Efficacy and Safety of Risperidone in the Treatment of Schizoaffective Disorder: Initial Results From a Large, Multicenter Surveillance Study

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Background: An adequate therapy for psychotic disorders needs to be effective against mood as well as psychotic symptoms. Analyses of data from clinical trials of risperidone in schizophrenia and small open-label studies in mania suggest that risperidone may have this broad efficacy profile. We present data on a 6-week trial of risperidone for the treatment of schizoaffective disorder that was part of a larger, 6-month surveillance study of patients with affective disorders.

Method: One hundred two patients suffering from schizoaffective disorder (DSM-IV or ICD-10) entered the trial. Inclusion criteria consisted of a current DSM-IV diagnosis of schizoaffective disorder, bipolar type; DSM-IV manic or mixed psychotic episode; and a Young Mania Rating Scale (YMRS) score > 7 for a mixed episode (> 20 for a manic episode). Assessments included the YMRS, the Positive and Negative Syndrome Scale (PANSS), the Hamilton Rating Scale for Depression (HAM-D), the 4-item Clinical Global Impressions (CGI) scale, and the UKU Side Effect Rating Scale subscale for neurologic side effects. For patients entering the study, open-label risperidone therapy was added to their existing regimens of mood-stabilizing treatments. Other antipsychotic drugs were not allowed.

Results: Ninety-five patients completed the 6-week trial. At week 6, the mean ± SD dose of risperidone was 4.7 ± 2.5 mg/day. The mean scores on the assessment scales at baseline and week 6 (unless otherwise stated) were as follows: YMRS, 22.7 and 4.7, an improvement of 18.0 points ($p < .0001$); PANSS (at baseline and week 4), 74.1 and 54.2, an improvement of 19.9 points ($p < .0001$); HAM-D, 14.0 and 7.4, an improvement of 6.6 points ($p < .0001$); CGI (at baseline and week 4), 2.6 and 1.7, an improvement of 0.9 points ($p < .0001$). At week 4, most patients had shown improvement in symptom severity, and 9.3% were completely symptom-free. There were no statistically significant differences between baseline and week 4 in the severity of extrapyramidal symptoms as measured by the UKU. Risperidone was well tolerated; side effects were few and generally mild.

Conclusion: The results to date with risperidone indicate that it may have both antipsychotic and mood-stabilizing properties. Despite the limitations of the open-label design, the results indicate that risperidone is a safe and effective therapy in combination with mood-stabilizers for the treatment of patients with manic, hypomanic, and depressive symptoms of mixed episodes in schizoaffective disorder, bipolar type.

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The traditional classification of medications as antipsychotic, antidepressant, or mood-stabilizing risks emphasizing one treatment benefit to the exclusion of other important benefits. Present-day understanding of psychiatric disorders encompasses the realization that many disorders manifest as a spectrum of symptoms.[1] Thus, within schizophrenia, schizoaffective disorder, and bipolar disorder, for example, the varied symptomatology of the illnesses often means that patients are treated simultaneously for both psychotic and affective symptoms. The novel antipsychotic risperidone may have usefulness in affective symptoms in addition to its widely acknowledged and robust efficacy against psychotic symptoms.[2,3]

Marder et al.[1] analyzed data from 2 double-blind trials with a combined total of 513 chronic schizophrenic patients according to the 5 dimensions of the Positive and Negative Syndrome Scale (PANSS)[4] derived by factor analysis, i.e., negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression.[5] The patients were randomly assigned to treatment with risperidone, haloperidol, or placebo. Risperidone brought about significantly greater improvements than haloperidol or placebo on all 5 dimensions; the advantages of risperidone were greatest for negative symptoms, uncontrolled hostility/excitement, and anxiety/depression.

Peuskens et al.[6] analyzed pooled data from 6 double-blind trials of risperidone versus haloperidol and placebo in 1254 patients with chronic schizophrenia. Symptoms indicative of mania were assessed by the PANSS excited and grandiosity items and by the excited cluster (excitement, hostility, uncooperativeness, and poor impulse control). Symptoms of anxiety and depression were assessed by the PANSS anxious/depressive cluster (somatic concern, anxiety, guilt feelings, and depression). Improvement in both manic symptoms and anxiety/depression symptoms were significantly greater with risperidone than with haloperidol or placebo. Among patients with manic symptoms at baseline, symptom reduction was significantly greater, and was significantly more rapid, with risperidone, and there were significantly fewer dropouts. Similar results were obtained in the patients with anxiety/depression symptoms.

A number of open-label studies of combined therapy[7–12] suggest that risperidone is also effective and well tolerated in acute mania. Tohen et al.,[10] for example, in an open trial of risperidone as adjunctive therapy in 15 manic patients resistant to conventional mood-stabilizing drugs, found significant improvements at 2 and 6 weeks, and a 6-month open study of 14 patients by Ghaemi and Sachs[13] indicated that add-on risperidone could be an effective antimanic therapy in bipolar patients who suffered "breakthrough" episodes despite adequate dosage of conventional mood stabilizers such as lithium and valproate. Risperidone may also be effective as monotherapy in manic patients; a double-blind trial by Segal et al.[14] in 45 acutely manic patients suggested that risperidone was of equivalent efficacy to haloperidol and lithium. In all 3 trials, risperidone was well tolerated, and no patients worsened.

Some reports have found induction of mania associated with risperidone treatment.[9,15,16] However, the trials were conducted in very small numbers of patients. Furthermore, in 2 of those studies,[15–16] patients were not being treated concurrently with mood-stabilizing medication.[15,16] In one study,[15] risperidone was titrated rapidly to a dose in excess of that usually used as a therapeutic dose, which may have caused induction of mania.

Table 1. Patients Recruited and Assessed[a]

Patients	N	% of N Recruited
Recruited	110	100.0
Excluded	8	7.3
YMRS score at baseline < 7	6	5.5
Age > 65 y	1	0.9
Baseline visit only	1	0.9
Patients beginning treatment	102	92.7
Withdrawn	7	6.4
Intolerance to medication	5	4.5
Lack of response	2	1.8
Patients completing treatment	95	86.4

[a]Abbreviation: YMRS = Young Mania Rating Scale.

Taking together the foregoing evidence, which suggests that risperidone has a broad range of efficacy against both schizophrenic and manic symptoms, we considered it appropriate to evaluate the effects of risperidone in schizoaffective disorder, bipolar type, as part of a large multicenter surveillance study of patients with affective disorders. The study continued for 6 months, but the results presented here are from the initial 6-week cutoff.

The study included patients with pure bipolar disorder. However, these patients have been excluded from this report to produce a preliminary assessment of risperidone in patients with schizoaffective disorder only, because the symptoms of this disorder are very similar to those of schizophrenia, an indication for which risperidone is currently approved.

METHOD

This study was performed by investigators who all had previous experience with clinical trials and in the management of patients with schizoaffective disorder and bipolar disorder. They were all given training in the instruments used to assess the efficacy of the trial, which included the Spanish versions of the Young Mania Rating Scale (YMRS), the Hamilton Rating Scale for Depression (HAM-D), the PANSS, the UKU Side Effect Rating Scale subscale for neurologic side effects, and the Clinical Global Impressions scale (CGI). All of these Spanish versions have been validated and widely used in previous studies.[17–19] Prior to beginning the trial, the protocol was presented at several meetings across Spain.

One hundred two patients suffering from schizoaffective disorder, bipolar type (DSM-IV,[20] ICD-10[21]), entered the study after giving their informed consent to the procedures used. Of these patients, 95 completed the 6 weeks of treatment. Reasons for noncompletion are listed in Table 1.

The inclusion criteria consisted of a current DSM-IV diagnosis of schizoaffective disorder, bipolar type; the most recent or current episode manic or mixed, with concurrent psychosis (DSM-IV)[20]; and a YMRS[22] score of

Table 2. Patient Characteristics[a]

Characteristic	Value
Sex	
Men	58 (57)
Women	44 (43)
Age, y	
≤ 20	5 (5)
21–30	35 (34)
31–40	34 (33)
41–50	16 (16)
51–60	9 (9)
> 60	3 (3)
Range (mean ± SD)	18–64 (35.7 ± 11.0)
Body weight, kg, mean ± SD[b]	
Men	75.4 ± 12.8
Women	65.3 ± 11.7
Total	70.7 ± 13.2
Patient status at baseline	
Inpatients	37 (36)
Outpatients	49 (48)
Day hospital	16 (16)
Employment status[c]	
Full-time	17 (17)
Part-time	9 (9)
Unemployed	3 (3)
Temporarily incapacitated	16 (16)
Permanently incapacitated	34 (34)
Disabled	5 (5)
Retired	3 (3)
Other	13 (13)
Severity of illness at baseline[d]	
Mild	3 (3)
Moderate	41 (40)
Severe	53 (52)
Very severe	5 (5)

[a]All values shown as N (%) unless specified otherwise. Percentages were calculated as a percentage of the total number of patients for whom data were available.
[b]Body weight not specified for 5 patients.
[c]Employment status not specified for 2 patients.
[d]Severity determined by score on the Clinical Global Impressions-Severity of Illness scale.

Table 3. Concomitant Medications[a]

Drug	Baseline (N = 102)	Day 7 (N = 102)	Day 14 (N = 100)	Week 4 (N = 99)	Week 6 (N = 95)
None	20 (19.6)	16 (15.7)	16 (16.0)	15 (15.2)	11 (11.6)
Lithium	31 (30.4)	35 (34.3)	37 (37.0)	34 (34.3)	31 (32.6)
Carbamazepine	14 (13.7)	14 (13.7)	17 (17.0)	18 (18.2)	18 (18.9)
Valproate	7 (6.9)	7 (6.9)	6 (6.0)	5 (5.1)	4 (4.2)
Antidepressant	7 (6.9)	9 (8.8)	4 (4.0)	6 (6.1)	6 (6.3)
Lithium + carbamazepine	7 (6.9)	4 (3.9)	3 (3.0)	3 (3.0)	4 (4.2)
Lithium + valproate	2 (2.0)	2 (2.0)	2 (2.0)	1 (1.0)	1 (1.1)
Lithium + antidepressant	6 (5.9)	6 (5.9)	6 (6.0)	7 (7.1)	8 (8.4)
Lithium + carbamazepine + antidepressant	0 (0)	0 (0)	1 (1.0)	1 (1.0)	2 (2.1)
Lithium + valproate + antidepressant	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (1.1)
Carbamazepine + valproate	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)
Carbamazepine + antidepressant	6 (5.9)	6 (5.9)	4 (4.0)	5 (5.1)	4 (4.2)
Valproate + antidepressant	2 (2.0)	3 (2.9)	3 (3.0)	3 (3.0)	5 (5.3)

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

greater than 20 points for a manic episode or greater than 7 points for a mixed episode.

Measures used to assess the efficacy of medication were the YMRS, the PANSS,[4] the HAM-D,[23] and the CGI.[24] Neurologic side effects were measured using the UKU Side Effect Rating Scale for extrapyramidal symptoms (EPS).[25] YMRS and HAM-D assessments were made at baseline and then at weeks 1, 2, 4, and 6, whereas all other measurements were made at baseline and week 4. Comparison between baseline and other measurements was made using the Wilcoxon test and the Friedman test.

Patients who had previously been treated with either haloperidol or pimozide were switched to risperidone by gradually introducing risperidone until an optimum dose was reached before gradually reducing the dose of the conventional neuroleptic over 3 or more days. Patients who were receiving clozapine had the dose gradually decreased over 15 days, with risperidone introduced from day 7 onward.

Patients entering the study were given risperidone in association with their existing mood-stabilizing treatments, which mostly included lithium, carbamazepine, or valproate, and in depressed patients, antidepressants, with selective serotonin reuptake inhibitors as the preferred choice. Most patients were started on 1.5 mg/day of risperidone and titrated to their optimum dose according to clinical response and tolerability.

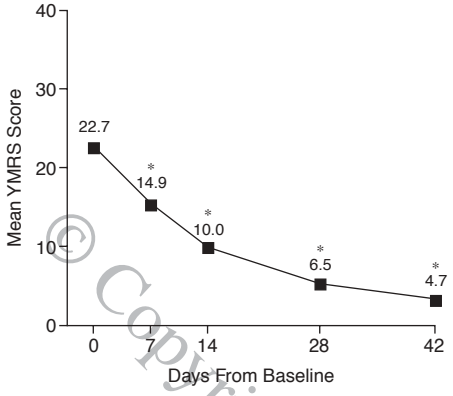
RESULTS

Subjects

Of an initial population of 110, 8 (7.3%) were excluded; 7 (6.9%) of the remaining 102 failed to complete the study. Reasons for exclusion and noncompletion are listed in Table 1. The demographic characteristics of the 102 patients who entered the study are shown in Table 2. The great majority of patients (96%) were moderately or severely ill at baseline (CGI). The mean ± SD YMRS score at baseline for all patients was 22.7 ± 10.2.

Table 3 shows the concomitant medications prescribed during the study. The most commonly prescribed treatment at baseline was lithium (N = 31, 30.4%), followed by carbamazepine (N = 14, 13.7%), and the most common combination was lithium plus carbamazepine (N = 7, 6.9%), followed by lithium plus an antidepressant (N = 6, 5.9%). Prescription of antidepressants was allowed in patients whose episodes showed either depressed or mixed symptoms, including those patients whose episodes were manic or hypomanic at the start of the trial but then became depressed or mixed during the study period. In cases in which the patient was psychotic and depressed, the combination of a mood stabilizer, risperidone, and an an-

Figure 1. Overall Change From Baseline in Mean Young Mania Rating Scale (YMRS) Score



*p < .0001 vs. baseline.

Figure 2. Mean Reduction in Young Mania Rating Scale (YMRS) Scores Between Consecutive Assessments

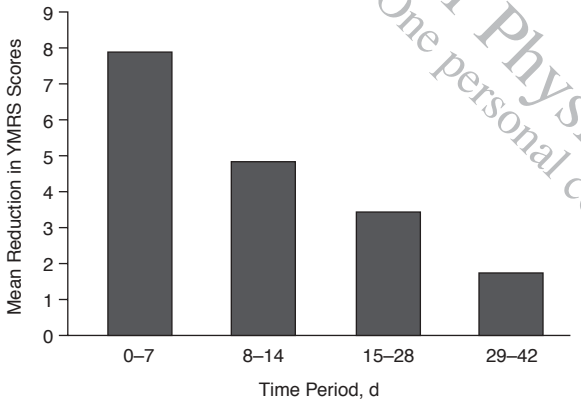
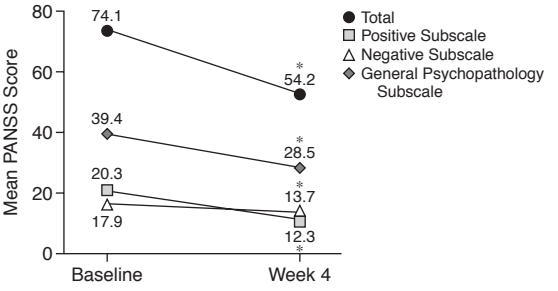
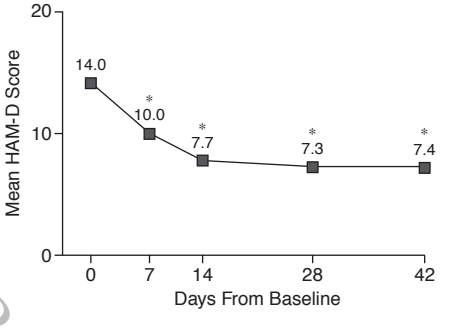


Figure 3. Change in Positive and Negative Syndrome Scale (PANSS) Total and Positive, Negative, and General Psychopathology Subscale Scores From Baseline to the 4-Week Assessment



*p < .0001 vs. baseline.

Figure 4. Overall Change in Mean Hamilton Rating Scale for Depression (HAM-D) Score



*p < .0001 vs. baseline.

tidepressant was given. The most commonly prescribed antidepressants at baseline were venlafaxine (N = 4, 3.9%) and mirtazapine (N = 4, 3.9%), followed by citalopram (N = 3, 2.9%) and fluvoxamine (N = 3, 2.9%). The mean dose of risperidone at week 6 was 4.7 ± 2.5 mg/day, and > 80% were receiving an optimal dose[26] of ≤ 6 mg/day.

Efficacy

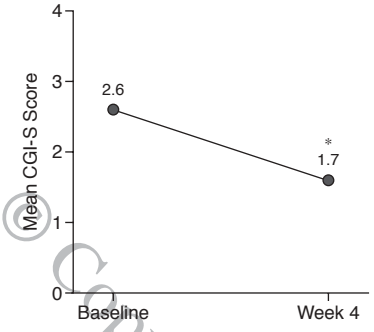
Figure 1 shows the mean YMRS score (N = 100) from baseline to week 6, and Figure 2 shows the mean reduction in YMRS scores that occurred between consecutive assessments up to 6 weeks. Numbers of patients may vary by rating scale because assessments were done at different timepoints (YMRS and HAM-D at baseline and weeks 1, 2, 4, and 6, the remainder at baseline and week 4). There was a highly significant improvement from 22.7 to 14.9 at 7 days (Wilcoxon, p < .0001) and a highly significant improvement in scores from baseline (22.7) to week 6 (4.7) (Friedman, p < .0001). With response defined as ≥ 50% improvement on the YMRS scale, 83.1% of patients were considered responders (per-protocol analysis of completers). This fell to 83.0% if an intent-to-treat analysis was employed.

Figure 3 shows PANSS total scores (N = 76) at baseline (74.1) and week 4 (54.2), demonstrating a highly significant improvement (Wilcoxon, p < .0001). Also shown are changes on the positive (from 20.3 to 12.3), negative (from 17.9 to 13.7), and general psychopathology subscales (from 39.4 to 28.5) of the PANSS, again with highly significant improvement on all 3 subscales (Wilcoxon, p < .0001).

Figure 4 shows mean scores on the HAM-D (N = 95). Again, there was a highly significant improvement from 14.0 at baseline to 10.0 at 7 days (Wilcoxon, p < .0001) and a highly significant improvement between baseline (14.0) and week 4 (7.4) (Friedman, p < .0001).

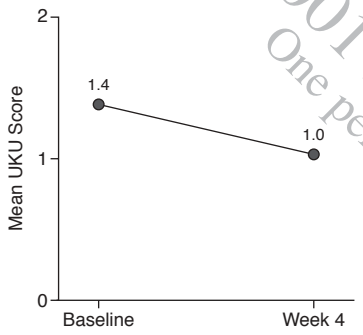
Figure 5 shows mean CGI scores (N = 102), with a highly significant improvement from 2.6 at baseline to 1.7 at week 4 (Wilcoxon, p < .0001). At the end of the study

Figure 5. Change in Mean Clinical Global Impressions-Severity of Illness Scale (CGI-S) Score From Baseline to the 4-Week Assessment



*p < .0001 vs. baseline.

Figure 6. Change in Mean UKU Side Effect Rating Scale Score From Baseline to the 4-Week Assessment



period, 9.3% of patients were symptom-free, and 87.5% of the patients (N = 64) were rated much improved (50%) or improved (37.5%). No worsening in overall clinical impression was witnessed.

Tolerability

The UKU subscale for neurologic side effects showed a decrease in mean score from baseline to week 4 (N = 64; Figure 6), although the change did not reach significance. The rates of dystonia, rigidity, hyperkinesia, hypokinesia, tremor, akathisia, and dyskinesia during the study were not significantly different from those at baseline, according to the UKU scores for these items. At the endpoint of the analysis, the number of patients who had shown appearance of depressive symptoms during the study was 13 (13%). Only 5 patients (5%) showed any exacerbation of mania as defined by any worsening in CGI score of 1 point or more. Thirteen adverse events were recorded in 7 patients; these are listed in Table 4. Four patients experienced more than 1 event. In addition, the study revealed no patients with tardive dyskinesia (TD).

Table 4. Adverse Events[a]

Event	Patients Experiencing the Event	Withdrawn From Study Due to Event
Gastrointestinal effects		
Vomiting	1 (1.6)	1 (1.6)
Nausea	1 (1.6)	1 (1.6)
Dyspepsia	1 (1.6)	1 (1.6)
Neurologic effects		
Drowsiness	3 (4.7)	2 (3.1)
Dizziness	1 (1.6)	0 (0)
Tremor	1 (1.6)	1 (1.6)
Anxiety	1 (1.6)	1 (1.6)
Physical effects		
Impotence	2 (3.1)	0 (0)
Increased weight	1 (1.6)	1 (1.6)
Other	1 (1.6)	1 (1.6)
Total no. of adverse events (%)	13 (20.3)	9 (14.1)
Total patients[b]	7 (10.9)	5 (7.8)

[a]All values shown as N (%) unless specified otherwise. Total N = 64.
[b]Four patients experienced more than 1 adverse event.

DISCUSSION

This open study of 102 patients indicates that risperidone has significant clinical and statistical efficacy when combined with conventional mood stabilizers in patients with manic, hypomanic, depressive, or mixed episodes of schizoaffective disorder, bipolar type. There was a favorable safety and tolerability profile, with no significant increase in EPS or TD and very low levels of initiation of depression or exacerbation of mania.

The study provides further evidence indicative of the efficacy and safety of risperidone in the treatment of affective symptoms. There are already indications that risperidone is effective against mood symptoms in chronic schizophrenia, in particular hostility/excitement and anxiety/depression,[1,6] in addition to its established robust efficacy against psychotic symptoms.[2,3]

A number of open studies indicate that risperidone is also effective and well tolerated in the treatment of acute mania occurring in bipolar disorder.[7–13] The present study of patients with schizoaffective disorder similarly supports a broader efficacy profile for risperidone, which has until recently been classified primarily as an antipsychotic.

In this study, the mean change in PANSS total scores from baseline to week 4 was a reduction of 19.9 points, slightly better than the reduction of 18.6 points from baseline to endpoint seen with 6 mg/day of risperidone in a combined analysis of the 2 pivotal North American trials in schizophrenia.[1] This finding suggests that the overall antipsychotic effect of risperidone in patients with schizoaffective disorder is similar to that in patients with schizophrenia. In addition, the changes in this study and the North American trials[1] on the negative subscale of the PANSS were also similar, with reductions of 4.2 and 3.4 points (dose = 6 mg/day), respectively.

Caution is always necessary in interpreting nonrandomized, uncontrolled, open studies, but the present results are supported by the analyses from double-blind trials in schizophrenia,[1] and it is also possible that the multicenter design might have mitigated observer bias.

Further bias may have resulted from the number of patients taking concomitant mood-stabilizing medication, since that medication could have been the underlying cause of the improvement in mood symptoms. 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.

Taking the evidence together, risperidone may have an efficacy profile suggestive of mood-stabilizing properties. The ideal properties of a mood stabilizer in schizoaffective disorder are that it should have clinical efficacy against the manic, hypomanic, depressive, and mixed symptoms of the disorder; it should not precipitate depression as some of the conventional antipsychotics might do[27]; and it should not precipitate mania as some antidepressants might do.[28,29] It should be safe and well tolerated in both short- and long-term use, and, since it is commonly used as an add-on therapy, it should be free from troublesome interactions. In addition, its use should not detract from the patient's quality of life by causing side effects such as TD, EPS, or oversedation. TD in particular is both disabling and stigmatizing and occurs in many patients with schizophrenia treated with conventional antipsychotics[30–33]; one study[33] found the prevalence of TD in that population to be anywhere between 12% and 37%. Furthermore, there is evidence that patients with affective disorder are even more prone to TD.[33–36]

Indications from the present study are that risperidone meets these criteria regarding the treatment of acute affective symptoms in schizoaffective disorder. The drug was well tolerated, with no significant increase in EPS or TD, and there was evidence of efficacy against manic, mixed, and depressive symptoms.

Concerns have been raised about worsening of mania with risperidone,[9,15,16] but at the end of the study manic symptoms had shown exacerbation in only 5% of patients. Given the fluctuating nature of schizoaffective disorder, these exacerbations were as likely to have occurred as part of the course of the illness as to have been caused by study medication.[8,10–12] The risk of worsening of manic symptoms was therefore low in this large, open study.

The above efficacy data apply specifically to patients with schizoaffective disorder. However, they are also possibly supportive of the potential use of risperidone in bipolar disorder, since symptoms such as mania and depression that are also seen in patients with bipolar disorder were well controlled by risperidone treatment in this study. The data are also, importantly, relevant to the treatment of affective symptoms in schizophrenia. Current understanding of schizophrenia favors a multidimensional model, in which affective symptoms feature prominently,[1,5] rather than the traditional positive/negative syndrome model.[4] Further, it is well recognized that affective symptoms in schizophrenia can be as troublesome and disabling as psychotic symptoms,[15,37,38] and patients and caregivers expect that treatment plans will attend to these symptoms.[1] In particular, patients with schizophrenia are especially prone to depressive symptoms and have a high suicide rate.[39,40] There is evidence, including the data presented in this report, that risperidone, as an antagonist of both serotonin and dopamine receptors, has a broader efficacy profile in schizophrenia than the conventional antipsychotic drugs, including efficacy against affective symptoms.[1,7] Its antidepressant properties have been associated with increased serotonin release related to α_2-adrenoceptor blockade.[41–43]

This study, therefore, provides further evidence for the efficacy of risperidone in the treatment of affective psychosis, specifically in the treatment of manic, depressive, and mixed symptoms. The treatment was safe and well tolerated, with no significant increase in EPS or TD and no induction of mania or depression. Risperidone, therefore, has both efficacy and safety advantages over the conventional neuroleptics, and also safety and tolerability advantages over other novel antipsychotics. It is, in particular, free from the risk of seizures and hematological toxicity posed by clozapine[44,45] and from the risk of weight gain and oversedation found with olanzapine.[46]

The mean dose of risperidone in this study was 4.7 ± 2.5 mg/day, and 88% of patients were taking doses of less than or equal to 6 mg/day, at which risperidone is thought to be safe and effective for the treatment of patients with schizophrenia and affective illnesses.[8,47,48] Therefore, risperidone is likely to be a useful addition to the growing number of drugs employed in the treatment of affective symptoms, which are present in schizophrenia, schizoaffective disorder, and affective illnesses including bipolar disorder. It shows good efficacy associated with a low propensity to produce harmful and unpleasant side effects.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), citalopram (Celexa), fluvoxamine (Luvox), haloperidol (Haldol and others), mirtazapine (Remeron), olanzapine (Zyprexa), pimozide (Orap), risperidone (Risperdal), venlafaxine (Effexor).

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