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Testing atypical depression definitions

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Abstract

The evidence supporting the DSM-IV definition of atypical depression (AD) is weak. This study aimed to test different definitions of AD. Major depressive disorder (MDD) patients (N = 254) and bipolar-II (BP-II) outpatients (N = 348) were interviewed consecutively, during major depressive episodes, with the Structured Clinical Interview for DSM-IV. DSM-IV criteria for AD were followed. AD validators were female gender, young onset, BP-II, axis I comorbidity, bipolar family history. Frequency of DSM-IV AD was 43.0%. AD, versus non-AD, was significantly associated with all AD validators, apart from comorbidity when controlling for age and sex. Factor analysis of atypical symptoms found factor 1 including oversleeping, overeating and weight gain (leaden paralysis at trend correlation), and factor 2 including interpersonal sensitivity, mood reactivity, and leaden paralysis. Multiple logistic regression of factor 1 versus AD validators found significant associations with several validators (including bipolar family history), whereas factor 2 had no significant associations.

Findings may support a new definition of AD based on the state-dependent features oversleeping and overeating (plus perhaps leaden paralysis) versus the current AD definition based on a combination of state and trait features. Pharmacological studies are required to support any new definition of AD, as the current concept of AD is based on different response to TCA antidepressants versus non-AD.

Key words: atypical depression, atypical features, bipolar II disorder, DSM-IV

Introduction

According to DSM-IV-TR (American Psychiatric Association, 2000), atypical depression (AD) is not a distinct disorder but a specifier of the major depressive episode (MDE) of bipolar and major depressive disorders (and dysthymic disorder). DSM-IV-TR criteria for the atypical features specifier always require mood reactivity plus overeating or weight gain, oversleeping, leaden paralysis, and interpersonal rejection sensitivity (at least two), and no melancholic or catatonic features. The diagnostic validity of this definition is currently unclear. The diagnostic validity of the Columbia group definition of AD (the basis of DSM-IV-TR criteria) is mainly based on treatment response (a better response to MAOIs than to TCAs) (Quitkin et al., 2003), and partly on latent class analysis (Kendler et al., 1996; Sullivan et al., 1998). This definition of AD has recently been questioned (Williamson et al., 2000; Posternak and Zimmerman, 2001, 2002; Angst et al., 2002; Benazzi, 2002; Parker et al., 2002). The Columbia group studies, and also community studies (using a definition of AD requiring only overeating and oversleeping), have the important limitation of being based on mainly non-bipolar depression samples (Horwath et al., 1992; Kendler et al., 1996; Rabkin et al., 1996; Levitan et al., 1997; Sullivan et al., 1998; Sotsky and Simmens, 1999; McGrath et al., 2000; Sullivan et al., 2002). In clinical studies, some AD symptoms (oversleeping, overeating, weight gain) were found to be more common in the

depression of bipolar disorders versus major depressive disorder (MDD) (Hantouche et al., 1998; Mitchell et al., 2001) and were often reported in standard textbooks comparing bipolar depression (mainly bipolar type I) and MDD (Goodwin and Jamison, 1990; Akiskal, 2002). Recent studies in mixed bipolar II disorder (BP-II) and MDD outpatient samples have shown that DSM-IV-TR AD is more common in BP-II (Agosti and Stewart, 2001; Benazzi, 2000a, 2002; Perugi et al., 1998, 2003; Angst et al., 2003), which is a common disorder in depressed outpatients (Akiskal et al., 2000; Benazzi, 2000a, 2003a; Akiskal and Benazzi, 2003; Hantouche et al., 1998; Angst et al., 2003; Manning et al., 1999; Dunner and Tay, 1993). The studies not finding more AD in BP-II versus MDD included a very small number of BP-II (McGrath et al., 1992; Rabkin et al., 1996; Robertson et al., 1996; Posternak and Zimmerman, 2002), or severe and inpatient depressions (Parker, 2000). In MDD samples, and in mixed BP-II and MDD samples, AD versus non-AD was often found to have a younger age at onset, more females, BP-II, axis I comorbidity, and family history of bipolar disorders (Horwath et al., 1992; Kendler et al., 1996; McGrath et al., 2000; Rabkin et al., 1996; Levitan et al., 1997; Sullivan et al., 1998; Sotsky and Simmens, 1999; American Psychiatric Association, 2000; Williamson et al., 2000; Angst et al., 2002; Benazzi, 2000a, 2002). However, age at onset of AD versus non-AD was not significantly different in a MDD sample (Asnis et al., 1995), and no gender difference was reported in mainly MDD community samples (Horwath et al., 1992; Levitan et al., 1997). Family history is an important diagnostic validator (Robins and Guze, 1970). There are few data on family history of AD. In mainly MDD samples, AD versus non-AD had greater or similar family history of depression, or greater family history of AD (Kendler et al., 1996; Rabkin et al., 1996; Sullivan et al., 1998; Matza et al., 2003). In mixed BP-II and MDD samples, AD had more family history of bipolar disorders versus non-AD (Perugi et al., 1998; Angst et al., 2002; Benazzi, 2002). Another important diagnostic validator is diagnostic stability over time (Robins and Guze, 1970), but AD had a moderate diagnostic stability (Levitan et al., 1997; Kendler et al., 1996; Angst et al., 2002).

The aim of the present study was to test the different definitions of AD by using DSM-IV-TR criteria symptoms.

Methods

More details on study methods can be found in previous reports (Benazzi and Akiskal, 2003a; Akiskal and Benazzi, 2003; Benazzi, 2003b).

Study setting

The setting was an outpatient psychiatry private practice, which may be more representative of the mood disorders (apart from bipolar I disorder) usually seen in clinical practice in Italy, because

- it is the first or second (after family doctors) line of treatment of mood disorders;
- the most severe and socially disadvantaged cases are usually seen in tertiary care centres;
- mood-disorder patients do not like to be treated in the national health service for fear of stigma; and
- most individuals can be treated by a private psychiatrist (fee-for-service), reducing a possible income bias.

This sample does not represent the whole spectrum of mood disorders and AD because all individuals were seeking professional help; the less severe community cases were not represented, as well as the more severe tertiary care cases.

Interviewer

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

Patients

Consecutive 348 BP-II and 254 MDD outpatients, presenting voluntarily for treatment of a major depressive episode (MDE), were assessed in the last 5 years. Substance-related and borderline personality disorders were excluded to avoid confounding the diagnosis of BP-II (Akiskal and Pinto, 1999). These patients are rare anyway in the present study setting (Benazzi, 2000b). Clinically significant general medical illnesses and cognitive disorders were also excluded. Patients had to have avoided psychoactive drugs for at least 2 weeks (few cases on small doses of benzodiazepines were included) in order not to include drug-induced pseudo-atypical symptoms like oversleeping and overeating. MDD and BP-II samples were combined in the analyses following previous studies on AD (McGrath et al., 1992; Levitan et al., 1997; Sullivan et al., 1998; Agosti

and Stewart, 2001; Angst et al., 2002; Benazzi, 2000a, 2002; Posternak and Zimmerman, 2002).

Interview methods

During the assessment visit the following instruments were used:

- the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (First et al., 1997) (SCID-CV) as modified by Benazzi and Akiskal (2003a); the question on racing thoughts was supplemented by the Koukopoulos and Koukopoulos' definition of crowded thoughts (the mind continuously full of non-stop thoughts) (Koukopoulos and Koukopoulos, 1999), following Kraepelin's description (1913, English translation 1921) of the grading of the thought disorders of hypomania;
- the Global Assessment of Functioning scale (GAF, in SCID-CV) for the MDE severity;
- the structured Family History Screen (Weissman et al., 2000) for assessing bipolar disorders family history in probands' first-degree relatives.

Often, family members or close friends supplemented clinical information during the interview, increasing the validity of BP-II diagnosis and family history (Akiskal et al., 2000; American Psychiatric Association, 2000). Systematic interviews about history of hypo-manic episodes were always conducted soon after diagnosis of MDE, before the assessment of study variables, in order to avoid a possible bias related to knowledge of bipolar signs. The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions). Wording of the sentences can be changed to improve and to check the understanding by the interviewed. This is an important advantage when compared with fully structured interviews because it reduces the BP-II false negatives (Dunner and Tay, 1993; Simpson et al., 2002; Benazzi, 2003c; Brugha et al., 2001). The skip-out instruction of the stem question on history of mood changes was not followed, in order to assess all past hypomanic symptoms, especially overactivity (increased goal-directed activity), following previous reports (Dunner and Tay, 1993; Simpson et al., 2002; Akiskal et al., 2003; Angst et al., 2003; Benazzi, 2003c; Benazzi and Akiskal 2003a, b). This behavioural change is easier to remember than mood changes (always required for the diagnosis according to DSM-IV-TR, and consequently easier to remember when overactivity had been remembered). The DSM-IV-TR diagnostic criteria for the *atypical features specifier* of the MDE were followed, always requiring mood reactivity plus increased eating or weight, increased sleeping, leaden paralysis, interpersonal rejection sensitivity (at least two), and no melancholic or catatonic features. *Atypical depression (AD)* was defined as an MDE with this specifier. *AD diagnostic validators* were female gender, young age at onset, axis I comorbidity, BP-II, bipolar (types I and II) family history, following previous reports comparing AD and non-AD (Horwath et al., 1992; Kendler et al., 1996; Rabkin et al., 1996; Levitan et al., 1997; Sullivan et al., 1998; Sotsky and Simmens, 1999; McGrath et al., 2000; Benazzi, 2000a, 2002; Angst et al., 2002). Several of the AD validators are also classic diagnostic validators, especially age at onset and family history (Kraepelin, 1921; Robins and Guze, 1970; Kendler, 1990; Akiskal, 2003; Angst et al., 2003). All the symptoms were present and directly assessed at the time of the interview.

Statistics

Univariate and multiple logistic regression were used to study associations and to control for confounding. Scaling of quantitative variables was age/10, onset/10, GAF/5, N atypical symptoms/1. Principal component factor analysis (varimax rotation, eigenvalue > 1, item loading > 0.40) was used to study correlations among atypical symptoms (a type of factor analysis often used in mood disorders studies: Bauer et al., 1991; Cassidiy et al., 1998; Dilsaver et al., 1999; Perugi et al., 2001; Swann et al 2001; Akiskal et al., 2001, 2003; Benazzi and Akiskal, 2003b). 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 0.01, to reduce the risk of type I error, following Rothman and Greenland (1998) and Altman et al. (2000).

Results

Frequency of AD was 43.0% (259/602). Logistic regression of AD versus non-AD is presented in Table 1. Logistic regression was controlled for age and sex, as some differences might have been related to these variables and not to AD. Atypical depression had significantly more BP-II, lower age and age at onset, more females, more MDE recurrences, more lasting MDE symptoms, fewer psychotic features, higher GAF, and

more bipolar family history. Among the MDE and atypical symptoms, apart from differences related to the definition of AD, AD had significantly more psychomotor agitation.

Factor analysis (Table 2) of MDE and atypical symptoms (in the entire sample) found three factors, on the basis of eigenvalues and inspection of the scree plot. Factor 1 including the reversed vegetative symptoms oversleeping, overeating and weight gain (and leaden paralysis at a trend correlation), negatively correlated with reduced eating and weight loss; factor 2 including interpersonal sensitivity and leaden paralysis among the atypical symptoms; factor 3 including mood reactivity among the atypical symptoms.

Factor analysis was then repeated including only the six DSM-IV-TR atypical symptoms in order to focus on the core symptoms of AD. Factor analysis of atypical symptoms (in the entire sample) (Table 3) found two factors: factor 1 including the reversed vegetative symptoms oversleeping, overeating and weight gain (and leaden paralysis at a trend correlation), and factor 2 including mainly personality features (interpersonal sensitivity and the related mood reactivity) plus leaden paralysis. Frequency of factor 1 was 14.6% (88/602), and that of factor 2 was 26.2% (158/602).

Table 1. Comparisons between atypical (AD) and non-atypical (non-AD) depression (controlled for age and sex)

	AD n = 259	non-AD n = 343	OR	95% CI
Variables	Mean(SD), %	Mean(SD), %		
MDD	28.9	52.1	0.4	0.2–0.6**
BP-II	71.0	47.8	2.3	1.6–3.3**
Age, years	40.3(12.9)	46.3(14.3)	0.7	0.6–0.8**
Female gender	73.3	58.8	1.9	1.3–2.7**
Age at onset first MDE, years	22.9(10.7)	29.5(13.7)	0.7	0.6–0.8**
> 4 MDEs	74.9	67.6	1.7	1.1–2.5**
MDE symptoms > 2 years	41.6	34.1	1.6	1.1–2.4**
Axis I comorbidity	58.3	45.1	1.3	0.9–1.9
Psychotic features	3.4	11.9	0.2	0.1–0.5**
GAF score	51.5(8.0)	49.6(10.3)	1.1	1.0–1.2**
Bipolar (type I + II) family history	45.6	24.2	2.3	1.5–3.6**
MDE symptoms				
Depressed mood	98.8	95.9	3.8	1.0–13.9*
Diminished interest	96.5	96.2	1.2	0.5–3.0
Weight loss	23.5	45.7	0.3	0.2–0.4**
Decreased eating	32.8	66.4	0.2	0.1–0.3**
Insomnia	75.6	82.5	0.7	0.4–1.1
Psychomotor agitation	33.5	23.3	1.6	1.1–2.3**
Psychomotor retardation	1.1	6.4	0.1	0.0–0.5**
Fatigue	94.9	82.5	4.4	2.1–7.7**
Worthlessness	58.6	61.8	0.7	0.5–1.1
Diminished ability to concentrate	79.5	68.5	1.4	0.9–2.3
Thoughts of death	45.9	52.4	0.7	0.5–1.0
Atypical symptoms				
Mood reactivity	100.0	76.3	nc	nc
Weight gain	37.4	1.4	37.8	15.0–95.2**
Increased eating	46.3	2.9	27.9	14.1–55.3**
Hypersomnia	64.0	7.5	21.1	12.8–34.6**
Leaden paralysis	72.5	17.7	11.6	7.7–17.3**
Interpersonal sensitivity	81.0	40.2	6.1	4.1–9.1**
N atypical symptoms	4.0(1.0)	1.4(0.7)	360.1	102.4–1266.5**

(MDD = major depressive disorder; BP-II = bipolar II disorder; MDE = major depressive episode; GAF = global assessment of functioning scale; OR = odds ratio; CI = confidence interval; * = $p < 0.05$; ** = $p < 0.01$; nc = not calculable)

Table 2. Factor analysis of major depressive episode and atypical symptoms in the entire sample

	Factor 1	Factor 2	Factor 3
Eigenvalue	3.0	1.7	1.3
Variance	17.5%	10.0%	7.6%
MDE symptoms			
Depressed mood	0.01	0.24	–0.10
Diminished interest	–0.04	0.17	0.12
Weight loss	–0.65	0.21	–0.18
Decreased eating	–0.74	0.11	–0.08
Insomnia	–0.32	0.38	0.01
Psychomotor agitation	0.01	0.43	0.01
Psychomotor retardation	0.00	–0.21	–0.53
Fatigue	0.05	0.42	0.02
Worthlessness	–0.00	0.09	–0.65
Diminished ability to concentrate	0.00	0.42	–0.27
Thoughts of death	–0.03	0.13	–0.58
Atypical symptoms			
Mood reactivity	0.26	0.05	0.59
Weight gain	0.76	0.14	–0.02
Increased eating	0.81	0.16	–0.00
Hypersomnia	0.53	0.26	0.06
Leaden paralysis	0.32	0.57	–0.01
Interpersonal sensitivity	0.14	0.47	0.01

(varimax rotation, eigenvalue > 1, item loading > 0.40)

As the DSM-IV-TR boundary between leaden paralysis and fatigue is not clear cut, factor analysis was recalculated including fatigue (as defined in DSM-IV-TR text) instead of leaden paralysis (as defined in DSM-IV-TR text). Results were similar to factor analysis results presented in Table 3.

To test which AD symptoms were more strongly associated with AD, multiple logistic regression was used (Table 4). All atypical symptoms were significantly and independently associated with the dependent variable AD.

To test which were the strongest and independent predictors of factor 1 and 2, multiple logistic regression was used (Table 5). Factor 1 was significantly associated with several AD validators, while factor 2 had no significant association with AD validators (Table 6).

Discussion

Frequency of AD in this outpatient, non-tertiary care, depression sample was relatively high (43%), and similar to previous community and tertiary-care studies (Angst et al., 2002; Perugi et al., 2003), supporting the representative nature of the study sample. Atypical depression, versus non-AD, had differences often reported in other studies (Horwath et al., 1992; Kendler et al., 1996; Rabkin et al., 1996; Levitan et al., 1997; Sullivan et al., 1998; Sotsky and Simmens, 1999; Benazzi, 2000a; McGrath et al., 2000; Williamson et al., 2000; Angst et al., 2002), such as more females, more BP-II, younger age at onset, and lower depression severity. An important finding was that AD had a higher family history of bipolar disorders (type I plus type II) versus non-AD. This finding was probably related to the inclusion in the study sample of many BP-II patients (it should be noted that in many previous studies BP-II patients were rare or absent), and to the systematic probing for history of BP-II in probands' relatives by the Family History Screen (Weissman et al., 2000). The Weissman et al. (2000) Family History Screen has an important advantage compared with some other commonly used family history instruments such as the Andreasen et al. (1977) and the FIGS by the National Institute of Mental Health (USA) (http, 2003) because these instruments can assess only mania, whereas the

Table 3. Factor analysis of atypical symptoms in the entire sample

	Factor 1	Factor 2
Eigenvalue	2.2	1.02
Variance	37.6%	17.1%
Mood reactivity	0.14	0.48
Weight gain	0.88	0.00
Increased eating	0.89	0.06
Hypersomnia	0.58	0.30
Leaden paralysis	0.33	0.51
Interpersonal sensitivity	–0.01	0.80

(varimax rotation, eigenvalue > 1, item loading > 0.40)

Table 4. Multiple logistic regression of DSM-IV AD versus all atypical symptoms

	OR	95% CI
Variable		
Mood reactivity	nc	nc
Weight gain	17.0	3.9–74.0**
Increased eating	45.5	11.8–174.4**
Hypersomnia	163.9	54.1–496.6**
Leaden paralysis	78.3	30.2–203.2**
Interpersonal sensitivity	83.2	27.1–255.5**

(OR = odds ratio; CI = confidence interval; * = $p < 0.05$; ** = $p < 0.01$; nc = not calculable)

Table 5. Multiple logistic regression of factor 1 (oversleeping plus overeating plus weight gain) versus AD validators (univariate logistic regressions were all significant, apart from female gender)

	OR	95% CI
Variable		
BP-II	1.3	0.8-2.1
Female gender	1.1	0.7–1.7
Young onset age	0.9	0.9–0.9*
Axis I comorbidity	1.7	1.1–2.6**
Bipolar family history	1.6	1.0–2.4*

(OR = odds ratio; CI = confidence interval; * = $p < 0.05$; ** = $p < 0.01$)

Table 6. Multiple logistic regression of factor 2 (mood reactivity plus leaden paralysis plus interpersonal sensitivity) versus AD validators (univariate logistic regressions were all significant, apart from onset and bipolar family history).

	OR	95% CI
Variable		
BP-II	0.8	0.2–2.6
Female gender	1.4	0.5–3.9
Young onset age	0.8	0.6–1.4
Axis I comorbidity	2.4	0.8–7.3
Bipolar family history	1.1	0.3–3.5

(OR = odds ratio; CI = confidence interval; * = $p < 0.05$; ** = $p < 0.01$)

Family History Screen can assess also hypomania. Previous reports on AD family history, some of which reported more depression or more AD in relatives, were based on mainly MDD samples, and bipolar (especially BP-II) family history was not assessed (Kendler et al., 1996; Rabkin et al., 1996; Sullivan et al., 1998; Matza et al., 2003). More bipolar family history in AD versus non-AD was also found by Angst et al. (2002) and by Perugi et al. (1998). More bipolar family history, as well as more BP-II, in AD versus non-AD, suggest a close link between AD and the bipolar spectrum.

Among the MDE symptoms, apart from the differences related to the definition of AD, AD had significantly more psychomotor agitation versus non-AD. According to DSM-IV-TR, psychomotor agitation can be an MDE symptom or a hypo-manic symptom. A previous study reported a link between AD and concurrent intra-MDE hypomanic symptoms (the depressive mixed state) (Benazzi, 2001). Also Akiskal (1996) described, in BP-II depression, a mixture of atypical and hypomanic symptoms. Akiskal's description of BP-II depression mirrors Hecker's description (1898, English translation by Koukopoulos, 2003), reporting that excitement (hypomanic) symptoms were often present during BP-II depression (a marker of this depression according to him). Hecker also observed that BP-II depression had frequently atypical symptoms. Textbooks and recent studies comparing bipolar (mainly bipolar I) depression and MDD reported more overeating and oversleeping in bipolar depression, but more retardation than agitation (Goodwin and Jamison, 1990; Mitchell et al., 2001; Akiskal, 2002).

Among the DSM-IV-TR atypical symptoms, differences were all significant between AD and non-AD, as expected, but it is noteworthy that the frequency of mood reactivity and interpersonal sensitivity in non-AD was high, a finding partly not supporting the inclusion of these symptoms in a definition of AD.

Focusing on the symptom structure of AD, factor analysis found two clearly different factors: a state-dependent reversed vegetative symptoms factor, and a mainly personality trait factor. Interpersonal sensitivity (and the related mood reactivity) has recently been reported to be a background personality feature present between the episodes of BP-II (Perugi et al., 2003).

DSM-IV-TR AD definition was tested by multiple logistic regression, in order to know which were the key symptoms of the syndrome. Results showed that all the symptoms were significantly and independently associated with AD, supporting the validity of the present combination of symptoms defining AD.

An attempt was made to find a core set of symptoms best defining AD. Multiple logistic regression showed that factor 1 (oversleeping plus overeating plus weight gain) was significantly associated with several independent AD validators (including an important validator like family history), whereas factor 2 showed no significant association with any AD validators. This finding may support a higher validity of a definition of AD mainly based on reversed vegetative symptoms. A feature further supporting this definition was that interpersonal sensitivity was present in many non-AD (40%), reducing its specificity, while the reversed vegetative symptoms were much more common in AD versus non-AD (odds ratios ranging from 12.8% to 95.2%), increasing the specificity of these symptoms.

It was also tested if the DSM-IV-TR unclear boundary between leaden paralysis (a severe loss of energy) and MDE fatigue (a less severe loss of energy) could have an impact on the results of factor analysis. Therefore, a second factor analysis was repeated including fatigue instead of leaden paralysis. Results were similar, suggesting that the key factor was loss of energy and not its severity.

This mixture of state and trait features may suggest that the current definition of AD should be improved, as suggested by different studies (Williamson et al., 2000; Posternak and Zimmerman, 2001, 2002; Angst et al., 2002; Benazzi, 2002; Parker et al., 2002). The reversed vegetative symptoms factor of AD corresponded to the definition of AD normally used in community studies, and also to that resulting from latent class analysis of MDE symptoms (Kendler et al., 1996; Sullivan et al., 1998). A definition of AD based only on reversed vegetative symptoms has been recently supported (Matza et al., 2003). Leaden paralysis had a trend correlation with the reversed vegetative symptoms, suggesting that it may be included in a new definition of AD.

These results could lead to a better insight into the biology of AD, as symptoms of a clearly different nature were present (vegetative and personality), which should have different basis and mechanisms. This combination of symptoms of a clearly different nature into a single syndrome raises questions about the validity of the current definition of AD. Furthermore, no biological concept is currently available supporting AD.

A definition of AD based only on the reversed vegetative symptoms had a frequency of 14.6%, much lower than the DSM-IV-TR AD definition (43%). It has to be seen if there are advantages in limiting the definition of AD only to the reversed vegetative symptoms (+/- leaden paralysis or loss of energy). From a practical point of view, oversleeping, overeating and weight gain are easier to diagnose by clinicians than a personality trait like interpersonal sensitivity. This may reduce the false positives (increasing the specificity). Loss of energy (severe as in leaden paralysis or less severe as in fatigue) is another symptom easy to diagnose. As it has been shown that no atypical symptom predicted better response to MAOI versus TCA (McGrath et al., 1992), and that it was the combination of symptoms that predicted this response, leaden paralysis or fatigue could also be included in a new definition of AD, on the basis of factor analysis results (trend correlation with the reversed vegetative symptoms). It has to be shown whether a definition including only these two or three symptoms meets the basic pharmacological validating feature of AD (better response to MAOI than to TCA).

All these different statistical analyses, apart from supporting the bipolar nature of AD, seem to support a definition of AD based mainly on reversed vegetative symptoms (perhaps including also leaden paralysis or loss of energy). Testing antidepressant response in any new AD definition versus DSM-IV AD would be required to support its validity. Some previous studies (Davidson et al., 1988; Thase et al., 1991) found that

AD requiring only oversleeping and overeating responded better to MAOI than to TCA, for the Columbia AD definition (very similar to the DSM-IV-TR AD definition). This new AD definition (based on oversleeping, overeating, and weight gain) was previously supported only by latent class analysis of community and mainly MDD patients (Kendler et al., 1996; Sullivan et al., 1998). As this AD definition is simpler and quicker to assess in clinical practice, it could take the place of the DSM-IV-TR 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). It could also be fruitful to re-analyse available pharmacological studies using this definition of AD.

Limitations and advantages

This was a private practice population and there was a single interviewer. Interviewer bias is possible. However, it may have been reduced by the present study variables being part of a larger set of variables systematically assessed during the first visit (for MDE) of all new patients during recent years, and by study aims not being known when data were collected. The interviewer inter-rater reliability for the diagnosis of bipolar II disorder was found to be k = 0.73 (Benazzi, 2003b). The interview was carried out by a clinician studying and treating mood disorders for a long time, using validated interviews, information from key informants, and systematically interviewing about past hypomania. All state-of-the-art instruments were administered in a systematic manner, in a very large clinical population, thereby limiting systematic bias. It was shown that use of semi-structured interviews reduced the false negative bipolar II and mood disorders (Dunner and Tay, 1993; Brugha et al., 2001; Simpson et al., 2002). These study features may have reduced study limitations (Goodwin and Jamison 1990; Akiskal et al., 2000). The finding of a high BP-II versus MDD ratio in the present study may be related to the use of advanced methods for probing for hypomania. The present study frequency of bipolar family history was in line with previous family history studies (Kupfer et al., 2002; Dunner, 2003).

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