

SPECIAL ISSUE

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Is depressive mixed state a transition between depression and hypomania?

Abstract *Background* Depressive mixed states (DMX), described systematically by Kraepelin, have recently been found common among depressed outpatients, with possible important impact on treatment. Study aim was to find if DMX in bipolar II disorder was often a transition period between depression and hypomania, as suggested by Kraepelin. *Methods* 194 consecutive bipolar II major depressive episode (MDE) outpatients were interviewed with the Structured Clinical Interview for DSM-IV. Hypomanic symptoms during the index MDE were systematically assessed. DMX was defined as a MDE plus > 2 hypomanic symptoms appearing during the MDE (not before it), following Akiskal and Benazzi (2003). History of depression-hypomania cycles and vice versa (without symptom-free intervals) was assessed. If DMX were a transition period, cycles should have been more common in bipolar II with DMX than in bipolar II without DMX. To test if there were differences between DMX with history of cycles and DMX without history of cycles, the two subgroups were compared on many clinical, family history, and temperamental variables. To test if there were differences between bipolar II with DMX and bipolar II without DMX, comparisons between the two subgroups were done on variables often reported to be typically found in bipolar disorders and to be diagnostic validators (young onset, many recurrences, atypical features of depression,

bipolar family history, temperamental mood lability, gender). *Results* DMX was present in 70.1 %, and history of cycles in 79.8 %. In bipolar II without index DMX (n = 58) history of cycles was present in 86.2 %; in bipolar with index DMX (n = 136) history of cycles was present in 77.2 % (p = 0.175). DMX with cycles was not significantly different from DMX without cycles on all study variables (apart from agitation). Bipolar II with index DMX, versus bipolar II MDE without index DMX, had significantly more depressions with atypical features, temperamental mood lability, and more females, while age of onset, recurrences, and bipolar family history were not significantly different. *Limitations* Single interviewer, cross-sectional assessment. *Conclusions* Findings do not support Kraepelin's view of DMX as a transition period between depression and hypomania, and a distinction between DMX with and without cycles. Findings only partly support DMX as a distinct subtype of bipolar II, which seems to require temperamental mood lability for its onset during a bipolar II MDE.

Key words depressive mixed state · depression · bipolar II disorder · cycle · hypomania

Introduction

Mixed states (i.e., the different combinations of hypo/manic and depressive symptoms during the same mood episode) were first described systematically by Weygandt (1899) and by Kraepelin (1913). Kraepelin described in detail mixed states, which he classified between the manic and depressive states of manic-depressive insanity (illness). Manic mixed states (mania plus depressive symptoms present during the same episode) were much more studied than depressive mixed states (depression plus manic/hypomanic symptoms present during the same episode, DMX) (Freeman and McElroy 1999). Recently, there has been a rebirth of studies on DMX. Perugi et al. (1997, 2001) described depressive mixed state in bipolar I disorder, Akiskal and Benazzi

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(2001a, 2001b, 2002, 2003, 2003c) described DMX in bipolar II disorder, following the clinical descriptions by Akiskal et al. (1977), Akiskal and Mallya (1987), Akiskal (1992, 1996), and Akiskal and Pinto (1999). According to Kraepelin (1913), the most important domains of manic-depressive insanity were mood, thought, and volition-activity. In mania and depression these domains displayed deviations in the same direction, i. e., excitement in mania and inhibition in depression. In mixed states excitement and inhibition were present concurrently, but the clinical picture was dominated by excitement (mania) or by inhibition (depression). Instead, in DSM-IV (1994) the diagnosis of mixed episode (classified under bipolar I disorder) requires that during the same period of time the criteria are met both for a manic episode and for a major depressive episode. In Kraepelin's mixed states, mania could have depressive mood (depressive mania), inhibition of thought (mania with poverty of thought), or inhibition of activity (inhibited mania); depression could have excitement of activity (excited depression), elevated mood (manic stupor), or excitement of thought (depression with flight of ideas). Kraepelin's description of manic/hypomanic thought disorder ranged from overcrowding of the mind by non-stop thoughts to a continuous flow of thoughts jumping from one topic to another. According to Kraepelin, mixed states were *most frequently* seen in the *transition periods* between hypomania/mania and depression. During the transition period, some opposite symptoms could be present in depression or in mania/hypomania, before the full syndrome of the opposite episode became evident. However, according to Kraepelin, mixed states could also appear infrequently as independent episodes. According to DSM-IV-TR (2000), mixed episodes can evolve from a manic episode or from a major depressive episode, or may arise *de novo*, and may remit or evolve into a major depressive episode (far less commonly into a manic episode). Some data suggest that manic mixed states could be independent episodes more frequently than suggested by Kraepelin. Manic mixed states were found to have clinical, family history, and temperamental differences versus pure manic episodes, and had some diagnostic stability over time (an important diagnostic validator (Robins and Guze 1970; Kendler 1980, 1990)) (Dell'Osso et al. 1991; Akiskal et al. 1998; Perugi et al. 2000; Woods et al. 2002).

Study aim was to find if DMX was related to depression-hypomania cycles in bipolar II disorder, as suggested by Kraepelin.

Materials and methods

Study setting

A general psychiatry outpatient private practice (a University of California at San Diego (USA) collaborating center). Private practice is more representative of mood disorder patients in Italy. The author's practice is a series of solo offices run by the author in different cities of the same region in northern Italy. As it is a general psychiatry prac-

tice it is unlikely that it had a concentration of uncommon and/or treatment-resistant patients (a skewed, not representative sample, as it is instead often the case for tertiary-care patients).

Interviewer

A senior clinical (20 years in practice) and mood disorder research psychiatrist.

Patients

Consecutive 194 bipolar II disorder outpatients, presenting spontaneously for major depressive episode (MDE) treatment without a recent (at least 2 months) hypomanic episode, were included in the last 2 years (sample features are presented in Table 1). Most patients were self-referred. Payment was fee for service, which almost all individuals can afford in Italy. Patients had to be without psychopharmacotherapy for at least two weeks when interviewed at the first visit to be included in the study, in order to exclude antidepressant-induced mixed states. Some patients presenting on low dose benzodiazepines (no more than 0.75 mg/day of alprazolam or equivalents) were however included. Current substance abuse and severe personality disorder patients were excluded, because of confounding the diagnosis of bipolar II and mixed states. Clinically significant general medical illness and cognitive disorders patients were excluded.

Interview method

Patients were interviewed by the author during the first visit (a cross-sectional assessment) with the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (kappa statistic 0.70–1.00) (First et al. 1997), and the Global Assessment of Functioning (GAF) scale (American Psychiatric Association 1994). Diagnosis of severe personality disorders was made following a semi-structured interview based on DSM-IV criteria (prevalence of severe personality disorders was found to be low with SCID-Axis II interviewing in the study setting (Benazzi 2000)). The SCID-CV is partly semi-structured and based on clinical evaluation (not on simple yes/no answers to structured questions). The wording of the sentences can be changed to improve/check understanding by the pa-

Table 1 Bipolar II sample features (n = 194)

Variables	mean (SD), % (N)
Female gender	68.5% (133)
Index age, years	41.8 (12.8)
Age of onset of first MDE	21.5 (9.3)
> 4 MDEs	82.4% (160)
Axis I comorbidity	55.1% (107)
Index MDE symptoms > 2 years	37.6% (73)
Index GAF	50.9 (9.6)
Index Psychotic features	8.2% (16)
Index Melancholic features	8.2% (16)
Index Atypical features	58.7% (114)
Index depressive mixed state	70.1% (136)
Depression-hypomania cycle history	79.8% (155)
Bipolar (I + II) family history	50.0% (97)
Temperamental mood lability	62.3% (121)
N hypomanic symptoms	3.2 (1.4)
Hypomania Interview Guide score	8.3 (3.6)

MDE major depressive episode; GAF global assessment of functioning scale

tient, and the final evaluation was based also on information from family members/close friends (often present during the interview).

■ **Diagnosis of past hypomania and of index depressive mixed state (DMX)**

Patients were systematically interviewed about past hypomanic and manic episodes. History of mania and hypomania was always investigated soon after the diagnosis of MDE before the assessment of study variables, in order to avoid a possible bias related to knowledge of signs of bipolarity. The SCID-CV skip-out instruction of the stem question about past elevated or irritable mood was not followed, as a negative answer would not allow the assessment of the other past hypomanic symptoms by requiring switching to a nonbipolar disorder assessment. This was done mainly to probe for past overactivity, as suggested by Angst et al. (2003). It was found that past overactivity was remembered more easily than past hypomanic mood by the patient, family members and close friends (Benazzi and Akiskal 2003a, b). In the present study the diagnosis of past hypomania always required hypomanic mood (according to DSM-IV), which resulted in it being easier to remember after having remembered a period of overactivity, even when at first the answer to the mood question had been negative. New questions were also asked after negative answers to questions on past overactivity and on elevated or irritable mood: "Did you have a period when you felt like a lion?" (a common saying in Italy), "Do you feel much better in summer?", "Do you feel much better soon before a depression or soon after it?". When the answer(s) was(were) positive, questions on past hypomanic symptoms were remade using different words, and also asking the patient to describe how behavior and mood were during that period. 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), to broaden the assessment of mental overactivity and because this question was found to be easier to understand by the patient compared to the SCID-CV question on racing thoughts. This definition of crowded thoughts was very similar to Kraepelin's description (1921, p 75) of the thought disorder which can be found in depression (an overcrowding of the mind by non-stop thoughts).

Family members and close friends were often present during the interview, and supplemented clinical information, especially during the probing for past hypomanic episodes (increasing reliability (Akiskal et al. 2000; American Psychiatric Association 2000)). Patients often did not report spontaneously about past hypomanic episodes, because hypomanic episodes are often pleasant periods of improved functioning or periods without marked impairment, often not seen as a disorder by patients (who can even view them as the true normality) (American Psychiatric Association 2000; Akiskal 2002a).

The DSM-IV 4-day minimum duration of hypomania for bipolar II diagnosis was not followed, because this cutoff was not based on data (Dunner 1998). Instead, at least 2 days of hypomania were required for the diagnosis of bipolar II, following previous reports supporting this cutoff (Akiskal 2002a; Angst et al. 2003; Akiskal et al. 2000; Cassano et al. 1992; Coryell et al. 1995; Akiskal et al. 1977; Akiskal 1996; Benazzi 2001c; Simpson et al. 2002). Most present study bipolar II patients had had more than one hypomanic episode (increasing reliability in retrospect (Akiskal et al. 2000)).

Presence of hypomanic symptoms during the index MDE was systematically assessed. This kind of assessment cannot be made by following strictly the SCID-CV structure. Hypomanic symptoms had to last at least 1 week, *appeared during the index MDE (not just before it)*, and were present at the time of the interview. A dimensional definition of index DMX (MDE plus concurrent hypomanic symptoms) was used, requiring more than 2 hypomanic symptoms. This dimensional definition of DMX had had clinical, psychometric, and family history validation (Benazzi and Akiskal 2001, 2003d; Benazzi 2001b, 2002, 2003; Akiskal and Benazzi 2003). To improve detection and assessment of hypomanic symptoms during MDE the Hypomania Interview Guide, Retrospective and Current Assessment Version (Williams et al. 1994, 2000) was used, as it covers all DSM-IV hypomanic symptoms.

■ **Definition of depression-hypomania cycles**

History of "depression-hypomania or hypomania-depression cycles without symptom-free intervals" was systematically assessed. To test if DMX were a transition period between depression and hypomania and vice versa (as suggested by Kraepelin) in bipolar II disorder, a comparison was made between frequency of depression-hypomania cycles in bipolar II with index DMX ($N = 136$) and frequency of depression-hypomania cycles in bipolar II without index DMX ($N = 58$). If DMX were a transition period, depression-hypomania cycles should have been more common in bipolar II with DMX. In order to test if there were differences between DMX with history of depression-hypomania cycles and DMX without history of depression-hypomania cycles, the two subgroups were compared on many clinical, family history, and temperamental variables. In order to test if there were differences between bipolar II with DMX and bipolar II without DMX, comparisons between the two subgroups were made on variables often reported to be typically found in bipolar disorders (young onset, many recurrences, atypical features of depression, bipolar family history, temperamental mood lability, gender) (Akiskal 2002a, b; Akiskal et al. 1983, 1995; Angst et al. 2003; Goodwin and Jamison 1990; Benazzi 1997, 2001b, 2001d; Baldessarini 2000; McMahon et al. 1994; Benazzi and Akiskal 2001, 2003; Perugi et al. 1998). Many of these variables were also variables suggested to validate a psychiatric diagnosis (family history, onset, course (recurrences), temperament) (Robins and Guze 1970; Kendler 1980, 1990; Akiskal 2002a, b; Angst and Gamma 2002).

■ **Family history**

Bipolar (type I and type II) family history was investigated with the Family History Screen (Weissman et al. 2000), a structured interview for psychiatric history of first-degree relatives, by interviewing the patient and often also one close relative.

■ **Temperamental mood lability**

Temperamental mood lability was assessed by using two of the items of the mood lability personality scale by Akiskal et al. (1995) ("mood often changes, happiness to sadness, without my knowing why", "have frequent ups and downs in mood, with and without apparent cause"). If at least one answer was positive, mood lability was recorded as present. These questions were similar to the question by Angst et al. (2003) used to assess mood lability ("would you say you were one of those persons who have frequent ups and downs").

Recurrences were divided into more than 4 MDEs and less than 5 MDEs, because many previous MDEs highly increased the risk of future recurrence (Kendler et al. 2001; Kessing et al. 1998).

■ **Check of diagnostic validity of bipolar II diagnosis**

Inter-rater agreement was checked. Recently interviewed MDE patients ($n = 15$) were recalled in 48 hours, and re-interviewed by a second psychiatrist (blind to the author's assessment results), from the same department and with a busy private practice (in order to make the test with a psychiatrist visiting private practice patients, who were the patients included in the present study). In the past, this psychiatrist had also performed research studies with the author. The psychiatrist, prior to the assessment of patients, was trained by the author about study interview methods, and diagnosis of bipolar II. The author checked the quality of the training by taking part to some interviews with the second psychiatrist. These patients were not included in the analysis of inter-rater agreement. The kappa statistic results were the following: agreement = 86.6%, expected agreement = 50.2%, kappa = 0.73, $z = 2.8$, $p = 0.0023$, showing substantial (0.61–0.80) agreement (according to the STATA 7 reference manual, the statistical software used in the study). The diagnostic validity of bipolar II diagnosed according to the present study methods was also tested by comparing it to major depressive disorder (MDD) on vari-

ables often reported to distinguish bipolar disorders versus MDD (onset, recurrences, atypical features of depression, DMX, bipolar family history, temperamental mood lability) (Akiskal 2002a, b; Akiskal et al. 1995; Angst et al. 2003; Goodwin and Jamison 1990; Baldessarini 2000; McMahon et al. 1994; Benazzi and Akiskal 2001, 2003).

Statistics

Means were compared by the t test, frequencies by Fisher's exact test. 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 0.05.

Results

Among 194 patients, DMX was present in 136 (70.1%). History of depression-hypomania cycles was present in 155 (79.8%). To test if there was a link between DMX and depression-hypomania cycles, history of depression-hypomania cycles was compared between bipolar II without index DMX ($n = 58$) and bipolar II with index DMX ($n = 136$). It showed that history of depression-hypomania cycles was present in 50 (86.2%) of bipolar II without DMX, and in 105 (77.2%) of bipolar II with index DMX (Fisher's exact test $p = 0.175$). DMX patients with ($n = 105$) and without history of depression-hypomania

cycles ($n = 31$) were compared (Table 2), to find if presence of cycles identified a distinct bipolar II subgroup. The only significant difference was more psychomotor agitation in DMX patients with cycles. To test if presence of DMX identified a distinct bipolar II subgroup, bipolar II with index DMX ($n = 136$) were compared to bipolar II without index DMX ($n = 58$) on key bipolar and diagnostic validator variables. This showed that bipolar II with DMX had significantly more depressions with atypical features, more temperamental mood lability, and more females, while age of onset, recurrences, and bipolar family history were not significantly different. Frequency of temperamental mood lability in bipolar II with cycles versus bipolar II without cycles was tested to determine if patients had confused mood lability with cycles. It resulted that temperamental mood lability was present in 60.6% ($n = 94$) of bipolar II with cycles ($n = 155$), and in 69.2% ($n = 27$) of bipolar II without cycles ($n = 39$) ($p = 0.360$).

Discussion

Kraepelin's view about mixed states as a transition period between depression and hypomania was not supported by the present findings. If, in bipolar II disorder,

Table 2 Sample of bipolar II with depressive mixed state (DMX) ($n = 136$). Comparison between DMX of bipolar II with history of depression-hypomania cycles (+Depr-Hypo cycle) and DMX of bipolar II without history of depression-hypomania cycles (−Depr-Hypo cycle)

Variables	+Depr-Hypo cycle (mean (SD), % (N)) $n = 105$	−Depr-Hypo cycle (mean (SD), % (N)) $n = 31$	t/Fisher	df	P
Female gender	76.1% (80)	67.7% (21)			0.357
Index age, years	41.5 (12.5)	42.2 (15.6)	−0.2	134	0.796
Age of onset of first MDE	20.7 (8.8)	22.0 (11.1)	−0.6	134	0.498
> 4 MDEs	86.6% (91)	70.9% (22)			0.055
Axis I comorbidity	50.4% (53)	64.5% (20)			0.120
Index MDE symptoms > 2 years	38.0% (40)	38.7% (12)			1.000
Index GAF	49.8 (9.6)	53.2 (8.3)	−1.7	134	0.076
Index Psychotic features	8.5% (10)	3.2% (1)			0.456
Index Melancholic features	8.5% (10)	0.0% (0)			0.116
Index Atypical features	64.7% (68)	61.2% (19)			0.832
Bipolar (I + II) family history	53.3% (56)	54.8% (17)			1.000
Temperamental mood lability	70.4% (74)	70.9% (22)			1.000
Irritability	70.4% (74)	74.1% (23)			0.822
Overactivity	11.4% (12)	19.3% (6)			0.245
Risky behavior	33.3% (35)	45.1% (14)			0.288
Less need for sleep	0.9% (1)	3.2% (1)			0.405
Psychomotor agitation	65.7% (69)	41.9% (13)			0.022
Grandiosity	0.0% (0)	0.0% (0)			
Distractibility	92.3% (97)	87.0% (27)			0.469
More talkativeness	37.1% (39)	19.3% (6)			0.083
Pressure to keep talking	0.0% (0)	0.0% (0)			
Flight of ideas	0.0% (0)	0.0% (0)			
Racing/crowded thoughts	88.5% (93)	93.5% (29)			0.523
N hypomanic symptoms	4.0 (1.0)	3.8 (0.8)	1.0	134	0.309
Hypomania Interview Guide score	10.4 (2.7)	9.9 (2.9)	0.8	134	0.374

MDE major depressive episode; GAF global assessment of functioning scale

Table 3 Comparisons between bipolar II with index depressive mixed state (DMX) and bipolar II without index DMX (no-DMX) on key bipolar and diagnostic validator variables

Variables	DMX (mean (SD), % (N)) n = 136	no-DMX (mean (SD), % (N)) n = 58	t/Fisher	df	P
Age of onset first MDE	21.0 (9.3)	22.9 (9.0)	-1.3	192	0.190
> 4 MDEs	83.0% (113)	81.0% (47)			0.837
Atypical features of depression	63.9% (87)	46.5% (27)			0.027
Bipolar (I + II) family history	53.7% (73)	41.3% (24)			0.158
Temperamental mood lability	69.1% (94)	41.3% (24)			0.000
Female gender	74.2% (101)	55.1% (32)			0.008

MDE major depressive episode

DMX were a transition period between depression and hypomania or hypomania and depression, there should have been a greater history of cycles. When compared to bipolar II without index DMX, history of depression-hypomania cycles was not significantly more common in bipolar II with index DMX. This finding was an indirect evidence against Kraepelin's view, strengthened by our definition of DMX which required no hypomania in the previous 2 months. The inclusion also of DMX with onset soon after hypomania would have allowed the estimate of the frequency of DMX associated with cycles compared to that of DMX not associated with cycles. The number of patients in each sample (bipolar II with and without index DMX) was large enough to reduce the risk of a type II error (missing a real difference). Alpha level was also kept low to reduce a type II error ($p = 0.05$).

When DMX with history of cycles was compared to DMX without history of cycles, no significant clinical, family history, and temperamental differences were found, which was another piece of evidence running against Kraepelin's view (one would have expected some important differences if DMX were related to a bipolar II subtype, i. e., bipolar II with history of depression-hypomania cycles). Bipolar II with history of cycles did not have significantly more temperamental mood lability than bipolar II without history of cycles, suggesting that patients did not confuse mood lability with cycles. Comparisons between bipolar II with and without index DMX only partly supported a distinction between the two (bipolar II with DMX had significantly more depressions with atypical features, more temperamental mood lability, and more females, while age of onset, recurrences, and bipolar family history were not significantly different). These findings suggest that an unstable mood trait background may be required for the onset of DMX. Age of onset, family history, and long-term diagnostic stability are probably the most important diagnostic validators (Akiskal 2002a, b; McMahon et al. 1994; Robins and Guze 1970; Kendler 1980, 1990; Angst and Gamma 2002). The present study found that bipolar II with index DMX was not significantly different from bipolar II without index DMX on age of onset and bipolar family history, partly not supporting the diagnostic validity of this subtyping of bipolar II. Long-term diagnostic stability would be an important piece of evidence

supporting the diagnostic validity of DMX as a subtype of bipolar II disorder. At present this information is lacking. It was shown that manic mixed state had some diagnostic stability (Dell'Osso et al. 1991; Akiskal et al. 1998; Perugi et al. 2000; Woods et al. 2002), which supported its diagnostic validity and its distinction from non-mixed mania. This finding might suggest that a similar finding could also be found in DMX, but only long-term follow-up studies will give the answer. Studies on larger, more powerful samples are also required to obtain more insight into this topic.

In conclusion, the present study findings do not support Kraepelin's concept of DMX as mainly a transition period between depression and hypomania.

■ Limitations

Single interviewer and cross-sectional assessment limited the validity of the findings. However, an interviewer bias is unlikely, as the variable "history of cycles" was included in the standard assessment without knowing the goal of the present study 2 years before, as part of a large set of variables systematically assessed during the first visit for MDE of each new patient. The bipolar II sample had the features often reported to distinguish bipolar versus unipolar MDD (younger onset, more recurrences, depressions with atypical features, DMX, bipolar family history), supporting the validity of the present interview. The interview used in the present study (the partly semi-structured SCID-CV) increased the probability of making a correct bipolar II diagnosis, as shown by previous studies comparing structured versus semi-structured interviews (semi-structured interviews showed higher validity and reliability) (Simpson et al. 2002; Aalto-Setälä et al. 2002; Eaton et al. 2000; Dunner and Tay 1993; Akiskal 2002a; Ghaemi et al. 2002; Brugha et al. 2001). Bipolar family history findings were in line with previous reports on family history of bipolar probands (Kupfer et al. 2002; Suppes et al. 2001). Collateral information from key informants increased the validity of bipolar II diagnosis in the present study (American Psychiatric Association 2000; Akiskal et al. 2000). The interviewer had been studying and treating bipolar II patients for many years, and all consecutive patients had a systematic and standard interview. About the

study setting, private practice is more representative of mood disorders than tertiary-care settings in Italy, because visits are not expensive (much reducing a bias related to income), because psychiatric patients often prefer to be treated outside the public (versus private) national mental health services for fear of stigma, and because the most severe patients are usually treated in the national health service or in the university. However, the sample cannot be seen as fully representative.

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