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The impact of the number of episodes on the outcome of Bipolar Disorder

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ABSTRACT – *Background:* Bipolar disorder is a highly recurrent severe psychiatric disorder. The number of episodes has been found consistently associated with poor outcome. It has been suggested that bipolar patients with long duration of illness and highly recurrent course show great impairment of global functioning.

Objectives: The aim of this study is to assess the clinical course and outcome of patients with bipolar disorder I and II with a high number of mood episodes.

Methods: We compared a group of bipolar I and II subjects whose number of episode was higher than ten (N = 167) with a similar-size representative sample of bipolar patients whose number of episodes was lower or equal than ten (N = 131).

Results: Bipolar patients with more than 10 episodes have a more severe outcome of bipolar disorder. Qualification and occupational status was clearly worse for the highly recurrent group which showed a predominance of depressive polarity.

Conclusions: These data suggest that bipolar patients with a highly recurrent course have significant functional impairment. With the passing of time, bipolar illness tends to be ruled by depressive features. Treatment strategies may need to address this issue.

Background

Bipolar illness is a lifelong psychiatric disorder which may carry severe impairment of patients' general functioning (Strakowski *et al.* 2000, Goldberg & Harrow 2004). In 1990, the World Health Organization studies reported that bipolar disorder is the sixth leading cause of worldwide disability (Lopez & Murrray 1998, World Health Organization 1999). Bipolar patients are "4 times more disabled than the general population" (Access Economics Report 2003); they have a variable course of illness and often do not experience complete recovery.

The course of bipolar disorder is typically episodic; the characteristic recurrence of the illness brings to personal and social costs that could also depend on the number of patient's episodes (Begley *et al.* 2001). Several studies have found high rates of recurrence in bipolar illness: it has been estimated that 50-90% of patients presents several bipolar episodes during the course of illness (Dion *et al.* 1988, Goodwin & Jamison 1990, Keck Jr. *et al.* 1995, Goldberg *et al.* 1995). The number of previous episodes has been found to be an important predictor of recurrence in bipolar disorder (Kessing *et al.* 2004). Poor occupational status after hospital discharge has been associated with the number of previous affective episodes (Tohen *et al.* 1990), and patients experience substantial impairment even in the absence of episodes (Gitlin *et al.* 1995). Moreover, the number of episodes may worsen the response to acute treatment in successive episodes (Swann *et al.* 2000).

Several investigations focused on the role of social and psychological risk factors in recurrence of bipolar disorder. For instance, bipolar patients were found prone to recurrence when socially disables. The clinical severity and the outcome of bipolar illness are generally associated to the number of episodes (Swann 2005): specifically, the number of episodes and the duration of illness have been found consistently associated with poorer outcome (Tohen *et al.* 1990, Goldberg *et al.* 1995).

Several studies have examined the outcome of bipolar disorder by using psychosocial variables. Data from 1450 patients showed that 30-60% of bipolar patients had detectable levels of psychosocial impairment (MacQueen *et al.* 2001). Long duration illness has been associated with impaired social functioning (Hajek *et al.* 2005).

In this study we compared a group of bipolar I and II patients with more than 10 episodes, with a group of bipolar I or II patients with a number of episodes equal or lower than 10. We hypothesized that the group of bipolar patients with more episodes would have a longer duration of illness, poorer outcome of bipolar disorder and worse social functioning.

Methods

All patients included in the present study were enrolled in the systematic follow up of the Bipolar Disorders Program of the Hospital Clinic and University of Barcelona which provides systematic and prospective collection of clinical, socio-demographic and treatment features of all patients included in the Bipolar Disorders Program. The Bipolar Disorders Program is a last-resort program providing care for difficult-to-treat bipolar patients derived from all over Spain but also provides clinical care to all bipolar patients coming from a specific catchment area *Eix-*

ample Esquerre in Barcelona. In order to be included in our database, the patients gave written informed consent for the collection of data. This study was approved by the Ethical and Research Committee of the Hospital Clinic. All the patients fulfilling DSM-IV criteria for bipolar type I and II disorder were selected from the database to assess the outcome implications of their illness course. Hence, patients were divided according to the number of lifetime episodes: higher (group 1) or lower or equal than ten (group 2). We chose this cut-off according to several authors who found that the mean rating for severity and outcome of depression and mania was associated with a history of more than 10 prior episodes (Nolen *et al.* 2004). One hundred sixty-seven patients (N = 167, 56.04 %) fulfilled criteria for the highly recurrent group, whilst one hundred thirty-one (N = 131, 43.96 %) were considered to belong to the second group. Both groups were compared regarding several clinical and socio-demographic variables. All patients were retrospectively assessed by means of the Structured Clinical Interview for DSM-IV-axis I and II (SCID-I and SCID-II, respectively) (First *et al.* 1997a, First *et al.* 1997b), in order to detect all possible psychiatric comorbid diagnoses. Several clinical and socio-demographic variables were obtained from the structured interviews with the patient and their relatives: age, age of onset, age of first hospitalization, number of hospitalizations, the number of lifetime episodes, treatment compliance, history of psychosis and suicidal behaviour. Several more variables were specifically assessed: predominant polarity of episodes, seasonality according to DSM-IV criteria, rapid cycling (DSM-IV criteria as well), physical illness, psychiatric history of first-degree relatives, episode polarity at onset, occupational functioning and employment qualification.

Both groups were compared using several statistic techniques, including the chi-square statistic with Yates correction or Fisher exact test for the comparison of categorical data and Student *t* test was used for dimensional variables. All statistics were two-tailed and significance was set at $p < 0.05$.

Results

There were no significant differences between the two groups regarding bipolar subtype. Comparison of quantitative and qualitative variables is shown in Table I and II respectively. Regarding predominant polarity of episodes, mania or hypomania predominance was more prevalent amongst the less recurrent patients (30.9% vs. 14.8%), whilst depression was strongly associated to more than 10 episodes (33.3% vs. 18.6%) ($p < 0.004$). Depressive onset was more common amongst less recurrent patients (71.9% vs. 58%) ($p < 0.02$). Less recurrent patients had a higher number of psychotic symptoms in their first episodes (37%) compared to the highly recurrent group (26.1%) ($p < 0.05$). We found significant differences regarding seasonal pattern, which was more prevalent amongst the highly recurrent group (32.5% vs. 16.4%) ($p < 0.003$). Rapid cycling was obviously more prevalent in the highly recurrent group (24.5% vs. 10.7%) ($p < 0.003$). We did not find any significant difference between both groups regarding axis I and II comorbidity, but axis III comorbidity was more prevalent amongst highly recurrent patients (40% vs. 24%) ($p < 0.005$). There was no specific association between family history of psychiatric disorders or suicide and long duration of the bipolar disorder, whilst family history of

affective disorders was more common in less recurrent patients (66.9% vs. 53.5%) ($p < 0.003$). Working for pay was more common amongst less recurrent group (64.9% vs. 48.5%) ($p < 0.006$). Regarding job qualification, we found a higher percentage of qualified patients in the less recurrent group (53.4% vs. 37.1%) ($p < 0.006$). As both groups differed in age, we performed an ANCOVA using age as a covariate, but differences remained significant anyway.

Table I
Comparison of the quantitative features of patients with and without history of high number of mood episodes.

Variable	BD with > 10 episode (N=167 Mean (±sd)	BD with < 10 episodes (N=131) Mean (±sd)	t	P
Age	48.36 (13.31)	34.67 (11.74)	-9.28	<.001
Age of onset	25.77 (10.98)	28.86 (11.45)	2.37	<.02
Age of first hospitalization	23.99 (19.54)	22.14 (16.20)	- .78	NS
N of manic episodes	2.63 (4.63)	1.87 (2.68)	- 1.45	NS
N of hypomanic episodes	5.48 (10.54)	2.91 (4.32)	- 2.27	<.03
N of depressive episodes	8.63 (9.83)	4.33 (4.67)	- 3.99	<.001
N of mixed episodes	.56 (1.41)	.39 (1.27)	- .95	NS
N of hospitalizations	1.66 (2.44)	1.26 (1.45)	- 1.43	NS
N of suicide attempts	.54 (1.27)	.44 (.98)	- .69	NS

NS = non significant.

Discussion

The impairment of global functioning seems to be strongly associated with the higher number of episodes and long duration of bipolar disorder. The results of this study show that these patients have higher levels of functioning impairment when compared to bipolar patients with short-duration illness. Particularly, we found that bipolar patients with long duration of illness reported lower employment qualification and occupational status. This finding is congruent with previous studies reporting that the number of episodes had a negative impact on social functioning (Tohen *et al.* 1990, Goldberg *et al.* 1995, MacQueen *et al.* 2000, Hajek *et al.* 2005). It is possible that the high number of episodes may determine brain long-lasting biochemical changes that could have some consequences on global functioning in bipolar patients (Young *et al.* 1993, Post 1993). Moreover, some investigators have found that cognitive dysfunctions could worsen psychosocial outcome and employment in bipolar illness (Zarate, Jr. *et al.* 2000, MacQueen *et al.* 2001, Martinez-Aran *et al.* 2004a). Patients with multi-episode bipolar disorder would be more prone to have cognitive impairment (Martinez-Aran *et al.* 2004b), and this fact may be on the basis of poor social and occupational adjustment.

Regarding clinical data, the highly recurrent group presented depression as predominant polarity of bipolar illness. This finding is congruent with the results of other investigators (Judd *et al.* 2002, Judd *et al.* 2003). Some possible explanations of this result are that the lower percentage of manic episodes could reflect a pattern inherent in the course of illness, or that treatments utilized in bipolar disorder would be more effective for mania than for depression; on

Table II
Comparison of the qualitative features of patients with and without history of high number of mood episodes.

Variables	BD with > 10 episodes (N = 167)		BD with > 10 episodes (N = 131)		x^2	p
	No.	%	No.	%		
Sex					2.44	NS
Male	64	38.3	62	47.3		
Predominant polarity					1.36	<.004
Mania or Hypomania	20	14.8	30	30.9		
Depression	45	33.3	18	18.6		
Without predominant polarity	70	51.9	49	50.5		
*Psychotic symptoms					.89	NS
Yes	92	55.8	79	61.2		
Psychotic symptoms in the first episode					3.96	<.05
Yes	42	26.1	47	37		
Life-events preceding first episode					.012	NS
Yes	90	55.6	68	56.2		
Seasonal pattern					9.81	<.003
Yes	53	32.5	21	16.4		
*Rapid cycling					9.30	<.003
Yes	40	24.5	14	10.7		
*Atypical depression					0.03	NS
Yes	33	22.1	27	23.1		
*Psychotic depression					.50	NS
Yes	29	25.9	25	30.5		
Subtype					2.71	NS
Bipolar I	102	61.1	92	70.2		
Bipolar II	65	38.9	39	29.8		
Comorbidity axis I					.33	NS
Yes	47	28.1	33	25.2		
Comorbidity axis II					1.73	NS
Yes	44	26.3	26	19.8		
Comorbidity axis III					8.35	<.005
Yes	66	40	31	24		
Family history of psychiatric disorders					1.72	NS
Yes	109	68.6	96	75.6		
Family history of affective disorders					5.31	<.03
Yes	85	53.5	85	66.9		
Family history of suicide					.02	NS
Yes	17	10.9	13	10.4		
Suicidal ideation					2.83	NS
Yes	111	69.4	76	59.8		
Attempted suicide					.40	NS
Yes	44	27.5	31	24.2		
Treatment adherence					.57	NS
Good	99	63.5	83	65.9		
Medium	43	27.6	30	23.8		
Poor	14	9	13	10.3		
Job qualification					7.91	<.006
Qualified	62	37.1	70	53.4		
Occupational status					7.98	<.006
Working for pay	81	48.5	85	64.9		
Hallucinations					.23	NS
Yes	43	25.7	37	28.2		
Depressive onset					6.25	<.02
Yes	120	71.9	76	58		
Substance use at present					.10	NS
Yes	88	54.7	66	52.8		

NS= non significant.
*Lifetime history of

the other hand, it may be possible that functioning impairment may itself have a role on development of depressive relapses (MacQueen *et al.* 2000). It has been reported that depression is usually the first and most frequent type of episode during the course of bipolar illness (Perugi *et al.* 2000). On the other hand, depressive phases have been associated to a worse occupational and social functioning (Bauer *et al.* 2001, Calabrese *et al.* 2004). Depression appears to be associated with disability and comorbidity (Vieta *et al.* 2001, Chengappa *et al.* 2005), and depressive polarity seems to have a strong impact on global functioning (Furukawa *et al.* 2000). Our study seems to confirm this relationship. There are several possible explanations for the link between high rates of depressive episodes and impairment of functioning. Some authors suggest that bipolar patients may be more likely to perceive depressive phases as more weakening than manic episodes (Calabrese *et al.* 2004); other authors suggest that unresolved depressive symptoms may contribute to incomplete symptomatic recovery and lead to major dysfunction and disability (Chengappa *et al.* 2005). Another possible explication to this finding is that depressive episodes are often associated with cognitive dysfunctions that may worsen global functioning along the course of bipolar illness.

In our results, depressive onset was more common amongst LD-BD patients, possibly because patients with a depressive onset had higher overall morbidity during the follow-up period (Turvey *et al.* 1999). On the other hand, the link between rapid cycling and long duration of the illness has been previously described elsewhere (Kupka *et al.* 2005). Interestingly, rapid-cycling itself may partly explain the high levels of functional impairment (Dean *et al.* 2004).

In this study we found a highly prevalence of seasonal pattern in patients with recurrent course of bipolar disorder. In the clinical practice, this finding would suggest the importance of primary prevention programs that should focus on the prevention of seasonal recurrences in this subgroup of bipolar patients. This could be achieved by enhancing treatment strategies immediately before the critical period.

In our sample, DSM-IV Axis III comorbidity was more prevalent amongst the most recurrent patients; in agreement with previous studies (Fagiolini *et al.* 2002, Fagiolini *et al.* 2003), it is possible to consider this finding as another risk factor of poorer functioning outcome amongst the bipolar patients.

The primary limitation of this study is that informations regarding the number of episodes and the age at onset of bipolar disorder were assessed retrospectively. Although our study was based on all available sources of information, in the retrospective history it may exist more potential bias than in prospective data. Moreover, it was not possible to evaluate the episode duration and his impact on global functioning versus the impact of absolute number of episodes on outcome. The two groups also differed on their age, but this was obviously a correlate of longer duration of illness. When age was controlled for, the results remained the same, suggesting that differences were not related to age but truly related to the impact of the number of episodes.

Despite these potential limitations, our study highlights the association between the duration of bipolar illness and functioning outcome. Since episodes seem to beget further episode (Kessing *et al.* 2004), it may be important to develop strategies for early diagnosis and for prevention of relapses. In

addition this study also suggests that bipolar patients with long duration of illness and higher number of episodes could benefit from rehabilitative intervention in order to minimize the functional impairment associated with bipolar illness. Moreover, our findings suggest that, with the passing of time, bipolar illness tends to be ruled by depressive features. Depressive polarity seems to have a strong impact on global functioning and such finding emphasizes the need to early recognize and treat depression in bipolar patients.

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