

# Risperidone: How Good Is the Evidence for Efficacy?

by Jeffrey A. Mattes

## Abstract

This article reviews the published literature evaluating the efficacy of risperidone. The literature includes three multicenter, double-blind studies that compared risperidone, haloperidol, and placebo, as well as three comparisons of risperidone with a standard neuroleptic. Efficacy of risperidone is reported, but most studies involved chronically hospitalized patients who were relatively refractory; the response to standard neuroleptics was not robust. Also, the reported superiority of risperidone on negative symptoms may be artifactual, since standard neuroleptics, because of extrapyramidal symptoms, can mimic or exacerbate negative symptoms. Finally, risperidone may have an antidepressant effect. It is as yet unclear whether risperidone is as effective as standard neuroleptics for positive schizophrenia symptoms in neuroleptic-responsive patients.

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This article reviews the published literature to evaluate the evidence for efficacy of risperidone. This issue is a major clinical concern if risperidone does not adequately control psychotic symptoms in many schizophrenia patients. It also concerns researchers involved in the development of other novel neuroleptics. This review focuses on aspects of available risperidone studies that suggest caution in assuming the drug to be as effective as standard neuroleptics for positive schizophrenia symptoms.

## Placebo-Controlled Comparisons

The largest U.S. study (388 patients) was reported by Marder and Meibach (1994) and showed the efficacy of risperidone to be at least that of haloperidol. However, there are some indications that the results might not accurately reflect the effect of risperidone in neuroleptic-responsive patients with schizophrenia.

The strongest indication was the marginal benefit from haloperidol. Although haloperidol-placebo comparisons often were statistically significant, the significance was caused primarily by the size of the sample, not by a robust haloperidol effect. For example, the mean score of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) for patients on haloperidol was 54.6 at baseline and 51.2 at endpoint, a mean change of only 3.3. This result was significantly different statistically from that of the placebo patients, whose BPRS scores increased 1.9 points on average; but this change is clearly of marginal clinical significance. The same conclusion is apparent from other ratings; for example, 22 percent of patients on placebo improved at least 20 percent on the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987), compared with 30 percent on haloperidol. Similarly, improvement on the Kane et al. (1988) criteria (20 percent reduction in BPRS score and either posttreatment Clinical Global Impression [CGI; Guy 1976] scale  $\leq$  mild or BPRS  $\leq$  35) occurred in 11 percent of patients on placebo and 22 percent of patients on haloperidol. Moreover, the evidence of haloperidol's efficacy was not apparent until patients had been on the drug for 1 month; before day 30, patients on haloperidol actually were doing worse than patients on placebo. Relatedly, these patients had been hospitalized an average of 29 weeks before entry into the study; thus, as a group, they were relatively chronic and refractory.

Marder and Meibach (1994) analyzed results, stratifying by length of hospitalization, and found that haloperidol was better than placebo only in patients hospitalized less than 1 month. (A patient hospitalized more than 1 month, in general, would have been treated with standard neuroleptics, thus would be relatively refractory.) The authors do not report what percentage of their patients were hospitalized less than 1 month, but it must have been a relatively small proportion given the mean duration of hospitalization, indi-

Very little change

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cating that the majority of patients were not responsive to haloperidol. In addition, the authors reported the effect of only the 6 mg dose of risperidone on patients hospitalized less than 1 month. They also reported only the total PANSS score, thus making it impossible to know which symptoms improved in this more acute subsample. Therefore, the effect of risperidone on neuroleptic-responsive symptoms remains unclear.

Chouinard et al. (1993) reported a similar multicenter Canadian study involving 135 inpatients at six sites. Again, there was impressive evidence that risperidone was superior to placebo and, in some comparisons, superior to haloperidol. The problems with interpreting this study are the same as for the U.S. study: the patients were a chronic, relatively refractory group who had been hospitalized an average of 2 years before the risperidone trial. Again, the evidence for efficacy of haloperidol was not robust. Thirteen of the 21 patients on haloperidol terminated their participation in the study early, 11 because of an insufficient response to medication (20 mg of haloperidol). Thus, only 8 patients on haloperidol finished the trial. It therefore is not clear that the patients who improved were responding to a neuroleptic effect of risperidone.

Borison et al. (1992) reported results of a double-blind study comparing risperidone, haloperidol, and placebo in 36 schizophrenia patients in a Veterans Affairs (VA) hospital. Apparently, these patients also were chronic (although duration of hospitalization is not specified); the average duration of illness ranged from 10 to 17 years. Response to prior neuroleptic medication was not specified. These authors reported impressive results demonstrating efficacy for risperidone compared with placebo and evidence of superiority compared with haloperidol. However, only 3 of 12 patients on haloperidol improved at least 20 percent on the BPRS. Also, at baseline, the risperidone patients were rated as more impaired on the CGI. Although elaborate statistical manipulations in such a small sample may be of questionable validity, the authors probably should have used a covariance analysis or stratified patients by baseline ratings to determine whether this baseline difference accounted for some of the evidence of efficacy and the reported superiority of risperidone.

One problem with both the large U.S. and the Canadian studies involves the emphasis on the total PANSS score as the primary efficacy measure. This measure (as intended) focuses more on negative symptoms than the BPRS, the more standard scale. Since haloperidol can mimic or exacerbate certain negative symptoms (e.g., extrapyramidal symptoms [EPS] such as akinesia), it may be predicted that neuroleptics that do not cause EPS may seem, artifactually, to have superior antipsychotic efficacy.

In addition, total scores on the PANSS or the BPRS

include ratings of several areas of psychopathology, not just typical schizophrenia symptoms. To evaluate specifically whether risperidone is having an antipsychotic effect, one could look at ratings of specific items. Lindenmayer (1994) had access to data from all three of the above studies and independently reported analyses by item. The results indicate statistically significant alleviation of positive symptoms by both haloperidol and risperidone, but improvement in negative symptoms only with risperidone. However, results are not presented in detail; for example, only significance levels are presented, not rating scale data or the total population sizes. Thus, the same reservations noted previously apply; specifically, statistical significance does not necessarily imply that either haloperidol or risperidone was of more than marginal clinical benefit.

## Comparisons Without Placebo

Three studies compared risperidone and a standard neuroleptic without a placebo group. These studies certainly are relevant but, because they had no placebo group, they can never be totally convincing in demonstrating efficacy (Leber 1991).

Müller-Spahn et al. (1992) and Peuskens (1995) reported a comparison of five doses of risperidone (1, 4, 8, 12, and 16 mg) with haloperidol (10 mg) in a total of 1,362 chronic schizophrenia patients from 15 countries with a 4-month median duration of the current hospitalization. As in the placebo-controlled studies, the beneficial effect of haloperidol was not robust. The mean improvement in the haloperidol patients on the PANSS-derived BPRS was only 8.1 points (standard deviation [SD] = 0.82; mean baseline BPRS score = 48.1), compared with improvement from 1 mg of risperidone (a dose assumed to be suboptimal) of 6.7 points (SD = 0.87; difference not statistically significant). In this study, haloperidol was significantly better than 1 mg of risperidone on some measures (e.g., BPRS thought disturbance, PANSS positive subscale, and CGI) but not on others (total PANSS and total BPRS). This result again suggests that the group was relatively refractory. Factors that make this study difficult to interpret, particularly the problematic effect of prior medication (e.g., 37% of patients were on depot neuroleptics shortly before the study) and the inadequately described patient population, are reviewed by Johnson and Johnson (1995).

This study (Müller-Spahn et al. 1992) specifically comments on evidence that risperidone might be particularly beneficial in patients with high levels of depression or anxiety. The sample was divided by high and low levels of anxiety/depression, and risperidone was shown to be more helpful in the high anxiety/depression subgroup. Con-

versely, the final report of this study (Peuskens 1995) showed no significant intergroup differences on the anxiety/depression cluster score.

Finally, although large samples are generally preferable, a sample of this size (1,362 patients) allowed for statistical significance with a relatively small medication effect such as the decreases in the total BPRS score on 1 mg and 16 mg of risperidone (6.7 and 9.7 points, respectively). This difference was statistically significant, but a difference of only 3 points has questionable clinical significance.

In another study, Claus et al. (1992) randomly assigned 44 schizophrenia patients to haloperidol or risperidone. This study also involved a chronic and refractory population; rating scores on haloperidol showed no improvement compared with baseline. Superior benefit was found for risperidone, but the risperidone group scored significantly worse at baseline than did the haloperidol group, and change scores were used in the analyses. Ratings at the end of the study were basically the same for haloperidol and risperidone, and the significant difference on change scores was caused strictly by the risperidone patients' higher scores at baseline. This study also used the PANSS scale, and the superiority of risperidone was not clearly due to improvement in positive schizophrenic symptoms.

Höyberg et al. (1993) randomly assigned 107 patients at 18 sites to risperidone (up to 15 mg/day [mean = 8.5 mg/day]) or perphenazine (up to 48 mg/day [mean = 28 mg/day]). Results showed generally equivalent benefit with some evidence of risperidone superiority on negative symptoms and hostility. However, the small number of patients per site and the lack of a placebo group increase the risk of Type II error (i.e., failing to find differences that do in fact exist). Also suggesting a Type II error, significant differences were not found in EPS between risperidone and perphenazine or in the use of antiparkinsonian drugs.

## Other Relevant Studies

Klieser et al. (1995) randomly assigned 59 patients to risperidone (4 mg), risperidone (8 mg), or clozapine (400 mg/day). Efficacy was equivalent in all groups; however, because there was no placebo group, this comparison is difficult to interpret. Also, 22 of the 39 patients on risperidone withdrew from the study before completing the full 28 days. Finally, improvement was not marked in any group; the mean change in BPRS score was only 11.4 (from a baseline mean of 52.6) in the 8-mg risperidone group (although improvement on 4 mg of risperidone averaged 16.8).

A study by Monfort et al. (1989) focused on patients with predominantly negative symptoms, thus, it does not speak to the issue of efficacy for abating positive symptoms. Finally, Dwight et al. (1994) and Sajatovic (1995) reported that risperidone precipitated or exacerbated mania in a total of 8 schizoaffective or bipolar patients, again suggesting an antidepressant effect.

## Discussion

It is possible, based on the available studies, that risperidone is not as effective as standard neuroleptics for typical positive schizophrenia symptoms (e.g., delusions, hallucinations, thought disorder) in schizophrenia patients. The studies to date have involved primarily chronic, refractory patients who have been marginally responsive to standard neuroleptics, although that degree of prior responsiveness has not been specified in most studies.

The placebo-controlled risperidone studies used the criteria of 20 percent improvement on the BPRS to indicate improvement, based on the Kane et al. (1988) criteria. However, the Kane et al. (1988) criteria were developed for the study of clozapine in refractory schizophrenia patients, and they were intended to show slight improvement, because even a small (20%) improvement might be significant in chronic, refractory patients. Earlier studies suggest that neuroleptic-responsive patients would be expected to improve much more than 20 percent on the BPRS.

It is beyond the scope of this article to review comprehensively all prior studies of BPRS changes in schizophrenia patients taking neuroleptics; Hedlund and Vieweg (1980) identified more than 100 such studies, but neither they nor other authors have summarized mean BPRS improvement scores (John Overall, personal communication, February 1996).<sup>1</sup> However, even a cursory review *not* selecting for studies with unusually large drug effects suggests that improvement has generally been much greater than that reported for haloperidol or risperidone in the risperidone studies. For example, Tuason et al. (1984)

<sup>1</sup>Parenthetically, Dr. Overall indicated that the version of the BPRS using ratings from 1 to 7 should be returned to the original 0 to 6 ratings (i.e., 18 should be subtracted) before calculating the percentage improvement. The change to the 1 to 7 ratings may have been made because older computer systems could not distinguish 0 from blank. However, the 1 to 7 ratings do not yield a ratio scale, that is, the minimum score is 18. The Kane et al. (1988) criteria used the 1 to 7 scale (without subtracting 18), as did the placebo-controlled risperidone studies; however, most other studies do not report whether they used the 0 to 6 or the 1 to 7 scale, making comparisons difficult. Converting to the 0 to 6 scale will increase the percentage improvement. For example, from the Marder and Meibach (1994) study, the mean 17.7 percent improvement in the 6-mg risperidone group would become a 26.6 percent improvement.

reported an average 59.5 percent improvement on the BPRS in a study comparing loxapine and chlorpromazine; Claghorn (1985) reported an average BPRS improvement of 35 percent in patients on molindone; and Gorham and Pokorny (1964) reported a mean BPRS improvement of 47.8 percent in patients on medication alone, compared with a 12.7 percent improvement in patients receiving psychotherapy alone. The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group (1964), in a study completed before the BPRS became standard, reported that 75 percent of 463 acutely ill schizophrenia patients had moderate to marked improvement on phenothiazines compared with 23 percent for patients on placebo. After receiving phenothiazines for 6 weeks, 46 percent of patients had only minor residual symptoms. VA hospital studies reviewed by Cole and Davis (1969), using the Multidimensional Scale for Rating Psychiatric Patients (MSRPP; Lorr et al. 1953), reported mean improvement ratings of approximately 32 percent.

It is problematic to compare studies, but it is apparent that the effect of haloperidol reported in the placebo-controlled risperidone studies is extremely small compared with prior reports of neuroleptic effects in acutely ill schizophrenia patients. Although the effect of risperidone is greater, it still is small compared with that of prior studies.

Response of the haloperidol group in the placebo-controlled risperidone studies is crucial. In this type of three-way comparison, it is necessary to demonstrate the expected difference between the standard medication (haloperidol) and placebo in order to characterize the effect of the novel drug. Also, without the expected effect of the standard drug, it is impossible to know whether the population being studied is similar to the population originally reported to have benefited from that type of medication. However, in the risperidone studies, haloperidol had only marginal benefit.

Before the use of clozapine, no neuroleptic drug had been marketed since molindone was introduced in 1974. (Note also that clozapine was tested only in treatment-refractory patients.) There is reason to think that patients similar to those who 20 to 40 years ago participated in studies of standard neuroleptics (that showed robust effects) are generally unavailable for current studies. The majority of schizophrenia patients now are treated with short hospitalizations at community or private psychiatric hospitals, making long-term institutionalized patients an increasingly atypical population.

Acute-care facilities (e.g., McLean Hospital) at one time conducted more inpatient neuroleptic studies. Thirty years ago, even medication-responsive, acutely ill patients often would be hospitalized for several months (Rosen et

al. 1976). At that time, insurance companies rarely were involved in managing care; a patient could be entered into a placebo-controlled study if the patient agreed and if the treating psychiatrist had an interest in research. Currently, most insurance companies do not pay for hospitalization if patients are in a placebo-controlled study, and hospital stays are much shorter. The result is that drug companies conduct most inpatient neuroleptic studies at VA and State hospitals where the cost of hospitalization is not borne by the drug company. Earlier neuroleptic studies also often used VA or State hospital populations; even at these facilities, however, the length of stay has decreased markedly over the past 25 years (Sunshine et al. 1991; McDuff and Keill 1992; Appleby et al. 1993). VA hospitals, although varying greatly in average length of stay, have not been immune to the financial and other pressures affecting private and other public facilities (Rosenheck and Massari 1991). Acutely ill VA patients who 20 to 40 years ago might have been hospitalized for several months now are often discharged in several weeks; they therefore are less available for studies (William Van Stone, M.D., personal communication, March 1996). The result is that most acutely ill, medication-responsive patients are not hospitalized long enough, in any setting, to participate in studies. Because of this situation, the patient population currently available for studies is different than that involved in earlier studies of neuroleptics. To remedy this problem, pharmaceutical companies would have to cover the cost of hospitalization for acutely ill patients involved in studies.

Regarding negative symptoms, the reported superiority of risperidone compared with haloperidol may result primarily from the relative lack of EPS from risperidone at the doses used. Carpenter et al. (1995) reviewed evidence suggesting that the superiority of clozapine in treating negative symptoms is true only for secondary negative symptoms, that is, those secondary to other causes, including neuroleptic side effects. They report no evidence of benefit from clozapine on primary negative symptoms. Other atypical neuroleptics also might be expected (to the extent that they are similar to clozapine) to reduce secondary but not primary negative symptoms. The available risperidone studies do not focus on this distinction. Moreover, if one assumes that risperidone has some beneficial effect on anxiety or depression, one would expect some evidence of superiority of risperidone on ratings of general psychopathology. This assumption is supported by Müller-Spahn et al. (1992); by Dwight et al. (1994) and Sajatovic (1995), who showed that risperidone can precipitate mania; and by Gelders (1989), who reviewed the evidence that serotonin- $S_2$  antagonists, including ritanserin and risperidone, have an antidepressant effect.

There are other suggestions in the recent literature

supporting the idea that risperidone may not be as effective as standard neuroleptics. For example, Stip et al. (1995), in a letter describing clinical experience with risperidone, reported an "awakening" effect. They described patients whose psychotic symptoms recurred, sometimes with manic features, after 3 to 6 months on risperidone. Similarly, there have been numerous reports (e.g., Horne and Miller 1995) of difficulties in changing patients from clozapine to risperidone; this difficulty, characterized by a resurgence of psychotic symptoms, has generally been attributed to withdrawal effects of clozapine, but insufficient efficacy of risperidone is another possibility. Janssen Pharmaceutica recently revised its recommendations (*Physicians Desk Reference* 1995, 1996) regarding switching patients from other neuroleptics to risperidone because of concerns about resurgent symptoms. (No prior reports of difficulties in changing from one neuroleptic to another are known to this author, suggesting an atypical effect of risperidone in neuroleptic-responsive patients.)

Risperidone does have dopamine-blocking activity, although some authors report less affinity for dopamine receptors than for typical neuroleptics (Farde et al. 1989). Risperidone thus would be expected to have some anti-psychotic effect. It might, at a sufficient dose (a dose resulting in dopamine blockade comparable to that obtained with typical neuroleptics), be expected to have an antipsychotic effect comparable to that of standard neuroleptics. However, at that dose, the advantages of risperidone (e.g., relative lack of EPS) might be lost, and the other pharmacological effects of risperidone (e.g., serotonin-blocking activity) might cause adverse events.

Theoretically, a purported advantage of risperidone is its blockade of serotonin- $S_2$  receptors. This theory has led to the development of a number of new neuroleptics, but it is only a theory, originally developed because of the  $S_2$ -blocking effect of clozapine. However, clozapine affects many neurotransmitter receptors, not just dopamine and serotonin, and there are competing theories to explain clozapine's superior benefit (Richelson 1994; Carpenter et al. 1995). Also, because risperidone does not inactivate ventral, tegmental, A10 dopamine neurons as standard neuroleptics and clozapine do (Richelson 1994), a finding of reduced efficacy for risperidone would highlight the importance of the A10 system in the genesis of positive schizophrenia symptoms.

It is important to emphasize that the available studies do not prove that risperidone is less effective than standard neuroleptics. Rather, the conclusion is that risperidone has not been evaluated extensively in neuroleptic-responsive schizophrenia patients and that clinicians should remember this fact when treating patients with risperidone. There appears to be a group of chronically

hospitalized refractory schizophrenia patients who do better on risperidone than on haloperidol; however, in this population the superiority of risperidone results largely from the lack of benefit from haloperidol. Further studies are needed on the efficacy of risperidone in neuroleptic-responsive and neuroleptic-naïve patients, as well as on primary negative symptoms. Risperidone may be particularly useful in certain situations, such as in patients with involitional mixed paranoid and depressive states, but its place in the psychiatric treatment armamentarium remains to be determined.

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