Olanzapine or Lamotrigine Addition to Lithium in Remitted Bipolar Disorder Patients With Anxiety Disorder Comorbidity: A Randomized, Single-Blind, Pilot Study

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Objective: The aim of the present randomized, single-blind, pilot study was to assess the efficacy of the addition of a second mood stabilizer, either olanzapine or lamotrigine, to lithium in patients with remitted bipolar disorder and comorbid anxiety disorder.

Method: Adult DSM-IV bipolar disorder patients with a current anxiety disorder and a Hamilton Rating Scale for Anxiety (HAM-A) score of 12 or higher, in remission from an affective episode for at least 2 months while on lithium maintenance treatment, were randomly assigned to receive 12 weeks of single-blind olanzapine 5 to 10 mg/day (N = 24) or lamotrigine 50 to 200 mg/day (N = 23) addition to lithium. The primary outcome measure was the HAM-A; secondary outcome measures were the Clinical Global Impressions-Severity of Illness scale and the Global Assessment of Functioning (GAF) scale. Data were collected from July 2005 to February 2007.

Results: Twenty-two patients in the olanzapine and 18 in the lamotrigine group completed the trial. Mean ± SD final doses of olanzapine and lamotrigine were, respectively, 7.7 ± 4.2 mg/day and 96.7 ± 46.7 mg/day in the intent-to-treat sample (N = 47). Both olanzapine and lamotrigine were effective in reducing HAM-A scores from baseline to endpoint (paired t test for completers: $t = 11.361$, $df = 21$, $p < .001$ for olanzapine and $t = 6.301$, $df = 17$, $p < .001$ for lamotrigine). Both drugs were also effective on the secondary outcome measures. Olanzapine was more effective than lamotrigine at weeks 6 and 12 with a last-observation-carried-forward analysis on all 3 outcome measures, while such differences disappeared on the HAM-A and GAF at week 12 with the visit-wise analysis.

Conclusions: The addition of a second mood stabilizer (olanzapine or lamotrigine) to lithium is effective in reducing anxiety symptoms in bipolar disorder patients with a co-occurring anxiety disorder.

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Anxiety disorders are the most prevalent co-occurring illnesses in patients with bipolar disorder,[1,2] even during sustained periods of euthymia.[3,4]

Anxiety disorder comorbidity impacts the clinical presentation and course of bipolar disorder in that it is associated with earlier age at onset of mood symptoms,[5–8] increased prevalence of suicidal behavior and substance abuse,[7–10] and diminished quality of life[4,7,8,11]; moreover, the presence of anxiety comorbidity has been consistently found to increase time to remission from affective episodes,[12–14] increase intensity of medication treatment,[12,15,16] and reduce the duration of time spent euthymic.[3,7,10,14]

The treatment of psychiatric, and specifically anxiety disorder, comorbidities in bipolar disorder is particularly challenging; unfortunately, it is not based on controlled data but is largely empirically based.[17–19] Antidepressants from virtually every class are effective in the treatment of most anxiety disorders, but their use in bipolar disorder patients is limited by the risk of switches into mania or cycle acceleration, and there is an ongoing debate regarding their cost-effectiveness in bipolar disorder.[20–22]

Ideally, an agent that provides both mood-stabilization and anxiolysis would be recommended; however, no randomized controlled trials have been conducted in patients with bipolar disorder and co-occurring anxiety disorder using mood stabilizers. Preliminary evidence suggests that olanzapine has an effect on anxiety symptoms asso-

ciated with bipolar disorder. In a large, randomized, double-blind, placebo-controlled trial[23] of olanzapine and olanzapine-fluoxetine combination in the short-term treatment of bipolar depression, changes in Hamilton Rating Scale for Anxiety (HAM-A) scores were used as secondary outcome measures; both treatments were significantly superior to placebo in reducing HAM-A total scores, with no differences between olanzapine (mean change ± SD = –5.5 ± 0.4) and olanzapine-fluoxetine combination (mean change ± SD = –7.0 ± 1.0). Moreover, olanzapine has been found to be effective, alone or in combination with antidepressants, in the treatment of primary or resistant anxiety disorders such as panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia.[24–34] Olanzapine, finally, is recommended by both the recent Expert Consensus Guidelines Series for bipolar disorder[35] and the Canadian Network for Mood and Anxiety Treatments guidelines for the management of patients with bipolar disorder[36] as an effective first-line treatment for subjects with bipolar disorder and co-occurring anxiety disorders.

Preliminary findings also suggest that lamotrigine may ameliorate some symptoms of posttraumatic stress disorder[37] and is effective in animal models of anxiety.[38] Another indication regarding the potential efficacy of lamotrigine in subjects with comorbid bipolar and anxiety disorders stems from a study by Grof[39]; he evaluated predictors of response to different mood stabilizers (in terms of affective symptoms) and found that lamotrigine responders had higher comorbidity rates for anxiety symptoms or disorders and specifically panic disorder. These results are in agreement with those of another study on differential predictors of response to lithium and lamotrigine, which also indicated a higher comorbidity rate for panic disorder or attacks in bipolar disorder subjects responding to lamotrigine.[40] These studies give strength to the hypothesis that olanzapine and lamotrigine, which have proved mood-stabilizing properties, might be effective also in reducing anxiety symptoms in subjects with bipolar disorder.

There is also a strong need to investigate the time sequencing of interventions directed at bipolar-anxiety comorbidity; all existing guidelines indicate that the initial goal in the pharmacologic management of patients with bipolar disorder and a co-occurring anxiety disorder is mood stabilization,[18] but no studies have been conducted on the efficacy of different compounds in treating anxiety symptoms or disorders in remitted bipolar disorder patients.

The aim of the present randomized, single-blind, pilot study was to assess the efficacy of the addition of a second mood stabilizer, either olanzapine or lamotrigine, to lithium in patients with remitted bipolar disorder and comorbid anxiety disorder.

METHOD

Sample

In order to be enrolled in the present study, patients had to fulfill the following criteria: (1) DSM-IV diagnosis of bipolar I disorder or bipolar II disorder, confirmed by the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-I/P)[41]; (2) euthymic (in remission) state for at least 2 months, prospectively confirmed by a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[42] total score less than 8 and a Young Mania Rating Scale (YMRS)[43] total score less than 13; the HAM-D-17 and YMRS had to be administered by one of the authors at least twice with an interval of at least 2 months; (3) aged 18 to 70 years; (4) a HAM-A[44] total score of 12 or higher with or without a SCID-I/P diagnosis of an anxiety disorder; and (5) lithium treatment. The following were exclusion criteria: (1) a present or previous diagnosis of schizophrenia or other psychotic disorders or an organic brain syndrome or medical illness that would contraindicate the use of olanzapine or lamotrigine; (2) substance dependence or use (except for nicotine) disorder within 30 days prior to screening; (3) being pregnant or nursing or a woman of childbearing potential not using adequate contraceptive measures; (4) history of nonresponse or intolerance to olanzapine or lamotrigine; (5) rapid cycling course; and (6) current active suicidal ideation (i.e., plan or intent) or recent (within 6 months) suicide attempts. Patients using antidepressants or benzodiazepines or other antianxiety medications during the 2 months of the prospective evaluation before study entry were excluded. It was also required that patients did not participate in any type of psychosocial interventions.

Patients were recruited from referrals to the Mood and Anxiety Disorders Unit of the University of Turin, Italy. A written informed consent was obtained for all patients prior to study enrollment after the procedure had been fully explained. The protocol was reviewed and approved by the local Ethical Committee of the ASO S. Giovanni Battista di Torino.

All eligible patients underwent a systematic face-to-face interview that consisted of structured and semi-structured components including the SCID-I/P, all rating scales (HAM-D-17, YMRS, HAM-A, Clinical Global Impressions-Severity of Illness [CGI-S],[45] and Global Assessment of Functioning [GAF][46]), and a physical examination, including electrocardiogram. Laboratory tests were performed, including complete blood count; thyroid, renal, and hepatic panels; and lithium serum levels. Patients with abnormalities in any of the blood parameters indicating a medical illness that was not stable at study entry or with lithium levels less than 0.6 or greater than 1.2 mmol/L were excluded and did not enter the single-blind, randomized, treatment-addition phase. Lithium levels were checked at least twice during the screening

phase, once at the beginning of the prospective observation and again when patients were randomly assigned (beginning of the single-blind treatment phase).

Design of the Study

All patients satisfying entry criteria were randomly assigned to receive single-blind olanzapine 5 to 10 mg/day or lamotrigine 50 to 200 mg/day addition to lithium; lithium dosage was maintained unchanged, and blood levels were monitored twice during the study (at week 6 and at the end of the study).

Olanzapine was started at 2.5 mg/day and then increased to 5 mg/day after 2 weeks; after an additional 2 weeks, olanzapine dosage could be increased according to clinical judgment up to a maximum of 10 mg/day, with a 2.5 mg per week adjustment. Lamotrigine was started at 25 mg/day and then increased to 50 mg/day after 2 weeks; after an additional 2 weeks, lamotrigine dosage could be increased according to clinical judgment to 100 mg/day and then to a maximum of 200 mg/day after an additional week.

Concomitant psychotropic medications were not allowed during the 12-week single-blind phase of the study.

Outcome Measures

The primary outcome measure was the change in the mean HAM-A[44] score from baseline to endpoint. Secondary outcomes were the change in severity of illness from baseline to endpoint according to the CGI-S[45] and GAF[46] scales.

In the early phase of the study, interrater reliability on the diagnosis of Axis I disorders with the SCID-I/P and on the HAM-D-17, YMRS, HAM-A, CGI-S, and GAF scores was ascertained. The interrater reliability was found to be good: Cohen's κ coefficient was greater than 0.80 for the presence of any current or lifetime Axis I disorder, and greater than 0.85 for all the rating scales' scores.

All rating scales (HAM-D-17, YMRS, HAM-A, CGI-S, and GAF) were administered to patients at baseline, at week 6, and at the end of the study (week 12). An investigator who was blind with respect to the current medication patients were taking administered rating scales independently. Moreover, patients were instructed not to reveal to this investigator their current treatment.

All adverse experiences volunteered by the patient or observed by the investigator were recorded at each visit by means of the UKU Side Effect Rating Scale.[47] The occurrence of severe side effects (as defined by the CGI-S efficacy index [item 3]), lack of compliance (missing more than 3 consecutive doses of the drug), or withdrawal of patient consent were criteria for the premature withdrawal of the patient from the study.

Data were collected from July 2005 to February 2007.

Statistical Analysis

The primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients who took at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment.

Between-group comparisons of demographic and baseline clinical characteristics of patients included were made with the Pearson χ^2 test for categorical variables and with the analysis of variance (ANOVA) for continuous variables. A p value less than .05 (2-tailed) was considered statistically significant. Paired t test was used to assess the likelihood of olanzapine and lamotrigine to change HAM-A, CGI-S, and GAF total scores from baseline to endpoint in completers.

Mean HAM-A, CGI-S, and GAF total scores at baseline and at weeks 6 and 12 for the olanzapine and lamotrigine groups were compared using the ANOVA; we performed a visit-wise analysis and a last-observation-carried-forward (LOCF) analysis. Drop-out rates were compared using the Pearson χ^2 test.

RESULTS

Sample

Fifty-six subjects were screened; 7 of them (12.5%) were excluded because of a previous diagnosis of schizophrenia (1 patient), alcohol abuse in the previous 30 days (2 patients), history of nonresponse to study medications (2 patients), a rapid cycling course (1 patient), and suicide attempts in the previous 6 months (1 patient).

Forty-nine patients fulfilled study criteria and were randomly assigned to receive olanzapine (N = 26) or lamotrigine (N = 23). Of these, 47 patients (24 in the olanzapine arm and 23 in the lamotrigine arm) received at least 1 dose of study medication and completed at least 1 postbaseline efficacy assessment and then were included in the intent-to-treat analyses; 2 patients did not present for the second visit and did not complete a postbaseline evaluation. Demographic and baseline clinical characteristics of this sample are reported in Table 1: no significant between-group differences were detected. All patients included in the study presented a current DSM-IV anxiety disorder. Current and lifetime SCID-I/P DSM-IV anxiety comorbidities are shown in Table 2: no differences were detected between the 2 study groups concerning the rates of anxiety disorder comorbidities.

Twenty-two patients in the olanzapine group and 18 in the lamotrigine group completed the 12-week trial; the proportion of dropouts due to any reasons did not differ in the 2 groups: 8.3% (N = 2) in the olanzapine and 21.7% (N = 5) in the lamotrigine groups ($\chi^2 = 1.655$; df = 1; p = .197). All patients dropped out between weeks 6 and 12; reasons for dropout were, for olanzapine, weight gain and somnolence (1 patient) and lack of compliance

Table 1. Demographic and Baseline Clinical Characteristics of Subjects With Bipolar Disorder and Comorbid Anxiety Disorder Included in the Study (ITT sample)

Characteristic	Olanzapine (N = 24)	Lamotrigine (N = 23)	ANOVA or χ^2		
			F or χ^2	df	p Value
Actual age, mean (SD), y	50.38 (10.38)	49.83 (11.58)	F = –0.171	45	.865
Gender, male, N (%)	13 (54.2)	12 (52.2)	χ^2 = 0.019	1	.891
Educational level, mean (SD), y	13.00 (2.70)	13.61 (3.53)	F = 0.666	45	.509
Marital status, N (%)			χ^2 = 0.771	2	.680
Married	17 (70.8)	15 (65.2)			
Divorced	2 (8.3)	1 (4.3)			
Never married	5 (20.8)	7 (30.4)			
Currently working, N (%)			χ^2 = 1.079	1	.299
Yes	18 (75.0)	14 (60.9)			
No	6 (25.0)	9 (39.1)			
Age at onset, mean (SD), y	24.67 (5.71)	25.43 (7.46)	F = 0.397	45	.693
Bipolar disorder subtype, N (%)			χ^2 = 0.011	1	.917
I	8 (33.3)	8 (34.8)			
II	16 (66.7)	15 (65.2)			
Length of illness, mean (SD), y	25.71 (13.38)	25.17 (12.61)	F = –0.141	45	.889
Time from last mood episode, mean (SD), mo	21.46 (16.20)	15.52 (15.88)	F = –1.268	45	.211
Lithium level, mean (SD), mmol/L	0.74 (0.16)	0.70 (0.12)	F = –1.133	45	.263
Lithium therapy length, mean (SD), mo	44.50 (38.90)	49.57 (44.44)	F = 0.416	45	.679

Abbreviations: ANOVA = analysis of variance, ITT = intent-to-treat.

Table 2. Current and Lifetime Anxiety Disorder Comorbidities

Disorder, N (%)	Olanzapine (N = 24)		Lamotrigine (N = 23)		χ^2 Statistic, Current			χ^2 Statistic, Lifetime		
	Current	Lifetime	Current	Lifetime	χ^2	df	p Value	χ^2	df	p Value
Panic disorder, with or without agoraphobia	8 (33.3)	8 (33.3)	9 (39.1)	9 (39.1)	0.171	1	.679	0.171	1	.679
Social phobia	5 (20.8)	5 (20.8)	4 (17.4)	4 (17.4)	0.090	1	.764	0.090	1	.764
Specific phobia	2 (8.3)	2 (8.3)	0 (0.0)	0 (0.0)	2.002	1	.157	2.002	1	.157
Obsessive-compulsive disorder	7 (29.2)	7 (29.2)	8 (34.8)	8 (34.8)	0.170	1	.680	0.170	1	.680
Generalized anxiety disorder	17 (70.8)	18 (75.0)	13 (56.5)	14 (60.9)	1.042	1	.307	1.079	1	.299

(1 patient) and for lamotrigine, hypomanic switch (1 patient), worsening of anxiety symptoms (3 patients), and lack of compliance (1 patient).

Mean ± SD final doses in the olanzapine and lamotrigine groups were, respectively, 7.7 ± 4.2 mg/day and 96.7 ± 46.7 mg/day in the intent-to-treat sample (N = 47) and 7.3 ± 3.4 mg/day and 102.8 ± 49.9 mg/day in the completer sample (N = 40).

Efficacy

In patients who completed the 12-week trial, both drugs were highly effective on the primary and secondary outcome measures. Patients in the olanzapine group showed a significant improvement over the 12-week study period on all rating scales (paired t test for mean HAM-A total score at week 12 as compared to baseline: t = 11.361, df = 21, p < .001; CGI-S: t = 9.054, df = 21, p < .001; and GAF: t = –3.096, df = 21, p = .005). Moreover, they also significantly improved on the HAM-D-17 (t = 4.228, df = 21, p < .001) and on the YMRS (t = 3.495, df = 21, p = .002). Patients in the lamotrigine group showed a significant improvement on all rating scales (paired t test for mean HAM-A total score at week 12 as compared to baseline: t = 6.301, df = 17, p < .001; CGI-S: t = 4.242, df = 17, p = .001; and GAF: t = –2.254, df = 17, p = .038). They also improved significantly on the HAM-D-17 (t = 4.582, df = 17, p < .001), while changes on the YMRS did not reach statistical significance (t = –.445, df = 17, p = .662). The effect of both treatments on HAM-A scores remained significant when the baseline HAM-D-17 and YMRS scores were controlled for (repeated-measures analysis of variance with HAM-D-17 and YMRS baseline scores as covariates: F = 8.263, df = 2, p = .001 for olanzapine and F = 4.622, df = 2, p = .018 for lamotrigine).

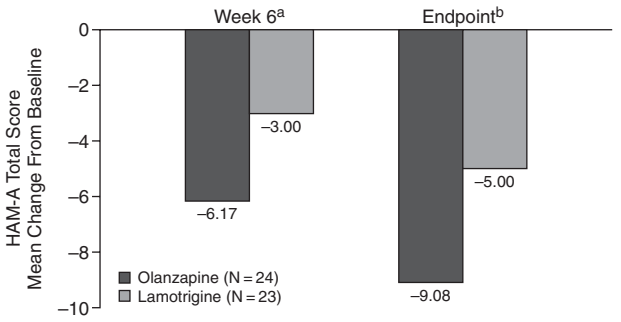
Both olanzapine and lamotrigine were effective in significantly reducing the following items of the HAM-A: anxious mood (paired t test at week 12 as compared to baseline: t = 13.096, df = 21, p < .001 for olanzapine and t = 4.592, df = 17, p < .001 for lamotrigine), tension (t = 10.887, df = 21, p < .001 for olanzapine and t = 6.872, df = 17, p < .001 for lamotrigine), fears (t = 5.700, df = 21, p < .001 for olanzapine and t = 4.123, df = 17, p = .001 for lamotrigine), insomnia (t = 9.238, df = 21, p < .001 for olanzapine and t = 5.050, df = 17, p < .001 for lamotrigine), general somatic symptoms–muscular (t = 2.592, df = 21, p = .017 for olanzapine and t = 2.380, df = 17, p = .029 for lamotrigine), general somatic symptoms–sensory (t = 4.161, df = 21, p < .001 for olanzapine and t = 3.063, df = 17, p = .007 for lamotrigine),

Table 3. Comparisons Between Mean Scores at Baseline, at Week 6, and at Endpoint: Visit-Wise and Last-Observation-Carried-Forward (LOCF) Analyses

	Olanzapine		Lamotrigine		ANOVA		
Measure	Mean	SD	Mean	SD	F	df	p Value
Visit-wise[a]							
HAM-A							
Baseline	17.46	2.00	17.48	3.64	0.001	1	.981
Week 6	11.29	3.34	14.48	4.23	8.248	1	.006
Endpoint	8.32	4.03	10.67	4.60	2.961	1	.093
CGI-S							
Baseline	3.58	0.65	3.78	0.52	1.333	1	.254
Week 6	2.63	0.88	3.26	1.01	5.334	1	.026
Endpoint	1.95	1.17	2.78	1.11	5.092	1	.030
GAF							
Baseline	71.08	10.06	66.00	10.06	3.000	1	.090
Week 6	74.58	8.93	67.57	10.33	6.228	1	.016
Endpoint	76.18	9.51	72.44	12.03	1.206	1	.279
HAM-D-17							
Baseline	6.42	1.06	6.26	1.29	0.206	1	.652
Week 6	5.38	1.84	5.52	2.04	0.067	1	.797
Endpoint	4.00	2.91	3.94	2.07	0.005	1	.946
YMRS							
Baseline	4.54	2.95	3.35	1.87	2.718	1	.106
Week 6	2.88	2.35	4.17	3.87	1.956	1	.169
Endpoint	2.64	2.42	3.89	3.14	2.029	1	.162
LOCF[b]							
HAM-A							
Baseline	17.46	2.00	17.48	3.64	0.001	1	.981
Week 6	11.29	3.34	14.48	4.23	8.248	1	.006
Endpoint	8.38	4.13	12.48	5.92	7.649	1	.008
CGI-S							
Baseline	3.58	0.65	3.78	0.52	1.333	1	.254
Week 6	2.63	0.88	3.26	1.01	5.334	1	.026
Endpoint	2.04	1.20	3.04	1.22	5.092	1	.030
GAF							
Baseline	71.08	10.06	66.00	10.06	3.000	1	.090
Week 6	74.58	8.93	67.57	10.33	6.228	1	.016
Endpoint	76.08	9.21	69.65	12.53	4.046	1	.050
HAM-D-17							
Baseline	6.42	1.06	6.26	1.29	0.206	1	.652
Week 6	5.38	1.84	5.52	2.04	0.067	1	.797
Endpoint	4.25	3.04	4.74	2.45	0.367	1	.548
YMRS							
Baseline	4.54	2.95	3.35	1.87	2.718	1	.106
Week 6	2.88	2.35	4.17	3.87	1.956	1	.169
Endpoint	2.67	2.33	4.70	4.58	3.712	1	.060

[a]Baseline: olanzapine, N = 24; lamotrigine, N = 23. Week 6: olanzapine, N = 24; lamotrigine, N = 23. Endpoint: olanzapine, N = 22; lamotrigine, N = 18.
[b]Olanzapine, N = 24; lamotrigine, N = 23.
Abbreviations: ANOVA = analysis of variance, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Figure 1. Improvement in HAM-A Scores From Baseline to Weeks 6 and 12 (endpoint) in Patients Taking Olanzapine Versus Lamotrigine (intent-to-treat sample, last-observation-carried-forward analysis)



[a]ANOVA: F = 7.168, df = 1, p = .010.
[b]ANOVA: F = 7.533, df = 1, p = .009.
Abbreviations: ANOVA = analysis of variance, HAM-A = Hamilton Rating Scale for Anxiety.

respiratory symptoms ($t = 2.160$, $df = 21$, $p = .042$ for olanzapine and $t = 2.380$, $df = 17$, $p = .029$ for lamotrigine), other autonomic symptoms ($t = 4.500$, $df = 21$, $p < .001$ for olanzapine and $t = 4.610$, $df = 17$, $p < .001$ for lamotrigine), and behavior during interview ($t = 5.684$, $df = 21$, $p < .001$ for olanzapine and $t = 5.532$, $df = 17$, $p < .001$ for lamotrigine).

Table 3 shows the comparative analyses (visit-wise and LOCF) of response to the 2 additional drugs in terms of mean HAM-A, CGI-S, and GAF scores at baseline, week 6, and week 12 (end of study). Mean HAM-D-17 and YMRS scores are also reported. With the visit-wise analysis, the 2 groups differed significantly in mean HAM-A scores at week 6, in mean CGI-S scores at both weeks 6 and 12, and in mean GAF scores at week 6. With the LOCF analysis, they differed at both weeks 6 and 12 on all 3 outcome measures (mean HAM-A, CGI-S, and GAF scores).

When examining response rates (response defined as a reduction ≥ 50% in the HAM-A total score at endpoint with respect to baseline), we did not find a significant difference between the 2 groups: 14 (63.6%) of 22 patients in the olanzapine group versus 7 (38.9%) of 18 patients in the lamotrigine group ($\chi^2 = 2.431$, $df = 1$, $p = .119$); neither did we find significant differences when considering remission rates (remission was defined as a final HAM-A total score ≤ 7): 12 (54.5%) of 22 patients in the olanzapine group versus 5 (27.8%) of 18 patients in the lamotrigine group ($\chi^2 = 2.903$, $df = 1$, $p = .088$).

Figure 1 shows the mean change from baseline to week 6 and endpoint in HAM-A scores according to treatments using the LOCF analysis: patients in the olanzapine group showed a mean ± SD decrease of 6.17 ± 2.90 points between baseline and week 6 and of 9.08 ± 3.76 points between baseline and endpoint, while subjects who received lamotrigine had a mean ± SD decrease of 3.00 ± 4.98 and 5.00 ± 6.19 points from baseline to week 6 and endpoint, respectively; both differences were statistically significant.

Other statistically significant differences between treatment groups in mean changes from baseline concerned CGI-S and YMRS scores; patients in the olanzapine group showed a mean ± SD decrease in the CGI-S of 0.96 ± 0.55

Table 4. Side-Effects Experienced by Patients Taking Olanzapine Versus Lamotrigine Addition (intent-to-treat sample)

Side Effect, N (%)	Olanzapine (N = 24)	Lamotrigine (N = 23)	Statistic χ^2	df	p Value
Sleepiness/sedation	3 (12.5)	0 (0.0)	3.071	1	.234
Weight gain	2 (8.3)	0 (0.0)	2.002	1	.489
Reduced duration of sleep	0 (0.0)	4 (17.4)	4.562	1	.050
Tension/inner unrest	0 (0.0)	5 (21.7)	5.839	1	.022
Reduced salivation	2 (8.3)	0 (0.0)	2.002	1	.489
Worsening of anxiety symptoms	0 (0.0)	3 (13.0)	3.344	1	.109

points between baseline and week 6 and of 1.54 ± 0.88 points between baseline and endpoint, while subjects who received lamotrigine had a mean ± SD decrease of 0.52 ± 0.89 and 0.74 ± 1.18 points from baseline to week 6 and endpoint, respectively (ANOVA, baseline versus week 6: F = 4.079, df = 1, p = .049; ANOVA, baseline versus endpoint: F = 7.034, df = 1, p = .011). Concerning YMRS scores, patients in the olanzapine group showed a mean ± SD decrease of 1.67 ± 1.99 points between baseline and week 6 and of 1.88 ± 2.49 points between baseline and endpoint, while subjects who received lamotrigine had a mean ± SD increase of 1.09 ± 3.88 and 1.35 ± 4.52 points from baseline to week 6 and endpoint, respectively (ANOVA, baseline versus week 6: F = 9.470, df = 1, p = .004; ANOVA, baseline versus endpoint: F = 9.275, df = 1, p = .004).

The profile of adverse events experienced by subjects in the 2 groups is shown in Table 4. Over 20% of subjects receiving lamotrigine (5/23) experienced an increase in tension and inner unrest; of them, one also experienced an increase in anxiety symptoms and another reported a reduced duration of sleep. There was a partial overlap between patients reporting an increase in anxiety symptoms and those with reduced duration of sleep: 2 of the 3 subjects with an increase in anxiety symptoms also reported a reduced duration of sleep (the other reported tension/inner unrest), while 2 of the 4 patients with reduced duration of sleep also reported an increase in anxiety symptoms. Overall, 8 patients (of 23, 34.8%) had at least 1 of the above-mentioned adverse events in the lamotrigine group. In these patients, the HAM-A mean ± SD total score remained unchanged (from 18.13 ± 3.14 at baseline to 16.13 ± 6.11 at week 6). Four of these patients dropped out before the completion of the study; in the remaining 4, however, the HAM-A score dropped significantly from beginning to endpoint (from 19.25 ± 3.86 to 8.75 ± 5.50, t = 6.754, df = 3, p = .007).

DISCUSSION

The aim of the present randomized, single-blind, pilot study was to assess the efficacy of the addition of a second mood stabilizer to lithium in remitted patients with bipolar disorder and comorbid anxiety disorder; our hypothesis was that anxiety symptoms would respond to the addition of a second mood stabilizer. If proved, the use of a second mood stabilizer instead of an antidepressant with proved efficacy in anxiety disorders would protect patients from the risk of switching into manic or mixed states or of cycle acceleration. We chose olanzapine and lamotrigine because preliminary evidence suggests their potential antianxiety effect,[23–34,37,38] and they are indicated as first-line mood stabilizer agents in the maintenance treatment of bipolar disorder, together with valproate, by existing guidelines.[48,49] We also performed a comparison of olanzapine versus lamotrigine addition, but we wanted to test primarily whether either of these medications was effective in reducing anxiety symptoms.

The results of our study indicate that both olanzapine and lamotrigine addition to lithium are effective in reducing HAM-A and CGI-S scores and in improving GAF scores, without worsening the course of bipolar disorder. This effect is evident even at rather low dosages of olanzapine and lamotrigine, approximately 7.5 mg and 100 mg/day, respectively. It has to be acknowledged, however, that a subsample of lamotrigine-treated subjects (35%) experienced side effects such as an increase in tension, an increase of anxiety symptoms, or a reduced duration of sleep, which are in the opposite direction of the hypothesized antianxiety effect of this compound, which needs to be further demonstrated.

Our study was a pilot one and was designed to investigate the potential efficacy of the 2 compounds when used in addition to a stable lithium treatment, so that we cannot conclude about the optimal dosages of the 2 drugs in relieving anxiety symptoms in bipolar disorder patients. The difference found in efficacy between the 2 groups at week 6, favoring olanzapine, may be tentatively explained by the slow upward titration of the dosages of lamotrigine with respect to olanzapine. While dosages as low as 5 mg/day of olanzapine, reached after week 2 in our study, have been reported to be effective (although when added to an antidepressant) in anxiety disorders[25,26,29,30] and might be sufficient to exert an effect, which is evident in our study as early as at week 6, the effect of lamotrigine on anxiety symptoms might be reached only at dosages of 100 mg/day, which were achieved later during the course of the trial. The analysis of the effect in completers (visit-wise) demonstrated a similar efficacy at week 12, confirming our hypothesis of a similar efficacy of the 2 compounds, with a difference only in latency of action, probably due to the time needed to reach safely adequate dosages of lamotrigine. Again, we have to acknowledge that our study was a pilot one and that we do not have sufficient information to draw conclusions about optimal dosages; neither do we have data concerning the reasons why the treating clinicians stopped titrating upward the

medications: the design of the study allowed them to decide according to response and tolerability.

Another question that our study does not address is whether different mood stabilizers, e.g., valproate or antipsychotics used in one phase of bipolar disorder, are effective in reducing anxiety symptoms in remitted bipolar disorder patients. An open-label, short-term and prophylactic (8 months) study of divalproex in 55 patients with rapid-cycling bipolar disorder, for example, simultaneously assessed response in co-occurring panic disorder or generalized anxiety disorder[50]: the majority of the patients achieved decreases in or remission of anxiety symptoms. Quetiapine also was found to be effective in reducing anxiety in patients with bipolar I or II depression in a secondary analysis from a randomized, double-blind, placebo-controlled study.[51] It is then possible that other drugs used in the treatment of different phases of bipolar disorder have an antianxiety effect.

Our study, however, is the first to examine the potential effect of an adjunctive mood stabilizer on anxiety symptoms in remitted patients with bipolar disorder and a co-occurring anxiety disorder. Since mood stabilizer therapy is the standard goal of maintenance treatment in bipolar disorder, it is appropriate in the majority of psychiatric comorbidities to defer starting new pharmacotherapy until the benefit of the mood stabilizer can be assessed. This is why we chose in this pilot study to investigate the efficacy of the addition of a second mood stabilizer only when lithium was found to be ineffective on anxiety symptoms: all patients included had anxiety symptoms despite a mean of 40 months on lithium treatment (and with checked plasma levels within the ranges suggested for maintenance therapy). Future studies will need to examine the advantages of instituting treatment for the comorbid anxiety disorder immediately versus delaying treatment until the mood disorder is under better control. It is also possible that different mood stabilizers have a specific efficacy for different subgroups of bipolar disorder patients (e.g., olanzapine or lamotrigine, and not lithium, for bipolar disorder patients with comorbid anxiety) and that the initial treatment with one of these mood stabilizers would reduce both mood and anxiety symptoms in bipolar disorder.

Our study has several limitations; first of all, the single-blind design will require confirmation in double-blind trials. The small sample size, moreover, prevented us from having a sufficient power to examine the effect of a second mood stabilizer addition to lithium in different anxiety disorders comorbid with bipolar disorder: future studies will need, first, to confirm our preliminary results and, second, to examine whether the effect is restricted to generalized anxiety or to, for example, obsessive-compulsive or panic symptoms. Our results might also not apply to all patients with bipolar and comorbid anxiety disorders; in fact, we recruited a sample of subjects who were in remission as shown by a HAM-D-17 score less than 8 and a YMRS score less than 13: our results do not apply, for instance, to patients who are unable to achieve and maintain euthymia and also present anxiety symptoms. Moreover, two thirds of our sample consisted of bipolar II disorder patients, while the majority of the studies investigating comorbidity with anxiety disorders and treatment of anxiety symptoms in bipolar disorder are primarily composed of subjects with bipolar I disorder; our sample was, moreover, about 10 years older than most studies, with two thirds of subjects married and working: it is thus possible that our results do not apply to all subjects with bipolar disorder and anxiety symptoms.

Another limitation of our study is the lack of data on mean weight gain or fasting glucose, cholesterol, or triglyceride levels throughout the study period. Given the availability of other antianxiety agents (such as benzodiazepines) or potential antianxiety agents (such as divalproex, gabapentin, or pregabalin) with a safer side effect profile, the metabolic risks of the potential use of olanzapine to treat anxiety symptoms need to be further evaluated. Finally, the study duration was only 12 weeks, which is insufficient to characterize the long-term effectiveness and, most of all, the tolerability of the 2 compounds in patients with bipolar and anxiety disorders. We found in the short-term a higher, although not statistically significant, drop out rate (21.7% versus 8.3%) and a higher side effect rate (specifically insomnia and tension/inner unrest) in patients assigned to receive lamotrigine; it is possible, however, that olanzapine side effects, such as weight gain or metabolic side effects, or even a worsening of obsessive-compulsive symptoms, will show later on during the course of the treatment.

Despite all these limitations, our results show that a second mood stabilizer (olanzapine or lamotrigine) added to lithium is effective in reducing anxiety symptoms in bipolar disorder patients with a co-occurring anxiety disorder. Given the high prevalence of bipolar-anxiety comorbidity and the negative impact of anxiety disorder comorbidity on the clinical course, quality of life, and treatment response of bipolar disorder patients, studies aimed at investigating treatment strategies in this subgroup of difficult-to-treat patients are highly warranted and have high clinical significance.

Drug names: divalproex (Depakote), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), pregabalin (Lyrica), quetiapine (Seroquel).

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