Eur Arch Psychiatry Clin Neurosci (2000) 250 : 249–253

ORIGINAL PAPER

F. Benazzi

Depressive mixed states: unipolar and bipolar II

Received: 16 February 2000 / Accepted: 31 May 2000

Abstract Depressive mixed states (DMS) (major depressive episodes with some hypomanic symptoms) are understudied, and not classified in DSM-IV. The study aim was to find prevalence of DMS among depressed outpatients, to study clinical differences between DMS and non-DMS, and relationships of DMS with unipolar and bipolar II. Ninety eight consecutive DSM-IV bipolar II and unipolar depressed outpatients were interviewed with the Structured Clinical Interview for DSM-IV. DMS was defined as an MDE with at least two concurrent hypomanic symptoms. DMS was present in 62.2 % of patients [48.7 % of unipolar, 71.9 % of bipolar II, (p=0.022)]. DMS had significantly fewer unipolar, more bipolar II patients, lower age at onset, and more atypical features than non-DMS. Bipolar II DMS had significantly more recurrences, more atypical features, and lower age at onset (trend) than unipolar DMS. Bipolar II DMS had (trend) lower age at onset and more atypical features than bipolar II non-DMS. High DMS prevalence has important treatment implications, as antidepressants may worsen DMS, and some antidepressant-resistant depressions may be DMS responding to mood stabilizers. DMS may be distinct from non-DMS, but not from unipolar and bipolar II disorders, and this distinction may be due mainly to high bipolar II prevalence in DMS.

Key words Depressive mixed state · Bipolar II · Unipolar · Prevalence · Outpatients

Introduction

DSM-IV mixed episode is a concurrent, full syndrome, manic and major depressive episode (American Psychiatric Association 1994). In DSM-IV there are no bipolar II mixed episodes. DSM-IV mixed episode is uncommon (Akiskal 1996). Manic episodes with less than syndromal depression were more common (Akiskal et al. 1998). Depressive mixed states (DMS) [major depressive episodes with some hypomanic symptoms (Akiskal et al. 1998)] are not classified in DSM-IV. Common features of DMS, reported in different bipolar populations, were irritability, agitation, racing thoughts, and increased talking (Akiskal and Mallya 1987; Akiskal 1992; Akiskal 1996; Goodwin and Jamison 1990; Koukopoulos et al. 1992; Perugi et al. 1997). Bipolar I patients were studied more than bipolar II patients. In Kraepelin's view, it was enough to have one of the three components of the affective states (psychomotor activity, mood and thinking) in a polarity opposite to the other two in order to have a mixed state (Akiskal et al. 1998). Symptomatic presentations of mixed states ranged from a single opposite-state symptom in the midst of a manic or depressive syndrome, to more complicated mixtures (Goodwin and Jamison 1990). Recent non-DSM-IV criteria for mixed mania (Freeman and McElroy 1999) and mixed depression (Koukopoulos and Koukopoulos 1999) have included a full manic or major depressive episode with at least two concurrent depressive or manic symptoms. DMS tended to be associated with bipolar II disorder and cyclothymic or hyperthymic temperament, while mixed mania tended to be associated with bipolar I disorder and dysthymic temperament (Akiskal 1996; Akiskal et al. 1998; Akiskal 1999). Mixed states might derive from intrusion of an affective episode into an opposite affective temperament (Akiskal et al. 1998). DMS might be part of a broad bipolar spectrum, between psychotic manic-depressive illness and unipolar depression (Akiskal 1996). Mixed states were frequently associated with substance-related disorders (which can confuse the differential diagnosis), and high suicide risk (Goodwin and Jamison 1990). They were often misdiagnosed and underdiagnosed (Perugi et al. 1997).

The aim of the present study was to find the prevalence of DMS among major depressive episode outpatients and to study if there were clinical differences between DSM

Dr. F. Benazzi (✉)
Via Pozzetto 17
48015 Castiglione di Cervia RA, Italy
Phone: +39 0335619 1852,
Fax: +39 0543 30069
E-mail: f.benazzi@fo.nettuno.itt

and non-DSM. Relationships of DSM with unipolar and bipolar II disorders were also studied.

Methods

The study was conducted by a senior psychiatrist, Department of Psychiatry, National Health Service, Forlì, Italy, with 16 years of experience in mood disorder treatment (more than 4000 personal visits per year, more than 400 new patients per year), and research work (Benazzi 2000, 1999a-i, 1997, in press a-c) in his outpatient private practice. The private setting was chosen because it is more representative of mood disorder patients spontaneously seeking psychiatric treatment in Italy, where it is the first or second (after family doctors) line of treatment of mood disorders, and where the most severe mood patients are usually treated in national psychiatric or university centers. Mood disorder patients from academic centers may not be representative of typical mood disorder patients (Goldberg and Kocsis 1999), and the bipolar patients reported in the literature are not representative of the larger universe of patients seen in clinical practice (Akiskal and Pinto 1999).

Ninety eight consecutive DSM-IV bipolar II and unipolar (major depressive and dysthymic disorder) outpatients, presenting for treatment of a major depressive episode (MDE), were included in the study during the last 8 months. There was no concurrent psychopharmacology, to avoid the inclusion of antidepressant-induced mixed states. Substance-related, and severe personality disorder patients (diagnosed by clinical interview following DSM-IV criteria) were not included, because they may be confused with bipolar II disorder and mixed states (American Psychiatric Association 1994; Akiskal 1992; Akiskal 1996; Goodwin and Jamison 1990; Blacker and Tsuang 1992). DMS was defined as an MDE with at least two concurrent hypomanic symptoms, following Akiskal's (1996), Freeman and McElroy's (1999), and Koukopoulos and Koukopoulos' (1999) definitions of mixed state. Patients were interviewed by the author during the first visit with the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version, Mood Disorder module (SCID-CV) (First et al. 1997) and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association 1994). Often, family members or close friends supplemented the clinical information during the interview. Axis I comorbid disorder diagnoses were made by the SCID-CV interview, when comorbid disorders were spontaneously reported by the patients, without systematic probing. This approach may have led to underreporting, but not to selection bias, because there was no reason to think that one group of patients was more likely than the other to report comorbid disorders. Variables from studies, comparing mixed mania with non-mixed mania and bipolar with unipolar patients, were studied: age, gender, age at onset of the first MDE, duration of illness, number of previous MDEs, chronicity (MDE / MDE without full interepisode recovery, lasting more than 2 years), number of patients with DSM-IV atypical, melancholic, and psychotic features, patients with axis I comorbid disorders, and MDE severity at intake (Akiskal et al. 1995; Coryell et al. 1995; Freeman and McElroy 1999). All patients were also interviewed with the SCID-CV for concurrent hypomanic symptoms.

Means were compared with the t test, and frequencies with the Fisher's exact test. Logistic regression was used to study associations. Statistics were calculated with STATA 5 statistical software (Stata Corporation, College Station, TX, 1997). All P values were two-tailed, and the probability level was $P < 0.05$.

The study was approved by the ethics committee, in accordance with 1964 Declaration of Helsinki, and all persons gave informed consent prior to inclusion in the study.

Results

DMS was present in 62.2 % (61/98) of patients. It was present in 48.7 % (20/41) of unipolar patients, and in 71.9 % (41/57) of bipolar II patients, a significant difference (p=0.022). The mean (SD) number of hypomanic symptoms was 2.7 (0.8), the median was 2, and range was 2–5. The most common hypomanic symptoms, present in more than 10 % of DSM patients, were racing thoughts (80.3 %), irritability (73.7 %), distractability (65.5 %), and more talkative (29.5 %).

Comparisons between DMS and non-DMS are presented in Table 1. DMS had significantly fewer unipolar patients, more bipolar II patients, lower age, lower age at onset, and more atypical features. As findings might be related to the high prevalence of bipolar II patients in DMS (lower age at onset and more atypical features were reported in bipolar II MDE versus unipolar MDE [Akiskal 1996; Benazzi 2000; Benazzi 1999e, f; Benazzi 1997]), logistic regression was used to determine if the differences were related to DSM, or to bipolar II, by controlling for bipolar II. Logistic regression showed that age and age at onset were still significantly different (p=0.002, p=0.036) and that

Table 1 Depressive mixed state (DMS) versus non-depressive mixed state (non-DMS)

Variable: mean (SD), % (n)	DMS (n 61)	non-DMS (n 37)	t / Fisher	df	p
Unipolar	32.7(20)	56.7(21)			0.022
Bipolar II	67.2(41)	43.2(16)			0.022
Female gender	70.4(43)	62.1(23)			0.506
Age (years)	40.8(13.9)	51.5(17.0)	3.3	96	0.001
Age at onset (years)	26.1(11.6)	33.0(15.8)	2.5	96	0.013
Duration of illness (years)	15.0(13.4)	18.6(13.9)	1.2	96	0.206
More than 3 MDEs	68.8(42)	72.9(27)			0.820
Chronicity	47.5(29)	48.6(18)			1.0
Axis I comorbidity	45.9(28)	40.5(15)			0.677
GAF	50.8(7.5)	51.3(8.5)	0.3	96	0.761
N depressive symptoms	7.4(1.8)	7.3(1.8)	0.2	96	0.790
Psychotic features	3.2(2)	10.8(4)			0.195
Melancholic features	18.0(11)	29.7(11)			0.215
Atypical features	37.7(23)	16.2(6)			0.039

Table 2 Bipolar II (BPII) versus unipolar (UP) depressive mixed state (DMS)

Variable: mean (SD), % (n)	BPII (n 41)	UP (n 20)	t / Fisher	df	p
Female gender	73.1(30)	65.0(13)			0.559
Age (years)	40.6(14.3)	41.0(13.5)	0.1	59	0.917
Age at onset (years)	24.2(11.0)	29.6(12.1)	1.7	59	0.086
Duration of illness (years)	16.6(12.6)	11.5(14.5)	1.4	59	0.163
More than 3 MDEs	80.4(33)	45.0(9)			0.008
Chronicity	48.7(20)	45.0(9)			0.793
Axis I comorbidity	46.3(19)	45.0(9)			1.0
GAF	50.7(7.8)	51.0(7.1)	0.1	59	0.885
N depressive symptoms	7.5(1.7)	7.5(2.0)	0.4	59	0.685
Psychotic features	2.4(1)	5.0(1)			1.0
Melancholic features	14.6(6)	25.0(5)			0.479
Atypical features	48.7(20)	15.0(3)			0.012

Table 3 Bipolar II depressive mixed state (BPII-DMS) versus bipolar II non-depressive mixed state (BPII- non-DMS)

Variable: mean (SD), % (n)	BPII-DMS (n 41)	BPII-non-DMS (n 16)	t / Fisher	df	p
Female gender	73.1(30)	68.7(11)			0.752
Age (years)	40.6(14.3)	52.9(17.4)	2.7	55	0.008
Age at onset (years)	24.6(12.6)	32.6(17.9)	1.9	55	0.061
Duration of illness (years)	16.6(12.6)	20.2(14.8)	0.9	55	0.360
More than 3 MDEs	80.4(33)	81.2(13)			1.0
Chronicity	48.7(20)	43.7(7)			0.776
Axis I comorbidity	46.3(19)	37.5(6)			0.767
GAF	50.7(7.8)	51.2(7.1)	0.2	55	0.824
N depressive symptoms	7.5(1.7)	7.6(1.7)	0.1	55	0.842
Psychotic features	2.0(1)	12.5(2)			0.187
Melancholic features	14.6(6)	31.2(5)			0.260
Atypical features	48.7(20)	18.7(3)			0.070

atypical features were no more significantly different (p=0.085). Comparisons between unipolar and bipolar II DMS are presented in Table 2. Bipolar II DMS had significantly more recurrences, more atypical features, and a trend for a lower age at onset. Hypomanic symptoms were not significantly different, apart from increased talking in bipolar II. Comparisons between bipolar II DMS and bipolar II non-DMS are presented in Table 3. In bipolar II DMS there was a trend for a lower age at onset (8 years difference) (p=0.0619), for more atypical features (30 % difference) (p=0.070), and age was significantly lower. The same comparisons between unipolar DMS (n=20) and unipolar non-DMS (n=21) did not find significant differences.

Discussion

Prevalence of DMS was high (62.2 %) among unipolar and bipolar II MDE outpatients. This finding has important treatment implications. Antidepressants were reported to worsen mixed depression and to induce mixed states, rapid cycling, and manic / hypomanic episodes in bipolar depression (Koukopoulos and Koukopoulos 1999; Kilzieh and Akiskal 1999; Akiskal 1996; Akiskal 2000). Some antidepressant-resistant depressions may be DMS, which respond to mood stabilizers, and are worsened by aggressive antidepressant treatment (Akiskal 2000). Comparisons between DMS and non-DMS showed significant differences in unipolar / bipolar II ratio, age at onset, and atypical features. Bipolar II patients were significantly more common in DMS than in non-DMS, and DMS was significantly more common in bipolar II than in unipolar patients. These findings suggest that bipolar II is more likely than unipolar disorder to have DMS. It is also important to note that DMS was common in unipolar patients (48.7 %). A finding suggesting that some unipolar patients may be "pseudounipolar" (i. e., they have some bipolarity traits), that some bipolar II patients may have been misclassified because history of hypomania may have low reliability (Dunner and Tay 1993), and that hypomanic symptoms may be common in unipolar patients, supporting a broad bipolar spectrum with few pure unipolar patients. These findings in unipolar patients are supported by reports that one in four becomes bipolar, and that many may be "pseudounipolar" (i. e., they have subtle hypomania during or following a depressive episode) (Akiskal 2000). DSM versus non-DMS had significantly lower age at onset and more atypical features. As findings might be related to the high prevalence of bipolar II patients in DMS (lower age at onset and more atypical features were reported in bipolar II MDE versus unipolar

MDE [Akiskal 1996; Benazzi 2000; Benazzi 1999e, f; Benazzi 1997]), logistic regression was used to determine if the differences were related to DSM, or to bipolar II, by controlling for bipolar II. Logistic regression showed that lower age at onset was related to DSM, while atypical features were related to bipolar II disorder. The lower age at onset of DMS versus non-DMS suggests that they may be distinct disorders, as differences in age at onset may support subtyping of mood disorders (McMahon et al. 1994). Comparisons between unipolar and bipolar II DMS showed findings reported in comparisons between unipolar and bipolar II MDE (lower age at onset, more recurrences, more atypical features) (Akiskal 1996; Benazzi 2000; Benazzi 1999e, f; Benazzi 1997), suggesting that DMS is not distinct from unipolar and bipolar II disorders. Comparisons between the small samples of bipolar II DMS and non-DMS showed, at a trend level, a lower age at onset and more atypical features in bipolar II DMS (statistically non-significant, but clinically significant), suggesting that bipolar II DMS may be a subtype of bipolar II disorder. The same comparisons between unipolar DMS and non-DMS did not find statistically or clinically significant differences, suggesting that the differences found between DMS and non-DMS were mainly due to bipolar II patients. In conclusion, these comparisons showed that DMS may be distinct from non-DMS, but not from unipolar and bipolar II disorders, and that this distinction may be due mainly to bipolar II patients.

Affective temperaments were not assessed, so the reported association with mixed states (Akiskal 1996) could not be tested. As a non-academic sample, like the present one, may be more representative of typical mood disorder patients (Goldberg and Kocsis 1999), results may have more general validity.

Limitations. It was an outpatient sample of moderate severity. There was a single interviewer, and assessment was non-blind and cross-sectional. Substance-related, and severe personality disorders were not included, making the sample less representative (but eliminating a source of bipolar disorder and mixed states misdiagnosis). Phenomenologically, hypomania is not clearly demarcated from mania in DSM-IV, and differential diagnosis depends on severity (Akiskal and Pinto 1999). Bipolar II patients underreport hypomania (Akiskal 1996). The distinction between unipolar and bipolar II is often retrospective, limiting reliability (Akiskal and Pinto 1999; Dunner and Tay 1993). Unless skillfully questioned about past hypomania, bipolar depression can be missed (Akiskal and Pinto 1999). A validated structured interview, a senior psychiatrist with clinical and research work in mood disorders (Benazzi 2000; Benazzi 1999a–i; Benazzi 1997; Benazzi in press a–c), presence of family members or close friends, standard assessment of all consecutive patients, and systematic questioning about past hypomania and current hypomanic symptoms may have reduced these limitations (Goodwin and Jamison 1990; Akiskal and Pinto 1999).

Advantages. Inclusion of outpatients only, no concurrent psychopharmacology, no substance-related disorders, comparison of unipolar and bipolar II patients, and a non-academic setting [mood disorder patients in academic centers may not be representative of typical mood disorder patients (Goldberg and Kocsis 1999)] are advantages of this study.

References

1. Akiskal HS (2000) Mood disorders: Clinical features. In: Sadock BJ, Sadock VA (eds) Kaplan & Sadock's Comprehensive Textbook of Psychiatry, seventh ed on CD-ROM. Lippincott Williams & Wilkins, Philadelphia, pp 28294–29391
2. Akiskal HS, Pinto O (1999) The evolving bipolar spectrum: prototypes I, II, III, and IV. In: Akiskal HS (ed) Bipolarity: beyond classic mania. Psychiatr Clin North Am 22: 517–534
3. Akiskal HS (1999) Spectrum of mixed states: with mania and with hypomania. Presented at the 152nd Annual Meeting of the American Psychiatric Association; Washington, DC, abstract no 46C
4. Akiskal HS, Hantouche EG, Bourgeois ML, Azorin JM, Sechter D, Allilaire JF, Lancrenon S, Fraud JP, Chatenet-Duchene L (1998) Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). J Affect Disord 50: 175–186
5. Akiskal HS (1996) The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 16 (suppl 1): 4S–14S
6. Akiskal HS, Maser JD, Zeller PJ, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin F (1995) Switching from "unipolar" to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 52: 114–123
7. Akiskal HS (1992) The distinctive mixed states of bipolar I, II, and III. Clin Neuropharm 15 (suppl 1, Pt. A): 632A–633A
8. Akiskal HS, Mallya G (1987) Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 23: 68–73
9. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Association, Washington, DC
10. Benazzi F (2000) Depression with DSM-IV atypical features: a marker for bipolar II disorder. Eur Arch Psychiatry Clin Neurosci 1: 53–55
11. Benazzi F (1999a) Bipolar versus unipolar psychotic outpatient depression. J Affect Disord 55: 63–66
12. Benazzi F (1999b) Prevalence and clinical features of atypical depression in depressed outpatients: a 467-case study. Psychiatry Res 86: 259–265
13. Benazzi F (1999c) A comparison of the age of onset of bipolar I and bipolar II outpatients. J Affect Disord 54: 249–253
14. Benazzi F (1999d) Gender differences in bipolar II and unipolar depressed outpatients: a 557-case study. Ann Clin Psychiatry 11: 55–59
15. Benazzi F (1999e) Prevalence of bipolar II disorder in atypical depression. Eur Arch Psychiatry Clin Neurosci 249: 62–65
16. Benazzi F (1999f) Atypical depression in private practice depressed outpatients: a 203-case study. Compr Psychiatry 40: 80–83
17. Benazzi F (1999g) Chronic atypical major depressive episode in private practice: unipolar and bipolar II. Acta Psychiatr Scand 100: 418–423
18. Benazzi F (1999h) Chronic depression subtypes: a 257 case study. Depress Anxiety 10: 81–84
19. Benazzi F (1999i) Bipolar II versus unipolar chronic depression: a 312-case study. Compr Psychiatry 40: 418–421
20. Benazzi F (1997) Prevalence of bipolar II disorder in outpatient depression: a 203-case study in private practice. J Affect Disord 43: 163–166
21. Benazzi F (in press a) Bipolar II depression in late life: prevalence and clinical features in 525 depressed outpatients. J Affect Disord

22. Benazzi F (in press b) Late-life atypical major depressive episode: a 358-case study in outpatients. Am J Geriatr Psychiatry
23. Benazzi F (in press c) Borderline personality disorder and bipolar II disorder in private practice depressed outpatients. Compr Psychiatry
24. Blacker D, Tsuang MT (1992) Contested boundaries of bipolar disorder and the limits of categorical diagnosis in psychiatry. Am J Psychiatry 149: 1473–1483
25. Coryell W, Endicott J, Maser JD, Keller MB, Leon AC, Akiskal HS (1995) Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 152: 385–390
26. Dunner DL, Tay KL (1993) Diagnostic reliability of the history of hypomania in bipolar II patients and patients with major depression. Compr Psychiatry 34: 303–307
27. First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured Clinical Interview for DSM-IV Axis I Disorders Clinician Version (SCID-CV). American Psychiatric Press, Washington, DC
28. Freeman MP, McElroy SL (1999) Clinical picture and etiologic models of mixed states. In: Akiskal HS (ed) Bipolarity: Beyond Classic Mania. Psychiatr Clin North Am 22: 535–546
29. Goldberg JF, Kocsis JH (1999) Depression in the course of bipolar disorder. In: Goldberg JF, Harrow M (eds) Bipolar Disorders. Clinical Course and Outcome. American Psychiatric Press, Washington, DC, pp 129–147
30. Goodwin FK, Jamison KR (1990) Manic-depressive Illness. Oxford University Press, New York, pp 48–49, 218–220, 241, 697
31. Kilzieh N, Akiskal HS (1999) Rapid-cycling bipolar disorder In: Akiskal HS (ed) Bipolarity: Beyond Classic Mania. Psychiatr Clin North Am 22: 585–607
32. Koukopoulos A, Koukopoulos A (1999) Agitated depression as a mixed state and the problem of melancholia. In: Akiskal HS (ed) Bipolarity: Beyond Classic Mania. Psychiatr Clin North Am 22: 547–564
33. Koukopoulos A, Faedda G, Proietti R, D'Amico S, de Pisa E, Simonetto C (1992) Mixed depressive syndrome. Encephale 18 (spec no 1): 19–21
34. McMahon FJ, Stine C, Chase GA, Meyers DA, Simpson SG, DePaulo JR (1994) Influence of clinical subtype, sex, and lineality on age at onset of major affective disorder in a family sample. Am J Psychiatry 151: 210–215
35. Perugi G, Akiskal HS, Micheli C, Musetti L, Paiano A, Quilici C, Rossi L, Cassano GB (1997) Clinical subtypes of bipolar mixed states: validating a broader European definition in 143 cases. J Affect Disord 43: 169–180