A. Montoya[1]
J. Pérez Sánchez-Toledo[2]
I. Gilaberte[1]
A. González-Pinto[3,7]
J. M. Haro[4,7]
E. Vieta[5,7]
M. Tohen[6]

Patterns of drug treatment for manic episode in the clinical practice. Outcomes of the Spanish sample in the EMBLEM Study

[1] Laboratorios Lilly
Spain
[2] Cambridgeshire and Peterborough Mental Health NHS Partnership Trust.
Department of Psychiatry
University of Cambridge
UK
[3] Psychiatry Department
Hospital Santiago Apóstol
Vitoria (Spain)
[4] Sant Joan de Déu-Serveis de Salut Mental
Sant Boi
Barcelona (Spain)
[5] Hospital Clinic
IDIBAPS
Universitat de Barcelona (Spain)
[6] Lilly Research Laboratories
Department of Psychiatry
Harvard Medical School/McLean Hospital
Belmont. Mass
[7] Red de Enfermedades Mentales REM TAP

Introduction. Although treatment for mania has been studied extensively in randomized clinical trials, there are few data that address how these patients are truly managed in clinical, functional, and economic terms in the psychiatric practice in Spain.

Objective. To determine prescribing patterns in Spain on the basis of the Spanish sample of bipolar patients in manic or mixed phase included as part of the pan-European EMBLEM Study.

Method. The EMBLEM Study recruited 3,681 patients, 312 of whom (8.47%) were included in Spain. Patients had to be adults with a diagnosis of bipolar disorder who were initiating treatment for a manic phase. They underwent evaluation using the Spanish versions of scales that measure severity of mania (the Young Mania Rating Scale, CGI-BP and the Hamilton Scale) and functional level (LCM, SLICE of LIFE). Information was collected regarding drug and treatment adherence variables.

Results. Prior to being admitted into the study, 42% of the patients were receiving polytherapy, 35% were on monotherapy, and 23% were not taking any medication whatsoever. Forty percent of the patients presented partial or total non-compliance with the treatment prescribed. During the first stage of the study, in the case of single-drug treatment, acute management for mania consisted of mean daily doses of 25 mg of olanzapine, 6.6 mg of risperidone, 9.5 mg of haloperidol, 165 mg of lamotrigine, 938.5 mg of valproate, and 909 mg of lithium, whereas when combined therapy was used, the following doses were used: olanzapine, 22.1 mg; risperidone, 7.3 mg; haloperidol, 12.3 mg; lamotrigine, 1,75.1 mg; valproate, 1,038.4 mg, and lithium, 1012.6 mg. Of those patients who were on monotherapy at the beginning of the study 51% were treated with a single drug, whereas 48% were receiving polytherapy. Among the participants who were receiving combined treatment when they began the study, almost all of them, 94%, were prescribed combined treatment. In the case of the hospitalized patients who made up 88% of the sample, the vast majority, 92%, had improved by the time the study was completed. Mean time to release from hospital was 24 days.

Discussion. In Spain, treatment for mania is essentially based on combined treatments, hospitalization, and antimania drugs that are prescribed at somewhat higher doses than those recommended in the corresponding prescribing information documents, which indicates that the clinical reality of this entity is far more complex than clinical trials conducted in experimental conditions suggest.

Key words:
Mania. Bipolar disorder. EMBLEM.

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Patrones de tratamiento farmacológico para el episodio maníaco en la práctica clínica. Resultados de la muestra española en el estudio EMBLEM

Introducción. Aunque el tratamiento de la manía ha sido estudiado profusamente en ensayos clínicos aleatorizados, existen pocos datos respecto al manejo real de estos pacientes en términos clínicos, funcionales y económicos en la práctica psiquiátrica en España.

Objetivo. Determinar, a través de la muestra española de pacientes bipolares en fase maníaca o mixta del estudio paneuropeo EMBLEM, los patrones de prescripción en España.

Método. El estudio EMBLEM reclutó a 3.681 pacientes, 312 de los cuales (8.47%) fueron incluidos en España. Los pacientes tenían que ser adultos con diagnóstico de trastorno bipolar que iniciaran tratamiento para una fase maníaca. Se les evaluó con las versiones españolas de escalas para la gravedad (Escala de Young, CGI-BP, Escala de Hamilton) y para la funcionalidad (LCM, SLICE de LIFE). Se recogió información sobre variables farmacológicas y de adherencia al tratamiento.

Resultados. Antes de entrar en el estudio, el 42% de los pacientes recibía politerapia, el 35% estaba en mono-

Correspondence:
Alonso Montoya
Laboratorios Lilly, España
Av. de la Industria 30
28108 Alcobendas (Madrid) (Spain)
E-mail: montoya_alonso@lilly.com

terapia y el 23% no tomaba ninguna medicación. Un 40 % de los pacientes incumplía total o parcialmente el tratamiento prescrito. Durante la fase inicial del estudio el manejo agudo de la manía fue a expensas, como monoterapia, de dosis medias diarias de: olanzapina, 25 mg; risperidona, 6,6 mg; haloperidol, 9,5 mg; lamotrigina, 165 mg; valproato, 938,5 mg, y litio, 909 mg, mientras que cuando fueron empleados en combinación las dosis fueron: olanzapina, 22,1 mg; risperidona, 7,3 mg; haloperidol, 12,3 mg; lamotrigina, 175,1 mg; valproato, 1.038,4 mg, y litio, 1.012,6 mg. De los pacientes que al inicio del estudio estaban en monoterapia, el 51% fueron tratados con un solo fármaco y un 48% recibió tratamiento combinado. De entre los pacientes que iniciaron el estudio recibiendo tratamiento combinado, el 94% continuó recibiendo tratamiento combinado. La gran mayoría de los pacientes (92%) mejoraron al término del estudio En el caso de los pacientes hospitalizados, los cuales conformaron el 88% de la muestra, el tiempo medio hasta el alta del hospital fue de 24 días.

Conclusiones. El tratamiento de la manía en España se sustenta fundamentalmente en tratamientos combinados, hospitalización y dosis de fármacos antimaníacos generalmente algo superiores a las recomendadas en las fichas técnicas, indicando que la realidad clínica es más compleja de lo que indican los ensayos clínicos realizados en condiciones experimentales.

Palabras clave:
Manía. Trastorno bipolar. EMBLEM.

INTRODUCTION

Pharmacological strategies make up the first line of treatment of bipolar disorder, with the specific objectives of reducing frequency, intensity and consequences of the episodes and of improving psychosocial functioning, among them[1]. Due to the complexity of the disorder, pharmacological management of bipolar disorder is becoming a daily challenge for the psychiatrist since each phase of the disease requires a different therapeutic approach[2].

Combination of drug agents more than single drug therapy is the treatment modality that prevails in persons who suffer bipolar disorder I, perhaps due to the complexity of the disorder and to the multiphasic nature of its clinical presentation[3].

Thanks to the information obtained in clinical trials in recent years, we have been experiencing changes in the trends of different drugs. Introduction of new treatment possibilities for bipolar disorder in recent years, especially for the treatment of acute mania[4-6], has undoubtedly increased the therapeutic options of psychiatry. However, based on this new knowledge, new doubts have arisen about how to translate/implement the new advances into the usual clinical practice.

Most of the clinical trials, due to their experimental nature, are conducted under very strict treatment conditions, such as the use of anti-mania agents almost exclusively in single drug therapy, with very flexible doses and very limited use of commitment medication[3,7].

Although it is clear that strict methodology must be used in the protocols in order to obtain valid results in regards to efficacy, what is not so clear is up to what point the data to of the clinical trials may be used to infer effectiveness in the conditions of usual clinical practice[7,8].

The current concept of therapeutic effectivity considers the impact of the drug agent and the control of several symptoms of the disease and the drug safety and tolerability[9]. It not only depends on the drug characteristics but also on other important factors that are generally not the object of the classical clinical trial studies. These may be clinical variability of the disorder, substance use, long-term treatment effects, dose variability as well as the combination of other drug and non-drug treatments[10].

Although the treatment of mania in bipolar patients during the usual clinical practice conditions has been examined in some studies, no observational (epidemiological) study that examines the real management of patients in the manic phase in clinical (seriousness of the symptoms), functional (work capacity, relationships, etc.) and financial (medical costs, etc.) terms study has been conducted in the psychiatric practice in Spain up to now.

In the EMBLEM study, data were collected on 3,536 patients in 15 European countries. This represents one of the most extensive studies in history, sample and territory on the bipolar disorder. In the present analysis, the pharmacological treatment patterns in the Spanish sample of 312 patients with manic or mixed episodes are studied in depth.

METHODOLOGY

Design

The European Mania in Bipolar Longitudinal Evaluation of Medication project (EMBLEM) is a multicenter, prospective and observational study designed to observe a sample of acute patients subjected to treatment for mania within the context of bipolar disorder in all Europe. Psychiatrists from 14 European countries (Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Holland, Norway, Portugal, Sweden, United Kingdom and Spain) recruited a sample of 3536 patients between December 2001 and June 2004. The study was divided into two stages, an acute phase (of three months) and the maintenance phase (longitudinal follow-up greater than three months). Spain only participated in the acute phase of the study. The EMBLEM study design was prospective and observational (not interventionist). Thus, there were no instructions regarding treatment. The deci-

sion to initiate or change the medication and the type of medication selected were completely independent of the study. This was limited to observing the treatment options and the outcomes instead of directing the treatment. The general methodology of the complete study has been described in detail in other articles[10,11]. This study was evaluated and approved by the ethics committees of the participating sites.

Participants

Those adult patients (older than 18 years) diagnosed of bipolar disorder who were receiving treatment indicated for a manic or mixed episode under usual clinical practice and who, in accordance with the criterion of the participating psychiatrists, were going to initiate or change the oral medication (without considering the dose changes) for treatment of manic/mixed episode of bipolar disorder were considered for enrolment in the study. Diagnosis to determine the manic/mixed episode was performed with standard diagnostic criteria (DSM IV, ICD 10 and clinical diagnosis). Those patients who were simultaneously participating in some other interventionist study could not be enrolled.

Objectives

The primary objective of EMBLEM was to evaluate changes in manic episode symptoms in patients treated with olanzapine, other antipsychotics, mood state stabilizers and combined treatments during the usual clinical practice. Other objectives were to examine functioning, symptomatic recovery, relapse rates and financial impact during the treatment.

Measurements

Sociodemographic and psychiatric history data were collected in order to characterize the patient sample, for example: age, gender, school level, age of onset of first effective episode, first contact with psychiatric services, first hospitalization, frequency and duration of subsequent hospitalizations as well as background of substance abuse and suicide attempts. Seriousness of the depressive or manic symptoms was evaluated with clinical scales such as the Spanish version of the clinical global impression scale for bipolar disorder (CGI-BP)[12], the Spanish version of the Young Mania Rating scale (YMRS)[3] and the 5 item Hamilton Depression scale (HAM-D-5) defined by component analysis by González Pinto et al. (2003)[14]. Functional deterioration in the impact of the disease in the functionality of the patients was evaluated with the Life Chart Methodology (LCM)[15] and with 2 items of the SLICE of LIFE[16] that assessed the functional status in terms of work functioning and life satisfaction. More information was collected on the housing conditions, civil status, number of dependents, social activity patterns and information regarding medication, such as ghosts and administration route, tolerability and adherence during the four weeks prior to the entry in the study. The clinical measures were evaluated on admission to the study, at 24 hours and during the 1st, 2nd, 3rd, 6th and 12th week.

Analysis

All the initial measurements of the study were included in an exploratory and descriptive type analysis.

OUTCOMES

Demographic data

A total of 55% of the 312 patients enrolled in this study were women with a mean age of 14 for years that decreased to 37.7 years in men. The highest educational level completed by the patients was: primary for 37% (n=113), secondary for 41% (n=125), and university for 20% (n=61). The demographic and baseline clinical data are shown in table 1.

Baseline clinical data

The profile of patients with bipolar disorder included in this sample was patients with moderate to serious mania, 88% of whom were patients hospitalized for treatment of a new manic/mixed episode. The remaining 12% received medication and follow-up in the outpatient consultations.

Onset age of the disorder was 28.1 years. The first manic or mixed symptoms were experienced at the mean age of 29.6 years while the depressive ones were revealed at 30 years, the medium of age being at 25.27 and 27 years, respectively.

The CGI BP general scale determined on admission to the study established mean seriousness of 4.6 (1.04) (moderate to noticeably ill), and the CGI BP mania scale mean score of 4.9 (0.91). The symptoms which were broken down and objectively quantified with the Young Mania Rating Scale (YMRS) supported the clinical opinion on the seriousness of the patients studied, with a mean global score of 30.6 (9.83). CGI depression grouped most of the patients (84%) in the grade of normal or not ill with a total mean score of 1.3 (0.3). The correlate of the depressive symptoms on the 5 item Hamilton Depression Scale (HAM-D 5 items) (González Pinto et al., 2003) reached a global mean score of 1.7 (2.01). A total of 53% (n=162) of the patients (n=307) had hallucinations and/or delusional ideas at some time of the episode. The hallucinations/delusional ideas on the CGI scale had a mean of 3.2 (1.77).

Table 1 Clinical and sociodemographic characteristics of patients enrolled in the Spanish sample of EMBLEM

Endpoint/characteristics	Patients with bipolar disorder (n = 312)
Mean age, years	41.3 ± 13.39
Gender, number (%)	
Masculine	140 (45)
Feminine	168 (55)
Civil status, number (%)	
Married	117 (38)
Never married	195 (62)
Educational level, number (%)	
Primary	113 (37)
Secondary	91 (30)
Pre-university	34 (11)
University	61 (20)
Clinical status, number (%)	
Hospitalized	273 (88)
Out-patient consultation	39 (12)
Onset age of BD, years	28.1 ± 10.08
First manic/depressive episode, number (%)	35 (14)
At least 1 previous manic/depressive episode	214 (86)
General CGI for BP, total score	4.6 ± 1.04
CGI mania	4.9 ± 0.91
CGI depression	1.3 ± 0.83
YMRS	30.6 ± 9.83
HAM-D 5	1.7 ± 2.01
Work functionality, number (%)	
Mild dysfunction	51 (16)
Moderate dysfunction	90 (29)
Serious dysfunction	60 (19)
Incapacity	48 (15)

BD: bipolar disorder; CGI: clinical global impression; YMRS: Spanish version of the Young Mania Rating Scale; HAM-D-5: 5 item Hamilton Depression Scale.

Comorbidity detected was fundamentally related with alcohol intake (10% abuse, less than 1% dependence) and cannabis (7% abuse, 1% dependence). Functional deterioration of the sample was high, with 19% (60) having, according to the investigator's opinion, serious difficulties in the work functioning during the year prior to admission in the study, 48% (149) reported they did not have any sentimental relationship and 13% that they did not interact in any activity during the 4 weeks prior to enrollment in the study.

PSYCHOPHARMACOLOGICAL TREATMENT

Prior to enrolment in the study

After analyzing data of 306 patients, 42% (129) of the patients received polytherapy before entering into the study, 35% (107) were receiving single drug therapy and 23% (70) did not take any medication. Table 2 shows the drug treatment for mania that the patients received before entering the study.

Single drug therapy was used at the expense of conventional antipsychotics with a percentage of 40% (43), lithium in 25% (27), atypical antipsychotics in 22% (24) and antiepileptics in 12% (13). The antipsychotics used most in single drug therapy were haloperidol (31), risperidone (11) and olanzapine (10) followed at more distance by quetiapine (2), other conventional ones (12) and other atypical ones (1).

As was mentioned in methodology of the EMBLEM study, inclusion depended on the initiation or change of oral medication for the treatment of a new manic/mixed episode. However, some of them received emergency intramuscular medication, in possible single drug therapy, basically conventional antipsychotics (n=91), followed by atypical ones (n=15) and benzodiazepines (n=10).

Examination regarding the number of medications taken by the study patients found that 70 patients (23%) did not

Table 2 Drug treatment prior to inclusion (n = 236)

	Patients with mania	
	n	%
Single drug therapy		
Typical antipsychotics	43	18
Atypical antipsychtics	24	10
Anti-convulsants	13	6
Lithium	27	11
Combined treatment		
Typical antipsychotics + atypical antipsychotics	17	7
Atypical antipsychotics + lithium	13	6
Atypical antipsychotics + anticonvulsants	10	4
Typical antipsychotics + lithium	12	5
Typical antipsychotics + anticonvulsants	13	6
Typical antipsychotics + atypical antipsychotics + anticonvulsants + lithium	2	<1
Other combinations	49	21

take any medication for the disorder, 107 (35%), as was previously stressed, were receiving single drug therapy, 81 patients (26%) had been prescribed two medications, 31 (10%) were taking three and 17 patients (6%) were being treated with four or more drugs.

Use of antidepressants for this population was scarce. Regarding the data for 310 patients, 57 received an antidepressant. Of these 40 had been prescribed an SSRI, 8 tricyclic antidepressants and 9 patients other types, however the MAOIs were not included among them.

Adherence to the medication prescribed showed 40% of the patients with compliance problems and 18% without any medication prescribed.

During the study

The mean daily doses of the drugs used during acute treatment of mania in this bipolar patient cohort were, as single drug therapy: olanzapine, 25 mg (SD: 12.1); risperidone, 6.6 mg (SD: 2.6); haloperidol, 9.5 mg (SD: 4.8); lamotrigine, 165 mg (SD: 141); valproate, 938.5 mg (SD: 512.4), and lithium, 909.0 mg (SD: 290), while when these were used in combination treatment, the doses were olanzapine, 22.1 mg (SD: 0.17); risperidone, 7.3 mg (SD: 3.98); haloperidol, 12.3 mg (SD: 9.5); lamotrigine, 175.1 mg (SD: 124.1); valproate, 1,038.4 mg (SD: 435.0), and lithium, 1,012.6 mg (SD: 316.6) (table 3).

Changes in the initial treatment

In half of the patients (50%), mean time to the first change in medication (the first time in which, after the baseline prescription, the medication of the patients was changed or discontinued) was 18 days. Table 4 shows the likelihood of change in initial treatment for mania in bipolar disorder patients.

Almost half (51%) of the patient who were receiving single drug therapy at the onset of the study were treated with single drug therapy while the other half (48%) received combined treatment. The change meant that only one patient (1%) remained without any treatment.

A total of 205 (94%) of the patients who initiated the study with combined treatment received multiple drug treatment while only 12 (5%) changed to single drug therapy and a minimum percentage remained without receiving any medication (1%) (table 3).

Change from single drug therapy to combined therapy was made in a mean time of 10.1 days (SD: 3.72) while change from those with combined therapy to single drug therapy occurred in 31.2 days (SD: 22.72).

Table 3 Mean daily doses of drugs used for the treatment of manic episode

Medication	Mean dose	SD
Prescribed as single drug therapy (mg/day)		
Olanzapine	25.0	12.1
Risperidone	6.6	2.6
Haloperidol	9.5	4.8
Lamotrigine	165.0	141.0
Valproate	938.5	512.4
Lithium	909.1	290.8
Prescribed in combination (mg/day)		
Olanzapine	22.1	10.17
Risperidone	7.3	3.98
Haloperidol	12.3	9.5
Lamotrigine	175.1	124.1
Valproate	1,038.4	435.0
Lithium	1,012.6	316.6

Efficacy

Most of the patients, 92% (n=288), improved at the end of the study while the course in 8% of them (n=24) was towards worsening (defined as an increase of at least 1 point in global CGI from a minimum of 3). Mean time required to reach a level of clinical improvement (defined as a decrease of at least 2 points on the global CGI) in 50% of the patients was 22 days. Figure 1 shows the change in scores of the clinical scales.

At the end of the study, the mean score on the general CGI BP decreased by approximately 2 points (from 4.9 to 2.3), and the CGI BP mania scale by almost 3 points (from 4.9 to 2.1) and there was practically no change on the CGI-

Table 4 Likelihood of change from initial treatment for manic episode

Patients who initiated with...	n	%
Single drug therapy (n = 93)		
Continued in single drug therapy		
Changed to combined treatment	45	48
Changed to with no prescribed medication	1	1
Combined treatment (n = 219)		
Changed to single drug therapy	205	94
Continued in combined treatment	12	5
Changed to with no prescribed medication	2	< 1

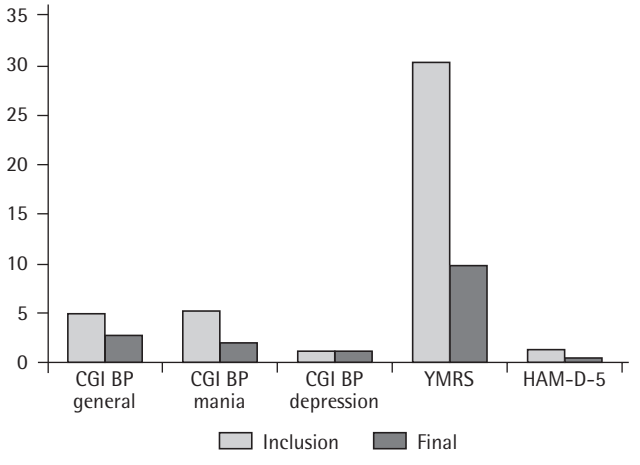

Figure 1 *Change in scores on CGI BP, YMRS and HAM-D-5.*

depression (from 1.3 to 1.2). In turn, the component hallucinations/delusional ideas on the CGI scale showed a change in the mean score from 3.2 to 1.4, and the mean time required to reach a level of clinical improvement (defined as a score under 4) in 50% of the patients was 15 days.

Symptoms quantified with the YMRS supported the changes observed by clinical impression on the seriousness of the patients studied, with a change in the mean global score of more than 20 points in relationship to the baseline score (from 30.6 to 8.9).

Finally, correlate of depressive symptoms in the HAM-D-5 changed from a mean global score of 1.7 to 0.4.

In the case of hospitalized patients, who accounted for 88% of the sample, mean time to discharge from the hospital was 24 days (SD: 14.45). Even though most of the patients showed symptomatic improvement, the initially documented functional deterioration in the sample still remained at significant levels at the end of the study. A total of 73% of the 79% of the patients considered by the therapist as patients with work dysfunction continued with some great dysfunction. This is to be expected in patients who have recently suffered a manic phase.

DISCUSSION

The present investigation describes the prescription patterns used for bipolar patients with acute mania in Spain. Given that the data were obtained from a sample that included several care sites in the Spanish national territory, these results cannot be attributed to a pattern of idiosyncratic prescription in a single geographic region.

When the results are analyzed, it should be observed that the patients enrolled in the study mostly required hospitalization, which testifies to the seriousness of the sample. This severity was confirmed in elevated mean scorers on the CGI scales for mania and YMRS. Assessments in regards to depressive symptoms were noticeably lower, suggesting a population in which manic symptoms predominated over mixed ones. More than half of the patients had psychotic symptoms at some time and the abusive comorbidity of substances with significant, especially with alcohol.

The high-levels of seriousness were reflected in very deteriorated functional patterns. As an indication, about 80% of the patients included presented some type of work dysfunction.

Treatment adherence of the sample was sufficient. Almost half of the patients had difficulties to comply with the prescribed medication. These results coincide with other studies in Spain[17] and their approach is being analyzed in search of improvements through psychoeducational and psychosocial models[18-21].

The proportions of patients in single and polytherapy prior to enrollment in the study were very balanced. Conventional antipsychotics stand out over the remaining therapeutic alternatives in single drug therapy. This could be explained partially by the fact that almost 100 patients were treated with parenteral classical antipsychotics in the emergency services before being hospitalized. Together with a conventional antipsychotics, lithium and atypical antipsychotics were the most common therapeutic alternatives in single drug therapy. About one fourth of the patients did not take any medication, data that rectifies the poor compliance, even more so when the number of the first episodes was low and the large majority had suffered at least one episode in the previous year.

At the onset of the study, single drug therapy was the treatment pattern chosen for one third of the patients included while the rest received combined treatment. Stability in these therapeutic regimes varied over time in the two new cohorts. In fact, half of the patients who began the study in single drug therapy changed to polytherapy after a mean of 10 days. However, only 5% of the patients who began with combined therapy changed to single drug therapy and this occurred at about 30 days of treatment. The differences in time to the change between both groups point to the possibility that the change from single to multiple drug therapy was due to the need for a therapeutic complement and in the second case to a simplification, once the acute symptoms partially subsided. In this regard, it is necessary to remember that half of the patients needed about 3 weeks to reach significant clinical improvement.

On the contrary to that which could be expected, the medication doses used in the patients who received single drug therapy were not greater than those used in polytherapy. There was also a tendency to prescribe higher doses in

most of the therapeutic alternatives (antipsychotics, lithium and anti-convulsants) when used in combination treatment. Use of antipsychotics was elevated and the use of olanzapine and risperidone in the majority of the cases stands out. In the specific case of olanzapine, the mean doses in both single drug as well as polytherapy were at about 25 mg/day, above the doses applied in controlled clinical trials[22,23].

In definitive, treatment of bipolar disorder is still a challenge that constantly confronts the psychiatrist in his/her clinical practice: It has multiple therapeutic approaches that are rarely effective when used as single drug therapy[24]. The growing number of controlled clinical studies in the manic phase supporting the use of drugs in single drug therapy, especially atypical antipsychotics[22,25] are not continued up in the routine clinical practice of our setting. Although an upward trend is observed, combined therapy continues to predominate. Experience acquired and confidence in terms of safety and tolerability with certain drugs influence the fact that the psychiatrist overcomes the dosage barriers imposed by the rigid methodologies of the clinical trials in certain cases, seeking optimum effectiveness in the patients of the real clinical world. In this sense, the outcomes of EMBLEM in Spain suggest that there is an important distance between the experimental data obtained in «ideal» patient samples, such as those who participate in randomized clinical trials, in whom comorbidity, suicidal risk or absence of disease awareness are excluded and the clinical reality that is reflected by the observational studies. In the latter, as the EMBLEM, it is clearly manifested that mania is a serious psychiatric picture that generally requires hospitalization and that frequently requires combined treatments at higher doses than those used in the controlled clinical trials.

REFERENCES

1. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217-24.
2. McElroy SL, Keck PE Jr. Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 2000;48:539-57.
3. Kupfer DJ, Frank E, Grochocinski VJ, Cluss PA, Houck PR, Stapf DA. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. J Clin Psychiatry 2002;63:120-5.
4. Bridle C, Palmer S, Bagnall AM, Darba J, Duffy S, Sculpher M, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. Health Technol Assess 2004;8:iii-iv, 1-187.
5. Mensink GJ, Slooff CJ. Novel antipsychotics in bipolar and schizoaffective mania. Acta Psychiatr Scand 2004;109:405-19.
6. Soldani F, Ghaemi SN, Baldessarini RJ. Research reports on treatments for bipolar disorder: preliminary assessment of methodological quality. Acta Psychiatr Scand 2005;112:72-4.
7. Vieta E, Carne X. The use of placebo in clinical trials on bipolar disorder: a new approach for an old debate. Psychother Psychosom 2005;74:10-6.
8. Haro JM, Edgell ET, Novick D, Alonso J, Kennedy L, Jones PB, et al; SOHO advisory board. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. Acta Psychiatr Scand 2005;111:220-31.
9. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209-23.
10. Haro JM, Os J, Vieta E, Reed C, Lorenzo M, Goetz I; the EMBLEM Advisory Board. Evidence for three distinct classes of «typical», «psychotic» and «dual» mania: results from the EMBLEM study. Acta Psychiatr Scand 2006;113:112-20.
11. Goetz I, Tohen M, Reed C, Lorenzo M, Vieta E, and the EMBLEM Advisory Board. Functional impairment in patients with mania: baseline results of the EMBLEM study. Bipolar Disord 2007;9:45-52.
12. Vieta E, Torrent C, Martínez-Arán A, Colom F, Reinares M, et al. A user-friendly scale for the short and long term outcome of bipolar disorder: the CGI-BP-M. Actas Esp Psiquiatr 2002;30: 301-4.
13. Colom F, Vieta E, Martínez-Arán A, García-García M, Reinares M, Torrent C, et al. Spanish version of a scale for the assessment of mania: validity and reliability of the young mania rating scale. Med Clin (Barc) 2002;119:366-71.
14. González-Pinto A, Ballesteros J, Aldama A, Pérez de Heredia JL, Gutiérrez M, Mosquera F, et al. Principal components of mania. J Affect Disord 2003;76:95-102.
15. Leverich GS, Post RM. The NIMH Life Chart Manual for Recurrent Affective Illness: the LCM. Monograph 1993.
16. Keller MB, Lavori PW, Friedman B, Nielsen E, EndicottJ, McDonald-Scott, et al. The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44: 540-8.
17. Vieta E, Herraiz M, Parramon G, Goikolea JM, Fernández A, Benabarre A. Risperidone in the treatment of mania: efficacy and safety results from a large, multicentre, open study in Spain. J Affect Disord 2002;72:15-9.
18. Colom F, Vieta E, Sánchez-Moreno J, Martínez-Arán A, Reinares M, Goikolea JM, et al. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. Bipolar Disord 2005;7(Suppl. 5):32-6.
19. Colom F, Lam D. Psychoeducation: improving outcomes in bipolar disorder. Eur Psychiatry 2005;20:359-64.
20. Sajatovic M, Davies M, Hrouda DR. Enhancement of treatment adherence among patients with bipolar disease. Psychiatr Serv 2004;55:264-9.
21. Berk M, Berk L, Castle D. A collaborative approach to the treatment alliance in bipolar disorder. Bipolar Disord 2004;6: 504-18.
22. Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, et al. Relapse prevention in bipolar I disorder: 18 month

comparison of olanzapine plus mood stabilizer v. mood stabilizer alone. Br J Psychiatry 2004;184:337-45.

23. Tohen M, Goldberg JF, González-Pinto Arrillaga AM, Azorin JM, Vieta E, Hardy-Bayle MC, et al. A 12 week double blind comparison of olanzapine versus haloperidol in the treatment of acute mania. Arch Gen Psychiatry 2003;60:1218-26.
24. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. CNS Drugs 2006;20:29-42.
25. Hirschfeld RMA, Keck PE, Kramer M, Karcher K, Canuso C, Eerdekens M, et al. Rapid antimanic effect of risperidone monotherapy: a 3 week multicenter, double blind, placebo controlled trial. Am J Psychiatry 2004;161:1057-65.