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Topiramate and divalproex in combination with risperidone for acute mania: a randomized open-label study

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Abstract

Mood stabilizers and atypical antipsychotics are commonly combined for the treatment of bipolar mania. The aim of this study was to compare the effectiveness and tolerability of topiramate and divalproex in combination with risperidone for treating acute mania patients in a naturalistic treatment setting. Seventy-four patients who met the DSM-IV criteria for bipolar mania were enrolled in this study. In order to assess the efficacy and the extrapyramidal symptoms (EPS), the Young Mania Rating Scale (YMRS), Clinical Global Impression (CGI) and Simpson–Angus Rating Scale (SARS) were measured at the baseline and at weeks 1, 3 and 6. From the baseline to the endpoint, the YMRS and CGI scores were reduced by 67.9% and 56.6% in the topiramate plus risperidone group (TPMG). The YMRS and CGI scores were also reduced by 63.7% and 58.2% in the divalproex plus risperidone group (DVPG). The weight and body mass index (BMI) increased significantly by 3.6% and 3.3% from the baseline to the endpoint in the DVPG, while they decreased by 0.5% and 0.4%, respectively, with no significant difference in the TPMG. There were no serious adverse events in either group. Despite the methodological limitations, topiramate was effective and tolerable for treating acute mania and may also be a promising alternative to a weight-gain liable mood stabilizer (MS) such as divalproex.

Keywords: Bipolar mania; Divalproex; Korean; Risperidone; Topiramate

1. Introduction

Divalproex has been reported to be effective in the short-term treatment of patients with mania, as evidenced by the results from many controlled clinical trials (Bowden et al., 1994; Freeman et al., 1992; Muller-Oerlinghausen et al., 2000; Pope et al., 1991). However, the blood level of divalproex should be monitored in order to achieve therapeutic range (Scott and Pope, 2002). Furthermore, divalproex has been associated with several side effects such

Abbreviations: ANCOVA, Analysis of Covariance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CGI, Clinical Global Impression; Cr, creatinine; DVPG, divalproex plus risperidone group; ECG, electrocardiogram; ITT, intent-to-treat population; LOCF, last observation carried forward; MS, mood stabilizer; SARS, Simpson–Angus Rating Scale; TPMG, topiramate plus risperidone group; YMRS, Young Mania Rating Scale.

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as tremors, weight gain and hepatic dysfunctions, which may result in nonadherence to the treatment (Chengappa et al., 2001; McIntyre et al., 2003).

A newer antiepileptic drug, topiramate, has some pharmacological advantages. Topiramate is minimally absorbed in the liver and mainly eliminated via kidney with a half-life of 19–23 h, requiring twice daily dose, which is favorable for adherence as well as the rapid absorption, minimal drug-interactions and good-bioavailability (Chengappa et al., 2001; Schneiderman, 1998).

A number of open and retrospective studies have reported that topiramate may be a promising alternative to traditional mood stabilizer (MS) in the treatment of bipolar mania. It was found that topiramate is effective in the short-term treatment of bipolar mania as either a combination regimen or as a monotherapy (Bozikas et al., 2002; Calabrese et al., 2001; Ghaemi et al., 2001; Guille and Sachs, 2002; Marcotte, 1998; McElroy et al., 2000). The long-term effect of topiramate in the treatment of bipolar mania has been also indicated in some open prospective and retrospective chart review studies (Vieta et al., 2003; Vieta et al., 2002). In addition, topiramate has been found to be useful in pediatric patients (DelBello et al., 2002), comorbid manic patients (Guille and Sachs, 2002) and the elderly (Madhusoodanan et al., 2002). In addition, recent studies has found topiramate to have an advantage in terms of weight gain, in which a significantly greater weight loss than a placebo was observed at all doses ranging from 64–384 mg/day in topiramate-treated patients (Ghaemi et al., 2001; Bray et al., 2003; Chengappa et al., 2002).

Overall, topiramate might have a similar acute and long-term antimanic efficacy in comparison with divalproex, while with regard to the side effects, topiramate would be expected show a more favorable profile than divalproex, particularly regarding weight gain. Thus far, there has not been a comparative study between topiramate and divalproex in the treatment of bipolar mania. Therefore, the primary purpose of this study was to examine the effectiveness and tolerability of adjunctive topiramate vs. divalproex in the treatment of patients with acute mania in an open label and randomized manner, and to extend the Western data on the effectiveness and tolerability of topiramate in the treatment of acute mania patients to the Asian population.

2. Methods

2.1. Subjects

Patients diagnosed with bipolar I disorder and a current episode of manic, according to the DSM-IV criteria (American Psychiatric Association, 1994), were enrolled in this study. All patients were recruited during the period from November 2002 to June 2003 in eight nationwide sites, including six university-based hospitals, one general hospital (tertiary care units) and one chronic mental institute in Korea, where they had been involved in some clinical trials including placebo-controlled and open studies. Written informed consent was obtained from all the subjects after they were giving extensive information on the study nature and methods.

Investigators' meetings for the study were held before and during the study, in which all investigators had to demonstrate their expertise in using the rating scales that were to be used in the study, and were given the study protocol and the methodology.

The inclusion criteria were as follows: (i) patients aged 18–65 years; (ii) DSM-IV diagnosis of bipolar I disorder with a current manic episode and a requirement for antipsychotic treatment based on the clinical experience or preference of the investigators; (iii) patients with a minimum score of 20 on the Young Mania Rating Scale (YMRS; Young et al., 1978); (iv) patients with medico-surgically stable condition as evidenced from the laboratory findings, a physical examination and medical history; (v) for female patients with childbearing potential, the subjects should guarantee the appropriate use of contraceptives. The exclusion criteria were as follows: (i) those who had confirmed organic brain diseases, including a history of cerebrovascular accidents, brain tumor or those with mental retardation; (ii) those who have a history of substance abuse or dependence within 1 month; (iii) those who have history of clozapine use within 1 month; (iv) those who have any other axis I DSM-IV diagnoses; (v) those who had used depot antipsychotics within one cycle before entering the study; (vi) a past history of hypersensitivity to the study medication; (vii) those who participated in clinical trials within 1 month before entering the study entry and those who were pregnant or were breast feeding. All patients were advised that they could withdraw from the study at any stage for any reason. Eighty-one patients initially entered a 3-day screening/washout period to determine their eligibility for randomization into the study. As a result of the meeting, along with the inclusion and exclusion criteria, a total of 74 patients with bipolar I disorder, manic, were finally enrolled.

2.2. Study design

The patients were randomly assigned to either the topiramate plus risperidone group (TPMG) or the divalproex plus risperidone group (DVPG) under an open-label condition. Topiramate, divalproex and risperidone were prescribed with flexible dosing schedules based on the investigators' experience and the patients' response from the baseline to week 6 (endpoint), although dosing recommendation was provided. The recommended starting dose of topiramate was 50 mg/day, and increase of 25–50 mg/day every 2–5 days was possible. The recommended starting dose of divalproex was 750 mg/day, and increase of 250–500 mg/day every 2–5 days was possible. The recommended starting dose of risperidone was 0.5–2 mg/

day, and increase was based on the clinicians' judgment. Antipsychotics other than risperidone were not permitted during the study. Lorazepam (oral formula) among the benzodiazepines up to a maximum of 4 mg/day was allowed to control agitation and was generally stopped after stabilization. Patients are not allowed to receive a lorazepam injection for 24 h before the completion of the rating scales. Antiparkinsonian drugs were allowed where needed. Other psychotropics were not permitted during the study period.

2.3. Assessment

The YMRS and Clinical Global Impression (CGI; Guy, 1976) scores were applied to measure the effectiveness. The neurological side effects were measured using the Simpson–Angus Rating Scale (SARS; Simpson and Angus, 1970). All assessments on the YMRS, CGI and SARS scores were run at the baseline, week 1, week 3 and endpoint. The primary measure of effectiveness was the change in the mean YMRS and CGI scores from the baseline to the endpoint. The last available postbaseline measurement was assigned as an endpoint (last observation carried forward, LOCF). Secondary effectiveness measures included a reduction in YMRS and CGI scores of 50% or more at the endpoint when compared to the baseline.

The vital signs were measured on each attendance of the patient. All adverse events attributable to or suspected to be related to the study drug were recorded at all assessment periods. Laboratory findings such as an electrocardiogram (ECG) and blood test were collected at the time of the baseline and endpoint.

2.4. Data analysis

Statistical analysis was performed using the SPSS 10.0 for Windows (SPSS, Chicago, IL) program. The data were analyzed on an intent-to-treat population (ITT, n=74). The LOCF (n=74) method was used for the endpoint efficacy analysis, requiring both the baseline score and at least one postbaseline score. All patients (n=74) who received at least one dose of the study medication were included for the safety analysis. An unpaired t-test, Fisher's Exact Test, Monte Carlo method for small cell and descriptive statistics were performed to compare the demographic and clinical variables where appropriate. Analysis of Covariance (ANCOVA) was performed to compare the mean changes in the YMRS, CGI and SARS scores between the two groups after controlling of the baseline values (sex, age, age at onset, number of past admission and diagnosis as covariates). Descriptive statistics was run for the group difference in the frequencies of side effects. ANCOVA was run to compare the mean changes in the laboratory measures between the two groups after controlling for the baseline values. All the statistical significance was two-tailed and set at $p<0.05$. Under an alpha value of 0.05 with two-tailed, the power of our sample was 80% in detecting an effect size (d) of 0.66, which corresponds to a difference in the YMRS of approximately 6.5 points between the two groups.

3. Results

3.1. Subjects

A total of 74 patients with bipolar manic episode were enrolled in this study (n=33 in TPMG; n=41 in DVPG), and 61 patients completed the study. Four patients withdrew at week 3 and nine withdrew at the endpoint. Reasons for the noncompletion were lack of response (n=2, 15.4%), side effects (n=4, 30.8%), noncompliance (n=2, 15.4%), protocol violations (n=2, 15.4%) and those lost to follow-up (n=3, 23.1%). Among of them, five (38.5%) were in TPMG and eight (61.5%) were in DVPG, which showed no statistical difference between the two groups (p=0.624).

There were no statistical differences in demographic and clinical data between the two groups. The mean age was similar between the two groups (37.5 years in TPMG; 37.6 in DVPG, p=0.960). Male was 45.5% (n=15) and 53.7% (n=22) in TPMG and DVPG, respectively (p=0.483). The baseline scores on rating scales were not different between the two groups. YMRS, CGI-s and SARS were 35.2 (p=0.482), 5.3 (p=0.480) and 0.2 (p=0.263) in TPMG, respectively, while 33.9, 5.5 and 0.5 in DVPG, respectively. This trend was same in age at onset between the two groups (29.3 years in TPMG; 28.8 years in DVPG, p=0.831). The differences in body mass index (BMI) and weight were not found between the two groups (24.1 kg/m^2 and 65.4 kg in TPMG; 24.6 kg/m^2 and 67.3 kg in DVPG; p=0.573 and p=0.388, respectively).

3.2. Medications

Within 1 year prior to entering the study, 44 (59.5%), 14 (18.9%), 56 (75.7%) and 8 (10.8%) patients had a history of MS, antipsychotic, antianxiety drug and antidepressant use, respectively. There were no group differences in previous medication history. In detail, the most common MS was lithium in the TPMG (n=15) and DVPG (n=17), respectively; the most common antipsychotic was olanzapine in the TPMG (n=2) and DVPG (n=4), respectively; the most common anxiolytic was alprazolam in the TPMG (n=17) and DVPG (n=21), respectively, and the most common antidepressant was paroxetine in the TPMG (n=2) and DVPG (n=3), respectively.

The medication doses during the study are shown in Table 1. The mean daily dose of risperidone during the study showed no group difference. Furthermore, the initial and exit doses of risperidone showed no group difference. The mean daily doses of lorazepam and beztropine were also not significantly different between TPMG and DVPG.

Table 1
Medication doses in topiramate plus risperidone group (TPMG) and divalproex plus risperidone (DVPG) in the study

	TPMG (n=33)	DVPG (n=41)	p value
Mean doses (mg/day)			
Mood stabilizer	220.6 (84.1)	908.3 (361.8)	–
Risperidone	3.4 (1.6)	3.3 (1.6)	0.735
Lorazepam	1.8 (0.7)	1.5 (0.7)	0.263
Benztropine	1.4 (0.5)	1.8 (0.7)	0.638
Starting doses (mg/day)			
Mood stabilizer	53.8 (25.1)	484.1 (178.7)	–
Risperidone	1.9 (1.0)	2.0 (1.0)	0.613
Exit doses (mg/day)			
Mood stabilizer	276.5 (158.3)	911.8 (356.7)	–
Risperidone	3.6 (1.9)	3.4 (1.8)	0.728

Values represent mean (standard deviation).

3.3. Effectiveness

From the baseline to the endpoint, the YMRS and CGI scores decreased significantly by 67.9% and 56.6% in TPMG (23.9±10.0, p<0.0001; 3.0±1.2, p<0.0001, respectively). The YMRS and CGI scores also decreased significantly by 63.7% and 58.2% in DVPG (21.6±10.3, p<0.0001; 3.2±1.2, p<0.0001, respectively), indicating no group difference (F=0.746, p=0.391; F=0.688, p=0.410, respectively), as shown in Fig. 1. The number of patients with a 50% reduction or more in the YMRS and CGI-s scores was 25 (75.8%) and 24 (72.7%) at the endpoint in the TPMG, respectively, and 29 (70.7%) and 30 (73.2%) at the endpoint in the DVPG, respectively, indicating no group difference (p=0.628; p=0.966, respectively). The number of patients entering remission (YMRS≤12) was 21 (63.6%) and 25 (61.0%) in the TPMG and DVPG at the endpoint, respectively, indicating no group difference (p=0.815).

3.4. Tolerability

No patient reported serious adverse events in the ITT population. Both treatments were generally tolerable, as shown in Table 2. As to extrapyramidal symptoms (EPS), including tremors, rigidity, dystonia and involuntary muscle contractions, about one third of the patients experienced EPS in both groups, respectively (Table 2). The mean change in the SARS score from baseline to endpoint in both the TPMG (p=0.069) and DVPG (p=0.975) was similar, indicating no group difference (F=2.021, p=0.160).

Table 2
Adverse events in topiramate plus risperidone group (TPMG) and divalproex plus risperidone (DVPG)

	TPMG (n=33)	DVPG (n=44)
Dizziness	7 (21.2)	0 (0)
Headache	6 (18.2)	2 (4.9)
Nausea	4 (12.1)	5 (2.4)
Paresthenia	3 (6.8)	0 (0)
Sedation	1 (3.0)	8 (19.5)
Concentration difficulty	1 (3.0)	6 (14.6)
Pruritis	0 (0)	1 (2.4)
EPS	9 (27.3)	13 (31.7)

Values represent number (%); EPS—extrapyramidal symptom.

Regarding weight change, 30 (73.2%) patients showed weight gain in the DVPG, while 15 (45.5%) patients experienced weight loss in the TPMG, at the endpoint. The weight (p<0.0001) and BMI (p<0.0001) increased significantly by 3.6% and 3.3% from the baseline to the endpoint in the DVPG, while it decreased by 0.5% and 0.4% with no significant difference in the TPMG (p=0.751; p=0.792, respectively), as shown in Fig. 2. ANCOVA (covariates=baseline weight and BMI, and age and sex) showed significant group difference in terms of the mean change in weight (F=14.90, p<0.0001) and the BMI (F=14.78, p<0.0001) from the baseline and endpoint.

As for liver function test, the aspartate aminotransferase (AST) was within the normal reference range at the endpoint in both groups. However, an increased alanine aminotransferase (ALT) level was found in two male patients (from 30 to 76 U/L; from 25 to 53 U/L) at the endpoint in DVPG, while an increased alanine aminotransferase (ALT) level was found in one female patient (from 28 to 69 U/L) in the TPMG. The blood urea nitrogen (BUN) and creatinine (Cr) levels were within the normal reference range at the

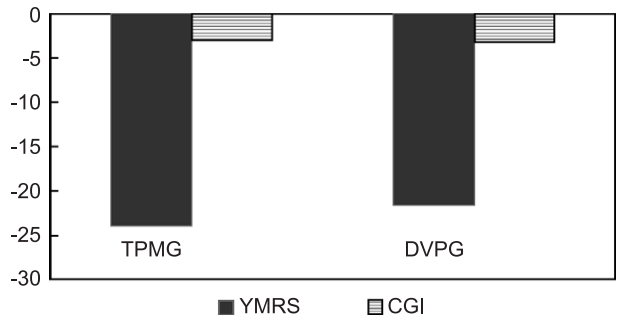

Fig. 1. The mean change in the YMRS and CGI scores from the baseline to the endpoint in the TPMG (topiramate plus risperidone group) and divalproex plus risperidone group (DVPG).

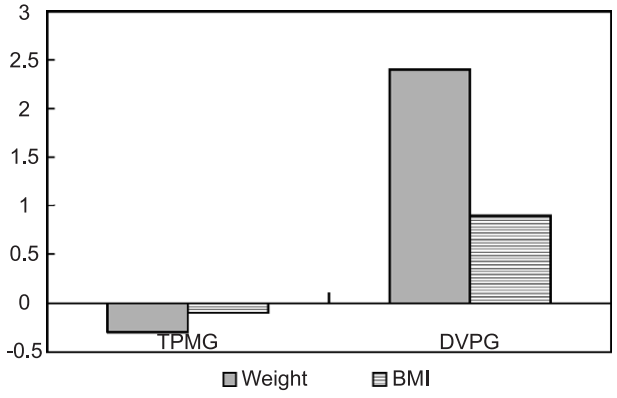

Fig. 2. The mean change in weight (kg) and the body mass index (BMI, kg/m^2) from the baseline to the endpoint in topiramate plus risperidone group (TPMG) and divalproex plus risperidone (DVPG).

endpoint in both groups. An ECG abnormality was not also found at the endpoint in both groups. However, we should keep in mind that the limitation of study design, such as the lack of monotherapy arm, would not allow us to provide accurate rate of side effects.

4. Discussion

4.1. Overall effectiveness

This study compared the effectiveness and tolerability over 6 weeks in patients with bipolar mania who received topiramate and divalproex along with risperidone. In this study, the YMRS and CGI scores significantly decreased in both group. The responder rate in the YMRS was 75.8% at the endpoint in the TPMG and 70.7% at endpoint in the DVPG, respectively. Furthermore, remission rate (YMRS≤12) was 63.6% in the TPMG and 61.0% in the DVPG at the endpoint, respectively. These positive results regarding the effectiveness in both groups are in accordance with other studies (Bowden et al., 1994; Freeman et al., 1992; Pope et al., 1991; Bozikas et al., 2002; Calabrese et al., 2001; Guille and Sachs, 2002; Marcotte, 1998; McElroy et al., 2000). Overall, the response rate in the TPMG and DVPG in this study was higher than in that of the placebo-treated group in controlled combination studies with mood stabilizers and risperidone (Sachs et al., 2002; Yatham et al., 2003), which overcome the limited interpretation of the results from an open study. Therefore, this study did not find any differences in the effectiveness in the acute mania treatment between the TPMG and DVPG.

4.2. Medication

The mean daily dose of topiramate during the study was similar to previous studies (Calabrese et al., 2001; McElroy et al., 2000; Chengappa et al., 2002). The overall suggested dose of topiramate add-on therapy for acute bipolar mania ranged from 100 to 400 mg/day, which was not confirmed but was proposed to be fairly tolerable even in rapid titrations, as reported in a phase II trial using a randomized allocation to 256 or 512 mg/day for a 10-day titration (Chengappa et al., 2001). Overall, the doses of the medications were of similar range compared to those of the Western data in the present study, indicating similar effectiveness and tolerability of topiramate and divalproex in the treatment of bipolar mania.

4.3. Tolerability

Excluding EPS and weight changes, the most and second most common adverse event was dizziness and headache, and central nervous system CNS-related side effects, which are similar to previous studies in the TPMG (Calabrese et al., 2001; Ghaemi et al., 2001; Guille and Sachs, 2002; Marcotte, 1998; Vieta et al., 2003; Vieta et al., 2002; Bray et al., 2003). In contrast, sedation and concentration difficulties were encountered in the DVPG. Nine (27.3%) and 13 (31.7%) patients in the TPMG and DVPG, respectively, experienced EPS, including tremor, rigidity, dystonia and involuntary muscle contractions. However, none of the subjects showed tardive dyskinesia during the study period, and the change in the SARS score from the baseline to the endpoint was found to be insignificant, suggesting that the topiramate/divalproex combination with risperidone for treating in bipolar mania was tolerable. Paresthesias were reported mainly in the hand and orofacial area in this study, where a similar region was observed in previous studies (Marcotte, 1998; McElroy et al., 2000). Other adverse profiles, including the BUN/Cr/AST/ALT/ECG, were not notable.

In line with our hypothesis, a significantly different effect on weight between the TPMG and DVPG was observed, indicating a superior profile in the TPMG. Weight loss by 0.5% (weight) and by 0.4% (BMI) was found in the TPMG at the endpoint, while weight gain by 3.6% and by 3.3% was found in the DVPG, respectively. This clearly contrasts topiramate with divalproex in terms of weight gain, which might affects the adherence to medication in bipolar mania (Chengappa et al., 2002). However, the results of topiramate on weight varied. Chengappa et al. (2002) reported that topiramate caused weight loss of 1.4% (1.2 kg) and BMI of 1.6% (0.5) over approximately 17 weeks with a mean dose of 260 mg/day. This is a similar trend of weight loss to our finding. Studies reported by Chengappa et al. (1999) and McElroy et al. (2000) reported 1.8 (0.8 kg) and 1.5 lbs (0.7 kg) in 1 week, respectively, while 9.4 lbs (4.3 kg) at week 5 and 3.5 lbs (1.6 kg) at week 10, respectively. Ghaemi et al. (2001) reported that topiramate lead to a weight loss of 14 lbs (about 6.4 kg) as a similar dose-related fashion to that reported in other studies (Chengappa et al., 1999; higher dose, higher weight loss), in which 50% of patients experienced weight loss. In detail, they demonstrated that the topiramate dose was higher in those who showed the higher weight loss (138.3 mg/day) than in those who did not (70 mg/day). Similarly, we found the possibility that dose of topiramate might have an impact on weight loss when subdividing into two groups with 300 mg/day or more/less, although there was a marginal difference (p=0.051). Some reports suggested that gender and the initial weight and BMI differences could influence the effect of topiramate on weight loss (Chengappa et al., 2001). In contrast to a previous finding, our study failed to find a correlation between the initial weight (p=0.077) and BMI (p=0.172) and weight loss as well as between gender and weight loss (weight, p=0.827; BMI, p=0.856). McElroy et al. (2000) reported that neither the initial weight nor the BMI was associated with weight loss, which is in line with our results. Finally, World Health Organization (WHO) expert consultation (2004) recently attempted redefine cutoff points for Asian population, but they concluded retaining of interna-

tional classification of BMI to Asian population because of the wide variation of the available data. However, it would be interesting how many patients show shift of BMI from normal range (18.5–24.9 kg/m^2) to preobese (25–29.9 kg/m^2) or obese (≥30 kg/m^2) between the two groups. In TPMG, 3.0% (n=1), 57.6% (n=19), 33.3% (n=11) and 6.1% (n=2) were in underweight, normal, preobese and obese BMI at baseline. None shifted to preobese BMI from the subjects with normal BMI at endpoint. One patient with underweight BMI shifted to normal BMI at endpoint. Some patients with preobese (n=2) and obese (n=2) BMI shifted to normal BMI at endpoint. Thus, the shift from one class to other lighter class was 12.1% (n=4) in total TPMG.

In DVPG, 4.9% (n=2), 58.5% (n=24), 24.4% (n=10) and 12.2% (n=5) were in underweight, normal, preobese and obese BMI at baseline. One patient with underweight BMI shifted to normal BMI at endpoint. Five patients with normal BMI shifted to preobese BMI at endpoint. One patient with preobese BMI shifted to normal BMI at endpoint. Thus, the shift from one class to other heavier class was 17.1% (n=7) in total DVPG.

4.4. Study design issues

The main strength of this study is that it is the first comparative study of the effectiveness and tolerability of topiramate vs. divalproex, using Asian samples. In addition, a homogenous group in a current manic episode was only included in order to reduce the heterogeneity of bipolar disorder. Finally, only risperidone as an antipsychotic combination was allowed in order to minimize the antipsychotic bias in effectiveness and tolerability profile. However, the only permitted antipsychotic was risperidone, which would give major limitation on the antimanic effect of topiramate because of known antimanic effects of risperidone as a monotherapy, although very limited data have been published so far. Sajatovic et al. (1996) failed to find the efficacy of risperidone monotherapy in a small pilot trial. All patients discontinued risperidone due to side effects or worsening of psychopathology; only one patient (21%) showed 50% reduction in YMRS, and the mean YMRS decrement was only 8% at endpoint. A controlled study (Segal et al., 1998) showed 57% improvement of manic symptom rating scale at endpoint, while high rate of EPS (similar with haloperidole monotherapy) and high dose of risperidone (6 mg/day) were reported. The most recent monotherapy study (Vieta et al., 2004; n=96) reported that 62.5% of patients met the responder criteria and 33.3% of patients met the remission criteria (YMRS≤12) at week 4, while 26% of patients showed relapse during 6-months follow-up. In comparison with those published data, we found a 68% decrease of YMRS at endpoint, and 25 patients (76%) and 21 patients (63.6%) met responder and remission criteria in the present study. These results may allow us to draw a careful conclusion on the effectiveness of topiramate in bipolar mania.

There were several methodological drawbacks in this study. This study did not include a control group so that the reduction in the YMRS and CGI scores may simply be due to the natural course of the disease. This study was a multicentre design, which might have had some observer biases. The treatment was set in a naturalistic design, although we restricted some medication regimens as a combination. Finally, a structured diagnostic interview for the disease was not included.

5. Conclusion

Despite the methodological limitations, this study demonstrated that either topiramate or divalproex in combination with risperidone is effective and tolerable for treating bipolar mania. In particular, topiramate was superior to divalproex with regard to the weight changes. Therefore, further studies with a controlled design are needed.

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