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ORIGINAL PAPER

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The continuum/spectrum concept of mood disorders: is mixed depression the basic link?

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Abstract *Background* Mixed states, i.e., opposite polarity symptoms in the same mood episode, question the bipolar/unipolar splitting of mood disorders, and support a spectrum view. Study aim was assessing the distribution of intradepressive hypomanic symptoms between bipolar-II (BP-II) and major depressive disorder (MDD) depressions, and testing a dose–response relationship between number of intradepressive hypomanic symptoms and bipolar family history. No bi-modality, and a dose–response relationship, would not support a categorical distinction. *Methods* Consecutive 389 BP-II and 261 MDD depressed outpatients were interviewed by the structured clinical interview for DSM-IV, hypomania interview guide, and family history screen, by a mood specialist psychiatrist, in a private practice. Intradepressive hypomanic symptoms were systematically assessed. Mixed depression was defined as the combination of depression and three or more intradepressive hypomanic symptoms, a validated definition. *Results* BP-II, versus MDD, had significantly more intradepressive hypomanic symptoms. The distribution of intradepressive hypomanic symptoms between BP-II and MDD was not bi-modal but normal-like, and a dose–response relationship was found between the number of intradepressive hypomanic symptoms and bipolar family history. *Conclusions* Study findings question the categorical division of BP-II and MDD, and may support the spectrum view of mood disorders.

Key words major depressive disorder · bipolar II disorder · spectrum · mixed depression · depressive mixed state

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Introduction

Mood disorders are categorically split in bipolar disorders and unipolar depressive disorders (American Psychiatric Association 2000). This division has been questioned by the continuum/spectrum concept of mood disorders, which includes overlapping and dimensional disorders ranging from bipolar-I (BP-I) and bipolar-II (BP-II) disorders to major depressive disorder (MDD). This topic has been recently reviewed (Benazzi 2005a, 2006).

According to Kendell and Jablensky (2003), finding a *bi-modal distribution* of distinguishing, cross-sectional symptoms between two related syndromes would support a categorical distinction. BP-II is the closest of the bipolar disorders to MDD, and it could be the one to compare to MDD. Mixed depression, i.e., the combination of depression and intradepressive manic/hypomanic symptoms, is much more common (so it is a distinguishing feature) in BP-I and BP-II versus MDD (Sato et al. 2003; Akiskal and Benazzi 2003, 2005a; Benazzi 2005b; Bauer et al. 2005; Mantere et al. 2004; Maj et al. 2003, 2006). *No bi-modality* in the distribution of the intradepressive hypomanic symptoms between BP-II and MDD depressions, and a *dose–response relationship* between number of intra-

depressive hypomanic symptoms and bipolar family history loading would not support a categorical distinction of these two disorders.

Study aim was to assess the distribution of intradepressive hypomanic symptoms between BP-II and MDD, and a dose–response relationship between intradepressive hypomanic symptoms and bipolar family history.

Methods

Detailed study methods can be found in previous reports (Benazzi 2003a; Benazzi and Akiskal 2003; Akiskal and Benazzi 2005b). The study was approved by local ethics committee, was performed according to 1964 Declaration of Helsinki, and all persons gave informed consent prior to inclusion in the study.

Study setting

An outpatient psychiatry private practice in northern Italy, a setting more representative of mood disorders usually seen in psychiatric clinical practice in this area (apart from the psychotic ones).

Interviewer

A clinical (21 years in practice) and mood disorder research psychiatrist, whose inter-rater reliability *k* for the diagnosis of BP-II had been previously tested, resulting 0.73 (Benazzi 2003a).

Patient population

Consecutive 389 BP-II and 261 MDD outpatients, presenting voluntarily for major depressive episode (MDE) treatment, were included in the last 6 years. Substance-related and borderline personality disorders were excluded because confounding the diagnosis of BP-II, and anyway rare in this setting. Clinically significant medical illnesses and cognitive disorders were excluded. Patients had to present off psychoactive drugs for at least 2 weeks (apart from a few individuals on small doses of benzodiazepines), in order not to have drug-induced or drug-suppressed intradepressive hypomanic symptoms.

Assessment instruments

During the first visit, the instruments used were (1) the structured clinical interview for DSM-IV Axis I disorders-clinician version (First et al. 1997) (SCID-CV, reported inter-rater reliability $k = 0.70–1.0$), modified by Benazzi and Akiskal (Benazzi and Akiskal 2003; Akiskal and Benazzi 2005b) to improve the probing for BP-II, (2) the global assessment of functioning scale (GAF) for assessing MDE severity, (3) the hypomania interview guide (Williams et al. 1994) (reported inter-rater reliability $k = 0.88$) to assess intradepressive hypomanic symptoms, (4) the family history screen (Weissman et al. 2000) (reported inter-rater reliability $k = 0.85$) for assessing bipolar (type I and II) family history in probands' first-degree relatives. Often, family members or close friends supplemented clinical information during the interview.

Interview methods

Systematic interviews about history of hypomanic and manic episodes were always conducted soon after the diagnosis of MDE, 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. Wording of the sentences can be changed to improve and to check the understanding by the interviewee. This is an important advantage versus fully structured interviews, because this interview method has been shown to reduce the false negative BP-II (Dunner and Tay 1993; Benazzi 2003b; Simpson et al. 2002).

Mixed depression (depressive mixed state) was defined as the combination of MDE (depression) and three or more DSM-IV-TR hypomanic symptoms (elevated mood and inflated self-esteem were always absent), a definition which had clinical, family history and psychometric validation (Akiskal and Benazzi 2003; Benazzi 2005b). Hypomanic symptoms had to appear during the MDE (i.e., an hypomanic symptom-free interval of at least 1 month before the MDE was required), to last at least 1 week, and to be present at the time of the interview. Sample features are presented in Table 1.

Testing study aim

To find if BP-II and MDD were distinct categories, Kendell and Jablensky (2003) method was followed, by looking for *bi-modality* in the distribution of the number of intradepressive hypomanic symptoms between BP-II and MDD depressions (MDEs). Intradepressive hypomanic symptoms were chosen because are much more common in BP-I and BP-II depression versus MDD depression (Sato et al. 2003; Akiskal and Benazzi 2003, 2005a; Benazzi 2005b; Bauer et al. 2005; Mantere et al. 2004; Maj et al. 2003, 2006; Perugi et al. 2001). If BP-II and MDD were distinct categories, this distribution should have been bi-modal. A *dose–response relationship* between number of intradepressive hypomanic symptoms and bipolar family history loading was also tested. Finding no dose–response relationship would not have supported a categorical distinction between BP-II and MDD.

Statistics

The distribution of the number of intradepressive hypomanic symptoms was studied by histogram method. ROC analysis was used to test the dose–response relationship. Logistic regression was used to study associations. STATA Statistical Software, Release 8.2, was used (Stata Corporation, College Station, TX, USA, 2003). *P* values were two-tailed, and alpha level was set at 0.01, to correct for multiple comparisons.

Table 1 Comparison between bipolar-II disorder (BP-II) and major depressive disorder (MDD) depressions (MDEs), by univariate logistic regression

Variables: mean (SD), %	BP-II $n = 389$	MDD $n = 261$	OR (95% CI)
Age, years	41.3 (12.9)	46.8 (14.8)	0.7 (0.6–0.8)**
Females	67.0	61.6	1.2 (0.9–1.7)
Age at onset of first MDE	22.8 (10.6)	31.8 (13.8)	0.5 (0.4–0.6)**
≥ 5 MDEs	78.9	58.2	2.6 (1.8–3.7)**
Current MDE symptoms for >2 years	37.5	34.8	1.1 (0.8–1.5)
Axis I comorbidity	54.2	47.5	1.3 (0.9–1.7)
Psychotic features	7.7	8.4	0.9 (0.5–1.6)
Melancholic features	12.0	13.0	0.9 (0.5–1.4)
Atypical features	52.6	28.7	2.7 (1.9–3.8)**
Mixed depression	64.5	32.1	3.8 (2.7–5.3)**
GAF	50.2 (9.2)	50.9 (9.6)	0.9 (0.8–1.0)
Bipolar (type I + type II) family history	44.7	15.3	4.4 (2.8–7.0)**
Number of intradepressive, non-euphoric, hypomanic symptoms	3.0 (1.4)	1.8 (1.2)	1.9 (1.6–2.2)**

(MDE = major depressive episode; GAF = global assessment of functioning scale; mixed depression: MDE plus ≥3 hypomanic symptoms; OR = odds ratio; 95% CI = 95% confidence interval; * = $P < 0.05$; ** = $P < 0.01$)

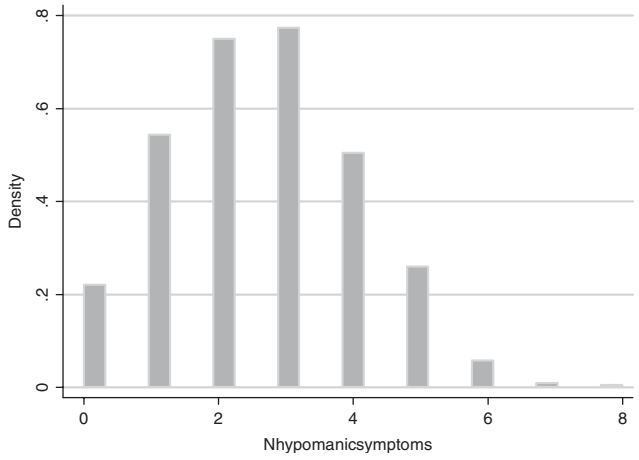

Fig. 1 Histogram of the distribution of the number of intradepressive hypomanic symptoms (Nhypomanicsymptoms) between bipolar II disorder and major depressive disorder

Results

Bipolar-II depression, compared to MDD, had significantly lower age at onset, more recurrences, more atypical and mixed depressions, more bipolar family history and more intradepressive hypomanic symptoms.

Figure 1 shows the distribution of the number of intradepressive hypomanic symptoms between BP-II and MDD depressions by the histogram method. No bi-modality was present.

Table 2 shows a dose–response relationship (by likelihood ratios) between the number of intradepressive hypomanic symptoms and bipolar family history loading, i.e., the higher was the number of intradepressive hypomanic symptoms, the higher was the bipolar family history loading.

Discussion

Comparisons between BP-II and MDD depressions showed significant differences on several classic diagnostic validators, such as bipolar family history, age at onset, course (recurrences), and clinical features (atypical symptoms, intradepressive hypomanic symptoms), following previous reports (Angst et al. 2003; Sato et al. 2003; Bauer et al. 2005; Benazzi 2005a, 2006). Differences on diagnostic validators could support a categorical distinction between BP-II and MDD.

Table 2 ROC analysis testing a dose–response relationship between number of intradepressive hypomanic symptoms and bipolar family history loading

Cut points	Sensitivity, %	Specificity, %	LR+	LR−
≥0	100.0	0.0	1.00	0.00
≥1	96.8	6.8	1.03	0.46
≥2	91.0	25.0	1.21	0.35
≥3	76.4	50.4	1.54	0.46
≥4	42.6	73.6	1.62	0.77
≥5	19.7	90.4	2.05	0.88
≥6	4.4	98.1	2.40	0.97
≥7	1.2	99.6	4.11	0.99
≥8	0.0	100.0	0.0	1.00

(LR+ = likelihood ratio positive; LR− = likelihood ratio negative)

According to Kendell and Jablensky (2003), the current best way of testing the categorical versus the dimensional approach to the classification of mental disorders would be to study if there is *bi-modality* in the distribution of some cross-sectional clinical features between two related syndromes. BP-II is the closest of the bipolar disorders to MDD. A clinical feature shown to distinguish the depressive syndromes of BP-II and MDD is a much higher frequency of intradepressive hypomanic symptoms in BP-II (Benazzi 2005b; Sato et al. 2003, Bauer et al. 2005). Instead, the distribution of the number of intradepressive hypomanic symptoms was not bi-modal as expected, but normal-like. This finding would not support a categorical distinction between BP-II and MDD. The study finding is complemented by a similar distribution of the *lifetime* manic/hypomanic symptoms in BP-I and MDD, and of the depressive symptoms of mania (Cassano et al. 2002; Bauer et al. 2005).

A *dose–response relationship* was found between intradepressive hypomanic symptoms and bipolar family history loading. If BP-II and MDD were distinct categorical disorders, such a relationship should not have been found.

The interpretation of study findings relies on the method used to define a categorical disorder. By using classic diagnostic validators, BP-II and MDD would seem to be distinct disorders. By using the 'bi-modality' and 'dose–response relationship' approaches, a continuum between BP-II and MDD would seem to be supported.

From a clinical practice point of view, study findings suggest a systematic assessment of intradepression hypomanic symptoms. Such a systematic assessment for mixed depression could be useful for the prevention of suicide (Bradvik and Berglund 2005), as mixed depression has been shown to be often present in suicide attempters before acting (Balazs et al. 2006), for preventing a worsening of depression by antidepressants used alone (i.e., not protected by mood stabilizing agents) (Koukopoulos et al. 2005), and for preventing a switching (Bottlender et al. 2004). The biology of mixed depression needs full investigation (Ehnvall et al. 2004).

Limitations

A single interviewer may have limited the validity of the findings. However, reliability of BP-II diagnosis, and BP-II correct diagnoses, were found to be higher when trained clinicians used semi-structured interviews as in the present study (Simpson et al. 2002; Dunner and Tay 1993). A clinician studying and

treating mood disorders for a long time, conducted the interview systematically using validated structured and semi-structured interviews for each new patient, often supplemented by key informants. Assessment of all consecutive patients in a systematic manner by validated instruments should have reduced the risk of systematic bias. The interviewer inter-rater reliability for the diagnosis of BP-II had been found to be acceptable (Benazzi 2003a). The validity of the interview method is supported by the close similarities found between a present setting BP-II sample and a BP-II sample of an independent group (Angst et al. 2005).

No-bimodality in the distribution of a distinguishing clinical feature such as the intradepressive hypomanic symptoms between BP-II and MDD depressions needs interpretation. If from one side it does not support a categorical distinction (as distinct disorders should have no, or only a little, overlap of symptoms) (Kendell and Jablensky 2003), from the other side it does not show that the two disorders are identical or very similar (although a 'significant' departure provides some evidence against the null hypothesis, a 'non-significant' departure does not provide evidence in favour of that hypothesis; the situation is rather that we have failed to find strong evidence against the null hypothesis) (Armitage et al. 2002). However, a dose–response relationship, such as that found in the present study, may more strongly support a BP-II/MDD continuum, which the lack of bi-modality suggests. A continuum/spectrum is not the sum of identical or similar disorders, it is the sum of disorders/subtypes, which share some common features but also have some distinguishing features.

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