement. These results also suggest that internalizing problems predict a more rapid transition through later stages of alcohol involvement on the way to development of an alcohol use disorder. Such a pattern suggests that alcohol may be more reinforcing for these individuals after a certain level of exposure (e.g., regular or heavy drinking) has been reached. The incentive-sensitization model of alcohol dependence (Robinson & Berridge, 1993), wherein the transition from "liking" the positive effects of alcohol to "wanting" or "craving" those effects is the key point in development of pathological alcohol use, may provide a helpful framework for thinking about these findings. Perhaps once individuals with internalizing problems begin drinking at a level where the pharmacological effects of alcohol are apparent, they make the transition from simply enjoying its positive effects to wanting or craving those effects more quickly than those

without internalizing problems. There is some evidence that reactivity to alcohol-related cues is enhanced under negative mood states, at least among alcohol-dependent individuals (Cooney et al., 1997; Litt et al., 1990), so perhaps individuals who are prone to experiencing negative affect are quicker to make the association between alcohol and its negatively reinforcing effects compared to individuals who experience negative affect less frequently. Although this model is speculative, it highlights the manner in which the more nuanced findings of developmentally-informed research might facilitate understanding of mechanisms driving the association between internalizing problems and alcohol use disorders.

Koob's (2003) neurobiologically-informed model of alcohol dependence is another theory that may be helpful in conceptualizing the mechanisms underlying stage-specific effects of internalizing symptoms on the development of alcohol use disorders. This model is particularly relevant to the later stages of alcohol involvement, including the end point of alcohol dependence. Broadly speaking, the model implicates dysregulation of brain stress systems during chronic alcohol withdrawal as the key process in the development of alcohol dependence. Koob posits that the progression to dependence is driven by escalating alcohol use that is aimed at relieving the symptoms of withdrawal. These withdrawal symptoms worsen with chronic use due to increasing dysregulation of the brain's stress systems, governed by the HPA axis and the extended amygdala (Heilig & Koob, 2007; Koob & Le Moal, 2008). There is evidence that internalizing psychopathology is associated with dysregulation in these same brain stress systems (Arborelius et al., 1999; LeDoux, 2007; Holsboer, 1989; Pervanidou, 2008; Van

den Bergh et al., 2008), and it has been proposed that individuals with internalizing disorders might be "neurobiologically prepared" for alcohol dependence due to the dysfunction already present in these areas (Kushner et al., 2011). However, as mentioned above, inferring a mechanism of action from the available evidence would be speculative. There is no direct evidence as of yet that would allow application of current etiological models of alcohol use disorders in articulating the "internalizing pathway" to alcohol dependence. However, with an approach that allows for the examination of the effects of internalizing symptoms on specific stages of alcohol use leading up to disorder it may be possible to obtain results that provide support (or do not provide support) for some of these stage-specific etiological mechanisms.

With that goal in mind, the current study aimed to provide the first investigation of the influence of early internalizing problems on the speed of transitions between alcohol involvement milestones in a prospective sample. This study utilized data from six waves of a large longitudinal study of children of parents with alcohol use disorders and demographically matched children of parents without alcohol use disorders. A measure of childhood/adolescent internalizing symptoms (collected at waves 1, 2, and 3, approximately ages 13, 14, and 15 respectively) served as the primary independent variable. The primary dependent variables included age of first use of alcohol as well as the length of three intervals of time elapsed between alcohol use milestones. The first interval was the total time from first use of alcohol to the first onset of any dependence symptom (e.g., withdrawal). This interval was then subdivided into two parts to be examined separately. The first part of the interval was the time period between first use

of alcohol and first binge (consumption of five or more alcoholic drinks on one occasion) and the second part of the interval was the time period between first binge and first alcohol dependence symptom.

It was hypothesized that individuals with higher levels of childhood/adolescent internalizing symptoms would consume their first alcoholic drink later than those with lower levels of internalizing and would transition more slowly from first drink to first binge (i.e., this interval would be longer among individuals higher in internalizing). This delay in onset and slower transition through early milestones has been implied in earlier studies (e.g., Kushner et al., 2011), but has not been explicitly tested as of yet; this was one novel contribution of the current study. It was also hypothesized that individuals with greater early internalizing would transition more quickly from first binge to first dependence symptom compared to their peers who were lower on early internalizing (i.e., the length of this interval would be shorter among those with higher internalizing). No directional hypotheses were made about the effect of internalizing symptoms on the length of the total time interval from first drink to first dependence symptom. Given that the hypothesized effects of internalizing on the early and later parts of this interval were in the opposite direction, this could result in an overall interval that is longer, shorter, or the same length for those with greater early internalizing versus less early internalizing.

Another novel contribution of the current study was the inclusion of covariates known to affect age of onset of alcohol use as well as the speed of transition to alcohol use disorders. Previous studies (including one in this dataset) have shown that family history of alcohol problems and externalizing symptoms predict both an earlier age of

first use of alcohol (Dawson, 2000; King et al., 2004) and an accelerated transition to alcohol use disorders once use has begun (Hussong et al., 2008); both of these variables were included as covariates in the current study. Some previous studies have also failed to account for the timing of prior milestones when examining the effects of internalizing problems on transitions through later milestones; the current study addressed this by controlling for age of onset of alcohol use when predicting the transition from first drink to first binge and from first drink to first dependence symptom. Age of first binge was included as a covariate when predicting the transition from first binge to first dependence symptom. If the effect of internalizing symptoms on the speed of a given transition can be accounted for by the age at which participants enter the interval, this would indicate that speed of transition is affected by developmental or environmental factors in addition to internalizing symptoms. If age at the earlier milestone cannot account for the effect of internalizing symptoms, this rules out developmental stage or age effects as an alternative explanation.

Finally, the moderating effects of gender were explored because conflicting findings have been reported regarding the influence of gender on the transition from first use of alcohol to the onset of alcohol use disorders (e.g., Johnson et al., 2005; Keyes et al., 2010; Randall et al., 1999).

METHOD

Sample Characteristics

The sample for the current study was drawn from a larger prospective study of children of parents diagnosed with alcohol use disorders and demographically matched control children (the Adult and Family Development Project; see Chassin et al. (1991)). The total size of the sample at wave 1 of data collection was 454, with 246 children of parents who met criteria for an alcohol use disorder (at least one parent met DSM-III criteria for alcohol abuse or dependence) and 208 controls. Some of the original target children had siblings who were recruited into the study at later waves, but the current study only utilized the original 454 target children to avoid data dependency issues. In order to be eligible for the study, participants were required to be 10.5-15 years old at wave 1 with parents who had Arizona residency and were either non-Hispanic Caucasian or Hispanic. The sample included 214 females (47.1%) and 240 males.

Procedure

Participants were recruited from the community, with parents who met criteria for alcohol use disorders identified through court and arrest records, community health organizations, and telephone screening. Matched control parents were identified via telephone screening in the neighborhoods from which parents with alcohol use disorders were recruited. Data was collected from children and parents using in person, computer-assisted interviews and questionnaires either at the family residence or in the laboratory. Retention through multiple follow-ups was high (see Table 1 for retention rates at each wave). Data from waves 1 through 6 was utilized in analyses.

Table 1. Mean Age and Retention Rate at Waves 1 through 6

	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6
Mean Age	13.22	14.17	15.17	20.37	25.70	31.51
(SD)	(1.44)	(1.44)	(1.44)	(1.36)	(1.62)	(3.21)
Percent of Original Sample Providing Data	N/A	98.9%	98.0%	89.6%	90.5%	93.3%

Measures

Achenbach Child Behavior Checklist – internalizing items

At Waves 1, 2 and 3, parents responded to a set of 28 items from the Child Behavior Checklist (CBCL; Achenbach, 1979) assessing past 3-month internalizing behavior in their child. These 28 items were selected because they loaded on the Internalizing factor for 12-16 year-old children of both genders (Achenbach, 1979). Children reported on a smaller subset of 7 of these items that loaded on the Internalizing factor for 12-16 year-old children of both genders. The parent items were scored on a three-point scale whereas the child items were scored on a five-point scale (with the purpose of increasing variability in responses; see Table 2 for mean scores from each reporter at each wave). Scores from the child reports were used to create internalizing factor scores for each participant (see "Data Analytic Plan" section below).

Achenbach Child Behavior Checklist – externalizing items

At waves 1, 2, and 3, parents responded to a set of 22 items from the Child Behavior Checklist (CBCL; Achenbach, 1979) assessing past 3-month externalizing behavior in their child. These 22 items were selected because they loaded on the Externalizing factor for 12-16 year-old children of both genders (Achenbach, 1979). Both children and parents reported on these 22 items. Parent items were again scored on a three-point scale and child items were scored on a five-point scale (see Table 2 for mean scores from each reporter at each wave). Scores from the parent reports were used to create externalizing factor scores for each participant (see "Data Analytic Plan" section below).

Table 2. Mean Internalizing and Externalizing Scores at Waves 1 through 3

Measure	Child Self-Report (1-5 Scale, Reverse Scored) Mean (SD)	Mother Report on Child (0-2 Scale) Mean (SD)	Father Report on Child (0-2 Scale) Mean (SD)
Internalizing Wv. 1	3.781 (.734)	.372 (.248)	.317 (.223)
Internalizing Wv. 2	3.835 (.743)	.365 (.266)	.319 (.227)
Internalizing Wv. 3	3.850 (.720)	.345 (.259)	.305 (.239)
Externalizing Wv. 1	4.349 (.490)	.316 (.247)	.290 (.242)
Externalizing Wv. 2	4.363 (.486)	.303 (.265)	.299 (.255)
Externalizing Wv. 3	4.307 (.507)	.301 (.255)	.300 (.267)

Onset of first drink and first binge

At waves 1, 2, and 3 of data collection (approximately ages 13, 14, and 15, respectively, see Table 1 for mean age at each wave), participants were asked at what age did they "first try an alcoholic beverage – more than just a few sips" and at what age did they "first drink five alcoholic drinks in a row." This information was used to create the "first drink" and "first binge" milestones for each participant (see "Alcohol involvement milestones" section below). At waves 4, 5, and 6 participants were also asked if they had consumed any alcohol and if they had consumed five or more drinks on a single occasion in the time between the current wave of data collection and the previous wave. This information from waves 4, 5, and 6 was used to estimate the age at which these milestones occurred for those who did not report any drinking or any binge drinking at waves 1 through 3 (again, see below).

Onset of first alcohol dependence symptom

At waves 4, 5, and 6 of data collection (approximately ages 20, 26, and 32.5, respectively), current DSM-III-R and DSM-IV diagnoses of alcohol dependence were determined using the computerized version of the Diagnostic Interview Schedule (C-DIS) (Robins et al., 1981). If a participant met criteria for alcohol dependence at a given wave, the earliest age at which any dependence symptom was experienced was recorded. This information was used to create the "first dependence symptom" milestone (see "Alcohol involvement milestones" section below).

Data Analytic Plan

Creation of internalizing and externalizing factor scores

Because agreement between parent and child ratings of internalizing behavior was quite low (e.g., correlation of .23 for child-mother reports and .20 for child-father reports at wave 1), a composite was not formed across reporters. Similarly, agreement between parent and child ratings of externalizing behavior was also somewhat low (e.g., correlation of .42 for child-mother reports and .34 for child-father reports at wave 1), so again the formation of a composite score across reporters was not warranted. Instead, only child reports of internalizing were used to create the internalizing variable and only parent reports of externalizing were used to create the externalizing variable.

Supporting the approach of using separate reporters, prior research has shown that children and adolescents self-report higher levels of internalizing problems compared to parent and teacher reports (Youngstrom, 2000) and that observer agreement is lower for ratings of child/adolescent internalizing problems compared to externalizing problems (De Los Reyes & Kazdin, 2005). This suggests that children and adolescents may have more insight into their own internal states compared to outside observers. Further, prior research has suggested that outside observers may be more reliable reporters of externalizing behavior in children and adolescents because externalizing behavior is overt and is highly salient to caregivers who are attempting to manage behavior (Stanger & Lewis, 1993).

The internalizing and externalizing variables took the form of factor scores, which were created using information from the first three waves at which internalizing and

externalizing behavior was assessed. Specifically, factor scores were computed for each subject by creating two separate three-level confirmatory factor analytic models in Mplus (Muthén & Muthén, 2010); one model for internalizing and one model for externalizing. Maximum likelihood estimation with robust standard errors was used as the estimation approach. Individual CBCL items (7 items at each wave for internalizing, 22 items at each wave for externalizing) loaded on three higher order latent factors (one for each wave of data collection). These three latent factors loaded on a single superordinate latent factor that represented symptoms across all three waves. Correlations between error terms for scores at adjacent time points (e.g. wave 1 with wave 2) were included in the models. Factor scores for these superordinate latent variables were utilized in the primary outcome analyses (score on the internalizing factor was the primary independent variable and score on the externalizing factor was a covariate).

Alcohol involvement milestones

Three alcohol involvement milestones were identified for each participant in the current study: 1) first consumption of an alcoholic drink, more than just a few sips (first drink), 2) first instance of five or more drinks on one occasion (first binge), and 3) onset of first symptom of alcohol dependence (only for those who met criteria for alcohol dependence at wave 4, 5, or 6). The age at which these milestones occurred was assessed at multiple waves (e.g., "at what age did you first try an alcoholic beverage?" was asked at waves 1, 2, and 3), so many participants had multiple values for the same milestone. In order to reduce potential recall bias, the milestone value was taken from the earliest wave at which a given behavior was reported. For example, if at wave 1 a participant

reported having their first drink at age 12, but at wave 2 reported that their first drink occurred at age 13, "12" would be the value assigned for age of first drink. Data was taken from the earliest possible wave because it was assumed that recall is more accurate when the behavior in question is more recent.

Some participants (approximately 33%) did not report the occurrence of their first drink or first binge at waves 1 through 3 (i.e., this milestone had not yet occurred by wave 3). For these participants, data from waves 4, 5, and 6 were utilized to estimate age of first drink and/or first binge. For example, if a participant did not report consuming an alcoholic drink at waves 1, 2, or 3, but at wave 4 reported consuming at least one drink in the past 5 years, that participant received a value for the "first drink" milestone equal to their age halfway between waves 3 and 4 of data collection (if this hypothetical participant was 15 years old at wave 3 and 20 years old at wave 4, they would have received "17.5" for their first drink value). Age of onset of first dependence symptom was assessed at waves 4, 5, and 6, and again the value for this milestone was taken from the earliest available wave.

The length of the intervals between alcohol use milestones was calculated by subtracting the age value of the "earlier" milestone in an interval from the age value of the "later" milestone. In the event that a participant reported a later milestone as occurring before an earlier milestone (e.g., first symptom of alcohol dependence reported as occurring at age 19 and first binge reported as occurring at age 20), the interval value was entered as "0," the logic being that the two events likely occurred at such a similar time that the order was recalled incorrectly. These reversed milestones made up

approximately 9% of all intervals calculated for all participants. A previous study employed a similar strategy with retrospective data from a single time point and found that the results were not affected (Kushner et al., 2011), providing some confidence that use of this approach with prospective data collected at multiple time points (which is less susceptible to recall bias) did not affect results. Additionally, analyses were replicated excluding cases in which the "later" milestone was reported as occurring more than two years before the "earlier milestone" in order to confirm that this strategy did not substantively change the results.

Primary analyses

Early internalizing symptoms (in the form of factor scores created from CBCL child reports of internalizing symptoms at waves 1, 2, and 3) were the primary independent variable in this study. The primary dependent variable was the speed of transition between various alcohol use milestones (first drink, first binge, and first dependence symptom). Covariates included COA status (whether the participant was recruited as a child of parent(s) with an alcohol use disorder), gender, and early externalizing symptoms (in the form of factor scores created from the CBCL parent reports of externalizing behavior at waves 1, 2, and 3). Age at the first milestone in each interval was also included as an additional covariate. For example, in the analysis of internalizing symptoms predicting the speed of transition from first drink to first binge, age of first drink was entered as a covariate. This was done to investigate whether any significant effect of internalizing symptoms on the speed of transition between milestones

was due in any part to the age or developmental stage at which an earlier milestone was reached.

First, COA status, gender, and externalizing symptoms were entered simultaneously into a linear regression predicting age of first drink. Internalizing symptoms were then added to the model to assess whether internalizing was a significant predictor of age of first drink above and beyond the effects of the covariates. Second, these same covariates (COA status, gender, and externalizing symptoms) were entered into a series of Cox regressions as predictors of speed of transition through 1) the total interval between first drink and first alcohol dependence symptom, 2) the interval between first drink and first binge, and 3) the interval between first binge and first dependence symptom. Internalizing symptoms were then added to these models to determine whether internalizing was a significant predictor of speed of transition through these intervals above and beyond the effects of the covariates. Next, age at the first milestone in each interval was added as a time-dependent covariate (see below) to the above models (at the covariate step) to determine whether internalizing remained a significant predictor of transition speed after accounting for age/developmental stage effects in addition to the effects of the other covariates.

Finally, gender was examined as a potential moderator of the effect of internalizing on transition speed. An interaction term of gender by internalizing symptoms was added to the above Cox regression models predicting the transition from first drink to first dependence symptom as well as the transitions from first drink to first binge and first binge to first dependence symptom. Although the gender by internalizing

interaction was of primary substantive interest, for completeness all possible 2-way interactions between gender and other predictors were included. If these interactions were not significant or marginally significant they were dropped from the model. In the event that any of the interactions between gender and internalizing were significant, the interactions were decomposed by running the models separately by gender.

Interpretation of results and inclusion of time-dependent covariates

In Cox regression, regression coefficients represent the relative effect of a predictor on the survival function (i.e., how long cases "survive" before an event of interest occurs) in a given time interval. A chi-square test statistic is provided for each regression coefficient, the significance of which indicates whether the regression coefficient is significantly different from zero in the population. Interpretation of significant coefficients in Cox regression involves examining the exponentiated regression coefficient, which is called the hazard ratio (or more generically, an odds ratio). The hazard ratio is the amount by which the odds of the event occurring (the hazard) at any point during the interval of interest are multiplied for every one-unit increase in the predictor. For example, in the case of this study, if the hazard ratio for internalizing symptoms were 2.0 in the analysis of the interval from first drink to first dependence symptom, this would indicate that the risk of onset of first dependence symptom at any point during the interval is doubled for each one-unit increase in internalizing symptoms. Given that Cox regression is modeling the instantaneous risk of the event of interest happening at any point during a given time interval, an increase in the hazard for a particular interval of time equates to less "survival" at every point during

the interval. In effect, an increase in the hazard results in a shortened survival time, which in this study equates to a more rapid transition between alcohol use milestones. Cox regression also assumes that the effects of covariates and predictors on survival rates are constant throughout the interval of interest (proportionality of hazards assumption). This assumption was tested by including the interaction of time with each covariate in each Cox regression model. If any of these interaction terms were found to be significant, the interaction term was included in the final model along with the main effect of that covariate (i.e., the variable was included as a "time-dependent covariate").

RESULTS

Descriptive Statistics for Alcohol Milestones

Table 3 contains descriptive data concerning the alcohol use milestones. Mean age of first drink was 13.58 (SD = 3.61), mean age of first binge was 16.67 (SD = 4.39), and mean age of first dependence symptom was 17.56 (SD = 2.82).

Model Fit Results for Internalizing and Externalizing Factor Scores

Adequate model fit was achieved in the CFA for the internalizing model (RMSEA = .046, CFI = .934, SRMR = .049). The initial externalizing model fit the data somewhat less well, so correlations between error terms for the same items at waves 1 and 3 were added. After adding these correlations, one item ("runs away from home") was found to have substantially lower loadings on the higher-order externalizing factors, particularly at waves 1 and 2 (standardized loadings of .11 at waves 1 and 2) compared to the other 21 items. Further examination revealed that this item was only endorsed by 1-3% of parents at each wave. Based on the low factor loadings and the infrequent endorsement, this item was removed from the factor model. This change, along with the addition of correlations between items at waves 1 and 3, resulted in a model with adequate fit (RMSEA = .043, CFI = .856, SRMR = .067). After this change, modification indices indicated that there were no major structural problems with the model (i.e., fit could only be improved by dropping more items), so the model was retained.

Table 3. Descriptive Statistics for Alcohol Milestones

Milestone	Mean	(SD)	N
Age of First Drink	13.58	3.61	414
Age of First Binge	16.67	4.39	362
Age of First Dep. Sx. Onset	17.56	2.82	157

Table 4. Internalizing Predicting Age of First Drink after Accounting for COA Status, Gender, and Externalizing

Variable	β	SE	*β*	*p*
Step 1: Covariates				
COA Status[a]	-1.204	.357	-.166	**.001**
Gender[b]	-.308	.351	-.043	.381
Externalizing Symptoms	-1.822	.597	-.152	**.002**
Step 2: Internalizing				
Internalizing Symptoms	-.749	.431	-.088	.083

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)
b. Gender was coded 1 = female, 2 = male

Does Greater Internalizing Predict a Later Age of First Drink?

As shown in table 4 (step 1) covariates of COA positive status (β = -.166, p = .001) and greater early externalizing (β = -.152, p = .002) were found to significantly predict an earlier age of first drink. Gender did not significantly predict age of first drink (β = -.043, p = .381). Contrary to hypotheses, greater early internalizing was not found to predict a later age of first drink after accounting for the effects of the covariates (see step 2 of Table 4). In fact, greater internalizing symptoms marginally predicted an earlier age of first drink (β = -.088, p = .083).

Does Internalizing Predict Speed of Transition from First Drink to First Dependence Symptom?

As shown in Table 5 (step 1), the covariates of COA positive status (OR = 1.789, p = .001) and male gender (OR = 1.961, p < .001) were found to significantly predict a faster transition from first drink to first dependence symptom. Greater early externalizing marginally predicted a faster transition from first drink to first dependence symptom (OR = 1.556, p = .055). As shown in Table 5 (step 2), greater early internalizing was found to significantly predict a faster transition from first drink to first dependence symptom (OR=1.544, p = .038) after accounting for the effects of the covariates. The odds ratio of 1.544 for internalizing indicates that for every one-unit change in internalizing symptoms, the hazard for first dependence symptom was multiplied by 1.544. This means that as internalizing symptoms increased, survival time from first drink to the onset of first dependence symptom decreased (i.e., transition speed increased).

Table 5. Internalizing Predicting Transition Speed after Accounting for COA Status, Gender, and Externalizing

	First Drink to Dep. Sx. (n=414)		First Drink to First Binge (n=414)		First Binge to Dep. Sx. (n=360)	
Variable	χ^2	Exp(β)	χ^2	Exp(β)	χ^2	Exp(β)
Step 1: Covariates						
COA Status[a]	10.664**	1.789	8.568**	1.384	6.890**	1.609
Gender[b]	15.227***	1.961	5.453*	1.288	10.563**	1.769
Externalizing Symptoms	3.679	1.556	1.206	1.208	2.597	1.490
Step 2: Internalizing						
Internalizing Symptoms	4.314*	1.544	2.147	1.218	3.749	1.503

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)

b. Gender was coded 1 = female, 2 = male

Early Stages of Alcohol Involvement: Does Greater Internalizing Predict a Slower Transition from First Drink to First Binge?

As shown in Table 5 (step 1), the covariates of COA positive status (OR = 1.384, p = .003) and male gender (OR = 1.288, p = .020) were found to significantly predict a faster transition from first drink to first binge, but greater early externalizing did not significantly predict a faster transition through this interval (OR = 1.208, p = .272). Contrary to hypotheses, greater early internalizing was not found to significantly predict a slower transition from first drink to first binge (OR = 1.218, p = .143). In fact, the positive odds ratio indicates that the effect was in the opposite direction than was hypothesized (although not significant).

Later Stages of Alcohol Involvement: Does Greater Internalizing Predict a Faster Transition from First Binge to First Dependence Symptom?

As shown in Table 5 (step 1), the covariates of COA positive status (OR = 1.609, p = .009) and male gender (OR = 1.769, p = .001) were found to significantly predict a faster transition from first binge to first dependence symptom, but greater early externalizing again did not significantly predict a faster transition through this interval (OR = 1.490, p = .107). In partial accordance with hypotheses, early internalizing was found to marginally predict a faster transition from first binge to first dependence symptom (OR = 1.503, p = .053). This effect was in the hypothesized direction but was not significant.

Effects of Age of First Drink and Age of First Binge

As noted above, Cox regression assumes that the effect of a given covariate/predictor on the survival function is constant over the time interval of interest

Table 6. Internalizing Predicting Transition Speed after Addition of First Drink/Binge to Model

	First Drink to Dep. Sx. (n=414)		First Drink to First Binge (n=414)		First Binge to Dep. Sx. (n=360)	
Variable	χ^2	Exp(β)	χ^2	Exp(β)	χ^2	Exp(β)
Step 1: Covariates						
COA Status[a]	12.489***	1.897	11.712**	1.468	3.768	1.447
Gender[b]	12.131***	1.836	4.078*	1.251	9.753**	1.735
Externalizing Symptoms	4.077*	1.608	2.866	1.344	2.139	1.441
Age of First Drink/Binge	27.571***	1.200	21.374***	1.089	7.872**	1.075
Age of First Drink/Binge*Time	35.751***	.963	21.039***	.982	32.653***	.956
Step 2: Internalizing						
Internalizing Symptoms	4.354*	1.553	2.542	1.241	2.722	1.430

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)

b. Gender was coded 1 = female, 2 = male

(proportionality of hazards assumption). This assumption was found to be violated when age of first drink and age of first binge were included as covariates in the above models, so these variables were included as time-dependent covariates. The inclusion of age of first drink and age of first binge at the covariate step of the above models did not change the nature of the findings (i.e., no significant internalizing effects became non-significant or vice-versa), although effect sizes changed somewhat (see Table 6). The largest change was in the analysis of the transition from first binge to first dependence symptom, where the OR for internalizing symptoms dropped from 1.503 to 1.430, and the *p* value changed from .053 to .099 after inclusion of age of first binge.

Moderation by Gender: Does the Effect of Internalizing on Transition Speed Differ by Gender?

As shown in Table 7, when a gender by internalizing interaction term was included in the above models (which included COA status, gender, externalizing symptoms, internalizing symptoms, and age of first drink/first binge), the interaction marginally predicted the transition from first drink to first dependence symptom (p = .077), significantly predicted the transition from first drink to first binge (p = .017), and did not significantly predict the transition from first binge to first dependence symptom (p = .255). None of the other gender by covariate interactions were significant; thus they were dropped from the models (all p values > .2). Given the presence of a marginally significant gender by internalizing interaction predicting the transition from first drink to first dependence symptom as well as the significant interaction predicting the transition from first drink to first binge, these analyses were re-run separately by gender. It was

Table 7. Full Model Including Gender by Internalizing Interaction

	First Drink to Dep. Sx. (n=414)		First Drink to First Binge (n=414)		First Binge to Dep. Sx. (n=360)	
Variable	χ^2	Exp(β)	χ^2	Exp(β)	χ^2	Exp(β)
COA Status[a]	11.649**	1.865	11.532**	1.471	4.042*	1.469
Gender[b]	16.235***	2.226	5.427*	1.314	12.605***	2.061
Externalizing Symptoms	2.690	1.480	2.170	1.300	1.496	1.361
Age of First Drink/Binge	28.981***	1.207	23.604***	1.095	9.765**	1.084
Age of First Drink/Binge*Time	36.551***	.962	22.595***	.981	32.855***	.956
Internalizing Symptoms	7.446**	2.249	7.599**	1.612	3.897*	1.835
Internalizing*Gender	3.137†	.477	5.710*	.522	1.298	.616

Note: † $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)

b. Gender was coded 1 = female, 2 = male

Table 8. Females Only: Internalizing Predicting Transition Speed after Accounting for COA Status, Externalizing, and Age of First Drink/Binge

	First Drink to Dep. Sx. (n=194)		First Drink to First Binge (n=194)		First Binge to Dep. Sx. (n=161)	
Variable	χ^2	Exp(β)	χ^2	Exp(β)	χ^2	Exp(β)
Step 1: Covariates						
COA Status[a]	7.431**	2.589	4.953*	1.461	3.406	1.914
Externalizing Symptoms	1.038	1.669	.908	1.344	.148	1.222
Age of First Drink/Binge	6.194*	1.189	.028	1.006	3.014	1.068
Age of First Drink/Binge*Time	10.144**	.956	3.159	.988	9.049**	.953
Step 2: Internalizing						
Internalizing Symptoms	6.968*	2.319**	6.180*	1.561	4.359*	1.980

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)

Table 9. Males Only: Internalizing Predicting Transition Speed after Accounting for COA Status, Externalizing, and Age of First Drink/Binge

	First Drink to Dep. Sx. (n=220)		First Drink to First Binge (n=220)		First Binge to Dep. Sx. (n=199)	
Variable	χ^2	Exp(β)	χ^2	Exp(β)	χ^2	Exp(β)
Step 1: Covariates						
COA Status[a]	5.177*	1.631	6.113*	1.448	.941	1.250
Externalizing Symptoms	3.080	1.600	2.349	1.384	2.065	1.510
Age of First Drink/Binge	23.342***	1.218	30.434***	1.129	4.719**	1.079
Age of First Drink/Binge*Time	26.993***	.961	17.008***	.979	21.198***	.954
Step 2: Internalizing						
Internalizing sx.	.085	1.092	.900	.813	.160	1.128

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

a. COA status was coded 0 = Control, 1 = child of alcohol-dependent parent(s)

found that greater early internalizing was a highly significant predictor of a more rapid transition through the entire interval (first drink to first dependence symptom) among females (see Table 8; OR = 2.319, p = .008) but was not a significant predictor of speed of transition through the full interval among males (see Table 9; OR = 1.092, p = .770). It was also found that greater early internalizing significantly predicted a faster transition through the early part of the interval (first drink to first binge) among females (see Table 8; OR = 1.561, p = .013) but not among males (see Table 9; OR = .813, p = .343).

The non-significant interaction between gender and internalizing for the later part of the interval (first binge to first dependence symptom) indicates that the effect of internalizing on the speed of this transition was not significantly different for men and women. However, given that greater early internalizing predicted a more rapid transition through the full interval as well as the early part of the interval among females, the effect of internalizing on the transition through the later part of the interval (first binge to first dependence symptom) was examined among women only in a post-hoc analysis. This was done in order to determine whether the observed effect of internalizing on the entire interval in women is driven by the observed effect in the early part of the interval or whether the effect of internalizing is significant in both parts of the interval. As shown in Table 8 (step 2), it was found that greater early internalizing was also a significant predictor of a faster transition through the later part of the interval among women (from first binge to first dependence symptom, OR = 1.980, p = .037). In other words, the observed rapid transition among females from first drink to first dependence symptom was not driven entirely by internalizing effects that were specific to the early stages of

alcohol involvement. Rather, the presence of early internalizing symptoms sped up the transition through both parts of the interval in females.

Replication of Results Excluding Cases with Negative Transition Times

Removal of cases with significant negative transition times (where the "later" milestone occurred more than 2 years before the "earlier" milestone) did not change the results relative to the analyses in the full sample. Greater early internalizing symptoms remained a significant predictor of a more rapid transition from first drink to first dependence symptom and a marginal predictor of a more rapid transition from first binge to first dependence symptom. In the gender-specific analyses removal of these cases did affect the significance of one result (in females). Specifically, internalizing was no longer a significant predictor of the transition from first binge to first dependence symptom (OR = 1.775, p = .100). However, the size of the effect remained substantial (OR of 1.775 with these cases removed versus an OR of 1.980 with these cases included).

DISCUSSION

The current study aimed to provide the first investigation in a prospective dataset of the effects of early internalizing symptoms on speed of transition through multiple stages of alcohol involvement. Previous studies have investigated this question using fully retrospective data from adults, and while the current study did utilize some retrospection, the longitudinal nature of the data allowed for more confidence in the accuracy of self-reported alcohol use milestones (because data was collected closer in time to the behaviors of interest). Another novel aspect of the current study was that the effects of internalizing were investigated after accounting for the effects of gender, family history of alcohol use disorders, and externalizing symptoms, all of which have been shown to be independent predictors of speed of transition to alcohol dependence (Keyes et al., 2010; Hussong et al., 2008). Additionally, age/developmental stage was included as a covariate in all analyses by controlling for the timing of the first milestone in each interval of interest. Previous studies of internalizing as a predictor of transition speed have controlled for some of these variables (e.g., Sartor et al. (2007) controlled for age at first drink and Kushner et al. (2011) included gender as a covariate), but this was the first study to control for the influences of all of these variables simultaneously, thus providing a rigorous test of the independent effects of internalizing on speed of transition through stages of alcohol involvement. Finally, this study also examined moderation of internalizing effects by gender, a question that prior studies have not investigated.

It was hypothesized that greater early internalizing symptoms would predict a later age of first use of alcohol, a slower transition from first drink to first binge, and a

faster transition from first binge to first dependence symptom. In general, these stage-specific hypotheses concerning the effects of internalizing were not supported. Rather, a pattern of results emerged suggesting that internalizing may be a more general risk factor that exerts its effects at all stages of alcohol involvement, and perhaps more so for women than for men. Specifically, it was found that greater early internalizing marginally predicted an earlier age of first drink, not a later age of first drink. Although this finding did not reach statistical significance, the direction of the effect was contrary to hypotheses. Also contrary to hypotheses, early internalizing did not predict a slower transition from first drink to first binge; in fact, the effect was again in the opposite direction (though not significant). Greater early internalizing marginally predicted a faster transition from first binge to first dependence symptom, so this hypothesis was partially supported. Finally, and perhaps most importantly, greater internalizing predicted a faster transition from first drink to first dependence symptom. No directional hypotheses were made concerning the effect of internalizing on the full interval from first drink to first dependence symptom, but this finding is highly informative given that stage-specific effects of internalizing were not found. Specifically, this result (in addition to the direction of internalizing effects observed for the early and later stages of the interval) suggests that early internalizing symptoms may predict a faster transition through all stages of alcohol involvement. In other words, the effects of internalizing symptoms do not seem to be specific to the early or later stages of alcohol involvement; the presence of early internalizing problems seems to shorten the entire interval.

Importantly, results from analyses in the full sample were qualified by the results of the moderator analyses. When moderation of the effect of internalizing by gender was examined, it was found that greater early internalizing significantly predicted a more rapid transition through the entire interval from first drink to first dependence symptom among women but not among men. Similarly, it was found that internalizing was a significant predictor of a rapid transition through the early part of the interval (first drink to first binge) among women only. The effect of internalizing on the transition through the later part of the interval (from first binge to first dependence symptom) was not found to differ significantly by gender, but in order to fully understand the nature of the effect in women, post-hoc analyses were conducted examining internalizing as a predictor of transition speed from first binge to first dependence symptom among women. This analysis showed that internalizing significantly predicted a more rapid transition through the later part of the interval just as it did in the early part of the interval, meaning that the effect of internalizing in women was not specific to a particular stage of alcohol involvement. Taken together, the results from the full sample as well as the moderator analyses suggest that internalizing is a general risk factor for rapid transition through early and later stages of alcohol use, and that this risk may be stronger for women than for men. Previous studies of the effects of internalizing on transition speed have not addressed this question of gender moderation, so this represents a novel finding of the current study (the implications of these results for future research are discussed later).

The finding that greater early internalizing symptoms predicted an earlier age of first drink was contrary to hypotheses, but consistent with results from some other studies

showing that various forms of early internalizing problems predict an earlier age of first alcohol use (King et al., 2004; Marmorstein et al., 2010; Costello et al., 1999). This hypothesis was based in part on Hussong's (2011) observation that some forms of internalizing could delay onset of use via social isolation (e.g., separation anxiety could lead to isolation from peers, limiting exposure to alcohol use among peers and delaying onset). However, the measure of internalizing problems used in the current study combined items that span both the anxiety and depression spectrum, meaning that it likely taps aspects of internalizing that do not involve isolation from peers and/or protection from high-risk environments. Hussong et al. (2011) foresaw the use of general measures of internalizing as a potential problem in investigations into the "internalizing pathway" to dependence, so perhaps the failure to support this hypothesis is not surprising. Specifically, Hussong et al. (2011) posited that different forms of internalizing may predict different trajectories of alcohol involvement over time. This is one limitation of the current study, and future studies should investigate the possibility that different forms of internalizing have different effects on transitions through stages of alcohol involvement.

The failure to support stage-specific hypotheses regarding the effects of early internalizing symptoms could perhaps also be attributed to the use of a general measure of internalizing symptoms, at least in part. It is possible that different forms of internalizing problems selectively affect speed of transition through particular stages of involvement with alcohol (again, as suggested by Hussong et al., 2011). However, the finding that internalizing symptoms in general predict a faster transition from the very

first use of alcohol to the first experience of a dependence symptom is noteworthy, because it suggests that a predisposition to experiencing negative affect in general may prime individuals to progress more quickly through all stages of alcohol involvement. If this is the case, this finding has significant implications for our theoretical understanding of the relationship between internalizing problems and alcohol use over the course of development, as well as implications for prevention and intervention.

The results of the current study suggest two possible kinds of mechanisms that might explain the effects of internalizing on speed of transition through various stages of alcohol involvement. First, it is possible that internalizing symptoms speed up these transitions via a single general mechanism that is active during all stages of involvement with alcohol. Second, although stage-specific hypotheses for the effects of internalizing were not supported, it is still possible that internalizing symptoms speed up transitions through different stages of alcohol involvement via different mechanisms (i.e., the mechanism is not the same in early stages of use as it is in later stages of use). In either case, general models of addiction articulated by other researchers (e.g., Koob, 2003; Robinson & Berridge, 1993) offer a helpful framework for interpreting the results of the current study and guiding future research in this area.

For instance, viewed through the lens of the incentive-sensitization model (Robinson & Berridge, 1993), the findings of the current study have interesting implications for the salience of alcohol-related cues and alcohol-related learning among those high in negative affect. As mentioned previously, it has been shown that negative mood states increase the desire to drink when presented with alcohol-related cues

(Cooney et al., 1997; Litt et al., 1990), so perhaps this increased salience of cues among those who frequently experience negative affect facilitates the learning of associations between alcohol use and the positive, reinforcing effects of alcohol. If this is the case, the crucial transition from passively "liking" the effects of alcohol to actively "wanting" or craving the positive effects of alcohol may happen more quickly among these individuals. Future studies could test this possibility by measuring relevant mediating variables of the effect of internalizing on increased transition speed during both early and later stages of use. One seemingly promising mediator is alcohol craving, which is nominated by Robinson and Berridge's (1993) incentive sensitization model as an important marker of the transition to pathological use. Additionally, craving has been shown to be higher among heavy drinkers compared to light drinkers (e.g., Field et al., 2008), suggesting that increased craving for alcohol use is an integral part of the development of pathological use over time. So, if it were found that craving increases more quickly after first use of alcohol or after first heavy use among those higher in internalizing symptoms, this could be interpreted as evidence for a more rapid transition from "liking" the positive effects of alcohol to "wanting" those effects among those high in negative affect.

Koob's (2003) neurobiological model of addiction also offers an intriguing framework for interpreting the results of the current study and guiding future research. Koob's model emphasizes the importance of withdrawal in the transition from non-pathological substance use to addiction. Specifically, the point at which substance use becomes primarily motivated by the goal of avoiding the unpleasant effects of withdrawal

(versus the goal of obtaining the positive effects of the substance) is identified as the threshold for addiction (Koob, 2003). This model seems especially well-positioned to explain rapid transitions through later stages of alcohol use among those high in internalizing (such as the transition from first binge to first dependence symptom in the current study). It has been observed that the state of alcohol withdrawal involves symptoms remarkably similar to those found in some internalizing disorders, such as trembling, excessive sweating, and anxiety (Roelofs, 1985), and that dysregulation in the same brain stress systems (such as the HPA axis) underlies both alcohol withdrawal and internalizing disorders (see Kushner et al., 2011). Perhaps internalizing symptoms predict a more rapid transition through later stages of use because individuals high in internalizing are predisposed to experiencing alcohol withdrawal due to pre-existing dysregulation in these brain systems. If this is the case, motivation for alcohol use might shift more quickly from obtaining the positive effects of alcohol to avoiding the negative effects of withdrawal among these individuals. Future studies could investigate this hypothesis by comparing the onset and severity of withdrawal symptoms after the initiation of alcohol use between those high in internalizing symptoms and those lower in internalizing. If severe withdrawal was reached more quickly among those high in internalizing, this could be interpreted as evidence for this particular mechanism.

In addition to possible theoretical implications, the results of the current study have the potential to inform prevention and intervention efforts among high-risk populations. Some existing interventions already target adults with both internalizing disorders and alcohol use disorders (e.g., Kushner et al., 2013; Najavitis et al., 2005), but

the finding in the current study that internalizing can speed up the transition through very early stages of use (at least among women) speaks to the need to address internalizing symptoms as a risk factor for alcohol problems early on in development, before alcohol use has progressed to more pathological levels. Given that substance use often onsets quite early in development (e.g., mean age of onset in the current study was 13.58), interventions targeting parents of children at high risk for internalizing (possibly via family history of internalizing) seem especially promising. Parent-focused interventions for adolescents at risk for externalizing problems have been shown to positively impact substance use outcomes (Dishion et al., 2002; Dishion et al., 2003), but there do not seem to be corresponding interventions targeting children with internalizing disorders with the goal of reducing alcohol use (Austin et al., 2005). Perhaps this is because the idea of internalizing problems as a risk factor for alcohol problems is not intuitive for parents (i.e., children with internalizing problems may not exhibit the same kinds of "risky" behavior as children with externalizing problems, such as associating with deviant peers). Perhaps interventions incorporating psychoeducation for parents about internalizing symptoms as a risk factor for subsequent alcohol problems would be helpful in preventing the development of pathological alcohol use in this population.

The finding of gender moderation in the current study is an especially intriguing area for future research. Interestingly, it calls to mind a long-standing and highly influential theoretical idea: Cloninger's typologies of alcohol dependence (Cloninger, 1987). In some ways, the results of the current study seem to resemble Cloninger's "Type I alcoholism," which is marked by traits of "anxious personality" and which he

explicitly states is the predominant form of alcoholism among women (however, Cloninger also asserts that Type I alcoholism onsets later in life, which clearly is not reflected in the results of the current study). Of course, the current results do not suggest that all pathological alcohol use among women is accompanied by internalizing problems, but they do suggest that internalizing symptoms are a particularly potent risk factor for a rapid transition to problematic use among women. Future studies should investigate this possibility in samples with a high prevalence of internalizing problems in both genders, as the current sample was not specifically recruited to meet this criterion. Given that analyses of moderation by gender in the current study were exploratory (i.e., no a-priori hypotheses were made about the moderating effects of gender), inferring mechanisms or causes for this gender difference are beyond the scope of the current study.

Although the results of the current study have important theoretical and practical implications, several limitations should be noted. First, although data were collected prospectively, some retrospection was still required on the part of the participants, especially regarding age of first dependence symptom. If, for example, a participant did not meet criteria for alcohol dependence until wave 5 (mean age of 25.7) but experienced their first dependence symptom at age 16, the length of retrospection in reporting this milestone could be a decade or more. That being said, the prospective nature of the data reduced retrospection compared to fully retrospective studies, which should lead to greater accuracy of data overall.

Another limitation of the current study is that the "first binge" milestone was not gender specific. That is, first "binge" was defined as first occasion of five or more drinks in a row for both men and women, which is not reflective of the National Institute on Alcohol Abuse and Alcoholism's definition of a "binge" as 5 drinks in a single occasion for males and 4 drinks for females (NIAAA, 2014). This could have affected the results of the current study because this may be a more severe milestone for women than for men (because it would indicate reaching a higher BAC on average for women). However, even if this milestone was more severe for women than for men, it still represents an intermediate stage of use between first use and the experience of dependence symptoms. Further, although this may have impacted the relative magnitude of the effects for women within particular intervals (early versus late), it seems unlikely that it would have impacted effects on the overall transition from first drink to first dependence symptom.

As detailed previously, some participants did not directly report an age of first drink or first binge at waves 1 through 3. If drinking or binge drinking was reported after wave 3 for these participants, data from waves 4 through 6 was used to estimate the age at which these milestones occurred. It is possible that this estimation strategy introduced error into the milestone estimates, although any error present should not have been systematic, given that the same estimation strategy was used for all participants without data at waves 1 through 3. Lending confidence to the estimation strategy used in the current study, the average ages of first drink and first binge in the sample were comparable to results obtained from multiple epidemiological studies of adolescents and young adults (e.g., Hingson et al., 2003; Johnson & Mott, 2001; Young et al., 2002).

This suggests that systematic bias was not introduced via the current estimation strategy. Age of onset of first dependence symptom was not estimated in this way for any participants, but comparing the values obtained for this milestone in the current study to epidemiological data increases confidence in the accuracy of this milestone. Most studies report age of onset of disorder rather than onset of first symptom, but nevertheless the values obtained in the current study (mean age of first dependence symptom was 17.5) are reasonable given that other studies have reported median age of onset of alcohol dependence to be 20.4 (DeWit et al., 2000) and 21.61 (Alvanzo et al., 2011). So although the average values in the current study were lower than in epidemiological samples, this makes some sense given that the current study was estimating onset of first symptom, which would presumably come before onset of disorder in many cases.

Finally, there were some cases in the current study where a participant reported a "later" milestone as having occurred before an "earlier" milestone (e.g., reporting age of first dependence symptom as 16 and age of first binge as 14). The majority of these "negative transitions" represented reversals of two years or less, and the general strategy employed in the current study was to set these negative transitions to zero and include these cases in analyses. The assumption was that these cases represented a recall error where one milestone occurred so close to the other in time that the order was recalled incorrectly. Supporting this assumption, the greatest number of these reverse transitions occurred for the transition from first binge to first dependence symptom, and first dependence symptom is the milestone at which retrospective distance could have been greatest (as mentioned previously). Further supporting the use of this strategy is the fact

that one recent study used this method of dealing with negative transitions and found that results were unaffected (Kushner et al., 2011), and when results in the current study were replicated after excluding all negative transitions of 2 years or more, only the significance of one post-hoc result was affected (internalizing no longer significantly predicted a more rapid transition from first binge to first dependence symptom among women, though the OR remained substantial).

In summary, the current study represents the first use of a prospective dataset to investigate the effects of early internalizing problems on speed of transition through various stages of alcohol involvement. Multiple variables known to affect speed of transition to alcohol dependence were included as covariates in analyses, and internalizing still emerged as a significant predictor of a more rapid transition from first use of alcohol to the onset of first dependence symptom. This effect was found to be stronger among women, and when the interval was broken down into early and late stages, internalizing predicted a more rapid transition through both stages among women. These findings have important implications for both our theoretical understanding of the relationship between alcohol use disorders and internalizing disorders as well as intervention and prevention efforts aimed at these problems. Future studies should seek to identify mechanisms through which early internalizing leads to faster transitions. Such studies may be helpful in identifying targets for prevention and intervention efforts. Additional studies examining potential interactions between internalizing and other risk factors (including those examined as covariates in the current study) also seem warranted,

as internalizing symptoms clearly do not act in isolation in speeding up transitions through various stages of alcohol involvement.

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