The Effects of Risperidone on the Five Dimensions of Schizophrenia Derived by Factor Analysis: Combined Results of the North American Trials

Stephen R. Marder, M.D., John M. Davis, M.D., and Guy Chouinard, M.D., F.R.C.P.(C.)

Background: In two double-blind trials conducted in North America, 513 patients with chronic schizophrenia received risperidone, haloperidol, or placebo. In the present study, combined data from the two trials were analyzed.

Method: Patients were randomly assigned to receive placebo, fixed doses of risperidone (2, 6, 10, and 16 mg/day), or 20 mg/day of haloperidol for 8 weeks. Factor analysis of scores on the Positive and Negative Syndrome Scale (PANSS) produced five dimensions (negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression), similar to the five dimensions of previous factor-analytic studies of PANSS data.

Results: Mean changes (symptom reductions) in PANSS factor scores from baseline to treatment Weeks 6 and 8 were significantly greater in patients receiving 6–16 mg/day of risperidone than in patients receiving placebo or haloperidol. The advantages of risperidone were greatest for negative symptoms, uncontrolled hostility/excitement, and anxiety/depression. Even at the lowest dose, 2 mg/day, risperidone was significantly ($p \leq .05$) superior to haloperidol in reducing negative symptoms. The differences in outcomes between risperidone and haloperidol on PANSS scores were not related to extrapyramidal symptoms.

Conclusion: Risperidone produced significantly ($p \leq .05$) greater improvements than haloperidol on all five dimensions. The large between-group differences on negative symptoms, hostility/excitement, and anxiety/depression suggest that risperidone and other serotonin/dopamine antagonists have qualitatively different effects from those of conventional antipsychotic agents.

(J Clin Psychiatry 1997;58:538–546)

Received April 8, 1997; accepted Aug. 26, 1997. From West Los Angeles Veterans Affairs Medical Center, Los Angeles, Calif. (Dr. Marder), The Psychiatric Institute, University of Illinois at Chicago (Dr. Davis), and Hôpital Louis-H. Lafontaine, Montréal, Québec, Canada (Dr. Chouinard).

Supported by the Janssen Research Foundation, Titusville, N.J., which also supplied the medication and placebo. The data analysis was performed independently by Dr. Davis without support from the Janssen Research Foundation.

The principal investigators in the North American trials were the following: Joyce Small, M.D., Indianapolis, Ind.; Richard Borison, M.D., Ph.D., Augusta, Ga.; John H. Krystal, M.D., West Haven, Conn.; Alan I. Green, M.D., Boston, Mass.; Jan Volavka, M.D., Orangeburg, N.Y.; Daniel Luchins, M.D., Chicago, Ill.; Robert Baker, M.D., and Nina Schooler, Ph.D., Pittsburgh, Pa.; Fred W. Reimherr, M.D., Salt Lake City, Utah; Rajiv Tandon, M.D., Ann Arbor, Mich.; Larry Ereshefsky, Pharm.D., and Janet True, M.D., San Antonio, Tex.; Jean-Pierre Lindenmayer, M.D., Bronx, N.Y.; James Garbutt, M.D., Raleigh, N.C.; Theodore Van Putten, M.D. (deceased), Los Angeles, Calif.; Jose M. Cañive, M.D., and Vicente Tuason, M.D., Albuquerque, N.M.; Joseph McEvoy, M.D., Butner, N.C.; B. D. Marshall, M.D., Camarillo, Calif.; John Carman, M.D., Atlanta, Ga.; John Herrera, Ph.D., and Michael Davidson, M.D., Elmhurst, N.Y.; John Rotrosen, M.D., New York, N.Y.; George M. Simpson, M.D., Philadelphia, Pa.

Guy Chouinard, M.D., F.R.C.P.(C.), Montreal, Québec; Barry Jones, M.D., F.R.C.P.(C.), Ottawa, Ontario; Gary Remington, M.D., Ph.D., F.R.C.P.(C.), Toronto, Ontario; David Bloom, M.D., F.R.C.P.(C.), and N. P. Vasavan Nair, M.D., F.R.C.P., Verdun, Québec; Donald Addington, M.B.B.S., F.R.C.P.(C.), Calgary, Alberta; G. William MacEwan, M.D., F.R.C.P.(C.), Port Coquitlam, B.C.; Raymond J. Ancill, M.D., F.R.C.P.(C.), Vancouver, B.C.

Reprint requests to: Stephen R. Marder, M.D., Psychiatry Service 116A, West Los Angeles VA Medical Center, Brentwood Division, 11301 Wilshire Boulevard, Los Angeles, CA 90037.

Two pivotal controlled trials of risperidone have been conducted in North America, the Canadian study of Chouinard et al.[1] and the United States study of Marder and Meibach.[2] In this report, we present the results of an analysis of the combined data from the two trials to determine whether risperidone differs qualitatively from the conventional neuroleptic haloperidol. Unlike haloperidol, risperidone blocks both serotonin 5-HT_{2A} and dopamine D_2 receptors, and the question is whether the additional pharmacologic property (5-HT_{2A} antagonism) could produce a qualitatively different set of antipsychotic actions from the conventional agents and enhance the overall antipsychotic effects of risperidone.

The development of risperidone has its roots in the 1950s when Woolley and Shaw[3] noted that lysergic acid diethylamide, which "calls forth in man mental distur-

bances resembling those of schizophrenia," acted as an antimetabolite of serotonin on smooth muscles, and thus proposed that serotonin was involved in the pathogenesis of schizophrenia. It was not until the late 1970s, however, that compounds with serotonin antagonist properties were developed.[4] In 1985, setoperone, a neuroleptic with potent 5-HT_2 antagonism but weak dopamine antagonism, was administered to patients with schizophrenia and found to ameliorate negative symptoms without causing extrapyramidal symptoms, and to have little effect on positive symptoms.[5] It was then shown that ritanserin, a pure 5-HT_2 antagonist, when combined with the dopamine antagonist haloperidol, improved negative symptoms in schizophrenic patients and reduced extrapyramidal symptoms.[6,7] At about the same time, Kane and coworkers[8] showed that clozapine, which also blocks 5-HT_2 receptors, was significantly and clinically more effective than a conventional neuroleptic in the treatment of chronic schizophrenia. In addition to risperidone and clozapine, a number of new 5-HT_2\D_2 antagonists are now approved for use (olanzapine and quetiapine) or are under investigation (sertindole and ziprasidone, for example) so that it is appropriate to investigate how each member of this new class of drugs differs clinically from conventional neuroleptics. Kapur and Remington[9] have recently reviewed the neural basis and clinical relevance of the serotonin-dopamine interaction.

The primary measure of treatment efficacy in the North American risperidone trial was the Positive and Negative Syndrome Scale (PANSS).[10] This is based on Crow's seminal paper[11] of 1980 in which he proposed that there were two predominant clusters of symptoms in schizophrenia, positive symptoms and negative symptoms. A number of authors have assessed Crow's hypothesized two-factor classification of schizophrenic symptoms (positive and negative), and all have concluded that the model is inadequate to explain the variance in these studies using several rating scales,[12–17] including the PANSS.[18–25] These studies include the factor analysis by Lindenmayer et al.[24] of the baseline PANSS scores of the patients in the present study. The factor-analytic studies of the PANSS produce five factors or dimensions of schizophrenia; thus, we investigated the differences between risperidone and haloperidol in the North American trials according to these five dimensions.

METHOD

Detailed descriptions of the study design, patient selection criteria, and efficacy and safety measures are included in the two reports of the North American trials[1,2] and will only be briefly described here. The two trials had identical protocols but separate investigator meetings, training sessions for raters, and monitoring, and were published separately. For this report, Dr. Davis performed a statistical analysis using the database from the North American trials. This analysis was carried out independently and without funding from the study's sponsor, the Janssen Research Foundation.

Study Design

The two parallel, randomized, double-blind, placebo-controlled multicenter trials were conducted at 20 centers in the United States and 6 centers in Canada. A total of 523 hospital patients (436 men and 87 women) with diagnoses of chronic schizophrenia participated. Ten subjects dropped out of the study at baseline and 1 had some missing data, so that the sample used in the present study was 512 or 513 subjects. The small number of women is due to the inclusion of a number of U.S. Department of Veterans Affairs medical centers (with mostly men) and, according to initially restrictive Food and Drug Administration guidelines at the beginning of the study, to the exclusion of women of childbearing potential. Approval was obtained from the institutional review board at each site and renewed annually, and each patient (and/or his or her legal representative when required) gave written, informed consent to participate in the trial.

Selection Criteria

Men and women inpatients aged 18 to 65 years with primary diagnoses of chronic schizophrenia (DSM-III-R[26]) and a PANSS total score between 60 and 120 were eligible for inclusion. Patients with clinically significant abnormal laboratory or electrocardiograph findings, histories of mental disorders other than chronic schizophrenia, epilepsy, alcoholism or drug abuse (within 6 months prior to selection), or clinically significant organic or neurologic disease were excluded.

Procedure

Patients were required to discontinue all psychotropic and antiparkinsonian medication and to enter a 7-day, single-blind, placebo washout period (28 days for patients receiving depot neuroleptics). Patients were permitted to proceed to the double-blind phase of the trial after 3 days of placebo washout if significant psychopathology emerged. The study protocols precluded the use of any psychotropic medication other than the study drugs, although chloral hydrate or a benzodiazepine and antiparkinsonian medication (biperiden or procyclidine) could be administered if required.

Patients were randomly assigned to one of six fixed-dose, parallel-treatment groups for 8 weeks: 2, 6, 10, or 16 mg/day of risperidone, 20 mg/day of haloperidol, or placebo. In the present investigation, we chose as the primary analysis the most conservative one, that is, responses to doses of 6 to 16 mg/day of risperidone, assuming a conventional dose-response curve where 6 to 16 mg/day of risperidone would be on the flat maximal-response part of

Table 1. Adjusted Mean Changes in Total PANSS and PANSS Factor Scores From Baseline to Weeks 6 and 8 in Patients Receiving Placebo (Plac), Risperidone, or Haloperidol (Hal), Effect Size Units, and Results of Analyses of Covariance[a]

	Adjusted Mean Changes in Scores					Risperidone 6–16 mg/d				Risperidone 2 mg/d				Haloperidol vs Placebo			Risperidone 6 mg/d			
		Risperidone				Effect Size		Effect Size		Effect Size		Effect Size		Effect			Effect Size		Effect Size	
PANSS	Placebo	6–16	6	2	Hal	vs Plac	t	vs Hal	t	vs Plac	t	vs Hal	t	Size	t	F	vs Plac	t[b]	vs Hal	t[b]
Total PANSS	–3.8	–14.1	–18.6	–5.3	–5.1	0.29	6.64‡	0.15	3.29†	0.12	2.79†	0.00	0.06	0.12	2.72†	16.20‡	0.53	6.98‡	0.31	4.05‡
1: Negative	0.2	–2.6	–3.4	–2.1	–0.1	0.15	3.44‡	0.14	3.10†	0.10	2.32*	0.11	2.04*	0.01	0.28	5.92‡	0.27	3.46‡	0.26	3.34†
2: Positive	0.9	–4.4	–5.7	–1.8	–2.3	0.26	5.96‡	0.10	2.31*	0.11	2.50*	–0.03	–0.50	0.13	2.98†	12.67‡	0.48	6.23‡	0.22	2.85†
3: Disorganized thought	0.1	–3.5	–4.6	–0.6	–0.2	0.26	5.99‡	0.09	1.99*	0.08	1.76	–0.08	–1.53	0.14	3.38‡	13.91‡	0.43	5.60‡	0.24	3.15†
4: Uncontrolled hostility/ excitement	0.2	–1.6	–2.5	0.3	–0.1	0.30	6.76‡	0.12	2.76†	0.12	2.61†	–0.04	–0.65	0.14	3.25†	16.66‡	0.47	6.21‡	0.29	3.77‡
5: Anxiety/ depression	–0.1	–1.8	–2.5	–0.3	–0.6	0.18	4.11‡	0.13	2.98†	0.10	2.26*	0.07	1.33	0.04	0.92	6.98‡	0.36	4.71‡	0.30	3.95‡

*p ≤ .05. †p < .01. ‡p < .001.
[a]Effect size = changes from baseline with risperidone minus the changes with haloperidol or placebo, divided by the pooled standard deviations.
[b]We do not present an F value as well as a t value for the two drug comparisons because F is equal to t^2.

the curve. As secondary analyses, we examined the optimal dose in the North American trials, 6 mg/day, and the lowest dose, 2 mg/day.

Assessments

Clinical interviews and PANSS assessments were conducted by a psychiatrist on each of seven visits: at selection, at baseline (after the placebo washout period), and at Weeks 1, 2, 4, 6, and 8. Investigators were trained in the use of the PANSS with the aid of videotapes of patient interviews; to participate in the trial, a minimum of 80% of their ratings of individual items were required to fall within ± 1 point of the consensus rating.

Severity of extrapyramidal symptoms was evaluated by means of the Extrapyramidal Symptom Rating Scale[27] (ESRS) at each visit. The same procedures as for the PANSS were used in training investigators in the use of the ESRS. To investigate the association between the occurrence of extrapyramidal symptoms and changes in PANSS factor scores, scores on two of the ESRS clusters (parkinsonism total, which is the sum of all parkinsonism items, and Clinical Global Impression-Severity of Parkinsonism scale[27] [CGI-Parkinsonism]) were analyzed. Results of an analysis of the total ESRS data in the combined North American trials are being published elsewhere.[28]

Statistical Analyses

A last-observation-carried-forward (LOCF) method was used in the analysis of the data, which included all randomized patients who had at least one observation during the double-blind phase of the trial. This analysis, which carried forward the last recorded observation for each patient who prematurely withdrew from the trial, was considered the primary efficacy analysis because it provides a more accurate and conservative assessment of efficacy than an observed-case analysis, which is based solely on patients who completed the trial. Our principal statistical method was analysis of covariance (ANCOVA) with four levels of the drug factor (placebo, haloperidol, and risperidone at 2 mg and 6–16 mg) and baseline as the covariant. Tables 1 and 2 show effect size units and results of ANCOVAs, which are presented as t values of simple contrasts. Results of the ANCOVAs of 6 mg/day of risperidone versus placebo and 6 mg/day of risperidone versus haloperidol are also presented in Table 1.

Kraemer[29] has noted that the power of statistical analysis can be increased without increasing the sample size by increasing the reliability of important ratings. Since improvement (reductions in PANSS scores) had started to level off at Weeks 6 or 8, we averaged the scores at Weeks 6 and 8 for certain endpoint analyses. This was done in order to have the most reliable measure, particularly in determining whether moderator variables such as extrapyramidal symptoms or background or clinical values might affect the results. If these variables were dichotomous, they were treated as a second factor, and if continuous, as a second covariant.

We performed a principal components analysis to extract the five factors, using equimax rotation on PANSS scores at selection and baseline (before and after the washout period); at Weeks 1, 2, 4, 6, and 8; and at Weeks 6 and 8 (average). We used the most common solution weighted by sample size to define which items entered each factor; each item was equally weighted in defining the factor scores. The equimax rotation was used to be consistent with most of the previous factor-analytic studies of the PANSS. We also performed varimax rotation, and the results were virtually identical with those from equimax rotation (data not shown).

RESULTS

Most of the patients were white (71%) men (83%) with a mean ± SD age of 37 ± 10.3 years (range, 18 to 67) and a DSM-III-R diagnosis of paranoid (56%) or undifferenti-

Table 2. Improvements in Individual PANSS Items With Risperidone Compared With Haloperidol (Effect Size Units) and Results of Analysis of Covariance

Item	Effect Size Unit	t
Passive social withdrawal	–0.60	4.0‡
Active social avoidance	–0.53	3.5‡
Hostility	–0.52	3.5‡
Depression	–0.44	3.3†
Emotional withdrawal	–0.44	3.1†
Disturbance of volition	–0.46	3.0†
Poor impulse control	–0.41	3.0†
Uncooperativeness	–0.32	2.7†
Blunted affect	–0.36	2.7†
Suspiciousness	–0.59	2.6†
Anxiety	–0.44	2.6*
Tension	–0.42	2.4*
Delusions	–0.47	2.1*
Lack of spontaneity	–0.34	2.0*
Somatic concern	–0.31	1.8
Difficulty in abstract thinking	–0.32	1.8
Unusual thought content	–0.39	1.8
Lack of judgment and insight	–0.29	1.5
Poor attention	–0.32	1.5
Excitement	–0.34	1.5
Mannerisms and posturing	–0.24	1.5
Preoccupation	–0.36	1.2
Hallucinatory behavior	–0.46	1.2
Grandiosity	–0.22	1.2
Motor retardation	–0.14	1.0
Poor rapport	–0.22	1.0
Stereotyped thinking	–0.22	0.9
Disorientation	–0.09	0.7
Guilt	–0.10	0.5
Conceptual disorganization	–0.26	–0.1

*p < .05. †p < 0.01. ‡p < .001.

ated (32%) chronic schizophrenia.[1,2] The mean age at onset of psychotic symptoms was 21.5 ± 5.8 years and age at the time of first psychiatric hospitalization 23.1 ± 6.5 years. The mean number of previous hospitalizations was 8.1 ± 7.2 and duration of the current hospitalization 48.0 ± 145.9 weeks. Almost half (46.2%) of the patients had a family history of mental illness. The patients' mean total PANSS scores at baseline ranged from 89.2 to 94.9 in the six treatment groups. There were no statistically significant differences between treatment groups with respect to sex, race, age, weight, height, type of schizophrenia, age at onset of psychotic symptoms, age at time of first psychiatric hospitalization, number of previous hospitalizations, or severity of illness (CGI-Parkinsonism, PANSS, and PANSS factor scores at baseline).

The 8-week treatment period was completed by 49.8% of the patients, including 31% of the patients in the placebo group, 41% of the haloperidol group, and 41%, 60%, 55%, and 61% of the patients receiving 2, 6, 10, and 16 mg/day of risperidone, respectively. Of the patients who withdrew from the study because of an insufficient response, most were receiving placebo (N = 51), 20 mg/day of haloperidol (N = 36), or 2 mg/day of risperidone (N = 41). Only 12 patients from the risperidone 6-mg group withdrew because of insufficient response.

Five Factors of Schizophrenia

Five factors were identified and labeled: (1) negative symptoms, (2) positive symptoms, (3) disorganized thought, (4) uncontrolled hostility/excitement, and (5) anxiety/depression. The items included in each factor are listed in Table 3. The negative symptoms factor is similar to the PANSS negative symptom cluster proposed a priori by Kay et al.,[10] except that the item "difficulty in abstract thinking" is now found in Factor 3 (disorganized thought), and "stereotyped thinking" is now found in Factor 2 (positive symptoms). The positive factor is also somewhat similar to the positive symptom cluster of Kay et al., except that three of the seven symptoms are in different factors: "conceptual disorganization" has been moved to Factor 3 and the items "excitement" and "hostility" to Factor 4 (uncontrolled hostility/excitement). Items in Kay and colleagues' original general psychopathology cluster are now found in Factors 3, 4, and 5.

The proposed five-factor structure was unchanged in patients receiving placebo (as expected) and was essentially the same during treatment with risperidone and haloperidol (Table 3). At almost all time points and for the Week 6 and 8 average, each item had its highest loading on the same factor as at baseline; exceptions are noted in the Table 3 footnote (the data are not shown for each time point in Table 3 but can be obtained from the authors).

Changes in PANSS Factor Scores

Figure 1 shows the mean changes in factor scores from baseline to Weeks 6 and 8 in patients receiving placebo, risperidone, or haloperidol. Risperidone improved symptoms on each of the factors, and the changes with risperidone at 6–16 mg/day were significantly greater than with placebo or haloperidol on each factor (Table 1).

Factor 1. Patients receiving 2 mg/day or 6–16 mg/day of risperidone showed a substantial reduction in negative symptoms, whereas an increase in symptoms was seen with haloperidol. This potent effect of risperidone on negative symptoms is also seen in the analysis of individual PANSS items (Table 2): risperidone had a significantly larger effect than haloperidol on five of the seven items included in the factor (passive social withdrawal, active social avoidance, emotional withdrawal, blunted affect, and lack of spontaneity).

Factor 2. A robust beneficial effect of haloperidol was seen on positive symptoms, but at Week 8, risperidone at 6–16 mg/day produced almost twice the reduction in symptoms as haloperidol.

Factor 3. Risperidone at 6–16 mg/day was significantly superior to haloperidol in ameliorating symptoms of disorganized thought. Both drugs, however, produced a substantial improvement, suggesting that thought disorder is affected by a property common to both drugs.

Factor 4. Uncontrolled hostility/excitement was substantially benefited by risperidone at 6–16 mg/day. Little

Table 3. PANSS Items Included in Each Factor at Treatment Weeks 6 and 8 (the Factor on Which Each Item Had Its Highest Loading)

	Factor Loadings		
Factor and Items	Placebo	Risperidone	Haloperidol
1: Negative symptoms			
Blunted affect	60	74	78
Emotional withdrawal	82	81	69
Poor rapport	76	64	73
Passive social withdrawal	78	82	76
Lack of spontaneity	73	80	78
Motor retardation	59	71	61
Active social avoidance	57	71	45[a]
% of variance	14	16	14
2: Positive symptoms			
Delusions	83	83	80
Hallucinatory behavior	52	69	45
Grandiosity	31[b]	61	72
Suspiciousness	64	55	60
Stereotyped thinking	65	50	62
Somatic concern	47	34[c]	55
Unusual thought content	83	84	79
Lack of judgment and insight	25[d]	55	41[e]
% of variance	13	14	15
3: Disorganized thought			
Conceptual disorganization	69	60	54
Difficulty in abstract thinking	69	66	73
Mannerisms and posturing	75	64	67
Poor attention	72	64	65
Disturbance of volition	69	41	52
Preoccupation	54	43[f]	30[g]
Disorientation	70	51	72
% of variance	15	12	12
4: Uncontrolled hostility/excitement			
Excitement	68	65	72
Hostility	88	82	79
Uncooperativeness	88	77	80
Poor impulse control	89	80	84
% of variance	14	13	15
5: Anxiety/depression			
Anxiety	71	83	70
Guilt	60	66	68
Tension	62	68	55
Depression	71	67	77
% of variance	8	10	10
Total % of variance	64	65	67

[a]Also loaded on Factor 4 (46).
[b]Also loaded on Factor 4 (43).
[c]Also loaded on Factor 5 (40).
[d]Also loaded on Factor 4 (36).
[e]Also loaded on Factor 4 (46).
[f]Also loaded on Factor 2 (52).
[g]Also loaded on Factor 2 (55).

change was seen with 2 mg/day of risperidone or haloperidol, and deterioration is evident in the placebo group. Risperidone was significantly superior to haloperidol on three of the four individual items included in this factor (hostility, poor impulse control, and uncooperativeness) (Table 2).

Factor 5. Symptoms of anxiety and depression were slightly reduced with placebo and haloperidol; in contrast, risperidone at both 2 mg/day and 6–16 mg/day produced considerable improvement. Significantly greater improvement with 6–16 mg/day of risperidone than haloperidol was seen on three of the four individual items included in this factor (depression, anxiety, and tension) (Table 2).

Risperidone at 2 and 6 mg/day. Risperidone at 2 mg/day was significantly superior to placebo on Factors 1, 2, 4, and 5 and significantly superior to haloperidol against negative symptoms (Factor 1) (Table 1). A curvilinear response to risperidone doses is apparent in Table 1—6 mg/day is superior to both lower and higher doses.

PANSS Total Scores

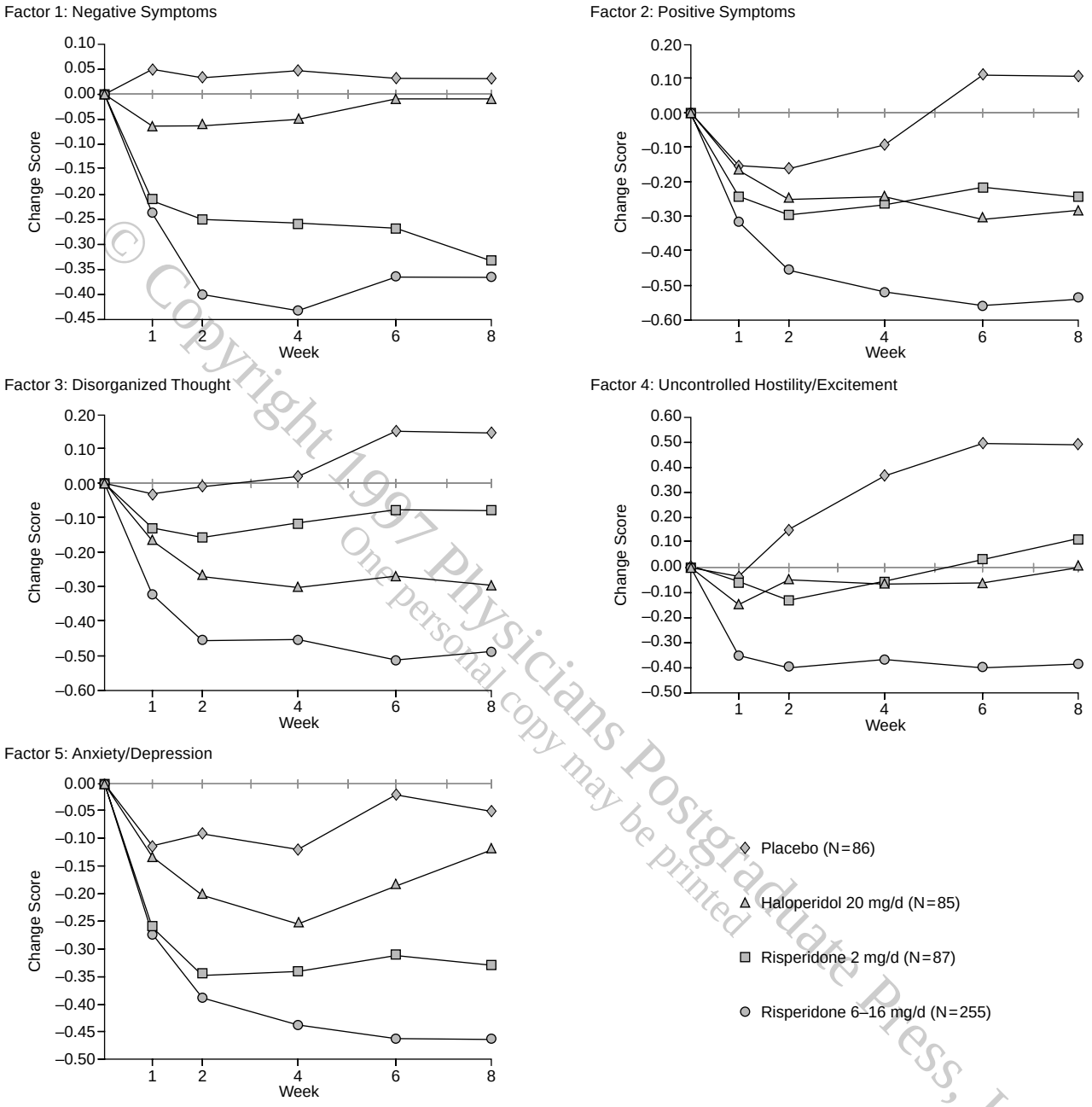
A rapid improvement in symptoms (PANSS total scores) is seen over the first 2 weeks in patients receiving 6–16 mg/day of risperidone, and this effect is maintained during the course of the trial (Figure 2). At Weeks 1 and 2 and thereafter, the reduction in total PANSS scores was significantly greater with 6–16 mg/day of risperidone than haloperidol (at Week 1, $t = 2.4$, $p = .02$; at Week 2 and later, $t > 3$, $p < .001$). The placebo patients deteriorated from Weeks 1 to 6 and then showed little change from Weeks 6 to 8. The responses to haloperidol and 2 mg/day of risperidone were similar. At Weeks 6 and 8, the reduction in total PANSS scores was twice as great with 6–16 mg/day of risperidone as with haloperidol (risperidone, –14.1; haloperidol, –5.1; $t = 3.3$, $p < .001$) (Table 1). Mean changes from placebo scores are shown in Figure 3.

Effects of Patient Characteristics on Treatment Response

To determine whether patient responses to treatment were affected by demographic or clinical differences, we performed two-way ANCOVAs on the following variables: sex of patient, age, race (white, black, other), schizophrenia diagnosis (paranoid, disorganized, or undifferentiated), high and low dichotomized baseline scores on each of the five factors and each of the 30 PANSS items, global severity (CGI-Parkinsonism scores) at baseline, number of hospitalizations per years at risk (years since first psychiatric symptoms), and early (< 21 years) versus late (≥ 21 years) onset of psychotic symptoms. None of these variables were significantly associated with differences in patient responses to risperidone, haloperidol, or placebo, with one exception: a higher score on the PANSS item "conceptual disorganization" was almost significantly associated with greater improvement with risperidone ($p = .07$). This is probably a chance association.

In their analysis of the data from the U.S. trial, Marder and Meibach[2] reported that, whereas 6 mg/day of risperidone was significantly superior to placebo (total PANSS scores) for all patients, regardless of duration of hospitalization, haloperidol was significantly superior to placebo only for patients hospitalized for less than a month. We examined whether patients with current hospitalization ≤ 1 week had a more favorable outcome on total PANSS and Factors 1 through 5 than patients hospitalized ≥ 2

Figure 1. Mean Changes in PANSS Factor Scores From Baseline to Week 8 (LOCF Analysis)



weeks and found no effect of hospital duration on the relatively better outcome in patients receiving 6–16 mg/day of risperidone than the other treatments. In each of the comparisons of changes in total PANSS scores and Factors 1 through 5, outcome was slightly better in newly admitted patients than in patients hospitalized ≥ 2 weeks in each treatment group, but none of the interactions of treatment group and length of hospitalization were statistically significant; that is, the relative effect of the various drug groups was not affected by hospital duration.

Extrapyramidal Symptoms and PANSS Factors

To determine whether there was an association between extrapyramidal symptoms and symptoms of schizophrenia, we performed a Pearson product-moment correlation analysis of scores on the two measures of parkinsonism (ESRS clusters) with the five PANSS factors. Mean parkinsonism total and CGI-Parkinsonism scores at selection and baseline (before and after the washout period) for all patients and at 1, 2, 4, 6, and 8 weeks for the placebo group were significantly correlated with Factors

Figure 2. Mean Changes in PANSS Total Scores From Baseline to Week 8 (LOCF Analysis)

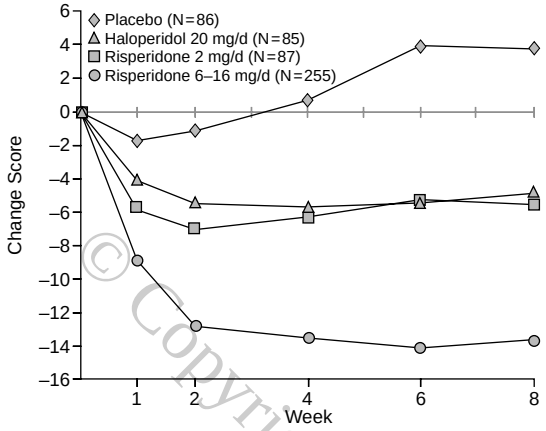
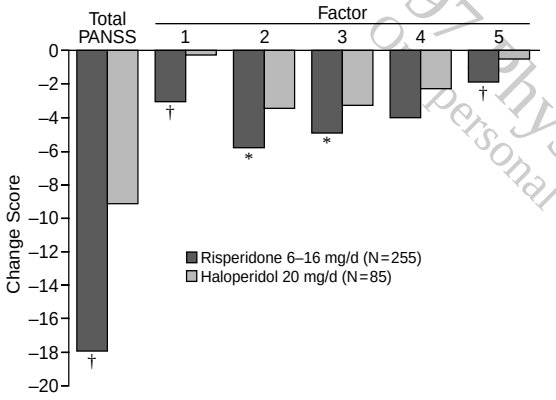


Figure 3. Mean Changes From Placebo Scores at Weeks 6 and 8 (LOCF Analysis)



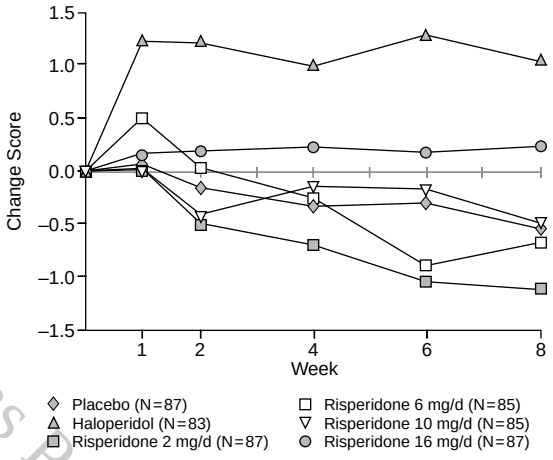
*p ≤ .05. †p < .01.

Table 4. Correlations of Two ESRS Clusters With PANSS Factor 1 (Negative Symptoms) and Factor 3 (Disorganized Thought) at Baseline (All Patients, N = 514) and at Treatment Weeks 1–8 (Placebo Patients Only, N = 86)

		Week				
Variable	Baseline	1	2	4	6	8
Parkinsonism total						
Factor 1	0.22‡	0.22*	0.12	0.19	0.24*	0.21
Factor 3	0.19‡	0.34†	0.28†	0.28†	0.29†	0.28†
Parkinsonism severity						
Factor 1	0.17‡	0.17	0.11	0.19	0.18	0.16
Factor 3	0.16‡	0.17	0.23*	0.28*	0.27*	0.24*

*p < .05. †p < .01. ‡p < .001.

Figure 4. Mean Changes in Parkinsonism Total Scores From Baseline to Week 8 (LOCF Analysis)



1 (negative symptoms) and 3 (disorganized thought) (Table 4). These correlations are statistically significant, but the magnitude is small (a correlation of .15 would account for about 2% of the variance). The other three factors were clearly unrelated to extrapyramidal symptoms.

Effects of Extrapyramidal Symptoms on Improvement

Figure 4 shows the effects of placebo, four doses of risperidone, and haloperidol (20 mg/day) on mean parkinsonism total scores during the 8 weeks of treatment. Haloperidol was associated with substantially more severe parkinsonism symptoms than placebo or risperidone. Severity of these symptoms tended to be higher at higher doses of risperidone, but at endpoint (Week 8) was similar in patients receiving placebo and 2–10 mg/day of risperidone.

Because baseline parkinsonism scores were significantly correlated with Factors 1 and 3 at baseline (Table 4), we held the effect of baseline constant by using the PANSS factor change scores and the maximum ESRS change scores with covariant adjustment for baseline; that is, using ANCOVA, we examined whether the occurrence of extrapyramidal symptoms (maximum scores on both parkinsonism total and severity of parkinsonism at any time point) altered the change scores of the five factors at Weeks 6 and 8 in patients receiving 6–16 mg/day of risperidone in comparison with the haloperidol group. Among the 10 comparisons, none were statistically significant (Table 5), indicating that treatment-related changes in factor scores were not influenced by these extrapyramidal symptoms.

We repeated the ANCOVA in patients stratified by whether they did or did not receive antiparkinsonian medications and found no effects on treatment outcome (changes in PANSS factors or total PANSS scores), nor did addition of this factor alter the failure of extrapyramidal symptoms to influence improvement (data not shown).

If extrapyramidal symptoms produce or aggravate negative symptoms, as has been proposed, patients treated with 10 or 16 mg/day, which produced more extrapyramidal symptoms than 6 mg/day, could be expected to have a lower improvement rate on negative symptoms than patients receiving 6 mg/day of risperidone. This was not the

Table 5. The Effects of Maximum ESRS Scores (Parkinsonism Total and Severity of Parkinsonism) on PANSS Factor Change Scores at Weeks 6 and 8 (N = 514)

Factor	t	p Value
1: Negative symptoms		
Parkinsonism total	0.52	.63
Severity of parkinsonism	–0.00	.99
2: Positive symptoms		
Parkinsonism total	–1.08	.28
Severity of parkinsonism	0.02	.99
3: Disorganized thought		
Parkinsonism total	–1.85	.07
Severity of parkinsonism	0.41	.68
4: Uncontrolled hostility/excitement		
Parkinsonism total	–0.75	.46
Severity of parkinsonism	–0.22	.83
5: Anxiety/depression		
Parkinsonism total	0.72	.43
Severity of parkinsonism	0.81	.42

case. There were significantly greater improvements with 6 mg/day than 10 or 16 mg/day on Factor 4 ($t = 2.3$, $p = .02$), Factor 5 ($t = 2.5$, $p = .01$), and total PANSS ($t = 2.15$, $p < .05$), but not on the other factors, although the differences were in the same direction (Factor 1, $t = 1.2$, $p = .22$; Factor 2, $t = 1.8$, $p = .07$; and Factor 3, $t = 1.8$, $p = .07$).

DISCUSSION

Dimensions of Psychopathology in Schizophrenia

Our findings agree with previous reports[18–25] indicating that psychopathology as measured by the PANSS can be described according to five dimensions (factors). Results of the factor analysis from our sample indicate that these factors represent negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression. Factor-analytic studies[14,30,31] of the Scales for the Assessment of Negative and Positive Symptoms (SANS and SAPS) clearly identified Factors 1, 2, and 3 of the present study but only included items relevant to these three factors (positive symptoms, negative symptoms, and disorganization). An important feature of the three-factor model is that it includes only symptoms that appear as part of the schizophrenic syndrome. However, hostility/excitement and anxiety/depression are common affective symptoms in schizophrenia, and since patients and their caregivers expect treatment plans to attend to these symptoms, we used the five-factor model to evaluate the effectiveness of risperidone and haloperidol.

In the present study, the factor structure was unchanged during 8 weeks of treatment with risperidone and haloperidol. In addition, the structure was stable over time in the placebo group, and, as Lindenmayer et al.[24] also noted, was essentially the same before the washout period, when most patients were receiving conventional neuroleptics, and just after washout. It appears that treatment with a conventional agent such as haloperidol or with a newer agent such as risperidone decreases the intensity of each factor without changing the factor structure or the pattern of correlations between items. A similar five factors were found in schizophrenic patients in Sweden by Lindström and von Knorring[19] and in Japan by Kawasaki et al.,[32] evidence of the cross-cultural stability of the factor structure.

Differential Responsiveness to Risperidone and Haloperidol

We found that improvement in all five dimensions with risperidone was not only consistent but substantially greater than in patients receiving haloperidol. The differential advantages of risperidone relative to haloperidol were greatest for negative symptoms, uncontrolled hostility/excitement, and anxiety/depression (Figure 1). The notion that the most important contrast between the two agents is in their effects on negative symptoms, hostility/excitement, and anxiety/depression is reinforced by the findings that risperidone at 2 mg/day was significantly more effective than haloperidol in reducing negative symptoms and that haloperidol was not significantly more effective than placebo for negative symptoms and anxiety/depression.

The different effects of risperidone and haloperidol are also seen in the comparison of the individual PANSS items (Table 2). In this analysis, the five items with the highest t values (in descending order) were passive social withdrawal, active social avoidance, hostility, depression, and emotional withdrawal. Again, these symptoms are not usually associated with the psychotic component of schizophrenia, suggesting that risperidone differs from haloperidol in its qualitative effects. These data also suggest that the newer antipsychotic is effective not only for socially withdrawn patients but also for those having difficulty with hostility and impulse control (Factor 4). Significantly greater improvement with risperidone than haloperidol was seen at Week 1, and indeed by Week 1, patients treated with risperidone showed greater improvement than haloperidol patients at Week 4; the cost implications of this more rapid response with risperidone are apparent.

The greater improvement in patients receiving risperidone as opposed to receiving haloperidol was not influenced by severity or chronicity of illness and was evident in all clinical subtypes as defined by high or low PANSS factor or item scores. Mattes[33] has recently suggested that the greater efficacy shown by risperidone than by haloperidol is seen only in the more chronic, treatment-resistant patients or in patients with severe negative symptoms or depression. However, we could find no evidence that any subtype of patient was more responsive to risperidone than any other.

According to the total PANSS data reported in Figure 3, the superiority of risperidone (6–16 mg/day) over placebo (change score, –17.9) was almost nine points greater

than that of haloperidol over placebo (–9.1). A nine-point difference is substantial enough to be considered of clinical significance.

Effects of Extrapyramidal Symptoms on Drug-Induced Improvement

We also investigated whether the differences in effects between the two drugs could be related to extrapyramidal symptoms. Four doses of risperidone were compared with a single daily 20-mg dose of haloperidol, a dose likely to result in substantial extrapyramidal symptoms, particularly akathisia and akinesia. The results of our analysis, however, suggest that the differences in outcome between the two agents cannot be explained by extrapyramidal symptoms: changes in PANSS factor scores at Weeks 6 and 8 were not influenced by the effects of treatment on extrapyramidal symptoms. We performed many other statistical analyses in our attempts to discover effects of extrapyramidal symptoms on changes in PANSS scores, but could find no appreciable and consistent evidence of this.

CONCLUSIONS

Our findings suggest that risperidone has important advantages compared with haloperidol. When administered in an effective dose range, risperidone produced greater improvements on all five dimensions of schizophrenia. This difference was most apparent on three dimensions (negative symptoms, uncontrolled hostility/excitement, and anxiety/depression), which suggests that risperidone—and perhaps other serotonin/dopamine antagonists—has qualitatively different effects from those of conventional neuroleptics.

Drug names: biperiden (Akineton), chloral hydrate (Noctec), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), procyclidine (Kemadrin), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25–40
2. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
3. Woolley DW, Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. Proc Natl Acad Sci U S A 1954;244: 228–231
4. Leysen JE, Niemegeers CJE, Tollenaere JP, et al. Serotonergic component of neuroleptic receptors. Nature 1978;272:168–171
5. Ceulemans D, Gelders Y, Hoppenbrouwers ML, et al. Effect of serotonin antagonism in schizophrenia: a pilot study with setoperone. Psychopharmacology (Berl) 1985;85:329–332
6. Reyntjens A, Gelders YG, Hoppenbrouwers ML, et al. Thymosthenic effects of ritanserin (R 55667), a centrally acting serotonin-S_2 receptor blocker. Drug Development and Research 1986;8:205–211
7. Gelders YG. Thymosthenic agents, a novel approach in the treatment of schizophrenia. Br J Psychiatry 1989;155:33–36
8. Kane J, Honigfeld G, Singer J, et al, and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
9. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996;153:466–476
10. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
11. Crow T. Molecular pathology of schizophrenia: more than one dimension of pathology? BMJ 1980;280:66–68
12. Van der Does AJ, Dingemans PM, Linszen DH, et al. Dimensions and subtypes of recent-onset schizophrenia: a longitudinal analysis. J Nerv Ment Dis 1995;183:681–687
13. Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. Br J Psychiatry 1987;151:145–151
14. Andreasen NC, Arndt S, Alliger R, et al. Symptoms of schizophrenia: methods, meanings, and mechanisms. Arch Gen Psychiatry 1995;52: 341–351
15. Schroder J, Buchsbaum MS, Siegel BV, et al. Structural and functional correlates of subsyndromes in chronic schizophrenia. Psychopathology 1995;28:38–45
16. Overall JE, Hollister LE, Pichot P. Major psychiatric disorders: a four-dimensional model. Arch Gen Psychiatry 1967;16:146–151
17. Lépine JP, Piron JJ, Chapatot E. Factor analysis of the PANSS in schizophrenia. In: Stefanis CN, Soldatos CR, Rabavilas AD, eds. Psychiatry Today: Accomplishments and Promises. Amsterdam, The Netherlands: Excerpta Medica; 1989
18. Kay SR, Sevy S. Pyramidical model of schizophrenia. Schizophr Bull 1990;16:537–545
19. Lindström E, von Knorring L. Principal component analysis of the Swedish version of the Positive and Negative Syndrome Scale for schizophrenia. Nordic Journal of Psychiatry 1993;47:257–263
20. Von Knorring L, Lindström E. Principal components and further possibilities with the PANSS. Acta Psychiatr Scand 1995;91(suppl 388):5–10
21. Bell MD, Lysaker PH, Beam-Goulet JL, et al. Five-component model of schizophrenia: assessing the factorial invariance of the Positive and Negative Syndrome Scale. Psychiatry Res 1994;52:295–303
22. Lindenmayer JP, Bernstein-Hyman R, Grochowski S, et al. Psychopathology of schizophrenia: initial validation of a five-factor model. Psychopathology 1995;28:22–31
23. Lindenmayer JP, Grochowski S, Hyman RB. Five factor model of schizophrenia: replication across samples. Schizophr Res 1995;14:229–234
24. Lindenmayer JP, Bernstein-Hyman R, Grochowski S. A new five factor model of schizophrenia. Psychiatr Q 1994;65:299–322
25. White L, Opler L, Lindenmayer JP, et al. Empirical evaluation of alternative models of schizophrenic symptoms. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 8, 1996; New York, NY: Abstract NR555:221
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
27. Chouinard G, Ross-Chouinard A, Annable L, et al. Extrapyramidal Symptom Rating Scale [abstract]. Can J Neurol Sci 1980;7:233
28. Simpson GM, Lindenmayer JP. Extrapyramidal symptoms in patients treated with risperidone. J Clin Psychopharmacol 1997;17:194–201
29. Kraemer HC. To increase power in randomized clinical trials without increasing sample size. Psychopharmacol Bull 1991;27:217–224
30. Andreasen NC, Arndt S, Miller D, et al. Correlational studies of the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms: an overview and update. Psychopathology 1995;28:7–17
31. Arndt S, Andreasen NC, Flaum M, et al. A longitudinal study of symptom dimensions in schizophrenia. Arch Gen Psychiatry 1995;52:352–360
32. Kawasaki Y, Maeda Y, Sakai N, et al. Evaluation and interpretation of symptom structures in patients with schizophrenia. Acta Psychiatr Scand 1994;89:399–404
33. Mattes JA. Risperidone: how good is the evidence for efficacy? Schizophr Bull 1997;23:155–161