ORIGINAL ARTICLE

Specificity of Bipolar Spectrum Conditions in the Comorbidity of Mood and Substance Use Disorders

Results From the Zurich Cohort Study

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Context: Although an association between mood disorders and substance use disorders has been well established, there is a lack of long-term prospective data on the order of onset and subtypes of mood disorders associated with specific substances and their progression.

Objective: To estimate the respective risks posed by subtypes of mood disorders or bipolar spectrum conditions for the subsequent development of substance use disorders.

Design: Six waves of direct diagnostic interviews were administered to a sample of young adults during a 20-year period. Mood disorders and syndromes assessed at each interview were used to predict the cumulative incidences of substance use disorders at subsequent interview waves.

Participants: We followed up 591 individuals (292 men and 299 women) who were selected at study enrollment from a representative sample of young adults in Zurich, Switzerland.

Main Outcome Measures: Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes, a semistructured clinical interview that collected data on the spectrum of expression of mood disorders and substance use and disorders for *DSM-III-R* and *DSM-IV* criteria.

Results: Individuals having manic symptoms were at significantly greater risk for the later onset of alcohol abuse/dependence, cannabis use and abuse/dependence, and benzodiazepine use and abuse/dependence. Bipolar II disorder predicted both alcohol abuse/dependence and benzodiazepine use and abuse/dependence. In contrast, major depression was predictive only of later benzodiazepine abuse/dependence.

Conclusions: In comparison with major depression, bipolar II disorder was associated with the development of alcohol and benzodiazepine use and disorders. There was less specificity of manic symptoms that tended to predict all levels of the substances investigated herein. The different patterns of association between mood disorders and substance use trajectories have important implications for prevention and provide lacking information about underlying mechanisms.

Arch Gen Psychiatry. 2008;65(1):47-52

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THE CO-OCCURRENCE OF mood and substance use disorders (SUDs) has been extensively documented in both clinical and community samples,[1-13] and the patterns of these associations differ considerably by disorder subtype. Alcohol dependence is more strongly associated with any mood disorder than either problematic use or abuse, and bipolar disorder is more strongly associated with any alcohol-related condition than either major depression or dysthymia.[6,9,11,14] Similar increases in magnitude are generally reported for drug dependence compared with abuse[5,6] and for bipolar disorder compared with major depression.[6,10]

Concerning the mechanisms underlying these forms of comorbidity, most controlled family studies[15-20] have found little or no support for the cross-transmission of SUDs with either bipolar disorder or major depression. Although some studies in twins have indicated that common genetic vulnerabilities may underlie major depression and alcoholism,[21] other research has found that shared etiologic factors underlying alcoholism, cannabis dependence, and major depression could be attributed to antisocial personality disorder.[22] The weak evidence for common etiologic factors underlying these different associations, therefore, suggests that causal mechanisms may be a more probable explanation. However, investigations of the most widely studied subtype of mood and SUD comorbidity, that is, major depression and alcohol dependence, have not

Table 1. Design of Zurich Cohort Study

Year	No. of Participants			Age (F/M), y	Assessment
	Women	Men	Total		
1978	2346	2201	**4547**	19/20	Screening
1979	299	292	**591**	20/21	Interview
1980	270	234	**504**	21/22	Questionnaire
1981	236	220	**456**	22/23	Interview
1986	232	225	**457**	27/28	Interview
1988	224	200	**424**	29/30	Interview
1993	215	192	**407**	34/35	Interview
1999	205	162	**367**	40/41	Interview

Abbreviations: F, female; M, male.

demonstrated unidirectional patterns either for the order of onset of these disorders[9,10,23,24] or for treatment response and syndrome severity changes as a function of comorbid disorder type.[23,25,26] This absence of uniformity has been attributed to the likelihood that multiple mechanisms of association are simultaneously active.[20] An alternative explanation is that current diagnostic boundaries do not sufficiently differentiate between profiles of comorbidity risk and, specifically, that a more careful separation of major depression from bipolar spectrum conditions may improve the prediction of secondary SUDs.[27]

Unlike the patterns observed for major depression, relatively consistent evidence has been found for causal associations underlying bipolar disorder and alcohol abuse/dependence. Ambulatory monitoring investigations have shown that while increases in depressed mood have little predictive value in explaining daily variation in alcohol use, diverse aroused states such as nervousness or happiness are highly significant predictors of such consumption.[28] Mania has also been shown to predict the later onset of alcohol dependence,[9] and recent epidemiological data suggest that the time to onset of the secondary syndrome is shorter in individuals with this form of comorbidity if the primary condition is bipolar disorder.[29] A direct causal model may, therefore, account for a large percentage of comorbidity between bipolar and alcohol use disorders, and potentially for major depression cases that fulfill broader criteria for bipolar spectrum conditions. This possibility is of particular importance in that a substantial percentage of individuals with lifetime major depression manifest bipolar disorder.[30-35]

Bipolar spectrum conditions are frequent in the general population[36] and remain associated with substance use disorders at levels below diagnostic thresholds.[37] However, the precise nature of these associations remains uncertain and may reflect several different underlying mechanisms. Aroused affect and expansive temperament characteristics, for example, may be largely specific to bipolar spectrum conditions while increasing the risk of abuse/dependence for a wide range of substances. This notion is consistent both with elevated risk behaviors and novelty seeking in patients with bipolar disorder[38,39] and with the high general prevalence of polysubstance dependence.[9,40-43] Conversely, a more limited causal phenomenon may require a match between mood symptoms and the pharmacologic properties of a given substance. This latter possibility is supported by observations that bipolar disorder may predict the onset of some forms of substance dependence[9] while having a fully opposite temporal relationship with others.[44] Discriminating between these alternatives, therefore, requires the prospective study of multiple classes of psychoactive substances in association with both major depression and bipolar spectrum conditions.

Despite considerable research on this topic, findings from epidemiological investigations are characterized by near-full reliance on retrospective estimates of disorder onset, and only a portion of studies have examined mood disorders in relation to multiple forms of SUD. The present prospective study was undertaken in an attempt to address these issues using the community-based sample of the Zurich Cohort Study. Young adults were interviewed directly in their homes 6 times during a 20-year period. Mood and SUDs, as well as subthreshold manifestations of these diagnostic categories, were assessed at each interview wave. The primary objectives were to examine the degree to which major depression and bipolar spectrum conditions may increase the risk of later onset of various forms of SUD and to assess the degree to which the observed patterns of comorbidity correspond to specific models of association.

METHODS

STUDY POPULATION

The Zurich Cohort Study is composed of a subset of 4547 individuals (2201 males and 2346 females) representative of the canton of Zurich in Switzerland who were screened using the Symptom Checklist-90 (SCL-90)–Revised.[45] The screening occurred in 1978, when male participants were aged 19 years and female participants were aged 20 years. To enhance the probability of cases, a 2-stage sampling procedure was used to identify 591 subjects (292 men and 299 women), two-thirds of whom scored at the 85th percentile or higher on the SCL-90 (high scorers) and one-third of whom were a random sample of individuals who scored below the 85th percentile.[46,47]

All subjects who met inclusion and exclusion criteria provided written informed consent or assent as appropriate, after receiving a complete description of the study and having an opportunity to ask questions. Diagnostic interviews were conducted in 1979, 1981, 1986, 1988, 1993, and 1999. Of the initial sample, 91% participated in at least 2 interviews; 82% in at least 3 interviews; 74% in at least 4 interviews; and 63% in at least 5 interviews. Sixty-nine percent of the original sample remained in the cohort during the 20-year study; 424 and 367 individuals participated in the 10- and 20-year interview waves, respectively (**Table 1**). Those who dropped out did not differ significantly in baseline measures of demographic characteristics or risk status at study enrollment, and no differences were observed in dropout rates for high and low scorers on the SCL-90.[48] Data were weighted to yield estimates of the population rates using coefficients that reflect the representation of the subjects with respect to the entire population assessed.

MEASURES

The diagnostic instrument used in the Zurich study was the Structured Diagnostic Interview for Psychopathologic and So-

matic Syndromes (SPIKE), a semistructured instrument that was developed for epidemiological studies.[49] Interviewers for the Zurich study were professional psychologists or psychiatrists with extensive experience in psychopathologic diagnosis and treatment. Initial training of interviewers involved group sessions to establish interrater reliability. After achieving an acceptable level of agreement, pairs of interviewers conducted sessions to establish pairwise reliability. Reliability was also maintained through periodic group sessions over the duration of the study. The interrater reliability of the SPIKE was $\kappa = 0.89$ and 0.91 for the symptoms of depression and anxiety (generalized anxiety disorder) and $\kappa = 0.90$ for the corresponding syndromal diagnoses.[50] The validity of the SPIKE has also been assessed by comparing physician ratings and medical records from local inpatient and outpatient settings with SPIKE diagnoses established by independent clinicians. High and moderate specificity levels were found for both threshold and subthreshold depression (0.90), anxiety (0.83), and mania (0.67).[51]

Information was collected on childhood characteristics, treatment history, psychiatric and somatic syndromes, and use and abuse of various substances. Symptoms, duration and frequency, subjective degree of distress, treatment, social consequences, history, age at onset, and family history were assessed for each syndrome. The core phenomenological probe for all of the syndromes was asked for each of the interim years between interviews in order to cover the entire assessment period. Screening probes were based solely on the major phenomenological features of each syndrome and were administered for each diagnostic category. Positive endorsement of the screening probe was followed by queries about specific symptoms and then by questions about symptom duration, frequency, and severity; treatment history; and impairment in work, social, and leisure activities. With this approach, diagnostic criteria for subthreshold syndromes and multiple systems of nosology could be applied. The classification of psychiatric disorders was based on the *DSM-IV* criteria for major depressive disorder, bipolar II (BP-II) disorder, and substance abuse/dependence. We also included subthreshold bipolar conditions that required either a reduced duration (<4 days) or number of symptoms (<4 symptoms) with impairment, referred to as *manic symptoms*.

ESTIMATION OF CUMULATIVE INCIDENCE

For analyses of cumulative incidence, mood disorders were classified according to a 4-level hierarchical variable, as follows: no mood disorder, major depressive disorder, manic symptoms, and BP-II disorder. With time, the highest level reached by each person was carried forward. For example, those who fulfilled criteria for manic/hypomanic symptoms at wave 3 and major depression at wave 4 were classified as having manic/hypomanic symptoms at wave 4. The frequency of respondents without a history of alcohol use was so small that the nonuse and use groups were combined for the initial level of alcohol exposure in trajectory analyses. Similarly, because of the small overall number of cases of cannabis and benzodiazepine abuse/dependence, these disorder categories were combined for each substance. Substance use disorders were, therefore, classified as follows: alcohol nonuse, abuse or dependence; cannabis nonuse, use, or abuse/dependence; and benzodiazepine nonuse, use, or abuse/dependence. At each time point, the dependent variable (substance use or abuse/dependence) was set to the highest value reached by the subject during each wave up to and including that wave. The principal independent variables (mood syndromes) represent the highest diagnostic level reached by the subject before that wave. The generalized ordinal logistic model used here (see the "Statistical Analysis" section) estimates odds ratios (ORs) for the association over these data points for each individual. Participants who met criteria for substance dependence at the initial interview were excluded from the analysis, including 2 individuals with alcohol dependence, 5 with benzodiazepine abuse/dependence, and 21 with cannabis abuse/dependence.

STATISTICAL ANALYSIS

A generalized ordinal logistic model was used to estimate the prospective effect of mood disorders on the development of subsequent SUDs. Unlike the proportional odds, this method estimates an equation for each cut point in the outcome measure, allowing the effect of the predictor variable to vary across the levels of the ordinal measure. Thus, separate measures of effect (ORs) can be estimated for each level, such as abuse/dependence, and these cut points can be understood as diagnostic thresholds. The OR for the alcohol abuse threshold, therefore, estimates the effect on abuse/dependence compared with nonuse or use; the effect for the dependence threshold estimates the effect on crossing the dependence threshold compared with nonuse, use, or abuse. The predictors were entered as indicator variables, setting no disorder as the referent category. The final models given herein include time (number of years in the study) and sex. Missing values were replaced with the last observed level for each variable that would bias the results negatively if subjects reached a higher level in a wave for which they were not assessed. Sampling weights were incorporated to account for the design, and robust variance estimates were calculated to account for the repeated measures. All analyses were conducted using commercially available software (SAS version 9, SAS Institute Inc, Cary, North Carolina, and STATA version 9, StataCorp LP, College Station, Texas).

RESULTS

PREVALENCE OF MOOD DISORDERS AND SUDs

The unweighted counts of participants meeting criteria for each of the mood disorder categories were as follows: no disorder (n=315), unipolar depression (n=87), manic symptoms (n=148), and BP-II disorder (n=41). The percentages of individuals in the cohort affected by mood and SUDs are given in **Table 2**. The cumulative incidence of major depressive disorder by 1993 was 9.7% of the total sample, and while no individual met criteria for bipolar I disorder by that year, 4.4% met criteria for BP-II and 23.5% had manic symptoms. Of the total sample, 17.9% met criteria for alcohol abuse/dependence by the last interview wave in 1999, 8% met criteria for cannabis abuse/dependence, and 3.4% met criteria for benzodiazepine abuse/dependence. The cumulative incidence of cannabis use never surpassed 18% of the cohort and remained relatively stable since the 1986 interview. In contrast, a small but steady progression in benzodiazepine use was observed at each wave, and most of the cohort (83.2%) had used benzodiazepines by the 1999 interview.

MOOD DISORDERS AS PREDICTORS OF SUD COMORBIDITY

Table 3 gives the generalized ordinal logistic model used to estimate the effect of mood disorders on subsequent substance use disorders. These associations were not significant for major depression and all categories of SUDs

Table 2. Cumulative Incidence of Mood Disorders and Substance Use Disorders[a]

Disorder	Year				
	1981	1986	1988	1993	1999
Mood					
Major depressive disorder	2.5	4.8	6.1	9.7	
Manic symptoms	1.8	17.0	22.4	23.5	
Bipolar II disorder	1.2	3.1	4.2	4.4	
Substance use					
Alcohol					
Abuse		10.6	10.6	8.4	9.2
Dependence		0.2	2.0	6.4	8.7
Cannabis					
Use		18.1	17.4	17.0	17.9
Abuse/dependence		6.4	7.4	7.9	8.0
Benzodiazepines					
Use		74.3	76.2	81.7	83.2
Abuse/dependence		2.5	3.5	3.6	3.6

[a]Values are given as weighted percentage.

Table 3. Mood Disorders as Predictors of Alcohol, Cannabis, and Benzodiazepine Use, Abuse, and Dependence[a]

Predictors	Abuse	Dependence
	Alcohol	
Major depressive disorder	1.8 (0.6-2.9)	2.2 (0.7-7.2)
Manic symptoms	2.4 (1.2-4.8)	4.4 (1.6-12.7)
Bipolar II disorder	9.1 (2.7-31.2)	21.1 (6.6-67.5)
No. of years	1.0 (1.0-1.1)	1.1 (1.1-1.2)
Male sex	6.3 (3.0-13.4)	12.5 (5.1-30.5)
	Use	**Abuse/Dependence**
	Cannabis	
Major depressive disorder	1.5 (0.7-3.6)	2.3 (0.7-6.9)
Manic symptoms	2.2 (1.2-4.1)	4.8 (2.0-11.6)
Bipolar II disorder	2.1 (0.8-6.0)	0.8 (0.2-3.7)
No. of years	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Male sex	2.4 (1.4-4.3)	3.1 (1.0-9.4)
	Benzodiazepines	
Major depressive disorder	2.7 (0.7-10.2)	13.2 (2.6-67.7)
Manic symptoms	3.6 (1.3-10.0)	11.5 (4.8-27.8)
Bipolar II disorder	6.9 (2.0-24.2)	14.1 (2.7-75.0)
No. of years	1.0 (1.0-1.1)	1.0 (0.9-1.0)
Male sex	0.3 (0.1-0.5)	0.7 (0.2-2.6)

[a]Values are given as odds ratio (95% confidence interval).

with the exception of benzodiazepine abuse/dependence (OR, 13.2; 95% confidence interval [CI], 2.56-67.67). In contrast, of all of the substances examined manic symptoms were highly consistent predictors of use or abuse/dependence. The magnitude of risk for later alcohol dependence (OR, 4.44; 95% CI, 1.55-12.73) was nearly twice that of alcohol abuse (OR, 2.41; 95% CI, 1.22-4.76), although the overall number of persons with manic symptoms who developed later alcohol abuse was greater than the number with alcohol dependence. The development of later cannabis abuse/dependence (OR, 4.82; 95% CI, 2.0-11.60) and benzodiazepine abuse/dependence (OR, 11.54; 95% CI, 4.80-27.78) was also significantly predicted by manic symptoms, as was general use of both substances.

The role of *DSM-IV* BP-II in predicting later alcohol abuse (OR, 9.11; 95% CI, 2.66-31.21) and dependence (OR, 21.05; 95% CI, 6.57-67.47), as well as benzodiazepine use (OR, 6.86; 95% CI, 1.95-24.19) and abuse/dependence (OR. 14.10; 95% CI, 2.65-75.09), is given in Table 3. In contrast to manic symptoms, this category of mood disorder did not predict the development of cannabis use or abuse/dependence.

COMMENT

PREDICTION OF SECONDARY DISORDERS

Past epidemiological research on the comorbidity of mood disorders and SUDs has been based almost exclusively on cross-sectional methods or retrospective estimates of disorder onset,[5,6,9-11,14,23,29] and few studies of any type have attempted to differentiate subthreshold bipolar conditions from major depression. Using longitudinal data and mutually exclusive categories of mood disorder, the present findings confirm the results of retrospective clinical and community studies of the strong association between bipolar disorder and the development of alcohol use disorders.[1-6,9-12,14] Moreover, the presence of manic symptoms was found to constitute a comprehensive risk factor for the future development of all categories of substance use or abuse/dependence investigated in this study. In comparison with major depression, the widespread association between manic symptoms and the full trajectory of all 3 substance categories provides new evidence for the specificity of bipolar disorder in the development of SUDs and further suggests that manic symptoms, even when below current diagnostic thresholds for hypomania, may be a powerful risk factor for these disorders. The patterns of association observed when carefully separating bipolar spectrum conditions from major depression also differed in important ways from previous population-based surveys. In particular, major depression was associated with an increased risk only of benzodiazepine abuse/dependence during the 2 decades covered by the study. The lack of association between major depression and later alcohol use disorders is in contrast to prospective epidemiological research that did not control for the influence of bipolar spectrum conditions[52] and may help clarify the inconsistent findings reported for this form of comorbidity.[20] However, the findings are convergent with previous observations in community samples of the lack of association between major depression and later cannabis abuse/dependence.[53]

MECHANISMS OF COMORBIDITY

Most previous family studies have demonstrated independent causes for alcohol dependence and mood disorders, and many investigations have, therefore, focused on causal explanations for these forms of comor-

bidity.[15-20] Among the potential causal mechanisms to be considered, the risk for several forms of SUD posed by bipolar diagnoses and manic symptoms indicates that self-medication is potentially less appropriate than more global explanatory models of association. The notion of self-medication assumes a contrast between the effects induced by a given substance and the nature of psychiatric symptoms experienced by the patient, therefore encouraging more targeted use of specific drug classes. Psychoeducation and other treatment approaches may, therefore, benefit from alternative models of substance use prevention in this population. In particular, these approaches may focus on reducing the use of diverse substances on the basis of the broad risks posed by temperamental and personality characteristics in persons with this disorder,[38,39] certain of which also aggregate in substance-dependent samples.[54]

This same causal model implicating behavioral, temperamental, or personality risk factors does not seem applicable to major depression, given its limited prospective association with most SUD categories. However, when compared with mutually exclusive groups of individuals with BP-II disorder or manic symptoms, major depression was independently associated with the later development of benzodiazepine abuse/dependence. In understanding this association, it is important to note that the percentage of individuals prescribed benzodiazepines is often greater than 50% in samples with mood disorders[55] and that a greater percentage of individuals prescribed benzodiazepines subsequently develop abuse compared with those who acquire this substance through other means.[56] The significant association of both bipolar disorder and major depression with benzodiazepine abuse/dependence, therefore, may be attributable in part to local prescription practices. Although the lack of association of BP-II disorder with cannabis use or abuse/dependence differs from findings observed for manic symptoms, the BP-II category also required a history of major depression, whereas subthreshold manic symptoms did not.

LIMITATIONS AND IMPLICATIONS

Several limitations of the study method should be considered in interpreting the present findings. Insofar as the cohort, the 20-year attrition rate of 38% may have implications for the generalization of the results to other populations, and the moderate sample sizes may have prevented the detection of smaller but clinically pertinent effects. The cohort was assessed through age 40 years, but the prospective nature of analyses limited the last assessment of mood disorders to age 35 years. While this is past the age of greatest risk for initial onset of most forms of mood disorder, it is possible that individuals fulfilling criteria, notably for BP-I, will be identified in future assessments. For these reasons, the findings may not be applicable to older cohorts and are limited to the clinical disorders and conditions described in the "Methods" section. The present method also does not permit the examination of specific factors such as impulsivity or other personality traits separately from bipolar spectrum conditions. The strategy for weighting of coefficients and the use of robust variance estimation yielded results that are representative of the reference population, but power remains limited for detecting the influence of sex and other individual differences. The analyses were also designed to examine the risk posed by mood disorders for the later onset of SUDs, with temporally primary manic symptoms and BP-II disorder, but bidirectional associations remain possible and should be examined in subsequent investigations. However, the emergence of mood syndromes after the onset of SUDs poses important questions about the nature of these clinical entities.

In terms of clinical implications, the prospective links observed between bipolar spectrum conditions and subsequent alcohol use disorders support recent interventions that incorporate both disorders in developing treatment strategies.[57] The present results further indicate that such treatment programs should be expanded to include a diversity of substance classes. Insofar as prevention of SUDs, consideration of BP-II disorder and manic symptoms is clearly merited, and early intervention in the form of psychoeducation and regular screening of substance use practices may be particularly beneficial in individuals with subthreshold manic symptoms. Although Angst et al[51] demonstrated that 16% of cohort participants with SUDs and 55% of those with mood disorders received treatment, the effect of services on the trajectories demonstrated in this sample remains an important question. Future studies will be required to examine this issue and the extent to which data from the present study have relevance for intervention and prevention in the transition to middle adulthood.

Submitted for Publication: December 3, 2006; final revision received July 27, 2007; accepted July 30, 2007.
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Author Contributions: Dr Merikangas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Financial Disclosure: None reported.
Funding/Support: This study was supported by grant 3200-050881.97/1 from the Swiss National Science Foundation.

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