

# A clinical study comparing manic and mixed episodes in patients with bipolar disorder

## Estudo clínico comparativo entre episódios de mania e mistos em pacientes com transtorno bipolar

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### Abstract

**Objective:** Mixed episodes have been described as more severe than manic episodes, especially due to their longer duration and their association with higher rates of suicide attempts, hospitalization and psychotic symptoms. The purpose of this study was to compare the severity between mixed and pure manic episodes according to DSM-IV criteria, through the evaluation of sociodemographic data and clinical characteristics. **Method:** Twenty-nine bipolar I patients presenting acute mixed episodes were compared to 20 bipolar I patients with acute manic episodes according to DSM-IV criteria. We analyzed (cross-sectionally) episode length, presence of psychotic symptoms, frequency of suicide attempts and hospitalization, Young Mania Rating Scale scores, Hamilton Depression Rating Scale scores and the Clinical Global Assessment Scale scores. **Results:** Young Mania Rating Scale scores were higher in manic episodes than in mixed episodes. There were no differences in gender frequency, CGI scores and rates of hospitalization, suicide attempts and psychotic symptoms, when mixed and manic episodes were compared. Patients with mixed episodes were younger. **Conclusion:** In our sample, mixed states occurred at an earlier age than manic episodes. Contrary to previous reports, we did not find significant differences between manic and mixed episodes regarding severity of symptomatology, except for manic symptoms ratings, which were higher in acute manic patients. In part, this may be explained by the different criteria adopted on previous studies.

**Descriptors:** Comparative study; Psychotic disorders; Bipolar disorder; Suicide, attempt; Hospitalization

### Resumo

**Objetivo:** Estados mistos têm sido descritos como mais graves que episódios de mania, especialmente pela maior duração dos episódios, maiores taxas de suicídio, hospitalização e sintomas psicóticos. O objetivo deste estudo foi comparar a severidade entre episódios mistos e mania pura definidos segundo critérios do DSM-IV, avaliando-se características clínicas e sociodemográficas dos pacientes. **Método:** Vinte e nove pacientes bipolares do tipo I em estado misto foram comparados a 20 pacientes bipolares do tipo I em episódio de mania aguda de acordo com os critérios do DSM-IV. Analisou-se transversalmente a duração dos episódios, presença de sintomas psicóticos, tentativa de suicídio, hospitalização, escores da Escala de Sintomas de Mania de Young, escores da Escala de Depressão de Hamilton e Escala de Avaliação Clínica Global. **Resultados:** As pontuações na escala de avaliação de mania de Young foram maiores nos episódios de mania quando comparadas às de episódios mistos. Não houve diferença estatisticamente significativa na frequência de gêneros, nas pontuações da CGI, nas taxas de hospitalização, tentativa de suicídio e sintomas psicóticos entre episódios mistos e de mania. Pacientes com episódio agudo misto tinham idade menor que pacientes em episódio agudo de mania. **Conclusão:** Em nossa amostra, episódios mistos ocorreram em idade menor que em episódios de mania. Ao contrário da literatura, não houve diferenças significativas entre episódios de mania e mistos no que se refere à severidade da sintomatologia, exceto para a pontuação de sintomas de mania, que foi maior em pacientes em mania aguda. Isto pode ser explicado, em parte, pela diferença nos critérios adotados por estudos anteriores.

**Descritores:** Estudo comparativo; Transtornos psicóticos; Transtorno bipolar; Tentativa de suicídio; Hospitalização

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## Introduction

In bipolar patients, mixed states have been reported to be more severe than manic episodes.<sup>1-2</sup> Mixed states have been reported to be associated with longer episode length,<sup>3</sup> higher frequency of hospitalization<sup>2</sup> and psychotic symptoms<sup>2,4</sup> when compared to pure manic episodes. More specifically, the occurrence of suicide attempts have been found to be higher among patients during mixed episodes in most studies that compared them to patients during manic states.<sup>5-8</sup>

The few comparative studies regarding manic and mixed states have used different diagnostic criteria. DSM-III-R mixed episode criteria<sup>9</sup> are as strict as DSM-IV criteria<sup>10</sup> regarding the number of depressive symptoms necessary for defining a mixed episode (at least five depressive symptoms). However, DSM-II-R and DSM-IV are more restrict than Cincinnati criteria,<sup>11</sup> which accept at least two depressive symptoms. When mixed episodes are defined by broad criteria, differences between the two types of episodes tend to diminish.<sup>8,12</sup>

Using broad criteria for mixed states, Akiskal et al.<sup>13</sup> reported that suicidal ideation and depressive mood are more frequent in mixed episodes when compared to manic episodes. Irritability has been found to be more frequent than depressive mood in mixed episodes.<sup>4,12</sup> Dell'Osso et al.<sup>14</sup> observed lower latency for hospitalization, more incongruent psychotic symptoms, and tendency to longer episodes in patients with history of mixed episodes compared to the ones without these episodes, they found no differences in CGI scores between the two groups.

Regarding manic symptoms, data are not uniform and different scales have been used: Swann et al. showed higher global rates of mania in non-treated inpatient adults with mixed episodes compared with patients with pure mania.<sup>15</sup> However, they applied a scale rarely used by other authors (Affective Disorders Scale [ADRS], Murphy et al.). Baker et al. described higher Young Mania Rating Scale (YMRS) scores in a large sample of patients with mixed episodes.<sup>16</sup> On the other hand, McElroy et al. found similar YMRS scores in manic and mixed episodes, using the Cincinnati or the DSM-III-R definition in patients who aged above 12 years.<sup>8</sup>

Mixed episodes are more frequent in adolescents than in adults.<sup>17-18</sup> Nonetheless, patients in mixed episodes were not found to be younger than patients in mania.<sup>3,8,12</sup>

We compared sociodemographic and clinical data of DSM-IV bipolar patients with manic and mixed episodes. We hypothesized that patients with mixed episodes defined by DSM-IV criteria would have episodes with greater severity than patients with manic episodes. Younger age at index episodes, higher occurrence of psychotic symptoms, suicide attempts and hospitalizations were considered indicators of greater severity.

## Method

We studied outpatients who have been followed up in average for five years at the Bipolar Research Program at the Institute

of Psychiatry, Universidade de São Paulo Medical School. The study was approved by the ethical review committee of the University Hospital. Written consent was obtained from all patients when in euthymia. Patients were diagnosed with bipolar disorder type I using the SCID-I/P (Structured Clinical Interview for DSM-IV)<sup>19</sup> and were assessed using the Young Mania Rating Scale (YMRS),<sup>20</sup> Hamilton Depression Rating Scale-31 items (HAM-D),<sup>21</sup> and the Clinical Global Assessment Scale (CGI).<sup>22</sup> These scales have been used in the literature as severity parameters by McElroy et al. and Baker et al., among others.<sup>8,16</sup> We selected bipolar patients that met DSM-IV criteria for acute mania, presented YMRS scores equal or higher than twelve during follow-up, and did not present mixed episodes in their past clinical history. The DSM-IV criteria for mixed episode were used. For each patient, the first mixed or manic episode during follow-up that met these criteria was considered the index episode. Only one episode was analyzed per patient. We also collected sociodemographic and clinical data such as age at index episodes, gender, and presence of psychotic symptoms, suicide attempts and hospitalization, the last three used in the literature as severity parameters.<sup>8,14</sup> This was a transversal study, based on data stored at each patient visit.

## 1. Statistic analysis

We applied the Kolmogorov-Smirnov test to ascertain if the distribution of the collected data was normal. Mean scores were compared using Student's t-test or the Mann-Whitney U test. We used the Chi-square or the Fisher's Exact test for categorical variables.<sup>23</sup>

## Results

### 1. Assessment

Sociodemographic data are presented in Table 1. Mean age at the index episode was significantly lower in patients in mixed episode compared to manic patients. Mixed state and manic groups did not differ in gender frequency.

### 2. Clinical data

Clinical data are displayed in Table 2. Manic patients had significantly higher YMRS scores than patients in mixed episode ( $p < 0.001$ ). Manic and mixed episodes had no statistically significant differences regarding episode length, presence of psychotic symptoms, suicide attempts and hospitalizations.

The following manic symptoms were significantly more frequent in manic episodes in comparison to mixed episodes: distractibility and racing thoughts, decreased need of sleep, lack of care with appearance, and lack of insight. There was no difference in the presence of irritability between mixed and manic episodes.

As expected, HAM-D scores were higher in patients in mixed episode compared to the ones in mania (Mean = 20.0,

**Table 1 - Sociodemographic data from patients with mixed and manic episodes**

	Mixed group n = 29	Manic group n = 20	p
Mean age at index episode: mean (SD)	34.8 (8.9)	42.0 (13.2)	0.002*
Gender Female: n (%)	21 (72.4%)	12 (80.0%)	0.540**

\* Mann-Whitney U test, \*\* Chi-Square test

**Table 2 - Clinical data of index mixed versus manic episodes**

	Mixed group n = 29	Manic group n = 20	p
Mean CGI Score (SD)	4.9 (0.6)	4.6 (1.0)	0.290**
Mean YMRS score (SD)	15.0 (4.8)	22.9 (9.5)	0.001**
Mean HAM-D score (SD)	20.0 (1.4)	2.7 (0.7)	< 0.001
Mean length of episode in days (SD)	40.2 (31.6)	41.6 (34.5)	0.680**
Psychotic symptoms: n (%)	9 (31.0%)	4 (20.0%)	0.520***
Hospitalization: n (%)	1 (3.4%)	1 (5.0%)	1.00***
Suicide attempts: n (%)	2 (6.9%)	0	0.52***

\*\* Mann-Whitney U-test, \*\*\* Fisher's exact test

SD = 1.4, versus Mean = 2.7, SD = 0.7;  $p = 0.001$ ). The main depressive symptoms in mixed episodes were insomnia, depressive mood, decrease in general activities including entertaining activities, somatic symptoms of anxiety, suicide ideation and guilt feelings.

## Discussion

Age at index episodes was significantly lower in patients in mixed episode compared to manic patients. Our results are in disagreement with other studies that have included inpatients.<sup>3,8,14</sup> However, Dilsaver et al.<sup>4</sup> studied mixed states according to DSM-III-R in out and inpatients and reported findings similar to ours. Himmelhoch and Garfinkel<sup>17</sup> have also noticed that mixed episodes occur at an earlier age. A younger age at the index episode can be considered as a severity marker, as the probability of a new episode is higher.<sup>12</sup>

We found similar gender frequencies in mixed and manic episodes, which is in agreement with the report from Perugi et al. who used DSM-III-R or Cincinnati criteria, the last requiring a smaller number of depressive symptoms for mixed episodes.<sup>3</sup> These findings were different from McElroy et al.'s, who have described a higher prevalence of women according to DSM-III-R criteria but not when Cincinnati Criteria were used, suggesting that women present more depressive symptoms during mixed episodes.<sup>8</sup> These conflicting results can be attributed to different methodologies used in the discrimination of the episodes. Our sample had a greater percentage of women and we did not detect a higher predominance of women with mixed episodes as described in the literature.

Length of mixed and manic episodes was similar to McElroy et al., but different from Dell'Osso et al. and Perugi et al., probably because our patients presented good adherence to treatment and were using mood stabilizers previously to the index episodes, avoiding a recrudescence of both episodes.<sup>3,8,14</sup>

The rate of psychotic symptoms was similar between groups, which has also been observed by Swann et al., but not by Dilsaver et al.<sup>4,12</sup> Rate of hospitalizations was similar to those found by McElroy et al. but different from Post et al.<sup>2,8</sup> Rate of suicide attempts during episodes was similar to Swann et al. and in disagreement with the results of Dilsaver et al.<sup>5,12</sup> The absence of differences between groups in these variables can be due to medication use and prompt access to treatment in our department.

Scores on YMRS found in this study were higher in manic episodes than in mixed episodes, similarly to Swann et al.'s findings. However, YMRS scores found in this study were smaller than in Baker et al.'s study, in which patients were free of medications before evaluation. Our results differed from McElroy et al.'s whose scores were similar between groups of patients with manic and mixed episodes.<sup>8,15-16</sup> As stated before, some studies show that manic patients have higher manic scores than patients with mixed episodes. A possible explanation for this is that patients in mixed episode may seek for treatment earlier than manic patients due to the presence of more severe depressive symptoms. The YMRS scores were relatively low in manic patients, including patients with psychotic symptoms. In a separate analysis, manic patients with psychotic symptoms scored significantly higher than manic patients without psychotic symptoms. CGI scores were similar between manic and patients in mixed episode.<sup>14</sup> These results are in disagreement with previous reports that mixed episodes are more severe than manic episodes.<sup>2</sup>

Depressive mood and insomnia were the two most common depressive symptoms in mixed episodes, differently from the report from Akiskal et al.,<sup>13</sup> who observed a higher occurrence of depressive mood and suicide ideation. Irritability was equally present in both groups, differing from some authors' findings who reported irritability to be more frequent in mixed episodes.<sup>24</sup>

In this study, there were no significant differences between manic and mixed episodes regarding severity of the episodes, except for manic symptoms severity scores. A possible explanation is that manic patients present less suffering than patients with depressive symptoms, and probably look for treatment later on than patients in mixed episode.<sup>25</sup> This delay would imply in higher manic scores in the patients with pure mania. Despite the relatively smaller YMRS scores in mixed episodes, we found that patients with mixed episodes and psychotic symptoms had higher manic symptoms scores compared to patients with mixed episodes and no psychotic symptoms ( $M = 19.56$ ,  $SD = 5.46$ , versus  $M = 14.02$ ,  $SD = 2.3$ ,  $p = 0.003$ , Mann-Whitney). We found large confidence intervals, what signalizes a possible type I error. To reduce this effect we would have had to significantly increase our sample, and this was not possible because we began the study with a defined number of patients. Our criteria were stricter than the ones used in other studies (Cincinnati criteria which require less depressive symptoms,<sup>11</sup> or Perugi's criteria<sup>3</sup> which require less symptoms and a shorter period of presentation). We observed a low frequency of suicide attempts and hospitalizations, probably because the majority of patients were under treatment. These low frequencies can lead to a higher probability of a type II error than previously estimated.

The results of this study do not support our initial hypothesis that mixed episodes are more severe than manic. This can be due to: the small sample size (which in part can be attributed to the methodology used); and to the use of medications that diminished the severity of the episodes. An analysis of the efficacy of therapeutic regimes was not included among our objectives due to our dependence on the patients' ability to recall previous treatments and their difficulty to distinguish antidepressants from other specific medications.

To our knowledge, this is the first controlled study analyzing Brazilian bipolar patients during mixed states. Despite the caveats described above, our results do not indicate that mixed episodes are more severe than manic ones. Future studies should evaluate whether the DSM-IV criteria for mixed states are the most appropriate one when comparisons with pure mania are conducted.

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