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ARTICLE

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Patterns of pharmacological maintenance treatment in a community mental health services bipolar disorder cohort study (SIN-DEPRES)

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Abstract

Maintenance therapy in bipolar disorder (BD) is usually required to prevent relapses and improve residual symptoms. Therefore, in this study, we describe patterns of pharmacological maintenance treatment and identify associated clinical features. This prospective multicentre epidemiological study recruited a cohort of 739 consecutive out-patients with clinically stable BD. Clinical stability was assessed at baseline with the Clinical Global Impression scale for BD and depressive symptoms with the Hamilton Depression Rating Scale. Psychotropic medications were classified and analysed according to their mechanism as well as use. Logistic regression models were used to examine the associations between pharmacological strategies and clinical features. Longer time since last episode [odds ratio (OR) 1.002, $p<0.0001$] and family history of psychiatric disorders (OR 1.911, $p=0.028$) were associated with lithium in monotherapy; manic polarity of the most recent episode (OR 3.300, $p=0.006$) and longer duration of clinical stability (OR 1.009, $p=0.034$) with antipsychotic in monotherapy; depressive polarity of the most recent episode (OR 2.567, $p=0.003$) and bipolar II disorder diagnosis (OR 2.278, $p=0.008$) with antidepressant combination; no ongoing psychiatric co-morbidity (OR 0.230, $p=0.004$) with lithium and anticonvulsant; manic polarity of the most recent episode (OR 3.774, $p<0.0001$) with lithium and antipsychotic; manic polarity of the most recent episode (OR 2.907, $p=0.028$) with lithium, anticonvulsant and antipsychotic. The pharmacological patterns followed published recommendations, except for the excessive use of antidepressants. This study reveals clinical factors closely related to prescription patterns.

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Key words: Bipolar disorder, community mental health services, cross-sectional studies, drug therapy.

Introduction

Bipolar disorder (BD) is a major mental health issue associated with considerable morbidity and mortality (Hirschfeld & Vornik, 2005). It is characterized by recurrent episodes of mania, hypomania, depression and mixed states separated by periods of relative euthymia. Treatments that can stabilize the acute mood swings in BD are available as is maintenance treatment. Since BD is a recurrent illness, a long-term prophylactic treatment is usually recommended (Suppes *et al.* 1991) and needed to uphold the initial therapeutic success. Maintenance therapy is expected to prevent relapses and reduce threshold symptoms,

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risk of suicide, cycle frequency and mood instability (APA, 2002). However, psychiatrists do not only assess the therapeutic effect but also the tolerability since it may be a long-term or even lifelong therapy (Vieta & Rosa, 2007).

Maintenance therapy is usually required in order to improve functioning and maintain quality of life since functional impairment has been related to residual symptoms (Joffe *et al.* 2004; MacQueen *et al.* 2000; Rosa *et al.* 2009; Wolf & Müller-Oerlinghausen, 2002). Patients with subclinical depressive symptoms present three to six times more functional impairment in various domains, such as work, housework and relationships with relatives and friends, than those who do not have these symptoms (Bonnín *et al.* 2012; Rosa *et al.* 2011). Therefore, the importance of identifying and appropriately treating these symptoms is widely acknowledged and thus patients can obtain complete disease remission and thereby improve their clinical outcomes in both the medium and long term (Perlis *et al.* 2006).

Several guidelines are available for the treatment of BD, covering both management of acute mood episodes and long-term prophylaxis (APA, 2002; Frye *et al.* 2011; Goodwin, 2009; Grunze *et al.* 2010; National Collaborative Centre for Mental Health, 2006; Suppes *et al.* 2005; Yatham *et al.* 2009). Although continuous efforts have been made to improve the management of this disease (Murru *et al.* 2011; Popovic *et al.* 2011), it is important to describe the current pharmacological strategies in clinical practice since BD may be one of the areas with a wide gap between evidence-based treatment as recommended by the guidelines and the actual hands-on clinical approach (Fountoulakis *et al.* 2005; Vieta & Rosa, 2007). According to the WHO, usual clinical practice should be assessed by means of drug utilization studies, which include an analysis of the prescription and use of medicinal products in the community with the final objective of defining optimal therapeutic practice (WHO Experts Committee, 1977).

The relevance of subclinical symptoms in long-term evolution led us to conduct a study in a large sample of clinically stable BD patients who attended a community health services setting. The main objectives were to obtain a cross-sectional estimation of the presence of subclinical depressive symptoms as reported elsewhere (Vieta *et al.* 2010*a*) and to describe maintenance drug utilization patterns, as reported herein. Scarce studies have focused on prescription in community health services. Moreover, most have centred on treatment patterns during acute phases of BD (Bellantuono *et al.* 2007; Montoya *et al.* 2010) or studies of mixed samples (Baldessarini *et al.* 2007; Ghaemi *et al.* 2006). Since clinical trials are not suitable for understanding treatment patterns, our objective with this naturalistic study was to explore the pharmacological patterns with relevant clinical features of BD.

Method

This was a prospective 16-week epidemiological study of a cohort of consecutive out-patients with clinically stable BD. The project was called SIN-DEPRES and was conducted at 88 community-based mental health services and private clinics across several geographical regions within Spain from April 2006 to March 2007. The sites involved were selected to make them representative of prescription patterns across Spain at the time of the survey by selecting eight consecutive patients from each centre and including a certain number of centres according to the population of the region. Fifteen centres were private psychiatric outpatient clinics and the rest community-based mental health centres. To really focus on maintenance treatment, acutely ill patients were excluded. Further details on the methodology are available elsewhere (Vieta *et al.* 2010*a*, *b*).

Subjects

The inclusion criteria for patients in this study were: aged $\geqslant$18 yr; well-established diagnosis of BD according to Diagnostic and Statistical manual of Mental Disorders criteria (DSM-IV); clinical stability for at least the previous month; presence of at least one acute affective episode during the 5 yr prior to inclusion in the study; given informed consent. Clinical stability was defined as a score of 'normal' or 'minimal' on both the depression and mania items of the Modified Clinical Global Impressions Scale for bipolar disorder (CGI-BP-M; Spearing *et al.* 1997; Vieta *et al.* 2002). Patients were excluded if no reliable information was available at the centre, they presented an acute affective episode at inclusion or suffered from another serious psychiatric condition, drug addiction, disorders of the central nervous system, organic brain disease, head trauma, dementia or an uncontrolled serious medical condition that could account for secondary depression (e.g. hypothyroidism). Patients who had suffered a single acute episode of BD and those participating in clinical trials were excluded.

The study included a sample of 761 BD I and II patients, 739 of whom were included in the final analysis. Those excluded ($n=22$) failed to meet the stability criteria, according to CGI-BP-M, did not

present with acute episodes within the last 5 yr or suffered from co-morbid medical conditions, such as hypothyroidism. In total, 733 of them were under treatment and were assessed in the study.

The study was approved by the Independent Ethics Committee of one of the participating centres, Hospital Clinic de Barcelona. All participants were informed about the study procedures and provided their written informed consent prior to inclusion.

Procedure

Data were obtained from the patients by means of a clinical interview and a psychiatric examination. The interview obtained information about socio-demographic and clinical data, including history of psychiatric disorders in first-degree relatives, history of treatments received and the degree of compliance and satisfaction with the treatment.

In order to determine clinical stability at baseline, all patients were assessed with the CGI-BP-M, taking into consideration the last month period (Spearing *et al.* 1997; Vieta *et al.* 2002). The 17-item Hamilton Depression Rating Scale (HAMD-17; Bobes *et al.* 2003; Maier *et al.* 1988) was also administered to evaluate the presence and severity of depressive symptoms at enrolment. In this context 'mild depression' at baseline was defined as a total score between 7 and 17 on the HAMD-17. Depressive symptoms were likewise evaluated at enrolment and end of study, using the Montgomery–Asberg Depression Rating Scale (Lobo *et al.* 2002; Montgomery & Asberg, 1979).

The recorded medication included all treatments being followed by the patient, including all drugs at prescribed daily doses. The patient's pharmacological maintenance treatment at baseline and for 4 months was encoded according to the Anatomical Therapeutic Chemical classification system (WHO, 2009). In order to study the pharmacological maintenance patterns of prescription, the medication prescribed at baseline was investigated in this study. Descriptive lists of drug utilization patterns relating to all assessable patients were produced. Treatment adherence was also documented according to the investigator's judgement based on the doses missed during a standard week (Weiden *et al.* 2004). Finally, the investigator recorded the patient's satisfaction with treatment on a 5-point Likert scale, ranging from 'not at all' to 'extremely satisfied'.

Data analysis

The sample size, as described elsewhere (Vieta *et al.* 2010*a*, *b*), was calculated in order to determine the prevalence of depressive symptoms among clinically stable BD out-patients.

In order to analyse the relationship between prescription patterns and clinical features of the disorder, therapeutic strategies were defined *a priori*, considering the generic therapeutic classification of agents, regardless of their approval for BD treatment: lithium, anticonvulsant or antipsychotic agents in monotherapy, combination of lithium with either anticonvulsants or antipsychotics or anticonvulsants with antipsychotics, combination of all three agents and combination with antidepressants. For this analysis, pharmacological strategies were classified as mutually exclusive. Gabapentin, topiramate and clonazepam were not considered anticonvulsant treatment prescribed for BD because of lack of evidence base for their use in this condition.

The clinical variables considered for the analysis were age, gender, marital status, educational level, occupational status, living conditions, BD type, clinical course of rapid cycling or seasonal pattern, past depressive episodes, polarity of the most recent episode according to DSM-IV-TR, age at first episode, number of episodes per year, time elapsed since the last episode, duration of the most recent episode, time elapsed since the last depressive episode, duration of the most recent depressive episode, duration of clinical stability, live events since last assessment, ongoing psychiatric co-morbidity, first degree relative psychiatric history and presence of depressive symptoms.

To analyse the differences between the described variables in each pharmacological strategy, analysis of variance or χ^2 tests were used, as appropriate, or their respective non-parametric tests if data did not fit a normal distribution. Then a logistic regression model was constructed for each pre-defined strategy to ascertain which clinical factors were associated with each strategy. The models were created according to Hosmer and Lemeshow advice to introduce one parameter for each 10 observed cases (Hosmer & Lemeshow, 2000).

Statistic analysis was conducted using the software Statistical Package for Social Sciences version 18.0 (SPSS Inc., USA). All p values reported were two tailed. Statistical significance was defined as $p < 0.05$.

Results

Sample characteristic

Most of the patients were diagnosed with BD type I ($n = 537$, 72.7%) (Table 1) and 88.2% ($n = 652$) had had a previous depressive episode. More than half of the

Table 1. Sociodemographic and clinical characteristics at baseline for all bipolar disorder (BD) patients

Variable	BD total ($n=739$)	
	Mean	S.D.
Age at enrolment (yr)	46.1	13.7
	n	%
Gender		
Male	295	39.9
Female	438	59.3
Marital status		
Married/stable partner	380	51.4
Single	234	31.7
Other situation	120	16.2
Educational level		
No education completed	47	1.9
Basic education	279	37.8
High school	386	31.9
University	162	21.9
Occupational status (yes)	291	39.4
Living situation		
Alone	105	14.2
With parents	177	24.0
With spouses/children	389	52.6
Residence/sheltered housing or in other situation	54	7.2
	Mean	S.D.
Time elapsed since last depressive episode (d)	889	1385
Age at first episode (yr)	29.7	11.8
Number of episodes per year	1.5	1.1
Time elapsed since last episode (d)	455.4	441.3
Duration of most recent episode (d)	74.1	70.3
Duration of clinical stability (months)	17.0	26.8
	n	%
BD		
Type I	537	72.7
Type II	202	27.3
Clinical course		
Rapid cycling	126	17.1
Seasonal pattern	261	35.5
Past depressive episodes (*yes*)	652	88.2
Polarity of most recent episode		
Depressive type (296.5 ×)	377	51.8
Manic type (296.46)	184	24.9
Hypomanic type (296.40)	127	17.2
Mixed type (296.6 ×)	46	6.2
Not specified (297.7)	4	0.5
Life events since last assessment	118	16.0
Ongoing psychiatric co-morbidity		
Substance abuse	109	14.7
Panic disorder	50	6.8
Non-specified anxiety disorders	48	6.5
Family history[a]		
Depressive disorder	254	34.4
BD	139	18.8
Substance abuse	58	7.8
Psychotic disorder–schizophrenia	50	6.8
Presence of mild/subclinical depression ($17 < \text{HAMD} \geqslant 7$)	125	16.9

HAMD, Hamilton Rating Scale for Depression.

[a] Psychiatric disorders on first degree relatives.

Table 2. Patterns of prescription and clinical features in bipolar disorder patients: qualitative and quantitative variables

	Pharmacological strategies $n=733$																	
Clinical features	Lithium monotherapy $n=76$		Anticonvulsant monotherapy $n=45$		Antipsychotic monotherapy $n=26$		Antidepressant combination $n=284$		Lithium & anticonvulsant $n=48$		Lithium & antipsychotic $n=95$		Anticonvulsant & antipsychotic $n=86$		Lithium & anticonvulsant & Antipsychotic $n=73$			
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Stats	*p* value
Age at enrolment (yr)	42.0	13.5	47.7	14.0	40.9	11.9	48.7	13.5	47.1	14.8	44.3	13.5	43.4	12.8	45.6	13.0	3.908	<0.0001***
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	Stats	*p* value
Gender (woman)	45	6.2	27	3.7	15	2.1	185	25.4	21	2.9	54	7.0	53	7.3	37	5.1	12.709	0.080
Marital status																	13.063	0.522
Single	26	3.6	15	2.1	12	1.6	76	10.4	12	1.6	36	4.9	30	4.1	26	3.6		
Married/Stable partner	38	5.2	24	3.3	12	1.6	149	20.4	29	4.0	45	6.2	42	5.8	36	4.9		
Other situation	11	1.5	6	0.8	2	0.3	58	8.0	7	1.0	13	1.8	13	1.8	11	1.5		
Educational level (high school or above)	48	6.7	28	3.9	12	1.7	144	20.0	26	3.6	51	7.1	39	5.4	46	6.4	10.007	0.188
Occupational status (Yes)	43	6.0	20	2.8	8	1.1	108	15.1	26	3.6	41	5.7	34	4.7	32	4.5	13.610	0.059
Living situation																	23.088	0.339
Alone	11	1.5	8	1.1	2	0.3	43	6.0	4	0.6	13	1.8	15	2.1	8	1.1		
With parents	20	2.8	8	1.1	11	1.5	56	7.8	11	1.5	31	4.3	19	2.6	21	2.9		
With spouse/children	39	5.4	24	3.3	11	1.5	163	22.6	29	4.0	44	6.1	41	5.7	36	4.9		
Residence/sheltered housing or in other situation	5	0.7	5	0.7	1	0.1	20	2.8	2	0.3	4	0.6	8	1.1	8	1.1		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Stats	*p* value
Time elapsed since last depressive episode (d)	1421.5	1774.3	601.8	695.3	1129.7	1754.8	567.8	1227.6	606.5	655.0	1288.7	2911.0	692.8	780.3	1310.6	1882.8	4.127	<0.0001***
Duration of most recent depressive episode (d)	98.4	92.8	68.5	61.0	83.8	62.2	95.7	119.9	97.5	75.7	84.8	60.7	59.5	40.7	78.2	62.7	1.748	0.095
Age at first episode	27.7	9.3	32.11	13.9	25.5	11.8	31.2	12.2	34.6	12.1	27.4	9.7	28.4	12.2	27.7	9.9	3.985	<0.0001***
Number of episodes per year	1.1	0.8	1.7	0.9	1.1	0.6	1.6	1.3	1.3	0.7	1.3	0.9	1.4	0.9	1.5	0.7	3.175	0.003**
Time elapsed since last episode (days)	800.2	494.8	517.2	468.0	489.5	491.5	384.2	409.8	483.4	421.2	460.6	462.6	371.3	343.7	380.3	407.4	9.096	<0.0001***
Duration of most recent episode (days)	72.7	79.1	67.0	61.9	65.5	52.7	80.8	83.0	87.5	77.6	67.2	50.2	64.1	49.3	70.2	55.5	1.137	0.337
Duration of clinical stability (months)	25.8	16.2	23.0	49.0	29.4	48.4	15.7	30.3	17.8	14.5	15.2	15.2	13.0	16.7	12.6	14.9	3.019	0.004**

	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	Stats	*p* value
Bipolar disorder															50.576	<0.0001***
Type I	64	8.7	33	4.5	22	3.0	169	23.1	35	4.8	82	11.2	63	8.6	65	8.9		
Type II	12	1.6	12	1.6	4	0.5	115	15.7	13	1.8	13	1.8	23	3.1	8	1.1		
Clinical course																		
Rapid cycling	8	1.1	8	1.1	9	1.2	56	7.6	3	0.4	10	1.4	18	2.5	14	1.9	13.559	0.060
Seasonal pattern	25	3.4	13	1.8	7	1.0	104	14.2	23	3.1	33	4.5	28	3.8	26	3.5	13.559	0.060
Past depressive episodes (yes)	60	78.9	37	82.2	20	76.9	274	96.8	42	87.5	75	78.9	76	88.4	63	86.3	39.795	<0.0001***
Polarity of most recent episode																	155.486	<0.0001***
Manic/mixed	44	6.0	26	3.6	20	2.7	68	9.3	13	1.8	73	10.0	53	7.3	58	8.0		
Depressive	31	4.3	19	2.6	6	0.8	214	29.4	35	4.8	21	2.9	32	4.4	15	2.1		
Life events since last assessment	9	1.2	8	1.1	3	0.4	54	7.4	7	1.0	11	1.5	12	1.6	10	1.4	5.325	0.620
Ongoing psychiatric comorbidity	19	2.6	9	1.2	8	1.1	77	10.5	7	1.0	26	3.5	30	4.1	26	3.5	14.481	0.043*
Family history[a]	46	6.3	21	2.9	9	1.2	160	21.8	21	2.9	43	5.9	41	5.6	49	6.7	18.004	0.012*
Presence of depressive symptoms (HAMD ⩾7)	9	1.2	9	1.2	7	1.0	49	6.7	7	1.0	12	1.6	20	2.7	12	1.6	7.408	0.388

HAMD, Hamilton Rating Scale for Depression.

[a] History of depressive disorder, bipolar, disorder, substance abuse, psychotic disorder or schizophrenia on first degree relatives.

* $p<0.05$, ** $p<0.001$, *** $p<0.0001$.

sample ($n=377$, 51.8%) presented with a depressive polarity in the most recent episode. Overall, patients were considered to adhere to the maintenance treatment ($n=618$, 83.6%). Moreover, most patients ($n=526$, 71.2%) were reportedly satisfied with their maintenance regimen. Further details on the description of sociodemographic and clinical data are available elsewhere (Vieta *et al.* 2010*a*).

Patterns of drug treatment

Most of the sample was under an antidepressant association strategy ($n=284$, 38.7%) (Table 2). Antidepressant combination patterns and types of antidepressants were classified according to the therapeutic strategies in Table 3. The combination strategies without antidepressants ($n=302$, 41.2%) were more prevalent than monotherapy ($n=147$, 20.0%). The most prevalent monotherapy was lithium ($n=76$, 10.4%). Significant differences were detected in the clinical features among the pharmacological strategies regarding age at enrolment ($F=3.908$, $p<0.0001$), BD type ($\chi^2=50.573$, $p<0.0001$), past depressive episodes ($\chi^2=39.795$, $p<0.0001$), polarity of the most recent episode ($\chi^2=155.486$, $p<0.0001$), ongoing psychiatric co-morbidity ($\chi^2=14.481$, $p=0.043$), family history ($\chi^2=18.004$, $p=0.012$), time elapsed since last depressive episode ($F=4.127$, $p<0.0001$), age at first episode ($F=3.985$, $p<0.0001$), number of episodes per year ($F=3.175$, $p=0.003$), time elapsed since last episode ($F=9.096$, $p<0.0001$) and duration of clinical stability ($F=3.019$, $p=0.004$; Table 2).

Relationship between prescription patterns and clinical features of BD

The results of the logistic regressions showed different factors that were significantly associated with each pharmacological strategy (Table 4).

The time elapsed since the last episode [odds ratio (OR) 1.002, 95% confidence intervals (CI) 1.001–1.002, $p<0.0001$] and a family history of psychiatric disorder (OR 1.911, 95% CI 1.071–3.412, $p=0.028$) were significantly associated with the possibility of following maintenance treatment with lithium in monotherapy. Age at enrolment was inversely related to the use of lithium in monotherapy (OR 0.975, 95% CI 0.954–0.997, $p=0.023$). No significant relationships were detected in the use of anticonvulsant in monotherapy. Manic polarity of the most recent episode (OR 3.300, 95% CI 1.497–9.346, $p=0.006$) and duration of clinical stability (OR 1.009, 95% CI 1.001–1.017, $p=0.034$) were significantly associated with the possibility of following maintenance treatment with an

Table 3. Antidepressant combination: pattern of pharmacological strategies

	Combination ($n=284$)		TCA ($n=29$)		SSRI ($n=134$)		SNRI ($n=89$)		Others ($n=32$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Lithium	46	16.2	7	2.5	17	6.0	17	6.0	5	1.8
Anticonvulsant	58	20.4	8	2.8	27	9.5	18	6.3	5	1.8
Antipsychotic	18	6.3	2	0.7	10	3.5	4	1.4	2	0.7
Lithium and anticonvulsant	34	12.0	3	1.1	17	6.0	8	2.8	6	2.1
Lithium and antipsychotic	37	13.0	2	0.7	17	6.0	14	4.9	4	1.4
Anticonvulsant and antipsychotic	47	16.5	3	1.1	24	8.5	17	6.0	3	1.1
Lithium, anticonvulsant and antipsychotics	34	12.0	3	1.1	18	6.3	11	3.9	2	0.7
Others	10	3.5	1	0.4	4	1.4	0	0	5	1.8

TCA, Tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitors.

antipsychotic in monotherapy. The maintenance treatment with an antidepressant combination with other agents was significantly associated with depressive polarity of the most recent episode (OR 2.567, 95% CI 1.370–4.809, $p=0.003$), bipolar II disorder diagnoses (OR 2.278, 95% CI 1.239–4.184, $p=0.008$), and age at enrolment (OR 1.051, 95% CI 1.020–1.084, $p=0.001$). Maintenance treatment with lithium combined with anticonvulsants was significantly related to age at first episode (OR 1.091, 95% CI 1.027–1.159, $p=0.005$) and inversely related to ongoing psychiatric co-morbidity (OR 0.230, 95% CI 0.085–0.627, $p=0.004$). With regard to the use of lithium combined with an antipsychotic as a maintenance treatment, a significant association was only shown with manic polarity of the most recent episode (OR 3.774, 95% CI 2.083–6.849, $p<0.0001$). Age at enrolment (OR 0.934, 95% CI 0.898–0.971, $p=0.001$) was significantly related to the possibility of following maintenance with treatment with anticonvulsants combined with antipsychotics. Finally, the use of combined treatment with the three agents as maintenance therapy was significantly associated with manic polarity of the most recent episode (OR 2.907, 95% CI 1.124–7.519, $p=0.028$).

Discussion

In this study several clinical features of bipolar patients were related to patterns of pharmacological maintenance strategies. Family history of psychiatric disorders, longer time since last episode and youth at the time of enrolment were associated with lithium monotherapy, manic polarity of the most recent episode and longer duration of clinical stability were associated with antipsychotic in monotherapy; depressive polarity of the most recent episode, BD type II diagnosis, and older age at the time of enrolment with antidepressant association strategy; older age at first episode and no ongoing psychiatric co-morbidity with lithium and anticonvulsant strategy; manic polarity of the most recent episode with lithium and antipsychotic strategy; youth at enrolment with anticonvulsant and antipsychotic strategy; and finally manic polarity of the most recent episode was associated with maintenance treatment with lithium, anticonvulsant and antipsychotic therapy.

Manic polarity of the most recent episode was related to maintenance treatment with antipsychotics in monotherapy, in combination with lithium or in combination with lithium and anticonvulsants. These results are in accordance with current guidelines, which recommend an approach to bipolar maintenance treatment based on the concept of predominant polarity (Colom *et al.* 2006; Goodwin, 2009; Nivoli *et al.* 2011*b*; Yildiz *et al.* 2011) or the nature of the preceding acute episode (Suppes *et al.* 2005).

On the other hand, depressive polarity of the most recent episode was associated with antidepressants combined with maintenance treatment. It is a matter of debate whether antidepressants should be prescribed in BD or not, particularly in long-term treatment, (Nivoli *et al.* 2011*a*; Valentí *et al.* 2011; Vieta *et al.* 2010*b*). On one hand, some guidelines do not recommend their use (APA, 2002; Frye *et al.* 2011; Yatham *et al.* 2009). Despite accepting that adjunctive antidepressants may be effective in the acute treatment of BD, it has been suggested that antidepressants do not appear to provide any additional benefit in long-term treatment of bipolar depression (Frye *et al.* 2011). For this reason, the NICE guidelines limit the use of

Table 4. Logistic regressions corresponding to maintenance pharmacological strategies in bipolar disorder (BD)

	β	OR	95% CI	p value
Strategies				
Lithium[a]				
Family history[b]	0.648	1.911	1.071–3.412	0.028*
Time elapsed since last episode	0.002	1.002	1.001–1.002	<0.0001***
Age at enrolment	−0.250	0.975	0.954–0.997	0.023*
Antipsychotic[c]				
Manic/mixed polarity of most recent episode	1.302	3.300	1.497–9.346	0.006**
Duration of clinical stability	0.009	1.009	1.001–1.017	0.034*
Antidepressant combination[d]				
Depressive polarity of most recent episode	0.943	2.567	1.370–4.809	0.003**
Bipolar II disorder	0.822	2.278	1.239–4.184	0.008**
Age at enrolment	0.050	1.051	1.020–1.084	0.001**
Lithium and anticonvulsant[e]				
Age at first episode	0.087	1.091	1.027–1.159	0.005**
Ongoing psychiatric co-morbidity	−1.468	0.230	0.085–0.627	0.004**
Lithium and antipsychotic[f]				
Manic/mixed polarity of most recent episode	1.329	3.774	2.083–6.849	<0.0001***
Anticonvulsant and antipsychotic[g]				
Age at enrolment	−0.069	0.934	0.898–0.971	0.001**
Lithium and anticonvulsant and antipsychotic[h]				
Manic/mixed polarity of most recent episode	1.066	2.907	1.124–7.519	0.028*

OR, Odds ratio; CI, confidence interval.

[a] Variables initially introduced in the model: age at enrolment, number of episodes per year, time elapsed since last episode, BD type, polarity of most recent episode, past depressive episodes and family history of psychiatric disorder; Hosmer and Lemeshow's test ($p = 0.850$).

[b] History of depressive disorder, BD, substance abuse, psychotic disorder or schizophrenia on first degree relatives.

[c] Variables initially introduced in the model: duration of clinical stability, and polarity of most recent episode; Hosmer and Lemeshow's test ($p = 0.438$).

[d] Variables initially introduced in the model: age at enrolment, age at first episode, time elapsed since last episode, time elapsed since last depressive episode, number of episodes per year, duration of clinical stability, BD type, polarity of most recent episode, ongoing psychiatric co-morbidity and family history of psychiatric disorder; Hosmer and Lemeshow's test ($p = 0.205$).

[e] Variables initially introduced in the model: Age at enrolment, age at first episode, ongoing psychiatric co-morbidity and family history of psychiatric disorder; Hosmer and Lemeshow's test ($p = 0.529$).

[f] Variables initially introduced in the model: age at enrolment, age at first episode, number of episodes per year, time elapsed since last episode, duration of clinical stability, BD type, past depressive episodes, polarity of most recent episode, family history of psychiatric disorder; Hosmer and Lemeshow's test ($p = 0.274$).

[g] Variables initially introduced in the model: age at enrolment, time elapsed since last episode, time elapsed since last depressive episode, number of episodes per year, duration of clinical stability, BD type, polarity of most recent episode, ongoing psychiatric co-morbidity; Hosmer and Lemeshow test ($p = 0.288$).

[h] Variables initially introduced in the model: age at enrolment, age at first episode, time elapsed since last episode, time elapsed since last depressive episode, BD type, polarity of most recent episode, ongoing psychiatric co-morbidity; Hosmer and Lemeshow's test ($p = 0.315$).

In the model performed for maintenance pharmacological anticonvulsant monotherapy, the variables initially introduced were number of episodes per year, time elapsed since last episode, duration of clinical stability and ongoing psychiatric co-morbidity. None was detected as a predictor.

* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

antidepressants at the minimal therapeutic dose in combination with prophylactic medication (National Collaborative Centre for Mental Health, 2006). On the other hand, however, the British Association for Psychopharmacology does not deny the obvious fact that prescribing antidepressants in maintenance

treatment is a widely spread clinical practice (Baldessarini *et al.* 2007) and suggests that there is not sufficient evidence to recommend the discontinuation of antidepressants (Goodwin, 2009).

In addition, a significant association in the same pharmacological strategy was found with the BD type II diagnoses. Given the major burden of the disease imposed by chronic depressive symptoms and recurrent depressive episodes in BD II (Judd *et al.* 2003; Solé *et al.* 2012), antidepressant prescription may be foreseeable (Pacchiarotti *et al.* 2011).

In the maintenance treatment with lithium in monotherapy, family history of psychiatric disorder seemed to be related to this strategy. It is commonly known that response to a given drug by a patient's relative is an important indicator for selecting the optimal treatment. In the case of lithium, familial clustering of response to treatment reportedly gave a significantly better response to lithium prophylaxis among relatives (Grof *et al.* 2002; Mendlewicz *et al.* 1973).

Moreover, youth at the time of enrolment was associated with lithium in monotherapy as well as with a combination of anticonvulsants and antipsychotics in contrast to the association between old age at enrolment with the antidepressant combination. These relationships could be explained as young patients are presumed not to have suffered the disorder for long. Therefore, neuroprogression in the disorder may not have progressed too long and first-line treatments, such as the former, which are initially prescribed, could still be effective (Yatham *et al.* 2009) in contrast to the latter, which is usually prescribed as a last resort.

Along the same lines, lithium is reported to better prevent relapses when introduced within the first 10 yr of illness (Franchini *et al.* 1999). Thus, patients under lithium monotherapy may show less severe evolution, which would not require treatment changes. For this reason patients under lithium monotherapy may present with a longer time since last episode.

The combination strategy with lithium and anticonvulsants was significantly associated with older age at first episode. It could be hypothesized that this may be due to a delay in the diagnosis in this subsample, a further progression of the disorder and, consequently, an ineffective monotherapy treatment (Hirschfeld *et al.* 2003). Moreover, this pharmacological strategy was inversely associated with psychiatric co-morbidity. We consider that this relationship results from the exclusion of anticonvulsants in this study, such as gabapetin, topiramate and clonazepam, which are generally used in other psychiatric disorders and in co-morbid conditions.

With regard to antipsychotics, an association was found between antipsychotic monotherapy and the duration of clinical stability, highlighting the suitability to use these drugs in maintenance treatment (Popovic *et al.* 2012; Vieta *et al.* 2011).

The present study has some limitations. Drug indications and prescription patterns vary across countries. However, a great effort was made to ensure the representativity of the sample across out-patient mental health settings in Spain. In fact, similar results at the prescription pattern were found in the different settings. Nevertheless, the results obtained in our country may not be fully generalizable to other countries, where attention and services to the patients may be differently distributed. Furthermore, it is important to bear in mind that this is a cross-sectional study and does not give a relationship of causality between the prescription pattern and clinical features. However, this study on maintenance treatment in BD may shed some light on this barely unexplored field. The results confirm that, in general, prescription patterns in BD are in line with published recommendations, except for the excessive use of antidepressants. This study also reveals clinical factors that may be closely related to prescription patterns, for which the evidence-based treatment may or may not be available, but which may help to build not only evidence-based but also experience-based guidelines.

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