

ORIGINAL PAPER

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Can only reversed vegetative symptoms define atypical depression?

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Abstract *Background* The definition of atypical depression (AD) has recently seen a rebirth of studies, as the evidence supporting the current DSM-IV atypical features criteria is weak. Study aim was to compare a definition of AD requiring only oversleeping and overeating (reversed vegetative symptoms) to the DSM-IV AD definition (always requiring mood reactivity, plus overeating/weight gain, oversleeping, leaden paralysis, and interpersonal sensitivity [at least 2]). *Methods* Consecutive 202 major depressive disorder (MDD) and 281 bipolar II outpatients were interviewed, during a major depressive episode (MDE), with the Structured Clinical Interview for DSM-IV. The DSM-IV criteria for AD were compared to a new AD definition based only on oversleeping and overeating, which was the one often used in community studies. Associations were tested by univariate logistic regression. *Results* The frequency of DSM-IV AD was 42.8 %, and that of the new AD definition was 38.7 %. DSM-IV AD, and the new AD definition, had almost all the same significant associations: bipolar II, female gender, lower age, lower age of onset, axis I comorbidity, depressive mixed state, MDE symptoms lasting more than 2 years, and bipolar family history. DSM-IV

AD was present in 86 % of the new AD definition sample. The new definition of AD was significantly associated with all the other DSM-IV AD symptoms not included in it. The new AD definition was strongly associated with DSM-IV AD (odds ratio = 17.8), and had sensitivity = 77.7 %, specificity = 90.5 %, positive predictive value = 86.1 %, negative predictive value = 84.4 %, and ROC area curve = 0.85, for predicting DSM-IV AD. *Conclusions* Results support a simpler definition of AD, requiring only oversleeping and overeating, and support the similar AD definition previously used in community studies. This definition is easier and quicker to assess by clinicians than the DSM-IV definition (mood reactivity and interpersonal sensitivity are more difficult to assess). Some pharmacological studies support this new AD definition (by showing better response to MAOI than to TCA, as shown in DSM-IV AD).

Key words atypical depression · bipolar II disorder · DSM-IV · oversleeping · overeating

Introduction

The current definition of atypical depression (AD) is based on DSM-IV criteria (American Psychiatric Association 1994), and comes from the Columbia group definition (Rabkin et al. 1996). In DSM-IV, AD is not a distinct mood disorder but a specifier of major depressive episode (MDE) occurring in depressive and bipolar disorders. DSM-IV criteria for AD always require mood reactivity, plus overeating/weight gain, oversleeping, leaden paralysis, and interpersonal rejection sensitivity (at least two), and no melancholic or catatonic features. Validity of this definition is mainly based on better antidepressant response to MAOI than to TCA and fluoxetine versus non-AD (Rabkin et al. 1996; McGrath et al. 2000), which is not a strong validator (Robins and Guze 1970; Akiskal 2002a,b; Kendler 1990,1980). A limitation of the current AD definition is that it was tested in mainly unipolar major depressive disorder (MDD) sam-

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ples (Rabkin et al. 1996; Williamson et al. 2000; McGrath et al. 2000; Sotsky and Simmens 1999; Levitan et al. 1997; Sullivan et al. 1998; Sullivan et al. 2002; Kendler et al. 1996; Horwath et al. 1992). Recent studies (Benazzi 1999a,b,c,d; Benazzi 2000a,b,c; Angst 1998; Perugi et al. 1998; Angst et al. 2003) found that DSM-IV AD was much more common in bipolar II versus unipolar [45.4% (in 251 bipolar II) vs 25.4% (in 306 unipolar) (Benazzi 2000c)]. The studies not finding more bipolar II in AD versus non-AD included a very small number of bipolar II (McGrath et al. 1992; Robertson et al. 1996; Posternak and Zimmerman 2002; Rabkin et al. 1996). The inclusion of bipolar II in AD studies is important because bipolar II is common (30 to 60%) among MDE outpatients (Akiskal et al. 2000; Akiskal 2002b; Benazzi 1997; Benazzi 2001a; Benazzi and Akiskal 2003; Hantouche et al. 1998; Cassano et al. 1992; Perugi et al. 1998; Angst 1996; Angst 1998; Angst et al. 2002; Angst et al. 2003). The place of mood reactivity among DSM-IV AD symptoms has been questioned (Rabkin et al. 1996; Nierenberg et al. 1998; Posternak and Zimmerman 2002; Angst et al. 2002; Benazzi 2002). The group of symptoms of DSM-IV AD has also been questioned, by showing that the symptoms did not have the same associations with some clinical variables (Posternak and Zimmerman 2001). This study was based on a mainly MDD sample (only 5.4% were bipolar II). Community studies definitions of AD, and definitions based on statistical analysis (latent class analysis) of MDE symptoms, included only oversleeping and overeating/weight gain (reversed vegetative symptoms) (Levitan et al. 1997; Horwath et al. 1992; Kendler et al. 1996; Sullivan et al. 1998; Sullivan et al. 2002). Sullivan et al. (1998) reported that "the correspondence between epidemiological derived typologies of atypical depression and DSM-IV major depression with atypical features is not yet known".

Study aim was to find the relationship between a new definition of AD (MDE plus oversleeping and overeating) and DSM-IV AD.

Methods

■ Study setting

A private outpatient psychiatry center was the study setting. This setting is more representative of mood disorder patients in Italy because it is the first (or the second, after family doctors) line of treatment of mood disorders, while national health services and university centers usually treat the most severe patients. Most persons can be visited by a private psychiatrist. Mood disorder patients in tertiary-care centers are not representative of patients usually treated in clinical practice (Akiskal and Pinto 1999; Ghaemi et al. 2000; Goldberg and Kocsis 1999; Post et al. 2001).

■ Patients and Interview

The interviewer was a senior clinical and mood disorder research psychiatrist. Consecutive 202 MDD, and 281 bipolar II outpatients, presenting spontaneously for MDE treatment, were included in the last three years. No psychopharmacotherapy was present before eval-

uation and in the previous two months, in order to avoid inclusion of antidepressant-induced mixed states (Akiskal 2002b), and of some drug-induced pseudo-atypical symptoms (like oversleeping, overeating, and weight gain). Study was approved by the ethics committee and performed according to ethical standards of 1964 Declaration of Helsinki. All persons gave informed consent prior to inclusion in the study. Substance abuse and severe personality disorder patients [found to have low prevalence in the study setting (Benazzi 2000d)] were not included, as confounding the diagnosis of bipolar II and mixed states (Akiskal et al. 2000). Clinically significant general medical illness and dementia patients were not included. 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), 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). Trained clinicians using semi-structured interviews made more correct diagnoses of bipolar II than interviewers using structured interviews, and had high interrater reliability (Brugha et al. 2001; Dunner and Tay 1993; Simpson et al. 2002). All patients were systematically SCID-CV interviewed for history of manic/hypomanic episodes, and for hypomanic symptoms during the index MDE. The SCID-CV structured question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition (1999) of crowded thoughts (head continuously full of ideas that the patient is unable to stop). The SCID-CV skip-out instruction of the stem question about past hypomanic mood was not followed, as a negative answer would not allow the assessment of the other hypomanic symptoms and especially of overactivity [found by Benazzi and Akiskal (2003) to increase bipolar II diagnoses]. History of mania/hypomania was always investigated soon after the diagnosis of MDE, and before assessment of study variables, avoiding bias related to knowledge of indicators of bipolarity (Akiskal et al. 2000; Akiskal 2002a,b; Goodwin and Jamison 1990; Baldessarini 2000; McMahon et al. 1994). Bipolar (type I+II) family history of first-degree relatives was investigated with the structured Family History Screen (Weissman et al. 2000), by interviewing patients and often also one first-degree relative. Depressive mixed state was defined as a MDE plus more than 2 concurrent hypomanic symptoms (Benazzi and Akiskal 2001). At least 2 days of hypomania were required for bipolar II diagnosis (Akiskal et al. 1977; Akiskal 1996; Akiskal et al. 2000; Akiskal 2002b; Angst 1998; Benazzi 2001c; Cassano et al. 1992; Coryell et al. 1995). Often, family members or close friends supplemented clinical information during the interview. Two definitions of AD were tested. The DSM-IV AD (a MDE with the atypical features specifier occurring in MDD or bipolar II, always requiring mood reactivity, plus overeating/weight gain, oversleeping, leaden paralysis, interpersonal rejection sensitivity (at least two), and no melancholic or catatonic features), and a new AD definition (a MDE with always the reversed vegetative symptoms oversleeping and overeating occurring in MDD or bipolar II). MDD and bipolar II samples were combined in the analyses following previous studies on AD (Angst et al. 2002; Posternak and Zimmerman 2002; Levitan et al. 1997; Sullivan et al. 1998; McGrath et al. 1992; Agosti and Stewart 2001; Benazzi 1999b,e; Benazzi 2000a,b; Benazzi 2001b). The two AD definitions were compared on variables often reported to distinguish AD and non-AD [gender, age, onset, bipolar II, axis I comorbidity, depressive mixed state (Benazzi 2001d; Benazzi in press; Akiskal and Benazzi 2003)], and on other sample variables. Sample features are reported in Table 1.

■ Statistics

Proportions were compared by the two-sample test of proportion. Univariate logistic regression was used to study associations, and to calculate sensitivity, specificity, and area under the ROC (receiver operating characteristic) curve. STATA Statistical Software, release 7, was used (Stata Corporation, College Station, TX, USA, 2001). P values were two-tailed, and alpha level was $P < 0.05$.

Table 1 Sample features (n = 483)

Variables	mean (SD) %
MDD	41.8
Bipolar II	58.1
Female gender	63.9
Age, years	44.0 (14.7)
Age of onset first MDE, years	26.6 (13.0)
GAF	50.7 (9.2)
MDE symptoms > 2 years	39.7
Axis I comorbidity	50.5
> 4 MDEs	72.6
Psychotic features	8.0
Melancholic features	13.6
Atypical features	42.8
Depressive mixed state	46.9
Bipolar family history	38.9

MDD major depressive disorder; MDE major depressive episode; GAF Global Assessment of Functioning scale

Results

Frequency of DSM-IV AD (bipolar II and MDD MDE with the atypical features specifier) was 207/483 (42.8%). DSM-IV AD was significantly more common in bipolar II versus MDD (53.7% in bipolar II versus 27.7% in MDD, 95% confidence interval (CI) 17.5% to 34.4%, $z = 5.6$, $p < 0.0001$). In the DSM-IV AD sample, frequency of atypical symptoms was the following: mood reactivity = 100% (by definition), weight gain = 35.2%, overeating = 45.4%, oversleeping = 63.7%, leaden paralysis = 71.4%, interpersonal rejection sensitivity = 84%. Univariate logistic regression results of DSM-IV AD (dependent variable) versus study variables are presented in Table 2. DSM-IV AD significant associations were the following: bipolar II, female gender, lower age, lower age of onset of the first MDE, axis I comorbidity, depressive

mixed state, MDE symptoms lasting more than 2 years from the index MDE, and bipolar family history. The frequency of the new definition of AD (MDE plus always oversleeping and overeating) was 187/483 (38.7%). In this AD sample, DSM-IV AD was present in 86%. The new AD definition was significantly more common in bipolar II versus MDD (65.1% versus 35.6%, 95% CI 20.8% to 38.1%, $z = 6.4$, $p < 0.0001$). Univariate logistic regression of the new definition of AD (dependent variable) versus the same variables of Table 2 found the following significant associations (Table 3): bipolar II, lower age, lower age of onset of the first MDE, axis I comorbidity, depressive mixed state, and bipolar family history. There was a trend ($p = 0.06$) for an association also with female gender. Associations of the new definition of AD (dependent variable) versus the other DSM-IV AD symptoms not included in its definition were tested. The new AD definition was significantly associated with mood reactivity (odds ratio = 6.5, 95% CI 2.9 to 14.6, $z = 4.5$, $p < 0.001$), leaden paralysis (odds ratio = 3.1, 95% CI 2.1 to 4.6, $z = 5.8$, $p < 0.001$), and interpersonal rejection sensitivity (odds ratio = 2.1, 95% CI 1.4 to 3.1, $z = 3.8$, $p < 0.001$). Logistic regression of DSM-IV AD (dependent variable) versus the new AD definition was tested, to find odds ratio, sensitivity, specificity, positive predictive value, negative predictive value, and area under the ROC curve of the new AD definition for predicting DSM-IV AD. Odds ratio was 17.8 (95% CI 11.0 to 28.8, $z = 11.7$, $p < 0.001$), sensitivity 77.7%, specificity 90.5%, positive predictive value 86.1%, negative predictive value 84.4%, and ROC area 0.85.

Discussion

Interviewer's bias is unlikely, as the present study variables were part of a larger set of variables systematically assessed during the first visit (for MDE) of new patients during recent years, and the present study goal was not

Table 2 Associations between DSM-IV AD and study variables, by univariate logistic regression

Variable	Odds ratio	95% CI	Z
Bipolar II	3.0	2.0 to 4.4**	5.6
Female gender	1.8	1.2 to 2.7**	3.1
Age	0.9	0.9 to 0.9**	-4.4
Age of onset	0.9	0.9 to 0.9**	-5.6
GAF	1.0	0.9 to 1.0	1.6
MDE symptoms > 2 years	1.4	1.0 to 2.1*	2.0
Axis I comorbidity	1.6	1.1 to 2.4**	2.8
> 4 MDEs	1.4	0.9 to 2.1	1.7
Depressive mixed state	2.8	1.9 to 4.2	5.5
Bipolar family history	2.4	1.5 to 3.9	3.7

CI confidence intervals; * = $p < 0.05$; ** = $p < 0.01$

MDE major depressive episode; GAF Global Assessment of Functioning scale

Table 3 Associations between the new AD definition (MDE plus always oversleeping and overeating) and study variables, by univariate logistic regression

Variable	Odds ratio	95% CI	Z
Bipolar II	2.3	1.6 to 3.4**	4.3
Female gender	1.4	0.9 to 2.1	1.8
Age	0.9	0.9 to 0.9**	-4.9
Age of onset	0.9	0.9 to 0.9**	-4.2
GAF	1.0	0.9 to 1.0	0.6
MDE symptoms > 2 years	1.0	0.7 to 1.5	0.3
Axis I comorbidity	1.7	1.2 to 2.5**	3.0
> 4 MDEs	1.1	0.7 to 1.8	0.8
Depressive mixed state	2.1	1.4 to 3.0**	3.9
Bipolar family history	1.8	1.1 to 2.8*	2.5

CI confidence intervals; * = $p < 0.05$; ** = $p < 0.01$

MDE major depressive episode; GAF Global Assessment of Functioning scale

known when the data were collected. The interview was performed 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. These study features may have reduced study limitations (Akiskal et al. 2000; Akiskal 2002b; Goodwin and Jamison 1990). Frequencies of DSM-IV AD and of the new AD definition were high and similar in the present study large mixed outpatient sample, in line with previous reports on samples including also 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. 2003). DSM-IV AD and the new AD definition were much more common in bipolar II versus MDD, in line with previous reports (Angst 1998; Angst et al. 2003; Benazzi 1999a,b,c,d; Benazzi 2000a,b,c; Perugi et al. 1998; Agosti and Stewart 2001; Akiskal 2002a,b). In community studies (which, however, did not assess bipolar II) using an AD definition requiring only oversleeping and overeating like the present one, AD did not have more bipolar I than non-AD (Sullivan et al. 1998; Levitan et al. 1997; Horwath et al. 1992). Two community studies did not assess bipolar disorders in AD (Kendler et al. 1996; Sullivan et al. 2002). These community studies have important limitations: bipolar II was not assessed, and fully structured interviews were used by nonclinician interviewers [which may reduce bipolar II diagnosis reliability and correct diagnoses (Brugha et al. 2001; Ghaemi et al. 2002; Simpson et al. 2002)]. In the present study, many new AD definition patients also met DSM-IV AD criteria (86%). DSM-IV AD and the new AD definition had very similar associations with the study variables, which were associations often found when comparing AD to non-AD in previous reports (Angst et al. 2002; Angst et al. 2003; 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; Benazzi 1999a,b,c,d; Benazzi 2000a,b,c). However, age of onset of AD versus non-AD was not significantly different in a unipolar sample (Asnis et al. 1995), and no gender difference was reported in some mainly unipolar community samples (Sullivan et al. 2002; Levitan et al. 1997; Horwath et al. 1992). The new AD definition had high specificity (90.5%), positive predictive

value (86.1%), and ROC area (0.85) for predicting DSM-IV AD. The two AD definitions were strongly associated (odds ratio = 17.8). Furthermore, the new AD definition was strongly associated with all the other DSM-IV AD symptoms not included in it. These findings support the validity of the new definition of AD compared to the DSM-IV definition. Testing antidepressant response in the new AD definition versus DSM-IV AD would further support its validity. Some previous studies (Thase et al. 1991; Davidson et al. 1988) found that AD requiring only oversleeping and overeating had better response to MAOI than to TCA, as it was shown for the Columbia AD definition (very similar to the DSM-IV AD definition). This new AD definition was previously supported only by latent class analysis of community and mainly unipolar MDE patients (Kendler et al. 1996; Sullivan et al. 1998; Sullivan et al. 2002). The present study tested its validity in a large clinical sample including many bipolar II patients, by comparing it to DSM-IV AD. The two AD definitions seemed very similar. As the new one is simpler and quicker to assess in clinical practice, it could take the place of the DSM-IV one, if it were found to have the same response to antidepressants versus non-AD (which, at present, is the main validating criterion of AD). A simpler AD definition could also improve its identification and treatment in primary care (Barkow et al. 2001; Antikainen et al. 2001).

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Table 4 Associations between the new AD definition (MDE plus always oversleeping and overeating) and DSM-IV atypical symptoms not included in this definition, by univariate logistic regression

Variable	Odds ratio	95% CI	Z
Mood reactivity	6.5	2.9 to 14.6***	4.5
Leadens paralysis	3.1	2.1 to 4.6**	5.8
Interpersonal sensitivity	2.1	1.4 to 3.1***	3.8

CI confidence intervals; * = $p < 0.05$; ** = $p < 0.01$

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