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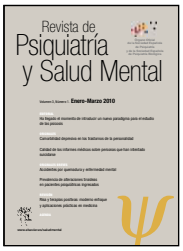

ORIGINAL ARTICLE

Diagnostic delay and differences by sex and clinical subtype in a cohort of outpatients with bipolar disorder

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KEYWORDS
Bipolar disorder;
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Abstract
Introduction: We describe the clinical and sociodemographic features at baseline of a cohort of bipolar patients included in a prospective study.
Methods: A total of 296 consecutive outpatients with bipolar disorder were recruited. Diagnosis relied on clinical judgment according to DSM-IV-TR criteria and the semi-structured MINI Interview. Retrospective data on the course of the disease and cross-sectional data on social adaptation (Social Adaptation Adjustment Self-Assessment Scale (SASS) and affective symptoms were collected. Affective symptomatology (euthymia, subsyndromal symptoms and episodes) was studied according to clinical criteria and the Hamilton Depression and Young rating scales. Differences between type I and II bipolar patients and between men and women were analyzed.
Results: The mean age was 48.8 years (95% CI 47.2-50.4); 56.8% were women and 43.2% were men. A total of 65.2% had a diagnosis of type I bipolar disorder and 23.3% of type II; 49.8% of the sample were euthymic, 32.7% had subsyndromal symptoms and 17.5% had had an affective episode. Diagnostic delay was 9.3 years (95% CI 8.2-10.3). In patients with type II bipolar disorder, the mean age (54.4 years; 95% CI 50.9-57.9 vs. 47.7 years; 95% CI 45.8-49.7, p=0.007), age at onset of illness (35.7 years; 95% CI 31.8-39.7 vs. 29.8 years; 95% CI 28-31.6, p=0.008) and age at diagnosis (47.7 years; 95% CI 44-51.3 vs. 37.9; 95% CI 35.9-39.8, p<0.0001) were higher than in patients with type I bipolar disorder. Manic polarity in the initial episode and psychotic episodes were more frequent in men, while depressive episodes and hypothyroidism were more frequent in women.
Conclusions: Our results confirm data published in our environment on sociodemographic and clinical variables but diagnostic delay in our study was longer. Compared with American samples, age at onset and at diagnosis were higher in our sample but comorbidity was much lower.

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PALABRAS CLAVE
Trastorno bipolar;
Características de la muestra;
Diferencias por sexos;
Comorbilidad;
Psicopatología asociada

Retraso diagnóstico y diferencias por sexo y subtipo clínico en una cohorte de pacientes ambulatorios con trastorno bipolar

Resumen
Introducción: Descripción de las características clínicas de una cohorte de pacientes bipolares al inicio de un seguimiento en un estudio prospectivo.
Metodología: Se incluyen 296 pacientes bipolares ambulatorios (criterios DSM-IV-TR y entrevista MINI). Se recogen datos retrospectivos del curso de la enfermedad y transversales de adaptación social (SASS) y de sintomatología afectiva (eutimia, síntomas subsindrómicos y episodios) según criterios clínicos y psicométricos con las escalas de HAM-D y de Young. Se estudian diferencias entre bipolares I y II y por sexos.
Resultados: La edad media es 48,8 años (IC95% 47,2-50,4), 56,8% son mujeres, 65,2% bipolares I y 23,3% bipolares II. 49,8% estaban eutímicos, 32,7% presentaba síntomas subsindrómicos y 17,5% sufría un episodio afectivo. El retraso diagnóstico es de 9,3 años (IC95% 8,2-10,3). La edad media en los bipolares II (54,4 IC95%50,9-57,9 vs 47,7 IC95% 45,8-49,7, p = 0,007), la de inicio de la enfermedad (35,7 IC95% 31,8-39,7 vs 29,8 IC95% 28-31,6 p = 0,008) y la de diagnóstico (47,7 IC95% 44-51,3 vs 37,9 IC95% 35,9-39,8, p < 0,0001) es más elevada que en los bipolares I. En los hombres es más frecuente iniciar la enfermedad con una fase maníaca y haber presentado episodios psicóticos mientras que las mujeres han tenido mayor número de episodios depresivos previos e hipotiroidismo.
Conclusiones: Nuestros resultados confirman los datos publicados en nuestro medio en cuanto a las características sociodemográficas y clínicas aunque en nuestro caso el retraso diagnóstico es mayor. En comparación con las muestras americanas, la edad de inicio y de diagnóstico es más tardía y la comorbilidad es mucho menor.

Introduction

Bipolar disorder (BD) affects over 2% of the general population[1] and is characterized by episodes of mania, hypomania, and depression. Despite advances in drug therapy, its course is characterized by frequent relapses, a tendency to become chronic, and significant functional impairment. Therefore, in a high percentage of cases, bipolar disorder is highly disabling, expensive, and associated with an unchangeable course and even a high risk of death, both from natural and non-natural causes.[2] For these reasons, the WHO reported it to be the 6th most common cause of medical disability in its report on the worldwide burden of the disease.[3]

In the last decade, several studies have been published[4-8] showing that the course of BD is not limited to the classic model affective, manic or depressive episodes in between which the patient has symptom-free periods. What really happens is that nearly half the time patients have symptoms which, unfortunately, are more commonly of the depressive type. The results of follow-up studies also show that most of the time patients suffer subsyndromal symptoms that, although less intense, cause significant functional impairment.[9]

There are hardly any evolutionary studies that look into the presence of affective episodes and subsyndromal symptoms in samples of the European population in general, and from Spain in particular, involving patients not originating from tertiary healthcare services. Therefore, in November 2004, our team began the follow-up of a cohort of bipolar outpatients under treatment with the aim of studying the presence of affective symptoms in a long-term follow-up.

This study describes the sociodemographic characteristics, clinical variables, social adaptation, and presence of affective symptoms of a cohort of bipolar outpatients at the time of inclusion in the follow-up study. Furthermore, the sample's clinical characteristics are analysed by their sex and clinical sub-type of bipolar disorder.

Method

Patient recruitment

The sample included patients who consecutively consulted two mental health centres and a specialist clinic at a general hospital, and agreed to participate in a prospective follow-up study into the naturalistic course of their disorder.[7,8] The patients were referred from primary care centres, hospital emergency departments, reference hospitals, and other specialist services. Data collection began in November 2004 and ended in November 2008.

Inclusion criteria:

- Met DSM-IV TR criteria for type I or type II bipolar mood disorder, unspecified polar disorder, bipolar-type schizoaffective disorder, or cyclothymic disorder. Confirmation of the clinical diagnosis of bipolar disorder by the MINI structured interview (MINI International Neuropsychiatric Interview), adapted to Spanish by L. Ferrando et al. (1998).
- Over 18 years of age.
- Gave informed consent.

Exclusion criteria:

- Mental retardation, brain damage or other organic disorders that presented cognitive deficit or deterioration.
- Pregnancy

The study was approved by the Ethics Committee at the La Princesa University Hospital of Madrid and the La Paz University Hospital of Madrid, and in all cases the patient's informed consent to participate in the study was obtained.

Data collection and measuring instruments

For the initial assessment, information was obtained from each patient and, where possible, from someone close to them who could provide useful information. The clinical diagnosis was performed via a non-structured interview, applying DSM-IV-TR criteria, and confirmed with the semi-structured MINI interview (Mini International Neuropsychiatric Interview[10]).

Clinical and sociodemographic variables were collected retrospectively (tables 1 and 2).

A psychopathological assessment was carried out at baseline to determine the presence of an affective pathology (affective episodes or subsyndromal symptoms) or euthymia. Clinical criteria were used for this as well as a psychometric assessment with the Hamilton Depression Rating Scale (HAM-D-21), the Young Mania Rating Scale, and the modified Global Clinical Impression Scale for bipolar disorder (CGI-BP-M).[11] We used the published recommendations and cut-off points established in other studies to establish cut-off points,[12-14] as well as recommendations on remission criteria.[15] We considered a score over 17 points on the HAM-D scale as an episode of depression, between 10 and 20 points on the Young scale as a hypomanic episode, and a score over 20 as a manic episode. Subsyndromal symptoms were considered to be scores from 7 to 17 on the HAM-D-21, and from 5 to 10 on the Young scale.

To study the predominant polarity, we followed the criteria defined by Colom et al[16] who consider the disorder predominantly manic when at least 2 thirds of the episodes meet the DSM-IV criteria for manic or hypomanic episodes, and predominantly depressive when at least 2 thirds of the episodes fulfil DSM-IV criteria for major depressive episodes or the DSM-IV research criteria for episodes of minor depression.

The inter-rater reliability in the administration of the scales was measured using Cohen's Kappa index and the SPSS 12.0 statistics software. The results were 0.826 (95% CI, 0.460-0.986) for the Hamilton scale, and 0.874 (95% CI, 0.552-0.990) for the Young scale. The overall Kappa index (Epidat 3.1 statistics software)[17] for the CGI-BP-M depression was 0.67 (95% CI: 0.32-1.01), 0.90 for the CGI-BP-M mania, and 0.78 for the overall CGI-BP-M.

Social functioning was assessed using the validated Spanish version[19] of the Social Adaptation Self-Evaluation Scale (SASS)[18] while the patient was not in an affective episode.

Data was also collected about current or prior consumption of toxic substances, patterns of clinical course (seasonal, rapid cycles), predominant polarity, comorbidity, body mass index (BMI), Global Activity Evaluation Scale (GAES), and current and previous treatment.

Statistical methods

Mean, standard deviation, median, and range were calculated with their respective confidence intervals for the quantitative variables, and percentages and confidence intervals were calculated for the qualitative variables from the patients' sociodemographic and clinical data. The groups were compared using a one way ANOVA, with the Bonferroni or Games-Howell adjustment for multiple comparisons of the quantitative variables, or with the student T test for the independent variables. The Chi-square test was used to compare differences in the quantitative variables between the groups, and z tests when more than 2 groups were compared. The level of significance was set at 0.05. The statistical analysis was performed with the SPSS 14.0 software.

Results

A total of 302 patients were recruited, 6 of whom were later excluded; 3 patients due to pregnancy (2 at the time of the baseline assessment and another during follow-up), 2 patients with moderate to severe comorbid Alzheimer's disease, and one patient due to a change of diagnosis. The final sample was composed of 296 patients with a mean age of 48.8 years (CI 95%, 47.2-50.4). Of these, 56.8% (168) were women and 43.2% (128) were men. The average duration of the disease since diagnosis was 8.7 years (95% CI, 7.7-9.7).

Sociodemographic characteristics (table 1)

In the study, 41.6% of the patients were married, 40% had a higher education, 49.8% had a qualified job, and 42.4% were actively employed at the time of the assessment. Over half of the sample lived with their own family (53.6%), while 22% lived with their parents. Only 2 patients, fewer than 1%, were living in institutions. Table 1 shows the sociodemographic data compared with those from other prospective studies.

Clinical characteristics (table 2)

Two-thirds of the patients had type I bipolar disorder (65.2%), 23.3% type II bipolar disorder, 5.1% unspecified

Table 1 Comparison of data with other cohorts of bipolar patients

	De Dios, Ezquiaga, García López et al N=296	Montes et al N=115	EMBLEM N=312	EPIDEP N=368	STEP-BD N=1000	SFBN N=261	TMAP N=409	Collab Dep Study N=146	Paykel et al N=204	Kessing L N=1719
Sex (%)										
Women	56.8	59.6	55	54.2	58.6	55.6	69.4	55.5	65	54.21
Men	43.2	40.4	45	45.8	41.4	44.4	30.6	44.5	35	45.7
Mean age	48.8	49.2	41.3	44.3	41.0	43.1	40.3	39.2	42.0	49.4
SD	14.3	14.6	13.39	13	12.6		10.6	13.7	11.0	
Marital status (%)										
Married	41.6	43.5	38	46.5	36.2	43.3	25.6	43.2		
Separated	14.8	12.2		17.4	23.5	24.5	42.3	24.0		
Single	40.2	37.4		32.9	35.2	30.7	30.9	32.9		
Widow/er	3.4	7.0		3.3	1.6	1.5	3.5			
Educational level (%)										
Primary	29.8	29.2	37	50.5	3.9	2.0	4.0	60.3		
Secundary	30.4	37.2	41	30.2	13.8	5.4	81.1			
University	39.9	33.6	20	19.3	82.3	92.6				
Occupational status (%)										
Employed	42.4	40.0		40.7	49.1	52.5	25.9			
Unemployed	11.2	8.7		13.3	22	6.5	12.0			
Disabled	18	14.8		27.1	15.3	21.1	74.1			

EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication project) Spanish sample (Montoya et al., 2007).
EPIDEP (Epidemiología del Trastorno Bipolar en población Española) Vieta et al., Poster presented at the XIII National Congress of Psychiatry, Madrid 2009.
STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder, Kogan et al., 2004).
SFBN (Stanley Foundation Bipolar Network, Suppes et al., 2001).
TMAP (Texas Medication Algorithm Project, Rush et al., 2003).
Collab. Dep Study (Collaborative Depression Study, Judd et al., 2002).

bipolar disorder, 4.4% schizoaffective disorder, and 2% cyclothymic disorder. The sample had high levels of comorbid disorders on all axes (32% on axis I, 23.3% on axis II, and 47.6% on axis III). Endocrine problems were the most common medical pathology. Over two-thirds of the patients were overweight or obese (68%), with a mean BMI of 27.40 (95%, CI, 26.8-28). Furthermore, 20.6% suffered from hypothyroidism.

From the onset of the first symptoms of the disease at 31 years of age (SD 13.8) until diagnosis (40.2 years, SD 15.5), 9.3 years elapsed (SD 9.2). Also of note is the 13.2-month delay between the diagnosis of bipolar disorder and the onset of treatment with mood stabilizers.

The mean number of episodes since the onset of the disease was 12.7 (SD 10.8), of which 3.14 were manic episodes, 5.2 hypomanic, 4.9 major depressive episodes, and 2.1 were mixed. A depressive episode was the most typical initial episode in 64.9% of patients, compared with 23% who began the disease with a manic phase, and 6.8% with a hypomanic episode. Forty-six percent of patients had a defined predominant polarity. This was main in 24% of the patients and depressive in 22%.

Over two-thirds of the sample (69.1%) had been hospitalized at some time, with a mean of 4 hospital admissions and a mean age for the first admission of 36.1 years (SD 14.3). A history of psychotic symptoms was observed in 53.9% of the patients and nearly a quarter (24.1%) had attempted suicide at some time.

A rapid cycle pattern in the last year was seen in 2.7% of the cases, and 13.6% had a seasonal pattern.

Over half (56.8%) of the sample had a family history of psychiatric disease, 48.1% of these were mood disorders.

Unlike in other studies, substance abuse was not that common in our sample; at the time of the initial visit only 7.2% of the patients were taking drugs, half of them cannabis. Furthermore, 8.9% of the patients met the criteria for alcohol abuse or dependence, and 47.5% were smokers.

Until their inclusion in the studies, the patients had received an average of 6.5 drugs (median 6), the most common being mood stabilizers (89%), and more specifically lithium (64.8%).

Global functioning (GAES scale)

A score ≥70 was obtained by 62.8% of the patients on the GAES. That is, they only had mild symptoms and good functioning. The mean score was 74.6 (95% CI, 72.8-76.4).

Table 2 Clinical characteristics of the sample

	Mean (95%CI) or n (%)
Diagnosis	
Type I Bipolar	193 (65.2%)
Type II Bipolar	69 (23.3%)
Unspecified bipolar	15 (5.1%)
Schizoaffective	13 (4.4%)
Cyclothymic	6 (2.0%)
Comorbidity (Axis I)	94 (31.8%)
Comorbidity (Axis II)	69 (23.3%)
Comorbidity (Axis III)	136 (47.6%)
Psychosocial Stress (Axis IV)	
None	177 (62.8%)
Problems with primary support group	47 (16.7%)
Problems related to the social environment	3 (1.1%)
Occupational problems	16 (5.7%)
Economic problems	11 (3.9%)
Problems related to dealings with the legal system or crime	1 (0.4%)
Other psychosocial and environmental problems	27 (9.6%)
Age of onset of affective pathology	31.1 (95% CI, 29.5-32.7)
Age of diagnosis of bipolar disorder	40.2 (95% CI, 38.6-41.9)
Disease evolution time (weeks)	18 (95% CI, 16.7-19.2)
Time until diagnosis (years)	9.3 (95% CI, 8.2-10.3)
Time between onset of pathology and starting treatment (years)	2.3 (95% CI, 1.7-3)
Number of previous episodes	
Total	12.7 (95% CI, 11.5-13.9)
Mania	3.1 (95% CI, 2.7-3.6)
Hypomania	5.2 (95% CI, 5.2-4.6)
Major depression	4.9 (95% CI, 4.9-4.3)
Minor depression	5.4 (95% CI, 4.4-6.5)
Mixed	2.1 (95% CI, 1.6-2.6)
Type of previous episodes	
Mania	196 (66.2%)
Hypomania	210 (70.9%)
Major depression	242 (81.8%)
Minor depression	131 (44.3%)
Mixed	69 (23.3%)
Predominant polarity	
Undifferentiated	160 (54.1%)
Manic	71 (24%)
Depressive	65 (22%)
Patients with episodes in the last year	
Mania	68 (23%)
Hypomania	97 (32.8%)
Major depression.	102 (34.5%)
Minor depression	57 (19.3%)
Mixed	28 (9.5%)
Any type	221 (74.7%)
Rapid cycling in the last year	8 (2,7%)
Number of previous admissions	4 (95% CI, 3.4-4.6)
Presence of previous psychotic symptoms	158 (53.9%)
History of suicide attempts	70 (24.1%)
Family history of psychiatric disease	
Any type	166 (56.8%)
Affective	139 (48.1%)
Suicide	37 (13.8%)

Social adaptation

The mean score on the social adaptation scale (SASS) was 38.9 (95% CI, 37.9-39.9), on the limit of what is considered normal social adaptation.

Psychopathological state in baseline assessment (fig. 1)

In the baseline assessment, 49.8% of the patients were in a euthymic state, 32.7% had subsyndromal symptoms, and 17.5% were in an episode. Depressive-type symptoms were the most common, 20.2% having subsyndromal symptoms, and 9.8% an episode of major depression. Subsyndromal symptoms of hypomania (7.3%), hypomanic symptoms (5.6%), and frank mania (1.4%) were less common. Furthermore, 5.2% had mixed subsyndromal symptoms, and 0.7% fulfilled the criteria for a mixed episode.

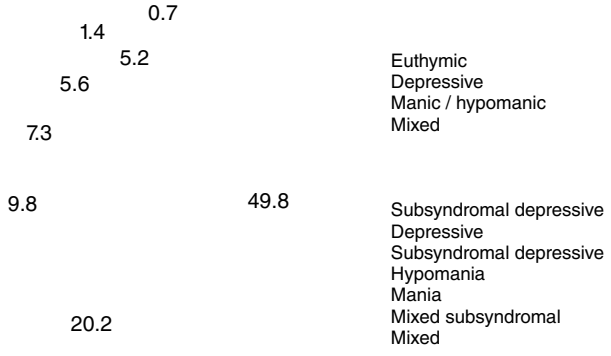

Figura 1 Affective state on baseline visit

The mean score on the HAM-D-21 was 6.9 points (95% CI, 6.1-7.7), 2.8 on the Young scale (95% CI, 2.3-3.3) and 3.4 on the overall CGI-BP-M (95% CI, 3.3-3.6).

Clinical differences between diagnostic subtypes (table 3)

The mean age of the type II bipolar patients (54.4 year, SD 14.6) was higher than that of type II patients (47.7 years, SD 14; *P*<.007), and than that of the schizoaffective patients (38.3 years, SD 6.8; P=.001). Patients with type II bipolar disorder were older than type I patients both at the onset of the first affective symptoms (35.7 years, SD 16.4) vs (29.7 years, SD 12.5) (*P*=.008), and when bipolar disease was diagnosed (mean: 47.6 years, SD 15.2) vs (37.8, SD 13.5) (*P*<.0001). Furthermore, there was a longer delay in the diagnosis of the disease in type II bipolar patients (12.1 years, SD 9.7) compared with type I patients (8.2 years, SD 8.9; *P*=.023), and also in the onset of treatment (3.4 years, SD 6.6 vs 1.9 years, SD 5.1; *P*=.024).

There were no differences in the total number of previous episodes between type I and type II patients, but type II patients did have a higher proportion of hypomanic (*P*=.005), major depressive (*P*=.005), and minor depressive (*P*=.009) episodes. There were also significant differences in predominant polarities; as expected, manic polarity was more prevalent among type I bipolar patients (*P*<.05), while depressive polarity was more common among type II bipolar patients (*P*<.05).

The percentage of patients requiring hospitalization was higher among type I bipolar patients (86.3%) and schizoaffective patients (100%) than among type II bipolar patients (30.9%; P<.0001). This is probably related to the higher proportion of type I patients with a history of psychotic symptoms (68.9% vs 15.9%) and of manic phases.

Table 3 Clinical differences between type i and type ii bipolar disorder

	Type I bipolar Mean (95%CI) or No. (%)	Type II bipolar Mean (95%CI) or No. (%)	*P*
Age	47.7 (45.8-49.7)	54.4 (50.9-57.9)	0.007
Age of onset of first affective symptoms	29.8 (28-31.6)	35.7 (31.8-39.7)	0.008
Age at diagnosis of bipolar disorder	37.9 (35.9-39.8)	47.7 (44-51.3)	<.0001
Delay in diagnosis (years)	8.2 (6.9-9.5)	12.1 (9.8-14.5)	0.023
Time between onset of pathology and starting treatment (years)	1.9 (1.2-2.7)	3.5 (1.9-5)	0.024
First affective episode with depression	100 (51.8%)	67 (97.1%)	<.05
Percentage of patients with previous admissions	164 (86.3%)	21 (30.9%)	<0.0001
Age when first admitted to hospital	34.9 (32.9-37.1)	47.9 (41-54.9)	<.0001
Previous psychotic symptoms	131 (68.9%)	11 (15.9%)	<.05
Family history of mood disorders	80 (42.6%)	43 (64.2%)	0.032
Affective state on baseline visit			
Euthymic	98 (52.7%)	34 (50.7%)	NS
Depressive symptoms	35 (18.8%)	16 (23.9%)	NS
Episode of depression	12 (6.5%)	9 (13.4%)	NS
Predominant polarity			
Manic/hypomanic	63 (32.6%)	2 (2.8%)	<.05
Depressive	29 (15%)	29 (44.6%)	<.05

Type I bipolar patients were first hospitalized at a younger mean age (34.9 years, SD 13.5) than type II patients (47.9 years, SD 16; $P<.0001$), although schizoaffective patients were admitted at even younger age (26.8 years, SD 6.8; $P=.0001$).

A family history of psychiatric disorders, in particular mood disorders, is more common in type II bipolar patients (64.2%) than in type I bipolar patients (42.6%) ($P=.03$).

There were no significant differences in the baseline psychopathological assessment according to the type of bipolar disorder in the percentage of patients in a euthymic state or with manic, hypomanic or depressive symptoms.

Neither were there differences in the level of functioning measured by the GAES between the different subtypes.

Differences by sex (table 4)

No significant differences were found in the sociodemographic variables (mean age, marital status, type of residence, educational level, occupational qualification, and working status) between men and women, except that more men (60.3%) had a qualified job than women (41.8%; $P<.05$).

No significant differences were found between men and women in the prevalence of type I and II bipolar disorder. However, women suffered more depressive episodes during the course of the disease than men (5.5, SD 5.7 vs 4.1, SD 3.9; $P=.02$), while manic episodes were more common among men (29.7% vs 17.9%; $P=.017$). Along the same lines, we observed that predominantly manic polarity was more common in men than in women ($P<.05$).

As expected, height and weight were significantly higher in men, but the male patients also had a higher BMI (mean MBI 28.19, SD 4.09 in men compared with 26.86, SD 4.9 in women; $P=.02$).

Hypothyroidism was significantly more common in women than in men (28% vs 10.9%; $P<.0001$).

There were no significant differences regarding the age at which men and women were first hospitalized, or the total number of admissions, or the number of admissions due to manic, depressive or mixed episodes.

Nearly a third (28.9%) of men began with a manic phase compared with 18.5% of women (P<.05), and 29.7% of men and 17.9% of women had had a manic phase during the previous year.

Psychotic symptoms were more common in men in the patients' psychiatric history (63% vs 47%; $P=.006$), but no differences existed, however, in the history of suicide attempts.

Both abuse and dependence on alcohol (P<.0001), and on other drugs ($P=.025$) was more frequent in men, both at the time of the assessment and in the past.

There were no significant differences between men and women in the level of functioning measured by the GAES, or in social adaptation, according to the scores on the SASS.

Significant differences did exist in the Hamilton scale scores. These scores were higher in women (8, SD 7.5 vs 5.6, SD 5.6; $P=.003$).

Discussion

We described the sociodemographic data and clinical characteristics of a sample of 296 patients from two mental health centres and a speciality clinic at a general hospital

Table 4 Differences by Sex

	Men	Women	*P*
	Mean (95% CI) or No. (%)	Mean (95% CI) or No. (%)	
BMI	28.2 (27.4-29)	26.9 (26.1-27.7)	0.02
Qualified job	76 (60.3%)	69 (41.8%)	<.05
Drug consumption			
Present	14 (11%)	7 (4.2%)	0.025
Past	36 (28.3%)	19 (11.4%)	0.0001
Alcohol Consumption			
Present	20 (15.9%)	6 (3.6%)	<.0001
Past	48 (47.5%)	12 (12.4%)	<.0001
Hypothyroidism	14 (10.9%)	47 (28%)	<.0001
History of psychotic symptoms	80 (63%)	78 (47%)	0.006
Manic initial phase	37 (28.9%)	31 (18.5%)	<.05
Predominant polarity			
Manic	38 (29.7%)	33 (19.6%)	<.05
Depressive	25 (19.5%)	40 (23.8%)	NS
Number of previous episodes			
Major depression.	4.1 (3.3-4.9)	5.5 (4.6-6.5)	0.024
Manic episodes in last year	38 (29.7%)	30 (17.9%)	0.017
HAM-D-21 score	5.6 (4.6-6.6)	8 (6.8-9.1)	0.003
Episode of depression at baseline assessment	7 (5.6%)	21 (13%)	<.05

that deal with bipolar outpatients referred by primary care doctors, hospital casualty departments, and the hospital units of the healthcare areas covered by these centres. This is an important difference between our cohort and those in other studies that come from tertiary centres and research centres.

However, the sociodemographic characteristics of our sample were similar to those of other clinical samples from America[4,20-22] or Europe[23,24] (table 1). When compared with other data published in Spain, the differences were even smaller.[25-27] In all the study populations there was a predominance of women, despite epidemiological data for the general population showing both sexes are affected to a similar extent, at least in type I bipolar disorder patients.[28] This could be interpreted that many men are not correctly diagnosed, or they do not go to psychiatric services for treatment. Also of note is the high percentage of patients with a higher education (40%), but in other samples, such as the STEP-BD[20] or the Stanley Foundation Bipolar Network,[21] the percentage is even higher (82% and 92%, respectively).

Two-thirds of our patients were diagnosed with type I bipolar disorder (65.2%), although the predominance of this disorder is even higher in other samples.[20,21,26,29] Only the study by Montes et al[26] has a similar percentage to ours. The inclusion of different clinical subtypes of bipolar disorder, such as schizoaffective disorder, unspecified bipolar disorder, and cyclothymic disorder, which were not included in other samples (e.g. EPIDEP study), may explain the lower percentage of type I bipolar disorder patients in our sample.

It must be highlighted that such a long time elapsed between the onset of the first symptoms and the diagnosis of bipolar disorder (9.3 years), longer than that found in other studies.[26,30] This may be because there was a higher proportion of patients with type II bipolar disorder in our sample. Delays in diagnosis have been observed in this substype. This has been associated with a worse response to treatment,[31] and highlights the difficulties that still exist in making a correct diagnosis in the early phases of the disease. The use of screening tools for hypomanic phases in patients with depression, such as the HCL-32 or the MDQ, which are easy to use and give satisfactory predictive results, could be of great clinical use[32,33] to reduce this long delay in diagnosis.

Although there were high rates of comorbidity in our sample, these rates referred to prevalence over the whole life (a third had another diagnosis on axis I and nearly 20% on axis II), our figures are much lower than those published in American populations.[1] Recent data from Spanish samples, although these referred to comorbidity at a specific time during the transversal assessment, are similar to the figures in our study.[34] The EPIDEP study[29] showed a comorbidity of psychiatric diseases of 27.6%. This is also true of the data for drug consumption. We found a comorbidity of 16% in our study, which is similar to the 14.7% in the EPIDEP study, and even higher than the figures in the extensive population sample in Kessing's study,[24] which studied all the population diagnosed with bipolar disorder in Denmark. However, our figures are much lower than those found in American samples.[1]

Again, it is worth highlighting the high prevalence of general pathologies in bipolar patients, in particular problems related to overweight. The mean BMI of 27.4 in our study is practically identical to that published recently by García Portilla et al.[35] In our sample, as in other studies,[36] overweight is more prevalent in men, unlike in the general population and in other psychiatric pathologies in which overweight is usually more common among women.[37]

The mean age at which the first symptoms appear (31 years) and at which the definitive diagnosis is made (40.2 years), confirm again that in European populations[23,24,26] the onset and diagnosis of the disease occurs later than in American ones.[38] Post's group[38] suggest that, while not being able to rule out bias due to recruitment, collection of information (usually retrospective), or availability of resources, these differences could be due to the higher incidence of a family history of bipolar disorder in American samples, and therefore, to a greater genetic burden. They could also be caused by the presence of more accumulated psychosocial risks such as a history of child abuse, or increased drug consumption.

Some data about the course of the disease, such as the high number of previous admissions (mean 12.7) and the evolution time of the disease (18 years), are also very similar to those reported in other studies (table 5). However, it is worth pointing out that a third of the patients in our study had not been previously hospitalized due to a psychiatric disorder, either because they suffered less severe forms of the disease or because they were diagnosed and treated before suffering severe complications.

Furthermore, the sample had acceptable levels of social adaptation and good global functioning. However, in the psychometric assessment, half of the sample was not in a euthymic state. This was a similar figure (48%) to that in the STEP-BD study[20] and in the sample from the Autonomous Community of Madrid (53%),[26] while in Paykel et al's sample there was a higher percentage of euthymic patients (65%).[23]

Comparing patients with type I or type II bipolar disorder, our results confirm those obtained from a recently published data cluster;[39] type I bipolar patients are younger when recruited to a study, begin to suffer from the disease earlier, and are diagnosed and treated sooner. Also, type I bipolar patients were hospitalized more often and suffered more previous psychotic symptoms, probably connected with the higher number of previous episodes of mania.

Depression is most commonly the first phase of the disease in all the subtypes of bipolar disorder. This is particularly true of type II bipolar disorder, as reported by other authors.[40]

Among the few differences observed between sexes was that women had less qualified jobs, clearly a case of cultural conditioning. Also, men started the disorder more frequently with an episode of mania and the women suffered more episodes of depression throughout the course of the disease, although no differences were found in the history of suicide attempts. As in other studies, we observed a higher prevalence of hypothyroidism among women and higher levels of substance abuse among men.

Table 5 Comparison of clinical data with other cohorts of bipolar patients

	De Dios, Ezquiaga, García López et al N=296	Montes et al N=115	EPIDEP N=368	STEP-BD N=1000	SFBN N=261
Type II Bipolar	65.2%	66.1%	71.3%	71%	81%
Type II Bipolar	23.3%	28.7%	28.7%	23.9%	16%
Time since onset	18 (11.5)	21.1 (12.4)		23.6	20.2
Delay in diagnosis (years)	9.3 (9.2)	7.6 (8.8)	5.8 (7.6)		
Polarity of first episode	Mania 23%	Mania 28.1%	Mania 25.5%	Mania or hypomania 26.1%	Mania or hypomania 19%
Depression 65%	Hypomania 2.6% Depression 66.7% Mixed 2.6%	Depression 62% Mixed 2.7%	Depression 52% Mixed 21%	Depression 52% Mixed 28%	
Total No. of episodes	12.7 (10.8)	16.7 (23.6)	7.25		
No. of admissions	3.99	3.1 (4.3)			
Current rapid cycling	2.7%	12.2%	9%	20%	18%
History of suicide attempts	24.1%	0.7 (1.7)		35.7%	30%
Family history of mood disorders	48.1%	54%			

Values presented as Means (95% CI) or No. (%).
EPIDEP (Epidemiología del Trastorno Bipolar en población Española) Vieta et al., Poster presented at the XIII National Congress of Psychiatry, Madrid 2009.
STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder, Kogan et al., 2004).
SFBN (Stanley Foundation Bipolar Network, Suppes et al., 2001).

The retrospective collection of data about the disease's evolution is a limitation of our study, which is a practically inevitable bias in clinical samples. We have tried to minimise this by also collecting clinical information from relatives and people close to the patients.

To sum up, we present here the baseline data from an extensive sample of patients with bipolar disorder that began a prospective follow-up in 2004. The patients were recruited from healthcare units specialized in dealing with bipolar disorder. The differences in clinical profile and outcome are shown in relation to other samples in the literature. Emphasis must be given to the long delay in making a diagnosis of bipolar disorder from the onset of the disease, in particular among patients with type II bipolar disorder, and also the high frequency of subsyndromal affective symptoms, especially depressive ones, in patients who were not in an episode. The clinical differences and difference in the course of the disorder are shown according to clinical subtypes and sex.

Conflict of interests

A grant from AstraZeneca Pharmaceuticals was used to perform the statistical analysis.

Dr Aurelio García has received funding and given conferences for AstraZeneca, Lilly, and Böehringer-Ingelheim.

Dr Elena Ezquiaga has received funding and given conferences for AstraZeneca, Lundbeck, Sanofi Aventis, and Böehringer-Ingelheim.

Dr Consuelo de Dios has received funding, has done consultancy work, and given conferences for AstraZeneca, Bristol-Myers-Otsuka, Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Lundbeck, Pfizer, Sanofi Aventis, Servier, Wyeth, and Böehringer-Ingelheim.

Dr Agud has given conferences for the following laboratories: Bristol-Myers-Otsuka, Eli Lilly, and GSK.

Dr Begoña Soler affirms that she has no conflict of interests.

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