Clinical Profile of an Atypical Antipsychotic: Risperidone

by John M. Davis and Nancy Chen

Abstract

Stimulated by Dawkins and colleagues’ (1999) and Remington and Kapur’s (2000) calls to develop clinical profiles of the new atypical antipsychotic drugs and by Mattes’s critiques (1997, 1998), we performed two sets of analyses for risperidone. First, we reanalyzed data from the North American risperidone trial: risperidone was superior to haloperidol to an equal degree in patients with and without the deficit syndrome, in patients with paranoid and nonparanoid schizophrenia, in treatment-resistant and treatment-responsive patients (patients hospitalized for longer and shorter periods), and in patients with or without weight gain. Moreover, risperidone was more effective than haloperidol on symptoms nonresponsive and responsive to haloperidol; its effects on negative symptoms were independent of its effects on extrapyramidal symptoms; and it was effective in treating depression in schizophrenia. Second, we performed a meta-analysis of 18 controlled risperidone trials: risperidone was consistently more effective than conventional antipsychotics in treating positive and negative symptoms.

Keywords: Atypical antipsychotics, risperidone, schizophrenia treatment, extrapyramidal side effects.


Dawkins and colleagues (1999) have suggested in this journal that trials of the new atypical antipsychotics conducted by pharmaceutical companies to obtain U.S. Food and Drug Administration approval fail to fully define the clinical profile of these agents. We agree. Clinical trials sponsored by drug companies focus on analysis of efficacy and safety using standard measures. The clinical profile of a newer antipsychotic agent is its differential efficacy in comparison with standard agents. Defining a clinical profile includes examining aspects of schizophrenia that are particularly helped by the newer agents and examining patient subgroups that particularly benefit (or do not benefit) from the newer agent, which may define indications for the new drug. We present results of the analyses of double-blind randomized studies of patients with schizophrenia to provide data relevant to constructing the clinical profile of one of the newer atypicals: risperidone. Our results also relate to some important questions about the efficacy of the newer atypical agents raised by Mattes (1997, 1998), Remington and Kapur (2000), and Geddes and colleagues (2000). The latter focused on how the haloperidol comparator dose affected efficacy.

To define the clinical profile, we performed several new analyses of raw data from two large randomized double-blind clinical trials comparing risperidone with haloperidol: one conducted in the United States and the other in Canada (Chouinard et al. 1993; Marder and Meibach 1994). Both trials were sponsored by Janssen Pharmaceutica and used the same protocol and basic design but differed in the investigators, protocol meetings, and investigator training. The greater power of a large sample size may help delineate true drug differences. These analyses include the following:

- Effects of risperidone on Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) items that were nonresponsive or responsive to haloperidol
- Effects of risperidone on putative serotonin- and dopamine-sensitive symptoms
- Differential effects of risperidone on symptoms of depression
- Whether the presence or absence of depression alters the response to risperidone or haloperidol
- Whether subtypes of schizophrenia respond differently to risperidone or haloperidol
- Effects of extrapyramidal symptoms (EPS) on clinical improvement
- Effects of duration of hospitalization (a measure of treatment resistance) on differential efficacy

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The 1997 critique of risperidone trials by Mattes is reviewed in a final section. In an appendix we add a note on power analysis.

Given that risperidone and all other new atypical drugs cost more than conventional neuroleptics, do they produce better results? If so, is this better efficacy due to an effect found in all schizophrenia patients or only in a subgroup? Is the better effect just a consequence of a lower incidence of EPS? Or is it independent of EPS? These questions are important to practice and to theory because the presumptive difference between the atypical and conventional antipsychotics is the serotonin 5HT 2 blockade. Risperidone is a particularly important drug for theory because it differs from conventional agents principally in this one pharmacological property.

Methods

North American Trial. Data from the Canadian and U.S. trials (Chouinard et al. 1993; Marder and Meibach 1994) were combined for these analyses. Both trials placed patients on a 1-week placebo lead-in or washout period. We used the same methods as in our previous analysis (Marder et al. 1997)—based on the five PANSS factors of schizophrenia: (1) negative symptoms, (2) positive symptoms, (3) disorganized thoughts, (4) impulsivity/hostility, and (5) anxiety/depression—and consequently we only briefly summarize the methods below. Analysis of covariance (ANCOVA) with baseline as covariate was used to compare the effects of placebo, haloperidol, and risperidone, using endpoint last-observation-carried-forward data. When overall F tests were significant (demonstrating that overall between-group differences were significant), comparisons between individual groups were made by simple contrast (expressed as t tests).

Patients in the North American trial were randomized to placebo; 20 mg/day of haloperidol; or 2, 6, 10, or 16 mg/day of risperidone. The optimal risperidone dose was 6 mg/day, which was also associated with few EPS. In the best-case and worst-case analyses, responses to 6 mg/day and to 6–16 mg/day of risperidone, respectively, versus placebo or haloperidol were assessed. The worst case assumes a linear dose-response curve that levels off once an optimal dose is achieved, while the best case assumes an inverted U-shaped curve on which lower and higher doses are less effective than the optimal dose. Because we wished to explore the effect of moderator variables on efficacy, almost all of our analyses were based on the worst-case scenario because it had the largest sample size. The single exception is that we present the results of the optimal 6 mg dose in figure 2, which is important to consider because the results place the worst-case scenario in perspective. The 2 mg dose was clearly less effective than the 6 mg dose. Results with the 2 mg dose are presented because they provide an estimate of a dose producing a benefit at about 50 percent of the optimal dose. We calculated the effect sizes of changes in PANSS points from the difference in PANSS total score (efficacy) between placebo and risperidone or haloperidol. The placebo/active-medication difference is a meaningful index of improvement because placebo-treated patients deteriorated almost 4 points (or 40%) on the absolute PANSS changes from baseline. The absolute PANSS changes from baseline as used by Mattes (1997) greatly underestimates the drug effect compared with placebo. Change scores were divided by the number of items in each factor to account for the uneven number of items in the factors (e.g., seven items for negative symptoms and four for anxiety/depression) (Marder et al. 1997).

Dimensional structure of schizophrenia. A large collection of consistent empirical literature now supports a five-dimensional model of schizophrenia—the five-factor structure of the PANSS (Kay and Sevy 1990; Lindenmayer et al. 1994; Marder et al. 1997)—including studies with the PANSS translated into other languages (Lindström and von Knorring 1993; Lançon et al. 1998). This was an important development because the original positive and negative subscales were constructed on a theoretical basis without empirical verification. The original negative subscale was confounded by the disorganized thoughts (cognitive) factor, thus distorting the clinical profile. Most important, the two-factor model misses three important dimensions of schizophrenia and is thus markedly incomplete. It is important to identify these symptom clusters correctly and then use them to help define the clinical profile.

Deterioration on placebo and during washout. Assessments of baseline characteristics were made at the screening visit and also after a 1-week washout period. To examine the degree of deterioration during the washout period, we analyzed the data of all patients at the screening and baseline evaluations. The question whether certain dimensions of schizophrenia deteriorate when the patient stops taking medication is addressed by focusing on the placebo patients. Do patients experience relapse in all aspects of the psychopathology at the same rate, or is there relapse in some aspects first? Selecting only the 86 placebo patients, we used paired t tests to
compare the degree of deterioration in the five factors as well as the individual items. To determine whether the same symptoms deteriorated in both the washout period and at endpoint, we correlated the change on each of the 30 items at the two time points.

Symptoms responsive and nonresponsive to a conventional neuroleptic. A few questions that should be asked about any new drug are: Does the new drug have a beneficial effect on symptoms untouched by the standard drug? Does it have a greater effect on symptoms that are improved by the standard drug? Or do both types of effects occur? The dimensional five-factor structure accounts for more than 50 percent of the variance of PANSS-measured symptoms. These clusters may miss important information; that is, the factors may not necessarily extract the most relevant information from the PANSS. For this reason we explored pharmacologically derived symptom clusters. To examine the effects of risperidone on PANSS items that were responsive and nonresponsive to a conventional neuroleptic, we constructed the haloperidol-responsive and the haloperidol-nonresponsive scales. The haloperidol-responsive items were determined by identifying the 13 items (PANSS items 1-4, 6, 7, 18, 23-26, 28, and 29) on which haloperidol was significantly superior to placebo ($p < 0.05$; ANCOVA with baseline as covariate). The haloperidol-nonresponsive items were the remaining 17 PANSS items on which haloperidol was not significantly superior to placebo (PANSS items 5, 8-17, 19-22, 27, 30). Each summed score was divided by the number of items in it (13 and 17) to derive an average change score per item. We present endpoint, intent-to-treat, last-observation-carried-forward data (average of weeks 6 and 8) and a time course of improvement on these two scales.

Dopamine- and serotonin-mediated effects. Risperidone differs from conventional neuroleptics such as haloperidol by blocking serotonin $5HT_2$ receptors as well as dopamine $D_2$ receptors. Antipsychotic effects specific to serotonin $5HT_2$ blockade can be identified as the effects produced by risperidone that are greater than those produced by haloperidol. We used pharmacological response as a tool to examine the difference between these two drugs. One difficulty is that the difference between risperidone and haloperidol could be due to another pharmacological property (e.g., the kinetics of dopamine binding—the rapidity of “time on” or “time off” of drug on $D_2$ receptors). For this reason, our use of the term “serotonin” in the text really refers to “serotonin/other” to indicate that we cannot say with certainty the mechanism of the difference between the two drugs. For convenience, we refer to these as the dopamine- and serotonin-sensitive symptoms. All but 2 of the 30 PANSS items appeared to carry some information ($p \leq 0.10$), so the haloperidol-nonresponsive items are suggestive of a serotonin effect.

We evaluated the beneficial effects of haloperidol versus placebo, risperidone versus placebo, and risperidone versus haloperidol on each item of the PANSS. We evaluated the symptoms that are helped by both risperidone and haloperidol, and the symptoms that are helped by risperidone only, with a much more stringent criterion that items must be statistically significant at the 0.01 level. First we measured the differences between haloperidol and placebo, risperidone and haloperidol, and risperidone and placebo directly. We also calculated the risperidone-haloperidol difference by subtracting the haloperidol-placebo difference from the risperidone-placebo difference. If these effects are transitive and additive, both methods should agree. There was excellent agreement between the two methods for estimating the difference between risperidone and haloperidol. To derive a dopamine-sensitive scale, we identified PANSS items on which haloperidol produced significantly ($p < 0.01$) greater improvement than placebo: items 1, 2, 3, 4, 23, 24, and 29 (each item weighted 1). We derived a serotonin-sensitive scale by identifying PANSS items on which risperidone produced significantly greater improvement ($p < 0.01$) than haloperidol: items 6, 8, 9, 11, 20, 22, 27, 28, and 30 (each item weighted 1). Because we had two estimates of the risperidone-haloperidol differences, we averaged them. On PANSS item 7 (hostility), the differences between haloperidol and placebo and risperidone and haloperidol were both statistically significant. We therefore calculated the respective size effects of the difference: mean improvement on haloperidol (or risperidone) minus mean improvement on placebo (or haloperidol) over the pooled standard deviation. In both the dopamine-sensitive and the serotonin-sensitive scales, the effect sizes were approximately equal (0.5). We therefore weighted the item 7 score by a size effect of 0.5 for both scales. We examined the effects of 2 mg, 6 mg, and 10–16 mg of risperidone, haloperidol, and placebo on the dopamine- and serotonin-sensitive scales. The serotonergic scale is substantially different from the haloperidol-nonresponsive scale because it includes only items on which risperidone produced a significantly greater effect than haloperidol. We hasten to add that the scales have not been validated and these should be regarded as exploratory analyses. Furthermore, differences may be due to something other than dopamine or serotonin. This approach is heuristically driven, not confirmatory, and the labels are labels of convenience for this operationally defined scale. Both scales measure somewhat the same thing but differ on the stringency of the exclusion criteria.
Effects on depression, schizophrenia subtypes, and the deficit syndrome. It has been proposed that atypical agents are particularly effective in patients not responding to conventional, and indeed Mattes has suggested that risperidone was ineffective in patients who responded to conventional agents. On the more general level, this question becomes: Are there subtypes of schizophrenia for which atypical drugs are indicated and other subtypes for which a conventional neuroleptic is indicated? We assessed a variety of methods of classifying schizophrenia patients by subtype to determine whether risperidone or haloperidol is particularly effective in one or another subtype. This analysis examines the interaction effect between diagnostic subtypes and drug conditions in an ANCOVA.

The effects of risperidone on patients with and without depression were evaluated by dichotomizing the patients as depressed or not depressed at baseline (scores of > 4 versus ≤ 4 on the depression item of the PANSS and entering this into the two-way ANCOVA). To address whether risperidone is superior to haloperidol only for certain subtypes of schizophrenia (Mattes 1997), the subtype was entered as a second factor into the ANCOVA. Another example of a meaningful subtype is paranoid versus nonparanoid schizophrenia. We explored whether risperidone was particularly effective and haloperidol less effective in patients with paranoid schizophrenia or vice versa.

The deficit syndrome is another important dimension of schizophrenia that is characterized by negative symptoms, with the emphasis on primary negative symptoms unresponsive particularly to conventional neuroleptics (Kirkpatrick et al. 1989). We derived a measure of the deficit syndrome from PANSS items (8–11, 13, and 30) and dichotomized patients as having (score of ≥ 4 on two or more items) or not having the syndrome at baseline.

To determine the effects of risperidone in schizophrenia patients with an affective component to the illness, we categorized patients as having predominantly schizomanic symptoms, schizodepressive symptoms, or both. We dichotomized PANSS items 4, 5, 8, 10, 20, and 21 (excitement, grandiosity, blunted affect, poor rapport, depression, and motor retardation) and the negative symptoms, disorganized thoughts, and impulsivity/hostility factors into high or low categories. Patients with predominantly manic symptoms met three or more of the following criteria: high scores on the excitement and grandiosity items and on the impulsivity/hostility factor, low scores on the motor retardation item and on the negative symptoms and disorganized thoughts factors, and less than 3 months of hospitalization. Patients with predominantly depressive symptoms met three or more of the following criteria: high scores on the motor retardation and depression items, low scores on the blunted affect and poor rapport items and on the disorganized thoughts factor, and less than 3 months of hospitalization. The "both" category consisted of patients who fell into both the manic and the depressive categories.

Effects of hospitalization duration, EPS, and weight gain. The population of patients studied in these two pivotal trials included a significant proportion of patients continuously hospitalized for long periods of time. We can infer that these patients were nonresponsive to conventional neuroleptics. The effect of duration of hospitalization on response to treatment was evaluated by dichotomizing this variable and entering it into the ANCOVA as a second factor in this now two-way ANCOVA (those hospitalized ≤ 4 weeks vs. those hospitalized > 4 weeks at study entry). This was considered the most relevant measure for identifying failure to respond to conventional neuroleptics.

To determine whether changes in the severity of EPS (Extrapyramidal Symptom Rating Scale [ESRS] scores) could explain the greater efficacy of risperidone compared with haloperidol, an ANCOVA with baseline as covariate was used to examine the effect of the maximum changes in total parkinsonism and clinical global impression (CGI) severity of parkinsonism scores on the change in PANSS total scores at weeks 6 and 8 in patients receiving risperidone, haloperidol, or placebo. The potential influence of antiparkinsonian medication on PANSS total scores and the five factors was examined by another ANCOVA that included whether or not patients received antiparkinsonian medications as a second factor in the model. The two ESRS measures of tardive dyskinesia (TD), total dyskinesia, and CGI severity of dyskinesia were almost perfectly correlated and hence were combined as a measure of TD seen throughout the trial. Patients were then classified as having no TD, questionable TD, and definite TD. This was entered into the two-way ANCOVA to examine the influence of risperidone, haloperidol, and placebo on improvement and TD (as a second factor), with baseline as covariate.

Atypical antipsychotics are associated with greater weight gain than conventional agents and thus it was of interest to determine whether weight gain was associated with improvement. To assess weight change, we calculated percentage changes in body mass index (BMI = weight [kg]/height$^2$ [m$^2$]) for each patient. We classified percentage changes in BMI into five categories: (1) weight loss less than 1 percent; (2) little or no change (between 1% loss and 1% gain); (3) mild weight gain (1.1%–5%); (4) moderate weight gain (5.1%–10%); and (5) more than 10 percent gain. The categorical weight change variable was entered into a two-way analysis of variance to examine its effects on treatment response.
Meta-Analysis of Risperidone Trials. The North American clinical trial clearly found risperidone to be superior to haloperidol. To determine whether this finding was something particular to the North American clinical trial or whether it was a general result of all or most controlled clinical trials, we performed a meta-analysis of the random-assignment double-blind controlled clinical trials of risperidone versus conventional neuroleptics. To avoid the file drawer problem (negative findings that remain unpublished), we included several unpublished studies, specifically that of Borison (1991), whose data were available on the Web site of the Cochrane Collaboration (Kennedy et al. 2001) as well as in company monographs. We also included two randomized open-label studies in our meta-analysis and examined whether there was any systematic difference between randomized double-blind and randomized open studies. Virtually all studies in this data base defined treatment response as a ≥ 20 percent reduction in the PANSS or Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) total scores, with the exception of the Emsley and colleagues (1999) study of first admission patients, which used a 50 percent criteria. Our meta-analysis included 16 double-blind randomized controlled trials and 2 randomized open-label studies that compared risperidone with conventional agents. These studies were identified by a computer-based search of the literature and by scanning reference lists of the study reports. Two of the trials are pertinent in extending the risperidone effect to acutely ill patients. Emsley and colleagues (1999) studied 183 first episode patients with schizophrenia, 99 receiving risperidone (mean dose 6.1 mg/day) and 84 receiving haloperidol (mean dose 5.6 mg/day). Blin and colleagues (1996) investigated patients in acute exacerbation of schizophrenia and with severe anxiety (Psychotic Anxiety Scale ≥ 34); 21 patients received a mean dose of 8.6 mg/day of risperidone and 20 patients received 9.2 mg/day of haloperidol for 4 weeks. We used the worst-case analysis in which all doses of risperidone from 4 to 16 mg/day were compared with conventionals (a conventional dose-response model).

Geddes and colleagues (2000) have suggested that an overly high dose of the comparator can produce decreased efficacy of the comparator and thus artifactually make the atypical better than the typical comparator. We entered the dose of haloperidol in a metaregression to see if it influenced haloperidol-risperidone differences.

Two meta-analysis techniques were used. The Peto method (Peto et al. 1977) analyzes pooled data of n studies from treatment responders and nonresponders. This method uses raw data for each patient and yields n sets of 2 × 2 tables of responders versus nonresponders for the study drug and its comparison. The Hedges and Olkin (1985) method analyzes the combined means and standard deviations (SDs) of improvement in the treatment and control groups in each trial. When SDs were not reported, they were estimated from data in three fixed-dose studies that used the same rating scales.

Supplemental Data Analysis. Further data analysis and discussion may be accessed on our Web site: http://www.psych.uic.edu/faculty/davis/risperidone.

Results

Clinical Profile of Risperidone Based on the North American Trial

Overall differences in efficacy. Efficacy in the North American trial (as in many others) was evaluated by means of the PANSS. For the reader who has not had extensive experience with the PANSS, the following may be used as a guideline for evaluating the significance of reported changes in PANSS scores: An improvement of 9–13 PANSS total points corresponds to a degree of improvement that a patient in acute psychotic exacerbation may achieve after 2 months of treatment based on the registrational studies of risperidone, olanzapine, quetiapine, sertindole, and ziprasidon (Chouinard et al. 1993; Marder and Meibach 1994; Zborowski et al. 1995; Beasley et al. 1996; Arvanitis and Miller 1997; Zimbroff et al. 1997; U.S. Food and Drug Administration 2001). A 9-point PANSS total improvement is equivalent to 0.3 points per item because the PANSS is a 30-item scale.

Risperidone was significantly superior to haloperidol on PANSS total and all five PANSS factors in both the worst-case (6–16 mg/day of risperidone; n = 255) and best-case (6 mg/day of risperidone; n = 85) analyses. In the worst-case analysis, the mean difference was 8.7 points (95% confidence interval [CI]: 3.4–14.0, p = 0.001). The mean difference between the risperidone 6 mg/day group and the placebo group was 22.0 points (95% CI: 15.5–28.5, p < 0.0001), while the haloperidol group improved by a mean of 9.0 points over placebo (95% CI: 2.5–15.5, p = 0.007). For the worst-case analysis, the mean difference between the risperidone 6–16 mg/day group and the placebo group was 17.7 points (95% CI: 12.4–23.0, p < 0.0001). We present only the best-case analyses in figure 2 because results of the worst-case analyses have been published (Marder et al. 1997, figure 3). In the best-case analysis, the mean difference in PANSS total score between the group receiving 6 mg/day of risperidone and the haloperidol group was 13.0 PANSS points (95% CI: 6.5–19.5, p = 0.0001), or 0.43 points per item. We emphasize that with this exception all the other analyses presented are worst-case analyses. The improvement with haloperidol as measured by changes in PANSS...
total scores was less than half that with risperidone in the best-case analysis (9.0 vs. 22.0, respectively) and about half that with risperidone (9.0 vs. 17.7) in the worst-case analysis (6–16 mg/day of risperidone). This is an important clinical difference that would surely be reflected in a considerable degree of social remission, and restoration of function and quality of life in patients treated with risperidone. The time course of improvement expressed as percent improvement for the PANSS total and five factor scores are presented in figures 1A and 1B on the Web site. Interestingly, patients on risperidone 6–16 mg/day exhibited much more improvement at week 1 than haloperidol at endpoint. We also evaluated the difference between the risperidone 6 mg dose and the combined 10–16 mg dose on PANSS improvement. This difference was just barely statistically significant: $t = 2.15$, $df = 252$, $p = 0.03$ (table 1 on the Web site).

To explore whether there was a natural cutoff point on the PANSS total score to identify responders versus nonresponders, we plotted the distribution of patients on PANSS total percentage improvement (figure 1). The figure shows that the distribution of patient improvement is

![Figure 1. Patient distribution versus Positive and Negative Syndrome Scale (PANSS) total percentage improvement for placebo, haloperidol, risperidone 2 mg/day, and risperidone 6–16 mg/day](image-url)
approximately normal for the four treatment groups (placebo, haloperidol, risperidone 2 mg, and risperidone 6–16 mg) with no indication of a bimodal distribution.

**Effects on Different Dimensions of Schizophrenia.** Risperidone was significantly superior to haloperidol on all five PANSS factors in both the best- and worst-case analyses (figure 2). The most marked differences between risperidone and haloperidol were on negative symptoms, impulsivity/hostility, and anxiety/depression. Mattes (1997) questioned risperidone’s greater efficacy on positive symptoms, but these analyses demonstrated that risperidone was substantially more effective than haloperidol on positive symptoms. Empirically, haloperidol was significantly superior to placebo on total PANSS ($t = 2.7, p = 0.007$) and on three of the five factors: positive symptoms ($t = 3.0, p = 0.003$), disorganized thoughts ($t = 3.3, p = 0.001$), and impulsivity/hostility ($t = 3.3, p = 0.001$) in this analysis.

**Figure 2. Effects of treatment on Positive and Negative Syndrome Scale (PANSS) total and factor scores in patients treated with placebo, haloperidol, or 2 mg/day or 6 mg/day of risperidone**

Deterioration on Placebo and in Washout Period. It is noteworthy that placebo patients deteriorated -3.9 points on the PANSS total score (-0.13 points per item) and on four of the five PANSS factors in figure 2. Indeed, 40 percent of the difference between haloperidol and placebo was deterioration in placebo scores and about 60 percent of that was improvement over baseline on haloperidol (0.17 points per item). The discussion by Mattes (1997, page 155) of haloperidol-induced changes from baseline is misleading in that it ignores the deterioration experienced by the placebo patients, which is almost as great as the improvement from baseline in the haloperidol patients.

Patients also became more symptomatic during the placebo lead-in washout period from screening to baseline evaluation. On the PANSS total score, patients deteriorated an average of 5.4 points ($t = 9.4, df = 512, p = 10^{-19}$). Examination of the individual PANSS items showed significant deterioration on 24 of the 30 items. Because the sample size is large ($n = 513$) at this point, the deterioration is

Note.—PANSS items were summed and divided by the total number of items.
Effect of Risperidone on Nonresponsive and Responsive PANSS Items. Does risperidone equally improve symptoms that are improved with haloperidol and also improve a greater variety of symptoms? The effects of placebo, haloperidol, and risperidone on the 17 items that were nonresponsive and the 13 items that were responsive to haloperidol are shown in figures 3A and 3B. At endpoint, risperidone at 6–16 mg/day was massively superior to haloperidol on the haloperidol-nonresponsive items \( t = 3.6, p = 0.0004 \), and risperidone at 2 mg/day was superior to placebo \( t = 2.7, p = 0.008 \). It is interesting to note that risperidone at 6–16 mg/day was also superior to haloperidol on the items that were responsive to haloperidol \( t = 2.3, p = 0.02 \). Risperidone appears to be a better haloperidol than haloperidol.

Effects Mediated by Dopamine and Serotonin. On both the dopamine-sensitive scale (items on which haloperidol produced a significantly greater improvement than placebo) and the serotonin-sensitive scale (items on which risperidone produced a significantly greater improvement than haloperidol), patients on placebo exhibited deterioration from baseline (figure 4). On the dopamine-sensitive scale, both haloperidol and risperidone (6 mg or 10–16 mg) produced highly significant improvements on the PANSS: risperidone 6 mg showed greater improvement over haloperidol, although the difference just missed statistical significance \( p = 0.06 \). On the serotonin-sensitive scale, haloperidol was not significantly better than placebo; risperidone at 6 mg significantly reduced PANSS scores by 0.7 points over placebo (CI: 0.4–1.1, \( p = 3 \times 10^{-4} \)); and even risperidone at 2 mg significantly reduced PANSS scores by 0.4 points (CI: 0.01–0.7, \( p = 0.04 \)). We remind the reader that the serotonin-sensitive scale may reflect some other property of risperidone and is a label of convenience because the conventional wisdom is that the serotonin \( 5HT_2 \) blockade property accounts for its differences from haloperidol.

Because haloperidol produces about a 9.3-point improvement on the PANSS total score or an average of 0.3 points per item (i.e., 9.3 divided by 30), risperidone produces 8.9 PANSS points improvement over and above that of haloperidol (0.3 average PANSS points). On the 17 haloperidol-nonresponsive items risperidone produced an improvement of 0.31 PANSS points per item. The greater improvement of risperidone over haloperidol on the haloperidol-nonresponsive items is of the same order of magnitude as the average improvement on PANSS total/per item, and this suggests that it is clinically important. For the selected serotonin-sensitive items an improvement of 0.46 PANSS points was observed. (The selection process elevated the average change.)

Rate of Response. Inspection of figures 3A and 3B (and figures 2A and 2B on the Web site) indicates that two phenomena are apparent. Risperidone produces a better response than haloperidol, manifested initially in the first 2 weeks, but then the response levels off. The patients on placebo deteriorate, and this deterioration is most marked in weeks 2–8 of the study. It is important to keep in mind in interpreting change of risperidone versus placebo that over time the change reflects both the initial rapid response to risperidone and the slower deterioration of the placebo group. The rate of response of negative symptoms, the serotonin scale, the haloperidol-nonresponsive scale, and
Figure 3. Time course of effects of placebo, haloperidol, and risperidone on the 17 PANSS items that were nonresponsive to haloperidol (3A) and the 13 items that were responsive to haloperidol (3B)

A: Nonresponsive Items

B: Responsive Items
the anxiety-depression factor is rapid and there is only a small amount of improvement after 2 weeks, when compared to baseline to risperidone.

**Depression.** Risperidone improved the depression symptomatology experienced by patients with schizophrenia. Risperidone at 6–16 mg/day produced almost half a point greater improvement on the PANSS depression item than haloperidol (95% CI: 0.2–0.8; ANCOVA with baseline as covariant, $F = 11.370$, $df = 1, 337$, $p = 0.0008$). The hypothesis that risperidone was effective only in depressed patients was not supported because risperidone was better than haloperidol to an equal degree on PANSS total and all five PANSS factors in patients with and without depression (depression is defined as a score of $>4$ on the PANSS depression item at baseline). A two-way ANCOVA found no significant differential effect of the high versus low depression subtype on improvements in total PANSS or the five factors; that is, there were no significant interactions of drug by depression ($F = 0.9, 1.8, 0.9, 1.8, 0.2, 0.4$, respectively, $df = 3, 504$). There was no significant main effect of depression on outcome ($F = 0.2, 0.7, 0.0, 0.4, 0.2, 0.8$, respectively, $df = 1, 504$). Additionally, in a one-way ANCOVA, there was no significant effect of depression defined by the PANSS depression item treated as a continuous variable and significance evaluated by $t$ tests ($t = 0.6, 0.7, 0.9, 0.4, 1.9, 0.8$, respectively).

**Schizophrenia Subtype.** Risperidone was superior to haloperidol to an equal degree among the paranoid and nonparanoid patients with schizophrenia. In other words, there were no significant effects of paranoid/nonparanoid diagnosis on the degree of risperidone or haloperidol response compared with each other or with placebo (the interaction of drug group and diagnosis for total PANSS and the five factors: $F = 0.5, 0.1, 1.0, 0.7, 0.8, 0.9$, respectively, $df = 3, 504$, $p = $ not significant [ns]). Nor were there any differences in the direct effects of paranoid status on overall outcome (total score and five factors all $F$ values $< 3.1$, $df = 1, 504$).
Clinical Profile of an Atypical Antipsychotic

Across all treatment groups, patients with the deficit syndrome showed less improvement on the PANSS negative symptoms factor than patients without the syndrome (F = 8.1, df = 1, 504, p = 0.005, two-way ANCOVA main effect of deficit state). This is consistent with Kirkpatrick and colleagues' hypothesis (1989). However, equal degrees of improvement were seen on the PANSS total and the other four factors in patients with and without the deficit syndrome in each of the four patient groups (placebo, 2 and 6–16 mg/day of risperidone, and haloperidol; in the 2-way ANCOVA, all F values < 1.2, df = 3, 504, p = ns).

Risperidone was more effective than haloperidol to an equal degree in subgroups of patients who were or were not predominantly manic, depressive, or both. In other words, the interaction effects of subgroup were not significant: for the schizomanic versus not subgroup, F = 0.41, 0.37, 0.24, 1.04, 0.15, and 0.33 for PANSS total, negative symptoms, positive symptoms, disorganized thoughts, impulsivity/hostility, and anxiety/depression; for the schizodepressive versus not subgroup, F = 1.06, 0.76, 0.51, 1.12, 1.12, and 0.79, respectively; and for the "both" versus "neither" subgroup, F = 0.49, 0.14, 0.41, 0.57, 0.81, and 0.13, respectively.

It is clearly possible that a new antipsychotic could be superior to conventional neuroleptics in only a subgroup of patients with schizophrenia. It is also possible that the magnitude of this superiority in one subgroup could be sufficient to make it appear that the new agent is superior for all patients. Thus it was important to examine whether the overall superiority of risperidone over haloperidol was not just an artifact of its possible superiority in a subgroup. This was not the case: there was no significant interaction between drug and any of the subtypes we examined. The results were similar when we examined subgroups defined by low or high scores on each symptom factor, the haloperidol-sensitive or haloperidol-resistant scale, and the serotonin- and dopamine-sensitive scales.

Effect of EPS on Improvement. To examine whether a reduction in the severity of EPS influenced improvements in negative symptoms or any other PANSS scores, the most critical comparison is between haloperidol, which caused the most EPS, and 6 mg/day of risperidone, which was associated with few EPS. No significant effects of overall drug-induced EPS on differences between risperidone and haloperidol in PANSS total scores or scores on the five factors could be found. In addition, neither the two EPS measures (total parkinsonism and CGI parkinsonism severity) nor the frequency of antiparkinsonian medication use had a significant effect on the differences between risperidone and haloperidol in PANSS total change score or on any of the five factors (table 1). Nor was it possible to find any evidence that the presence of TD influenced improvements in PANSS total or factor scores as a direct effect (F = 0.3, 0.3, 0.1, 0.6, 0.1, 0.2; df = 1, 346; all ns) or on differential improvements with risperidone (2 and 6–16 mg), haloperidol, or placebo (interaction F = 0.3, 0.4, 0.1, 0.9, 1.4, 1.3; df = 3, 346; all ns). We tested to see if the greater EPS seen with risperidone 10–16 mg could explain why this dose range was less efficacious than 6 mg risperidone. We found no evidence to support this hypothesis (tables 2 and 3 on Web site).

Duration of Hospitalization. In this analysis we explored whether risperidone was particularly effective in patients who had been resistant to treatment with conventional neuroleptics (i.e., those who had been hospitalized for longer than 1 month, an analysis relevant to what Remington and Kapur [2000] call "the refractory question"). Duration of hospitalization before receiving the study medications was 1 week in 35 percent of the patients, 2–4 weeks in 22 percent, 5 weeks to 2 years in 33 percent, and more than 2 years in 9 percent. The 1-week group responded better to treatment overall (doses of risperidone, haloperidol, or placebo) than the group hospitalized 2 weeks or longer. More than half of the patients had been hospitalized for 1 month or less; these patients generally tended to do better in all treatment groups than those hospitalized for longer periods. These variables, however, did not influence the degree to which risperidone was superior to haloperidol or haloperidol was superior to placebo. No significant between-treatment differences in responses (changes in PANSS total scores and scores on the five PANSS factors) were noted between patients who had been hospitalized for 1 month or less and patients hospitalized for periods longer than 1 month (figure 5). Risperidone was superior to haloperidol to the same degree in each of the compared duration groups. There were no interactions between hospitalization duration and PANSS total score or any of the five factors.

We also examined other classifications of patients, other cutoff points for length of hospitalization, and other variables such as number of hospitalizations per year at risk (defined as current age minus age at first psychotic episode) and age of onset. We found no interaction between treatment outcome and drug response.

Weight Gain and Improvement. To explore whether risperidone-induced improvement was linked to weight gain, we evaluated the interaction between drug and weight gain. Did patients who experienced the greatest weight gain do particularly well with risperidone?

In patients receiving placebo, risperidone (2 and 6–16 mg/day), and haloperidol, weight gain tended to be associated with improvement; in other words, the direct effect of BMI category (significant weight gain, moderate weight gain, mild weight gain, little or no weight change, and
weight loss) on clinical improvement was significant ($F = 7.0; \text{df} = 4, 490; p = 0.00002$). However, the interaction between weight gain and treatment (2 or 6–16 mg of risperidone, haloperidol, or placebo) on improvement was not significant. Indeed, there was not even a trend toward an interaction ($p = 0.861$), which indicates that weight gain appeared to be disassociated from drug-induced improvement.

Because weight gain is a common factor shared at least by some atypical antipsychotic drugs, it is possible that the weight gain might be mediated by serotonin blockade. Thus it could be expected that improvement on the serotonin-sensitive subscale would be correlated with weight gain. However, there was no interaction between weight gain and treatment on the serotonin-sensitive subscale ($F = 0.875; \text{df} = 8, 412; p = 0.538$). In addition, no significant interaction with weight gain was observed for the dopamine-sensitive score, the haloperidol-responsive or -nonresponsive scale, or any of the five factors.

**Meta-Analysis of Risperidone versus Conventional Agents.** Means and SDs of the improvement scores were available for 19 studies (figure 6). We used the Hedges-Olkin method with Comprehensive Meta-Analysis (1.0.16; Borenstein and Rothstein 1999) of the randomized studies to demonstrate that risperidone was superior to typical neuroleptics with an effect size of 0.26 (95% CI: 0.19–0.33; $t = 7.3; p = 3 \times 10^{-12}$). We evaluated the effect of the 17 double-blind versus two open-label studies and found that it just missed statistical significance ($p = 0.07$). The effect size was 0.22 for the double-blind randomized studies alone. Geddes and colleagues (2000) have suggested that a higher dose of haloperidol may be less effective than lower doses. Thus, he postulated that a higher dose of haloperidol comparator may falsely increase the difference between an atypical and the typical comparator. We evaluated dose of comparator as a continuous variable using MetaWin (2.0; Rosenberg et al. 2000) and found a marginal effect of haloperidol dose as a continuous variable (coefficient for slope = 0.017, $t = 7.3; p = 3 \times 10^{-12}$). The results of 18 studies for which responder-nonresponder data were available are presented in table 2. Almost all randomized controlled clinical trials of risperidone versus typical antipsychotics use the 20 percent

Table 1. The effect of EPS (total parkinsonism and CGI parkinsonism severity) and their treatment with antiparkinsonian agents on improvement with 6 mg/day of risperidone or haloperidol

<table>
<thead>
<tr>
<th>Joint effect of both EPS</th>
<th>PANSS total</th>
<th>Negative symptoms</th>
<th>Positive symptoms</th>
<th>Disorganized thoughts</th>
<th>Impulsive hostility</th>
<th>Anxiety/depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F$ value</td>
<td>0.51</td>
<td>0.10</td>
<td>2.02</td>
<td>1.85</td>
<td>0.64</td>
<td>2.28</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.60</td>
<td>0.91</td>
<td>0.14</td>
<td>0.16</td>
<td>0.53</td>
<td>0.11</td>
</tr>
<tr>
<td>Total parkinsonism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t$ value</td>
<td>0.43</td>
<td>0.07</td>
<td>-0.19</td>
<td>0.59</td>
<td>0.57</td>
<td>1.59</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.67</td>
<td>0.94</td>
<td>0.85</td>
<td>0.56</td>
<td>0.57</td>
<td>0.11</td>
</tr>
<tr>
<td>CGI parkinsonism severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t$ value</td>
<td>-0.94</td>
<td>0.24</td>
<td>-1.24</td>
<td>-1.69</td>
<td>-1.09</td>
<td>-0.18</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.35</td>
<td>0.81</td>
<td>0.22</td>
<td>0.09</td>
<td>0.28</td>
<td>0.85</td>
</tr>
<tr>
<td>Antiparkinsonian agent (direct effect)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F$ value</td>
<td>0.07</td>
<td>0.08</td>
<td>0.48</td>
<td>0.73</td>
<td>1.79</td>
<td>0.02</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.80</td>
<td>0.77</td>
<td>0.49</td>
<td>0.39</td>
<td>0.18</td>
<td>0.88</td>
</tr>
<tr>
<td>Interaction of risperidone vs. haloperidol with antiparkinsonian agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F$ value</td>
<td>0.32</td>
<td>0.04</td>
<td>0.83</td>
<td>0.71</td>
<td>0.49</td>
<td>0.18</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.57</td>
<td>0.84</td>
<td>0.36</td>
<td>0.40</td>
<td>0.49</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Note.—CGI = Clinical Global Impression; EPS = extrapyramidal symptoms; PANSS = Positive and Negative Syndrome Scale.

1. The $F$ value evaluates the statistical significance of whether the maximum changes in scores on both total parkinsonism and CGI parkinsonism severity influence the difference in improvement with 6 mg of risperidone compared with 20 mg of haloperidol.

2. For these contrasts, the $t$ tests evaluate each of the EPS variables on the difference in drug response. The $t$ test would be significant if there was an association between severity of EPS and a lesser response to haloperidol.

3. The $F$ test for the direct effects tests whether use of an antiparkinsonian agent affected the overall response to both risperidone and haloperidol. That is, do patients who receive antiparkinsonian drugs have a lesser clinical response irrespective of which antipsychotic they receive?

4. The $F$ test for interaction evaluates whether the use of antiparkinsonian drugs had a negative effect on response to haloperidol with respect to risperidone (i.e., there was an interaction of PANSS response and type of drug).
improvement on the BPRS and PANSS as the definition of clinical response. Emsley and colleagues (1999) used a 50 percent improvement in a study of first admission patients, and we included this study in our meta-analysis as well. Sixteen of the 18 studies were randomized double-blind studies, and 2 studies were randomized open studies. The Peto odds ratio of 1.6 showed that risperidone was superior to haloperidol (95% CI: 1.4–1.8; z = 6.2; p = 2 × 10^{-10}). Excluding the two open studies, the Peto odds ratio of 1.5 was slightly less but yielded essentially the same result. The difference between blinded and open randomized studies was not statistically significant (p = 0.07), but, this difference aside, the open studies yielded a higher odds ratio. To explore the dose of comparator, we did a metaregression on 14 studies that used haloperidol as a comparator for which dose information was available. The MetaWin program for meta-analysis treating dose of haloperidol comparator as a continuous variable yielded a slope coefficient of 0.04 (p = 0.05).

Fifteen studies reported means and SDs of the improvement scores observed with risperidone and typical neuroleptics for the positive and negative subscale. Our meta-analysis using Comprehensive Meta-Analysis’s implementation of the Hedges and Olkin algorithm found that risperidone produced significantly more improvement than typicals, with an effect size of 0.16 for positive symptoms and 0.20 for negative symptoms (p = 10^{-5} and 10^{-7}, respectively; table 3). Differences between randomized open and randomized controlled studies were not statistically significant: positive symptoms (Q = 0.27, df = 1, p = 0.60) and negative symptoms (Q = 2.7, df = 1, p = 0.10). Using MetaWin, we failed to find that dose of haloperidol comparator had a significant effect on positive symptoms (slope coefficient = -0.0004, p = 0.96) and negative symptoms (slope coefficient = 0.018, p = 0.09).

### The Mattes Critique

Mattes (1997) wrote a provocative critique of the risperidone studies. We feel he asked a number of important questions and therefore undertook our reanalysis of the

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**Table 2. Percentages of treatment responders among patients treated with risperidone or conventional neuroleptics in the worst-case (all doses) analyses and results of Peto odds-ratio analyses.**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Risperidone</th>
<th>Neuroleptic</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blin et al. 1996</td>
<td>62</td>
<td>81</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>Borison et al. 1991</td>
<td>106</td>
<td>57</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>Bouchard et al. 2000</td>
<td>165</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cavallaro et al. 2001</td>
<td>29</td>
<td>60</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Česková &amp; Švestka 1993</td>
<td>62</td>
<td>45</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Chouinard et al. 1993</td>
<td>89</td>
<td>53</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Claus et al. 1992</td>
<td>42</td>
<td>33</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Csernansky and Okamoto 2000</td>
<td>365</td>
<td>75</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>Emsley et al. 1999</td>
<td>182</td>
<td>63</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Høyberg et al. 1993</td>
<td>101</td>
<td>74</td>
<td>59</td>
<td>15</td>
</tr>
<tr>
<td>Huttunen et al. 1995</td>
<td>98</td>
<td>58</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>Mahmoud and Engelhart 1998</td>
<td>675</td>
<td>64</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td>Marder and Meibach 1994</td>
<td>251</td>
<td>49</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Mesotten 1991 (unpublished data)</td>
<td>60</td>
<td>54</td>
<td>72</td>
<td>-18</td>
</tr>
<tr>
<td>Min et al. 1993</td>
<td>35</td>
<td>63</td>
<td>74</td>
<td>-11</td>
</tr>
<tr>
<td>Peuskens et al. 1995</td>
<td>1,126</td>
<td>62</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>Wirshing et al. 1999</td>
<td>65</td>
<td>18</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Zhang et al. 2001</td>
<td>78</td>
<td>76</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>3,591</td>
<td>60</td>
<td>49</td>
<td>11</td>
</tr>
</tbody>
</table>

1. Risperidone versus conventional neuroleptics: Peto odds ratio = 1.6 (95% CI: 1.4–1.8); z = 6.2, p = 2 × 10^{-10}.
2. Effect of dose of comparator: Q = 2.8, df = 1, p = 0.09 (Comprehensive Meta Analysis); coefficient for slope = 0.04, p = 0.05 (MetaWin).
3. Minor discrepancies in Difference column due to rounding.
4. Data obtained from the Cochrane Collaboration (Kennedy et al. 2001).
Table 3. Summary results of worst-case meta-analyses of risperidone versus conventional neuroleptics (Hedges-Olkin method)

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>n</th>
<th>Effect size</th>
<th>95% confidence intervals</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS total</td>
<td>19</td>
<td>3,643</td>
<td>0.26</td>
<td>0.19–0.33</td>
<td>7.27</td>
<td>10^-12</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>15</td>
<td>3,363</td>
<td>0.16</td>
<td>0.09–0.24</td>
<td>4.37</td>
<td>10^-5</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>15</td>
<td>3,363</td>
<td>0.20</td>
<td>0.13–0.28</td>
<td>5.45</td>
<td>10^-7</td>
</tr>
</tbody>
</table>

Note.—PANSS = Positive and Negative Syndrome Scale. Tests for heterogeneity were not significant for all three tests; therefore, fixed-effects models were used.

Figure 5. Improvements in total Positive and Negative Syndrome Scale scores (drug-placebo differences) in patients treated with 6–16 mg/day of risperidone or 20 mg/day of haloperidol for ≤ 1 month or > 1 month (t = 0.13, p = 0.90)

Figure 6. Meta-analysis of 19 randomized studies comparing risperidone with haloperidol

North American clinical trial in part to obtain data relevant to his critique. Mattes proposed that risperidone is not necessarily more effective than haloperidol for positive symptoms of schizophrenia in acutely ill neuroleptic-responsive patients because patients of the North American clinical trial may have consisted of chronically hospitalized patients who were, by definition, unresponsive to conventional neuroleptics. We do not dispute Mattes’s suggestion that this risperidone trial included many typical neuroleptic-resistant patients. Indeed, each study of a new antipsychotic tends to include patients refractory to some degree to all previous antipsychotics. Furthermore, extremely disturbed schizophrenia patients cannot reasonably give informed consent or cooperate in typical blinded placebo-controlled studies. We cannot examine patient groups that have not been studied. However, in patients that have been studied we can look at this dimension to see if it alters differential response to risperidone versus haloperidol in the North American clinical trial and in our meta-analysis of the randomized studies from the world literature.

The crux of Mattes’s reasoning was that in studies conducted from the 1960s through the 1980s conventional neuroleptics produced a high rate of improvement among patients with schizophrenia who were acutely ill and presumably neuroleptic sensitive. Mattes cites four examples. First, in the National Institute of Mental Health (NIMH) collaborative study (1964), treatment with phenothiazines for 6 weeks resulted in marked improvement in 75 percent of acutely ill schizophrenia patients, compared with 23 percent given placebo. It should be noted, however, that approximately 50 percent of the patients in this study were experiencing their first psychotic episode, a stage of the illness when there is a greater likelihood of responding. Moreover, only patients who completed the study were included in this analysis, which would tend to markedly inflate the percentage of responders. Second, in a 4-week study of loxapine and chlorpromazine, Tuason and colleagues (1984) reported an average 59.5 percent of “maximum possible improvement” in BPRS scores; this measure is not at all comparable to percentage improvement. Third, in an open study, Claghorn (1985) reported that 35 percent of patients treated with molindone improved on the BPRS. Neither of the two latter trials was placebo controlled. Mattes also speculated that the reported superiority
of risperidone for negative symptoms might be an artifact of reduced EPS with risperidone doses. However, we were unable to demonstrate any relationship between changes in PANSS total or factor scores and drug-induced EPS (table 1). It is impossible to make meaningful and valid comparisons between the recent controlled risperidone studies and trials of conventional neuroleptics using radically different methods; most of these were open, observed-case complete analyses (rather than endpoint, last-observation-carried-forward analyses) that used various methods to calculate improvement. Nevertheless, the questions raised by Mattes were clinically and substantively important.

In their study of first admission patients, Emsley and colleagues (1999) reported that the improvement rate with risperidone was very slightly higher (nonsignificant) than with haloperidol. We agree with Mattes that the absolute improvement in first admission patients is much greater than in more chronic patients in the risperidone, haloperidol, and placebo groups. First admission patients of the Emsley and colleagues study differ in three ways from the more typical chronic patients entering randomized trial: (1) they are in their first episode, (2) some may present a version of psychotic illness that does not progress to chronic schizophrenia, and (3) they are fully in an acute episode as opposed to partially relapsed. Blin and colleagues (1996) found that risperidone produced a much greater improvement than haloperidol, but both drugs produced a greater improvement from baseline than that found in less symptomatic patients. We note that these patients show a much greater symptomatic improvement than do the typical chronic patients, suggesting that reasons (1) and (2) are pertinent. Because negative symptoms may be less prominent in first episode patients and their drug response may be different from that of chronic patients, more studies are needed.

We also performed a meta-analysis of data from the double-blind random-assignment studies of quetiapine and sertindole and found that their effects were equal to that of haloperidol (Davis et al. 1998). If the superiority of risperidone were an artifact of using haloperidol-unresponsive patients, as suggested by Mattes, then all atypicals should be superior to haloperidol, and this was not the case.

Discussion

The choice of drug to treat a patient with schizophrenia is one of the most important decisions made by clinicians. The National Schizophrenia Guideline Development Group of the United Kingdom (Geddes et al. 2000) recommends typical neuroleptics as first line treatment. In contrast, Guidelines of the American Psychiatric Association (1997) and of the NIMH Schizophrenia Patient Outcome Research Team (Lehman and Steinwachs 1998) recommend either conventional or atypical antipsychotics as first line treatment. More recent guidelines by panels of experts place atypicals as first line treatment (primarily because of a side effect advantage), although conventions are still rated as first line for certain indications (Pearsall et al. 1998; McEvoy et al. 1999; Miller et al. 1999; Osser and Zarate 1999). These guidelines often equivocate as to whether atypical antipsychotics are more efficacious than conventional agents, and some experts deny that there is any difference in efficacy. We feel that the aforementioned evidence demonstrates that risperidone produces a substantially greater improvement than haloperidol. Previous meta-analyses have underestimated the risperidone-comparator difference because they included the suboptimal 1 or 2 mg dose in their comparisons (Leucht et al. 1999).

We find that risperidone benefits a substantial number of PANSS items that are untouched by haloperidol. We feel this broader-based efficacy is clinically important and note that the benefit in PANSS points is approximately the same as the benefit in average PANSS points produced by haloperidol over placebo. We speculate that the pharmacological difference between risperidone and typical neuroleptics is possibly due to differences in the serotonin 5HT2, blockade property or "time on" and "time off" on D2 receptors. In short, we suggest risperidone is more efficacious than typical neuroleptics because of its beneficial effect on a wider range of symptoms. We feel the difference in EPS is clinically more important than the efficacy difference but that the efficacy difference is clinically meaningful and another reason to argue that certain atypicals (in this case, risperidone) should be considered as first line treatment. The present results are useful in providing basic data for the correlation of the pharmacological profile with the clinical profile (the pharmacological question).

Remington and Kapur (2000) have recently proposed that two questions need to be considered when evaluating the atypical antipsychotics. One is whether the new agent can produce a greater antipsychotic effect in responders than the older agents; they refer to this as the "antipsychotic size question." The other is whether these agents can induce even a partial response in patients who have been refractory to treatment with the older agents; they refer to this as the "refractory question." We provide evidence to show that risperidone is substantially superior to haloperidol in the entire patient group (the size question). The notion that atypical antipsychotics are superior to conventional in only a population of nonresponders (a type of refractory question) is reasonable. Empirically, however, we could not find a subgroup of patients with schizophrenia for whom risperidone was superior to haloperidol to a greater degree than that seen in other patients. Our search for patient subtypes and symptom
clusters was based on a cross-sectional analysis of PANSS data. A longitudinal identification of subtype (e.g., deficit state) might capture phenomena not fully identified here. We emphasize this limitation of the analysis. We cannot rule out the possibility that a better measure of some of the constructs might reveal a differential drug response. Only prospective studies of patients whose response to drug A is measured and who are then randomized to drug A or B can answer this question.

The precedent of using clozapine for patients who do not respond to conventional has focused attention exclusively on nonresponders. We feel responders are important as well. After all, it is these patients who will be discharged into the community with a good chance of rehabilitation. Negative symptoms, depression, and impaired thought processes interfere with occupational and family roles. Impulsivity and hostility can seriously jeopardize a person’s functioning in the community. By the same token, it may be important to treat patients with atypical drugs early in the course of their disease so that negative symptoms do not develop and social deterioration can be (hopefully) prevented, a question that must be studied in a controlled trial.

The greater risperidone efficacy observed was independent of EPS or weight gain. One limitation of this study was that 20 mg haloperidol was used, which is considered a high dose by contemporary standards. By the same token, the dose used has an advantage because it allows an exploration of haloperidol-produced EPS on the differential efficacy of risperidone versus haloperidol. We found no statistical evidence that the difference between high-dose haloperidol and risperidone or between high-dose risperidone (10–16 mg) and 6 mg risperidone could be explained as a consequence of EPS (table 2 on Web site).

In our meta-analysis, we essentially replicate the finding of Geddes and colleagues (2000) on the effect of the dose of haloperidol comparator, although most of our metaregressions just missed the 0.05 level of significance, and Geddes and colleagues just made the 0.05 level in their findings. We feel this effect is small and will explore it more thoroughly in a different publication presently being prepared.

The first of the dimensions of schizophrenia to deteriorate is the impulsivity/hostility dimension. Our inference is that these patients are unable to inhibit acting on their frequent psychotic impulses. This is reflected by impulsivity and by uncooperativeness, hostility, and excitement. A practical implication is that these symptoms may be an early warning of impending deterioration and warrant quick action if observed. We observed the same phenomena in the olanzapine clinical trial data base (Davis and Chen 2001).

**Conclusions**

Results of these analyses can be used to construct a preliminary clinical profile of an atypical antipsychotic, as suggested by Dawkins and colleagues (1999). In their table 2, Dawkins and her coworkers summarize the clinical profiles of various atypical agents in a semiquantitative scale (−, +, ++, etc.). We have attempted to refine such a profile more exactly by a quantitative data-based statistical analysis. In the reexamination of data from the North American trial, risperidone was significantly more effective than haloperidol in the treatment of schizophrenia, and haloperidol was significantly more effective than placebo.

Symptoms that were refractory to haloperidol were shown to respond to risperidone. A substantial part of the superiority of risperidone is due to it improving symptoms not benefited by typicals. Risperidone produced an improvement in a wider range of symptoms than haloperidol, but symptoms sensitive to haloperidol also responded better to risperidone. Changes in EPS or weight gain had no influence on efficacy comparisons that favored risperidone over haloperidol. Risperidone was superior to this conventional neuroleptic in patients hospitalized for both shorter and longer periods (a measure of neuroleptic resistance), in patients with diagnoses of both paranoid and nonparanoid schizophrenia, and in both deficit and nondeficit schizophrenia. Risperidone was also found to reduce symptoms of depression in patients with schizophrenia.

The meta-analysis of all relevant risperidone trials consistently demonstrated that risperidone is more effective than conventional neuroleptics both overall and on positive and negative symptoms. This result is not an artifact of one trial but a consistent finding of many.

**Appendix. Power to detect a clinical difference**

Because in our analyses of the North American trial we failed to find a differential effect of diagnostic subtype, symptom cluster, EPS, treatment duration, or weight gain, it is pertinent to consider the power needed to detect a difference. A large random-assignment double-blind study such as the North American trial provides parameters for the estimation of the power to detect such differences in future studies. We feel that it is important to define the clinical profiles of the novel antipsychotics, and we here present a power analysis, with the hope that it will help in the design of such studies.

Based on the worst-case analysis, the sample size needed to detect a significance level of 0.05 with 80
percent power of detecting a difference between risperidone and placebo would be about 23 patients per group (or 46 patients) for PANSS total score and 90, 20, 33, 28, and 60 patients, respectively, for the five PANSS factors. To detect a difference between risperidone and haloperidol, 94, 104, 190, 202, 116, and 106 patients per group for PANSS total and five factors would be required. The sample size needed to detect an interaction of some other grouping variable on the outcome on total score and the five factors would be similar. To detect a change produced by another grouping variable by 2, 4, 6, 8, and 10 PANSS points as either a direct effect or an interaction with the treatment variable, sample sizes of 1,683, 422, 188, 107, and 69, respectively, would be required. While we made power calculations on the parameters from analysis of covariance of risperidone at 6–16 mg, haloperidol, risperidone at 2 mg, and placebo, we would recommend that a good approximation of the SD of the covariate-adjusted PANSS total endpoint score is 21, a parameter that can be entered along with estimated mean changes for power analysis of similar populations of persons with schizophrenia.

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