

## Original Articles

# The Manic-Depressive Mixed State: Familial, Temperamental and Psychopathologic Characteristics in 108 Female Inpatients

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**Summary.** Data on 108 hospitalized bipolar I women were analyzed to characterize those whose course was marked with at least one mixed episode (i.e. an episode with concomitant manic and depressed features) on the basis of various anamnestic and cross-sectional clinical features in comparison with those without mixed episodes. Our data revealed a later age of appearance of the first mixed episode in the course of bipolar illness with a tendency to recur true to type; greater prevalence of mood incongruent psychotic features; lower frequency of hyperthymic temperament; and familial depressive, rather than bipolar, disorders. These characteristics tend to identify the mixed state as a distinct longitudinal pattern of manic-depressive illness.

**Key words:** Mixed state – Bipolar I disorder – Depressive temperament – Hyperthymic temperament

## Introduction

The manic-depressive mixed state is traditionally considered as the simultaneous existence of “opposite” symptoms of manic-depressive illness. Such coexistence of depressive and manic features may be observed at the beginning or at the end of an episode, when mood is particularly likely to change to the opposite polarity; sometimes a mixed state appears during the switch process, when some aspects of the previous phase overlap with prodromal symptoms of the new one. Nevertheless, the diagnosis of mixed state is made when the manic and depressive syndromes coexist during the same episode, a clear polarity not being distinctly identifiable. The mixed state is usually characterized by a more severe psychopathological condition than a pure affective episode, with frequent delusions and hallucinations. Kraepelin (1921)

described it as “... a morbid state ... composed by flight of ideas, excitement and anxiety ... at the same time ideas of sin and persecution are usually present.”

Although the existence of such mixed states has long been known (Deron 1928), few studies have been carried out on this topic in recent years (Himmelhoch et al. 1976a, b; Himmelhoch 1979; Nunn 1979; Evans and Nemeroff 1983; Krishnan et al. 1983; Zubenko et al. 1984; Cohen et al. 1988; Tandon et al. 1988; Adler 1989; Kontaxakis et al. 1989; Post et al. 1989). It is likely that the clinical heterogeneity of this condition and its resistance to traditional treatments (Post et al. 1985; Himmelhoch 1986; Keller et al 1986; Secunda et al. 1987; Prien et al. 1988) have largely contributed to a long disregard of such a frequent presentation of bipolar disorder.

The mixed state, a polymorphous picture, requires a careful differential diagnosis from most mental disorders. It is often misdiagnosed as a nonaffective psychotic illness and even schizophrenia. Mixed states can also be deceptive in their nonpsychotic presentation, manifesting themselves as “atypical depression,” “hysteroid dysphoria” or “panic disorder”. Though mood symptoms are usually relevant, the affective nature of this condition may be difficult to recognize by a purely cross-sectional evaluation. Anamnestic data regarding family history and prior course of illness can facilitate the diagnosis. The aim of this study, carried out on inpatients with severe mixed states, was to identify particular longitudinal and psychopathological aspects of bipolar I disorder with mixed episodes compared with those forms of the illness characterized by more homogeneous, classical or pure affective episodes.

## Patients and Method

This study is part of a longitudinal collaborative project on affective disorders between the Universities of Pisa, Italy, and Mem-

phis, Tenn. USA. The project has an ambulatory component (Cassano et al. 1989), as well as the inpatient component (Dell'Osso et al. 1989a) from which the present communication derives. We investigated 213 patients suffering from a primary mood disorder, consecutively admitted to the female ward of the Psychiatric Clinic at the University of Pisa for a manic, depressive or mixed episode according to DSM-III-R (1987). The data on 108 patients who met the criteria for bipolar I disorder (those with at least one manic episode), representing 50.7% of our sample, were analyzed in order to characterize the mixed states on the basis of various longitudinal and cross-sectional clinical features.

Data were collected on familial, temperamental, anamnestic and clinical parameters based on a special Italian adaptation (Dell'Osso et al. 1989a) of the Mood Clinic Data Questionnaire (MCDQ), extensively used in research at the University of Tennessee (Akiskal et al. 1978). As recommended by the MCDQ, we used a semistructured face-to-face interview, lasting 60–120 min and well accepted by patients. Data concerning psychiatric history were also collected from family members and all other relevant sources (i.e. social workers, physicians, others relevant informants) and systematically recorded. Previous hospital records and physicians' clinical notes completed the collection of retrospective data. The family history concerning affective disorders was investigated using the Research Diagnostic Criteria-Family History Version by Andreasen et al. (1977).

The affective temperaments were assessed by the method of Akiskal and Mallya (1987) derived from Schneider's (1958) description of depressive and hyperthymic types. Onset of illness was defined in three ways (Roy-Byrne 1985): first subjective symptoms, first treatment, and first hospitalization. With regard to the course of illness, we included only the episodes that required psychiatric observation or treatment.

As for cross-sectional features, we assessed many variables, such as age, latency of hospitalization (i.e. interval between onset of episode and admission to hospital), duration of episode, psychosocial stressors and psychopathologic and social functioning just before the index episode (using the GAF scale of DSM-III-R 1987). The psychopathologic cross-sectional profile was assessed by the Clinical Global Improvement (CGI) Scale, the Brief Psychiatric Rating Scale (BPRS) and the Hamilton Rating Scale for Depression (HRSD). As for the diagnostic criteria for the mixed state, no existing approach seems to cover adequately this polymorphic condition. In the present study, the diagnosis of mixed state was made in the conditions that were characterized by a major depressive syndrome in the context of a classic manic picture (according to DSM-III-R criteria). The depressive component was assessed on the basis of the score (more than 15 in the first 17 items) of HRSD (Hamilton 1967). Opposite affective symptoms had to coexist for at least 2 weeks. Following Prien et al (1988), the DSM-III-R criterion A of alternating manic and depressive features was not used, because of possible overlap with rapid cycling bipolar illness. According to the draft of the International Classification of Disease, Xth edition (World Health Organization 1988), at least one prior manic episode was required.

The final diagnosis was made on the basis of all the above information by two senior psychiatrists in our team (LDO and GFP), who assigned consensus diagnoses during a briefer face-to-face interview.

After acute symptoms had been controlled, the patients were discharged, and subsequent visits were made after 2 weeks, 6 weeks and 6 months.

For historical data analysis, the patients were subdivided into two groups:

- (1) Mixed pattern (M): patients with index or past mixed episode. Since past history of mixed episodes is difficult to establish reliably, this judgement was almost entirely reserved to the cases where such history could be documented by past hospital records.
- (2) Straight bipolars (SB): patients with depressive or manic index episode, with no documented mixed states as defined above (Nunn 1979).

The historical data regarding onset and course of illness was further analyzed by subdividing the sample on the basis of polarity of the first episode into three subtypes: depressive onset, manic onset, and mixed onset.

For the analysis of the index episode the sample was subdivided into three groups: patients with mixed index episode (MI), SB with depressive index episode (SD) and SB with manic index episode (SMan).

The data were processed at the Center for Clinical Psychopharmacological Data Documentation (CCPDD) of the Institute of Psychiatry of Pisa University (Cassano et al. 1985), by Statistical Analysis System (S.A.S.) with *t*-test, Chi-square, Fischer's exact test and analyses of variance. We conservatively used two-tailed statistics.

## Results

### Historical Data

Mixed pattern (M) was found in 49 of 108 patients (45.4%), 33 (30.5%) actually suffering from mixed episode, and 16 (14.9%) with an index depressive or manic episode and at least 1 anamnestic mixed episode. Among 59 straight bipolars (SB), 18 (16.6%) were admitted for a depressive episode and 41 (38%) for a manic one; by definition none of them had a history of mixed state. Mean age was 43.5 ( $\pm 14.9$ ) in M and 40.3 ( $\pm 14.3$ ) in SB.

As shown in Table 1, there were no differences between M and SB as regards affective familial loading in first-degree relatives, whether in individual members or taken in toto. Interestingly, however, depressive disorders were more frequent in the relatives of mixed pattern patients and bipolar disorders in the relatives of straight bipolars. There were no differences between the two groups in family history of suicide or suicidal attempts.

Little attention has been paid in the literature to the premorbid temperament in mixed states. In this study, whereas hyperthymia was significantly more frequent in SB, depressive temperament was more common in M (Table 2).

As regards age at onset, age at first depressive and at first manic episode (Table 3), no significant differences

**Table 1.** Rates of family history for mood disorders and suicide

	M (n = 49) %	SB (n = 59) %	df	$\chi^2$
First-degree relatives				
Father	28.5	30.5	1	0.10
Mother	24.5	25.5	1	0.87
Sibs	22.4	28.9	1	1.11
Offspring	8.2	15.2	1	2.37
Diagnosis				
Bipolar disorders	14.0	30.6	1	7.95**
Depressive disorders	35.3	19.4	1	6.36*
Unspecified mood disorders	24.5	30.5	1	0.90
Suicide or suicidal attempts	20.5	18.7	1	0.10

\*  $P < 0.05$ ; \*\*  $P < 0.01$

**Table 2.** Temperament

	M ( <i>n</i> = 49)		SB ( <i>n</i> = 59)		<i>df</i>	$\chi^2$
	<i>n</i>	%	<i>n</i>	%		
Depressive	7	14.3	4	6.8	1	1.65
Hyperthymic	8	16.3	20	34	1	4.30*

\*  $P < 0.05$ **Table 3.** Age at onset

	M ( <i>n</i> = 49)		SB ( <i>n</i> = 59)		<i>t</i>	<i>P</i>
	<i>X</i>	SD	<i>X</i>	SD		
Onset	27	10.2	28.2	11.2	0.5570	0.58
First depressive episode	27.6	9.7	29.8	12.2	0.9386	0.35
First manic episode	30.6	11.1	32.6	12.2	0.7113	0.48
First mixed episode	39.2	14.3	*			

\* Absent by definition

**Table 4.** Characteristics of episodes according to polarity of onset

Onset	Depressive ( <i>n</i> = 67)		Manic <sup>a</sup> ( <i>n</i> = 26)		Mixed ( <i>n</i> = 12)		<i>P</i>
	<i>X</i>	SD	<i>X</i>	SD	<i>X</i>	SD	
Age at onset	27.7	11.2	25.8	8.4	33.2	13.4	n.s.
No. of manic episodes	2.6	3.5	4.2	3.8	0.8	1.4	0.05 <sup>b</sup> 0.006 <sup>d</sup>
No. of depressive episodes	5.5	2.2	1.7	3.1	0.5	0.8	0.001 <sup>b</sup> 0.001 <sup>c</sup>
No. of mixed episodes	0.8	1.1	0.2	0.5	1.8	1.4	0.02 <sup>b</sup> 0.001 <sup>c</sup> 0.001 <sup>d</sup>
Total episodes	9.2	7.2	6.1	5.8	3.2	1.9	0.04 <sup>b</sup> 0.004 <sup>c</sup>

<sup>a</sup> Three B I patients had hypomanic onset<sup>b</sup> Depressive onset vs manic onset<sup>c</sup> Depressive onset vs mixed onset<sup>d</sup> Manic onset vs mixed onset

were observed between M and SB. In patients with the M pattern, however, the mean age of the first mixed episode (39.2 years) was much later in the course of the illness than that of the first depressive (27.6) and manic (30.6) episodes.

Polarity of onset was depressive in 65.3% of M and in 59.3% of SB, manic in 8.2% of M and in 37.3% of SB ( $df = 1$ ,  $\chi^2 = 24.09$ ,  $P < 0.01$ ), hypomanic in 2% of M and in 3.4% of SB; in 24.5% of M the illness onset was mixed.

As regards prior episodes, 56.7% of all episodes in M and 53.2% in SB were depressive.

The analysis of prior manic episodes confirms the trend to a lower number (16.1%) of pure manic episodes in M than in SB (46.8%;  $df = 1$ ,  $\chi^2 = 21.86$ ,  $P < 0.01$ ); although

there was no significant difference in the overall percentages of episodes with psychotic features (M = 33.3%; SB = 30.0%), in M there was a significantly higher percentage of mood-incongruent psychotic features (71.8% vs 30.2 in SB;  $df = 1$ ,  $\chi^2 = 34.63$ ,  $P < 0.001$ ), while in SB there was a significantly higher percentage of mood-congruent psychotic features (69.7% vs 28.2 in M;  $df = 1$ ,  $\chi^2 = 34.46$ ,  $P < 0.001$ ). Mixed episodes represented 27.2% of all previous episodes in M and were characterized by a high percentage of psychotic features (58.8%), often mood incongruent (60%).

As for interepisodic characteristics, full remission was observed in 44.9% of M and in 44.1% of SB; partial remission with mild depressive symptoms or chronic depression were recorded in 20.4% of M and in 13.6% of SB; 32.7% of M and 23.7% of SB showed mild irregular oscillations of mood; overall 2% of M and 18.6% of SB showed hypomanic residuals.

The historical data regarding onset and course of illness was further analyzed by subdividing the sample on the basis of polarity of the first episode into three subtypes: depressive onset ( $n = 67$ ), manic onset ( $n = 26$ ) and mixed onset ( $n = 12$ ). Only in 3 patients there was a hypomanic onset. In the three subtypes there was a significant prevalence of episodes of the same polarity as at onset. Thus, the greatest mean number of depressive anamnestic episodes was found in the depressive onset subtype; the same goes for the manic onset subtype that showed the highest number of manic episodes; in the mixed onset subtype, mixed episodes were also significantly more numerous.

Significant differences were also observed as regards the number of episodes: the depressive onset subtype showed the highest number of episodes and the mixed onset the lowest (Table 4).

### Index Episode

Eighteen SB (16.6%) showed a depressive index episode (SD) and 41 (38%) a manic one (SMan); these subgroups were compared with 33 patients (30.5%) presenting a mixed episode at index evaluation (MI).

Actual age, duration of illness (interval between the first symptoms and the actual age), latency of hospitalization (interval between onset of index episode and hospitalization) and length of episode in the three groups are shown in Table 5. Although the difference among the groups was not statistically significant, latency of hospitalization and length of episodes were clearly longer in mixed patients.

Statistically significant differences also emerged from the comparison of the percentages of index episodes with psychotic features among the three groups; the comparison between mood congruent and incongruent features between the three groups also reached statistical significance. In particular, 63.2% of mixed psychotic episodes were incongruent, and 36.8% were congruent; by contrast, 37.5% of manic psychotic episodes were incongruent, and 62.5% congruent (Table 6).

No differences were found in the percentage or in the severity of psychosocial stressors occurring in the year

preceding the current episode (39.3% in MI vs 38.9% in SD vs 34.4% in SMan). The mean score on Axis V (GAF Scale) was 53.4 in the MI, 42 in the SD and 44.2 in SMan, indicating a somewhat better psychosocial and occupational functioning in MI than in the other two groups in the year before the index episode.

As regards the psychopathologic profile, the HRSD factors and the total score of mixed patients showed no significant difference from that of pure depressives. This was in part definitional, because for the entry criteria, the MI had to have an HRSD level compatible with clinical depression.

Although the CGI scores were essentially the same in MI (5.5), SD (5.5) and SMan (5.4), the mean total score of BPRS was higher in MI suggesting that the mixed state is more severe than the pure affective episode of

either of the two polarities (Table 7). Analysis of the mean factors scores of BPRS revealed that MI and SD did not differ in the "Anxiety/Depression" factor, but that they showed a significantly higher score than SMan. The mean score for the "Anergia" factor was significantly lower in MI than in SD, and significantly higher than in SMan; thus, the mean score of "Activation" factor in MI is significantly higher than in SD and significantly lower than in SMan. Similarly the MI mean scores of "Thought Disturbance" and "Hostility/suspiciousness" factors were in an intermediate position between those of SD (lower) and those of SMan (higher).

## Discussion

In agreement with the literature (Winokur et al. 1969; Nunn 1979; Himmelhoch et al. 1986) and with a previous study conducted on a smaller sample (Dell'Osso et al. 1989b), 30.5% of bipolar I female inpatients were diagnosed as suffering from a mixed index episode, and the percentage of patients with a mixed pattern rose to 45.4% when past mixed episodes were taken into consideration. The high percentage of mixed states in our sample is probably gender-related (Himmelhoch et al. 1976b; Nunn 1979; Secunda et al. 1987).

Among the anamnestic characteristics of the mixed pattern (i.e. patients with an index or past mixed episode) in our sample, there was a heavy family loading for depressive disorders, and in some cases, in accordance with Himmelhoch et al. (1976b), double heredity, i.e. for bipolar illness and for depressive disorders. Moreover, compared with the more classic bipolar episodes that arose from the background of a hyperthymic temperament, the mixed state more often arose from that of a depressive temperament, which may have added a dysphoric component to the manic phases.

The illness began as a mixed state in about one-fourth of the sample; in most of the remaining cases the onset was depressive. The higher prevalence in our sample of depressive onset is probably gender-related (Angst 1978; Roy-Byrne 1985). It is of interest that M showed a significantly lower percentage of manic onset in com-

**Table 5.** Index episodes

	MI (n = 33)	SD (n = 18)	SMan (n = 41)	F	P
	X	X	X		
Index age	42.3	47.9	37.1	3.68	0.03 <sup>a</sup>
Length of illness (years)	15.4	17.2	9.8	4.01	0.02 <sup>b</sup>
Latency of hospital- ization (weeks)	12.6	7.4	6.6	1.78	0.17
Length of episode (months)	4.1	2.0	2.9	1.69	0.19

<sup>a</sup> SD > SMan

<sup>b</sup> SD = MI > SMan

**Table 6.** Psychotic features at index episode

	MI (n = 33)	SD (n = 18)	SMan (n = 41)	df	$\chi^2$
	%	%	%		
Psychotic episodes	52.8	21.0	55.8	2	30.31** <sup>a</sup>
Congruent	36.8	100.0	62.5		
Incongruent	63.2	0.0	37.5	2	90.6**

<sup>a</sup> MI = SMan > SD

\*\*  $P < 0.01$

**Table 7.** BPRS Factors and total scores at index episode

	MI (n = 33)		SD (n = 18)		SMan (n = 41)		T	P
	X	SD	X	SD	X	SD		
Anxiety/Depression	327.3	16.1	369.4	21.8	151.8	14.4	49.48	0.0001 <sup>a</sup>
Anergia	201.5	14.9	273.6	20.1	134.8	13.3	17.36	0.0001 <sup>b</sup>
Thought disturbance	187.9	16.4	136.1	22.2	269.5	14.7	14.52	0.0001 <sup>c</sup>
Activation	296.7	19.4	195.9	26.3	389.0	17.4	19.70	0.0001 <sup>d</sup>
Hostility/suspiciousness	232.1	22.5	155.4	30.5	260.6	20.2	4.13	0.02 <sup>e</sup>
Total	44.5	1.4	41.7	1.9	41.8	1.3	1.22	0.30

<sup>a</sup> SD = MI > SMan

<sup>b</sup> SD > MI > SMan

<sup>c</sup> SMan > SD = MI

<sup>d</sup> SMan > MI > SD

<sup>e</sup> MI = SMan > SD

parison with SB; this kind of onset seems to be replaced by a mixed one in M. The finding of a much higher mean age of the first mixed episode confirms Kraepelin's observation (1921) of the later onset of the first mixed episode, which is usually preceded by one or more pure episodes. Thus, it would appear that, after a period of recurrence of opposite pure phases, bipolar disorder, especially in females and for yet unknown reasons, mixes these opposite poles into a mixed presentation.

With reference to the course of illness, M compared with SB were characterized by largely mixed or depressive episodes, often with psychotic congruent or incongruent features. For this reason, mixed states are often underdiagnosed and treated as schizophrenic (Akiskal and Puzantian 1979) or borderline disorders (Akiskal and Mallya 1987).

When the sample was subtyped on the basis of polarity of the first episode, a marked correlation emerged between onset polarity and polarity of recurrences; furthermore, the depressive-onset subtype was characterized by the highest mean number of episodes, while in the mixed-onset subtype, although the duration of illness was longer, the lowest number of episodes was found, as observed by Prien et al. (1988). Thus, the polarity of onset identified subgroups characterized by a specific course pattern and appeared to be a reliable predictor of polarity and number of subsequent episodes.

As for cross-sectional features, patients with a mixed index episode (MI) had an actual age and duration of illness intermediate between straight bipolars with a depressive index episode (SD) and straight bipolars with a manic index episode (SM).

At the index episode, the percentages of psychotic features were quite similar for mixed and manic patients but, just as anamnestic episodes, mood-incongruent psychotic episodes were more frequent in the mixed and mood-congruent episodes were prevalent in manic patients.

In agreement with Prien et al. (1988), a broad spectrum of depressive symptoms contributed to the difference between the pure manic and the mixed group. As if to confirm the "mixed" nature of this condition, mean scores for the "Activation" and "Anergia" factors in MI were situated in an intermediate position between those of straight depressed and straight manic patients. The resulting clinical picture was characterized by a polymorphous psychopathology, corresponding to the mixed pattern. This was further suggested by the total score for BPRS, which was higher, though not significantly so, in mixed than in straight bipolars, irrespective of whether they were manic or depressive.

Despite these indices of classic severity, the high mean score of the GAF Scale in MI indicates a relatively good psychosocial and occupational functioning just before the index episode; this could have prognostic significance, since it would predict a return to the previous level of adjustment and might serve as a useful criterion for differential diagnosis from schizophrenic patients, together with the longitudinal aspects already described, such as the affective family history and the presence of prior

pure mood episodes. As for phenomenological aspects, the simultaneous existence of opposite affective symptoms, even though variously combined, provides a common denominator for these states.

In conclusion, because of its special cross-sectional features, its longitudinal aspects and, particularly, its tendency to recur with the same characteristics, the mixed state may be considered as a distinct longitudinal pattern of manic-depressive illness.

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