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ORIGINAL PAPER

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Gender differences in bipolar-II disorder

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Abstract Gender differences in bipolar-II disorder (BP-II) are understudied. *Study aim* was to test if there were gender differences in the clinical and family history features of BP-II. *Methods* Consecutive 374 BP-II private practice outpatients were interviewed by a senior psychiatrist using the Structured Clinical Interview for DSM-IV, modified to improve the detection of BP-II (by Benazzi and Akiskal 2003, J Affect Disord 73:33–38), the Montgomery Asberg Depression Rating Scale (MADRS), the Hypomania Interview Guide, and the Family History Screen. Logistic regression was used to study associations and control for confounding. Alpha level was set at 0.05; P was two-tailed. *Results* Females represented 67.3 % of the group. The female to male ratio was independent of age. Females were more common in younger onset BP-II. Females, versus males, had significantly lower age at onset, more axis I comorbidity, atypical depressions, intra-depression hypomanic symptoms (i. e., mixed depression), and family history of suicidal behavior. On the MADRS, females had more sadness, loss of energy, loss of interest, and suicidal ideas. The symptom structure of hypomanic episodes was similar between females and males. *Limitations* Single interviewer, outpatient sample, private practice study setting. *Discussion* Clinical differences were found between BP-II females and males. Differences were found only on the depressive pole of the disorder. However, the magnitude of the differences had not a strong clinical significance, suggesting that at present, on the basis of the variables and the population studied, there is little ground to support a female BP-II depression.

Key words bipolar II disorder · gender · female · male

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Introduction

Gender differences in bipolar disorders are understudied, especially in bipolar-II disorder (BP-II) (McElroy 2004). Reviews (McElroy 2004; Shulman et al. 2002; American Psychiatric Association 2000; Goodwin and Jamison 1990) reported the following findings between bipolar females and males: not more females than males in bipolar-I disorder (BP-I); more females in BP-II; more depressive episodes than manic and hypomanic episodes in females; mania and hypomania equally common in females and males; more rapid cycling in females; more depressive symptoms in mania (mixed mania) and hypomania in females; more mixture of depressive and hypomanic symptoms in females; more seasonal depressions and atypical depressions in females; similar age at onset; more suicide attempts in females; less non-alcohol substance abuse in females; more alcohol abuse in females.

Gender differences in BP-II are understudied. In a 251 BP-II sample (Benazzi 1999a, b, 2000a), independent from the present study sample and including fewer variables, BP-II had more females than males, and females had a significantly lower age at onset, more atypical depressions, and more axis I comorbidity. Frequency of females was not significantly different between BP-II and major depressive disorder (MDD) atypical depressions, but female atypical depression had a significantly lower age at onset (findings replicated by Angst et al. 2002).

Underdiagnosis and misdiagnosis of BP-II as MDD are common in clinical practice (American Psychiatric Association 2002; Angst et al. 2003; Benazzi 2003a). In community and clinical samples, the BP-II to MDD ratio may be near one (Angst et al. 2003; Hantouche et al. 1998; Manning et al. 1999; Benazzi 2003a). BP-II is also a persistent disorder with inter-episode neuropsychological deficits (Clark and Goodwin 2004; Gutierrez and Scott 2004).

Study aim was to test if there were gender differences in BP-II depression and hypomania, for the first time in-

cluding in the analyses intra-depression hypomanic symptoms.

Methods

Detailed study methods can be found in previous reports (Akiskal and Benazzi 2003; Benazzi and Akiskal 2003a; Benazzi 2003b). The study was approved by the local ethics committee, was performed according to the ethical standards of 1964 declaration of Helsinki, and all persons gave informed consent prior to inclusion in the study.

Study setting

An outpatient psychiatry private practice. This setting is more representative of the mood disorders usually seen in clinical practice in Emilia-Romagna region, northern Italy (apart from the psychotic ones), on the basis of the author's working experience in both the public and private sector. This is because 1) private practice is the first or second (after family doctors) line of treatment of most mood disorders, 2) the most severe and socially disadvantaged individuals are usually seen in psychiatric tertiary-care centers (national health services, university centers), 3) mood disorder patients do not like to be treated in the national health services for fear of stigma, and 4) most individuals can be treated by a private psychiatrist (fee-for-service), reducing a possible income bias.

Interviewer

A senior clinical (20 years in practice) and mood disorder research psychiatrist.

Patient population

Consecutive 374 BP-II outpatients, presenting voluntarily for major depressive episode (MDE) treatment, were included in the last 6 years. Substance-related and borderline personality disorders were excluded due to confounding of the diagnosis of BP-II (due to the high background mood instability of these disorders, Akiskal and Pinto 1999), and which are anyway rare in the study setting (Benazzi 2000b). Clinically significant general medical illnesses and cognitive disorders were also excluded.

Assessment instruments

Only patients presenting without psychopharmacotherapy (for at least 2 weeks, apart from a few cases on small doses of benzodiazepines, in order not to have drug-induced or drug-suppressed hypomanic symptoms in depression) were included. When presenting for the first time (first visit), before starting any treatment, the following instruments were used: 1) the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV, reported inter-rater reliability $\kappa = 0.70–1.0$, First et al. 1997), as modified by Benazzi and Akiskal (2003a) to improve the detection of BP-II (i. e., to reduce the false negatives) by focusing the probing for history of hypomania more on overactivity; the question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition of crowded thoughts (i. e., mind continuously full of non-stop thoughts) (Koukopoulos and Koukopoulos 1999), following Kraepelin's description (1913, English translation by Barclay 1921) of the grading of the thought disorders of hypomania; 2) the Global Assessment of Functioning scale (GAF, in the SCID-CV) and the MADRS (Montgomery Asberg Depression Rating Scale, Montgomery and Asberg 1979) for assessing MDE severity; 3) the Hypomania Interview Guide (HIG, reported inter-rater reliability $\kappa = 0.88$, Williams et al. 1994) to assess intra-MDE hypomanic symptoms; 4) the structured Family History Screen (reported inter-rater reliability $\kappa = 0.85$, Weissman et al. 2000) for assessing family history of suicidal behavior and bipolar disorders in probands' first-degree relatives. Often, family members or close friends supplemented clinical information during the interview, increasing the validity of BP-II diagnosis and family history (Akiskal et al. 2000).

Interview methods

Systematic interviews about history of hypomanic/manic episodes were always conducted soon after the diagnosis of MDE and before the assessment of study variables, in order to avoid a possible bias related to knowledge of bipolar signs. The SCID-CV is partly semi-structured and based on clinical evaluation. This is an important advantage versus fully structured interviews because it reduces the false negative mood disorders, especially BP-II (Dunner and Tay 1993; Simpson et al. 2002; Benazzi 2003d). The skip out instruction of the stem question on history of mood changes was not followed, in order to assess all past hypomanic symptoms, especially overactivity (increased goal-directed activity), following previous reports showing that this approach reduced the false negative BP-II (Akiskal et al. 1977; Dunner and Tay 1993; Angst et al. 2003; Benazzi and Akiskal 2003a; Simpson et al. 2002; Benazzi 2003c). This behavioral change is easier to remember than mood changes (always required for the diagnosis of BP-II according to DSM-IV-TR). Mood changes were easier to remember when overactivity had been remembered.

Mixed depression was defined as an MDE plus three or more concurrent intra-MDE hypomanic symptoms, according to a definition which has clinical, family history, and psychometric validation (Akiskal and Benazzi 2003; Benazzi and Akiskal 2003b; Benazzi 2005; Mantere et al. 2004; Sato et al. 2003).

Symptom structure of hypomania was assessed during remission (i. e., GAF > 80 for at least one month), by probing for history of hypomania.

Data analysis

Logistic regression was used to study associations and to control for confounding (STATA 8.2). The chi-squared test was used to compare frequencies. P value was two-tailed, and alpha level was set at 0.05, not correcting for multiple comparisons because of the exploratory nature of the study (i. e., no a priory hypotheses).

Results

Females represented 67.3 % of the group. BP-II median age was 40 years. Frequency of females did not change according to this cutoff or to a lower one (age 30 years): in the group with age < 40 years (n = 177 BP-II) females were 63.2 %, in the group with age > 39 years (n = 197 BP-II) females were 71 % ($\chi^2 = 2.3$, df = 1, p = 0.121); in the group with age < 30 years (n = 116 BP-II) females were 72.3 %, in the group with age > 29 years (n = 298 BP-II) females were 66.1 % ($\chi^2 = 1.0$, df = 1, p = 0.299). There were only 7 BP-II with age < 20 years.

BP-II median age at onset was 20 years. Frequency of females was significantly higher when onset was lower than 20 years: in the group with onset < 20 years (n = 171 BP-II) females were 74.2 %; in the group with onset > 19 years (n = 203 BP-II) females represented 61.5 % ($\chi^2 = 6.8$, df = 1, p = 0.009).

Females and males were compared on clinical and family history features: age, age at onset of the first MDE, GAF, MDE recurrences, current MDE symptoms for more than 2 years, axis I comorbidity, psychotic, melan-

cholic and atypical features, mixed depression, bipolar (type 1 and 2) family history, suicidal behavior family history, MDE symptoms, intra-MDE hypomanic symptoms (elevated mood and increased self-esteem absent by definition). Females had significantly lower age at onset, more axis I comorbidity, atypical depressions, mixed depressions, psychomotor agitation, and family history of suicidal behavior (Table 1).

Comparisons between females and males on MADRS scores of index MDE are presented in Table 2. Females had significantly higher scores on sadness, loss of energy, loss of interest, and suicidal ideas. There was a statistically significant but clinically nonsignificant greater severity in females. Repeating the comparisons of Tables 1 and 2 by logistic regression controlled for MADRS severity did not change the findings.

No significant gender differences were found on symptom structure, duration, and functioning of past hypomania.

Discussion

The present study found that females were not more common than males according to age. Instead, younger onset BP-II had more females than males.

Females had lower age at onset, more axis I comorbidity, and more atypical depressions. Females were found to have more mixed depressions versus males, which may make them more vulnerable to antidepressant-related mood instability (Altshuler et al. 1995; Koukopoulos and Koukopoulos 1999; Akiskal and Pinto 1999; Bottlender et al. 2004).

Suicidal behavior is common in mood disorders, especially in BP-II (Rihmer and Pestality 1999). Females showed more severe suicidal ideation on the MADRS, coupled with higher family history of suicidal behavior (a known risk factor of suicide). These findings suggest that BP-II females may be at higher risk of suicidality than males.

The structure of hypomania was similar between females and males. It was the depressive pole of the disorder which showed some gender differences.

Limitations

Statistically significant differences were found between females and males, but the magnitude of the differences did not show a strong clinical significance. A single interviewer may bias results. However, the interviewer's inter-rater reliability for the diagnosis of BP-II was found to be adequate (Benazzi 2003c). An interviewer bias is unlikely as study variables were systematically recorded at a time when the study goal had not been planned. Because of the setting (private practice), and the population studied (non-tertiary care outpatients, exclusion of patients with substance abuse and border-

Table 1 Comparisons between females (F) and males (M) on clinical and family history features (only the significant findings are reported)

Variables: mean (SD); %	F n = 252	M n = 122	OR	95% CI	P
Age at onset first MDE, years	21.9 (10.3)	24.3 (10.8)	0.8	0.6–0.9	0.041
Axis I comorbidity	58.7	45.0	1.7	1.1–2.6	0.013
Index atypical depression	57.5	44.2	1.7	1.1–2.6	0.016
Index mixed depression (MDE plus ≥ 3 hypomanic symptoms)	68.6	52.4	1.9	1.2–3.0	0.002
Suicidal behavior family history	10.9	3.4	3.4	0.99–11.9	0.050
Psychomotor agitation	37.3	26.2	1.6	1.03–2.6	0.035

MDE major depressive episode; *OR* odds ratio; *95% CI* 95% confidence interval

Table 2 Comparisons of MADRS items between females (F) and males (M)

Variables, mean (SD)	F	M	OR	95% CI	P
Apparent sadness	3.3 (1.4)	2.7 (1.5)	1.27	1.05–1.5	0.011
Reported sadness	3.5 (1.3)	2.9 (1.3)	1.38	1.1–1.7	0.003
Inner tension	3.3 (1.0)	3.3 (1.0)	1.0	0.8–1.3	0.661
Reduced sleep	2.4 (1.9)	2.6 (2.0)	0.9	0.8–1.09	0.488
Reduced appetite	1.3 (1.7)	1.1 (1.5)	1.1	0.9–1.3	0.251
Concentration difficulties	3.0 (1.6)	2.6 (1.3)	1.18	0.99–1.4	0.053
Lassitude	3.3 (1.4)	2.8 (1.2)	1.28	1.06–1.5	0.010
Inability to feel	3.6 (1.6)	3.0 (1.6)	1.28	1.08–1.5	0.003
Pessimistic thoughts	3.2 (1.4)	2.8 (1.5)	1.1	0.9–1.3	0.082
Suicidal thoughts	1.4 (1.3)	0.8 (1.1)	1.49	1.17–1.9	0.001
Total score	28.8 (8.7)	25.0 (9.2)	1.28	1.08–1.5	0.003

MADRS Montgomery Asberg Depression Rating Scale; *OR* odds ratio; *95% CI* 95% confidence interval

line personality disorder), the validity of the findings may be limited to this subgroup of BP-II. In tertiary care, and in inpatients, findings may be different because the BP-II in these settings are different from the present study sample (i. e., more severity, more substance abuse, more personality disorders). This distinction of BP-II into two subgroups was made by Akiskal et al. (2003). One group was called "sunny" because hypomanic episodes frequently had improved functioning, and there was a relative inter-episode mood stability. This group was well described by Hecker (1898, English translation by Koukopoulos 2003), who worked in private practice. The other group was called "dark", because hypomanic episodes frequently had reduced functioning, there was risk-taking, and there was high inter-episode instability of mood, thinking, and behavior.

Advantages

Large BP-II sample. Systematic, standard assessment of all new patients. Innovative assessment of hypomanic symptoms during depression. Experienced clinician doing all the interviews. The systematic use of validated structured and semi-structured interviews, supplemented by key informants, should have reduced the risk of bias.

Conclusions

Findings showed clinical differences between females and males, but the type of differences, the number of differences, and the magnitude of the differences, did not seem to support a subtyping of BP-II according to gender. Study findings may suggest looking for other variables, and to test the present study variables in different settings, in order to find if there are gender differences in BP-II.

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