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A longitudinal study of the order of onset of alcohol dependence and major depression☆

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Abstract

Alcohol dependence and major depression commonly occur together; however, few studies have assessed prospectively the magnitude of the risk that one disorder imparts on the subsequent occurrence of the other. We used data from the first two waves of the Epidemiologic Catchment Area community survey ($n = 14\,480$) to estimate the odds of either major depression or alcohol dependence being followed by the other disorder after 1 year of follow-up. The odds of developing major depression associated with low, medium, and high levels of alcoholic symptoms at baseline were 1.66, 3.98, and 4.32 for females ($P < 0.001$), and 1.19, 2.49, and 2.12 for males ($P = 0.026$). Conversely, odds ratios indicating the 1-year follow-up risk of incident alcohol dependence within low, medium, and high categories of baseline depressive symptomatology were 2.75, 3.52, and 7.88 for females ($P < 0.001$) and 1.50, 1.41, and 1.05 for males ($P = 0.091$). Individuals with alcohol dependence appeared more likely to meet lifetime diagnostic criteria for both disorders after 1 year than individuals with depression. These results suggest that both alcohol dependence and major depression pose a significant risk for the development of the other disorder at 1 year. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Alcohol dependence and major depression commonly occur together (Deykin et al., 1987; Regier et al., 1990; Grant and Harford, 1995). The risk of alcohol dependence is significantly higher among individuals with depression than in the general population (Kessler et al., 1996); conversely, depression is more prevalent among individuals with alcohol dependence than without alcohol dependence (Kessler et al., 1997). The comorbidity of these two conditions is likely to remain a significant public health problem because rates of both disorders are increasing at younger ages (Klerman and Weissman, 1989; Helzer et al., 1990; Burke et al., 1991; Blazer et al., 1994; Wittchen et al., 1994), a pattern observed in multiple countries (Helzer et al., 1990; Cross-National Collaborative Group, 1992), and because early onset disorders are associated with an increased risk of secondary psychiatric conditions (Christie et al., 1988; Rohde et al., 1991; Giaconia et al., 1994; Kasch and Klein, 1996). Morbidity is also more severe in the context of co-occurring disorders than when either condition is present singly; for example, both violence (Swanson et al., 1990) and suicidal behavior (Rohde et al., 1991; Cornelius et al., 1995, 1996) are more likely among individuals with both disorders.

The co-occurrence of alcohol dependence and depression is particularly high in clinical samples (Lynskey, 1998). In a survey of 6355 patients receiving treatment for addiction, Miller et al. (1996) observed that the lifetime prevalence of depression was 43.7%. This finding is consistent with results from the COGA study by Schuckit et al. (1997), in which the lifetime prevalence of major depressive disorder among treatment-seeking alcoholics was 42.2%. However, the prevalence of de-

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pression that occurred prior to alcohol dependence was markedly lower (5.3%), as was the prevalence of depression occurring outside of the context of alcohol dependence (11.5%). These results highlight the importance of distinguishing the pattern of onset in studies investigating whether one disorder may be causally related to the other.

In a cross-sectional study of depressed outpatients, Abraham and Fava (1999) found that 31% of subjects had a comorbid substance use disorder. The order of onset of the drug dependence and depression depended on the class of substance abused. Alcohol dependence was more likely to follow major depression than precede it, supporting the hypothesis that alcohol served as self-medication in depression. However, since comorbidity between alcohol dependence and other psychiatric disorders is a significant predictor of treatment seeking (Wu et al., 1999), studies based on treated samples may overestimate the association between alcohol dependence and depression in the general population due to the selection of more severe cases into treatment (Berkson, 1946).

The association between alcohol dependence and major depression has been demonstrated by several large-scale, cross-sectional surveys of mental illness based on community samples. Helzer and Pryzbeck, in a report from the first wave of the community Epidemiologic Catchment Area (ECA), indicated that the odds of meeting DSM-III criteria for major depression were 1.8 times higher for respondents with alcohol dependence compared with non-alcoholic subjects (Helzer and Pryzbeck, 1988). The risk of depression was higher among female alcoholics than male alcoholics. Kessler et al. (1994) reported a similar pattern of associations in the National Comorbidity Survey (NCS), a nationally representative survey of 8098 respondents that assessed the presence of DSM-III-R disorders using the Composite International Diagnostic Interview. Compared with non-depressed respondents in the NCS, the lifetime odds of alcohol dependence were significantly elevated for both men (2.95) and women (4.05) with major depression (Kessler et al., 1997). Conversely, NCS data indicated a twofold increase in the lifetime odds of depression among subjects with alcohol dependence (Kessler et al., 1996). Results from the National Longitudinal Alcohol Epidemiologic Survey, a nationally representative survey of 42 862 individuals that assessed the presence of DSM-IV disorders, indicated that the lifetime odds of alcohol dependence were 3.56 times higher for subjects with DSM-IV major depression (Grant and Harford, 1995).

Taken together, previous studies are suggestive of a two- to fourfold increase in risk of the occurrence of either secondary alcohol dependence or depression given the presence of one of these disorders. However, longitudinal data are needed in order to verify the temporal associations between comorbid disorders. The present study was conducted in order to assess whether the association between alcohol dependence and depression might have a causal link by examining whether the presence of one disorder significantly predicts the development of the other disorder after 1 year. The multiwave data from the ECA are well suited to address this question since the ECA was based on a community sample interviewed at two points in time. The specific objectives of the present study are to determine whether primary alcohol dependence poses an increased risk for secondary major depression, and whether primary major depression presents an increased risk for the development of secondary alcohol dependence. We hypothesized that, since comorbid alcohol dependence and depression are common, both diagnoses would pose an increased risk for a secondary disorder. We also examined whether subclinical levels of alcoholism and depression were risk factors for DSM-III major depression and alcohol dependence, respectively.

2. Methods

2.1. Sample

The ECA survey was conducted by investigators at the following five academic sites between 1980–1985: Duke, Johns Hopkins, UCLA, Washington University, and Yale (methods described previously; Regier et al., 1984; Eaton and Kessler, 1985); its goal was to characterize the prevalence of mental illness in the United States. While the ECA recruited individuals from the general population as well as from clinical and institutional settings, this report is based entirely on the community sample ($n = 18\,571$). The eligible study population for the present report is comprised of the 14 480 respondents (78%) who were re-interviewed after 1 year. Since the primary objective of this study is to examine, separately, the risk factors for a first-time diagnosis of alcohol dependence and major depression, the analytic sample was restricted as follows to exclude prevalent cases. In assessing the risk factors for incident alcohol dependence, the 1028 subjects who met DSM-III criteria for a lifetime diagnosis of alcohol dependence at the baseline interview were excluded. Similarly, 577 subjects meeting DSM-III criteria for lifetime major depression at the baseline interview were not included in the analysis of risk factors for incident major depression.

Characteristics of the baseline and 1-year follow-up samples of the non-institutionalized ECA participants are presented in Table 1. The actual count of individuals in each category is presented along with the corresponding weighted percentages. The mean age of subjects upon ascertainment was 43 years (range, 18–96

years); approximately one-third of the sample was represented in each of the three age categories. Slightly more than one-half of the respondents were female (53%), and the majority was Caucasian (69%). Most respondents were in the second and third Socio-economic SES quartiles, although slightly more than 15% of subjects were in the highest and lowest SES categories, respectively. As shown in Table 1, the demographic characteristics of the sample at the 1-year follow-up interview were virtually identical to those of the entire baseline sample.

2.2. Diagnoses of alcohol dependence and major depression

Subjects were administered the Diagnostic Interview Schedule (DIS) upon ascertainment and again after 1 year (Robins et al., 1981). The DIS was designed for use by non-clinician interviewers to determine psychiatric diagnoses according to DSM-III (American Psychiatric Association, 1980). The DIS algorithm codes subjects as having major depression who have dysphoric mood plus two or more weeks of symptoms from at least four of the following categories: weight or appetite changes, sleep disturbance, loss of interest or pleasure, psychomotor changes, fatigue, worthlessness, trouble concentrating or thinking, and suicidal thoughts. DSM-III hierarchy rules were applied such that a diagnosis of depression was not assigned in the context of bereavement or in the presence of psychotic symptoms and organic brain disorder. For a diagnosis of alcohol dependence, DSM-III criteria require either a pattern of pathological use or impairment in social or occupational functioning plus having tolerance or withdrawal symptoms. As DSM-III criteria for alcohol dependence do not require the clustering of symptoms within a specified time frame, each symptom is assessed on a lifetime basis.

Table 1
Characteristics of the ECA sample at baseline and at 1 year[a]

	Baseline		1 Year	
	Number	Percent	Number	Percent
Age				
18–30	4778	33	3724	33
31–50	5018	33	4062	34
>50	8766	34	6686	34
Ethnicity				
Caucasian	12 176	69	9553	70
African–American	4301	19	3465	20
Hispanic	1433	9	997	8
Other	454	3	354	3
SES quartile				
1 (low)	4472	17	3322	16
2	6166	33	4682	32
3	5199	32	4244	33
4 (high)	2587	17	2143	18
Sex				
Male	7617	47	5837	46
Female	10 954	53	8643	54
ECA Site				
Duke University	3921	16	3087	16
Johns Hopkins University	3481	15	2768	15
UCLA	3131	21	2363	20
Washington University	3004	23	2574	26
Yale University	5034	25	3688	24
Total	18 571		14 480	

[a] Percentages are weighted; numbers indicate the actual count of individuals in each category.

The psychometric properties of the DIS have been evaluated in many ways. For example, DIS diagnoses of alcohol dependence made by non-clinician and clinician interviewers were compared, and their chance-corrected agreement, indexed by kappa (κ) (Cohen, 1960), was relatively high (0.68 and 0.86 in studies by Helzer et al. (1985) and Robins et al. (1981), respectively). The temporal stability of DIS alcohol dependence has been studied in test–retest studies conducted over multiple time frames. Semler et al. (1987) showed that the agreement between two lifetime diagnoses of alcohol dependence made, an average, 1.7 days apart was 0.66 (κ) with an expanded version of the DIS. Vandiver and Sher (1991) conducted a test–retest study of DIS lifetime diagnoses of alcohol dependence and found a similar level of agreement ($\kappa = 0.67$) for diagnoses made nine months apart. Diagnoses of alcohol dependence made by the DIS have also been compared with those generated by other instruments; kappa between the DIS and the SADS-L (Endicott and Spitzer, 1978) was 0.66 in a study by Hasin and Grant (1987b). Goethe and Fischer (1995) also demonstrated a high level of association between the DIS and the Michigan Alcoholism Screening Test (correlation $= 0.79$).

The reliability of DIS diagnoses of depression is generally lower than of alcohol dependence. Kappa values for non-clinician and clinician-administered DIS diagnoses of depression ranged between 0.33 and 0.63 in the studies already cited (Robins et al., 1981; Helzer et al., 1985). In the test–retest study conducted by Semler et al. (1987), kappa for DIS diagnoses of depression made a few days apart was 0.66, whereas it was 0.41 in the 9-month study of Vandiver and Sher (1991); however, Vandiver and Sher reported a higher level of reliability (0.64) of DIS depression using a different measure of agreement (Yule, 1912). In comparisons of the DIS with the SAD-L, kappa values for depression were quite variable, ranging from 0.13 (Hasin and Grant, 1987a) to 0.74 (Hesselbrock et al., 1982).

2.3. Analytic procedures

Analyses were conducted separately for the incidence of alcohol dependence and depression, which were defined as lifetime disorders absent at the Wave 1 interview and subsequently present at the Wave 2 interview. Multivariate logistic regression was used to estimate the association between baseline (Wave 1) and Wave 2 diagnoses. Regression coefficients were exponentiated to obtain odds ratios, which have the interpretation of the odds of meeting diagnostic criteria for the outcome disorder among subjects at each covariate level compared with the reference level. All models excluded prevalent cases of the outcome disorder and were estimated separately for females and males. We considered subclinical symptoms of the outcome disorder as potential confounders in situations where they preceded the baseline disorder of interest. Thus, while it was necessary to control for symptomatology that occurred prior to Wave 1, it was important to avoid controlling for symptoms that occurred during the follow-up period as those symptoms lie along the causal pathway of the outcome disorder (Rothman and Greenland, 1998). We accomplished this by comparing the age of first symptom onset for both conditions and creating two indicator variables: one for alcoholic symptoms preceding depressive symptoms and the other for depressive symptoms preceding alcohol symptoms. The onset of depressive symptoms was assessed by the DIS item which asks subjects their age at which they first had a period of 2 weeks or longer when they felt sad and experienced other depressive symptoms, and was obtained from all respondents who reported depressed mood along with symptoms from at least three other categories. The DIS item that ascertained the onset of alcoholic symptoms asked subjects to indicate the earliest age at which they had any alcoholic symptom, and was obtained from all respondents who reported at least one such symptom.

In addition to prior alcoholic and depressive symptoms, we also controlled for the presence of a DSM-III diagnosis of substance dependence and the following demographic factors: age, gender, and socio-economic status (SES). Age was categorized into three groups: 18–29, 30–49, and >50. Self-reported race was categorized as Caucasian, African–American, Hispanic, and Other. The ECA household measure of socio-economic status was used in these analyses; it was constructed based on the combined percentiles of occupational status, educational attainment, and household income (described previously by Regier et al. (1993)). Finally, we controlled for two features of the ECA design in all of the analyses: (1) the ECA site and (2) whether or not the DIS was administered to an informant proxy rather than directly to the subject (Regier et al., 1984). Analyses were conducted in SUDAAN (Shah et al., 1997) in order to account for the clustered sampling design used in the ECA study, and were weighted in order to account for differential selection probabilities of respondents. The ECA sampling weight also standardizes the study population to the age, race, and sex distribution of the United States according to the 1980 census and adjusts for non-response (see Kessler et al. (1985) for a detailed description of the ECA sampling weights).

3. Results

3.1. Risks for alcohol dependence at 1 year

Results of sex-specific logistic regression models predicting alcohol dependence are shown in Table 2. As already mentioned, these analyses were conducted among subjects without a lifetime history alcohol dependence at Wave 1. Model I includes a single indicator for a DSM-III depression diagnosis, whereas Model II has indicators for the level of depressive symptoms. For both sexes, there was no significant association between a diagnosis of major depression at baseline and alcohol dependence after 1 year. However, the odds of alcohol dependence were elevated in relation to the level of baseline depressive symptoms; this association was highly significant for females ($\chi^2 = 24.3$, degrees of freedom (df) $= 3$, $P = < .001$) and marginally significant for males ($\chi^2 = 6.5$, df $= 3$, $P = 0.091$). Compared with females and males without depressive symptoms, the adjusted odds of alcohol dependence corresponding to 1–3, 4–6, and 7+ depressive symptoms were 2.57, 3.52, and 7.88 higher for females, and 1.50, 1.41, and 1.05 higher for males. These results suggest that depressive symptoms pose a risk for becoming dependent on alcohol, that this risk is associated with mild depression, and that, for females, it increases with the severity of depression. As expected, the presence of alcoholic symptoms preceding depressive symptoms was strongly associated with subsequent alcohol dependence, as was a lifetime diagnosis of substance dependence.

3.2. Risks for major depression at 1 year

Risk factors for major depression at 1 year were assessed among those subjects without a lifetime history of depression at the baseline interview. Adjusting for demographic and clinical factors, the increased odds of depression after 1 year of follow-up associated with baseline alcohol dependence (Table 3, Model I) were significant for both females ($\chi^2 = 26.7$, df $= 1$, $P < 0.001$; odds ratio (OR), 3.52; 95% confi-

Table 2
Odds of alcohol dependence at 1-year follow-up by baseline factors[a]

Parameter	Model I[b]				Model II[b]			
	Female		Male		Female		Male	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
DSM-III depression diagnosis								
Yes	2.15	0.76–6.05	0.62	0.27–1.40				
No	1.00	–	1.00	–				
Chi-square (P), df = 1	2.2 (n.s.)		1.4 (n.s.)					
Number of depressive symptoms								
7+					7.88	2.86–21.70	1.05	0.35–3.15
4–6					3.52	1.86–6.66	1.41	0.69–2.87
1–3					2.75	1.52–5.00	1.50	1.08–2.08
None					1.00	–	1.00	–
Chi-square (P), df = 3					24.3 (<0.001)		6.5 (0.091)	
Alcoholic symptoms preceding depressive symptoms								
Yes	31.96	11.67–87.53	7.91	3.17–19.75	20.66	7.58–56.30	3.32	0.87–12.72
No	1.00	–	1.00	–	1.00	–	1.00	–
Chi-square (P), df = 1	47.3 (<0.001)		20.5 (<0.001)		36.5 (<0.001)		3.2 (0.074)	
Lifetime DSM-III substance dependence at baseline								
Yes	5.42	2.14–13.75	2.50	1.31–4.77	4.59	1.73–12.18	2.22	1.13–4.38
No	1.00	–	1.00	–	1.00	–	1.00	–
Chi-square (P), df = 1	13.2 (<0.001)		8.0 (0.005)		9.7 (0.002)		5.52 (0.019)	

[a] Also controlling for age, socio-economic status, ethnicity, ECA site, and proxy informant.
[b] In addition to the clinical and demographic covariates, Model I includes an indicator variable for the presence of a DSM-III diagnosis of major depression at the Wave 1 interview, whereas Model II includes three variables representing the number of depressive symptoms present at baseline.

dence interval (CI), 2.16–5.72) and males ($\chi^2 = 5.3$, df = 1, $P = 0.021$; OR, 1.77; 95% CI, 1.08–2.91). Model II, estimated with indicator variables for alcoholic symptoms rather than a diagnosis of alcohol dependence, revealed that the adjusted odds of depression at 1 year were significantly increased for subjects at higher levels of alcoholic symptomatology at baseline. The odds of depression corresponding to 1–3, 4–6, and 7 or more alcoholic symptoms were 1.66, 3.98, and 4.32 for females ($\chi^2 = 34.2$, df = 3, $P < 0.001$) and 1.19, 2.49, and 2.12 for males ($\chi^2 = 9.3$, df = 3, $P = 0.026$). While premorbid depressive symptoms were highly associated with depression, a lifetime diagnosis of substance dependence was not predictive of depression independent of alcoholic symptoms.

3.3. Risks of a secondary diagnosis due to primary alcoholism or primary depression

The order of onset of alcohol dependence and depression among individuals with both disorders has important implications for treatment, public health planning, and basic and clinical research (Schuckit and Monteiro, 1988; Abraham and Fava, 1999). Identifying the most likely pathway from primary to secondary disorders may be useful for the prevention of secondary disorders (Kessler and Price, 1993). Accordingly, we used logistic regression to compare the risk for developing secondary depression or alcohol dependence among individuals with primary alcoholism versus those with primary depression in an analysis restricted to the subset of respondents with a single lifetime diagnosis of either disorder at baseline ($n = 1421$). The dependent variable was an indicator of a first-time occurrence of either secondary depression or alcohol dependence after 1 year of follow-up. In addition to the covariates already described, we also controlled for the age of onset of the primary disorder. The objective of this analysis was to determine whether the risk of comorbidity between alcohol dependence and depression was related to their order of onset. Among males, the odds of a secondary disorder were 1.34 times higher (95% CI, 0.32–5.59) for alcoholics compared with depressives; among females, alcoholics were 7.51 times more likely to develop a secondary disorder than depressives (95% CI, 2.82–19.98). These results suggest that, among women, primary alcohol dependence is a far more likely

forerunner of major depression than primary depression is for secondary alcoholism.

4. Discussion

4.1. Constraints of the present study

There are several constraints to this study. The reliability of DIS diagnoses is imperfect. For example, the agreement between Wave 1 and Wave 2 lifetime diagnoses of major depression was only 0.44 (κ) among a subsample of the Los Angeles ECA site. While a perfect level of agreement is not expected due to true change occurring between the two interviews, there was inconsistency in the data insofar as individuals who had lifetime diagnoses at Wave 1 failed to have lifetime diagnoses at Wave 2. Sher and Trull suggested that a number of factors may account for the instability of diagnoses over time, including the tendency of respondents to report fewer symptoms upon re-interview (Robins, 1985; Sher and Trull, 1996) and the issue of near-threshold levels of symptomatology (Rice et al., 1992). In the reliability study conducted by Vandiver and Sher (1991), the authors examined this problem of diagnostic instability and indeed found that many discordant diagnoses were among individuals with a borderline number of symptoms. Respondents with discordant Wave 1–Wave 2 diagnoses (false negatives at Wave 2) reflect the measurable part of the inconsistency in DIS diagnoses. In all likelihood, a portion of individuals with Wave 2 lifetime disorders were incorrectly classified as incident cases because their disorder was not picked up by the DIS at Wave 1 (false positives at Wave 1). The likely consequence of this misclassification is the attenuation of regression coefficients (Armstrong, 1990), leading to an understimation of the actual risk between alcohol dependence and major depression.

A second difficulty in studies of self-report is the subjects' imperfect recollection of their age at symptom onset (Farrer et al., 1989; Rogler et al., 1992), which could have limited the study's ability to control for

Table 3
Odds of major depression at 1 year follow-up by baseline factors[a]

Parameter	Model I[b]				Model II[b]			
	Female		Male		Female		Male	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
DSM-III alcohol dependence diagnosis								
Yes	3.52	2.16–5.72	1.77	1.08–2.91				
No	1.00	–	1.00	–				
Chi-square (P), df = 1	26.7 (<0.001)		5.3 (0.021)					
Number of alcohol dependence symptoms								
7+					4.32	1.92–9.75	2.12	0.90–5.00
4–6					3.98	2.37–6.69	2.49	1.26–4.92
1–3					1.66	1.05–2.64	1.19	0.76–1.88
None					1.00	–	1.00	–
Chi-square (P), df = 3					34.2 (<0.001)		9.3 (0.026)	
Depressive symptoms preceding alcoholic symptoms								
Yes	3.00	1.32–6.82	8.03	3.28–19.66	2.28	0.96–5.43	5.92	2.44–14.35
No	1.00	–	1.00	–	1.00	–	1.00	–
Chi-square (P), df = 1	7.2 (0.007)		21.7 (<0.001)		3.6 (0.57)		16.2 (<0.001)	
Lifetime DSM-III substance dependence at baseline								
Yes	1.58	0.80–3.16	1.51	0.52–4.34	1.37	0.70–2.70	1.38	0.50–3.84
No	1.00	–	1.00	–	1.00	–	1.00	–
Chi-square (P), df = 1	1.8 (n.s.)		0.6 (n.s.)		0.9 (n.s.)		0.4 (n.s.)	

[a] Also controlling for age, socio-economic status, ethnicity, ECA site, and proxy informant.
[b] In addition to the clinical and demographic covariates, Model I includes an indicator variable for the presence of a DSM-III diagnosis of alcohol dependence at the Wave 1 interview, whereas Model II includes three variables representing the number of alcoholic symptoms present at baseline.

premorbid symptomatology. Wittchen et al. (1989) conducted a test–rest study of the DIS age of onset questions and found that the intra-class correlation for age of depression onset was between 0.49 and 0.77, and for alcohol dependence was 0.74. These results indicate a moderate to high level of reliability of the age of onset questions for both depressive and alcoholic symptoms. We examined this issue in the ECA dataset by computing the correlation between the Wave 1 and Wave 2 age of onset questions; they were 0.87 and 0.75 for the age of first depressive symptoms and alcoholic symptoms, respectively. We also found that, among ECA respondents reporting both alcoholic and depressive symptoms, 81% reported the same symptom chronology at both interviews.

A question may be raised if the reliability of the DIS is compromised among substance abusers because of a failure to discriminate between secondary major depression and acute depression directly caused by a toxic effect of the drug abused. However, the DIS does distinguish whether depressive symptoms were the direct result of alcohol use (Regier et al., 1990). The reliability of psychiatric diagnoses among substance abusing patients may also vary according to the diagnostic methodology used, as indicated by a review by Weiss et al. (1992) showing that differences in interview techniques, timing of interviews, and divergent diagnostic criteria contributed to substantial disagreement of psychiatric diagnoses in this population. Given the difficulty of assessing mental disorders among substance abusers, diagnostic instruments other than the DIS may enhance the reliability of the diagnosis of depression when it exists contemporaneously with alcohol dependence. Such instruments have since been developed for use among active substance abusers that aim to determine whether symptoms were caused by substance use (Hasin et al., 1996a).

Finally, the generalizability of our results may be compromised by the sampling design of the ECA, which was conducted in five geographic locations. Prevalence estimates of psychiatric diagnoses from the five-site ECA differ considerably from the nationally representative NCS (Regier et al., 1998). However, strong associations between alcohol dependence and depression were found in nationally representative surveys conducted after the ECA (Grant et al., 1996; Kessler et al., 1996, 1997), suggesting that the predictive associations between these two disorders are likely to apply to the population as a whole.

4.2. Summary and conclusions

This report of data from the Epidemiologic Catchment Area survey indicates that baseline symptoms of depression or alcohol dependence increase the risk of developing alcohol dependence or depression, respectively, at 1 year. These two paths to dual diagnosis of alcohol dependence and depression appear to be defined by dose–response relationships in which the greater degree of symptoms of the first diagnosis at baseline predicts more strongly the appearance of the second diagnosis at 1 year. The odds of developing major depression were elevated among subjects with increasing levels of alcoholic symptomatology. Conversely, the odds of meeting diagnostic criteria for alcohol dependence during the follow-up period significantly increased according to the level of baseline depressive symptoms, although this association was much more pronounced among females. The effects of one diagnosis preceding another were observed after just 1 year of follow-up; we speculate that, were these risks to persist over time, their magnitude would increase. A short-lived effect of one on the other is less likely, but possible. Were this to be the case, we would speculate the presence of a time-sensitive, and perhaps genetically driven, neurotoxic effect of alcohol on limbic centers modulating mood.

While dose–response relationships were found between primary and secondary disorders, a higher risk for a secondary disorder was indicated for major depression in primary alcoholics. This risk was statistically significant among female alcoholics, who were more than seven times as likely to develop depression as were depressives to become alcoholic. Thus, the development of depression in primary alcoholics is a significant public health problem. While this does not discount the finding that alcohol may be used as self-medication in primary depression (Khantzian, 1997; Abraham and Fava, 1999), there is little firm evidence suggesting that treatment of 'primary' depression has a benefit on 'secondary' alcohol dependence (Nunes et al., 1994; Petrakis et al., 1998).

The association between alcohol dependence and depression may be due, in part, to the depressive effects of alcohol that often remit following discontinuation of its use (Hasin et al., 1996b). Similarly, it is plausible that the psychosocial consequences of problem drinking may be 'depressogenic,' and that these psychosocial consequences may themselves be exacerbated by alcohol misuse. In addition, both disorders may share a common etiology. Winokur and colleagues found a high degree of familiarity between alcohol dependence and depression, although the degree of familiarity was much stronger for women than men (Winokur and Coryell, 1991; Coryell et al., 1992). Using genetically informative samples, other investigators have attempted to decompose the covariation between alcohol dependence and major depression into genetic and environmental components, and have reported that a substantial portion of this covariation may be due to

shared genes (Kendler et al., 1993, 1995; Tambs et al., 1997).

Our finding that the risk of developing depression after the onset of alcoholism is higher than the risk of developing alcoholism after depression is consistent with results from the National Comorbidity Survey indicating that primary alcohol dependence was more common than primary depression among subjects with both disorders (Kessler et al., 1997). However, in the NCS, alcohol dependence was more likely to precede depression among men, although it was just as likely to precede as to follow depression among women. Future studies will be needed to assess the relative importance of these and potentially other causal pathways.

Finally, our analyses suggest that subclinical levels of alcohol dependence and major depression significantly predicted development of the other disorder. This finding implies that the recognition and treatment of symptoms that may not meet full diagnostic criteria may prevent the emergence of secondary psychiatric disorders. These results further suggest a potential epidemiologic advantage of Likert-type scales of symptoms over binary coding of the presence or absence of specific diagnoses. This may be especially relevant for major depression in light of research indicating the dimensional nature of this condition (Kendler and Gardner, 1998). It may also be that the relationship between depression and alcohol dependence is strongest among individuals with subclinical levels of depressive symptomatology. This possibility is consistent with our finding that subthreshold depressive symptoms predict alcohol dependence much more strongly than a DSM-III diagnosis. In our sample, 44% of respondents who reported seven or more lifetime symptoms of depression at Wave 1 failed to meet diagnostic criteria for major depression; nonetheless, these individuals were at significant risk for developing alcohol dependence.

Further research is needed that examines the temporal ordering of alcohol dependence and depression, and assesses the relationship between the orders of onset of both disorders and their subsequent patterns of recurrence. Schuckit and Monteiro (1988) suggest that a hierarchy of symptoms should be established based on symptom chronology, and that the course of disease depends on which disorder was the primary one. This is so because patterns of remission and relapse differ in the presence of secondary disorders. Brown et al. (1995) found that the course of illness among subjects hospitalized for comorbid depression and alcoholism was different in those individuals with primary depression versus those with primary alcoholism. Medication management of depressive symptoms was not necessary in primary alcoholics after a period of detoxification; however, depressive symptoms did require psychotropic medication in primary depressives even after a period of sustained abstinence. Hasin et al. (1996b) reported in 1996 on 127 patients who were dually diagnosed with alcohol dependence and depression and followed for 5 years. Approximately 80% of patients whose alcoholism remitted also experienced a remission of their depressive symptoms, whereas only 40% of patients without a remission in their alcohol dependence experienced a remission of depression. Similarly, only those subjects who maintained their remission from alcohol dependence were able to avoid a relapse of depression. Mueller et al. (1994) observed virtually identical results in a 10-year follow-up study of depressed alcoholics and non-alcoholics. These data suggest that the depressogenic effects of alcohol may be ameliorated upon detoxification. On the other hand, depression did persist in a substantial number of patients regardless of their remission status from alcohol dependence.

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