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ORIGINAL PAPER

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Should mood reactivity be included in the DSM-IV atypical features specifier?

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Abstract *Background* The definition of atypical depression is still an unsolved issue. DSM-IV atypical features specifier criteria always require mood reactivity, but why mood reactivity should be included is unclear. The study aim was to test whether mood reactivity should be included in DSM-IV atypical features specifier. *Methods* Consecutively, 164 unipolar and 241 "soft" bipolar II major depressive episode (MDE) outpatients were interviewed with the Structured Clinical Interview for DSM-IV. The DSM-IV criteria for atypical features specifier were strictly followed. Associations were tested by univariate logistic regression. *Results* MDE with atypical features was present in 41.4 % of patients. Bipolar II disorder was significantly more common in patients with atypical features. MDE with atypical features was significantly associated with bipolar II, female gender, lower age of onset, more axis I comorbidity, fewer psychotic features, and more depressive mixed states. In the whole sample, mood reactivity was significantly associated with all the atypical symptoms, apart from leaden paralysis, and all the other atypical symptoms were significantly associated with each other. In the bipolar II sub-sample, mood reactivity was associated with many, but not all, atypical symptoms, while in the unipolar sub-sample it was associated with no atypical symptom. Atypical symptoms were significantly more common in mood reactive than in non-mood reactive patients, apart from leaden paralysis. Bipolar II disorder and mood reactivity were strongly associated. *Conclusions* Results may support the inclusion of mood reactivity in the DSM-IV atypical features specifier for bipolar II disorder, but not for unipolar depression.

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Introduction

The definition of atypical depression (AD) is still unclear (Angst et al., in press a; Rabkin et al., 1996). Different definitions can be found (Rabkin et al., 1996; Williamson et al., 2000; McGrath et al., 2000; Sotsky and Simmens, 1999; Levitan et al., 1997; Sullivan et al., 1998; Kendler et al., 1996; Horwath et al., 1992; Thase et al., 1992). In DSM-IV (American Psychiatric Association, 1994), AD is a major depressive episode (MDE) specifier of depressive (unipolar) and bipolar disorders. DSM-IV AD always requires mood reactivity, plus overeating/weight gain, oversleeping, leaden paralysis, and interpersonal sensitivity (at least two). DSM-IV AD criteria come from Columbia University studies showing, in mainly unipolar samples, better response to MAOI than to TCA and fluoxetine (McGrath et al., 2000; Rabkin et al., 1996). Latent class analysis also supported AD validity (Sullivan et al., 1998; Kendler et al., 1996).

Why mood reactivity should always be present in DSM-IV AD is unclear (Nierenberg et al., 1998). Rabkin et al. (1996) review did not include mood reactivity among the symptoms suggested to define AD. When only mood reactivity was present, MAOI were not more effective than TCA (Quitkin et al., 1989). Mood reactivity was not correlated with AD symptoms in one study (Posternak and Zimmerman, 2002), but it was associated with AD symptoms in another study (Angst et al., in press a). Most studies on AD had mainly unipolar samples (Rabkin et al., 1996; Williamson et al., 2000; McGrath et al., 2000; Sotsky and Simmens, 1999; Levitan et al., 1997; Sullivan et al., 1998; Kendler et al., 1996; Horwath et al., 1992). Recent studies (Benazzi, 1999a,b,c,d; Benazzi, 2000a,bc; Angst, 1998; Perugi et al., 1998; Angst et al., in press b) found that DSM-IV AD was much more common in bipolar II vs unipolar [45.4 % (n = 251) vs 25.4 % (n = 306) (Benazzi, 2000c)]. As bipolar II was

common (30 to 60 %) among MDE outpatients (Akiskal et al., 2000; Benazzi, 1997; Benazzi, 2001a; Benazzi and Akiskal, in press; Hantouche et al., 1998; Cassano et al., 1992; Perugi et al., 1998; Angst, 1996), inclusion of bipolar II in AD studies is important.

The study aim was to test whether mood reactivity should be included in the DSM-IV atypical features specifier. The inclusion of a large sample of bipolar II increases the validity of the findings.

Methods

The study was conducted by the author in his private outpatient psychiatry center (a University of California in San Diego (USA) collaborating center). Private practice could be more representative of mood disorder patients in Italy (possibly also in the USA (Ghaemi, 2001)), because it is the first (or second, after family doctors) line of treatment of mood disorders, and national health services and university centers usually treat the most severe patients. Most persons can be visited by a private psychiatrist. Authorities believe that mood disorder patients in tertiary care centers are not representative of usual clinical practice (Akiskal and Pinto, 1999; Ghaemi et al., 2000; Goldberg and Kocsis, 1999; Post et al., 2001). However, the study sample was not compared with an epidemiological sample, which is the only way to know how representative any sample is of a population.

Consecutively 164 unipolar (major depressive disorder (MDD), and MDD superimposed on dysthymic disorder) and 241 bipolar II outpatients were included in the last three years. Study was approved by ethics committee and performed according to ethical standards of 1964 Declaration of Helsinki. All persons gave informed consent prior to inclusion in the study. MDD and MDD superimposed on dysthymic disorder were combined in one group (Angst et al., 2000; Judd and Akiskal, 2000). No psychopharmacotherapy before evaluation avoided antidepressant-induced mixed states (Akiskal and Pinto, 1999), and drug-induced pseudoatypical symptoms (like hypersomnia and weight gain). Current substance abuse and severe personality disorder patients were not included (Benazzi, 2000d). Clinically significant general medical illness and dementia patients were not included. Patients were interviewed by the author during the first visit with the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (First et al., 1997), and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994). The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions), increasing bipolar II correct diagnoses (Dunner and Tay, 1993). Patients were systematically interviewed for history of manic/hypomanic episodes, and for hypomanic symptoms during the index MDE. The SCID-CV skip-out instruction of the question about past periods of hypomanic mood was not followed, as it was shown (Benazzi and Akiskal, in press) that systematic assessment of all past hypomanic symptoms increased the frequency of bipolar II diagnoses. History of mania/hypomania was always investigated soon after making the diagnosis of MDE to avoid a possible bias related to knowledge of signs of bipolarity (Akiskal et al., 2000; Goodwin and Jamison, 1990; Baldessarini, 2000; McMahon et al., 1994). DSM-IV 4-days minimum duration of hypomania for bipolar II diagnosis (a cut-off not based on data (Dunner, 1998)) was not followed. At least 2 days of hypomania were required for bipolar II diagnosis, on the basis of previous reports (Akiskal et al., 2000; Akiskal, 1996; Benazzi, 2001b; Angst, 1998; Cassano et al., 1992; Akiskal et al., 1977; Coryell et al., 1995). These bipolar II patients, not strictly following DSM-IV, could be called "soft" bipolar II (following Akiskal, 1996, and Angst et al., in press b). Most present study bipolar II patients had had more than one hypomania. Often, family members or close friends supplemented the clinical information during the interview.

Study variables (Coryell et al., 1995; Benazzi and Akiskal, 2001; Akiskal et al., 1995) are presented in table 1. DSM-IV criteria for atypical features were strictly followed. Depressive mixed state was defined as a MDE plus three or more (DMX3) concurrent hypomanic symptoms, following Benazzi and Akiskal (2001), and Benazzi (Benazzi, 2001c; Benazzi, in press). More details on study methods can be found in previous reports of the author (see references).

Table 1 Sample features (bipolar II (BPII) versus unipolar (UP))

Variables: mean(SD), %	BPII n = 241	UP n = 164	t/z	df	P
Female gender	67.2 %	60.3 %	1.4		0.1546
Age, years	41.9(14.1)	47.1(15.5)	−3.4	403	0.0005
Age of onset first MDE, years	22.9(10.8)	32.1(14.5)	−7.3	403	0.0000
GAF score	50.4(9.0)	50.8(9.2)	−0.4	403	0.6637
MDE symptoms > 2 years	44.3 %	33.5 %	2.1		0.0294
Axis I comorbidity	55.1 %	46.9 %	1.6		0.1050
> 4 MDEs	80.9 %	59.7 %	4.6		0.0000
Psychotic features	8.7 %	7.9 %	0.2		0.7754
Melancholic features	13.6 %	18.2 %	−1.2		0.2088
Atypical features	53.5 %	23.7 %	5.9		0.0000
DMX3	59.3 %	26.8 %	6.4		0.0000

Statistics

Means were compared with the t test, and proportions with the two-sample test of proportion. Univariate logistic regression was used to study associations. STATA Statistical Software, Release 7, was used (Stata Corporation, College Station, TX, USA, 2001). Two-tailed $P < 0.05$ was used.

Results

MDE with DSM-IV atypical features was present in 168 outpatients (168/405, 41.4 %). Bipolar II disorder was present in 76.7 % of MDE patients with atypical features, and in 47.2 % of MDE patients without atypical features ($z = 5.9$, $P = 0.0000$). Associations between atypical features and study variables are presented in Table 2. MDE with atypical features was significantly associated with bipolar II, female gender, lower age of onset, more axis I comorbidity, fewer psychotic features, and more DMX3. Associations among atypical features symptoms in the whole sample are presented in Table 3. Mood reactivity was significantly associated with all atypical features symptoms, apart from leaden paralysis (4/5). All the other atypical symptoms were significantly associated with each other. Associations among atypical features symptoms in the bipolar II sub-sample are presented in

Table 2 Associations between DSM-IV atypical features specifier and study variables, by univariate logistic regression

Variable	Odds ratio	Z	P
Unipolar	0.2	−5.8	0.000
Bipolar II	3.6	5.8	0.000
Female gender	2.0	3.2	0.001
Age of onset first MDE	0.9	−5.3	0.000
> 4 MDEs	1.4	1.6	0.093
Axis I comorbidity	1.6	2.5	0.010
GAF	1.0	1.5	0.133
Psychotic features	0.2	−3.0	0.002
DMX3	3.0	5.2	0.000
MDE symptoms > 2 years	1.3	1.4	0.162

Table 3 Association between DSM-IV atypical features specifier symptoms in the whole sample, by univariate logistic regression (odds ratio, * = P < 0.05, ** = P < 0.01)

	MR	WG	IA	H	LP
WG	3.1*				
IA	9.3**	83.7**			
H	4.6**	8.8**	9.4**		
LP	1.5	3.0**	3.5**	2.6**	
IRS	2.2**	2.0*	1.7*	2.4**	2.4**

(*MR* mood reactivity, *WG* weight gain, *IA* increased appetite, *H* hypersomnia, *LP* leaden paralysis, *IRS* interpersonal rejection sensitivity)

Table 4 Association between DSM-IV atypical features specifier symptoms in the bipolar II sub-sample, by univariate logistic regression (odds ratio, * = P < 0.05, ** = P < 0.01)

	MR	WG	IA	H	LP
WG	3.9				
IA	5.3*	69.6**			
H	5.2**	6.2**	6.5**		
LP	1.3	3.1**	3.4**	2.0**	
IRS	3.2**	1.1	1.0	1.4	2.2**

(*MR* mood reactivity, *WG* weight gain, *IA* increased appetite, *H* hypersomnia, *LP* leaden paralysis, *IRS* interpersonal rejection sensitivity)

Table 5 Associations among DSM-IV atypical features specifier symptoms in the unipolar sub-sample, by univariate logistic regression (odds ratio, * = P < 0.05, ** = P < 0.01)

	MR	WG	IA	H	LP
WG	1.4				
IA	NC	98.3**			
H	3.1	18.5**	18.5**		
LP	1.4	1.5	2.4	3.4**	
IRS	1.2	4.4*	2.9*	4.1**	2.0*

(*MR* mood reactivity, *WG* weight gain, *IA* increased appetite, *H* hypersomnia, *LP* leaden paralysis, *IRS* interpersonal rejection sensitivity, *NC* not calculable)

Table 4. Mood reactivity was significantly associated with 3/5 atypical symptoms. The other atypical symptoms were often, but not always, significantly associated with each other (7/10). Associations among atypical features symptoms in the unipolar sub-sample are presented in Table 5. Mood reactivity was not significantly associated with any atypical symptom. The other atypical symptoms were often, but not always, significantly associated with each other (8/10). Comparisons of atypical features symptoms between mood reactive and non-mood reactive MDE patients are presented in Table 6. Atypical features symptoms were significantly more common in mood reactive than in non-mood reactive MDE patients, apart from leaden paralysis. Given the strong significant association between bipolar II disorder and DSM-IV atypical features, the association between bipolar II and mood reactivity was tested. Logistic regression of bipolar II disorder versus mood reactivity found odds ratio = 2.0, z = 2.6, p = 0.009.

Table 6 Comparison of DSM-IV atypical features specifier symptoms between mood reactive (MR) and non-mood reactive (N-MR) major depressive episode (MDE) patients

Atypical symptoms	MR = 344	N-MR = 61	Z	P
Weight gain	18%	6.5%	2.2	0.0249
Increased appetite	24.1%	3.2%	3.6	0.0002
Hypersomnia	33.4%	9.8%	3.7	0.0002
Leaden paralysis	40.9%	31.1%	1.4	0.1489
Interpersonal sensitivity	62.5%	42.6%	2.9	0.0035

Discussion

MDE with DSM-IV atypical features specifier was present in 41.4% of outpatients, in line with previous reports including bipolar patients (Benazzi, 1999a,b,c,d (samples independent from the present one); Benazzi, 2000a,b,c (samples independent from the present one); Angst, 1998; Perugi et al., 1998; Angst et al., in press b). Bipolar II disorder was significantly more common in MDE patients with DSM-IV atypical features than in MDE patients without DSM-IV atypical features, in line with previous reports (Angst, 1998; Angst et al., in press b; Benazzi, 1999a,b,c,d; Benazzi, 2000a,bc; Perugi et al., 1998; Agosti and Stewart, 2001). In community studies (which did not assess bipolar II) AD did not have more bipolar I than non-AD (Sullivan et al., 1998; Levitan et al., 1997; Horwath et al., 1992). One community study did not assess bipolar disorders in AD (Kendler et al., 1996). These community studies have important limitations. AD was not assessed according to DSM-IV criteria, bipolar II disorder was not assessed, fully structured interviews were made by lay interviewers (semi-structured interviews by medical interviewers provided more valid assessment of mood disorders than structured interviews by non-medical interviewers (Brugha et al., 2001)), and reliability of bipolar diagnosis was low compared to a clinicians' diagnosis (Ghaemi et al., 2002). Sullivan et al. (1998) reported in the abstract that "the correspondence between epidemiological derived typologies of atypical depression and DSM-IV major depression with atypical features is not yet known". When bipolar II disorder was carefully assessed in a community study, it was more common in AD vs non-AD (Angst et al., in press a). Some atypical symptoms (overeating, weight gain, hypersomnia) were more common in bipolar I vs unipolar disorder in inpatients (Serretti et al., 1998), but melancholic features (and also mood non-reactivity and reduced eating) were reported to be more common in bipolar (I+II) vs unipolar in/outpatients (Parker et al., 2000) (according to DSM-IV, a diagnosis of atypical features cannot be made if there are melancholic features). Diagnostic stability (Coryell et al., 1995), different family history (Goodwin and Jamison, 1990; Coryell, 1999), and linkage studies (McMahon et al., 2001) suggest that bipolar I and bipolar II may be distinct disorders which should be studied separately. No more bipolar II in AD vs non-AD was reported in

some clinical samples (Robertson et al., 1996; Posternak and Zimmerman, 2002), but these bipolar II samples were very small (n = 10, n = 28), limiting the power of the studies. In the present study, MDE with the DSM-IV atypical features specifier was significantly associated with bipolar II, female gender, lower age of onset, more axis I comorbidity, fewer psychotic features, and more DMX3, in line with previous reports (Rabkin et al., 1996; Williamson et al., 2000; McGrath et al., 2000; Sotsky and Simmens, 1999; Levitan et al., 1997; Sullivan et al., 1998; Kendler et al., 1996; Benazzi and Akiskal, 2001; Horwath et al., 1992). However, age of onset of AD vs non-AD was not significantly different in a unipolar sample (Asnis et al., 1995), and no gender difference was reported in mainly unipolar community samples (Levitan et al., 1997; Horwath et al., 1992).

Mood reactivity was significantly associated with all DSM-IV atypical features symptoms, apart from leaden paralysis (4/5), in the whole sample. All the other atypical symptoms were significantly associated with each other (10/10) in the whole sample. However, when the analysis was made in the bipolar II and unipolar subsamples, results were partly different. In the bipolar II sub-sample mood reactivity was significantly associated with 3/5 atypical symptoms, while in the unipolar subsample it was significantly associated with no atypical symptom (0/5). In the two sub-samples the other atypical symptoms were often, but not always, significantly associated with each other (7/10, 8/10). Given the strong association between bipolar II disorder and the DSM-IV atypical features specifier found in the present study and in previous studies (Angst, 1998; Angst et al., in press a,b; Benazzi, 1999a,b,c,d; Benazzi, 2000a,b,c; Perugi et al., 1998; Agosti and Stewart, 2001), the association between bipolar II and mood reactivity was tested by logistic regression, finding a strong association. The results of the present study in the bipolar II sub-sample are line with Angst et al. (in press a) finding of significant associations between mood reactivity and the other DSM-IV atypical features symptoms. The results of the present study in the unipolar sub-sample are also in line with Posternak and Zimmerman (2002) finding of a lack of correlation between mood reactivity and the other atypical symptoms (leading the authors to question the inclusion of mood reactivity in the DSM-IV atypical features specifier). In these two studies, unipolar and bipolar II patients were combined in the analysis, as it was done in Table 3. An important difference between these two studies is the number of bipolar II patients included, which was very small in the study by Posternak and Zimmerman (2002). In the present study, a large number of bipolar II patients was included, making it more comparable to the study by Angst et al. (in press a). However, contrary to these two studies, unipolar and bipolar II sub-samples were also studied separately (Tables 4 and 5), leading to interesting findings which could explain the opposite findings of the above two studies. The results of the present study seem to suggest that the inclusion of mood reactivity among the symptoms of the atypical features may be different in bipolar II vs unipolar depression. In bipolar II depression, mood reactivity could be included in the atypical features, while in unipolar depression it could not be included. This conclusion is also supported by differences found between bipolar II AD and unipolar AD (lower age of onset, fewer psychotic features, and less chronicity in bipolar II, different associations between the early- and late-onset subtypes) (Benazzi, 1999a,b,c,d; Benazzi, 2000a). Interview by trained clinicians may be an important variable related to different findings in similar studies. The present study interview was made by an experienced clinician studying and treating mood disorders, while in the study by Posternak and Zimmerman (2002) the interview was performed by psychologists or a college graduate. Clinicians were reported to make more correct assessments than non-medical interviewers (Brugha et al., 2001).

Comparisons of DSM-IV atypical features symptoms between mood reactive and non-mood reactive MDE patients found that atypical symptoms were much more common in mood reactive than in non-mood reactive MDE patients, apart from leaden paralysis. This finding seems to support the inclusion of mood reactivity in the DSM-IV atypical features specifier, but it was mainly related to the bipolar II sub-sample. AD better response to MAOI than to TCA was not related to any AD symptom (McGrath et al., 1992), and when only mood reactivity was present MAOI was not more effective than TCA (Quitkin et al., 1989). AD better response to MAOI was not always found, and it was also reported that mood non-reactivity responded better to MAOI (Zisook et al., 1985; Davidson et al., 1991). These pharmacological studies do not seem to support the inclusion of mood reactivity in DSM-IV AD criteria, but were based on mainly unipolar samples. The results of the present study suggest that mood reactivity could be included in the atypical features in bipolar II disorder, but not in unipolar (MDD) depression. This conclusion is supported by the reported strong association between interpersonal sensitivity and bipolar II disorder (Perugi et al., 1999; Akiskal et al., 1995), as mood reactivity may be related to interpersonal sensitivity. In the present study mood reactivity was strongly associated with interpersonal sensitivity in the bipolar II sample only.

The present study low frequency of non-mood reactive patients (61/405) was related to the setting (the median GAF score of the sample was 50), where very severe patients are usually not treated (non-reactivity of mood is a fundamental symptom of melancholic features, which are usually present in severe MDE patients (American Psychiatric Association, 2000; Parker, 2000), and melancholic features were present in only 13 to 18 % of study patients).

A limitation of the present study is that comparisons with other studies following DSM-IV 4-days minimum duration of hypomania for bipolar II diagnosis (versus 2 days in the present study) may not be valid. However, it was shown that bipolar II with short hypomania (less

than 4 days) had features similar to DSM-IV bipolar II (Benazzi, 2001b; Angst et al., in press b). The finding of more bipolar II in the present study may be related to the different minimum durations of hypomania, which could have led to underdiagnosis of bipolarity in other studies.

Use of a single interviewer limited the validity of the findings. Bipolar II and unipolar sample features were in line with the reported typical features distinguishing bipolar from unipolar (onset, recurrences, AD, family history) (Benazzi and Akiskal, 2001; Akiskal et al., 2000; Goodwin and Jamison, 1990; Baldessarini, 2000; McMahon et al., 1994), supporting the validity of the interview. The interview was conducted by an experienced clinician studying and treating mood disorders, using a validated structured/semi-structured interview, information from key informants, and systematically interviewing about past hypomania. DSM-IV AD criteria were strictly followed. However, a single interviewer bias may be possible. In the diagnosis of bipolar II disorder, clinical evaluation by clinicians trained on bipolar II diagnosis led to more correct diagnoses than strict structured interviewing (Dunner and Tay, 1993), and semi-structured interviews by clinicians provided more valid assessment of mood disorders than structured interviews by non-medical interviewers (Brugha et al., 2001). These study features may have reduced study limitations (Akiskal et al., 2000; Goodwin and Jamison, 1990). DSM-IV minimum duration of hypomania, and the SCID-CV skip-out instruction, were not followed, which could make the present study not fully comparable to previous ones. However, recent studies (Angst et al., in press b; Benazzi, 2001b; Benazzi and Akiskal in press) did find similarities between DSM-IV bipolar II and bipolar II diagnosed not following DSM-IV hypomania duration and SCID-CV guidelines.

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