

Research report

Predominant polarity in bipolar disorder: Diagnostic implications

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Abstract

Background: It has been reported that patients with bipolar disorder (BD) remain about 10 years symptomatic before the correct diagnosis is made. This fact is particularly important for patients with predominantly depressed polarity who tend to be diagnosed as suffering from unipolar major depressive disorder and treated with antidepressants. The present study was carried out to assess clinical differences between predominantly manic and depressed BD patients with a special focus on the time that patients remained undiagnosed.

Methods: Clinical and socio-demographic characteristics were obtained from a sample of 149 euthymic bipolar outpatients. Patients were divided into depressive or manic predominance of polarity. Clinical features, number of years undiagnosed (NYU) and occupational functioning were assessed in the two groups.

Results: Forty-five patients were classified as a “Depressive Polarity” whilst forty-seven were considered as “Manic Polarity”. Depressive Polarity was associated with a longer delay to be diagnosed ($F=14.43$, $df=89$, $p=0.001$). The predominantly depressive patients tended to present a depressive onset of illness, earlier age of onset, longer duration of illness and higher number of suicide attempts than manic polarity patients.

Conclusion: There was a marked clinical difference between predominantly manic and depressive bipolar patients. Predominantly depressive polarity is associated with a longer delay in receiving a correct diagnosis and effective treatment which has an important impact on the management of the illness.

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1. Introduction

There is an emerging body of evidence suggesting that the predominance of polarity is a valid prognostic parameter and may help clinicians to take on long-term

decisions (Judd et al., 2003; Calabrese et al., 2004; Colom et al., 2006; Quitkin et al., 1986; Perlis et al., 2006). In a recent paper it has been suggested that about 50% of bipolar patients present a “predominant polarity”, meaning that over two thirds of episodes are restricted to one pole of the illness (Colom et al., 2006). Predominance of polarity has important therapeutic implications for the long-term treatment of these

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patients. This seems to be particularly true whenever the therapeutic choice is concerned, as it seems that predominantly depressed patients would benefit from differential approaches such as a more frequent use of lamotrigine (Vieta and Rosa, 2007).

There are clinical differences between patients with predominant manic polarity from patients with predominant depressive episodes. In one hand, the presence of substance misuse, psychotic symptoms, hospitalizations and cognitive impairment are more frequent among patients with manic polarity (Judd et al., 2002; Post et al., 2003; Colom et al., 2006; Daban et al., 2006; Martinez-Aran et al., 2007; Martinez-Aran et al., 2004a). On the other hand, as the illness progresses predominantly depressive patients experience a higher number of suicide attempts and also a greater amount of stressful life events (Colom et al., 2006; Daban et al., 2006). Moreover, in the depressive polarity, the first episode is often depressive, and frequently includes melancholic features. In addition, a seasonal pattern is more likely to occur in patients with predominantly depressive polarity (Daban et al., 2006; Goikolea et al., 2007).

BD is often under/misdiagnosed and many times a long gap takes place between the first observed symptoms and the time that a clearly defined diagnosis is given to patients by a clinician (Hirschfeld et al., 2005). The most common misdiagnosis is unipolar major depressive disorder (Hirschfeld et al., 2005; Ghaemi et al., 1999; Post, 2005). This is particularly important because patients with predominantly depressed polarity are likely to be treated with antidepressants increasing the risk of manic switch and rapid cycling, thereby worsening the long-term course of the illness (Goodwin and Jamison, 1990; Ghaemi et al., 1999). In addition, lack of effective treatment would predispose patients to illness recurrence and the development of chronic subsyndromal symptoms which in turn are associated with poor cognitive and functioning outcomes (Torrent et al., 2006; Martinez-Aran et al., 2007).

The present study was designed to assess clinical differences between predominantly manic and depressed BD patients with a special focus on the time that patients remained undiagnosed.

2. Methods

Ninety-two DSM-IV-TR bipolar patients were enrolled for at least five years in the systematic prospective follow-up of the Bipolar Disorders Program of the Hospital de Clinicas de Porto Alegre (HCPA), Brazil. In this systematic follow-up patients are interviewed at least once every three months to collect relevant clinical data. Data collection was initiated in March 2002 and it is still

going on. The systematic prospective follow-up was approved by the Ethical and Research Committee of the HCPA. Depressive predominant polarity was defined according to a previous study conducted in Spain (Colom et al., 2006) as at least two third of a patient's past episodes fulfilling the DSM-IV criteria for Major Depressive episode. Manic/hypomanic predominant polarity was defined as at least two thirds of past episodes fulfilling DSM-IV criteria for manic or hypomanic episodes. The patients that did not meet criteria for either predominant polarity were excluded from the analysis. Mixed episodes were accounted for as well but were not considered as a part of depressive polarity or manic polarity. Diagnosis was assessed at baseline using the Structured Clinical Interview for DSM-IV-TR (SCID, First et al. 1999a,b). Episodes were prospectively assessed using the DSM-IV check –list for mania, hypomania, mixed episodes and depression. Clinical variables included number and polarity of previous episodes, hospitalizations, age of onset, age of first hospitalization, polarity of the first episode, history of psychosis, rapid cycling and suicidal behaviour were assessed from a questionnaire obtained with the patients and their relatives. The number of years undiagnosed (NYU) was also analysed. The NYU was obtained subtracting the age when patients received the diagnosis of BD by a mental health professional from the age of onset as defined by the patient (Gazalle et al., 2005a). Demographic data, psychiatric comorbidities and psychiatric history of first degree relatives were also assessed. Social and occupational functioning was assessed using the Global Assessment of Functioning (GAF).

3. Statistics

Groups (depressive and manic polarity) were compared regarding clinical and social demographic variables. Statistical methods consisted of Chi-square statistics with Yates correction or Fisher's exact test for comparisons of categorical data, and the Student's *t* test for dimensional variables which were normally distributed. Linear regression analysis was performed to examine the relationship between the number of years undiagnosed (NYU) and predominant polarity as the predictive variable. The HAM-D, YMRS and HAM-A scores were used as the confounding factors. All statistics were two-tailed, and significance was set at $p < 0.05$.

4. Results

Fifty seven out of 149 were excluded from the study because they did not present any specific predominant

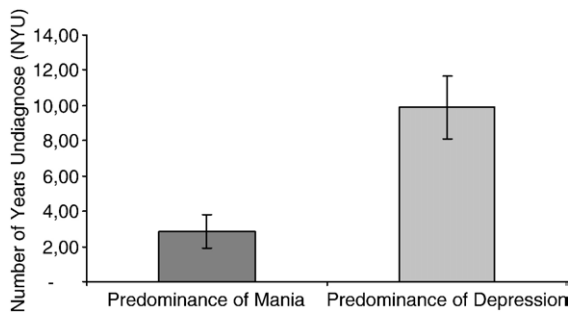


Fig. 1. Number of Years Undiagnosed (NYU) and predominant polarity.

polarity according to our definition. Forty-five (24.2%) patients were classified as having Depressive Polarity, forty-seven (25.3%) were considered as having Manic Polarity. Depressive Polarity was strongly associated with a higher number of years undiagnosed (NYU) ($F = 14.43$, $df = 89$, $p = 0.001$), as shown in Fig. 1. Table 1 shows the results after comparing Manic and Depressive Polarity regarding demographic variables, work situation, clinical variables and pharmacological treatment. Depressive polarity was more prevalent amongst bipolar II patients and was strongly associated with depressive onset of BD. Regarding the quantitative clinical variables, the age of onset of bipolar disorder was lower for depressive polarity patients (24.22 ± 1.97) than manic polarity patients (29.33 ± 11.86 ; $p = 0.044$). Depressive polarity patients showed a longer duration of illness (DP: $20.07 \pm 11.27 \times$ MP: 15.52 ± 8.96 ; $p = 0.038$) and a higher number of suicide attempts (DP: $2.13 \pm 2.24 \times$ MP: 1.18 ± 1.23 ; $p = 0.039$) than manic polarity patients. No differences were found between groups regarding age and gender. A high proportion of the patients with either manic (84.1%) or depressive polarity (89.4%) were working at the time of assessment. There was no difference between groups regarding the GAF scores. Finally, we did not find differences between groups regarding rapid cycling, substance abuse and family history of psychiatric disorder.

Using a linear regression model, predominant polarity was the only variable that showed significant statistical association to NYU and this model explained 13% of the variance ($F = 3.22$, $R^2 = 0.13$, $\beta = 0.38$, $df = 85$, $p = 0.001$).

5. Discussion

The present study confirms most of the findings by the Spanish Group (Colom et al., 2006) and gives further support to the concept of predominant polarity in the context of bipolar illness. It also shows that

depressive predominant polarity is associated with a longer delay in receiving a correct diagnosis in a sample of bipolar patients. This is probably due to the fact that patients who are predominantly depressed tended to be diagnosed as suffering from unipolar depression (Suppes et al., 2005; Solomon et al., 2006). In average, the delay before the accurate diagnosis is made and appropriate treatment is initiated in bipolar patients can be up to 10 years (Hirschfeld et al., 2003) and this delay appears to be related to higher risk for current depressive symptoms and lower quality of life (Gazalle et al., 2005a,b). Similarly to previous studies, we also found that depression was the most common first-episode polarity in predominantly depressive patients which could increase the probability of an inaccurate diagnosis (Perugi et al., 2000; Daban et al., 2006).

There are several factors that contribute to the misdiagnosis of BD as unipolar major depressive disorder. First, many bipolar patients, especially during hypomanic episodes experience heightened mood, elevated self-esteem, increased physical/mental activity and they fail to perceive their symptoms as pathological (Perlis, 2005). Indeed, it seems that a state of “anosognosia” seems to be an important correlate of manic psychopathology (Gazalle et al., 2007). As a consequence, most of the patients look for assistance when they are suffering from depressive episodes. Some patients report that they have always been depressed or underreport important symptoms such as racing thoughts, increased speech production or excessive irritability or aggressive behaviour (Hirschfeld et al., 2003). On the other hand, there is also a lack of understanding about bipolar disorder among the doctors/professionals. Several studies have reported that bipolar patients consulted 3.3 psychiatrists before being diagnosed with BD (Ghaemi et al., 1999). Previous studies suggest a careful history-taking is necessary to allow for the recognition of BD and the use of the structured clinical interview is recommended in order to better assess symptoms of depression, mania or hypomania. In addition, the use of collateral informants, such as friends or family members might help the clinician to enhance the accuracy of the diagnosis (Perlis, 2005).

Depressive symptoms in both bipolar and unipolar patients are phenomenologically similar and this might impair the accuracy of the diagnosis of BD during depression (Perlis, 2005; Benazzi, 2006). There are some symptoms such as irritability, hypersomnia and psychomotor agitation that are more frequent in BD, especially BD-II than unipolar depression (Benazzi, 2006). A careful inspection of clinical features such as course of illness, age of onset, characteristics of past episodes, presence of

Table 1
Differential features between bipolar patients with manic (MP) and depressive (DP) predominant polarity

	MP (n=45)	DP (n=47)	t	p
	N(%)	N(%)		
Female	66.7%	85.1%	4.29	0.38
Activity Working	84.1%	89.4%	10.37	0.11
	MP (n=45)	DP (n=47)	Chi Square	p
	N(%)	N(%)		
BPI	43(95.55%)	36(76.60%)	6.81	0.009
BPII	2(4.4%)	11(23.04%)		
Manic onset	21(46.66%)	10(21.74%)	12.46	0.014
Depression onset	14(31.11%)	31(67.39%)		
Mixed onset	7(15.55%)	4(8.69%)		
Hypomania onset	1(2.22%)	-		
Present substance abuse preceding first episode	2(4.44%)	3(6.52%)	0.189	0.664
Rapid cycling	10(22.22%)	12(27.27%)	0.305	0.581
Alcohol	11(24.44%)	9(19.15%)	0.379	0.538
Street drugs	12(26.66%)	8(17.02%)	1.257	0.262
Family history of psychiatric disorder	34(75.55%)	36(78.26%)	0.094	0.759
Family history of THB	11(24.44%)	9(19.56%)	0.316	0.574
Family history of depression	8(17.77%)	13(28.26%)	1.408	0.235
Family history of suicide	9(20%)	11(23.91%)	0.203	0.652
<i>Treatment</i>				
Lithium	41(91.11%)	40(85.10%)	0.787	0.375
Carbamazepine	22(48.88%)	28(59.57%)	1.058	0.304
Valproate	34(75.55%)	29(61.70%)	2.044	0.153
Lamotrigine	2(4.44%)	3(6.39%)	0.168	0.682
Antipsychotics	14(31.11%)	12(25.53%)	0.353	0.552
Antidepressants	18(40.00%)	6(12.76%)	8.843	0.003
Benzodiazapines	24(53.33%)	15(31.91%)	4.319	0.038
	Mean (SD)	Mean (SD)	t	p
Age	44.27±11.66	44.70±11.55	-0.18	0,858
Education level	9.78±4.59	8.89±3.71	1.01	0.32
Age of onset	29.33±11.86	24.22±1.97	2.048	0,044
Age of first hospitalization	34.80±12.45	30.18±11.53	1.647	0,104
Duration of illness	15.52±8.96	20.07±11.27	-2.11	0,038
Total number of episodes	16.34±12.82	18.07±18.09	-0.473	0.638
Number of manic episodes	11.66±9.77	4.49±6.21	3.871	0.001
Number of hypomanic episodes	0.54±2.13	0.32±1.08	0.594	0.554
Number of depressive episodes	4.14±5.92	13.27±12.45	-3.966	0.001
Number of hospitalizations	4.11±4.22	3.76±5.10	0.353	0,725
Number of suicide attempts	1.18±1.23	2.13±2.24	-2.113	0,039
HAM-A	9.35±7.63	13.57±8.34	-2.53	0,052
HAM-D	7.84±6.53	10.63±7.06	-1.97	0.013
YMRS	5.70±7.25	3.56±3.38	1.79	0,076
GAF	63.33±13.62	61.89±15.04	0.48	0.63

psychosis, hyperphagia and family history of mania or hypomania could reduce the underdiagnosis and misdiagnosis of BD (Akiskal et al., 1983).

Another important factor is the difficulty in diagnosing bipolar disorder in the face of comorbidity with other psychiatric disorders. Anxiety disorders, alcohol or/and substance abuse and personality disorders are very

common in BD (Regier et al., 1990; Vieta et al., 2001; Vieta et al., 2000; Akiskal et al., 2006). There are symptoms such impairment in attention, sleep disturbance and racing thoughts that can be associated with both mood disorders and anxiety disorders (Perlis, 2005). Previous studies reported that patients with depressive symptoms experienced more anxiety symptoms than manic patients

(Perlis, 2005; Simon et al., 2006). Moreover, symptoms of anxiety and depression are difficult to tease apart and it is very challenging to identify clear cut anxiety disorders in patients who are acutely depressed (Kauer-Sant'anna et al., 2007; Mitchell et al., 2007). In the present study an analysis of anxiety comorbidity was not feasible due to the small sample size.

The extensive gap between the treatment-seeking and appropriate diagnosis leads to serious consequences. In the absence of effective treatment, patients may experience a greater number of episodes and/or more subsyndromal affective mood symptoms. Recurrent mood episodes appear to have negative effects on the cognitive functioning as well as on the psychosocial functioning (Zarate et al., 2000; Hirschfeld et al., 2003; Rosa et al., 2007; Martinez-Aran et al., 2004a,b). Previous studies have reported that functional impairment is associated with depressive symptoms (Calabrese et al., 2004; Fagiolini et al., 2005; Depp et al., 2006). However, a large proportion of patients experience some degree of impairment even during remission (Depp et al., 2006; Tohen et al., 2000; Martinez-Aran et al., 2007). In our sample, the GAF scores were similar in both groups, which is consistent with previous findings in the Spanish sample (Colom et al., 2006), suggesting that both depressive and manic polarity patients present the same level of functioning. Another consequence is that bipolar patients misdiagnosed as unipolar depression are likely lead to be treated with antidepressant monotherapy. The use of antidepressants treatment in these patients has been associated with a higher risk of drug-induced mania/mixed switches and rapid cycling-episodes which in turn may yield treatment-resistance and poor outcomes (Ghaemi et al., 1999).

BD has been clearly associated with elevated risk of suicidal ideation and attempts, with death due to suicide estimated to occur in 10–15% of patients (Post, 2005; Simon et al., 2006). As expected, we found that depressive predominant polarity was associated with a higher number of suicide attempts (lifetime). In addition, patients with depressive predominant polarity experienced lower age of onset of BD, higher number of the depressive episodes and hospitalizations, characterizing a more severe and chronic profile of illness. These clinical characteristics complemented by the long delay in receiving an accurate diagnosis and effective treatment might be related to the higher rates of suicide attempts. Nonetheless, these findings highlight the importance of prophylactic treatment to depression. In this context, mood stabilizers with depression-prevention profiles or “class B” stabilizers added to the formerly existing “class A” and “C” stabilizers (Ketter and Calabrese, 2002; Vieta, 2004; Colom et al., 2006) are recommended, especially if supplemented with psychoso-

cial interventions, such as psychoeducation and family intervention (Colom et al., 2003; Reinares et al., in press).

6. Limitation

Although we included patients with reliable information and further verification through relatives and records was performed, a limitation of this report is that part of the the information was collected retrospectively.

7. Conclusion

In conclusion, the marked clinical differences between predominantly manic and depressive bipolar patients were again highlighted in the present study. In accordance to a similar study with a Spanish sample (Colom et al., 2006), there was a clear predominant depressive or manic polarity in around half bipolar patients which results in important clinical and therapeutic implications. Patients with predominant depressive polarity experienced a long delay in receiving a correct diagnosis and effective treatment, which may engender a more severe course of illness.

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Conflict of Interest

Declaration of interest: The authors declare no conflicts of interest related to the content of this article.

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