A Double-Blind, Randomized Study Comparing the Efficacy and Safety of Sertindole and Risperidone in Patients With Treatment-Resistant Schizophrenia

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Objective: The comparative efficacy of second-generation antipsychotics has yet to be fully elucidated in patients with treatment-resistant schizophrenia. The objective of this study was to examine the efficacy and safety of sertindole, compared to risperidone, in this patient population.

Method: In this multicenter, phase 3, randomized, double-blind, parallel-group study, only patients with *DSM-IV* schizophrenia who had failed an adequate antipsychotic treatment within the previous 6 months and who had not responded positively to haloperidol during screening were eligible for enrollment. The primary efficacy variable was change in Positive and Negative Syndrome Scale (PANSS) from baseline to final assessment. Weekly assessments included the PANSS, the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), and the Clinical Global Impressions (CGI) scale. The study was conducted between June 1996 and April 1998.

Results: Of the 321 patients randomly assigned to double-blind treatment, 217 patients completed the study (sertindole, n/n = 142/216 [66%]; risperidone, n/n = 75/105 [71%]). The main reason for withdrawal in both groups was ineffective therapy. The between-group difference in PANSS total score was not statistically significant and both groups showed improvement, with mean changes of −18.6 in the sertindole group and −20.9 in the risperidone group based on observed cases and −12.0 and −19.0, respectively, based on the last-observation-carried-forward method for imputing missing data. There were no statistically significant differences between the groups in any of the secondary end points: PANSS positive and negative subscales, CGI scores, BPRS total scores and positive symptom subscale scores, and SANS total scores. Patients reported similar levels of adverse events and treatment-emergent adverse events (TEAEs), except for extrapyramidal syndrome-related TEAEs, which were more common in the risperidone-treated group. Prolongation of the QTc interval was observed significantly more frequently with sertindole treatment.

Conclusions: Sertindole and risperidone are effective and well-tolerated in patients with treatment-resistant schizophrenia. Sertindole offers an alternative treatment option for refractory patients in Europe given its good EPS profile, favorable metabolic profile, and comparable efficacy to risperidone.

J Clin Psychiatry 2011;72(2):194–204

Submitted: *August 23, 2007; accepted August 20, 2009.*
Online ahead of print: *July 27, 2010 (doi:10.4088/JCP.07m03733yel).*
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Schizophrenia is a disabling psychiatric condition that is characterized by severe disturbances in affect, thought, perception, and behavior. The positive and negative symptoms of schizophrenia are often accompanied by cognitive, suicidal, and violent symptoms that are inherently more difficult to treat with pharmacotherapy.[1] A large proportion of patients with schizophrenia remain refractory, or only respond partially, to antipsychotic medication.

Conventional antipsychotic drugs have been available since the 1950s, and they can produce complete remission of positive symptoms, that is, delusions and hallucinations, in 70%–80% of patients with early-phase schizophrenia.[2] However, they are largely ineffective against the negative symptoms of schizophrenia and also often induce high levels of unwanted side effects, such as extrapyramidal syndrome (EPS).[3,4] Negative symptoms often result in the patient's experiencing long periods of impaired functioning, while unpleasant side effects may result in poor adherence to treatment and an increased risk of relapse and readmission to hospital.[5] Even though second-generation antipsychotics may be comparatively efficacious against positive symptoms, as well as seemingly having some advantages in terms of negative and cognitive symptoms, at least 20% of patients with schizophrenia are still not fully responsive to any of the currently available medications.[6]

There are limited data on the comparative efficacy of the second-generation antipsychotics in patients with treatment-resistant schizophrenia, and (with the exception of clozapine) any form of hierarchy has yet to be fully elucidated. This shortage of data may be attributable to inadequate definitions of treatment resistance or the inherent difficulties in performing clinical trials in patients with severe or refractory schizophrenia.[1] Nevertheless, there is consistent evidence to support the use of clozapine in patients with treatment-resistant schizophrenia,[6–9] and in recent years, data on the efficacy of other second-generation antipsychotics in treatment-resistant schizophrenia have been published. Olanzapine has demonstrated similar efficacy to chlorpromazine and superior efficacy to haloperidol and risperidone in treatment-resistant patients.[8,10,11] However, olanzapine and risperidone have also been found to have similar efficacy in treatment-resistant patients.[12] One study reported a similar efficacy of risperidone compared to clozapine.[13] However, clozapine was more efficacious than risperidone in 3 other trials.[14–16] Buckley et al[17] compared quetiapine with haloperidol in patients with poorly responsive schizophrenia. They reported significantly more responders on

the Clinical Global Impressions-Severity of Illness (CGI-S) scale with quetiapine treatment than with haloperidol.[17] Methodological differences between the above studies make drawing comparative conclusions from the data difficult, while addition of a consideration of side effects adds a further difficult dimension to the choice of antipsychotic therapy.

The advantages of the second-generation antipsychotics over the conventional antipsychotics in terms of efficacy are still under debate, and there is a growing body of evidence that a major disadvantage of second-generation antipsychotics is their propensity to cause weight gain. Weight gain is a particular concern, as it can have a number of long-term health implications, such as diabetes, dyslipidemia, and coronary heart disease. Wirshing et al[18] investigated the relative weight gain liabilities of clozapine, risperidone, olanzapine, sertindole, and haloperidol in patients with schizophrenia. Clozapine and olanzapine caused the most weight gain, and risperidone caused intermediate weight gain. Sertindole had less associated weight gain than haloperidol.[18] These findings are supported by other studies that have shown relatively low treatment-associated weight gain with sertindole.[19–21] Consequently, selecting effective management of the treatment-resistant population is a complex question affected by many issues, not least the potential balance between efficacy and side effects, which are well-known to be linked to treatment compliance.[5,22]

Sertindole is a second-generation, nonsedating antipsychotic that is effective against positive and negative symptoms of schizophrenia.[20,23–25] Sertindole has a high affinity for dopamine D_2, serotonin 5-HT_2, and α_1-adrenergic receptors,[26,27] selectively binding to dopamine receptors in the mesolimbic rather than the striatal regions.[26,28–30] Sertindole has therefore been considered to have a low propensity for the induction of EPS. In several large placebo-controlled studies, the incidence of EPS in patients treated with sertindole was found to be comparable with that of placebo.[24,25,31] This low propensity to induce EPS may translate into other benefits for patients, such as improved adherence and fewer relapses and hospital readmissions.[21,32]

Sertindole was licensed in the United Kingdom (UK) in 1996 but was withdrawn in 1998 due to concerns about its effect on the QT interval. The UK Adverse Reactions Online Information Tracking system registered what appeared to be an unusually high ratio of serious cardiac arrhythmias and sudden cardiac deaths in relation to total adverse drug reactions. In 2001, the Committee for Proprietary Medicinal Products (now the Committee for Medicinal Products for Human Use) lifted the suspension on sertindole after considering data from 7 epidemiologic studies, including more than 10,000 patients, which demonstrated that the mortality rates among sertindole-treated patients are comparable with those of other antipsychotics.[33]

Risperidone is an effective antipsychotic that binds to central dopamine D_2 and 5-HT_2 receptors.[34] It has higher affinity for nigrostriatal dopaminergic neurons than sertindole has,[35] and it produces dose-dependent EPS, although not to the same degree as the conventional antipsychotics.[36]

A recently published study of the treatment of moderate-to-severe schizophrenia compared sertindole with risperidone.[20] Despite being terminated early (due to the suspension of sertindole), this study demonstrated significant benefits of sertindole over risperidone in the observed cases data set for mean change in the Positive and Negative Syndrome Scale (PANSS) total scores (sertindole: -37.6 ± 18.8; risperidone: 31.5 ± 17.3, $P \leq .05$), and in both observed cases and last observation carried forward (LOCF) data sets for treatment of negative symptoms as indicated by improvements in PANSS negative subscale scores (LOCF, $P \leq .05$; observed cases, $P \leq .001$). Both treatments achieved similar results in CGI, Drug Attitude Inventory, and Global Assessment of Functioning scores. Tolerability was good in both groups; fewer patients in the sertindole group experienced EPS, but significantly more were found to have QT prolongation and abnormal ejaculation volume.[20]

The objective of the study reported here was to examine the efficacy and safety of sertindole in patients with treatment-resistant schizophrenia, using risperidone as a comparator. The study took place around the time of the sertindole suspension in the UK, and it aimed to expand on the existing data. Following its reintroduction in the UK, sertindole represents a second-generation antipsychotic treatment whose role in the management of patients with treatment-resistant schizophrenia has yet to be clearly defined, and it may address the need for an alternative treatment in clinical practice.

METHOD

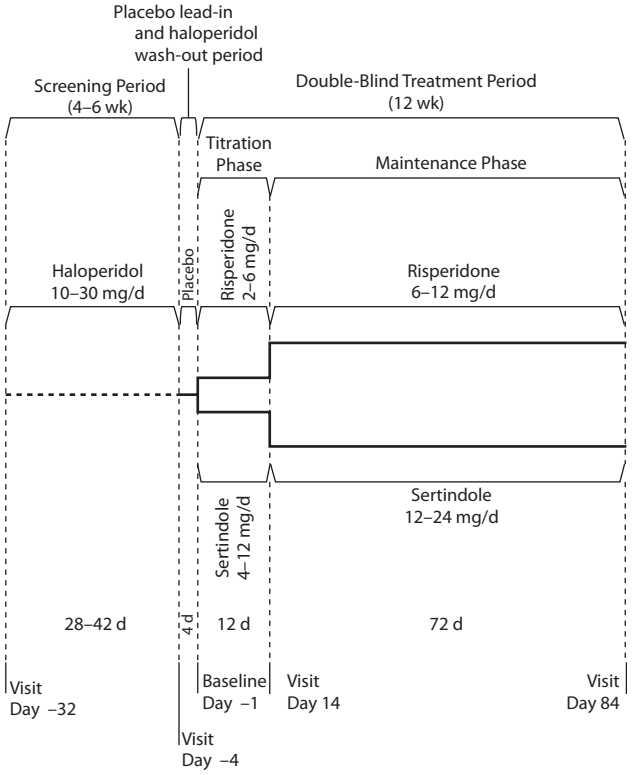
This phase 3, randomized, double-blind, parallel-group study was carried out in 34 centers in the US and Canada between June 1996 and April 1998. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Patients participated in a 4- to 6-week screening and prospective haloperidol-treatment period, followed by a single-blind, placebo lead-in period (4 days), before being randomly assigned in a 2:1 ratio to sertindole or risperidone and entering the 12-week, double-blind treatment phase (Figure 1).

Inclusion/Exclusion Criteria

Before enrollment, patients were required to give informed consent and to be capable of cooperating with assessments. Patients were eligible for screening if they were aged 18 to 55 years, had a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[37] primary diagnosis of schizophrenia, and had failed 1 adequate antipsychotic treatment in the previous 6 months.

The main criteria for exclusion were a response to haloperidol expressed as a $\geq 25\%$ reduction in the PANSS[38] total score at the end of the screening period (day −4), a response to any antipsychotic treatment in the previous 6 months, failure to respond to clozapine after at least 8 weeks of treatment, a PANSS total score < 60 at screening, and a QT or QTc interval > 500 msec. Other exclusion criteria included

Figure 1. Study Design



a primary psychiatric diagnosis other than schizophrenia; a clinically significant somatic disorder or other medical problem requiring frequent changes in medication; previous psychosurgery; abnormal neurologic or clinically significant laboratory findings; hepatic impairment; suicidal tendencies; a recent history of substance or alcohol abuse; positive hepatitis B or HIV status; recent use of investigational drug; and concomitant use of ketoconazole, itraconazole, or quinidine.

Study Treatments and Procedures

In the screening period, patients received haloperidol 10 to 30 mg/d (prescribed according to the investigators' discretion) for 4 to 6 weeks. A minimum of 10 mg/d for 3 weeks was required. Patients who responded positively to haloperidol treatment (≥ 25% reduction in PANSS total score) were not randomly assigned into subsequent phases, that is, patients were only eligible for random assignment if they had failed 1 adequate antipsychotic treatment in the previous 6 months and failed to respond adequately to haloperidol treatment during the screening period, constituting treatment failure to at least 2 antipsychotic agents before random assignment (except for patients initially enrolled because haloperidol-treatment had failed). This initial screening ensured that all patients entered into the double-blind treatment phase of the study were treatment-resistant. Patients were admitted to hospital at the start of the 4-day lead-in period (day –4), haloperidol was titrated down, and patients received placebo from day –2. Patients were discharged from the hospital during the titration phase 10 days later (day 7).

At the end of the lead-in phase, which also served to wash out haloperidol, patients were randomly assigned to the 12-week double-blind treatment phase if:

- they were resistant to haloperidol treatment
- they continued to show positive symptoms (Brief Psychiatric Rating Scale (BPRS) positive symptom subscale[39]: hallucinatory behavior, unusual thoughts, conceptual disorganization, and suspicion) as assessed by a total rating of ≥ 8 on any 2 of the items
- they had an acceptable level of involuntary movements (assessed by Abnormal Involuntary Movement Scale (AIMS)[40]: a score of ≤ 3 was required on all items).

Patients were randomly assigned in a 2:1 ratio to receive oral sertindole once daily or oral risperidone twice daily. Initial daily dosing was 4 mg sertindole or 2 mg risperidone, and doses were increased by 4 mg or 2 mg, respectively, every third day, up to the minimum treatment dose (12 mg/d and 6 mg/d, respectively). The same titration schedule was followed until the optimal or maximum dose was reached (maximum daily doses: 24 mg for sertindole and 12 mg for risperidone). Both sertindole- and risperidone-treated patients had the study drug adjusted by the investigator to achieve an optimal therapeutic response. The mean daily dose was 18.1 mg/d for sertindole-treated patients and 9.0 mg/d for risperidone-treated patients. (The mean modal dose was 19.9 mg/d and 9.4 mg/d, respectively.)

Blinding

Investigators were supplied with a randomization schedule and a set of sealed treatment assignment envelopes. Codes were unbroken throughout the study, unless the investigator felt it was necessary to reveal the identity of the study medication to provide optimal treatment to the patient in the event of an emergency. To maintain blinding throughout the study, capsules of both study drugs were identical in appearance and were supplied in identical weekly blister packs. Because risperidone requires twice-daily dosing (morning and afternoon), a daily placebo capsule was added to the sertindole blister packs to conceal the identity of the medication.

Concomitant Medication

A number of concomitant medications were allowed to control other psychiatric and motor symptoms:

- lorazepam (up to 10 mg/d) for agitation
- chloral hydrate (up to 3 g/d) for insomnia
- benztropine mesylate for EPS (assessed using the Simpson-Angus Scale (SAS).[41]
- benztropine mesylate or propranolol for akathisia (assessed using the Barnes Akathisia Scale (BAS).[42]

Chloral hydrate and lorazepam could not be used in the 8-hour period prior to assessment with the psychiatric rating scales. Benztropine mesylate was administered either on the judgment of the clinician or when the patient reported

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discomfort due to EPS symptoms, and benztropine mesylate or propranolol were administered either on the judgment of the clinician or when the patient reported discomfort due to akathisia symptoms. Patients were always assessed on the SAS before treatment with benztropine mesylate for EPS and always assessed on the BAS before treatment with benztropine mesylate or propranolol for akathisia. The need for continued treatment was re-evaluated every 7 days.

Assessments: Psychiatric Rating

Following a detailed medical and psychiatric history and baseline physical and neurologic examinations, assessments of psychiatric status were carried out weekly during the double-blind treatment phase using 4 scales:

- the PANSS[38]
- the BPRS[39]
- the SANS[43]
- the CGI scale.[44]

These scales were chosen in order to assess improvement in both positive and negative symptoms, as well as the overall improvement of the patient (CGI scale)

Modified versions of the PANSS and BPRS scales were used in the analysis, whereby a value of 1 was subtracted from each item score for both scales (PANSS being a 30-item scale with positive and negative subscales and BPRS being an 18-item scale with a positive subscale) such that the absence of symptoms was coded as zero. Therefore, scores presented for the PANSS and BPRS may be less than expected for a treatment-resistant schizophrenia population (PANSS total scores were assessed on a scale of 0 to 180 rather than 30 to 210, and BPRS total scores were assessed on a scale of 0 to 108 rather than 18 to 126). Hence, the *mean change* in scores presented will be comparable to those achieved in other studies, while the data for *percentage reductions* presented will differ from those in comparable studies and will need to be taken in the context of these modified scales.

Only investigators who had been trained for this study conducted rating sessions. For each patient, the CGI score was performed by the same assessor throughout the study and, when possible, the same assessor was also used for the PANSS, BPRS, and SANS assessments.

Assessments: Movement Rating

Effects of treatment on motor function and movement were measured using 3 movement rating scales:

- the AIMS[40]
- the SAS[41]
- the BAS.[42]

Other Assessments

In addition to the standard hematologic and biochemical safety evaluations, blood pressure and electrocardiograms (ECGs) were monitored every 2 weeks to study episodes of postural hypotension and QT_c prolongation.

Compliance was assessed by the investigator.

Study End Points

The primary efficacy variable was the change in PANSS total score from baseline to final assessment. The study reported the mean change from baseline and the proportion of patients achieving predefined improvements.

Secondary efficacy variables comprised the change from baseline on the PANSS negative and positive subscales, the BPRS total score, the SANS total score, and the CGI-S and Global Improvement (CGI-I) scores. Appropriate subscale scores of each were also analyzed.

It was considered that a treatment period of 12 weeks would be sufficient to show a treatment response in the positive and negative symptoms of schizophrenia.

Statistical Analyses

Statistical analysis was carried out using the SAS system, version 6.12 or later (SAS Institute Inc, Cary, North Carolina). Analysis of the primary end point was based on an analysis of covariance (ANCOVA) incorporating factors for treatment group, study center, and baseline PANSS total score. An ANCOVA was also used for all secondary outcomes except CGI-I score, which was analyzed using the nonparametric Cochran-Mantel-Haenszel mean score statistic. All hypothesis testing was 2-tailed, with a significance level of 5%.

The following data sets were used for statistical analysis:

- *All-patients-treated set* (APTS) comprised all randomly assigned patients who took at least 1 dose of double-blind medication (n = 321).
- *Intent-to-treat set* (ITT) comprised all patients in the APTS who had an efficacy assessment at baseline and at least once after the receipt of double-blind medication (n = 317).

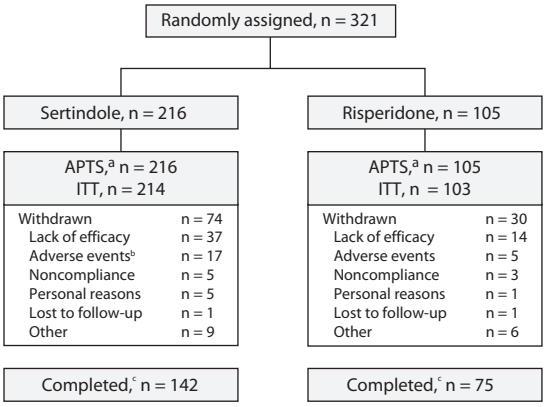
Primary efficacy analysis was based on the ITT population using last-observation-carried-forward (LOCF) data to compensate for early dropouts. All efficacy analyses were also carried out for the observed cases data set. The observed cases data only include patients who actually attended visits and completed assessments. In the event of missing interim data for an individual item of the PANSS, BPRS, or SANS, the score was estimated by using the average score obtained in other assessments. However, this estimation was only done if fewer than half of the assessments were missing.

Safety Analyses

All adverse events (AEs) and TEAEs were recorded, as were discontinuations. A TEAE was defined as any AE that began or worsened on or after day 1. Adverse events included TEAEs, as well as events that began prior to, but ended on or after, day 1.

Adverse events were coded using version 3 of the Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary.[45] Analyses of movement rating scales, AEs, and laboratory data were based on the APTS. Comparisons of the proportion of patients who experienced treatment-emergent EPS were made using Fisher exact test.

Figure 2. Patient Disposition



[a] The all-patients-treated set (APTS) comprised all randomly assigned patients who took at least 1 dose of double-blind medication.
[b]One patient in the sertindole-treated group had an adverse event leading to discontinuation before week 1.
[c]Completed is defined as: the patient was taking sertindole or risperidone at the time the sponsor discontinued the study, or the patient completed the 12-week treatment period.
Abbreviations: APTS = all-patients-treated set, ITT = intent to treat.

Determination of Sample Size

On the basis of previous studies,[25,46] the difference between sertindole and risperidone in treatment-resistant patients was expected to be 75% of the difference between sertindole and placebo, which was determined as a 10-point change from baseline in the PANSS total score. It was also estimated that there would be an SD of 23 points. Therefore, a total sample size of 400 patients and a 2:1 ratio of sertindole to risperidone would give the study 87% power to detect a difference of 7.5 points with an SD of 23 points.

RESULTS

Patient Disposition

The study was terminated prematurely for administrative reasons surrounding the uncertain approvability status of the medication at that time.

Of the 379 patients screened, 321 patients met the entry criteria for the double-blind phase of the study and were randomly assigned to receive sertindole or risperidone treatment (sertindole, n = 216; risperidone, n = 105). Of these patients, the mean haloperidol dose was 18.7 mg/d (SD = 7.5) in the sertindole-treated group and 17.7 mg/d (SD = 7.4) in the risperidone-treated group. Of the 321 patients randomly assigned, a total of 217 patients completed the 12 weeks of treatment (sertindole, n = 142 [66%]; risperidone, n = 75 [71%]). This included 7 patients who were prematurely discontinued as a result of study termination. A total of 104 patients discontinued prematurely (Figure 2). The main reason for withdrawal in both groups was ineffective therapy, 17% (37/216) in the sertindole-treated group and 13% (14/105) in the risperidone-treated group.

No statistically significant differences between the 2 treatment groups were noted in the proportion of patients using lorazepam during the study to help control agitation (sertindole, 78% (167/214); risperidone, 79% (81/103)). There were no clinically relevant differences between the treatment groups in terms of concomitant medications initiated during the study.

Table 1. Baseline Demographic Characteristics of 321 Patients With Treatment-Resistant Schizophrenia Randomly Assigned Double-Blind to Sertindole or Risperidone

Characteristic	Sertindole, n = 216	Risperidone, n = 105
Age, mean (SD), y	38.9 (9.0)	38.7 (7.3)
Age, median, y	39	39
Sex, men, %	78	78
Weight, mean (SD), kg	82.2 (19.4)	85.0 (21.3)
Age at diagnosis, n[a]	211	97
Mean (SD), y	22.0 (6.3)	22.3 (6.3)
Median, y	20	21

[a]Data on age at diagnosis were missing for 5 patients in the sertindole-treated group and 8 patients in the risperidone-treated group.

Baseline Demographics

The baseline demographic characteristics of the randomly assigned patient population are shown in Table 1. There were no significant differences in the baseline parameters, although the mean weight at baseline was lower for women in the sertindole group (82.2 kg, SD = 24.0) than for the women in the risperidone group (89.6 kg, SD = 21.1).

Large proportions of the patients in both the sertindole and risperidone groups were overweight at baseline with mean body mass index (BMI) values of 27.7 kg/m^2 (SD = 6.6) and 28.6 kg/m^2 (SD = 7.5), respectively. The women in particular had high BMI values at baseline, more so in the risperidone group (33.7 kg/m^2 [SD = 7.5] versus 31.2 kg/m^2 [SD = 8.9] in the sertindole group).

The psychiatric history was similar for both groups, with the most common primary diagnosis being paranoid schizophrenia according to *DSM-IV* paragraph 295.30 (61% in the sertindole-treated group; 64% in the risperidone-treated group). There were no clinically significant differences between the 2 treatment groups regarding baseline neurologic examination or vital signs.

The majority of patients (over 85%) in both groups had ongoing medical conditions. There was >5% difference for the following conditions: sertindole group patients had more gastrointestinal conditions, while risperidone-treated patients had more endocrine and metabolic conditions, drug allergies, and surgical histories.

Efficacy

Mean PANSS total scores. Both treatment groups showed a similar improvement in mean PANSS total scores (Table 2). On the basis of the OC data set, the mean changes were −18.6 for the sertindole-treated group versus −20.9 for the risperidone-treated group. For the LOCF data set, the difference between the treatment groups was greater (−12.0 for the sertindole group and −19.0 for the risperidone group). There was no statistically significant difference between the treatment groups in the mean change from baseline to final assessment in either the OC or the LOCF data sets (Figure 3).

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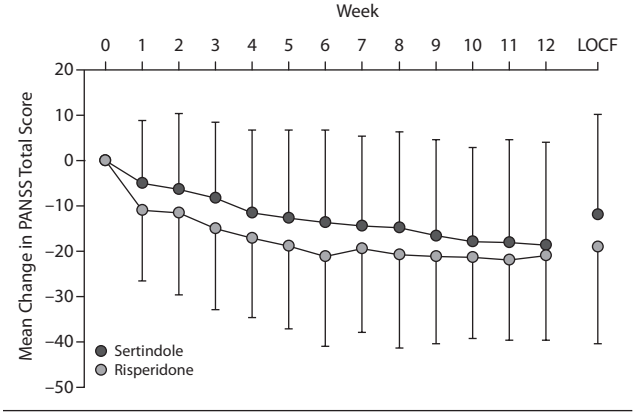
Table 2. Change From Baseline to Week 12 in the Modified PANSS, Modified BPRS, SANS, and CGI-S Scores (ITT population)

	Sertindole						Risperidone					
			Mean Change to Week 12						Mean Change to Week 12			
	Baseline		Observed Cases		LOCF		Baseline		Observed Cases		LOCF	
Scale	n	Mean (SD)	n	Change (SD)	n	Change (SD)	n	Mean (SD)	n	Change (SD)	n	Change (SD)
PANSS												
Total	213	68.1 (18.1)	122	−18.6 (22.7)	213	−12.0 (22.1)	102	71.7 (22.1)	64	−20.9 (18.7)	102	−19.0 (21.3)
Positive	213	17.6 (5.4)	122	−5.3 (6.8)	213	−3.3 (6.9)	102	18.5 (6.8)	64	−6.2 (5.9)	102	−5.8 (6.3)
Negative	213	18.4 (6.2)	122	−4.0 (6.9)	213	−2.5 (6.5)	102	19.1 (6.6)	64	−4.3 (5.1)	102	−3.7 (5.9)
BPRS												
Total	213	36.8 (10.5)	122	−11.1 (13.0)	213	−7.0 (13.1)	101	38.7 (12.0)	65	−12.2 (11.4)	101	−10.9 (12.7)
Positive	213	12.6 (3.5)	122	−3.6 (4.5)	213	−2.4 (4.6)	101	13.3 (3.6)	65	−3.6 (4.1)	101	−3.5 (4.5)
SANS total	162	56.9 (21.7)	108	−9.1 (19.0)	162	−7.5 (18.2)	84	59.2 (20.9)	59	−12.1 (16.9)	84	−10.3 (19.0)
CGI-S	213	5.1 (0.8)	122	−0.8 (0.8)	213	−0.5 (0.9)	101	5.3 (0.8)	65	−0.9 (1.0)	101	−0.8 (1.0)

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness, ITT = intent to treat, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale, SANS = Scale for the Assessment of Negative Symptoms.

Figure 3. Mean Change From Baseline to Each Evaluation in PANSS Total Score (observed cases data set, with Week 12 score for LOCF data set)



PANSS positive and negative subscales. Both treatment groups showed a similar mean change in PANSS positive and negative subscale scores, and—as with the PANSS total score—the differences between the groups were not statistically significant (Table 2).

BPRS total and positive symptom subscale. Both treatment groups showed an improvement from baseline to final assessment of mean BPRS total score and BPRS positive symptom subscale score (Table 2), but the between-group differences were not statistically significant.

CGI-S score. There was no statistically significant difference between the two treatment groups for mean improvement in CGI-S scores (Table 2).

SANS total score. Both treatment groups showed a reduction in mean SANS total score (Table 2), but the difference between the groups was not statistically significant.

Predefined improvements in modified PANSS and BPRS total scores. Table 3 shows the proportions of patients achieving predefined improvements from baseline to final assessment as measured on the modified PANSS and BPRS total scores. The percentages of patients achieving ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% improvement in the modified PANSS and BPRS total scores were greater in the risperidone group for all categories of improvement, with a trend for smaller differences between treatment groups in categories of greater improvement. The difference in mean change from baseline to final assessment between the treatment groups for each of the categories was significantly different in favor of risperidone for the groups of patients achieving ≥ 10% and ≥ 20% improvement in modified PANSS and BPRS total scores.

Table 3. Patients Achieving Prespecified Improvements on the Modified PANSS, Modified BPRS, and CGI Global Improvement Scale (ITT population)

	Sertindole		Risperidone	
Outcome	n	%	n	%
Reduction from baseline to final assessment in PANSS total score	n = 213		n = 102	
≥ 10%	119	55.9	72	70.6*
≥ 20%	96	45.1	59	57.8*
≥ 30%	75	35.2	47	46.1
≥ 40%	48	22.5	32	31.4
≥ 50%	35	16.4	20	19.6
Reduction from baseline to final assessment in BPRS total score	n = 213		n = 101	
≥ 10%	121	56.8	74	73.3*
≥ 20%	98	46.0	60	59.4*
≥ 30%	80	37.6	49	48.5
≥ 40%	57	26.8	37	36.6
≥ 50%	45	21.1	26	25.7
CGI-I rating	n = 214		n = 102	
At least very much improved	11	5.1	2	2.0
At least much improved	57	26.6	34	33.3
At least minimally improved	123	57.5	64	62.7

*$P \leq .05$ versus sertindole (ANCOVA).

Abbreviations: ANCOVA = analysis of covariance, BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement, ITT = intent to treat, PANSS = Positive and Negative Syndrome Scale.

CGI-I scale. On the CGI-I scale, a greater number of sertindole-treated patients were rated at least *very much improved*, compared to the risperidone-treated group (5.1% [n = 11/214] versus 2.0% [n = 2/102], respectively), while the trend was reversed for the categories of at least *much improved* and at least *minimally improved* (Table 3).

Safety

The percentage of randomly assigned patients experiencing AEs was similar for both groups: 90.3% (n/n = 195/216) of sertindole-treated patients and 89.5% (n/n = 94/105) of

Table 4. Treatment-Emergent Adverse Events in Either Treatment Group and Mean Change From Baseline to Final Assessment for Movement Rating Scales (APTS)[a]

	Sertindole (n = 216)		Risperidone (n = 105)	
COSTART Description	n	%	n	%
TEAEs with an incidence ≥ 10%				
Patients with at least 1 TEAE	185	85.6	89	84.8
Headache	63	29.2	29	27.6
Insomnia	39	18.1	17	16.2
Vomiting	37	17.1	14	13.3
Dyspepsia	34	15.7	9	8.6
Rhinitis	33	15.3	21	20.0
Abnormal ejaculation	25	14.8	5	6.1
Nausea	28	13.0	14	13.3
Somnolence	25	11.6	15	14.3
Dizziness	23	10.6	12	11.4
Pain	20	9.3	11	10.5
Infection	15	6.9	11	10.5
Accidental injury	15	6.9	11	10.5
Akathisia	11	5.1	12	11.4
EPS-related TEAEs with an incidence ≥ 5%				
EPS	45	20.8	38	36.2**
Akathisia	11	5.1	12	11.4
Extrapyramidal syndrome	5	2.3	10	9.5*
Increase in saliva	6	2.8	6	5.7
	(n = 195)		(n = 95)[b]	
Movement rating scales	Baseline Mean	Mean Change (SD)	Baseline Mean	Mean Change (SD)
SAS	3.0 (3.8)	−1.3 (3.5)	3.4 (4.2)	−1.4 (3.6)
BAS	2.2 (2.9)	−1.1 (3.1)	2.3 (2.9)	−0.9 (2.8)
AIMS	3.7 (4.7)	−1.2 (3.8)	3.3 (4.1)	−0.8 (4.1)

[a]The number of patients in the randomized population served as the denominator for calculating rates of adverse events, except for gender-specific adverse events.
[b]Except for AIMS score, n = 96.
*$P \leq .05$ versus sertindole from Fisher exact test.
**$P \leq .01$ versus sertindole from χ^2 test.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, APTS = all-patients-treated set, BAS = Barnes Akathisia Scale, EPS = extrapyramidal syndrome, COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms, SAS = Simpson-Angus Scale, TEAE = treatment-emergent adverse event.

risperidone-treated patients. The proportion of patients experiencing TEAEs was also similar: sertindole 85.6% (n/n = 185/216); risperidone 84.8% (n/n = 89/105). Treatment-emergent adverse events with an incidence ≥ 10% in either treatment group are listed in Table 4. The overall pattern of occurrence of TEAEs was similar for both groups except for abnormal ejaculation, dyspepsia, and vomiting, which were higher in the sertindole-treated group, and akathisia, rhinitis, infection, and accidental injury, which were higher in the risperidone-treated group. None of these differences were statistically significant.

Serious adverse events. Nineteen patients (sertindole, n = 14 [6.5%]; risperidone, n = 5 [4.8%]) had a total of 21 serious adverse events (SAEs) during the study, 16 in the sertindole-treated group and 5 in the risperidone-treated group. The most common SAEs were accidental overdose, 1.9% (4/216) in the sertindole group and 1.9% (2/105) in the risperidone group; suicidal tendency, 0.9% (2/216) in the sertindole group and 1.9% (2/105) in the risperidone group; and depression, 1.4% (3/216) in the sertindole group. Most were judged by the investigators to be unrelated to the study drug.

Withdrawals. The proportion of patients who withdrew due to AEs was similar in both groups: 17 (8%) in the sertindole group and 5 (5%) in the risperidone group. Of the 17 sertindole-treated patients who withdrew due to an AE, 3 were due to ECG abnormalities, 5 to QT interval prolongation, and 2 to tachycardia. All of these were deemed to be *probably* related to the study drug, except 1 of the ECG abnormalities, which was classified as being *possibly* related. No deaths occurred in the double-blind treatment period.

Treatment-related EPS. Although there were no statistically significant differences in the proportion of patients who discontinued, continued, or started taking anti-EPS medication in this study, the proportion of patients who experienced at least 1 EPS-related TEAE was significantly lower in the sertindole-treated group than the risperidone-treated group (20.8% [45/216] versus 36.2% [38/105]; $P \leq .01$) (Table 4). Sertindole-treated patients experienced significantly fewer EPS events ($P \leq .05$) and although not more than 5% of patients reported joint disorder, there were significantly more joint disorder events in the risperidone-treated group (0.5% [1/216] versus 4.8% (5/105); $P \leq .05$). There were numerically fewer cases of, but non-significant differences in the frequency of, akathisia and increase in saliva production events in the sertindole-treated group compared with the risperidone-treated group (Table 4).

Movement disorders. Both groups showed an improvement from baseline to final assessment for all movement rating scales: SAS, BAS, and AIMS. There were no statistically significant differences between the treatment groups (Table 4).

Weight gain. At last assessment, sertindole-treated patients had gained a mean 3.1 kg (SD = 4.5) whereas risperidone-treated patients had gained a mean 2.5 kg (SD = 3.3) (Table 5). Clinically significant weight gain (≥ 7% increase) was seen in 40 patients in the sertindole group (25%) compared with 14 patients (16%) in the risperidone group. This difference was not significant.

Laboratory values. Mean glucose, cholesterol, and triglyceride concentrations increased slightly in both treatment groups (Table 5). For blood glucose and cholesterol concentrations, the mean increase was higher in the risperidone group than in the sertindole group, and vice versa for triglyceride concentrations. For glucose, total cholesterol, and triglyceride concentrations, the proportion of patients moving from a baseline value of *normal* to *markedly high* at last assessment was similar for both treatment groups (approximately 10%–14%; data not shown).

Table 5. Change in Weight and Metabolic Laboratory Values From Baseline[a]

	Sertindole			Risperidone		
		Mean Change (SD)			Mean Change (SD)	
Measurement	Baseline, Mean (SD)	Week 12	Last Assessment	Baseline, Mean (SD)	Week 12	Last Assessment
Laboratory values, mg/dL	n = 200	n = 116	n = 200	n = 97	n = 60	n = 97
Glucose	100.6 (30.0)	1.8 (32.0)	6.0 (38.6)	100.4 (35.1)	3.8 (20.8)	6.3 (23.1)
Total cholesterol	187.9 (35.0)	3.2 (28.4)	3.9 (28.8)	177.0 (37.0)	8.1 (27.3)	4.0 (24.9)
Triglycerides	170.2 (117.6)	5.5 (89.8)	21.4 (141.0)	162.3 (124.4)	8.7 (76.7)	−0.2 (91.3)
Weight, kg						
All	n = 162	n = 89	n = 162	n = 86	n = 53	n = 86
	82.6 (19.9)	3.9 (4.6)	3.1 (4.5)	84.4 (21.1)	2.4 (3.1)	2.5 (3.3)
Men	n = 127	n = 68	n = 127	n = 66	n = 41	n = 66
	82.6 (18.4)	3.9 (4.7)	3.1 (4.6)	82.8 (21.1)	2.6 (3.3)	2.5 (3.3)
Women	n = 35	n = 21	n = 35	n = 20	n = 12	n = 20
	82.5 (24.9)	4.2 (4.1)	3.1 (3.9)	89.6 (21.1)	1.8 (2.4)	2.6 (3.4)

[a]Only patients with baseline and postbaseline values are included.

Vital signs. There were no apparent trends within or between the treatment groups regarding change from baseline in sitting systolic or diastolic blood pressure or pulse rate.

ECG findings. Sertindole had a tendency to prolong the QTc interval in some patients. The mean change from baseline in QTc value (Fridericia correction) was significantly higher for sertindole-treated patients (22.7 ± 22.4 msec) than for risperidone-treated patients (4.1 ± 15.6 msec; $P \leq .05$), and there were statistically significant between-group differences in the numbers of patients having a ≥ 60 ms change in QT or QTc (29 and 39, respectively, in the sertindole group and 4 and 4, respectively, in the risperidone group).

One patient in the sertindole-treated group and none in the risperidone group had a $QT_{max} \geq 500$ msec and 8 and 1, respectively, had a $QTc_{max} \geq 500$ msec. These differences between treatment groups were not statistically significant.

QTc prolongation as a TEAE was reported in 9 sertindole-treated patients (4.2%) and 1 risperidone-treated patient (1.0%). The difference was not statistically significant.

DISCUSSION

This is the first study to be published comparing sertindole and risperidone in patients with treatment-resistant schizophrenia. The results demonstrated that both treatments were effective in improving symptoms in this patient population, as measured by change in the PANSS total score from baseline to final assessment, although no statistically significant difference was seen between the treatment groups. The only significant difference between the treatment groups was in the percentage of patients achieving ≥ 10% and ≥ 20% improvement in modified PANSS and BPRS total scores, which was in favor of risperidone. Care should be exercised when reviewing the responder rates in this study, as they may not be directly comparable to those observed in other studies due to the range of the modified PANSS and BPRS scales used in this study, which may differ from those used in other studies (see *Method*). Findings were similar for the other study end points, with both groups showing measurable improvement in PANSS positive and negative subscale scores, BPRS total and positive subscale scores, CGI-I and CGI-S scores, and SANS total scores, with no significant difference between the 2 treatments. Failure to detect any significant difference between the 2 groups could be due to the fact that the study was underpowered relative to the target recruitment of 400 patients due to the premature termination of the study.

Despite the fact that this study was conducted in the late 1990s and that it was terminated early, the insights to be gained are still of value today, particularly with the recent reintroduction of sertindole in Europe. The design of this study allowed for titration of both agents and also for dose decreases, which ensured that patients were given optimal doses of either study drug, and the efficacy and safety/tolerability measures examined are pertinent to the clinical monitoring required in accordance with today's guidelines for the use of antipsychotics, as well as each drug's Summary of Product Characteristics. Both sertindole and risperidone have good tolerability and safety profiles. One of the few significant safety differences in this study was seen in the effect on QT interval prolongation, which has been a cause for concern with sertindole.[19] However, a large number of clinical and epidemiologic studies involving about 15,000 patients since this study was terminated have found that there is no evidence of increased cardiac or all-cause mortality as a result of sertindole treatment.[47,48] It now appears that most antipsychotics can cause dose-related prolongation of the QTc interval, but there is not a clear-cut relationship between this QTc interval prolongation and the development of ventricular tachyarrhythmia.[49] Further information on this issue will soon be available from the Sertindole Cohort Prospective (SCoP) study, a pragmatic, partially-blinded, randomized, controlled study comparing sertindole and risperidone treatment under normal conditions of use. The first primary end point in the SCoP study was all-cause mortality and the second primary endpoint was the incidence of serious cardiac adverse events. The SCoP study involved almost 10,000 patients and 15,000 years of patient exposure. Preliminary results indicated no excess mortality in the sertindole group compared to the risperidone group.[50]

Patients treated with second-generation antipsychotics have an increased risk of drug-induced weight gain, which

may vary depending on the specific antipsychotic used.[51] Weight gain is a significant issue for schizophrenia patients that can result in noncompliance and increase the risk for development of diabetes.[18] In this study, the mean weight gain from baseline was 3.1 kg in the sertindole-treated group compared with 2.5 kg in the risperidone-treated group. The proportion of patients with a clinically significant weight increase (≥ 7%) was larger in the sertindole-treated group than the risperidone-treated group, but the difference was not significant. These results are consistent with other studies suggesting that risperidone and sertindole do not cause excessive weight gain, but, in contrast to other study outcomes, the 2 treatment groups experienced similar degrees of weight gain.[52–54] This result may be attributed to the large proportions of the patients in both the sertindole group and risperidone group who were overweight at baseline. The women in particular had high BMI values at baseline.

The laboratory mean values at baseline were in keeping with what one expects to see in an overweight population. In both treatment groups, blood glucose levels were slightly above the cutoff of the International Diabetes Federation (IDF) (100 mg/dL) for constituting a risk factor contributing to metabolic syndrome[55] although this value is somewhat lower than the corresponding cutoff (110 mg/dL) suggested by US National Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATP III).[56] Mean triglyceride concentrations were also well above both the IDF and NCEP-ATP III upper limit (150 mg/dL) for constituting a risk factor contributing to metabolic syndrome. However, neither the mean triglyceride nor the total cholesterol concentrations approached clinically abnormal values according to the thresholds set out by the NCEP-ATP III (200 mg/dL and 240 mg/dL, respectively). Mean changes from baseline to week 12 or last assessment for fasting glucose, total cholesterol, and triglyceride concentrations were all relatively small and in favor of sertindole, except for the change to final assessment in triglyceride concentration, which was 21.4 mg/dL for sertindole and –0.2 mg/dL for risperidone. Both mean changes, however, were associated with large SDs.

Earlier studies have demonstrated that the incidence of EPS with sertindole is similar to placebo.[24,25,54] In this study, patients in the sertindole-treated group experienced significantly fewer treatment-related EPS, in particular EPS and joint disorder, than risperidone-treated patients. However, because of the refractory nature of this population, the dose of risperidone was higher than that which might be used in a less refractory schizophrenia population (mean = 9.0 mg/d). The occurrence of EPS is a major factor in low compliance with antipsychotic treatment,[5] and sertindole could, therefore, offer benefits over some of the other second-generation antipsychotic agents that are associated with higher levels of EPS.

Sertindole has been shown in earlier studies to be more effective than haloperidol in the relief of the negative symptoms of schizophrenia.[23] The current study, although prematurely terminated, suggests that efficacy of sertindole and risperidone against negative symptoms may be comparable in patients with treatment-resistant schizophrenia. This finding is in contrast to a more recently published study, in which superior efficacy of sertindole over risperidone was demonstrated in the treatment of moderate-to-severe schizophrenia.[20]

This study provides supporting evidence of overall comparable tolerability, with greater incidence of EPS-related TEAEs in risperidone-treated patients, and greater incidence of QT prolongation in sertindole-treated patients, both of which were also observed in the study by Azorin et al.[20] The study also provides confirmation of similar tolerability through demonstrating equal proportions of lorazepam use for the management of agitation in both treatment groups.

The management of patients who fail to respond to an initial course of an antipsychotic remains a considerable challenge. Changing antipsychotics when one treatment is ineffective or causes intolerable side effects is common. The clozapine arm of phase 2 of the CATIE study showed that clozapine was still significantly more effective than the other treatments offered.[57] In the other arm, which did not use clozapine as a treatment option, risperidone and olanzapine were more effective than quetiapine and ziprasidone.[58] In fact, risperidone is one of the compounds with the most evidence of superiority over conventional antipsychotics.[18,58–60] Therefore, the comparable efficacy of sertindole with risperidone in this context is notable.

The current study provides evidence of a role for both sertindole and risperidone in treatment-resistant patients. It remains to be ascertained whether sertindole is effective for patients who have been previously unsuccessfully treated with risperidone.

The limitations of this study include the use of modified PANSS and BPRS scales in the analysis. While these modifications do not impact on mean change in these scales (or subscales thereof), they do impact on percentage changes in scores, and caution must be exercised in comparing these data to studies that use the validated versions of the scales. Data on the tolerability of haloperidol during the 4- to 6-week screening period are not included, nor do we comment on how poor tolerability might have impacted on assessment of patients' eligibility for random assignment. This study is reported in light of the need for a range of treatment options in schizophrenia (including both moderate-to-severe and treatment-resistant schizophrenia) and in light of the reintroduction of sertindole in Europe. It is a limitation that this study was undertaken in the 1990s, reflecting the restricted choice of treatment alternatives at that time, and, therefore, the use of haloperidol and risperidone 12 mg twice a day may not be current standard clinical practice. The agents and doses used limit the translation of these results to current clinical practice, although the outcomes may be generalizable to sertindole's role in treatment-resistant populations, and they invite accumulation of comparable study data using current treatment options and regimens.

A general limitation of studies investigating treatment resistance in schizophrenia is varying definitions of the term

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treatment resistance with regard to how many antipsychotic treatments have failed, over what period of time treatment has been unsuccessful, and inclusion and exclusion criteria. This study's exclusion criteria included 'total PANSS score < 60 at screening' using the validated PANSS scale, which might be regarded as a low threshold for defining treatment resistance. The intention was to avoid being restrictive in recruitment of patients and to include subjects who may have shown an incomplete response to previous antipsychotic treatments. This is an important group for inclusion in such studies as, despite not meeting the strictest criteria for treatment resistance, incomplete treatment response may lead to treatment nonadherence.

CONCLUSION

In this study, sertindole and risperidone were both beneficial in patients with treatment-resistant schizophrenia. Both drugs have a good safety profile and are well-tolerated. Although more sertindole-treated patients experienced prolongation of the QTc interval, there were no differences between groups in the proportion of patients experiencing QT_{max} and $QTc_{max} \geq 500$ msec.

The heterogeneity of patients with schizophrenia is well known, and there is a real need for an array of antipsychotic medications, as the individual response is not predictable. Given the good EPS profile, favorable metabolic profile, and efficacy comparable to risperidone seen here, sertindole offers another valuable treatment option for refractory patients.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), itraconazole (Sporanox and others), ketoconazole (Ketozole, Nizoral, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal, InnoPran, and others), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Kane** is a consultant to or on advisory boards for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, Eisai, Eli Lilly, Lundbeck, Intracellular, Janssen, Johnson & Johnson, Merck, Myriad, Novartis, Otsuka, Pfizer, Pax, Proteus, Rules-Based Medicine, Takeda, Targacept, Vanda, Wyeth; and is a stock shareholder in MedAvante. **Dr Potkin** is a consultant, has received grant/research support and honoraria from, and participates in speaker/advisory boards for Abbott, Janssen, Bristol-Myers Squibb, Pfizer, Merck, Novartis, National Institutes of Health, Ono, Organon, Roche, Sumitomo, Wyeth, Vanda, AstraZeneca, and Otsuka. **Dr Daniel** is employed by United Biosource, which has received contracts from or sought contracts from Lundbeck within the last 12 months. **Dr Buckley** has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, National Institute of Mental Health, Pfizer, Solvay, and Wyeth; is a consultant to Abbott, Alamo, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, Merck, Roche, Solvay, and Wyeth; and has received honorarium/expenses from Abbott, Alamo, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Pfizer.

Funding/support: This research was supported by Abbott Laboratories, Abbott Park, Illinois, and H. Lundbeck A/S, Copenhagen, Denmark.

Previous presentation: Data were presented as a poster at the 20th International Congress on Schizophrenia Research; Savannah, Georgia; April 2–6, 2005.

Acknowledgment: The authors gratefully acknowledge the assistance of Jonas Eberhard, MD, in the preparation of this manuscript. Dr Eberhard is employed by H. Lundbeck A/S. He participated in the editing and writing as did all coauthors.

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