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One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder

Rosa AR, González-Ortega I, González-Pinto A, Echeburúa E, Comes M, Martínez-Àran A, Ugarte A, Fernández M, Vieta E. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder.

Objective: The aim of this 1-year follow-up study was to compare functional outcome as well as clinical differences between patients with first- and multiple-episode bipolar disorder.
Method: Bipolar disorder patients with first ($n = 60$) and multiple episodes ($n = 59$) were recruited from two hospitals in Spain. The Functioning Assessment Short Test (FAST) was used to assess functioning. The Hamilton Depression Rating Scale (HAMD) and the Young Mania Rating Scale (YMRS) were administered to assess mood symptoms.
Results: As expected, patients with first episode experienced a greater functioning compared to patients with multiple episodes (11.26 ± 10.94 vs. 26.91 ± 13.96; $t = 6.436$, $P < 0.001$). There were significant demographic and clinical differences between both groups. Baseline depressive symptoms ($F = 9.553$, df = 4, 102; $P < 0.001$) and age ($F = 14.145$, df = 4, 103; $P < 0.001$) were significantly associated with poor functional recovery at 6-month and 12-month assessment, respectively, in a group of patients with multiple episodes.
Conclusion: Our data give support to the model of staging in bipolar disorder, showing that the enduring neurotoxicity of repeated episodes may contribute to sustained impairment in multiple areas of psychosocial functioning.

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Key words: functioning; functional impairment; functional recovery; first-episode bipolar; multiple-episode bipolar; staging model

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Significant outcomes

- Patients with first-episode bipolar disorder had better functioning than those with multiple-episode bipolar disorder in areas such as autonomy, occupation, cognition, interpersonal relationships and leisure time.
- Baseline depressive symptoms were associated with poor functioning at 6-month period in a group of patients with multiple episodes.
- Our findings are consistent with the model of staging in bipolar disorder, showing that the toxic effects of mood episodes may contribute to sustained impairment in multiple areas of psychosocial functioning.

Limitations

- Naturalistic design: most patients were recruited from in-patient settings
- First-episode patients may be getting more intensive support given that their care has been prioritized by the local healthcare authorities.
- The effects of medication may be different according to subgroup (first episode vs. multiple episode).
- Some baseline clinical differences were found between groups that might have had some influence on functional outcome.

Introduction

Bipolar disorder has been associated with a marked impairment in psychosocial functioning (1–7). Patients show difficulties in multiple areas of functioning (independent living, interpersonal relationships, occupational and educational achievement, recreational enjoyment, and sexual activity) that appear early in the course of the illness (8–12). The functional impairment may continue for prolonged periods, even when patients with bipolar disorder are in clinical remission (3, 13–17). Therefore, psychosocial dysfunction among bipolar disorder is not limited to symptomatic periods, but may be enduring or result in sustained disability, which contributes to high personal suffering and socioeconomic costs to society (18, 19).

Longitudinal studies of patients with bipolar disorder indicate that functional recovery is more difficult than symptomatic improvement (6). The European Mania in Bipolar Evaluation of Medication (EMBLEM) study results show that 64% of patients achieved remission, whereas only 34% achieved functional recovery during the 2-year follow-up after an acute episode (20). However, the knowledge about factors related with psychosocial outcomes in patients with bipolar disorder is limited. Clinical factors such as subclinical depressive symptoms (4, 5, 14) and number of depressive (21) or mixed episodes (22) seem to have a clear negative impact on functioning. Furthermore, cognitive impairment (23–25), low social support perceived by the patient, as well as dysfunctional beliefs or cognitive schemas appear to play a significant role in functioning of patients with bipolar disorder(5). Although insight impairment is common among first episode patients, especially when they experience manic symptoms, a recent study did not find relationship between unawareness of having a mental disorder and functioning (26).

Some studies report that functional outcome in first-episode patients are typically less adverse than those of multiple-episode patients, and treatment is more effective if patients are not already chronically ill (27). In addition, functional impairment seems to increase with the number of previous episodes and longer illness duration (28–30). Such evidence is consistent with the staging model theory, which suggests a progression of bipolar disorder from prodromal (latent period) to more severe and refractory presentations (stage 4) as a consequence of the cumulative exposure to acute episodes, and specific treatments should be contemplated for each stage (31–33).

Hence, a better understanding of the functional outcome and clinical differences between first- and multiple-episode patients, at different points of the course of the illness, would permit more effective treatments for disability (27).

Aims of the study

The main aim of this study was to assess functional outcome in first-episode vs. multiple-episode patients with bipolar disorder in a 12-month follow-up study. Secondarily, we also examined clinical differences between both groups.

Material and methods

Patients

A multicenter study with long-term follow-up was conducted on patients with bipolar disorder enrolled prospectively in the Santiago Apóstol Hospital of Vitoria (22) and in the Bipolar Disorders Program of the Hospital Clinic of Barcelona (34–36) because of experiencing first or multiple episodes of bipolar disorder. First episode was defined as the first lifetime occurrence of a manic, depressive, or mixed episode. Multiple episodes were defined as the occurrence of at least two lifetime episodes. Both sites have specific 'First-episode Programs' and take care of acutely as well as chronically ill in- and out-patients. Multiple-episode patients were randomly selected from a pool of over 600 patients with bipolar disorder. All subjects met diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) (37) for bipolar disorder I, II, or not specified. Patients on psychological therapy were not included. All participants who provided informed consent ($N = 119$) were included in the study. Subjects with mental retardation or cerebral organic disorders were excluded. Ethical approval of the study was obtained by the Ethics Committees of the two hospitals.

Assessment

Diagnosis of bipolar disorder was determined at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (38) according to DSM-IV diagnostic criteria. These interviews were carried out independently by experienced clinicians. The data on interrater reliability obtained with these interviews in this study were satisfactory (kappa = 0.91 and kappa = 0.88 respectively).

The sociodemographic and clinical variables of patients recorded at baseline included gender, age,

marital status, educational level, employment status, living conditions, age at onset, bipolar subtypes, episode onset, hospitalizations, history of suicide attempts, alcohol and substance abuse, and axis I comorbidity. Pattern of medication prescribed was also collected consisting of a mood stabilizer (predominantly lithium or valproate), antipsychotics, antidepressants, and others.

Manic and depressive symptoms were evaluated with the Young Mania Rating Scale (YMRS) (39) and the Hamilton Depression Rating Scale (HDRS-21) (40) respectively. Symptomatic recovery was defined as a score of eight or less on the HDRS-21 and a score of five or less on YMRS. The Functioning Assessment Short Test (FAST) (41) was used to assess functional outcome of patients. The FAST has been validated in both multiple-episode (41, 42)) and first-episode patients (43).

All patients were evaluated with this protocol at baseline, at six months, and at one year, during follow-up.

Statistical analysis

SPSS for Windows, version 16.0, was used for the statistical analyses. Sociodemographic and clinical characteristics of patients were calculated with descriptive analysis. Differences between first-episode patients and multiple-episode patients were analyzed by Pearson's chi-square test for categorical variables and Student's *t*-test for continuous variables. Analysis of covariance (ANCOVA) was used to adjust for demographic (age) and mood symptoms (YMRS and HDRS) that were significantly different between groups.

Results

Baseline patient characteristics

A total of 119 patients with bipolar disorder were recruited for the 1-year follow-up outcome study, 60 of whom were on first mood episode. There were differences between the groups on the number or patients who completed the 1-year follow-up study (*multiple episodes:* 76.27% vs. *first episode:* 100%, $P < 0.001$). Patients with multiple episodes were significantly older than patients with first episode (46.73 ± 15.05 vs. 29.73 ± 10.34, $P < 0.001$) and had higher level of education (44.1% vs. 25%, $P = 0.023$). Moreover, a greater percentage of patients with first episode were single compared to patients with multiple episodes (71.7% vs. 43.9%, $P = 0.012$), and more of them lived with their parents (55% vs. 34.7%, $P = 0.019$). There were no differences regarding age at onset between patients with first episode (28.33 ± 10.30) and multiple episodes (29.83 ± 13.22) ($P = 0.501$). All subjects with first episode were in-patients compared to 54 (91.5%) of those with multiple episodes ($x^2 = 5.308$, $P = 0.027$). Axis I comorbidity was more prevalent in first-episode group compared to those with multiple episodes (41.7% vs. 34%, $P = 0.002$). First-episode patients had significantly higher baseline YMRS total scores (29.93 ± 12.16 vs. 13.07 ± 11.17, $P < 0.001$) and HDRS total scores (18.30 ± 7.82 vs. 12.57 ± 8.94, $P < 0.001$) compared to patients with multiple episodes. As expected, higher number of episodes was observed in patients with multiple episodes than in those with first episode (11.98 ± 8.58 vs. 1.30 ± 0.62, $t = 9.617$; $P < 0.001$). Other baseline sociodemographic and clinical characteristics are listed in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients with first or multiple episodes of bipolar disorder

	First episode (*n* = 60)		Multiple episode (*n* = 59)		Overall (*n* = 119)		First vs. multiple	
	N	%	*N*	%	*N*	%	χ^2	*P*
Demographic variables								
Sex (female)	24	40	32	54.2	56	47.1	2.42	0.120
Educational level								
College	15	25	26	44.1	41	34.5	0.029	0.035
Primary/high school	45	75	33	55.9	78	65.5		
Marital status								
Single	43	71.7	25	43.9	68	58.1	10.927	0.012
Married	14	23.3	22	38.6	36	30.8		
Separate	2	3.3	9	15.8	11	9.4		
Widow	1	1.7	1	1.8	2	1.7		
Employment status								
Active	51	85	15	28.3	66	58.4	45.882	<0.001
Unemployed	9	15	17	32.1	26	23		
Disability	0	0	15	28.3	15	13.3		
Retirement	0	0	6	11.3	6	5.3		
Living conditions								
Alone	2	3.3	5	10.2	7	6.4	9.997	0.019
Own family	16	26.7	24	49	40	36.7		
Parents	33	55	17	34.7	5	45.9		
Other	9	15	3	6.1	12	11		
Clinical variables								
Diagnosis								
Bipolar I	39	65	49	86	88	75.2	30.079	<0.001
Bipolar II	0	0	8	14	8	6.8		
Unspecified	21	35	0	0	21	17.9		
Episode (baseline)								
Depressive	2	3.3	27	45.8	29	24.4	56.211	<0.001
Hypomania/Mania	16	26.7	28	47.5	44	37		
Mixed	42	70	4	6.8	46	38.7		
Inpatient	60	100	54	91.5	114	95.8	5.308	0.027
History of suicide attempts	8	13.3	24	47.1	32	26.9	15.758	<0.001
Alcohol abuse	15	25.0	9	15.25	36	30.25	10.092	0.018
Cannabis abuse	23	38.3	5	8.47	10	8.4		

Table 2. Functional outcome

	6 months					12 months				
	First episode		Multiple episode			First episode		Multiple episode		
Outcome measure	M	SD	M	SD	*t* (*P*)	M	SD	M	SD	*t* (*P*)
Overall functioning	15.20	10.55	29.11	18.04	5.085 (<0.001)	11.26	10.94	26.91	13.96	6.436 (<0.001)
Autonomy	3.03	3.16	4.72	4.10	2.475 (0.015)	2.08	3.07	3.73	3.00	2.747 (0.007)
Occupational functioning	3.88	3.97	9.22	6.68	5.239 (<0.001)	3.46	4.66	9.40	6.57	5.408 (<0.001)
Cognitive functioning	3.10	3.05	5.68	4.29	3.732 (<0.001)	2.05	2.77	5.13	3.46	5.064 (<0.001)
Financial issues	1.01	1.53	1.22	1.85	0.646 (0.520)	0.71	1.36	1.20	1.47	1.736 (0.086)
Interpersonal relationships	2.81	3.07	5.48	4.06	3.970 (<0.001)	1.95	2.54	4.77	3.63	4.686 (<0.001)
Leisure time	1.35	1.49	2.77	1.65	4.840 (<0.001)	1.00	1.34	2.64	1.74	5.459 (<0.001)

M, mean; SD, standard deviation.

Functional outcome at 6- to 12-month assessments

Patients with first episode experienced better overall functioning than those with multiple episodes, which was evident at 6-month and 12-month follow-up. Specifically, they showed higher levels of autonomy, better work, and lower cognitive complaints compared with other group. Greater capacity to enjoy their relationships and leisure time was also seen in patients with first episode than those with multiple episodes (see Table 2). This pattern of functioning was observed either in 6-month or 12-month assessments.

Effects of age and affective symptoms at 6-month assessment

It has been reported that age and depressive symptoms may affect functioning in bipolar disorder (4, 44). To control for these effects, individual ANCOVAS were performed with age, HDRS, and YMRS scores as covariates. Thus, after adjusted analysis, not only group but also depressive symptoms were significantly associated with poor overall functioning ($F = 9.553$, df = 4, 102; $P < 0.001$). With regard to specific domains, group (first vs. multiple) and depressive symptoms were also related to occupational functioning ($F = 9.736$, df = 4, 102; $P < 0.001$), interpersonal relationships ($F = 6.041$, df = 4, 102; $P < 0.001$), and leisure time ($F = 8.399$, df = 4, 102; $P < 0.001$). Cognitive complaints were associated with group and age ($F = 5.127$, df = 4, 102; $P = 0.001$). The differences between both groups on the autonomy domain were lost after controlling for age and mood symptoms.

Effects of age and affective symptoms at 12-month assessment

Significant differences were observed on the autonomy ($F = 4.665$, df = 4, 103; $P < 0.002$) and occupational domains ($F = 8.611$, df = 4, 103; $P < 0.001$) between both groups even after controlling for potential confounders. However, other domains such as cognitive complaints ($F = 8.406$, df = 4, 103; $P < 0.001$), interpersonal relationships ($F = 7.711$, df = 4, 103; $P < 0.001$), leisure time ($F = 12.012$, df = 4, 103; $P < 0.001$), as well as overall functioning ($F = 14.145$, df = 4, 103; $P < 0.001$) were also associated with group and age. Either depressive or manic symptoms did not affect overall functioning or life-specific domains.

Symptomatic recovery

At 6-month assessment, similar rates of symptomatic recovery (defined by HDRS < 8 and YMRS < 5) were found between both groups (42.4% vs. and 40%, $P = 0.656$). However, a significantly greater percentage of patients in first-episode group had symptomatic recovery compared to those with multiple episodes at endpoint (62.7% vs. 44.9%, $P = 0.005$).

Table 3. Patterns of medication use

	First episode		Multiple episode		Overall		First vs. multiple	
	n	%	*n*	%	*N*	%	χ^2	*P*
Mood stabilizers								
No	34	56.7	0	0	34	28.57	35.440	<0.001
Lithium	19	31.7	31	77.5	50	42.01		
Valproate	3	5	6	15	9	7.56		
Others	4	6.7	3	7.5	7	5.88		
Antipsychotics								
No	19	31.7	13	22	32	26.89	4.538	0.103
Atypical	26	43.3	37	62.7	63	52.94		
Typical	15	25	9	15.3	24	20.16		
Antidepressants								
No	55	91.7	40	67.8	105	88.23	11.294	0.010
IRSS	4	6.7	11	18.6	15	12.60		
Tricyclic	0	0	3	5.1	0	0		
Other	1	1.7	5	8.5	6	5.04		
Benzodiazepines	30	50	38	64.4	68	57.14	2.521	0.080
Antiparkinsonian	21	35	5	8.5	26	21.84	12.969	0.002

Patterns of medication use

Significant differences were also observed between both groups regarding the number of medications. Patients with multiple episodes received higher number of medications than those with first episode at baseline (2.76 ± 0.60 vs. 2.12 ± 0.55, $P < 0.001$) and endpoint (1.83 ± 1.50 vs. 1.40 ± 0.69, $P = 0.048$) (see Table 3).

Discussion

Bipolar disorder is a highly recurrent condition, but the psychosocial impact of multiple episodes has rarely been the focus of outcome studies. The majority of such studies have analyzed first (12, 45)- or multiple-episode patients (42, 46) separately, and very few of them have distinguished functional recovery from syndromal remission (10, 47, 48). The present 1-year follow-up study compared outcome in patients with first vs. multiple episodes, showing a greater functional and symptomatic recovery in the former. In particular, patients with first episode showed a higher level of autonomy, better work performance, and greater capacity to enjoy their relationships and leisure time related to those with multiple episodes. However, after accounting for the effects of age and mood symptoms, we found that baseline depressive symptoms appear to have an important contribution to the functional impairment, particularly through the six-month period. Emerging data have also demonstrated a strong relationship between depressive symptoms and functional impairment in bipolar disorder patients with multiple episodes (6, 7, 9, 46). Moreover, a Canadian study in first-episode patients with bipolar disorder showed that depressive symptoms (even if subsyndromal), and the absence of remission, were the best predictors of functional impairment (49). Together with previous studies, our findings suggest that depressive symptoms, particularly in a subgroup of patients with multiple episodes, may significantly interfere with the individual's life, particularly, regarding the performance of interrelationships and work functioning, and this effect may persist for at least six months after an acute episode. Consequently, it is especially important to treat depressive symptoms in order to improve psychosocial functioning.

Consistent with previous studies (27, 48), we found significant baseline clinical differences between both groups, which probably have some impact on long-term outcome. For instance, patients with first episode were younger and received less complex treatment regimens than other group, which may be associated with less cognitive complaints and greater overall functioning. Our data are also consistent with the model of staging for bipolar disorder, suggesting that the number of episodes is an important contributor to the stage progression of the illness from less to more severe presentations and consequently poor outcome (31–33, 35). Therefore, early diagnosis and appropriate intervention may play a role in preventing the neuroprogressive course of bipolar illness (9, 50). With regard to neurobiological correlates, Strakowski et al. (51) showed that patients with multiple episodes experienced more abnormalities in brain circuits involved in mood regulation and cognition than those with first episode (51). Progressive changes in neurotrophins (BDNF) and cytokines were also observed from early to late stage of bipolar illness (12). Furthermore, neurocognitive studies have shown that repeated episodes predict cognitive function, suggesting that relapses play an important role on neuropsychological performance (52, 53) and consequently psychosocial functioning (24, 54). In terms of treatment response, Berk et al. (55) reviewed twelve controlled randomized clinical trials in bipolar disorder, showing that individuals with fewer episodes (1–5 episodes) were more likely to show a better treatment response compared to those with more episodes (55). Additionally, lithium treatment response seems to be greater in patients in the early phase of the disorder (56). Likewise, some psychological interventions are more effective in the early (less than 10 episodes) compared to late stages of bipolar illness (57–59). Finally, recurrence has been also associated with an increased risk of suicide (21). To sum up functional impairment may be a consequence of enduring neurotoxicity of the mood episodes and consequently neurostructural abnormalities, which is clearly more evident in those individuals in the later stages of bipolar disorder.

In conclusion, the present study showed that patients with first episode experienced greater functioning in multiple domains than those with multiple episodes. Baseline depressive symptoms may contribute to 6-month poor functioning, especially in a group of patients with multiple episodes. Furthermore, our findings are in accordance with the staging model theory showing that greater cognitive complaints and functional impairment may be a consequence of repeated mood episodes and, therefore, emphasizing the importance of early interventions. The therapeutic approach, therefore, should integrate pharmacological and psychosocial interventions, including aspects such as autonomy and social activity and, ultimately, functional recovery.

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Declaration of interest

Professor Eduard Vieta has served as consultant, advisor, or speaker for the following companies: Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Johnson and Johnson Janssen, Jazz, Lundbeck, Merck-Sharp and Dohme, Novartis, Organon, Otsuka, Pfizer Inc, Sanofi-Aventis, Servier, Takeda and UBC. Ana González-Pinto has received grant support, acted as consultant, or given presentations for the following pharmaceutical companies: Almirall (Barcelona, Spain), Astra-Zeneca, Bristol-Myers-Squibb, Otsuka, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Sanofi-Aventis, Lundbeck, Novartis, Organon, Schering-Plough, Spanish Ministry of Science and Innovation, Department of Health of the Basque Government, University of the Basque Country and Pfizer. The other authors report no conflicts of interest.

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