Risperidone Safety and Efficacy in the Treatment of Bipolar and Schizoaffective Disorders: Results From a 6-Month, Multicenter, Open Study

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Background: The goal of this study was to assess the efficacy and safety of risperidone in bipolar and schizoaffective disorders.

Method: 541 patients entered this open, multicenter, 6-month study. Patients were entered provided that they fulfilled DSM-IV criteria for bipolar disorder or schizoaffective disorder, bipolar type, during a manic, hypomanic, mixed, or depressive episode. Risperidone was added to any previous mood-stabilizing medication that the patients were taking. Efficacy was assessed with the Young Mania Rating Scale (YMRS), the Hamilton Rating Scale for Depression (HAM-D), the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impressions scale (CGI). Extrapyramidal symptoms (EPS) were assessed using the UKU Side Effect Rating Scale.

Results: 430 patients completed the study. Addition of risperidone produced highly significant improvements ($p < .0001$) on the YMRS and HAM-D at both 6 weeks and 6 months and on the CGI and the scales of the PANSS at both 4 weeks and 6 months. There was a significant reduction in UKU total and subscale scores at 6 months. The mean dose of risperidone was 3.9 mg/day. There was no single case of new-emergent tardive dyskinesia, and there was a very low incidence of exacerbation of mania within the first 6 weeks (2%). Adverse events were few and mostly mild, the most frequent being EPS and weight gain.

Conclusion: This large study provides additional evidence that risperidone is effective and well tolerated when combined with mood stabilizers in the treatment of bipolar disorder and schizoaffective disorder, bipolar type. Previous concerns about exacerbation of manic symptoms were not confirmed.

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Because of the wide spectrum of symptomatology, complex psychiatric conditions such as bipolar disorder and schizoaffective disorder frequently need more than one drug for adequate control of symptoms. In bipolar disorder, an antipsychotic drug or an antidepressant is commonly added to lithium or to another mood stabilizer during acute phases,[1] and in schizoaffective disorder, the combination of an antipsychotic and an antidepressant is usual practice.[2] However, combining some medications with lithium can cause problems with drug interactions such as increased neurotoxicity[3,4]; further, some of the combinations commonly used are often ineffective.[4,5] Traditional classification of medications as antipsychotic, antidepressant, or mood stabilizing emphasizes one treatment benefit to the exclusion of other important benefits. Thus, in bipolar and schizoaffective disorders for example, control of psychotic/manic symptoms must go hand in hand with treatment and prevention of affective symptoms.

Risperidone, a benzisoxazole compound, is a novel antipsychotic drug with proven efficacy against both the positive and negative symptoms of schizophrenia.[6] It is

generally well tolerated, with a low potential for extrapyramidal and other adverse events.[7–9] In addition to its efficacy against psychotic symptoms, risperidone seems to be effective against affective symptoms (anxiety and depression) in schizophrenia.[10] Thus, it may have a broader efficacy profile than commonly thought, encompassing a range of symptoms not normally associated with the term *antipsychotic*. Evidence for this contention comes from a number of studies in both schizophrenia and bipolar disorder.

A number of open-label studies,[11–16] 1 double-blind study of monotherapy,[17] and 2 still unpublished double-blind add-on trials[18,19] suggest that risperidone is also effective and well tolerated in the treatment of the manic phase of bipolar disorder. In an open-label study as adjunctive therapy in 15 manic patients resistant to conventional mood-stabilizing drugs, risperidone showed significant improvements at 2 and 6 weeks.[14] A 6-month open study by Ghaemi et al.[15] showed that adjunctive risperidone was an effective antimanic therapy in bipolar patients who experienced "breakthrough" episodes despite adequate dosage of conventional mood stabilizers such as lithium and valproate. Risperidone was shown to be as effective as haloperidol and lithium in the treatment of 45 acutely manic patients in a double-blind study by Segal et al.[17] In all 3 studies, risperidone was well tolerated, and none of the patients experienced a worsening of their condition. Finally, 2 still unpublished, randomized, placebo-controlled studies on adjunctive risperidone to mood-stabilizers have been performed.[18,19] Both trials showed active antimanic properties for the drug.

In addition to clinical studies indicating a broad efficacy profile, there is biochemical evidence that risperidone may have antidepressant properties. A series of animal experiments has shown that risperidone potently increases serotonin (5-HT) availability in the frontal cortex, a property it shares with many antidepressant drugs, such as the selective serotonin reuptake inhibitors (SSRIs).[20,21] It is suggested that this enhanced 5-HT output may be of particular relevance for the treatment of schizophrenia when associated with depression, and of schizoaffective disorder.[20,21]

Taking these 3 lines of evidence together, we conducted a large, multicenter, open study to further assess the efficacy and safety of risperidone in the treatment of schizoaffective and bipolar disorders. Preliminary 6-week results from 1 subsample of patients taken from this study have previously been reported.[22] With this longer follow-up, we tried to address not only the long-term efficacy of treatment with risperidone, but also the safety, as some concerns have been raised about risk of tardive dyskinesia and induction or worsening of mania with risperidone treatment.[23]

METHOD

Five hundred forty-one patients with bipolar disorder or schizoaffective disorder entered the study after receiving a full explanation of the procedure and giving their written informed consent to take part. Criteria for inclusion were a DSM-IV[24] diagnosis of a manic, hypomanic, depressive, or mixed episode, a need for antipsychotic treatment as assessed by the investigator on the basis of his or her experience, and a Young Mania Rating Scale (YMRS)[25] score of 20 points or more for manic patients and 7 points or more for hypomanic, mixed, and schizoaffective patients. Depressed patients had to score higher than 17 on the Hamilton Rating Scale for Depression (HAM-D).[26] Diagnosis was assessed by means of a checklist of DSM-IV criteria for bipolar disorder or schizoaffective disorder, bipolar type, and mania, hypomania, mixed episode, or major depression. Risperidone was given in combination with lithium, anticonvulsants, and antidepressants in doses according to clinical response and tolerability. Antipsychotics were not allowed except for risperidone. The addition of another mood stabilizer was not allowed, either, but mood stabilizers could be tapered after remission of the index episode, according to the decision of the clinician. Antidepressants could be added throughout the 6-month follow-up if the patient met DSM-IV criteria at any point. Therefore, the dose of existing medications was maintained stable with clinical response to minimize the likelihood of any carryover effect.

Measures used to assess the efficacy of medication were the YMRS (for manic symptoms), the 17-item HAM-D (for symptoms of depression),[26] the Positive and Negative Syndrome Scale (PANSS, for psychotic symptoms),[27] and the Clinical Global Impressions scale (CGI).[28] The primary efficacy variable was the magnitude of reduction in YMRS score, which indicates an improvement in manic symptoms for manic, hypomanic, and mixed patients. A responder analysis was also performed, with responders defined as those patients who showed a 50% reduction in YMRS scores from baseline to endpoint and a decrease in CGI score of at least 2 points, except for purely depressed patients, who were defined according to a 50% reduction in HAM-D score. Extrapyramidal symptoms (EPS) were measured using the UKU Side Effect Rating Scale.[29]

The overall assessment period was 6 months; measurements of YMRS and HAM-D scores were performed at baseline and then at weeks 1, 2, 4 (month 1), 6, 12 (month 3), and 24 (month 6; endpoint). The other measurements of efficacy and tolerability (PANSS, CGI, UKU) were performed at baseline and weeks 4, 12, and 24. Analyses of efficacy were performed in an intent-to-treat approach. Adverse events reported by the patients were collected throughout the 6-month follow-up. To address safety concerns about the risk of exacerbation of mania or depression after the introduction of risperidone, any manic or depressive episode emerging within the first 6-week follow-up was considered as potentially drug related, and this issue is reported and discussed in the Tolerability section. Relapses or recurrences appearing after the 6-week

Table 1. Patient Characteristics (N = 541)

Characteristic	Value[a]
Sex	
Male	249 (46.0)
Female	292 (54.0)
Age, y, mean ± SD (range)	40.1 ± 12.6 (18–64)
Body mass index, kg/m^2, mean ± SD (range)	25.5 ± 4.2 (16.1–45.7)
Patient status	
Inpatient	189 (34.9)
Outpatient	280 (51.8)
Day hospital	72 (13.3)
Occupational status	
Employed	219 (40.5)
Unemployed	34 (6.3)
Disabled	189 (34.9)
Retired	18 (3.3)
Housewives	47 (8.7)
Students	23 (4.3)
Other	11 (2.0)

[a]All values shown as N (%) unless specified otherwise.

Table 2. Diagnoses (N = 541)

Diagnosis	N	%
Schizoaffective disorder, bipolar type	183	33.8
Bipolar I disorder	299	55.3
Bipolar II disorder	45	8.3
Bipolar disorder NOS	14	2.6
Type of current episode		
Manic	249	46.0
Mixed	31	5.7
Hypomanic	45	8.3
Depressed	33	6.1
Schizomanic	183	33.8

Table 3. Reasons for Patient Discontinuation

Variable	N	%
Eligible for evaluation	541	100.0
Early discontinuation	111	20.5
Lack of efficacy	30	5.5
Lost to follow-up	22	4.1
Physician's decision	22	4.1
Adverse event	16	3.0
Patient's decision	7	1.3
Patient moved	6	1.1
Noncompliance	3	0.5
Other	5	0.9

Table 4. Concomitant Drugs

	Baseline (N = 541)		Month 6 (N = 430)	
Drug	N	%	N	%
None	114	21.1	75	17.4
Lithium	195	36.0	155	36.0
Carbamazepine	60	11.1	48	11.2
Valproate	46	8.5	28	6.5
Antidepressants	34	6.3	33	7.7
Lithium + carbamazepine	32	5.9	19	4.4
Lithium + valproate	12	2.2	8	1.9
Lithium + antidepressants	25	4.6	30	7.0
Lithium + carbamazepine + antidepressants	2	0.4	4	0.9
Lithium + valproate + antidepressants	...	...	1	0.2
Carbamazepine + valproate	...	...	1	0.2
Carbamazepine + antidepressants	13	2.4	14	3.3
Carbamazepine + valproate + antidepressants	1	0.2	2	0.5
Valproate + antidepressants	7	1.3	12	2.8

cut-off were also collected, and the rates at the endpoint are discussed in the Efficacy section. These a priori definitions, though arbitrary, may be useful to separate psychiatric side effects from failures in prophylactic efficacy of the treatment.

The study was performed by investigators who all had previous experience in clinical trials and in the management of patients with schizoaffective disorder and bipolar disorder. Prior to beginning the study, the protocol was presented at several meetings across Spain, and the raters had to demonstrate their skills in the use of all the measures.

RESULTS

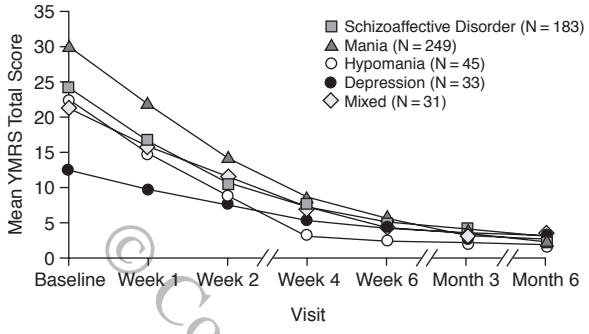
Subjects

Of 598 patients recruited, 57 (9.5%) were excluded because they did not meet all the inclusion criteria, and 111 (20.5%) of the remaining 541 failed to complete the study. The majority of patients excluded were schizoaffective patients presenting with acute, purely psychotic episodes. The demographic characteristics of the 541 patients who entered the study are shown in Table 1. Most patients were suffering from either bipolar I disorder (N = 299, 55.3%) or schizoaffective disorder, bipolar type (N = 183, 33.8%). Patients' diagnoses and type of current episode are shown in Table 2. The majority of patients (N = 503, 93.0%) were moderately to very severely ill at baseline (CGI), and the mean YMRS score at baseline was 25.6. A total of 430 patients completed the study. The reasons for noncompletion are shown in Table 3.

Medications

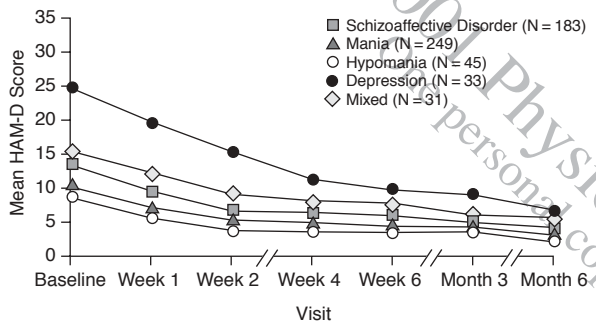
Table 4 shows the concomitant drugs patients received in combination with risperidone at baseline and at 6 months. The most common drug prescribed as monotherapy at baseline and month 6 was lithium. The most common combination therapy at baseline was lithium plus carbamazepine, but at month 6 was lithium plus antidepressants. The most commonly prescribed antidepressant at baseline and at 6 months was venlafaxine (N = 17). The mean ± SD dose of risperidone at baseline was 4.0 ± 2.9 mg/day and 3.9 ± 2.6 mg/day at month 6. The mean dose of risperidone used by subgroup was 4.3 ± 2.8 mg/day for manic patients, 4.0 ± 2.9 mg/day for schizoaffective patients, 2.9 ± 1.9 mg/day for patients with hypomania, 4.2 ± 3.0 mg/day for patients with mixed episodes, and 1.6 ± 2.3 mg/day for depressed patients.

Figure 1. Change in Young Mania Rating Scale (YMRS) Scores by Diagnostic Subgroup[a]



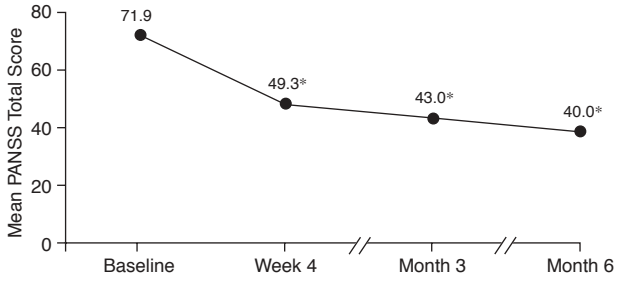
[a]p < .0001 vs. baseline for all groups at each subsequent visit except for patients with depression (p < .05 vs. baseline at each subsequent visit).

Figure 2. Change in Hamilton Rating Scale for Depression (HAM-D) Scores by Diagnostic Subgroup[a]



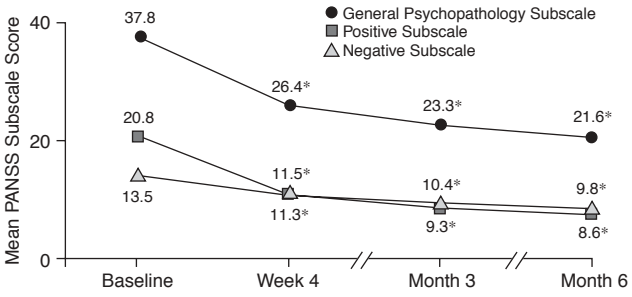
[a]p < .0001 vs. baseline for all groups at each subsequent visit.

Figure 3. Change in Positive and Negative Syndrome Scale (PANSS) Total Scores



*p < .0001 vs. baseline.

Figure 4. Change in Scores on the Positive, Negative, and General Psychopathology Subscales of the Positive and Negative Syndrome Scale (PANSS)



*p < .0001 vs. baseline.

Efficacy

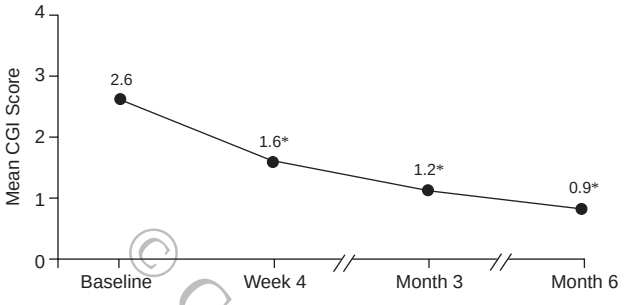
Risperidone was associated with significant improvements in all efficacy measures at 6 months. Moreover, many of the scales showed significant improvements as early as week 1. Mean scores on the YMRS decreased from 25.6 ± 10.7 at baseline to 7.2 ± 8.1 at week 4 and continued to decline to 2.4 ± 4.6 at the endpoint at 6 months (Wilcoxon signed-rank test: p < .0001). The decreases in scores were significant from week 1 onward (Wilcoxon: p < .0001). Figure 1 shows YMRS scores by diagnostic subgroup from baseline to month 6. There was a significant improvement from baseline at day 7 in all 5 groups (Wilcoxon: p < .05 for patients with depression; p < .0001 for all the other diagnostic subgroups), and this was maintained at subsequent assessments. There was a significant fall in scores throughout the study period (Friedman 2-way analysis of variance: p < .0001) in the schizoaffective, manic, hypomanic, mixed, and depressed patients.

Overall, mean HAM-D scores declined significantly from 12.8 ± 7.9 at baseline to 4.1 ± 4.8 at 6 months (Wilcoxon: p < .0001). This significance was apparent at every visit from week 1 onward. Figure 2 shows scores on the HAM-D from baseline to month 6 by diagnostic group. In all 5 groups, there was a significant improvement from baseline at day 7 (Wilcoxon: p < .0001), and this was maintained at subsequent assessments. There was a significant fall in scores throughout the study period (Friedman: p < .0001) in the schizoaffective, manic, hypomanic, mixed, and depressed patients.

Mean total scores on the PANSS declined from 71.9 ± 25.1 at baseline to 49.3 ± 19.1 at week 4 (Wilcoxon: p < .0001) and continued to decline to 40.0 at 6 months (Friedman: p < .0001). Figure 3 shows the total PANSS scores from baseline to month 6. At week 4, there were statistically significant differences from baseline in all groups (Wilcoxon: p < .0001). This improvement continued in all groups to month 6 (Friedman: p < .0001). Figure 4 shows the change on the positive, negative, and general psychopathology subscales of the PANSS. As with the total scores, there was a highly significant improvement from baseline to week 4 in all 3 subscales (Wilcoxon: p < .0001), continuing to month 6 (Friedman: p < .0001).

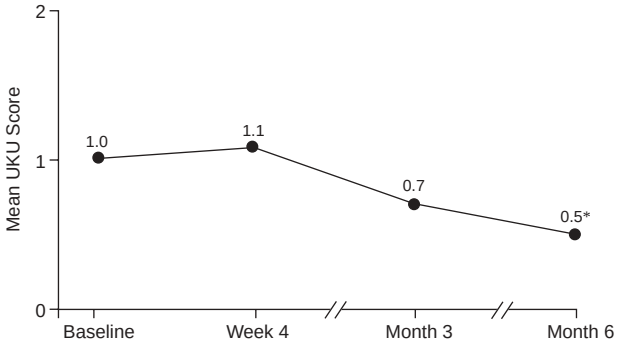
Figure 5 shows CGI scores from baseline to month 6 for the total population. There was a significant improvement from baseline at week 4 (Wilcoxon: p < .0001) and

Figure 5. Change in Clinical Global Impressions Scale (CGI) Scores



*p < .0001 vs. baseline.

Figure 6. Change in UKU Side Effect Rating Scale Scores



*p < .0001 vs. baseline.

a significant fall in scores throughout the study period (Friedman: p < .0001).

Furthermore, according to CGI, at baseline no patients were completely free from symptoms, and only 5.1% of patients were rated as "mildly ill." At endpoint, however, 44.3% of patients were showing no symptoms of mania or depression and a further 30.2% of patients were "mildly ill." This corresponded with a decrease in the percentage of severely and very severely ill patients from 59.5% at baseline to 10.2% at month 6.

Using an intent-to-treat analysis with response defined as a ≥ 50% reduction in YMRS score and at least a 2-point reduction in CGI score, 76% of manic, schizomanic, mixed, and hypomanic patients were considered responders and 24% of patients were considered nonresponders. For depressed patients, a ≥ 50% reduction in HAM-D score was observed in 69%.

During the 6-month follow-up, 136 patients (25.1%) experienced relapses into a mood state different from that at the start of the trial. Of these, at endpoint, 87 patients (16.1%) had presented with a depressive episode, 39 (7.2%) met DSM-IV criteria for a manic episode, and 10 (1.8%), for a mixed episode.

Tolerability

Risperidone was well tolerated throughout the 6-month study. Figure 6 shows the changes in EPS as measured by UKU scores from baseline to month 6. There was a significant reduction in total scores at month 6 as compared with baseline (Wilcoxon: p < .0001) and a significant fall in scores throughout the study period (Friedman: p < .0001). There were improvements on all subscale scores, represented by significant reductions throughout the study period in the dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia UKU subscale scores. There were no cases of new-emergent tardive dyskinesia.

Seventy-two nonextrapyramidal adverse events were recorded in 46 (8.5%) of the 541 patients who received trial medication, with 17 patients (3.1%) experiencing more than one event. These are shown in Table 5. The most common were increase in weight (13 patients, 2.4%), drowsiness (7 patients, 1.3%), impotence (4 patients, 0.7%), and dysarthria (4 patients, 0.7%). Of the 72 adverse events, 23 (31.9%) were considered mild, 36 (50.0%) were moderate, and 7 (9.7%) were severe. Six (8.3%) of the adverse events were not classified in terms of severity.

Forty-seven adverse events (65.3%) were considered probably or very probably related to the medication; for a further 9 adverse events (12.5%), the relationship was considered possible. The adverse effects considered very probably due to the medication (11 events, 15.3%) were impotence and hypotension (in 2 patients each) and somnolence, fatigue, tremor, dysarthria, palpitations, and vertigo (in 1 patient each).

A total of 33 adverse events (45.8%) led to withdrawal from the study (16 patients, 3.0%). The most common reasons for withdrawal were drowsiness (3 patients), increase in weight (3 patients), and vomiting (2 patients). In the overall opinion of the investigators, the tolerability of medication in patients was generally excellent (51.5%) or good (40.4%). There was a very low incidence of exacerbation of mania or depression. At 6-week cutoff, only 10 patients (1.8%) had experienced an exacerbation of manic symptoms and 16 (3.0%) had experienced an early switch into depression.

DISCUSSION

The results of this open study in 541 patients show that risperidone at a mean dose of 3.9 mg/day was associated with statistically significant improvements in YMRS scores and that it is clinically effective when combined with conventional mood stabilizers for the treatment of patients with bipolar and schizoaffective disorders. Risperidone was well tolerated; it was not associated with a significant increase in EPS or tardive dyskinesia, and there were very few cases of potential exacerbation of mania or depression.

Although the results of open-label studies should be interpreted with caution due to the bias inherent in the de-

Table 5. Most Common Adverse Events, Excluding Extrapyramidal Symptoms (total N = 541)[a]

Reaction	N (%)	Severity	Relation to Medication	Study Withdrawal, N (%)
Drowsiness	7 (1.3)	3 mild, 1 moderate, 1 severe	4 probable, 1 very probable	3 (0.6)
Weight increase	13 (2.4)	5 mild, 5 moderate	2 possible, 8 probable	3 (0.6)
Dizziness	3 (0.6)	1 mild, 2 moderate	1 remote, 2 probable	2 (0.4)
Impotence	4 (0.7)	1 mild, 2 moderate, 1 severe	2 probable, 2 very probable	1 (0.2)
Hypotension	3 (0.6)	1 mild, 2 moderate	1 probable, 2 very probable	1 (0.2)
Vomiting	3 (0.6)	1 mild, 1 moderate, 1 severe	3 probable	2 (0.4)
Dysarthria	4 (0.7)	1 mild, 3 moderate	1 possible, 1 probable, 1 very probable	2 (0.4)
Other	4 (0.7)	2 moderate, 2 severe	1 remote, 2 probable, 1 very probable	4 (0.7)

[a]A total of 72 nonextrapyramidal adverse events were experienced. Severity was not specified for 6 of the 72 events. A total of 33 adverse events led to study withdrawal; 10 patients attributed study withdrawal to more than 1 event.

sign, our results are supported by other open[11–16] and double-blind[17–19] studies in bipolar disorder which indicate that risperidone is effective against affective and particularly manic symptoms as well as being a proven antipsychotic. Furthermore, the multicenter design of our study may have helped to mitigate against single investigator bias. Another potential source of bias is the fact that patients were receiving concomitant mood stabilizers and, in some cases, antidepressants in conjunction with risperidone. These mood stabilizers and antidepressants may have been responsible for some or all of the improvement in mood symptoms seen during the trial. However, patients may have been receiving their concomitant medication for an extended period of time prior to entering the study, and there were no marked changes in the overall percentage of patients taking each class of drug as the study progressed. Therefore, the sudden marked improvements in manic, depressive, and psychotic symptoms and clinical impression were more likely to have been due to the additional drug, i.e., risperidone.

Despite these reservations, the evidence from this and previous studies indicates that risperidone is an effective treatment for schizoaffective disorder and bipolar disorder and that it may exhibit some of the properties of a mood stabilizer. A mood stabilizer for bipolar or schizoaffective disorder should ideally have the following properties: it should possess clinical efficacy against the manic, hypomanic, depressive, and mixed symptoms of the disorder; it should not precipitate depression as is sometimes seen with the conventional neuroleptics[30]; it should not precipitate mania, a common event that it is believed to happen with certain antidepressants; since it is commonly used in combination therapy, it should not cause problems with drug interactions[4,31]; it should be well tolerated in both short- and long-term use; and it should not adversely affect the patient's quality of life by causing disabling or stigmatizing adverse events such as EPS, tardive dyskinesia, or oversedation.

The results from our study suggest that risperidone might have the properties of a mood stabilizer in the treatment of schizoaffective disorder and bipolar disorder. Of course, such an assumption would be much more strongly supported by a double-blind, randomized long-term trial comparing risperidone with placebo and/or lithium. However, within the limitations of an open-label study, there was clear evidence of efficacy against mania as measured by the YMRS and against depression as measured by the HAM-D, together with efficacy in psychotic symptoms as measured by the PANSS. The treatment of one pole of the illness did not induce an early switch to the other, and at the endpoint, the rate of recurrence was quite low (25%). The uncontrolled design of the study does not allow for comparisons, but from the literature we know that this figure is not high.[32]

In terms of tolerability, the level of EPS fell significantly during treatment. This is in concordance with several other reports that also found reductions in EPS during treatment with risperidone, even in patients who had not previously received other antipsychotic medication.[33–35] There was a low level of other adverse events and, as in other studies, the indications are that risperidone was well tolerated when used in combination with other drugs and that it is free from troublesome drug interactions.[36–40] The low rate of sexual dysfunction and galactorrhea, however, might be influenced by the tendency of some patients to underreport such symptoms, either by a feeling of shame or because of their ignorance about a possible relationship between the symptoms and the medication.

Tardive dyskinesia and EPS are unpleasant and can even be life-threatening.[41] The favorable results with risperidone in terms of very low levels of these adverse events suggest that risperidone is likely to have considerable benefits in terms of patient quality of life compared with the conventional neuroleptics, which induce EPS and tardive dyskinesia in a high proportion of patients[42,43] leading to a high dropout rate[44] and yet are still widely used in bipolar disorder.[30,45] The benefits are likely to be especially valuable in patients with bipolar disorder who, it is thought, may be more prone to developing tardive dyskinesia.[41,43,46,47] However, a longer follow-up would be needed to ensure that the risk for tardive dyskinesia is so low with risperidone.

In the past, it has been suggested that risperidone might be associated with induction or worsening of mania in some patients[23]; however, at the end of the acute treatment period, defined as the first 6 weeks after the introduction of risperidone, only 1.8% of the patients were found to have experienced exacerbation or induction of manic symptoms. Given the fluctuating nature of schizoaffective disorder and bipolar disorder, these symptoms were more likely to be due to the course of the illness than to be drug induced. Furthermore, previous studies have suggested that the risk of induced mania with risperidone is probably no greater than with any other antipsychotic.[10,12,14–16]

The mean dose at endpoint of 3.9 mg/day that was used in this study is very similar to the target dose of 1 to 4 mg/day recommended in various reports.[12,34,35,48,49] This is interesting since no target dose was indicated to the investigators at the beginning of the study, and therefore it supports from a naturalistic perspective the validity of those recommendations.

The efficacy of risperidone against depression, as shown by improvements in HAM-D scores, may be related to its property of increasing availability of 5-HT in the frontal cortex.[20,21] However, one should keep in mind that several patients were taking antidepressants at the same time.

Risperidone is classified as an antipsychotic and is indicated for the treatment of schizophrenia. This large, long-term study supports that risperidone is also effective in reducing the manic, hypomanic, depressive, mixed, and psychotic symptoms of bipolar disorder and schizoaffective disorder. Risperidone was also found to be safe and well tolerated, with no evidence of induction of tardive dyskinesia, life-threatening EPS, or significant worsening of mania.

In conclusion, in this large, 6-month study, risperidone has shown clinically and statistically significant efficacy in the treatment of mania, hypomania, depression, and mixed and psychotic symptoms in patients with bipolar and schizoaffective disorders. Despite the limitations inherent to the open design, this large naturalistic study suggests that risperidone may be a valuable option for the treatment of bipolar disorder and schizoaffective disorder. Evidence-based medicine that derives from studies of patient populations selected to gain marketing approval for new psychopharmacologic drugs is increasingly distinct from the experience of treating patients in clinical psychiatric practice.[50] Thus, observational studies give worthy complementary information about the efficacy and safety of psychiatric treatments in the real world. The effectiveness of risperidone in the treatment of bipolar spectrum disorders shown in this study might be indicative of mood-stabilizing properties, although long-term, controlled clinical trials are needed to confirm this suggestion.

Drug names: carbamazepine (Tegretol and others), haloperidol (Haldol and others), risperidone (Risperdal), venlafaxine (Effexor).

REFERENCES

1. Prien RF, Potter WZ. NIMH workshop report on treatment of bipolar disorder. Psychopharmacol Bull 1990;26:409–427
2. Azorin JM. Long-term treatment of mood disorders in schizophrenia. Acta Psychiatr Scand 1995;388(suppl):20–23
3. Janicak PG. Copharmacy strategies for bipolar disorder. Psychiatr Ann 1998;28:357–364
4. Silverstone T, Romans S. Long term treatment of bipolar disorder. Drugs 1996;51:367–382
5. Montgomery S. The treatment of bipolar disorder: current limitations and future prospects. J Bipol Dis 1997;1:20–22
6. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
7. Borison RL, Pathiraja AP, Diamond BL, et al. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull 1992;28:213–218
8. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Pharmacol 1993; 13:25–50
9. Davis JM, Janicak PG. Risperidone: a new, novel (and better?) antipsychotic. Psychiatr Ann 1996;26:78–87
10. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American studies. J Clin Psychiatry 1997;58:538–546
11. Madhusoodanan S, Brenner R, Araujo L, et al. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995;56:514–518
12. Jacobsen F. Risperidone in the treatment of affective illness and obsessive compulsive disorder. J Clin Psychiatry 1995;56:423–429
13. Sajatovic M, DiGiovanni SK, Bastani B, et al. Risperidone therapy in treatment-refractory acute bipolar and schizoaffective mania. Psychopharmacol Bull 1996;32:55–61
14. Tohen M, Zarate CA, Centorrino F, et al. Risperidone in the treatment of mania. J Clin Psychiatry 1996;57:249–253
15. Ghaemi SN, Sachs GS, Baldassano CF, et al. Acute treatment of bipolar disorder with adjunctive risperidone in outpatients. Can J Psychiatry 1997; 42:196–199
16. Vieta E, Gasto C, Colom F, et al. Treatment of refractory rapid cycling bipolar disorder with risperidone [letter]. J Clin Psychopharmacol 1998;18: 172–174
17. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomised controlled study. Clin Neuropharmacol 1998;21:176–180
18. Sachs G. Safety and efficacy of risperidone versus placebo as add-on therapy to mood-stabilizers in the treatment of manic phase of bipolar disorder. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1999; Acapulco, Mexico
19. Yatham L. Safety and efficacy of risperidone as combination therapy for the manic phase of bipolar disorder: preliminary findings of a randomized, double-blind study (RIS-INT-46). Presented at the 22nd annual meeting of the Congress of the College of International Neuropsychopharmacology; July 19–13, 2000; Brussels, Belgium
20. Hertel P, Nomikos GG, Schilström B, et al. Risperidone dose-dependently increases extracellular concentrations of serotonin in the rat frontal cortex: role of α_2-adrenoceptor antagonism. Neuropsychopharmacology 1997;17: 44–55
21. Hertel P, Nomikos GG, Svensson TH. Risperidone inhibits 5-hydroxytryptaminergic neuronal activity in the dorsal raphe nucleus by local release of 5-hydroxytryptamine. Br J Pharmacol 1997;122: 1639–1646
22. Vieta E, Herraiz M, Fernández A, et al. Efficacy and safety of risperidone in the treatment of schizoaffective disorder: results from a large, multicentre surveillance study. J Clin Psychiatry 2001;62:623–630
23. Dwight MM, Keck PE, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 1994;344:554–556
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
25. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability,

validity, and sensitivity. Br J Psychiatry 1978;133:429–435
26. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychiatry 1967;6:278–296
27. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
28. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976: 218–222
29. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of adverse events in neuroleptic-treated patients. Acta Psychiatr Scand 1987;334(suppl):1–100
30. Keck PE Jr, McElroy SL, Strakowski SM, et al. Factors associated with maintenance antipsychotic treatment of patients with bipolar disorder. J Clin Psychiatry 1996;57:147–151
31. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder. Am J Psychiatry 1994;151(suppl 12):1–36
32. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111
33. Jeste DV, Klausner M, Brecher M, et al. A clinical evaluation of risperidone in the treatment of schizophrenia: a 10-week, open-label, multicenter study. Psychopharmacology (Berl) 1997;131:239–247
34. Kopala LC, Good KP, Honer WG. Extrapyramidal signs and symptoms in first-episode schizophrenia: response to low-dose risperidone. J Clin Psychopharmacol 1997;17:308–313
35. Simpson GM, Lindenmayer J-P. Extrapyramidal symptoms in patients treated with risperidone. J Clin Psychopharmacol 1997;17:194–201
36. Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry 1996;57(suppl 11):12–25
37. de Leon J, Bork J. Risperidone and cytochrome P450 3A [letter]. J Clin Psychiatry 1997;48:450
38. Sommers DK, Snyman JR, van Wyk M, et al. Lack of effect of amitryptyline on risperidone pharmacokinetics in schizophrenic patients. Int Clin Psychopharmacol 1997;12:141–143
39. Avenoso A, Facciolá G, Scordo MG, et al. No effect of citalopram on plasma levels of clozapine, risperidone and their active metabolites in patients with chronic schizophrenia. Clin Drug Invest 1998;16:393–398
40. Collaborative Working Group on Clinical Trial Evaluations. Atypical antipsychotics for treatment of depression in schizophrenia and affective disorders. J Clin Psychiatry 1998:59(suppl 12):41–45
41. Casey DE, Rabins P. Tardive dyskinesia as a life-threatening illness. Am J Psychiatry 1978;135:486–488
42. Faurbye A, Rasch PJ, Petersen PB, et al. Neurologic symptoms in pharmacotherapy of the psychoses. Acta Psychiatr Scand 1964;40:10–27
43. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol 1988:8:52S–56S
44. Van Putten T. Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 1974;31:67–72
45. Brotman MA, Fergus EL, Post RM, et al. High exposure to neuroleptics in bipolar patients: a retrospective review [CME]. J Clin Psychiatry 2000;61: 68–72
46. Hunt N, Silverstone T. Tardive dyskinesia in bipolar affective disorder. Int J Clin Psychopharmacol 1990;6:46–50
47. Jeste DV, Caligiuri MP. Tardive dyskinesia. Schizophr Bull 1993;19: 303–315
48. Tooley PJH, Zuiderwijk P. Drug safety: experience with risperidone. Adv Ther 1997;14:262–266
49. Luchins DJ, Klass D, Hanrahan P, et al. Alteration in the recommended dosing schedule for risperidone. Am J Psychiatry 1998;155:365–366
50. Stahl SM. Does evidence from clinical trials in psychopharmacology apply in clinical practice? [BRAINSTORMS] J Clin Psychiatry 2001;62:6–7