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ORIGINAL PAPER

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Frequency of bipolar spectrum in 111 private practice depression outpatients

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Abstract *Background* Mood disorders included into the bipolar spectrum are increasing, and overactivity (increased goal-directed activity) has reached the status of mood change for the diagnosis of hypomania in the recent studies by Angst (2003) and Akiskal (2001). *Study aim* was to find frequency of bipolar spectrum in remitted depressed outpatients by including sub-syndromal hypomania. *Methods* 111 depression-remitted outpatients were interviewed for history of hypomania and hypomanic symptoms with the Structured Clinical Interview for DSM-IV-Clinician Version (a partly semi-structured interview), as modified by Benazzi and Akiskal (2003). Bipolar I patients were not included. All past hypomanic symptoms (especially overactivity) were systematically assessed. Wording of the questions could be changed to increase/check understanding. Sub-syndromal hypomania was defined as an episode of overactivity (increased goal-directed activity) plus at least 2 hypomanic symptoms. *Results* Frequency of bipolar II (BPII) was 68/111 (61.2 %, 95 % confidence interval 52 % to 69.8 %), frequency of major depressive disorder (MDD) was 43/111. The most common hypomanic symptom was overactivity. In the MDD sample, sub-syndromal hypomania was present in 39.5 % (15.3 % of the entire sample), and had 4 median symptoms. Bipolar spectrum frequency was 76.5 % (95 % confidence interval 67.9 % to 83.5 %). Overactivity had higher sensitivity than elevated mood for predicting BPII diagnosis. *Limitations* Single interviewer. *Conclusions* By systematic probing more focused on past overactivity than mood change, and by inclusion of sub-syndromal hypomania, bipolar spectrum frequency was higher than the near 1 to 1 ratio versus MDD reported up to now (Angst et al. 2003). Given the wide confidence interval, the value in the depression population should be around 70 %. Better probing skills by clinicians, and use of semi-structured interviews could much reduce the current high underdiagnosis of BPII and related disorders in usual clinical practice.

Key words bipolar II disorder · hypomania · bipolar spectrum · depression

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Introduction

In DSM-IV-TR (American Psychiatric Association 2000) mood disorders are classified into distinct categories – bipolar and depressive disorders. Bipolar disorders are divided into categories – bipolar I, bipolar II (BPII), cyclothymic, and bipolar nos disorders. This categorical classification of mood disorders runs against Kraepelin's unitary (continuity, spectrum) classification of hypo-manic and depressive states under manic-depressive insanity (1921). DSM-IV-TR reports (p. xxxi) that a categorical classification requires *"clear boundaries between classes"*. The validity of DSM-IV (and of ICD-10, World Health Organization 1992) classification of mood disorders has been questioned on clinical grounds (Akiskal 2003). Lack of clear boundaries ("zones of rarity") between different DSM-IV syndromes does not support psychometrically a categorical classification, while it supports a dimensional classification (Kendell and Jablensky 2003). A dimensional approach to bipolar (and depressive) disorders is supported by longitudinal course, showing fluctuating severity, number, and duration of symptoms (Judd and Akiskal 2003; Judd et al. 2003; Judd and Akiskal 2000). The Goodwin and Jamison (1990) review supported a bipolar spectrum, which included major depressive disorder (MDD) plus bipolar signs (young onset, many recurrences, atypical depression, bipolar family history, antidepressant-associated switching) (Ghaemi et al. 2002). Links (i. e., midstream mood states) between MDD and BPII (the closest to MDD of the bipolar disorders) have recently been

found, supporting the Akiskal (2003) and Goodwin and Jamison (1990) bipolar spectrum concept. MDD plus anger (Benazzi in press a), MDD plus young onset (Benazzi 2003 a), MDD plus atypical features (Benazzi 2003 a), MDD plus hypomanic symptoms during a major depressive episode (MDE) (depressive mixed state, Akiskal and Benazzi 2003), and MDD plus many MDE recurrences (Benazzi 2002 a) showed bipolar features (Angst et al. 2003; Angst and Gamma 2002; Akiskal 2002; Akiskal 2003; Ghaemi et al. 2002; Goodwin and Jamison 1990; McMahon et al. 1994; Akiskal and Benazzi 2003). Recent definitions of the bipolar spectrum are by Akiskal and Pinto (1999), Angst et al. (2003), and Ghaemi et al. (2002). Akiskal and Pinto included bipolar I, BPII, bipolar III, and bipolar IV (depressive mixed state), Angst et al. included BPII and minor bipolar disorders, Ghaemi et al. included MDD (no history of mania/hypomania) plus bipolar signs. Different diagnostic criteria of hypomania are partly at the root of the broad bipolar spectrum. DSM-IV requires a minimum duration of 4 days, but this cut-off is not data-based (Dunner 1998), while a cut-off of 2 days is supported by data (Akiskal 1996; Benazzi 2001 a; Angst et al. 2003; Angst 1998; Cassano et al. 1992; Perugi et al. 1998; Coryell et al. 1995; Akiskal et al. 1995; Akiskal and Benazzi 2003; Akiskal 2002; Akiskal et al. 2000). One DSM-IV symptom of hypomania – overactivity (increased goal-directed activity) – was found to be as important as mood change for the diagnosis of hypomania (in DSM-IV, mood change must always be present, while overactivity not) on the basis of clinical, family history, and psychometric findings (Angst et al. 2003; Angst and Gamma 2002; Akiskal et al. 1977; Akiskal et al. 1995; Akiskal et al. 2001; Akiskal et al. 2003 a; Hantouche et al. 2003; Benazzi and Akiskal 2003 a,b; Bauer et al. 1991; Goodwin and Jamison 1990). In Kraepelin's description of hypomania (1921), overactivity ("increased busyness") had a high status, like mood change and racing thoughts (mood, activity, and thinking were his fundamental domains of manic-depressive insanity). Antidepressant-associated hypomania (not classified as BPII according to DSM-IV) was found to be closely linked to spontaneous hypomania (Akiskal et al. 2003 b; Akiskal et al. 1983). Family and twin studies partly support the validity of the bipolar spectrum (Kelsoe 2003).

Study aim. To find the frequency of bipolar spectrum in a depression outpatient sample (not including bipolar I disorder), including sub-syndromal hypomania in its definition.

Materials and methods

Study setting

A general psychiatry outpatient private practice (a University of California at San Diego (USA) collaborating center). Private practice is more representative of mood disorders in Italy, because it is first or second (after family doctors) line of treatment of mood disorders, because psychiatric patients often prefer not to be treated in the public national health service (NHS) (for fear of stigma related to these places), and because the most severe patients are usually seen in the NHS and in University mood disorder units. This private practice is a series of solo offices in different cities of northern Italy. As it is a general psychiatry practice it is unlikely that it has a concentration of uncommon and/or treatment-resistant patients (a skewed, non-representative sample, as it is instead often the case for tertiary-care patients). Payment is fee for service, which almost all individuals can afford (reducing a possible bias related to income).

Interviewer

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

Patients

111 consecutive major depressive episode (MDE)-remitted (with psychoactive drug treatment) outpatients were included in two recent months. DSM-IV diagnoses not included in the study sample: substance-related disorders and borderline personality disorder (because confounding the diagnosis of BPII (Akiskal and Pinto 1999), and because rare in the study setting (Benazzi 2000a)), bipolar I disorder (because study aim was to focus on minor bipolar disorders, and because they are a minority in the study setting (Benazzi 1997, 2001b)), psychotic disorders, cognitive disorders, mental disorders due to a general medical illness, and clinically significant general medical illness. Most patients were self-referred. Remission was defined as no depression or hypomania symptoms and full recovery of functioning for at least one month. Interviewing during remission improves identification of BPII (Akiskal et al. 2000; Akiskal 2002; Hantouche et al. 1998). Sub-syndromal hypomanic episode was defined as an episode of hypomanic symptoms (at least 2) not meeting DSM-IV criteria for hypomania (because the number of symptoms was below DSM-IV cut-off, or because mood change was not present), following Angst et al. (2003) and Judd and Akiskal (2003). Overactivity (increased goal-directed activity) had priority in the diagnosis of sub-syndromal hypomania, following clinical, psychometric, and family history findings supporting its bipolar nature (Akiskal et al. 2003 a; Angst et al. 2003; Hantouche et al. 2003; Benazzi and Akiskal 2003 a,b,c; Bauer et al. 1991; Akiskal et al. 1977; Angst and Gamma 2002; Dunner et al. 1976 a,b; Goodwin and Jamison 1990). Study was approved by the ethic committee, and performed according to ethical standards of the 1964 Declaration of Helsinki. All persons gave informed consent prior to inclusion in the study.

Interview method

Patients were interviewed during a follow-up visit (a cross-sectional assessment) with the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First et al. 1997), as modified by Benazzi and Akiskal (2003), and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association 1994). The SCID-CV inter-rater reliability kappa is 0.70–1.0 (First et al. 1997), and the interviewer inter-rater agreement kappa is 0.73 (Benazzi in press b). Diagnosis of borderline personality disorder was done following a semi-structured interview based on DSM-IV criteria (prevalence of borderline personality disorder was found to be low (12 % in BPII, 1.5 % in MDD) with SCID-Axis II structured interviewing in the same study setting (Benazzi 2000a)). The SCID-CV is a partly semi-structured interview based on clinical evaluation (not on simple yes/no answers to structured questions). The wording of the questions can be changed to improve/check understanding (according to its manual), and the final evaluation was based also on information from family members/close friends (often present during the interview).

Diagnosis of past hypomania

History of hypomania was systematically assessed. The SCID-CV skip-out instruction of the stem question about past mood change was not followed, because a negative answer would not allow the assessment of all hypomanic symptoms by requiring switching to a nonbipolar disorder assessment. The aim was to focus the probing more on past overactivity (increased goal-directed activity) than mood change, as suggested by Angst et al. (2003), Akiskal et al. (1977, 2001, 2003 a), and Benazzi and Akiskal (2003 a,b). Diagnosis of hypomania always required mood change (according to DSM-IV), which resulted in easier to remember after remembering past overactivity, even when at first the answer to the mood stem question had been negative. New questions were also asked after negative answers to questions on past overactivity and on past mood change: "did you have a period when you felt like a lion?" (a common saying in Italy), "do you usually feel much better in summer?", "do you usually feel much better soon before a depression or soon after it?" When the answer(s) was (were) positive, questions on all past hypomanic symptoms were re-made using different words, and also asking the patient to describe how behavior and mood were during that period. The SCID-CV structured question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition (1999) of crowded thoughts (i. e., head continuously full of ideas that the patient is unable to stop), to broaden the assessment of mental overactivity and because this question was found to be easier to understand by the patient compared to the SCID-CV question on racing thoughts. This definition of crowded thoughts was similar to Kraepelin's description (1921, p 75) of a thought disorder of depression (i. e., mind overcrowding by non-stop thoughts). Family members and close friends, often present during the interview, supplemented clinical information (increasing reliability of BPII diagnosis (Akiskal et al. 2000, American Psychiatric Association 2000)). The DSM-IV 4-days minimum duration of hypomania for BPII diagnosis was not followed, because this cut-off was not based on data (Dunner 1998). Instead, at least 2 days of hypomania were required for the diagnosis, following reports supporting this cut-off (Akiskal 2002; Angst et al. 2003; Akiskal et al. 2000; Cassano et al. 1992; Coryell et al. 1995; Akiskal et al. 1977; Akiskal et al. 1995; Akiskal 1996; Benazzi 2001 a; Simpson et al. 2002). Most BPII had had more than one hypomania (increasing reliability (Akiskal et al. 2000)).

Statistics

Logistic regression was used to study associations. STATA Statistical Software, Release 7, was used (Stata Corporation, College Station, TX, USA, 2001). P values were two-tailed, and alpha level was set at 0.05.

Results

Frequency of BPII was 61.2 % (68/111, 95 % confidence interval 52 % to 69.8 %). BPII and MDD hypomanic features are presented in Tables 1 and 2. The most common hypomanic symptom in BPII was overactivity, which was more common than mood change. Most BPII had had hypomania/s lasting at least 4 days (the DSM-IV cut-off), and most had had more than one episode. In the MDD sample, many had had sub-syndromal hypomanic episodes. In MDD, the median number of hypomanic symptoms was 3; the most common ones were racing/crowded thoughts and irritability. In the MDD sample (Table 3) reporting episodes of overactivity (17/43 MDD, 39.5 %), many (n = 15) had had more than one sub-syndromal hypomanic episode. The median number of symptoms was 4 in this sample. This sample of MDD plus sub-syndromal hypomania with overactivity was 15.3 % (17/111, 95 % confidence interval 9.8 % to 23.2 %) of the entire sample (BPII + MDD). The bipolar spectrum frequency, resulting from the sum of the 68 BPII and the 17 MDD plus sub-syndromal hypomania with overactivity was 76.5 % (95 % confidence interval 67.9 % to 83.5 %).

Logistic regression, to test sensitivity and specificity of overactivity for predicting BPII diagnosis (dependent variable), found odds ratio = 11.0, p = 0.000, 95 % confidence interval 3.9 to 25.4, sensitivity = 86.7 %, specificity = 60.4 %. Logistic regression, to test sensitivity and specificity of elevated mood for predicting BPII diagno-

Table 1 Clinical features of past hypomanic episodes of the remitted bipolar II sample (n = 68)

Index mean (SD) age (years)	40.9 (12.2)
Index median age	38.5
Female gender	60.2 %
Elevated mood	60.2 %
Irritable mood	55.8 %
Increased self-esteem	58.8 %
Reduced need for sleep	52.9 %
More talkativeness	63.2 %
Racing/crowded thoughts	55.8 %
Distractibility	61.7 %
Increased goal-directed activity (overactivity)	86.7 %
Psychomotor agitation	52.9 %
Risky behavior	63.2 %
Mean (SD) N symptoms	5.6 (1.9)
Median N symptoms	5.5
Duration of episode/s > 3 days	78.6 %
Duration of episode/s > 1 week	67.2 %
Duration of episode/s > 4 weeks	29.5 %
> 1 episode	80.8 %

Table 2 Clinical features (past hypomanic symptoms, past sub-syndromal hypomanic episodes) of the remitted major depressive disorder sample (n = 43)

Index mean (SD) age (years)	39.9 (12.9)
Index median age	37
Females	55.8 %
Elevated mood	13.9 %
Irritable mood	51.1 %
Increased self-esteem	27.9 %
Reduced need for sleep	13.9 %
More talkativeness	13.9 %
Racing/crowded thoughts	62.7 %
Distractibility	60.4 %
Increased goal-directed activity (overactivity)	39.5 %
Psychomotor agitation	25.5 %
Risky behavior	34.8 %
Mean (SD) N symptoms	3.3 (1.9)
Median N symptoms	3
> 1 sub-syndromal episode	73.8 %

Table 3 Clinical features (past hypomanic symptoms, past sub-syndromal hypomanic episodes) of the remitted major depressive disorder sample plus history of overactivity (n = 17)

Index mean (SD) age (years)	41.5 (12.5)
Index median age	45
Females	52.9 %
Elevated mood	11.7 %
Irritable mood	47.0 %
Increased self-esteem	47.0 %
Reduced need for sleep	17.6 %
More talkativeness	29.4 %
Racing/crowded thoughts	64.7 %
Distractibility	64.7 %
Overactivity	100 %
Psychomotor agitation	17.6 %
Risky behavior	41.1 %
Mean (SD) N symptoms	4.2 (1.9)
Median N symptoms	4
> 1 sub-syndromal episode	88.2 %

sis (dependent variable), found odds ratio = 9.3, p = 0.000, 95 % confidence interval 3.4 to 25.2, sensitivity = 60.2 %, specificity = 86 %. Logistic regression, to test sensitivity and specificity of irritable mood for predicting BPII diagnosis (dependent variable), found odds ratio = 1.2, p = 0.627, 95 % confidence interval 0.5 to 2.6 (as the association was not significant, sensitivity and specificity could not be calculated).

Discussion

Results showed a high frequency of bipolar spectrum in this MDE-remitted outpatient sample. It resulted that 3 in 4 patients were bipolar spectrum by including MDD plus sub-syndromal hypomanic episodes with overactivity. Not including MDD plus sub-syndromal hypomanic episodes with overactivity, frequency of BPII was in line with many previous reports (Akiskal and Benazzi 2003; Angst et al. 2003; Hantouche et al. 1998; Angst 1996; Perugi et al. 1998; Akiskal 2002; Akiskal 1996; Akiskal and Mallya 1987; Benazzi 1997; Benazzi 2000 b). MDD plus sub-syndromal hypomanic episodes with overactivity was included in the bipolar spectrum on the basis of clinical, psychometric, and family history findings supporting the bipolar nature of overactivity and that overactivity could have the priority given by DSM-IV to mood change for the diagnosis of hypomania (Akiskal et al. 2003 a; Angst et al. 2003; Akiskal et al. 1977; Benazzi and Akiskal 2003 a,b; Hantouche et al. 2003; Dunner et al. 1976 a,b; Goodwin and Jamison 1990). MDD sub-syndromal hypomanic episodes with overactivity had also 4 median concurrent hypomanic symptoms, further supporting its clinical validity. These study results in a clinical sample are very similar to the recent community study findings by Angst et al. (2003), using different methods, which were the following: 59.4 % BPII frequency in a MDD + BPII sample, 44.5 % frequency of MDD plus past overactivity in the MDD sample, and 18 % frequency of MDD plus past overactivity in the entire sample. Sub-syndromal hypomanic episodes were found to meet the criteria for "caseness" in the ECA community study (Judd and Akiskal 2003). Sub-syndromal hypomania in adolescents had negative outcomes, supporting its clinical validity (Lewinsohn et al. 2002). Akiskal and Benazzi (2003) found that, by including into the bipolar spectrum MDD plus more than 2 hypomanic symptoms present during the index MDE (depressive mixed state), bipolar spectrum frequency was 69.2 % (261/377). The bipolar nature of depressive mixed state (MDE plus intra-episode hypo/manic symptoms not meeting full criteria for hypo-mania) was validated by clinical, family history, and psychometric findings (Akiskal and Benazzi 2003; Sato et al. 2003; Benazzi 2002 b; Benazzi and Akiskal 2001, 2003 c; Benazzi 2003 b, c; Perugi et al. 1997,2001; Koukopoulos and Koukopoulos 1999; Akiskal and Mallya 1987; Akiskal and Pinto 1999). Following Ghaemi et al. (2002) definition of bipolar spectrum disorder (MDD plus bipolar signs [not including overactivity!]), bipolar spectrum frequency was 65.5 % to 71.8 % in a previous study (Benazzi 2003 c). Akiskal and Mallya (1987) reported a 50 % bipolar spectrum frequency in an outpatient sample using criteria stricter than the present ones. Even by applying different criteria, bipolar spectrum frequency was around 70 % in the depressed outpatients of different studies. Underdiagnosis of BPII was reported (Ghaemi et al. 2002), and was related to DSM-IV narrow diagnostic criteria (American Psychiatric Association 2002).

The present study results cannot be related to the different cut-off of hypomania duration (4 days in DSM-IV vs 2 days in the present study), as most BPII had a duration of hypomania longer than 4 days.

Overactivity had higher sensitivity but lower specificity than elevated mood for predicting BPII diagnosis. If having fewer false negatives (i. e., high sensitivity) is seen as more important for the clinician than having fewer false positives (i. e., high specificity), overactivity seems more useful than elevated mood for the diagnosis of BPII.

BPII studies were reported to be limited by low BPII diagnostic reliability (Coryell 1999; Andreasen et al. 1981; Mazure and Gershon 1979; Keller et al. 1981; Rice et al. 1986). Recent studies, using semi-structured interviews by clinicians instead of the fully structured interviews by nonclinicians used in previous studies, found low agreement between the two types of interviews, many false negatives using fully structured interviews, and high inter-rater reliability of BPII diagnosis (Aalto-Setala et al. 2002; Eaton et al. 2000; Brugha et al. 1999; Helzer et al. 1985; Dunner and Tay 1993; Simpson et al. 2002; Ghaemi et al. 2002). These findings are supported by long-term high diagnostic stability of BPII (Coryell et al. 1995; Akiskal et al. 1995) when diagnosis was made by trained clinicians using a semi-structured interview.

Frequency of BPII in depressed outpatients was found to be high (around 50 %) when the interviewers were clinicians using semi-structured interviews (Hantouche et al. 1998; Perugi et al. 1998; Benazzi 1997, 2000 b; Akiskal and Benazzi 2003; Akiskal et al. 2000; Angst 1996; Angst et al. 2003). A clinician using a semi-structured interview can assess all past hypomanic symptoms, especially overactivity (Akiskal et al. 1977; Angst et al. 2003; Benazzi and Akiskal 2003 a,b). Bypassing skip-out instructions related to mood change questions increased the frequency of BPII correct diagnoses by 33 % (from 45 % to 60 % BPII in depressed outpatient samples) (Benazzi and Akiskal 2003 a; Akiskal and Benazzi 2003).

Present study frequency of BPII (61.2 %, 95 % confidence interval 52 % to 69.8 %), diagnosed when depression was remitted, was similar to that found when the same interview was done at intake during a moderate severity MDE in the larger intake sample (Akiskal and Benazzi 2003). This finding supports the validity of BPII diagnosis done during MDE assessment when MDE is not too severe.

Limitations

Single interviewer limited validity of the findings. However, the interviewer inter-rater BPII reliability is high (Benazzi in press b), as well as that of the SCID-CV. Use of a semi-structured interview increased reliability and correct BPII diagnosis. Key informants increased validity of BPII diagnosis (American Psychiatric Association 2000; Akiskal et al. 2000). The interviewer had been studying and treating BPII for many years. All consecutive remitted patients had a systematic and standard interview. It is not known what the picture of the non-remitted patients was. Therefore, the present study findings must be related only to a group of psychoactive drug MDE-remitted BPII and MDD.

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