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Artículo original

Pharmacological treatment outcomes in Latin American patients with bipolar I disorder

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RESULTADOS DEL TRATAMIENTO FARMACOLÓGICO EN PACIENTES LATINOAMERICANOS CON TRASTORNO BIPOLAR I

RESUMEN

Objetivo: este estudio evaluó los resultados de pacientes latinoamericanos con diagnóstico de trastorno bipolar I (episodio maniaco o mixto) que incluyeron en su tratamiento olanzapina comparados con los que no fueron medicados con este antipsicótico. *Material y métodos:* participaron pacientes de 7 países de Latinoamérica, valorados durante 12 meses. Las variables principales de medición fueron: periodo para la remisión de los síntomas maniacos (lapso de hospitalización después de remisión y tiempo de recaída con un episodio maniaco o depresivo). Se compararon resultados clínicos solamente incluyendo datos de las visitas de pacientes que continuaron con el tratamiento de la basal. *Resultados:* se incluyeron 516 pacientes tratados con olanzapina y 246 con otros tratamientos. El 67.5% de la totalidad de los pacientes habían experimentado un episodio maniaco mientras que el 31.9% restante había sufrido al menos un episodio mixto. El periodo para la remisión de los síntomas maníacos fue similar en ambos grupos. El lapso para la hospitalización y recaída con episodio maniaco, pero no en episodio depresivo fue significativamente más largo en pacientes tratados con olanzapina comparados con el grupo no tratado con este medicamento. También se obtuvieron resultados similares en la aparición de eventos adversos y mejoría estadística significativa en la calidad de vida en ambos grupos. *Conclusiones:* la inclusión de olanzapina en el tratamiento del trastorno bipolar I puede permitir a los pacientes latinoamericanos mantener la efectividad y respuesta al tratamiento a largo plazo.

Palabras clave: trastorno bipolar, Latinoamérica, olanzapina, resultado del tratamiento.

ABSTRACT

Objective: this study assessed treatment outcomes of Latin American patients with bipolar I disorder (manic or mixed episodes) who included olanzapine in their treatment regimen compared with patients who did not. *Materials and methods:* patients from seven Latin American countries participated in this prospective, observational, noninterventional, open-label study

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conducted over 12 months. Main outcome measures were: (i) time to remission of manic symptoms (Young Mania Rating Scale (YMRS) ≤ 12), (ii) time to hospitalisation after remission, and (iii) time to relapse with a manic (YMRS ≥ 15) or depressive (Montgomery-Åsberg Depression Rating Scale (MADRS) ≥ 15) episode. Comparisons of clinical outcomes only included data from visits where patients continued to use their baseline treatment. *Results:* at baseline, 516 patients included olanzapine in their treatment and 246 did not; 67.5% of all patients had a manic episode and 31.9% had a mixed episode. Time to remission of manic symptoms was similar between groups (log-rank *P*-value = 0.133). Time to hospitalisation (log-rank *P*-value < 0.0001) and relapse with a manic (log-rank *P* value = 0.0002), but not a depressive (log-rank *P*-value = 0.363) episode was significantly longer in the olanzapine group compared with the non-olanzapine group. Similar rates of treatment-emergent adverse events and statistically significant improvements in quality of life (12-Item Short Form Health Survey) were observed in both groups. *Conclusions:* inclusion of olanzapine in bipolar I disorder therapy may allow patients from Latin America to maintain clinically effective and long-term responses to treatment.

Key words: bipolar disorder, Latin America, olanzapine, treatment outcome.

Bipolar I disorder is a complex mood disorder characterised by intermittent manic, depressive or mixed episodes, with or without residual interepisodal symptoms. Pharmacological treatment of bipolar I disorder is primarily concerned with symptomatic remission and prevention of symptomatic relapse[1]. This strategy aims to encourage long-term adherence to medication and, ultimately, to improve patients' quality of life. Despite the numerous treatment options available, the risk of a recurrent episode in patients with bipolar I disorder is high[2,3].

Olanzapine is a second generation antipsychotic drug that is available for the treatment of acute manic or mixed episodes in adults with bipolar disorder. The efficacy and tolerability of olanzapine for the treatment of acute manic or mixed episodes and in the prevention of relapse into mania or depression has been established in several randomised controlled trials (RCT) comparing olanzapine monotherapy with placebo[4-6], anticonvulsants[7], other antipsychotics[8,9] and lithium [10,11]. Olanzapine has also been assessed in two large, multi-centre observational studies[12,13]. However, most of these studies were conducted in the USA, Europe and other non-European countries and may not be applicable to Latin American populations. This proposition is supported by findings from a *post hoc* analysis of RCT data where the response to antipsychotic therapy in Latin American patients with acute mania was compared with patients from the USA and Europe[14]. In this RCT, significantly more patients from the USA and Europe experienced remission of manic symptoms with olanzapine compared with haloperidol, but no significant differences in remission rates remission between olanzapine and haloperidol were observed in Latin American patients. Moreover, the adverse event profile of each medication was significantly different between the Latin American patients compared with patients from the USA and Europe. To our knowledge, no studies have prospectively assessed the effectiveness and tolerability of olanzapine for treatment of bipolar I disorder in Latin American countries and little is known about patient treatment patterns in this region.

This observational study of patients from Latin America with bipolar I disorder was designed to compare the clinical outcomes of those who included olanzapine in their treatment regimen with those who did not. The specific objectives of this study were: (i) to determine the pharmacological treatment patterns for acute manic or mixed episodes of bipolar I disorder in a real-life clinical setting; (ii) to determine the clinical outcomes of treatment in terms of remission from symptoms, and hospitalisation and relapse after remission; and (iii) to assess the quality of life of patients during the study.

MATERIALS AND METHODS

Study design and setting

The Health Outcomes in Manic Episode and Stabilization study (Study F1D-BL-HGKJ) was a 12-month prospective, observational, noninterventional, open-label study. Patients from seven countries in Latin America (Argentina, Chile, Colombia, Costa Rica, México, Peru and Venezuela) were assessed from May 2003 to February 2005. Although this study intended to include patients from Brazil, progress in this country was not possible because of local regulations regarding observational studies at the time of study. All medication was prescribed with the usual standard of care at each site and at the sole discretion of the participating psychiatrist. There were no restrictions on dosage of medication, polypharmacy, concomitant medications or route of administration. Patients could

switch between treatment groups at any stage of the study. Patients were followed-up within the normal course of care and assessments were made at the baseline visit and every 4 months (± 4 weeks) thereafter. Additional follow-up visits were conducted at discharge (for inpatients), remission and relapse. Ethics approval to conduct the study was obtained, where appropriate, from each participating country in accordance with local requirements. All patients gave informed consent before participating in the study.

Study population

Patients (inpatients, outpatients or in an ambulatory setting) were included in the analyses if they were 18 years of age or older, and met the revised Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[15] criteria for bipolar I disorder (manic or mixed episode) in the normal course of care, and were eligible to initiate or change an oral medication to treat a manic or mixed episode of bipolar disorder.

Outcome measures

Patient demographic data and psychiatric history were assessed at baseline and the use of psychotropic medication and clinical status were assessed at each visit. The use of psychotropic medication was summarised for the following groups: first generation antipsychotics, second generation antipsychotics, lithium, anticonvulsants and antidepressants. The median daily dose (minimum, maximum) of the most commonly used psychotropic medications during the study was reported. Clinical status was measured using the Young Mania Rating Scale (YMRS)[16] and the Montgomery-Åsberg Depression Rating Scale (MADRS)[17]. Investigators were trained in both scales and inter-rater reliability tests were performed.

The number and type of treatment-emergent adverse events (TEAEs) were recorded at each follow-up visit. Quality of life was assessed at baseline and at the final visit using the 12-item Short Form (SF-12) Health Survey[18], which comprised a Physical Component Summary Score (PCS) and a Mental Health Component Summary Score (MCS).

The main outcomes of interest were: (i) first remission (YMRS ≤ 12), (ii) first hospitalisation after first remission, and (iii) relapse either as the next new manic episode (YMRS ≥ 15) or the next new depressive episode (MADRS ≥ 15) after first remission.

Statistical analysis

Two main treatment groups for comparison were established at baseline: (i) the olanzapine group (i.e., patients prescribed olanzapine either as monotherapy or in combination with other psychotropic medication) and (ii) the non-olanzapine group (i.e., patients prescribed any psychotropic medication other than olanzapine either as monotherapy or in combination with other psychotropic medication). Treatment groups were analysed using the on-drug population (i.e., grouped by treatment prescribed at baseline and only including data from visits where patients continued to use their baseline treatment) and the baseline treatment population (i.e., grouped by treatment prescribed at baseline for all visits).

Differences between the treatment groups at baseline were analysed using Fisher's exact test or the Monte Carlo simulation for N = 10,000 (categorical variables) and Wilcoxon's test (for continuous variables).

Differences in the time to remission, hospitalisation and relapse between the on-drug treatment groups were analysed using unadjusted Kaplan-Meier analysis and the log-rank test to compare curves. The likelihood of remission, relapse and hospitalisation (hazard ratio and 95% confidence interval [CI]) were assessed using Cox proportional hazards modelling to further examine on-drug treatment group differences. The model included the on-drug treatment groups, baseline hospitalisation status and a propensity score. Propensity scoring[19] was implemented to control for selection bias and examined the following a priori defined baseline covariates: age, sex, body mass index, marital status, employment status, hospitalisation status, rapid cycler status, presence of psychiatric comorbidity, presence of psychotic symptoms, exhibition of hostility / aggression, past or current substance abuse, history of suicide attempts, previous treatment with lithium, previous electroconvulsive therapy, previous psychotherapy, past hospitalisation, current episode (manic, mixed or none), receiving intramuscular medication for current episode, number of baseline adverse events, and baseline YMRS, MADRS and SF-12 (MCS and PCS) scores. Weighted marginal structural modelling (MSM)[20] was implemented as a sensitivity analysis for the likelihood analyses to take into account treatment switching and patient discontinuation in the baseline treatment groups. Propensity scoring was used to account for selection bias with the set of covariates described above. Adjusted number needed to treat (NNT) and the

associated CI was calculated in the on-drug treatment groups for time to event outcomes using estimated survival probabilities from the Cox proportional hazards models[21]. NNTs were reported only if the 95% CIs were statistically significant.

Changes in SF-12 PCS and MCS during the study were analysed using baseline treatment groups rather than on-drug treatment groups as quality of life was only assessed at baseline and at study endpoint. Within-group changes from baseline to endpoint SF-12 scores were analysed using an analysis of covariance based on data with the last-observation-carried-forward (LOCF) approach. Baseline scores of an a priori list of candidate covariates were adjusted for confounding when the changes from baseline of those scores were analysed. The model included baseline treatment group, baseline hospitalisation status and a propensity score based on the covariates described above.

Data were analysed using SAS® Version 8.2 and Version 9.1 for Windows (SAS Institute, Cary, NC). Missing data were excluded from percentage calculations and differences were considered statistically significant at the 5% level of significance.

RESULTS

Patient disposition and baseline characteristics

A total of 766 patients participated in the study and, of these, 762 were eligible for analysis. Four patients were excluded from the analysis because they were younger than the age inclusion criterion. Of the patients eligible for analysis, 67.5% (514 / 762) completed the study. The most common reasons for discontinuation were: visit did not occur within 4 weeks before or after the scheduled visit (10.0%, 76 / 762), participating psychiatrist discontinued (7.7%, 59 / 762) and patient changed to a different psychiatrist (4.2%, 32 / 762). The treatment groups at baseline comprised 516 patients in the olanzapine group and 246 patients in the non-olanzapine group.

Most patients were from México and approximately two-thirds of the patient population were female (table 1). At baseline, 67.5% (514 / 762) of all patients had a manic episode and 31.9% (243 / 762) had a mixed episode. In addition, 50.5% (385 / 762) had psychotic symptoms and 28.6% (218 / 762) were inpatients (table 1). The mean duration of illness was 13.0 ± 11.4 years and 14.7% (112 / 762) of patients were classified as rapid cyclers. On average, patients had moderate symptoms of mania (YMRS score) with relatively little depression (MADRS score), and moderate SF-12 physical and mental component scores (table 1).

Table 1. Patient demographics and characteristics at baseline.

Characteristic	All patients	Baseline treatment groups		
		Olanzapine	Non-olanzapine	*P*-value
	N = 762	n = 516	n = 246	
Age, mean ± SD years	41.0 ± 13.7	40.2 ± 14.0	42.7 ± 12.9	0.008
Female, n (%)	490 (64.3)	317 (61.4)	173 (70.3)	0.023
Body Mass Index, mean ± SD kg/m^2	26.9 ± 5.1	26.4 ± 4.6	27.9 ± 5.9	0.007
(min, max)	(16.2, 51.4)	(16.4, 43.0)	(16.2, 51.4)	
Country of origin, n (%)				< 0.001
México	529 (69.4)	408 (79.1)	121 (49.2)	
Argentina	83 (10.9)	36 (7.0)	47 (19.1)	
Chile	53 (7.0)	14 (2.7)	39 (15.9)	
Colombia	40 (5.2)	20 (3.9)	20 (8.1)	
Venezuela	30 (3.9)	23 (4.5)	7 (2.8)	
Peru	20 (2.6)	12 (2.3)	8 (3.3)	
Costa Rica	7 (0.9)	3 (0.6)	4 (1.6)	
Current episode, n (%)				
Manic	514 (67.5)	342 (66.3)	172 (69.9)	0.455
Mixed	243 (31.9)	169 (32.8)	74 (30.1)	
Inpatients, n (%)	218 (28.6)	114 (22.1)	104 (42.3)	< 0.001
Concurrent psychotic symptoms, n (%)	385 (50.5)	267 (51.7)	118 (48.0)	0.353
Rapid cycler [a], n (%)	112 (14.7)	84 (16.3)	28 (11.4)	0.080
Duration of illness, mean ± SD years	13.0 (11.4)	12.3 (11.4)	14.5 (11.3)	0.005
Psychiatric comorbidity, n (%)	411 (53.9)	300 (58.1)	111 (45.1)	< 0.001
Current substance abuse, n (%)	28 (3.7)	20 (3.9)	8 (3.3)	0.837
Current alcohol abuse, n (%)	50 (6.6)	30 (5.8)	20 (8.1)	0.273
Rating Scales, mean ± SD				
Total YMRS[b] score	28.7 ± 9.6	28.6 ± 9.7	28.8 ± 9.2	0.975
Total MADRS[c] score	13.6 ± 9.5	14.2 ± 9.3	12.4 ± 9.8	0.002
SF12[d], Physical component score	44.6 ± 8.8	43.9 ± 8.8	46.0 ± 8.6	0.003
SF12, Mental component score	40.2 ± 11.5	39.8 ± 11.3	41.0 ± 12.0	0.224

[a]Rapid cycler = At least four episodes of a mood disturbance in the previous 12 months that meet the DSM-IV-TR criteria for a major depressive, manic, mixed, or hypomanic episode. [b]YMRS = Young Mania Rating Scale, from 0 to 60 (highest severity). [c]MADRS = Montgomery-Åsberg Depression Rating Scale, from 0 to 60 (highest severity). [d]SF-12 = 12-Item Short Form Health Survey, from 0 to 100 (highest quality of life). Missing data are not included in percentage calculations.

Although the overall depression rating (MADRS) was low, patients in the olanzapine group had significantly greater MADRS scores and significantly shorter duration of illness than patients in the non-olanzapine group (table 1). In addition, significantly more patients in the olanzapine group had one or more psychiatric comorbidities and significantly fewer were inpatients compared with the non-olanzapine group.

Pharmacological treatment patterns

There was a high degree of polypharmacy; patients were prescribed multiple combinations of antipsychotic agents, anticonvulsants, lithium and antidepressants. Before patients entered the study, the

most commonly prescribed medications were anticonvulsants (48.2%, 367 / 762) and first generation antipsychotics (41.2%, 314 / 762), followed by lithium (26.6%, 203 / 762), second generation antipsychotics (22.4%, 171 / 762) and antidepressants (18.6%, 142 / 762).

Only 16.7% (127 / 762) of patients were prescribed monotherapy at the baseline visit. An anticonvulsant combined with a first or second generation antipsychotic was the most commonly prescribed combination therapy (figure 1). The most commonly prescribed medications in the olanzapine group at baseline were: an anticonvulsant and second generation antipsychotic (26.7%, 138 / 516), a second generation antipsychotic (14.7%, 76 / 516), and an anticonvulsant, second generation antipsychotic and lithium (10.3%, 53 / 516). The most commonly prescribed medications in the non-olanzapine group at baseline were: an anticonvulsant and first generation antipsychotic (13.0%, 32 / 246), an anticonvulsant, first generation antipsychotic and lithium (11.4%, 28 / 246), and a first generation antipsychotic and lithium (11.0%, 27 / 246).

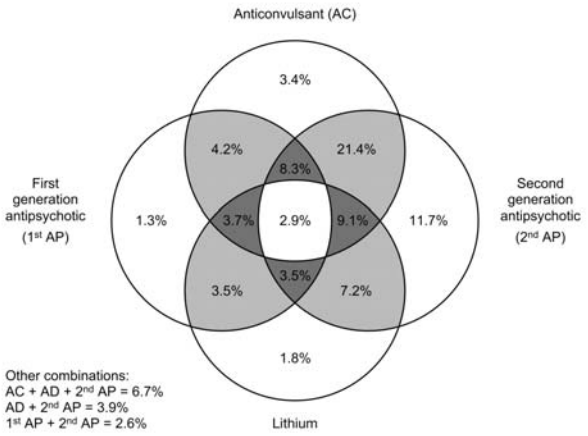

Figure 1. Pharmacological treatments prescribed for bipolar I disorder at baseline for all patients who participated in the study (N = 762). Medication classes prescribed for less than 1% of patients are not shown. AC = anticonvulsant, AP = antipsychotic, AD = antidepressant.

The median (minimum, maximum) oral doses of the psychotropic medication provided an indication of the diverse prescribing patterns in Latin American clinical practice settings. The median (minimum, maximum) oral doses of the most frequently used antipsychotics during the study were: haloperidol 15 (0.5, 90) mg/day, levomepromazine 25 (6.5, 200) mg/day, olanzapine 10 (2.5, 30) mg/day, and risperidone 3 (0.5, 12) mg/day. The median (minimum, maximum) oral doses of the most frequently used anticonvulsants were: valproic acid 800 (100, 2500) mg/day, clonazepam 2 (0.5, 15) mg/day, and carbamazepine 600 (100, 1200) mg/day. The median (minimum, maximum) oral doses of fluoxetine and lithium were 20 (10, 90) mg/day and 900 (150, 1800) mg/day, respectively.

Clinical outcomes

Similar percentages of patients in the on-drug treatment groups experienced remission of either manic or mixed symptoms during the study (table 2). The median time to remission of manic symptoms was 77 (95%CI 57 to 93) days for the olanzapine group and 43 (95%CI 36 to 65) days for the non-olanzapine group. The median time to remission of mixed symptoms was 94 (95%CI 84 to 105) days for the olanzapine group and 60 (95%CI 42 to 73) days in the non-olanzapine group. Despite the numerical difference in the median time to remission between groups, there was considerable variation in time to remission within each group and the times to remission of manic (log-rank *P*-value = 0.133; figure 2) or mixed (log-rank *P*-value = 0.430) symptoms between groups were not statistically significant. The likelihood of remission of manic or mixed symptoms was similar between the on-drug treatment groups (table 3). Sensitivity analysis suggested that when treatment switching and patient discontinuation were taken into account in the baseline treatment groups, the likelihood of achieving remission for patients in the olanzapine group was significantly higher compared with patients in the non-olanzapine group (table 3).

The rate of hospitalisation after remission of symptoms was low in both on-drug treatment groups

Table 2. Event rates of clinical outcomes for patients analysed by on-drug treatment groups.

Outcome	Olz group n / N (%) patients	Non-olz group n / N (%) patients
Remission		
Manic symptoms (YMRS [a] = 12)	404 / 516 (78.3%)	190 / 246 (77.2%)
Mixed symptoms (YMRS [a] = 12 and MADRS[b] = 10)	387 / 516 (75.0%)	179 / 246 (72.8%)
First hospitalisation after first remission	11 / 415 (2.7%)	30 / 239 (12.6%)
Relapse after first remission		
Any episode (YMRS = 15 or MADRS = 15)	62 / 415 (14.9%)	73 / 239 (30.5%)
Manic episode (YMRS = 15)	31 / 415 (7.5%)	46 / 239 (19.2%)
Depressive episode (MADRS = 15)	47 / 415 (11.3%)	41 / 239 (17.2%)
Mixed episode (YMRS = 15 and MADRS = 15)	6 / 415 (1.4%)	8 / 239 (3.3%)

[a]YMRS = Young Mania Rating Scale, from 0 to 60 (highest severity). [b]MADRS = Montgomery-Åsberg Depression Rating Scale, from 0 to 60 (highest severity). Olz = olanzapine.

(table 2). Patients in the olanzapine group were hospitalised significantly later after remission compared with patients in the non-olanzapine group (log-rank *P*-value < 0.0001; figure 2). The median time to hospitalisation could not be calculated as less than 50% of patients were hospitalised. The likelihood of hospitalisation was significantly lower for patients in the olanzapine group compared with patients in the non-olanzapine group (table 3).

Table 3. Comparison of the likelihood* of remission of symptoms, hospitalisation or relapse between the olanzapine and non-olanzapine groups.

Outcome	On-drug treatment groups [a] Hazards ratio (95%CI)		*P*-value	Baseline treatment groups [a] Hazards ratio (95%CI)		*P*-value
Likelihood of remission						
Manic symptoms (YMRS [b] = 12)	0.97	(0.80 to 1.17)	0.717	0.57	(0.40 to 0.83)	0.003
Mixed symptoms (YMRS [b] = 12 and MADRS [c] = 10)	0.92	(0.76 to 1.11)	0.384	0.67	(0.49 to 0.94)	0.019
Likelihood of hospitalisation after first remission	3.86	(1.88 to 7.93)	< 0.001	5.50	(2.57 to 11.8)	< 0.001
Likelihood of relapse after first remission						
Any episode (YMRS = 15 or MADRS = 15)	1.96	(1.36 to 2.82)	< 0.001	3.27	(1.83 to 5.86)	< 0.001
Manic episode (YMRS = 15)	2.10	(1.31 to 3.37)	0.002	3.05	(1.48 to 6.30)	0.003
Depressive episode (MADRS = 15)	1.36	(0.76 to 2.42)	0.301	1.91	(1.05 to 3.46)	0.034
Mixed episode (YMRS = 15 and MADRS = 15)	1.37	(0.45 to 4.18)	0.582	3.46	(0.94 to 12.7)	0.061

[a]Analysis of likelihood of events included (i) Cox proportional hazards modeling using the on-drug treatment groups and (ii) weighted marginal structural modelling using the baseline treatment groups to take into account treatment switching and patient discontinuation during the study (sensitivity analysis). [b]YMRS = Young Mania Rating Scale, from 0 to 60 (highest severity). [c]MADRS = Montgomery-Åsberg Depression Rating Scale, from 0 to 60 (highest severity). CI = confidence interval.

Fewer patients in the olanzapine on-drug group relapsed with a manic episode compared with patients in the non-olanzapine on-drug group (NNT = 8 [95%CI 5 to 29]; table 2). Compared with patients in the non-olanzapine group, patients in the olanzapine group took significantly longer to relapse with any episode (log-rank *P*-value = 0.0004) or with a manic (log-rank *P*-value = 0.0002) episode, but not with a depressive episode (log-rank *P*-value = 0.363) or a mixed episode (log-rank *P*-value = 0.246; figure 2). The likelihood of relapsing with any episode or a manic episode was significantly lower for patients in the olanzapine group compared with the non-olanzapine group (table 3). The likelihood of patients relapsing with a depressive episode or a mixed episode was similar between on-drug treatment groups. Sensitivity analysis suggested that when treatment switching and patient discontinuation were taken into account in the baseline treatment groups, the likelihood of a relapse with a new depressive episode, but not a mixed episode, was significantly lower for patients in the olanzapine group compared with the non-olanzapine group (table 3).

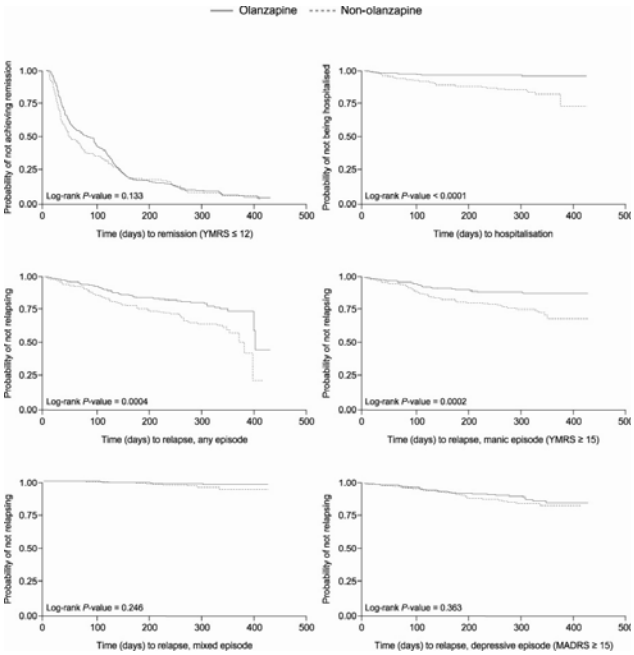

Figure 2. Kaplan-Meier survival curves for the (i) time to remission (11-item Young Mania Rating Scale [YMRS] d" 12), (ii) time to first hospitalisation after remission and (iii) time to first relapse with: any episode (YMRS e" 15 or 10-item Montgomery-Åsberg Depression Rating Scale [MADRS] e" 15), a manic episode (YMRS e" 15), a mixed episode (YMRS e" 15 and MADRS e" 15) or a depressive episode (MADRS e" 15). Treatment groups were the olanzapine and non-olanzapine on-drug treatment groups.

Adverse events

Similar percentages of patients reported at least one TEAE in the olanzapine (93.6%, 351 / 375) and non-olanzapine (91.6%, 175 / 191) on-drug treatment groups. The most commonly reported TEAEs were weight gain, increased appetite and somnolence (table 4). These events were reported more frequently in the olanzapine group compared with the non-olanzapine group. Tremor, muscular rigidity and myalgia were reported less frequently in the olanzapine group compared with the non-olanzapine group (table 4).

Similar percentages of patients in the olanzapine (34.0%, 66 / 194) and non-olanzapine (31.7%, 40 / 126) on-drug groups experienced clinically significant weight gain (≤ 7% increase from baseline) at the end of the study (*P* = 0.716).

Six deaths occurred during the study; four in the olanzapine group and two in the non-olanzapine group. No deaths were suicides.

Patients in both baseline treatment groups reported an increase in the severity of suicidal thoughts (MADRS Item 10 score) during the study (olanzapine

group = 16.4%, 72 / 439; non-olanzapine group = 14.9%, 32 / 215).

Quality of life

Table 4. Most frequently reported treatment-emergent adverse events in each on-drug treatment group[a].

Treatment-emergent adverse event	Olanzapine group % (n / N)		Non–olanzapine group % (n / N)	
Weight gain	65.2	(182 / 279)	37.5	(51 / 136)
Increased appetite	51.8	(147 / 284)	36.2	(51 / 141)
Somnolence	43.4	(109 / 251)	28.2	(40 / 142)
Headache	19.2	(52 / 271)	19.1	(29 / 152)
Asthenia	18.7	(57 / 305)	16.1	(26 / 161)
Loss of libido	18.1	(53 / 293)	13.2	(20 / 151)
Weight loss	13.0	(43 / 331)	6.2	(11 / 178)
Cognitive deficit	12.5	(31 / 248)	13.3	(19 / 143)
Tremor	11.0	(33 / 301)	23.9	(39 / 163)
Nausea	10.2	(34 / 332)	13.3	(22 / 166)
Muscular rigidity	9.2	(26 / 282)	16.4	(27 / 165)
Myalgia	8.2	(27 / 329)	11.5	(20 / 174)

[a] On-drug treatment groups were based on the treatment prescribed at baseline and only included data from visits where patients continued to use their baseline treatment. Data are presented for treatment-emergent adverse events that occurred at e" 10.0%. Missing data were not included in percentage calculations.

Patients in both baseline treatment groups had experienced a significant improvement in quality of life by study end. For the olanzapine group, the mean change in SF-12 PCS was 1.46 (95%CI 0.78 to 2.13; $P < 0.0001$) and the mean change in SF-12 MCS was 4.00 (95%CI 3.06 to 4.93; $P < 0.0001$). For the non-olanzapine group, the mean change in SF-12 PCS was 1.02 (95%CI 0.05 to 1.98; $P = 0.039$) and the mean change in SF-12 MCS was 4.86 (95%CI 3.52 to 6.20; $P < 0.0001$).

DISCUSSION

This is the first clinical practice study to prospectively assess treatment patterns and outcomes in the management of manic or mixed episodes in patients from Latin America with bipolar I disorder. There was a high degree of polypharmacy in our patient population, with anticonvulsants and either first or second generation antipsychotics being the most commonly prescribed medications. The time to remission of manic or mixed symptoms was similar between patients who included olanzapine in their treatment regimen and continued to use olanzapine for the study duration compared with patients who did not. However, patients who included olanzapine took significantly longer to relapse with a manic episode or to be hospitalised post-remission. In addition, patients who included olanzapine in their treatment regimen were less likely to relapse with a manic episode and were less likely to be hospitalised after remission or relapse with a manic episode compared with those who did not include olanzapine in their treatment. Although patients in both groups experienced similar rates of TEAEs and improved quality of life, weight gain, increased appetite and somnolence were reported more frequently in patients who included olanzapine in their treatment regimen. These findings suggest that inclusion of olanzapine in the treatment of bipolar I disorder may allow patients to maintain a clinically effective and long-term response to treatment compared with patients who use other antipsychotic medication. However, the high degree of polypharmacy in the study population limits the association of the favourable clinical outcomes to olanzapine alone.

While several RCTs have compared either remission of symptoms or prevention of relapse with olanzapine to specific treatment groups[7,22], few studies have been conducted under conditions that reflect clinical practice, where a high degree of polypharmacy is present and many patients have significant psychiatric comorbidities[12,13,23]. The longer time to relapse with a manic episode in patients who included olanzapine in their treatment regimen in our study confirms findings from an 18-month RCT comparing olanzapine combined with lithium or valproate to lithium or valproate monotherapy[22], where patients randomised to receive olanzapine combination therapy had a significantly longer time to symptomatic relapse with any episode (YMRS ≤ 15 or 21-item Hamilton Rating Scale for Depression ≤ 15) than those who received monotherapy. However, generalisation of these findings to daily practice can be problematic because the stringent inclusion criteria and controlled treatment groups used in RCTs may not be relevant to day-to-day clinical practice.

Overall, treatment patterns in our population are indicative of the high degree of polypharmacy that characterises management of bipolar I disorder worldwide. The frequent use of anticonvulsants and first or second generation antipsychotics was similar to bipolar I disorder treatment patterns reported from Europe and other non-European countries[12,13], but differs from those reported from the USA, where lithium and an anticonvulsant is the most frequently used combination therapy[24]. Regional differences in the treatment of bipolar I disorder may reflect the different

treatment guidelines used in Latin America compared with other countries, and the differences in characteristics between patient populations. Similar to other observational and noninterventional studies of patients with bipolar mania in Europe and non-European countries[12,13], patients in our study experienced moderate to severe symptoms of mania, with relatively low depressive symptoms. In addition, more than half of all patients had psychiatric comorbidities. However, in contrast to these studies, there was a higher percentage of women and a lower percentage of inpatients in our study population.

The adverse event profile in our study was consistent with those reported in similar non-interventional studies conducted mostly in Europe and other non-European countries[12,13]. Consistent with earlier studies[7,9,11], patients who included olanzapine in their treatment experienced a greater frequency of somnolence, weight gain and increased appetite compared with those who did not include olanzapine. This is supported by findings from the post hoc analysis of RCT data, suggesting that a significantly higher rate of patients from Latin America experience somnolence with olanzapine compared with patients from the USA and Europe[14]. These data suggest that Latin American patients may experience greater increases in weight with olanzapine compared with patients from Europe and the USA[14]. Therefore, patients should be counselled that olanzapine is associated with weight gain and should have their weight monitored regularly.

Few studies have assessed the long-term effect of psychotropic treatment on the quality of life of patients with bipolar I disorder[25]. The mean baseline SF-12 physical and mental health scores for our population were remarkably similar to the SF-12 component scores reported for patients with bipolar I disorder from the USA[26,27]. This is possibly a reflection of the high proportion of patients with manic episodes and relatively mild symptoms of depression[27]. In our study, all patients experienced small, but statistically significant improvements in the physical and mental components of the SF-12 quality of life scale. This finding suggests sustained improvements in clinical outcomes contribute, at least in part, to improvement in quality of life, irrespective of the type of treatment received.

This is the first large-scale, long-term study to prospectively assess treatment outcomes in patients with bipolar I disorder from Latin America. The findings from this study are clinically relevant to the Latin American population because the observational, non-interventional study design reflects the usual standard of care in this region. However, because treatment groups reflected actual clinical practice, the high rates of polypharmacy and treatment switching make it difficult to attribute the findings directly to olanzapine alone. In an effort to overcome the potential bias that may have arisen from the high degree of treatment switching and patient discontinuation in this study, clinical outcomes were assessed using the on-drug treatment population (i.e.; in those patients who remained in the same treatment group for all visits). These findings were confirmed by the sensitivity analysis where the potential bias arising from the high degree of treatment switching and patient discontinuation were accounted for in the baseline treatment groups using MSM[28,29]. The issue of unmeasured confounding, as a result of the potential effects of selection bias arising from the lack of randomisation, is a clear limitation in this study. Also, the lack of control for the high degree of polypharmacy in the study limits the association of the favourable clinical outcomes to olanzapine alone. Kaplan-Meier analysis of the comparisons of the time to remission, hospitalisation and relapse were not adjusted for baseline differences between treatment groups. Therefore, it is possible that these findings were confounded by baseline differences (e.g., approximately twice as many patients in the non-olanzapine group were inpatients at baseline compared with patients in the olanzapine group). However, analyses of the likelihood of an event occurring were adjusted for all known and collected confounders, including inpatient status, and these analyses resulted in similar differences between groups as the time to event analyses. In addition, although the potential for observer bias is also a limitation in this study, no incentive was provided to investigators to prescribe treatment or favourably assess patients in one treatment group over the other.

CONCLUSIONS

In conclusion, inclusion of olanzapine in the treatment regimen of patients from Latin America with bipolar I disorder may be an effective option for maintaining favourable long-term outcomes. Whilst all patients experienced improved quality of life during the study, patients who included olanzapine in their treatment regimen experienced a greater frequency of weight gain as an adverse event. Although this study is representative of patients treated in clinical practice, the favourable findings cannot be ascribed to

olanzapine alone because of the high degree of polypharmacy in the patient population.

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