1-Year Follow-Up of Patients Treated With Risperidone and Topiramate for a Manic Episode

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Background: The safety and efficacy of the combination of risperidone and topiramate in the long-term treatment of mania were assessed in a 12-month, multicenter open study.

Method: Subjects (N = 58) who met DSM-IV criteria for bipolar disorder and for a manic episode received both risperidone and topiramate for the treatment of their manic symptoms. Patients with mixed episodes were excluded. Risperidone could be discontinued at any point, but patients had to be on topiramate therapy for at least 12 months to be considered completers. Efficacy was assessed with the Young Mania Rating Scale (YMRS) and a modified version of the Clinical Global Impressions for Bipolar Disorder (CGI-BP-M). Safety was assessed with systematic collection of side effect data, weight, and the Hamilton Rating Scale for Depression (HAM-D) scores, to address the risk of switch into depression.

Results: 41 patients (70.7%) completed the study. There was a significant improvement on the YMRS ($p < .001$) and the CGI-BP-M subscales for manic symptoms ($p < .005$) and long-term outcome ($p < .005$) from week 2 onward. Relapse rates were significantly lower during the 12-month study period compared to the precedent year ($p < .0001$). There was no increase in depressive symptoms as measured by the HAM-D. 37 patients (63.8 %) experienced at least 1 adverse event, the most frequent of which was somnolence (N = 7, 12.1%). At endpoint, the patients' mean weight had decreased an average of 1.1 ± 0.4 kg.

Conclusion: Despite the limitations inherent to the open design, this naturalistic study suggests that the combination of risperidone and topiramate may be a valuable option for the short- and long-term treatment of mania.

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Risperidone is licensed in several countries, including Spain, for the adjunctive treatment of mania with mood stabilizers. To date, no single randomized, double-blind trial has established its efficacy in monotherapy for the treatment of mania, so its use is generally limited as an adjunct during the first weeks of therapy because it has been shown to be more efficacious and have a faster onset of action than mood stabilizers alone.[1,2] While the combination of risperidone and lithium, valproate, or carbamazepine has been tested in double-blind trials[1,2] and large observational studies,[3] there is no single report on the combination of risperidone with other drugs that are believed to have mood-stabilizing properties. This poses the question of what to do with patients who may benefit from adjunctive risperidone but are intolerant of or unresponsive to the conventional mood-stabilizing drugs, such as lithium, valproate, or carbamazepine. To the best of our knowledge, there are no data on the efficacy and safety of risperidone-lamotrigine or risperidone-topiramate cotherapy.

Topiramate is an anticonvulsant that might have mood-stabilizing properties, according to several open studies and case series.[4–6] However, a randomized, double-blind monotherapy study on the efficacy of topiramate in acute mania did not show any difference from placebo on the primary efficacy measure,[7] and thus, the antimanic efficacy of this drug remains unproven. With the present

study, we tried to address the efficacy and safety of the combination of a well-established antimanic adjunctive drug, risperidone, and a potential mood stabilizer such as topiramate for the long-term treatment of patients who could not take the available standard treatments (lithium, valproate, or carbamazepine).

METHOD

Study Subjects

This study was conducted from October 2000 to March 2002 by a network of clinicians who were intensively trained in the use of the rating instruments and the protocol. This network is involved in several observational studies addressed to assess the effectiveness of the available drugs in the treatment of bipolar disorders in actual clinical practice conditions; it encompasses a number of centers across Spain, including the 17 that were involved in this specific study: Hospital Virgen del Rocío (Sevilla); Hospital Son Dureta (Palma de Mallorca); Hospital General de Valencia, Hospital Clínico de Salamanca, Hospital de Bellvitge, Hospital del Mar, Hospital Cruz Roja, Institut Municipal de Psiquiatria, and Hospital Clinic (Barcelona); CSM Fuenlabrada, CSM Móstoles, Hospital Princesa, and CSM Alcalá de Henares (Madrid); CSM Pumarin (Asturias); Ambulatorio Vargas (Cantabria); CSM Valverde (Huelva); and Hospital Cruces (Bilbao).

For patients who deserve alternative treatments to the standard ones, informed consent is required to prospectively collect the data concerning treatment response and tolerability. More than 2000 patients are believed, approximately, to attend the settings involved, though data are selectively collected for specific treatment protocols. The Ethics and Research Board of the Hospital Clinic of Barcelona approved the protocol.

This study enrolled 58 bipolar I manic patients with a history of poor response or intolerance to lithium, valproate, and carbamazepine, who were subsequently treated with a combination of risperidone and topiramate for an acute manic episode. Poor response or intolerance to standard treatments was addressed by interview with the patient and confirmed insofar as all 3 drugs had been tried in the past, either in monotherapy or in combination, and withdrawn because of lack of efficacy or side effects. Since we wanted to address not only acute manic efficacy, but also long-term outcome, the endpoint was preestablished at 1 year. To be enrolled, the patients had to be between 18 and 65 years old, fulfill DSM-IV criteria for bipolar disorder and for a manic episode, have a Young Mania Rating Scale (YMRS)[9] score above 20, and provide reliable data on the course of the illness during the previous year. For this reason, only subjects with documented medical records and family reports for the previous year were included. As mixed states are viewed by several authors as a separate entity, bipolar patients with mixed episodes were not included.[8] Pregnant or lactating women, women using ineffective contraceptive methods, or patients suffering from severe organic illnesses were excluded.

Assessments

All patients were assessed at baseline and as long as possible, according to treatment response, for up to 1 year. Assessments were performed at weeks 2 and 4 and at months 3, 6, 9, and 12.

At baseline, demographic and clinical data, including careful assessment of the course of the illness during the previous 12 months, DSM-IV criteria, rating scales, and weight, were systematically collected in the case report forms. The instruments used were the Spanish version of the YMRS,[9] the 17-item Hamilton Rating Scale for Depression (HAM-D),[10] and the Modified Clinical Global Impressions for Bipolar Disorder (CGI-BP-M),[11] which is a reduced version of the CGI-BP[12] for the assessment of response to treatments with potential effects on manic symptoms, depressive symptoms, and prevention of relapse. The reliability of the YMRS across the network's sites has been proved to be high.[9]

Relapses and adverse event data were systematically collected at every visit on all patients, including those dropping out during the study, and were intended to be followed-up for 1 year for the assessment of relapse/recurrence. Weight and body mass index were also recorded at every visit.

In all cases, both risperidone and topiramate were introduced at the same time or with a 48-hour maximal time difference. The recommendation focused on risperidone to address the acutely manic symptoms and on topiramate for longer-term stabilization and prevention of relapse by means of a slow titration (25–50 mg/day increase every 3–5 days), but the final decision was always up to the clinician. Thus, risperidone could be tapered off at any time during the 1-year follow-up study, but the patients had to be maintained on topiramate for 1 year to be considered completers. The recommendations were not mandatory, and the treating clinician could decide to go faster or slower regarding titration, could target a higher or a lower dose according to treatment response and tolerability, and could maintain or stop risperidone as an adjunct as long as he felt that it was more beneficial for the patient. Benzodiazepines were allowed throughout the 1-year follow-up study.

Statistical Analyses

The principal analyses of efficacy measures were conducted on an intent-to-treat basis, meaning that data for all participants who were treated and who had at least 1 postbaseline assessment were included in the analyses. Wilcoxon test was used to compare baseline with postbaseline/endpoint ratings and weight. Significance was set at 2-tailed $p < .05$.

RESULTS

Participant Characteristics

This study recruited 58 acutely manic bipolar I patients (28 men and 30 women) with a mean ± SD age of 40.8 ± 11.2 years and a duration of illness of 15.2 ± 9.3 years. The patients had a mean of 3.8 ± 4.6 previous lifetime hospitalizations and 1.8 ± 1.2 episodes during the prior 12 months.

Their mean body weight was 73.9 ± 13.0 kg (162.9 ± 28.7 lb), and their body mass index (BMI) was 26.5 ± 4.5. A majority of the patients were initially treated on an inpatient basis (N = 38, 65.6%), 33 (56.9%) had psychotic symptoms, 13 (22.4%) had a history of suicide attempts, and 25 (43.1%) had any kind of substance abuse.

Of 58 patients recruited, 17 (29.3%) failed to complete the study. The reasons for noncompletion are shown in Table 1.

Table 1. Reasons for Discontinuation Among 58 Patients Treated With Combination Risperidone and Topiramate

Variable	N	%
Lost to follow-up	7	12.1
Side effects	5	8.6
Lack of efficacy	3	5.2
Poor compliance	1	1.7
Other	1	1.7
Total early discontinuation	17	29.3

Efficacy

There was a significant reduction in the YMRS and HAM-D scores from week 2 onward (Wilcoxon $p < .001$ and $p < .005$), as shown in Figure 1. From a baseline mean YMRS score of 29.0 ± 5.5, there was an average decrease of 6.2 points at week 2, 16.5 at week 4, 21.4 at month 3, 24.1 at months 6 and 9, and 26.2 at the 1-year endpoint. Improvements from week 2 onward were also observed in CGI-BP-M subscale scores for manic symptoms (Wilcoxon $p < .005$) and long-term outcome (Wilcoxon $p < .005$) but not for the depressive symptoms subscale (Wilcoxon p = NS).

Using intent-to-treat (ITT) analysis with response defined as a ≥ 50% reduction in YMRS score and remission defined as a YMRS score below 8, at the 1-year endpoint, there were 36 responders (62.0%) and 35 patients (60.3%) in remission. During the study period, 15 patients (25.9%) had a relapse. Of these, at endpoint, 9 patients (15.5%) had presented with a depressive episode, 4 (6.9%) met DSM-IV criteria for mania, 1 (1.7%) for hypomania, and 1 (1.7%) for a mixed episode. The mean number of episodes during the 1-year prospective assessment was 0.5 ± 0.2 (excluding from the denominator those lost to follow-up), which was significantly lower than the mean number of episodes during the preceding year (1.8 ± 1.5) for this sample (Wilcoxon $p < .0001$). The difference remained significant when the sample was split between patients on risperidone-topiramate cotherapy (Wilcoxon $p = .02$) and patients only on topiramate treatment at the endpoint (Wilcoxon $p < .01$).

Safety

Only 5 patients (8.6%) dropped out because of side effects, particularly cognitive disturbances (N = 2, 3.4%), akathisia (N = 1, 1.7%), galactorrhea (N = 1, 1.7%), and somnolence (N = 1, 1.7%). The incidence of any adverse event was 63.8% (N = 37). The most common ones were somnolence (N = 7, 12.1%), paresthesia (N = 6, 10.3%), dizziness (N = 5, 8.6%), tremor (N = 5, 8.6%), weight loss (N = 5, 8.6%), extrapyramidal disorder (N = 5, 8.6%), and gastrointestinal (N = 5, 8.6%) and cognitive disturbances (N = 4, 6.9%), as shown in Table 2. One patient presented with tardive dyskinesia during the study.

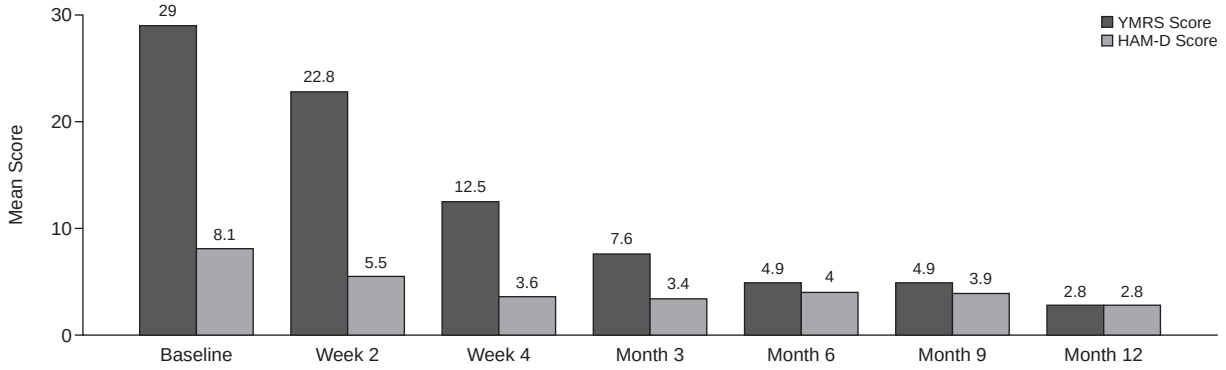
There was no increase in depressive symptoms as measured by the HAM-D. In fact, significant improvements were observed throughout the 12-month period in HAM-D scores ($p < .005$), even though this was not confirmed with the CGI-BP-M depression subscale (p = NS). During the first 4 weeks of the study, 3 patients (5.2%) had a switch to depression and 1 (1.7%) had a manic relapse.

Although only 5 patients complained of weight loss as an adverse event, 27 patients (46.6%) had actually lost weight after 12 months. The mean change in weight was –1.1 ± 0.4 kg (–2.4 ± 0.9 lb) for the whole sample. The mean body mass index decreased from 26.5 ± 4.5 at baseline to 26.1 ± 4.3 at endpoint. There was a statistically significant correlation between weight loss and improvement in manic symptoms as measured with the YMRS (Pearson $r = 0.5023$, $p = .01$).

Medication Doses

The mean doses received by the participants during the trial were 2.7 ± 1.7 mg/day of risperidone and 236.3 ± 138.1 mg/day of topiramate. Figure 2 shows the mean doses of each drug at every study point. No patient discontinued risperidone therapy within the first 2 weeks, 8 (13.8%) discontinued between weeks 2 and 4, 6 (10.3%) between week 4 and month 3, 6 (10.3%) between months 3 and 6, 8 (13.8%) between months 6 and 9, and 3 (5.2%) between months 9 and 12. At the 12-month endpoint, 27 patients (46.6%) were taking both risperidone and topiramate, 14 (24.1%) were taking only topiramate, and 17 (29.3%) had dropped out. Thus, the mean duration of risperidone cotherapy was 29.4 ± 9.7 weeks (6.9 months). Figure 3 shows the proportion of patients remaining on cotherapy at every visit. Reasons for discontinuation of risperidone but not topiramate were clinician's decision (N = 10, 17.2%) and side effects (N = 4, 6.9%), basically amenorrhea (N = 3, 5.2%) and sexual dysfunction (N = 1, 1.7%).

Figure 1. Mean Change in Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HAM-D) Scores for 58 Manic Patients Treated With Risperidone and Topiramate[a]

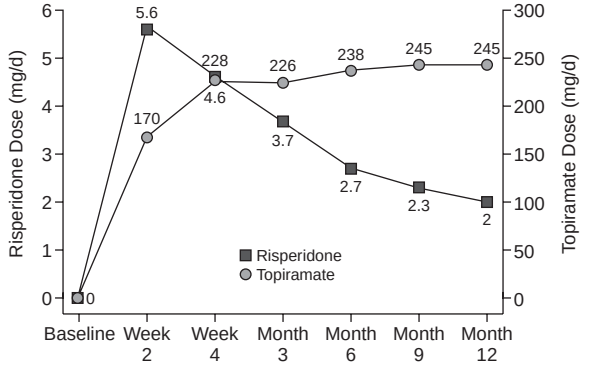


[a]These scores show statistically significant improvements ($p < .001$) from week 2 onward in manic symptoms (YMRS) without worsening depressive symptoms (HAM-D) throughout a 12-month period.

Table 2. Adverse Events During the 12-Month Risperidone-Topiramate Cotherapy Study in Mania (N = 58)

Variable	N	%
None	21	36.2
Somnolence	7	12.1
Paresthesia	6	10.3
Dizziness	5	8.6
Tremor	5	8.6
Weight loss	5	8.6
Extrapyramidal disorder	5	8.6
Gastrointestinal	5	8.6
Cognitive disturbances	5	8.6
Amenorrhea	3	5.2
Weight gain	3	5.2
Akathisia	3	5.2
Headache	3	5.2
Hair loss	2	3.4
Anxiety	2	3.4
Sexual dysfunction	2	3.4
Insomnia	2	3.4
Other	10	17.2

Figure 2. Mean Dose of Risperidone and Topiramate During 12-Month Follow-Up Study of 58 Manic Patients

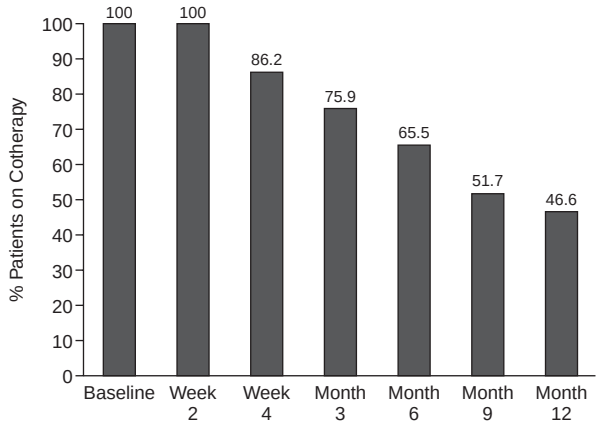


DISCUSSION

This pilot study is the first to address the safety and the efficacy of the combination of risperidone and topiramate in the short- and long-term treatment of bipolar mania. The treatment paradigm in this condition is more and more combination therapy rather than monotherapy. Combination therapy may be advantageous as far as synergies in mechanisms of action and efficacy can be observed, but on the other hand it may carry additional safety risks and interactions, which can be evaluated through open studies such as this. The results from this study suggest that risperidone and topiramate can be safely combined and that significant improvements in manic symptoms can be observed from the first assessment after baseline until the 12-month endpoint.

This study has several limitations that should be considered. The first and most important is the open design and the absence of a control group. However, results from other open, multicenter studies from some of the authors on the efficacy and safety of several drug combinations have been confirmed in all cases by double-blind, randomized clinical trials. For instance, a large open study on risperidone plus mood stabilizer cotherapy in mania[3] showed strikingly similar positive results to 2 double-blind trials comparing this combination with placebo plus mood stabilizers.[1,2] Results of a positive open study on olanzapine as add-on therapy in mania[13] were also confirmed by a randomized, double-blind trial of olanzapine plus mood stabilizers versus placebo plus mood stabilizers.[14] Furthermore, a negative open study from our group showed no benefit from add-on gabapentin in manic patients taking lithium,[15] and the same results were observed in a double-blind, randomized, placebo-controlled add-on trial.[16] We believe that our well-trained and experienced investigators may have helped to mitigate against spurious positive results in this study. Another limitation is

Figure 3. Percentage of Patients Remaining on Risperidone Plus Topiramate Cotherapy Throughout the Study Period (N = 58)



inherent to the combination therapy design that makes it difficult to separate the effects of each drug. However, 53.4% patients discontinued risperidone and were maintained well with topiramate monotherapy, so that some experience can be gained from their outcome. A third limitation is that compliance was not assessed by blood-checking, but only by patients' reports. However, we think that the significantly positive correlation that we observed between YMRS score decrements and weight loss can only be explained by means of compliance. On the other hand, the advantage of naturalistic studies is that they enroll less biased samples, including patients with comorbidity and suicide risk, who are usually excluded from clinical trials.

Besides showing efficacy in the short-term, with significant improvements in YMRS and CGI-BP-M mania subscale scores, the combination of risperidone and topiramate seemed to maintain efficacy over a long period of time (1 year), since there was no subsequent increase in YMRS scores. Furthermore, when the number of episodes during the study period was compared with the number of episodes in the precedent year, significant differences emerged suggesting a mood-stabilizing effect of risperidone-topiramate cotherapy and perhaps, attending to the relapse rate of the patients who discontinued risperidone and remained in remission, of topiramate monotherapy as well.

The side effects that emerged during the study were mainly those already reported separately for risperidone[17] and topiramate[18] in manic patients, suggesting that both drugs can be safely combined. In fact, most studies have found the combination of risperidone with mood stabilizers to be reasonably safe,[1–3] and the same seems to apply to the combination of topiramate with antipsychotics.[4,6] One particular side effect of topiramate, which may actually become desirable in some patients, is weight loss. We found particularly interesting the fact that, despite risperidone treatment, which is usually associated with mild-to-moderate weight gain,[19] the combination of topiramate and risperidone had an almost neutral effect on weight with average loss of about only 1 kg (2.2 lb). According to this result, topiramate may neutralize the tendency of certain drugs, particularly risperidone, to induce weight gain in bipolar patients. If this suggestion is confirmed in further studies, topiramate could become a good choice for the prophylaxis of the weight gain that is frequently associated with several psychiatric treatments. The positive correlation between weight loss and improvement in manic symptoms as measured with the YMRS is likely to be explained by means of compliance.

Although a few case reports suggested that risperidone might be associated with induction or exacerbation of mania in some patients,[20] further controlled trials[1,2] and large observational studies[3] have not supported this concern, and the present study is no exception. Furthermore, the risk of switching to depression was also very low: only 5.2% during the first 4 weeks, and 15.5% for the 12-month follow-up.

As shown in Figure 2, mean modal doses of risperidone were as high as 5.6 mg/day at week 2 and as low as 2 mg by the endpoint. In the 2 double-blind add-on trials,[1,2] doses were slightly below 4 mg/day, although placebo-controlled trials, even when add-on, usually differ from the actual doses used in routine clinical conditions. In fact, in our large open add-on study,[3] the mean risperidone dose was around 5 mg/day. From week 2 onward, the mean dose of risperidone in the present study went progressively down as a plateau was reached with topiramate. This pattern suggests that the clinicians used risperidone as the main treatment for acute manic symptoms and titrated topiramate up to around 250 mg/day, most likely looking for prophylactic effects. Hence, the clinicians seemed to be more confident in the acute antimanic properties of risperidone than topiramate.

The issue of the duration of the antipsychotic treatment deserves further attention. Although antipsychotics, particularly conventional neuroleptics, are believed to be unnecessary or even deleterious in the prophylaxis of bipolar illness, the fact is that they are widely used long term.[21] With atypical antipsychotics, concerns about tardive dyskinesia and negative effects on the course of the illness are probably less important, and claims about their potential mood-stabilizing properties are being made.[3,13,22,23] For this reason, it is difficult to separate in the present report the potential prophylactic effects of topiramate and risperidone. Besides, the absence of a comparison group treated with placebo or with lithium makes it difficult to ascertain whether there was any real benefit from the prophylactic treatment, although previous studies have reported consistently higher relapse rates.[24] From

the results of this observational, long-term prospective study, we can only conclude that the clinicians decided that roughly half of the patients deserved combination treatment for 1 year, and that 1 in 4 could stay well with topiramate monotherapy.

In conclusion, this long-term, multicenter, open, prospective observational study suggests that risperidone and topiramate can be effectively and safely combined in the treatment of mania, although the prophylactic efficacy of both risperidone-topiramate cotherapy and topiramate monotherapy remains to be confirmed in randomized, double-blind trials.

Drug names: carbamazepine (Tegretol and others), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine, (Zyprexa), risperidone (Risperdal), topiramate (Topamax).

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