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ORIGINAL PAPER

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Is the association of alcohol use disorders with major depressive disorder a consequence of undiagnosed bipolar-II disorder?

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Abstract *Background* There is emerging evidence that there is a spectrum of expression of bipolar disorder. This paper uses the well-established patterns of comorbidity of mood and alcohol use disorder to test the hypothesis that application of an expanded concept of bipolar-II (BP-II) disorder might largely explain the association of alcohol use disorders (AUD) with major depressive disorder (MDD). *Method* Data from the Zurich study, a community cohort assessed over 6 waves from ages 20/21 to 40/41, were used to investigate the comorbidity between mood disorders and AUD. Systematic diagnostic criteria were used for alcohol abuse, alcohol dependence, MDD, and BP-II. In addition to DSM criteria, two increasingly broad definitions of BP-II were employed. *Results* There was substantially greater comorbidity for the BP-II compared to major depression and for alcohol dependence compared to alcohol abuse. The broadest concept of BP-II explained two thirds of all cases of comorbidity of AUD with major depressive episodes (MDE). In fact, the broader the definition of BP-II applied, the smaller was the association of AUD with MDD, up to non-significance. In the majority of cases, the onset of bipolar manifestations preceded that of drinking problems by at least 5 years. *Conclusions* The findings that the comorbidity of mood disorders with AUD was primarily attributable to BP-II rather than MDD and that bipolar symptoms usually preceded alcohol problems may encourage new approaches to prevention and treatment of AUD.

Key words alcohol use disorders · alcohol abuse · alcohol dependence · bipolar II disorder · major depression · comorbidity

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Introduction

There is emerging evidence from prospective studies of community and clinical samples that a substantial proportion of individuals with lifetime major depression may in fact manifest bipolar disorder [1–3, 5, 17, 20, 21]. Application of a broader concept of bipolar disorder (i.e., by including overactivity as one of the core criteria rather than mood elevation or irritability as the sole criterion, and omitting a duration threshold) suggests that approximately 50% of all mood disorders may be more appropriately classified as bipolar II disorder [5]. Rates of major depression may be artificially elevated because of the delayed recognition of hypomanic symptoms as pathological, under-reporting of hypomanic symptoms, which subjects experience as normal, and the high threshold for the diagnosis of hypomania in the DSM-IV [5]. This has relevance for our approach to investigating the association with alcohol use disorders.

Patterns of co-occurrence of alcoholism and mood disorders (both MDD and BP disorders) have been well-established in clinical [10, 30] and community samples [3–5]. The magnitude of the association between mood and alcohol use disorders (AUD) differs substantially according to subtypes of both disorders. For example, alcohol dependence has been found to be far more strongly associated with mood disorders and with most other comorbid conditions, than either problematic alcohol use or abuse [23].

Convergent evidence from large-scale population-based studies has demonstrated a greater association of alcohol dependence [7, 12, 19, 28] with bipolar disorder than with major depressive disorder. Moreover, the NCS study reported that alcohol dependence-mania comorbidity was greater in males than in females (e.g., OR = 12.0 for males, OR = 5.0 for females) [19]. In one of the largest samples to date, Grant et al. [15] confirmed that the association of AUD was consistently higher with mania and hypomania than with MDD or dysthymia [16]. The clinical significance of alcohol use-mood disorder comorbidity is reflected in the increased prevalence of bipolar disorder among alcohol-dependent subjects who had attempted suicide [26, 27].

Therefore, the major aim of this study is to test whether lowering bipolar-II (BP-II) diagnostic thresholds will lead to a reduction in comorbidity between major depression and alcoholism. Further, we propose that a stepwise broadening of the diagnostic criteria for bipolar disorder would not weaken its association with AUD.

Methods

Sample

The Zurich study sample was selected from 4,547 subjects (2,201 males, 2,346 females) of age 19/20, representative of the canton of Zurich in Switzerland. These subjects were screened in 1978 with the Symptom Checklist 90-R (SCL-90-R) [11] in order to oversample persons with high global severity indices (GSI) who would be more likely to develop psychiatric syndromes. A stratified random sample of 591 subjects (292 males, 299 females) was selected for interview and subsequent follow-up. Two-thirds of the cohort consisted of high scorers (defined as those with scores > the 85th percentile on the GSI). The remaining third were a random sample of those with scores below the 85th percentile. The screening took place in 1978 when the male participants were 19 and the females 20 years of age. Six interview waves were conducted across 20 years, as shown in the Table 1. The interviews assessed a broad range of psychiatric and somatic syndromes and symptoms, including questions about duration, frequency and treatment as well as subjective impairment and distress. Across 20 years the attrition rate was 38% (men 44%, women 31%); 91% of the subjects were interviewed at least twice.

Diagnostic criteria

Diagnoses were derived by computer algorithm from the answers given in the interviews. Alcohol abuse and dependence were classified according to DSM-IV criteria (1994). This retrospective classification was possible because the interview's assessment of alcohol consumption and its consequences was not limited to diagnostic criteria. Major depressive episodes (MDE) were defined by DSM-III criteria (in the first two interviews 1979 and 1981) and DSM-III R criteria (1987) in the last four interviews (1986, 1988, 1993, 1999). Mania was defined according to DSM-IV criteria. BP-II disorder required the presence of a MDE plus hypomania. Hypomania/mania was not assessed at the initial interview in 1979. A formal diagnosis of hypomania based on DSM-IV and strict criteria was applied from the third to the sixth interview. Hypomania was defined in three different ways: (1) DSM-IV criteria, requiring elevated mood plus 3 of 7 criterial symptoms of mania plus a minimum duration of four days; (2) "strict" criteria, requiring 3 of 7 DSM-IV criterial symptoms, but not its time criterion of 4 days, and in addition behavioural consequences (subjectively perceived problems [financial consequences, trouble with the police, etc.] and critical remarks by significant others about a behavioural change); and (3) "broad" criteria, requiring the presence of any hypomanic symptoms without any time restriction and omitting the behavioural consequences. These three sets of criteria for hypomania were used to define three corresponding categories of BP-II: DSM-IV, strict, and broad, all requiring in addition the presence of a MDE. In the last four interviews (1986–1999), in which the number of manic symptoms was assessed, all subjects meeting broad criteria manifested at least 2 of 7 criterial symptoms of mania. Details on the validity of definitions 2 and 3 have been published [5].

Age of onset was evaluated retrospectively after having assessed the whole syndrome and defined as the first manifestation of the syndrome; the latter did not have to qualify for the diagnosis.

Statistical analysis

Prevalence rates and standard errors were computed with adjustment for sample stratification. Lifetime prevalence rates (cumulative lifetime incidence) refer to the total of the six 1-year prevalence rates across the six interviews. Associations between each mood disorder subtype and alcohol abuse and dependence were assessed using logistic regression models, adjusting for stratified sampling and sex. For group comparisons, χ^2-tests, Fisher's exact tests and Kruskal–Wallis tests were applied. Analyses were conducted using SAS for Windows version 8.01 and Stata 8.0.

Table 1 Design of Zurich cohort study

Year	Females	Males	Total *N*	Age (F/M)	Assessment
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

Table 2 Cumulative prevalence rates of alcohol use and BP-II disorders

Diagnoses	M + F	Males	Females	P (χ^2)
	Prevalence rates % (SE)			
Alcohol use disorders				
All	17.9 (2.3)	28.0 (3.9)	8.0 (2.2)	0.000
Dependence	8.7 (1.6)	14.5 (3.0)	3.1 (1.2)	0.000
Abuse	9.2 (1.8)	13.5 (3.0)	5.0 (1.9)	0.000
MDE	22.4 (2.4)	16.9 (3.1)	27.7 (3.7)	0.03
BP-II disorder				
DSM-IV	1.7 (7.6)	0.3 (0.2)	2.9 (1.5)	0.000
Strict	5.3 (1.3)	4.1 (1.5)	6.5 (2.1)	0.33
Broad	11.0 (1.8)	9.2 (2.4)	12.6 (2.7)	0.36

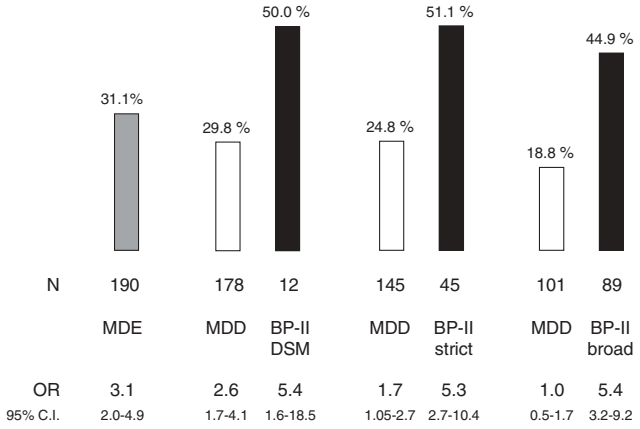

Fig. 1 Proportion of subjects with alcohol abuse/dependence in mood disorder subgroups based on varying definitions of BP-II disorder. OR = Odds ratio (adjusted for sex and stratified sampling), MDE = Major Depressive Episode, MDD = Major Depressive Disorder, BP = Bipolar Disorder

Results

Prevalence of AUD and BP-II

The sex-specific lifetime prevalence rates of AUD and BP-II according to the varying definitions given above are presented in Table 2. Eighteen percent of the sample fulfilled criteria for AUD. The prevalence of BP-II increased monotonically across the 3 increasingly broad sets of criteria, with 1.7% for the DSM-IV criteria, 5.3% for the strict, and 11.0% for the broad criteria. Males had greater rates of both alcohol abuse and dependence than females. By contrast, females had significantly higher rates of DSM-IV MDE and BP-II. The sex difference diminished as the definition of bipolar disorder broadened.

Sex, alcohol dependence and alcohol abuse

Table 3 presents the sex-specific associations between AUD and major mood disorders. The association between AUD and mood disorders was consistently stronger in females than in males. This was true for both alcohol dependence and abuse. For both males and females the association of mood disorders with alcohol dependence was also consistently stronger than with alcohol abuse. For both men and women, the associations between AUD and MDD decreased markedly in step with the broadening of the diagnostic concept of BP-II.

AUD according to the varying definitions of BP-II

Figure 1 shows the rates of AUD among subjects with mood disorders, subdivided according to MDE and the varying definitions of bipolar disorder. AUD was much more strongly associated with BP-II than with MDD, irrespective of the definition of bipolar disorder (DSM-IV, strict or broad criteria). Using increasingly broad definitions of bipolar disorder, the association between AUD and MDD decreased from 29.8% for DSM-IV BP-II disorder to 18.8% for the broadest concept of BP-II. With the broadest definition of BP-II, the association between MDD and AUD ceased to be significant

Table 3 Associations (odds ratios = OR) of alcohol abuse, dependence with mood disorders by sex

	Mood disorder	N	% with alcohol abuse	OR	95% CI	P	% with alcohol dependence	OR	95% CI	P
Men	MDE[a]	72	15.3	1.3	0.6–2.6	0.581	34.7	3.8	2.0–7.1	0.000
	BP-II DSM-IV	4	25.2	2.3	0.2–22.7	0.481	75.0	5.8	1.6–20.2	0.006
	Remaining MDE	68	14.7	1.2	0.5–2.6	0.674	32.3	2.9	1.7–4.9	0.000
	BP-II strict	21	23.8	2.1	0.7–6.3	0.166	38.1	5.8	2.8–11.8	0.000
	Remaining MDE = MDD	51	11.8	0.8	−0.4–2–3	0.852	33.3	2.4	1.4–4.2	0.002
	BP-II broad	36	19.4	**1.7**	0.7–4.1	0.281	44.4	**4.8**	2.7–8.5	0.000
	Remaining MDE = MDD	36	11.1	**0.8**	0.3–2.6	0.786	25.0	**1.9**	0.95–3–6	0.071
Women	MDE	118	6.8	2.1	0.7–6.3	0.174	12.7	5.2	1.8–14.5	0.002
	BP-II DSM-IV	8	12.5	4.2	0.4–39.4	0.213	12.5	5.0	0.52–49.0	0.164
	Remaining MDE	110	6.4	2.0	0.6–6.1	0.230	12.5	5.1	1.8–14.7	0.002
	BP-II strict	24	12.5	4.2	0.96–17.9	0.055	29.2	14.5	4.1–50.6	0.000
	Remaining MDE = MDD	94	5.3	1.6	0.5–5.5	0.425	8.5	3.3	1.0–10.3	0.043
	BP-II broad	53	13.2	**4.4**	1.4–13.8	0.010	18.9	**8.2**	2.7–25.2	0.000
	Remaining MDE = MDD	65	1.5	**0.5**	0.05–3.8	0.471	7.7	2.9	0.8–10.5	0.098

[a]MDE = Major Depression Episode

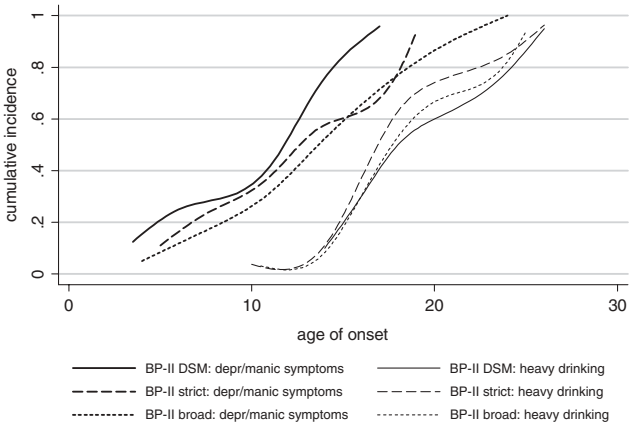

Fig. 2 Cumulative age of onset of first depressive/manic episode and heavy drinking, for three increasingly broad definitions of BP-II disorder. For each definition, depressive/manic manifestations tend to precede the occurrence of heavy drinking

(OR = 1.0, 95% CI = 0.5, 1.7). Despite the broadening of the concept of bipolarity the association between AUD and BP-II remained absolutely stable (OR = 5.4).

Temporal sequence of BP-II and AUD

We compared the ages of the onset of the first depressive/manic episode and the start of heavy drinking in subjects who developed both BP-II and AUD at any later time. This intra-individual comparison was made for the three different definitions of BP-II. Using the broad definition of BP-II, 23 of 34 cases (68%) manifested an affective episode before the onset of heavy drinking; the mean age of onset was 12.9 years (SD 5.03) for bipolarity and 18.2 years (SD 4.19) for heavy drinking. Using the strict definition of BP-II, the first affective episode preceded the onset of heavy drinking in 13 of 19 cases (68%); the mean age of onset was 12.3 years (SD 5.74) for bipolarity and 17.8 years (SD 4.28) for heavy drinking. Finally, all 6 cases with the DSM definition of BP-II (who also had AUD) manifested an affective episode earlier than heavy drinking; the mean age of onset for bipolarity was 9.5 years (SD 6.09), and that for heavy drinking 18.8 years (SD 4.58).

Figure 2 shows the cumulative distribution of ages of onset of the first affective episode and heavy drinking in the three increasingly broad groups of BP-II. In each group, the curve for BP-II is shifted towards earlier ages compared to the curves showing the onset of heavy drinking.

The number of subjects with AUD increased from 14 (at the age of 20–22) to 51 at the age of 40. At the same time, the number of BP-II cases decreased from 47 (at 20–22) to 31 at the age of 40. This finding further supports the view that bipolar symptoms precede and may contribute to the development of AUD.

Discussion

Applying a spectrum concept of BP-II disorder, which resulted in an increasing proportion of MDD subjects being classified as BP-II, we found that the association between MDD and AUD progressively diminished and ultimately disappeared with the broadest definition of BP-II. Whereas 93.5% of AUD cases had MDD according to DSM-IV criteria, the figure was only 53% of the AUD cases had MDD with our broadest definition of bipolar disorder. Our findings also confirm that the association between alcoholism and mood disorders was far greater for alcohol dependence than for abuse, particularly in men. This supports prior family study research suggesting that women have a lower threshold for expression of alcoholism than men [24].

Another key finding of our study relates to the time sequence of the onset of symptoms of AUD and BP-II. Affective episodes preceded heavy drinking in most cases. In the majority of cases the onset of BP occurred before age 20, whereas at this age AUD was a minor problem but grew quickly in the third decade of life. In the prospective period from age 20/21 to 40/41 changes from BP-II to AUD were several times more frequent than the reverse (data not shown).

These findings could have major implications for risk factor research and the prevention of AUD. If our findings are replicable and, in particular, if BP-II disorder tends to manifest first in the comorbid sequence, this could have a substantial impact on the prevention of AUD, especially in women. Application of broad rather than strict diagnostic criteria would allow earlier and more accurate identification of individuals at risk. The administration of instruments for the self-assessment of hypomania/mania in cases of depression [4, 18] could greatly help to identify bipolar subjects, to initiate early prophylactic treatment and to reduce their risk of developing secondary alcohol and drug abuse/dependence.

In terms of clinical implications, our findings have relevance for both diagnosis and treatment. The finding that AUD are predominantly associated with bipolar disorder suggests the need to screen for bipolarity in all subjects with alcohol problems. Such screening could also apply in the evaluation of dual diagnoses in people with schizophrenia or schizo-affective with substance use disorders [9, 25, 29]. Increased vigilance in the detection of bipolarity among those who have already developed dependence, could be used to select treatment modalities that address both the mood and substance problems. Indeed, there is emerging evidence for the success of this approach in a growing number of studies [8, 13]. Future studies will be required to examine the extent to which data from the present study have relevance for intervention in the transition to early and mid adulthood.

Finally, these findings have important implications for etiologic studies; particularly those which seek to identify genetic factors underlying mood disorders or alcoholism. Although evidence regarding the extent to which comorbidity between alcoholism and bipolar disorder is attributable to share common underlying genetic risk factors is inconclusive [6, 22, 24], none of the prior family and genetic studies employed the spectrum concept of bipolar disorders [14]. Therefore, results of earlier studies may have underestimated the extent to which bipolar disorder and alcoholism have familial links.

The findings of this study should be considered in the context of the following limitations: (a) subjects were aged 20/21 when the study started; the data on age of onset are therefore partially retrospective; (b) differences in diagnostic information available across six interview waves (DSM-III and DSM-III-R major depression); (c) the 20-year attrition rate of 38%; (d) the relatively small sample size of this cohort; which inter alia did not allow assessment of rare disorders.

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