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ORIGINAL PAPER

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Validating Angst's "ups & downs" personality trait as a new marker of bipolar II disorder

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Abstract *Background* Angst has recently found an association between the bipolar spectrum and a personality trait called "ups & downs", defined by the question "would you say you were one of those people who have frequent ups and downs?". *Study aim* was to find the frequency of "ups & downs" in a large sample of bipolar II (BPII) and major depressive disorder (MDD), and to test its association with BPII. *Methods* Consecutive 89 MDD and 89 BPII outpatients were interviewed, during a major depressive episode (MDE), with the Structured Clinical Interview for DSM-IV, as modified by Benazzi and Akiskal (2003). Hypomanic symptoms during MDE were systematically assessed. The association between "ups & downs" (defined by Angst's question) and BPII was tested versus bipolar validators (young onset, many recurrences, atypical depression, depressive mixed state [MDE plus 3 or more concurrent hypomanic symptoms, following Akiskal and Benazzi's definition (2003)], and bipolar family history. Associations were tested by univariate and multivariate logistic regression (STATA 7). *Results* "ups & downs" was present in 62.9 % of BPII and in 33.7 % of MDD (ratio = 1.86, p = 0.0001). All bipolar validators were significantly more common in BPII versus MDD. Sensitivity and specificity of bipolar validators for predicting BPII, including "ups & downs", showed that "ups & downs" had a balanced combination of sensitivity (62.9 %) and specificity (66.2 %) (i. e., sensitivity not too low compared to specificity and vice versa) for predicting BPII, and that it was strongly associated with BPII (odds ratio = 3.3, 95 % CI 1.8–6.1). Multivariate analyses found that "ups & downs" independently and significantly predicted BPII among the other bipolar validators. Patients did not confuse "ups & downs" with many past MDEs, as the association with BPII did not change when controlled for recurrences. *Conclusions* Findings suggest that Angst's "ups and downs" might be a new marker of BPII. Its simple question might be useful to clinicians to better detect the highly underdiagnosed BPII during assessment of depression.

Key words ups and downs · temperament · bipolar II disorder · depression

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Introduction

A recent study by Angst et al. (2002, 2003a) found that a personality trait called "ups & downs" was a strong predictor of bipolar spectrum disorders. Assessment of "ups & downs" was made by the question "would you say you were one of those people who have frequent ups and downs?" (Angst et al. 2003a). There is a relationship between "ups & downs" and Akiskal et al. (1995) mood lability temperament. Mood lability temperament (Akiskal et al. 1995) was a strong predictor of the switching of major depressive disorder (MDD) to bipolar II disorder (BPII). Among its features there was frequent instability of mood. Akiskal et al. (1995) defined frequent instability of mood by two questions, similar to that of Angst for "ups & downs" (Angst et al. 2003a).

Mood instability as a personality trait related to bipolar disorders is not a new finding. Kraepelin (1921) and Hecker (1898, translation into English by Koukopoulos 2003) reported that, between manic/hypomanic attacks and depressive attacks of "manic-depressive insanity" (including today DSM-IV BPII) and "cyclothymia" (corresponding to today DSM-IV BPII), mood was frequently unstable. Kraepelin (1921) stated that mood instability was a fundamental temperamental state of "manic-depressive insanity", the root of the attacks of the illness, and listed it among the basic features of "manic-depressive insanity". Kraepelin defined "cyclothymic temperament" as "frequent fluctuations to the

manic or to the depressive side", and his description ("people who constantly oscillate hither and thither between the two opposite poles of mood") was very similar to Angst's "ups & downs". According to Kraepelin, this temperament was an "invariable introduction to the slightest forms of manic-depressive insanity which run their course outside institutions" (who were the "cyclothymia"-BPII outpatients seen by Hecker in private practice).

More recently, cyclothymic temperament was described by Akiskal et al. (1977, 1979), Akiskal and Mallya (1987), and by Akiskal et al. (1998). Among its features there was frequent instability of mood. Cyclothymic temperament was found to be significantly more common in BPII versus MDD (44.4% versus 4.4%) (Hantouche et al. 1998). There is a similarity between the mood instability of cyclothymic temperament definition by Akiskal, and Angst's "ups & downs". All these studies on temperaments (mood lability, cyclothymic, "ups & downs") require mood instability, and point to a relationship with bipolar disorders. A study assessing different types of premorbid personalities in mood and non-mood disorders found that the "manic type" was more common in bipolar I, and that the "melancholic type" was more common in BPII and unipolar depressive patients (von Zerssen et al. 1994).

The study of personality traits/disorders in BPII clearly still needs a lot of research by independent groups. Akiskal has been doing very important work for many years in this field, following Kraepelin's temperamental "fundamental states" (which he viewed as the "deeper cause" of "manic-depressive insanity") (1921, p 117). Studies on personality in BPII and other mood disorders may have an important impact on the genetics of these disorders (Fridman et al. 2003). Family studies have shown that, among the relatives of bipolar disorders probands, there is an increased frequency not only of mood disorders (both bipolar and unipolar) but also of mood personality traits/disorders (Kelsoe 2003). Kraepelin viewed mood temperaments as the root of mood disorders.

Study aim was to find the frequency of "ups & downs" in a large sample of BPII and MDD, and the relationship between "ups & downs" and BPII.

Materials and methods

Study setting

An outpatient psychiatry private practice (a University of California at San Diego (USA) collaborating center) was the study setting. Private practice is more representative of mood disorders usually seen in clinical practice in Italy: it is the first or the second (after family doctors) line of treatment of mood disorders, while university and national mental health (NHS) services usually treat the most severe (and less representative) patients. In Italy people do not like to be treated for mood disorders in the NHS for fear of stigma. Most individuals can visit a private psychiatrist (reducing a possible selection bias related to income).

Interviewer

The interviewer was a senior (20 years in practice) clinical and mood disorder research psychiatrist.

Patients

A total of 89 consecutive MDD, and 89 BPII outpatients, presenting voluntarily for major depressive episode (MDE) treatment, were included in the last 2 years. Substance-related and borderline personality disorders were excluded because they confound the diagnosis of BPII and mixed states (Akiskal and Pinto 1999). In the present study setting, prevalence of BPII and MDD with borderline personality disorder was found to be very low (Benazzi 2000a). DSM-IV rapid cycling BPII diagnoses were excluded (and were also few in the sample), to avoid the possibility that patients confused this unstable disorder with "ups & downs". Clinically significant general medical illnesses and cognitive disorders were also excluded. The study was approved by the ethic committee, performed according to ethical standards of the 1964 Declaration of Helsinki, and all individuals gave informed consent prior to inclusion in the study.

Interview method

All patients were interviewed during the first visit 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 (2003a) to focus the probing for history of hypomania more on past overactivity (increased goal-directed activity) than on mood change (in line with Angst et al. 2003b; Akiskal et al. 1977, 2001; Dunner and Tay 1993). The Global Assessment of Functioning (GAF) scale (American Psychiatric Association 1994) was used to grade index MDE severity. Bipolar (type I and type II) family history was investigated with the Family History Screen (Weissman et al. 2000), a structured interview for psychiatric history of first-degree relatives, by interviewing the patient and often also one first-degree relative.

The DSM-IV 4-days minimum duration of hypomania for BPII diagnosis was not followed, because this cutoff was not based on data (Dunner 1998). Instead, at least 2 days of hypomania were required for the diagnosis of BPII, following previous reports supporting this cutoff (Akiskal 2002; Angst 1998; Angst et al. 2003b; Akiskal et al. 1977, 1979, 2000; Benazzi 2001a; Cassano et al. 1992; Coryell et al. 1995; Judd et al. 2003).

Most present study BPII patients had had more than one hypomania, increasing reliability and validity of BPII diagnosis (Akiskal et al. 2000). Often, family members or close friends supplemented clinical information during the interview, increasing reliability and validity of BPII diagnosis (Akiskal et al. 2000; American Psychiatric Association, 2000).

All patients were systematically interviewed about history of hypomanic and manic episodes. History of mania and hypomania was always investigated soon after the diagnosis of MDE before assessment of study variables, in order to avoid a possible bias related to knowledge of signs of bipolarity (Ghaemi et al. 2002). Inter-rater agreement of the interviewer for BPII diagnosis was $\kappa = 0.73$ (Benazzi 2003a). This kappa-statistic was similar to that found in a study on reliability of BPII diagnosis using methods similar to those used in the present study (semi-structured interview by trained clinicians) (Simpson et al. 2002). SCID-CV inter-rater kappa statistic was reported to range between 0.70 and 1.00 (First et al. 1997).

The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions). The wording of the sentences can be changed when unclear to patient or when the interviewer is in doubt about understanding. The SCID-CV skip-out instruction in the stem question about history of elevated or irritable mood was not followed, as a negative answer would not allow the assessment of the other past hypomanic symptoms. This was done mainly to probe for past overactivity when the answer to the stem question on mood was negative. It was found (Benazzi and Akiskal 2003) that past overactivity was easier to remember than past mood change by patient, family members and close friends. It must

be noted that in the present study the diagnosis of past hypomania always required mood change (according to DSM-IV), which however made it easier to remember after remembering overactivity, even when at first the answer to the mood question had been negative. The utility of probing for history of hypomania by focusing more on overactivity than on mood change was reported (Angst et al. 2003b; Akiskal et al. 1977, 2001; Dunner and Tay 1993).

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 easier to understand by patients compared to the SCID-CV question on racing thoughts. This definition of crowded thoughts was similar to Kraepelin's description of a thought disorder of depression (i. e., overcrowding of the mind by non-stop thoughts) (1921, p 75). Presence of hypomanic symptoms during the index MDE was systematically assessed. Hypomanic symptoms had to last at least 1 week, to appear during the index MDE, and to be present at the time of the interview. The Hypomania Interview Guide-Current Assessment Version (Williams et al. 1994, 2000) was used to improve assessment of hypomanic symptoms during the index MDE, as it covers all DSM-IV hypomanic symptoms.

Depressive mixed state was defined as a MDE plus 3 or more concurrent hypomanic symptoms. This definition had had clinical, family history, and psychometric validation and replication (Benazzi and Akiskal 2001; Benazzi 2001b, 2002, 2003b; Akiskal and Benazzi 2003a, 2003b; Sato et al. 2003; Sato et al. 2003 in press; Judd et al. 2003).

MDE recurrences were divided into more than 4 MDEs and less than 5 MDEs, on the basis of data showing that bipolar disorders and MDD with more than 4 MDEs had a similar high probability of recurrence (Kendler et al. 2001; Kessing et al. 1998).

Testing the association of "ups & downs" with BPII

"Ups & downs" was assessed by Angst's question "would you say you were one of those people who have frequent ups and downs?" of mood (specified) (Angst et al. 2003a). The association between "ups & downs" and BPII was tested by studying of the association between BPII and bipolar and psychiatric diagnosis validators (age of onset, many recurrences, atypical features of depression, depressive mixed state, bipolar family history) (Kraepelin 1921; Hecker 1898; Angst and Gamma 2002; Akiskal 2003; Akiskal et al. 1995; Akiskal and Benazzi 2003a; Benazzi 2000b; Goodwin and Jamison 1990; McMahon et al. 1994; Ghaemi et al. 2002; Robins and Guze 1970; Kendler 1980.1990).

Statistics

Means were compared by t test; frequencies were compared by chi-squared test. Associations were tested by univariate and multivariate logistic regression, and by forward stepwise multiple logistic regression. STATA Statistical Software, Release 7, was used (Stata Corporation, College Station, TX, USA, 2001). P values were two-tailed, and the alpha level was set at 0.05.

Results

"Ups & downs" was common in both BPII and MDD, and significantly more common in BPII versus MDD (ratio = 1.86) (p = 0.0001) (Table 1). All bipolar validators were significantly more common in BPII versus MDD (Table 1).

Sensitivity and specificity of bipolar validators including "ups & downs" for predicting BPII (Table 2) showed that bipolar family history had the highest specificity (82.5 %). However, the best combinations of sensitivity and specificity (i. e., sensitivity not too low compared to specificity and vice versa) were shown by depressive mixed state and by "ups & downs". Both multivariate logistic regression and stepwise multiple logistic regression found that "ups & downs" independently and significantly predicted BPII among all the other bipolar validators.

To test if patients might have confused "ups & downs" with many past MDEs (because logistic regression between "ups & downs" and more than 4 MDEs had found odds ratio = 2.6, 95 % CI = 1.3 to 5.0, p = 0.003), logistic regression of BPII versus "ups & downs" was controlled for MDE recurrences. MDE recurrences were a possible confounding factor because they are also associated with BPII. The result was odds ratio = 2.7, 95 % CI = 1.4 to 5.2, p = 0.002. The interaction between "ups & downs" and MDE recurrences was not significant (p = 0.149) (Table 3).

As Angst et al. (2003a) did not find an association between "ups & downs" and bipolar family history, associations between "ups & downs" and bipolar (type I + type II) family history, and mood disorders family history were tested by univariate logistic regression (Table 4). In the entire sample, family history of bipolar disorders was present in 26.5 %, and family history of mood disor-

Table 1 Comparisons between bipolar II (BPII) and major depressive disorder (MDD) on bipolar validators, and "ups & downs" (*T* test; *X2* chi-squared test; *DF* degrees of freedom)

Variables: mean (SD), N (%)	BPII n = 89	MDD n = 89	T/X2 DF = 176 DF = 1	P
Index age, years	41.8 (11.5)	45.8 (13.3)	2.1	0.033
Female gender	65 (73 %)	52 (58.4 %)	4.2	0.040
Index GAF	51.1 (9.3)	51.2 (9.7)	0.0	0.944
BIPOLAR VALIDATORS				
Index depressive mixed state	64 (71.9 %)	43 (48.3 %)	10.3	0.001
Index atypical features	57 (64 %)	38 (42.6 %)	8.1	0.004
Age at onset of first MDE, years	21.7 (9.5)	31.9 (12.7)	6.0	0.000
> 4 MDEs	73 (82 %)	44 (49.4 %)	20.8	0.000
Bipolar (I + II) family history	34 (38.2 %)	13 (14.6 %)	13.1	0.000
"ups & downs"	56 (62.9 %)	30 (33.7 %)	15.2	0.000

MDE major depressive episode; *GAF* global assessment of functioning scale

Table 2 Univariate logistic regression of bipolar II (dependent variable) versus bipolar validators

Variables	Odds ratio	95 % CI	SE	SP	ROC
Onset	0.9	0.9 to 0.9***	84.0	44.4	0.70
> 4 MDEs	3.1	2.1 to 4.6***	81.2	42.3	0.61
Atypical features	2.7	1.9 to 3.8***	55.0	69.1	0.62
Depressive mixed state	3.4	2.4 to 4.9***	62.5	67.4	0.64
Bipolar family history	4.7	2.9 to 7.6***	50.2	82.5	0.66
"ups & downs"	3.3	1.8 to 6.1***	62.9	66.2	0.64

*** $p < 0.001$; *95 % CI* 95 % confidence interval; *MDE* major depressive episode; *SE* sensitivity; *SP* specificity; *ROC* area under ROC curve

Table 3 Multivariate logistic regression of bipolar II (dependent variable) versus bipolar validators (likelihood ratio test, X2 = 58.6, P = 0.0000)

Variables	Odds ratio	95 % CI
Onset	0.9	0.9 to 0.9**
> 4 MDEs	3.8	1.7 to 8.5**
Atypical features	1.0	0.5 to 2.2
Depressive mixed state	1.6	0.7 to 3.5
Bipolar family history	2.7	1.1 to 6.7*
"ups & downs"	2.1	1.0 to 4.4*

* $p < 0.05$; ** $p < 0.01$; *95 % CI* 95 % confidence interval; *MDE* major depressive episode

Table 4 Forward stepwise multiple logistic regression of bipolar II (dependent variable) versus bipolar validators (likelihood ratio test, F = 13.8, P = 0.0000) (atypical features were deleted by the stepwise variable selection)

Variables	Coefficient	95 % CI
Onset	–0.0	–0.0 to –0.0**
> 4 MDEs	0.2	0.1 to 0.3**
Depressive mixed state	0.1	–0.0 to 0.2
Bipolar family history	0.1	0.0 to 0.3*
"ups & downs"	0.1	0.0 to 0.2*

* $p < 0.05$; ** $p < 0.01$; *95 % CI* 95 % confidence interval; *MDE* major depressive episode

ders in 70 %. Logistic regression of "ups & downs" versus bipolar family history found an odds ratio = 1.2, 95 % CI = 0.6 to 2.5, p = 0.462. Logistic regression of "ups & downs" versus mood disorders family history found an odds ratio = 2.1, 95 % CI = 1.0 to 4.0, p = 0.028.

Discussion

It was found that Angst's personality trait "ups & downs" was common in depressed outpatients, and that it was much more common in BPII versus MDD. This finding is line with the much higher frequency of cyclothymic temperament (which includes mood instability) in BPII versus MDD found by Hantouche et al. (1998).

Univariate and multivariate analyses showed that "ups & downs" was a strong and independent predictor of BPII. Therefore, it might be added to the current list of most important bipolar validators (including young onset, many recurrences, atypical features of depression, depressive mixed state, bipolar family history, and cyclothymic temperament). Findings are in line with Angst et al. (2003a), showing that "ups & downs" was a strong and independent predictor of bipolar spectrum disorders (including BPII), and with Akiskal et al. (1995) study showing that mood lability (which included two items similar to "ups & downs") was a strong predictor of the switching of MDD to BPII. Angst et al. (2003a) found that "ups & downs" was not associated with a family history of bipolar disorders. In multivariate logistic regression, "ups & downs" resulted significantly associated with BPII even if bipolar family history was included in the model. This finding suggests that "ups & down" was not associated with bipolar family history (a finding replicated in the univariate logistic regression analysis), which is in line with Angst et al. (2003a). This finding does not agree with the significant association found between cyclothymic temperament and bipolar family history (Akiskal et al. 1977, 2003b). These different findings may be related to the definition of cyclothymic temperament, which includes not only instability of mood, but also instability of behavior, thinking, energy, and sleep (Akiskal et al. 2003b). However, "ups & downs" was associated with a family history of mood disorders in the present sample, supporting its link with mood disorders.

The balanced combination of sensitivity and specificity for predicting BPII shown by "ups & downs" suggests that it could become a useful marker in clinical practice. Its usefulness for clinical practice is further strengthened by its quick and simple assessment question. BPII is in need of clinical markers because it is highly underdiagnosed in clinical practice (Akiskal 2002; Akiskal et al. 2000; Ghaemi et al. 2002). DSM-IV-TR reports a 0.5 % community prevalence of BPII, while Angst (1998) and Angst et al. (2003b) reported an 11 % community prevalence, which was similar to that of MDD. This near 1 to 1 ratio found between BPII and MDD was also found in clinical samples carefully and systematically assessed for history of hypomania by expert clinicians (Akiskal and Benazzi 2003a; Hantouche et al. 1998; Dunner and Tay 1993; Manning et al. 1999; Benazzi 1997, 2001c). Hypomania is often a period of improved functioning (Hecker 1898; Dunner and Tay 1993; Akiskal 2002; American Psychiatric Association 2000; Benazzi 2003 in press), and it is therefore often seen by BPII patients (and often also by family members and doctors) as a period of well being ("I felt like a lion" is a common saying in Italy to describe that state by few clear words). Therefore, BPII patients usually present for treatment of depression, and during clinical assessment usually do not spontaneously report about past hypomania. Consequently, skillful questioning by the clinician is required to detect a history of past hypomania (Akiskal 2002). The current structured interviews often

used by nonclinicians highly underdiagnose BPII (Akiskal 2002; Benazzi and Akiskal 2003; Simpson et al. 2002; Ghaemi et al. 2002; American Psychiatric Association 2002; Benazzi 2001d), while semi-structured interviews by expert clinicians increase the detection of BPII and other mood disorders (Dunner and Tay 1993; Benazzi and Akiskal 2003b; Brugha et al. 2001). Some BPII clinical markers could be useful to induce the clinician to suspect BPII, then leading to a careful assessment of past hypomania. Among them, young onset, many MDE recurrences, bipolar family history are usual markers dependent on memory, limiting utility when depression is severe (which leads to memory impairment and negative cognitive bias) and when no informant is present. Current cross-sectional BPII clinical markers, which can easily be detected during assessment of depression, are DSM-IV atypical features and depressive mixed state (Benazzi 2000b, 2003c). Angst's "ups & downs" might be added to this list of BPII markers, and, given its simple feature, it could become an important and quick screening question to detect BPII during assessment of depression.

As "ups & downs" was significantly associated with MDE recurrences (and recurrences were also associated with BPII), its association with BPII was controlled for recurrences (a possible confounding factor), to test if patients might have confused having had many recurrences with "ups & downs". It resulted that the association between BPII and "ups & downs" remained significant, suggesting that patients did not confuse recurrences with "ups & downs". This finding supports the validity of Angst's question for "ups and downs".

The relationships between "ups & downs" and rapid cycling BPII (not included in the present sample) should be studied, as patients could not be able to distinguish them. However, rapid cycling and ultra-rapid cycling BPII were often reported to be present in less than 20 % of BPII (Maj 2001; Kilzieh and Akiskal 1999), while "ups & downs" was present in 63 % of the present study BPII sample. Depression is the main problem in BPII rapid cycling (Maj 2001; Kilzieh and Akiskal 1999). As the present study patients did not confuse history of many MDEs with "ups & downs", it is possible that the same could occur also in rapid cycling BPII (which patients might distinguish also because it is a period usually not lasting for most of the life as instead a personality trait does). Studies on this topic are clearly needed.

Studies on the association between "ups & downs" and other mental disorders are required to determine if "ups & downs" is a specific marker of BPII and if it is also a risk factor of other mental disorders.

Limitations

A single interviewer limited the validity of the findings, but his inter-rater kappa-statistic for BPII diagnosis was high. Reliability of BPII diagnosis was found to be high and similar to the present one when the interview was semi-structured and performed by trained psychiatrists (Simpson et al. 2002), supporting the present study methods. BPII and MDD sample features were in line with the features often reported to distinguish bipolar disorders and MDD (Akiskal 2002, 2003; Goodwin and Jamison 1990; Akiskal and Benazzi 2003a; McMahon et al. 1994), supporting the validity of the interview. The interview was conducted by a clinician studying and treating mood disorders for a long time, using validated structured/semi-structured interviews, information from key informants, and systematically interviewing about past hypomania. Clinicians using semi-structured interviews made more correct BPII diagnoses compared to structured interviews (Dunner and Tay 1993), and made more valid assessments of mood disorders than structured interviews by nonclinician interviewers (Brugha et al. 2001). These study features may have reduced study limitations (Akiskal 2002; Akiskal et al. 2000; Goodwin and Jamison 1990). The present study frequency of bipolar disorders among first-degree relatives was in line with previous studies (Coryell 1999; Kupfer et al. 2002; Suppes et al. 2001).

"Ups & downs" was assessed during a state of depression. Information obtained during depression about the past may be biased by its negative cognitive bias (Akiskal et al. 2000). However, the negative cognitive bias of depression is related to its severity (Akiskal et al. 2000), and most present study depressions were not too severe (mean GAF = 51). Furthermore, information was often supplemented by interview of key informants. Importantly, patients did not confuse past MDEs with "ups & downs", supporting the validity of the assessment of this personality trait during a nonsevere depression. These study features should have increased the validity of the assessment of this personality trait during depression. Further study is needed about the validity of the assessment of "ups & downs" during depression.

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