Aripiprazole for Treatment-Resistant Schizophrenia: Results of a Multicenter, Randomized, Double-Blind, Comparison Study Versus Perphenazine

John M. Kane, M.D.; Herbert Y. Meltzer, M.D.; William H. Carson, Jr., M.D.; Robert D. McQuade, Ph.D.; Ronald N. Marcus, M.D.; and Raymond Sanchez, M.D.; for the Aripiprazole Study Group

Objective: Treatment-resistant schizophrenia poses a major therapeutic challenge. This multicenter, double-blind, randomized study compared the efficacy and safety of aripiprazole and perphenazine in treatment-resistant patients with schizophrenia.

Method: Schizophrenia patients (DSM-IV diagnosis) with a history of antipsychotic resistance underwent 4 to 6 weeks of open-label treatment with olanzapine or risperidone to confirm treatment resistance. Only patients who completed this open-label period and failed to respond (< 20% improvement in Positive and Negative Syndrome Scale [PANSS] total score or a Clinical Global Impressions-Severity of Illness score ≥ 4) entered the 6-week, double-blind treatment phase. In all, 300 patients with confirmed treatment resistance were randomly assigned to aripiprazole (15–30 mg/day) or perphenazine (8–64 mg/day). The primary outcome measure was change in PANSS score from baseline. The study was conducted between August 30, 2000, and March 18, 2002.

Results: Both aripiprazole and perphenazine treatment were associated with clinically relevant improvements in PANSS total scores from baseline. After 6 weeks, 27% of aripiprazole-treated patients and 25% of perphenazine-treated patients were responders (≥ 30% decrease in PANSS total score or a Clinical Global Impressions-Improvement score of 1 or 2). Perphenazine-treated patients had a higher incidence of extrapyramidal symptom–related adverse events, mean increases (i.e., worsening) in extrapyramidal symptom rating scale scores, and a higher rate of elevated prolactin levels than aripiprazole (57.7% vs. 4.4%, $p < .001$). Improvements in quality of life considered to be clinically relevant (≥ 20% improvement in Quality of Life Scale score) occurred in 36% of the aripiprazole-treated patients and in 21% of those treated with perphenazine ($p = .052$).

Conclusions: Aripiprazole and perphenazine, at the doses used here, can improve the symptoms of schizophrenia in treatment-resistant patients who have failed to respond to olanzapine or risperidone.

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Received June 20, 2006; accepted Dec. 13, 2006. *From the Zucker Hillside Hospital and The Albert Einstein College of Medicine, Glen Oaks, N.Y. (Dr. Kane); the Division of Psychopharmacology, Psychiatric Hospital at Vanderbilt, Nashville, Tenn. (Dr. Meltzer); Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, N.J. (Drs. Carson and McQuade); Bristol-Myers Squibb Co., Wallingford, Conn. (Dr. Marcus); and Bristol-Myers Squibb Co., Paris, France (Dr. Sanchez).*

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Various analyses of these data have been presented at the 24th meeting of the Collegium Internationale Neuro-Psychopharmacologicum, June 20–24, 2004, Paris, France; 17th annual congress of the European College of Neuropsychopharmacology, October 9–13, 2004, Stockholm, Sweden; 157th annual meeting of the American Psychiatric Association, May 1–6, 2004, New York, N.Y.; 12th Biennial Winter Workshop on Schizophrenia, February 7–13, 2004, Davos, Switzerland; 16th annual congress of the European College of Neuropsychopharmacology, Sept. 20–24, 2003, Prague, Czech Republic; and 156th annual meeting of the American Psychiatric Association, May 17–22, 2003, San Francisco, Calif.

Dr. Kane is a consultant to Abbott, Bristol-Myers Squibb, Janssen, Eli Lilly, Pfizer, Wyeth, and AstraZeneca; has received honoraria from Bristol-Myers Squibb and Janssen; and is on the speakers bureaus of AstraZeneca, Abbott, Bristol-Myers Squibb, and Janssen. Dr. Meltzer is a consultant to and has received grant support from ACADIA, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Sanofi, and Solvay; has received grant support from Sepracor and Organon; has received honoraria from Janssen, Pfizer, Bristol-Myers Squibb, Eli Lilly, and AstraZeneca; and is a consultant to Alamo and Merck. Drs. Carson and McQuade are employees of Otsuka, and Dr. McQuade is a stock shareholder in and former employee of Bristol-Myers Squibb. Drs. Marcus and Sanchez are employees of Bristol-Myers Squibb, and Dr. Sanchez is a stock shareholder in Bristol-Myers Squibb.

Study investigators are listed at the end of the article.

Corresponding author and reprints: John M. Kane, M.D., Zucker Hillside Hospital and The Albert Einstein College of Medicine, 75-59 263rd St., Glen Oaks, NY 11004 (e-mail: psychiatry@lij.edu).

Managing patients with schizophrenia who fail to respond to antipsychotic treatment is a major clinical and public health care challenge. Patients with treatment-resistant schizophrenia are, by definition, highly symptomatic and have poor social function. These patients are frequent users of mental health services, on both an inpatient and an outpatient basis.[1]

As many as 30% of patients with schizophrenia derive little or no benefit from existing antipsychotic treatments and are classified as "treatment resistant."[1–3] In addition, clinical trials of antipsychotic treatments indicate that between 20% and 30% of patients who are compliant suffer a relapse in their condition during the first 1 to 2 years on

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maintenance therapy.[2] A recent naturalistic study showed that even with atypical antipsychotics, relapse occurs in up to 9% of patients within 3 to 12 months after an initial response.[4] Even when adherence with the use of long-acting medication is controlled for, a significant proportion of patients will relapse within a year.[5]

The introduction of clozapine represented a breakthrough in the management of treatment-resistant schizophrenia. Current treatment guidelines recommend that patients should be treated with clozapine monotherapy after failure to respond to trials with 2 other antipsychotics.[6,7] Clozapine provides some improvement, for a large proportion of patients with treatment-resistant schizophrenia, in positive and negative symptoms, cognitive function, excitement, and depression.[8,9] Of note, 39% of patients with treatment-resistant schizophrenia have shown improvement in positive symptoms after 4 weeks of treatment with clozapine.[10] However, clozapine treatment is associated with a number of limitations, such as seizures[11] and myocarditis,[12] and is also known to produce agranulocytosis in 0.5% to 1% of patients.[13] This leads to a requirement for regular blood monitoring, which severely limits its acceptability.[14,15]

The limitations associated with clozapine therapy have led to examination of the effects of other atypical agents in patients with treatment-resistant schizophrenia. Some studies suggest that risperidone and olanzapine may offer some improvements in symptoms in treatment-resistant patients.[16–26] More recently, Kane et al.[27] compared ziprasidone and chlorpromazine in patients with confirmed treatment resistance to open-label haloperidol (≤ 30 mg/day). Response rates (based on change in Positive and Negative Syndrome Scale [PANSS]–derived (Brief Psychiatric Rating Scale [BPRS] total score) were similar for the 2 treatment groups (≥ 30% decrease: ziprasidone, 47%; chlorpromazine, 46%). However, the findings of these studies to date are limited by the lack of controlled studies involving well-defined, prospectively confirmed, treatment-resistant populations. In addition, most of these studies only included patients who failed to respond to typical agents, despite the widespread use of atypical agents in clinical practice in the United States and their increasing use in Europe. This underlines the need to identify new antipsychotic agents that can be used in patients who are unresponsive to, or intolerant of, typical and atypical therapies.

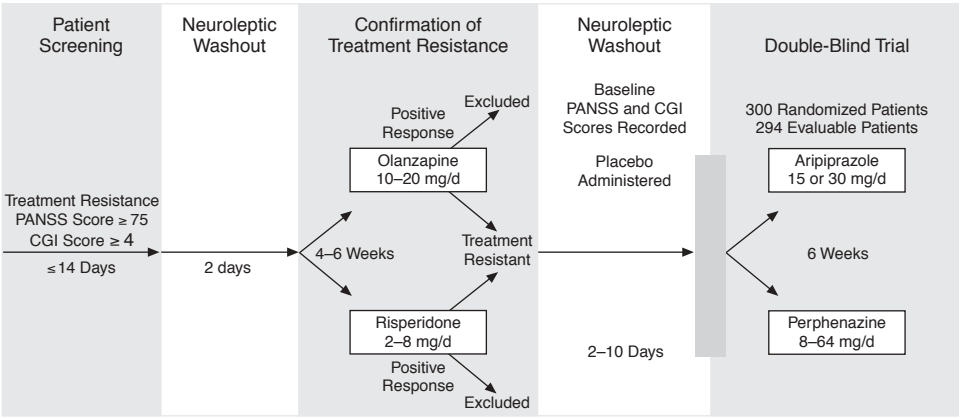
Aripiprazole is a recently introduced atypical antipsychotic agent, with a novel mechanism of action. Aripiprazole is a D_2-receptor partial agonist,[28] a 5-HT_{2A} receptor antagonist,[29] and a partial agonist at the 5-HT_{1A} receptors.[30] In clinical studies in patients with non–treatment-resistant schizophrenia, aripiprazole doses of 10 to 30 mg/day are efficacious and well tolerated.[31–33] A recent review of clinical studies showed that aripiprazole significantly decreased relapse over both the short term and medium term compared with placebo, and produced better compliance with the study protocol.[34]

This double-blind, multicenter study was designed to examine the efficacy, safety, and tolerability of aripiprazole versus perphenazine in a well-defined population of patients with treatment-resistant schizophrenia. Although there is no universally accepted definition of treatment-resistant schizophrenia, it is commonly defined as the failure to respond to trials of 2 different antipsychotic agents, given in sufficiently high doses, with a 3- to 6-week treatment period usually being considered adequate to assess response.[3,6,35] In this study, this history-based definition of treatment resistance was used for the enrollment of patients. To increase the validity of the study, the treatment resistance was further confirmed by treatment with olanzapine or risperidone, and only those patients who failed to respond in this phase continued the study and were eligible to be randomly assigned to aripiprazole or to the conventional antipsychotic perphenazine. Perphenazine was chosen as the active comparator as it is a typical antipsychotic that is relatively well tolerated and is not widely used, minimizing the probability that the patients enrolled in the study would have been exposed to it previously. After completion of this study, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study results were reported, showing comparable efficacy of perphenazine to risperidone, quetiapine, and ziprasidone, but lower than that of olanzapine.[36] However, it is unclear what proportion of the patients were treatment resistant, and concerns have been raised regarding the dose equivalence used in the trial.

METHOD

This randomized, double-blind study was conducted at 59 centers throughout the United States and Canada between August 30, 2000, and March 18, 2002. Patients > 18 years of age who had schizophrenia (DSM-IV criteria) and were classified as being treatment resistant were eligible to participate in the study. Treatment resistance was defined as failure to experience satisfactory symptom relief despite at least 2 periods of treatment (each lasting at least 6 weeks) with adequate doses of antipsychotic agents (one of which had to be a typical antipsychotic) during the 2 years prior to the study. In addition, patients should not have experienced satisfactory symptom relief with their most recent course of antipsychotic therapy. Patients also had to meet the following disease severity criteria: a PANSS[37] total score ≥ 75 and a score of ≥ 4 on at least 2 of the items of conceptual disorganization, suspiciousness, hallucinatory behavior, or delusions and a Clinical Global Impressions-Severity of Illness (CGI-S)[38] score ≥ 4. Patients had to have been treated as an outpatient for at least 1 continuous 3-month period during the 2 years prior to study entry. All patients gave written

Figure 1. Flow of Patients Through the Study Phases



Abbreviations: CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale.

informed consent to participate, and institutional review board approval was obtained for the study.

Patients who met any of the following criteria were excluded from the study: a DSM-IV diagnosis of schizoaffective disorder, residual schizophrenia, or bipolar disorder; clinical presentation or history consistent with delirium, dementia, amnesic or other cognitive disorders; refractory response to prior clozapine treatment administered at therapeutic doses for 6 weeks; previous unsatisfactory response to perphenazine; likelihood to require prohibited concomitant therapy during the study; current or recent psychoactive drug or alcohol abuse or dependence; a history of suicidal attempts or serious suicidal thoughts; known allergy or hypersensitivity to study drugs; treatment with an investigational drug within 4 weeks of the washout phase; previous enrollment in an aripiprazole clinical study. Patients were also excluded if they had any other acute or unstable medical condition or were pregnant or lactating.

All enrolled patients were subjected to a 2- to 14-day screening period, including a minimum 2-day neuroleptic washout period, to assess their eligibility for entry into the study. Patients meeting the inclusion and exclusion criteria listed above entered an open-label treatment period with risperidone or olanzapine to confirm their resistance to neuroleptic treatment (Figure 1). Patients received either risperidone 2 to 8 mg/day (for those with a history of recent failure with olanzapine) or olanzapine 10 to 20 mg/day (all others) for 4 to 6 weeks. Patients started treatment at the lowest medication dose: in the olanzapine group, dose adjustments to 15 or 20 mg/day could be made at 1-week intervals, whereas in the risperidone group, 2-mg/day increases in dose could be made every 1 to 2 days. PANSS and CGI ratings were evaluated every 2 weeks during this period. Patients who showed significant improvement (defined as a reduction in PANSS total score of ≥ 20% and a CGI-S score of 1–3) at any time were discontinued from the study. Enrolled patients and/or their representatives were made aware prior to the study that they would not be eligible to enter the double-blind treatment phase if they responded during open-label therapy. These patients were followed for 1 additional visit to ensure continuation of appropriate treatment.

At week 6, patients who showed no significant improvement, and had received at least 15 mg/day olanzapine or 6 mg/day risperidone for a minimum of 3 weeks, were considered to be treatment resistant and entered a single-blind, placebo washout period lasting for 2 to 10 days. Those patients who continued to meet the eligibility criteria at the end of this period were randomly assigned to double-blind treatment with aripiprazole (15–30 mg/day) or perphenazine (8–64 mg/day) for 6 weeks (Figure 1).

Patients on aripiprazole started at 15 mg/day, and dose adjustments could be made to 30 mg/day at the end of week 1. Perphenazine was started at 8 mg/day and could be increased to 16 mg/day on day 4, if needed. At the end of week 1, additional increases in perphenazine dose (in 8-mg/day increments) could be made at 4- to 7-day intervals up to 64 mg/day. Perphenazine doses greater than 8 mg/day were administered twice daily. Incremental dose reductions were also permitted during the study, provided that patients remained within the permitted dose range (perphenazine, 8–64 mg/day; aripiprazole, 15–30 mg/day).

Efficacy and Safety Evaluations During Double-Blind Treatment

Rating scales for the assessment of efficacy included PANSS and CGI measures. The primary outcome measure was the mean change in PANSS total score from baseline (i.e., the end of the placebo washout) to the end of the

study (week 6 of double-blind treatment). Secondary efficacy measures included mean changes in scores from baseline to study endpoint for PANSS-derived Brief Psychiatric Rating Scale (BPRS)[39] core score and CGI-S score, mean CGI-Improvement (CGI-I) score at week 6, and the percentage of patients who responded to treatment (defined as a ≥ 30% decrease in the PANSS total score or a CGI-I score of 1 or 2). Quality of life (QoL) was evaluated using the Quality of Life Scale (QLS), a 21-item, clinician-administered interview.[40] A clinically important improvement in QoL was defined as a ≥ 20% improvement in QLS total score from baseline.[41]

Safety and tolerability assessments included a review of adverse event reports (including intercurrent illness), vital sign measurement, electrocardiogram (ECG), body weight, concomitant medication use, and the results of physical examinations and laboratory tests. Extrapyramidal symptoms were assessed using the Simpson-Angus Scale (SAS),[42] the Abnormal Involuntary Movement Scale (AIMS),[43] and the Barnes Akathisia Rating Scale (BAS) (global clinical assessment item).[44]

Concomitant Medication

The concomitant use of neuroleptic agents (other than those specified in the protocol), antidepressants, mood stabilizers (e.g., lithium, valproate), propranolol and other β-adrenergic blocking agents (for the treatment of akathisia), and diphenhydramine and other antihistamines (for the treatment of agitation, anxiety, and insomnia) was prohibited during all 4 phases of the study. Concomitant benzodiazepine use was prohibited, except for lorazepam (up to 4 mg/day) for anxiety or insomnia. Anticholinergic medications for extrapyramidal symptoms (EPS) were permitted up to a maximum dose, equivalent to 6 mg/day of benztropine, except during the placebo washout phase.

Statistical Methods

The planned sample size of 250 evaluable patients was intended to yield 90% power to detect a difference of 9.5 between the 2 treatments, assessed as the mean change in PANSS total score from baseline to week 6 (assuming a standard deviation of 23).

Statistical analyses were only performed on efficacy and safety data from the double-blind treatment period. The safety sample included all randomized patients who took at least 1 dose of study medication. The efficacy sample included all patients in the safety sample with at least 1 postrandomization efficacy evaluation. The primary analysis was of last observation carried forward (LOCF) data, with observed case (OC) analyses performed to corroborate these data.

Continuous efficacy data were evaluated using analysis of covariance. Statistical models included the score at randomization as the covariant and study center and treatment as main effects. For each measure, 95% confidence intervals were calculated for the treatment difference between the perphenazine and aripiprazole groups at week 6. Categorical efficacy data (CGI-I score, response rate, and discontinuation rate) were evaluated using the Cochran-Mantel-Haenszel procedure. In addition, a 95% confidence interval was calculated for the ratio of response rates between the perphenazine and aripiprazole groups at week 6.

Adverse events, abnormal vital signs, and potentially clinically relevant ECG and laboratory test results were listed. Changes from baseline were calculated for selected vital signs, ECG, laboratory parameters, and the 3 EPS assessment scales. In addition, analysis of covariance was used to analyze changes from randomization at each scheduled visit in SAS total score, AIMS total score, BAS global clinical assessment item, serum prolactin levels, and body weight.

RESULTS

Disposition of Patients Through the Study Phases

In all, 512 patients underwent screening, and, of these, 416 entered the open-label treatment phase with olanzapine or risperidone to confirm nonresponse to antipsychotic medication (Figure 1). Only patients who completed this period and failed to respond to treatment were allowed to proceed with the study.

Overall, 334 patients (80%) completed this 6-week treatment period. Only 9 patients (2%) were discontinued from the study for showing a response to treatment (olanzapine, N = 4; risperidone, N = 5). The other reasons for discontinuation were adverse event (N = 23; 6%), patient withdrew consent (N = 20; 5%), lost to follow-up (N = 11; 3%), lack of efficacy (N = 10; 2%), patient unreliability (N = 4; 1%), and other known cause (N = 5; 1%).

A total of 300 patients entered the double-blind, aripiprazole versus perphenazine treatment phase. The baseline demographic characteristics of these patients are shown in Table 1. Three patients (aripiprazole, N = 1; perphenazine, N = 2) did not receive study medication and were excluded from the safety analysis. A further 3 patients (all aripiprazole) were excluded from the efficacy analysis because they lacked a postrandomization efficacy rating. The QLS analysis included 207 patients (aripiprazole, N = 104; perphenazine, N = 103); the other patients were excluded due to a lack of baseline or postrandomization data.

In all, 225 patients (75%) completed the 6 weeks of therapy—110 in the aripiprazole group and 115 in the perphenazine group. Among the 75 patients who discontinued treatment prematurely, adverse events were the most common reason for discontinuation (N = 33; Table 2). There were no significant differences between treatments in terms of the rate of discontinuations (p = .86). At the end

Table 1. Baseline Demographic Characteristics of Patients Randomly Assigned to the Double-Blind Treatment Phase

Characteristic	Aripiprazole (N = 154)	Perphenazine (N = 146)	Total (N = 300)
Gender, N (%)			
Male	114 (74)	94 (64)	208 (69)
Female	40 (26)	52 (36)	92 (31)
Ethnicity, N (%)			
White	76 (49)	75 (51)	151 (50)
Black	33 (21)	38 (26)	71 (24)
Asian/Pacific Islander	5 (3)	3 (2)	8 (3)
Hispanic/Latino	33 (21)	23 (16)	56 (19)
Other	7 (5)	7 (5)	14 (5)
Age, mean (SE), y	42.6 (1.0)	41.6 (0.9)	42.1 (0.7)
Weight, mean (SE), kg	83.7 (1.9)[a]	84.9 (1.6)	84.3 (1.2)
Schizophrenia type, N (%)			
Paranoid	108 (70)	107 (73)	215 (72)
Disorganized	4 (3)	10 (7)	14 (5)
Undifferentiated	42 (27)	29 (20)	71 (24)
Age at time of first hospitalization, mean (SE), y[b]	22.6 (0.5)	22.9 (0.7)	22.8 (0.4)

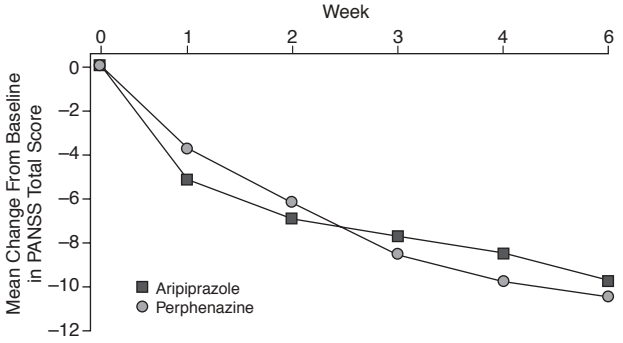
[a]N = 152.
[b]Aripiprazole, N = 145; perphenazine, N = 138; total, N = 283.

Table 2. Patient Disposition During the 6-Week Double-Blind Treatment Phase, N (%)

Disposition	Aripiprazole (N = 154)	Perphenazine (N = 146)	Total (N = 300)
Completed	110 (71)	115 (79)	225 (75)
Discontinued			
Adverse event	22 (14)	11 (8)	33 (11)
Lack of efficacy	10 (6)	8 (5)	18 (6)
Patient withdrew consent	3 (2)	8 (5)	11 (4)
Other known cause[a]	9 (6)	4 (3)	13 (4)

[a]Includes patient unreliability (N = 6), lost to follow-up (N = 5), positive drug screen (N = 1), and discontinued per family's request (N = 1).

Figure 2. Change From Baseline to Week 6 in PANSS Total Score (LOCF)



Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Table 3. Efficacy Results at Endpoint (LOCF)

	Aripiprazole (N = 150)		Perphenazine (N = 144)	
Measure	Mean	95% CI	Mean	95% CI
PANSS total score				
Baseline	97.5	95.0, 100.0	99.5	97.0, 102.1
Change at week 6	–9.8	–13.2, –6.3	–10.5	–14.0, –7.0
PANSS-derived BPRS core score				
Baseline	17.2	16.7, 17.7	17.6	17.0, 18.1
Change at week 6	–2.0	–2.7, –1.3	–2.0	–2.7, –1.3
CGI-S score				
Baseline	5.0	4.9, 5.2	5.0	4.8, 5.1
Change at week 6	–0.3	–0.5, –0.2	–0.3	–0.5, –0.1
CGI-I score				
Score at week 6	3.7	3.4, 3.9	3.5	3.3, 3.7

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

of the study, the majority of aripiprazole-treated patients were receiving aripiprazole 30 mg/day (92.8%) (mean dose, 28.8 mg/day). The mean dose of perphenazine at the end of treatment was 39.1 mg/day, with 19.1% of the patients receiving the maximum dose (64 mg/day) at endpoint.

Efficacy Evaluations

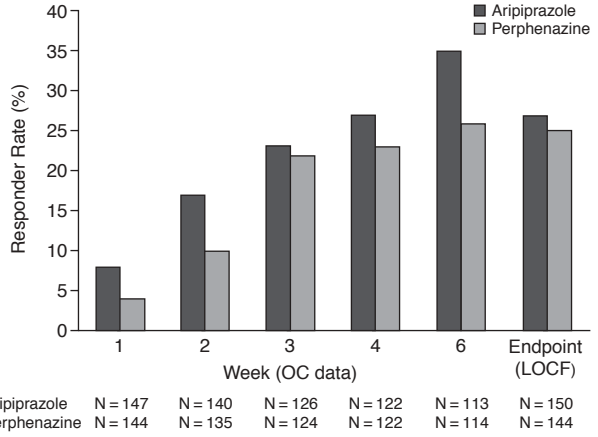
Treatment with either aripiprazole or perphenazine was associated with clinically relevant improvements in PANSS total score from baseline to week 6 (Figure 2). Patients receiving aripiprazole therapy showed a mean decrease in PANSS total score from baseline of 9.8, whereas those receiving perphenazine showed a mean decrease of 10.5 (Table 3). The difference between the 2 groups was not statistically significant.

The mean decreases in PANSS total scores seen with aripiprazole and perphenazine treatment were similar whether patients had received olanzapine or risperidone during the open-label treatment phase. During open-label treatment, mean PANSS total scores increased from baseline (i.e., end of screening) values in both the risperidone and olanzapine treatment groups (+3.5 and +3.2, respectively, for patients randomly assigned to double-blind treatment).

Aripiprazole and perphenazine treatments were each associated with improvements in other efficacy measures, although the differences between the 2 treatments were not statistically significant (Table 3). PANSS-derived BPRS core showed decreases in mean score from baseline to endpoint (LOCF and OC analyses) with both aripiprazole and perphenazine treatment. Mean CGI-S scores also decreased in both treatment groups, and the beneficial effect of the treatments was reflected in CGI-I scores. After 6 weeks of aripiprazole therapy, the mean CGI-I score was 3.7, and in the perphenazine treatment group it was 3.5.

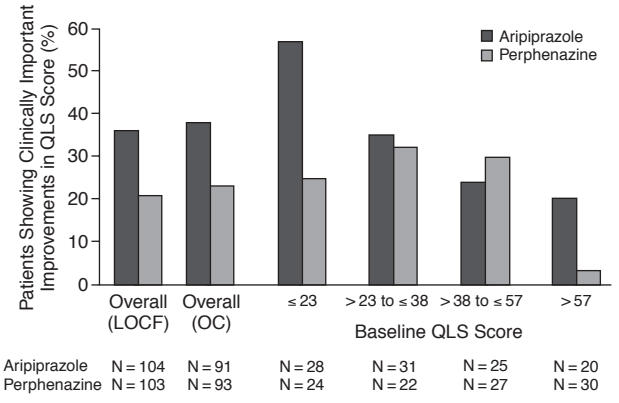
Overall, 27% (N = 40) of aripiprazole-treated patients and 25% (N = 36) of perphenazine-treated patients were

Figure 3. Percentage of Treatment Responders Through the Study (OC) and at Endpoint (LOCF)



Abbreviations: LOCF = last observation carried forward, OC = observed cases.

Figure 4. Proportion of Patients Showing ≥ 20% Improvement in Quality of Life Scale (QLS) Score From Baseline



Abbreviations: LOCF = last observation carried forward, OC = observed cases.

classified as treatment responders, according to CGI or PANSS measures after 6 weeks (LOCF analysis; Figure 3). As data collected over the 6-week treatment period show, there was a cumulative rise in the number of patients responsive to treatment with time. OC analysis at week 6 showed responder rates of 35% for aripiprazole and 26% for perphenazine (Figure 3).

Quality of Life Assessment

The mean changes in QLS score from baseline were similar in the aripiprazole (1.7) and perphenazine (2.6) groups, with no between-group statistical significance. The proportion of patients experiencing a clinically important improvement in QLS (≥ 20% increase in QLS score from baseline) was higher in the aripiprazole group (36%) than in the perphenazine group (21%; LOCF data): this difference approached statistical significance ($p = .052$). The difference between the groups reached statistical significance for the OC dataset (aripiprazole, 38%; perphenazine, 23%; $p < .05$).

When patients were stratified according to baseline QLS scores, there were more than twice as many responders with aripiprazole treatment (57%) compared with perphenazine (25%) among patients with poor QoL at baseline (QLS score ≤ 23) (Figure 4).

Table 4. Incidence of Treatment-Emergent Adverse Events (≥ 5% of patients in either treatment group) During the Double-Blind Comparison of Perphenazine and Aripiprazole, N (%)

Adverse Event	Aripiprazole (N = 153)	Perphenazine (N = 144)
Insomnia	37 (24.2)	30 (20.8)
Agitation	25 (16.3)	24 (16.7)
Headache	25 (16.3)	13 (9.0)
Psychosis	18 (11.8)	14 (9.7)
Anxiety	16 (10.5)	18 (12.5)
Dyspepsia	16 (10.5)	9 (6.3)
Creatine phosphokinase increased	9 (5.9)	4 (2.8)
Akathisia	6 (3.9)	13 (9.0)
Extrapyramidal syndrome	5 (3.3)	9 (6.3)
Somnolence	4 (2.6)	10 (6.9)
Lightheadedness	2 (1.3)	10 (6.9)
Accidental injury	2 (1.3)	9 (6.3)

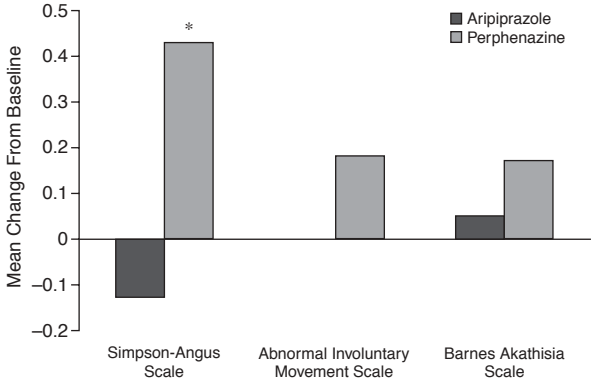
Safety Results

The majority of adverse events were mild to moderate in intensity. The most frequently reported adverse events were insomnia, agitation, and anxiety in the perphenazine group and insomnia, agitation, and headache in the aripiprazole group. Table 4 shows treatment-emergent adverse events that occurred in at least 5% of patients during double-blind treatment.

A total of 56 patients (19%) experienced at least 1 serious adverse event during the 6-week double-blind treatment phase (aripiprazole, N = 32 [21%]; perphenazine, N = 24 [17%]). The most commonly reported serious adverse event was psychosis (aripiprazole, N = 15 [9.8%]; perphenazine, N = 9 [6.3%]). This finding is not unexpected in a treatment-resistant study population such as this. There were no deaths during any phase of this study.

Extrapyramidal symptoms. The incidence of EPS-related adverse events was higher among perphenazine-treated patients (19.4%; N = 28) than among those receiving aripiprazole (13.7%; N = 21). Akathisia and extrapyramidal syndrome each occurred in more than 5% of patients receiving perphenazine (9.0% and 6.3%, respectively), whereas the corresponding values for the aripiprazole group were lower (akathisia 3.9%, extrapyramidal syndrome 3.3%). In addition, more patients received concomitant medication for EPS in the perphena-

Figure 5. Change From Baseline to Week 6 in Scores on Extrapyramidal Symptom Rating Scales (LOCF)



*p = .04 aripiprazole vs. perphenazine.
Abbreviation: LOCF = last observation carried forward.

zine group (N = 40, 27.8%) than in the aripiprazole group (N = 27, 17.6%).

Over the 6-week treatment period, SAS scores showed a mean improvement from baseline in the aripiprazole group, but worsened in the perphenazine group (Figure 5). The mean change from baseline to endpoint during double-blind treatment differed significantly between the aripiprazole and perphenazine groups (p = .04). Changes in AIMS and BAS scores were not significantly different between the treatment groups (Figure 5).

Prolactin. Mean prolactin levels were elevated in both groups at baseline (aripiprazole, 33.4 ng/mL; perphenazine, 35.8 ng/mL). Mean prolactin levels decreased during treatment with aripiprazole (–28.2 ng/mL), but showed almost no change with perphenazine (–0.3 ng/mL); this difference was statistically significant (p < .001). In all, 57.7% of patients (79/137) receiving perphenazine showed potentially clinically significant high levels (i.e., above the upper limit of normal) compared with 4.4% of patients (6/135) receiving aripiprazole (p < .001).

Electrocardiogram. Differences were also noted between treatment groups with respect to ECG safety data. There was only 1 reported clinically significant ECG abnormality (first-degree atrioventricular block) in the aripiprazole group compared with 15 clinically significant abnormalities in the perphenazine group. None of the patients treated with aripiprazole or perphenazine had a clinically significant prolonged QTc interval (≥ 450 msec and ≥ 10% increase from baseline) evaluated using the FDA Neuropharmacology Division correction formula ($QT/RR^{0.37}$).

Body weight. There was no significant difference between treatments in terms of weight change during treatment. Patients in both the perphenazine group and the aripiprazole group showed a mean decrease in body weight (–1.52 kg and –2.19 kg, respectively). Less than 2% of the total patient group experienced a potentially significant increase in body weight (≥ 7% from baseline) over the 6-week double-blind phase of the study.

Vital signs and laboratory parameters. The review of vital signs revealed no significant safety issues for either aripiprazole or perphenazine. The incidence of potentially clinically significant laboratory abnormalities during the study was low (except for prolactin elevation, discussed above), with most abnormalities seen in only 1 or 2 patients. The most frequently reported finding was an abnormal total creatinine phosphokinase value (perphenazine, N = 7; aripiprazole, N = 12). Two patients receiving perphenazine treatment discontinued due to vital sign abnormalities (syncope; bradycardia), and 2 patients in the aripiprazole group discontinued due to elevated creatinine phosphokinase levels.

DISCUSSION

A significant proportion of patients with schizophrenia have a history of resistance to antipsychotic agents, leading to poorer functional outcome and more expensive health care costs. The results of this study show that aripiprazole and perphenazine, at appropriate doses, can bring significant improvement in the signs and symptoms of schizophrenia in some such patients.

This study enrolled a well-defined population of patients with prospectively confirmed, treatment-resistant schizophrenia. The patients included in this study had a history of resistance to antipsychotic treatment and then underwent 4 to 6 weeks of prospective, open-label treatment with either olanzapine or risperidone therapy to confirm antipsychotic resistance. Patients who entered double-blind therapy had, therefore, failed to respond to previous trials with at least 2 different antipsychotic agents and had confirmed resistance to at least 1 atypical (olanzapine or risperidone) antipsychotic treatment. In addition, patients in this study could receive anticholinergic agents, allowing optimization of perphenazine treatment to give this treatment group the best chance for success.

However, as with any study, there are limitations to this analysis. This was a short-term study. Effects on negative symptoms and QoL take time to develop, and the treatment duration may have been insufficient to adequately evaluate these parameters. However, over the 6-week treatment period, both the atypical antipsychotic, aripiprazole, and the phenothiazine agent, perphenazine, were found to be effective in reducing the positive symptoms of schizophrenia in these treatment-resistant patients. Positive and Negative Syndrome Scale and CGI-S efficacy measures showed mean improvements from baseline with both aripiprazole and perphenazine treatments; no statistically significant differences were

detected between the 2 groups. A similar number of patients in the 2 treatment groups met the a priori criteria for treatment response. At the end of treatment, 27% of patients receiving aripiprazole and 25% of those receiving perphenazine responded to treatment. Among patients who completed the 6-week study, the response rates were 35% with aripiprazole and 26% with perphenazine. The absence of a placebo treatment group or a subtherapeutic dose of aripiprazole or perphenazine raises the question of whether the response to both drugs in this study was a true drug effect. However, the design of this study, whereby patients had failed to respond to prior treatment with risperidone or olanzapine, suggests that the observed improvements do represent an efficacy response to aripiprazole and perphenazine. It is noteworthy that the mean dose of aripiprazole utilized in this study, 28.8 mg/day, is at the higher end of the dose range (10–30 mg/day) that has been shown to provide efficacy in non–treatment-resistant patients with schizophrenia.[31–33]

Although these results show that only around one quarter of treatment-resistant patients responded to aripiprazole therapy, these findings should be considered in the context of the patient population included in the study—i.e., those with confirmed resistance to olanzapine or risperidone. In the open-label treatment phase used to confirm treatment resistance, only 2% of olanzapine-treated patients and 3% of risperidone-treated patients were discontinued due to prespecified response criteria. The low response rate to these atypical agents in the open-label phase is of note and is comparable to the response rates observed in previous studies that included patients who failed to respond to typical agents.[1,2] However, this observation is not wholly unexpected given that the open-label phase was designed to confirm treatment resistance and that patients in this phase may have been treated previously with, and shown resistance to, atypical antipsychotics including risperidone and olanzapine (but not aripiprazole or the typical agent, perphenazine).

In a landmark study with clozapine, patients with a history of treatment resistance underwent single-blind haloperidol therapy for 6 weeks to confirm treatment resistance, and those who failed to respond to haloperidol were randomly assigned to double-blind treatment with clozapine or chlorpromazine.[2] Overall, 30% of clozapine-treated patients were classified as responders (> 20% reduction in BPRS score plus a final BPRS score ≤ 35, or final CGI score ≤ 3) compared with 4% of chlorpromazine-treated patients. In a comparison study of olanzapine and chlorpromazine therapy, which also included a 6-week haloperidol treatment period to confirm resistance, 7% of olanzapine-treated patients and no chlorpromazine-treated patients met the response criteria (≥ 20% improvement from baseline in BPRS total score and a posttreatment CGI score ≤ 3 or a posttreatment BPRS score ≤ 35).[1] In a small comparison study that used a 2-week fluphenazine treatment period to confirm poor treatment response, clozapine produced greater improvements in some efficacy measures than risperidone.[23]

A recent small study in patients with confirmed treatment-resistant schizophrenia compared the efficacy of risperidone, quetiapine, and the typical agent fluphenazine.[25] Patients who had previously failed to respond to at least 2 different antipsychotics underwent 4 to 6 weeks of treatment with olanzapine or a typical antipsychotic (other than fluphenazine) to confirm treatment resistance, before randomization to study medication for 12 weeks. Response rates (≥ 20% decrease in BPRS score) were 23% for risperidone, 25% for quetiapine, and 15% for fluphenazine and were, therefore, similar to those reported here for aripiprazole. However, the majority of the randomized patients received typical agents (N = 33) rather than olanzapine (N = 7) during the initial study period to confirm treatment resistance.

Other studies assessing the efficacy of olanzapine and risperidone in patients with treatment-resistant schizophrenia have also reported improved treatment response rates in some cases.[16,19–23] More recently, Kane et al.[27] used a 6-week period of open-label haloperidol (≤ 30 mg/day) treatment to confirm resistance in a comparison study of ziprasidone and chlorpromazine. Response rates (based on change in PANSS-derived BPRS total score) were similar for the 2 treatment groups (≥ 30% decrease: ziprasidone, 47%; chlorpromazine, 45%). However, interpretation of the results of these studies is limited by the fact that treatment resistance was not well defined and studies use differing definitions of response. In some studies, enrollment criteria include patients who are intolerant of, rather than nonresponsive to, antipsychotic therapies and so include patients who could not be described as refractory to treatment.[16,17,19,20,22] In addition, few studies include an initial antipsychotic treatment period to confirm that patients entering the comparison phase of the study are treatment resistant.

A further consideration is the fact that the majority of trials in treatment-resistant schizophrenia only include patients who failed to respond to typical agents, even though the use of atypical antipsychotics is widespread in the United States and increasing in Europe. This may limit the applicability of findings from these studies to clinical practice. To date, clozapine has been shown to be effective in treating patients who have failed to respond to olanzapine therapy,[18] whereas a small open-label study suggests that olanzapine is effective in risperidone-resistant patients.[19] Olanzapine has also shown modest response rates (> 20% reduction in BPRS score [extracted from the PANSS] plus a final BPRS score ≤ 35, or final CGI score ≤ 3) (16.7%) in an open-label study involving patients resistant to typical antipsychotics and either risperidone or clozapine therapy.[26] Results from the current study suggest that aripiprazole may provide an alternative

treatment option for patients who are resistant to other atypical agents.

The similar response rates observed with aripiprazole and perphenazine treatment raise interesting questions for the management of patients with treatment-resistant schizophrenia. As atypical antipsychotic therapy becomes widespread, replacing typical agents as first-line treatments for schizophrenia, the proportion of patients who have failed to respond to recent trials of atypical agents will continue to grow. Increasingly, therefore, effective treatments will be required for patients who are nonresponsive to atypical therapies. Results from the current study suggest that at least some typical agents may provide an effective alternative for some of these patients. The fact that in this study, responses were seen with both a typical agent and a novel atypical agent raises the possibility that, for some treatment-resistant patients at least, a typical neuroleptic such as perphenazine, at an adequate dose, may produce a response, albeit with a greater risk of tardive dyskinesia. Perphenazine has recently been compared with atypical antipsychotics for the long-term treatment of schizophrenia in the CATIE study.[36] In this trial, perphenazine was associated with similar time to discontinuation for all reasons as the atypical agents. However, in the CATIE trial, perphenazine was associated with the second-highest rate of discontinuation due to adverse events (after olanzapine).[36] The dose of perphenazine used in this study was twice that of the CATIE study, reflecting the treatment-resistant nature of this population—a higher dose would be expected to produce more adverse events, which could subsequently impact on patient QoL.

Although aripiprazole and perphenazine showed similar response rates and improvements in efficacy measures in this study, the improved tolerability of aripiprazole therapy over perphenazine suggests that it has some advantages for this patient population. Tolerability issues with an antipsychotic medication may lead to treatment discontinuation.[45] In this study, perphenazine treatment was associated with more EPS-related adverse events than aripiprazole, and EPS rating scales scores worsened from baseline with perphenazine treatment. In addition, more patients in the perphenazine group received concomitant anticholinergic medication than in the aripiprazole group. Extrapyramidal symptoms are known to be associated with reduced compliance with antipsychotic therapy, whereas the development of EPS during antipsychotic therapy is a predictor of reduced likelihood of response to treatment.[46,47] Perphenazine treatment was also associated with a significantly higher incidence of hyperprolactinemia over the 6-week study than aripiprazole treatment (57.7% vs. 4.4%). Mean prolactin levels also remained elevated with perphenazine treatment, but decreased to within normal limits with aripiprazole. Hyperprolactinemia may be associated with sexual dysfunction, with symptoms including gynecomastia, amenorrhea, and galactorrhea,[48] all of which may adversely affect treatment compliance during long-term maintenance therapy. The low liability for EPS and lack of prolactin elevation observed with aripiprazole is consistent with reports from previous short- and long-term aripiprazole clinical trials.[31,32,49–51]

Aripiprazole and perphenazine had comparable and small positive effects on QoL, with similar mean improvements from baseline in QLS scores with both treatments. Almost twice the proportion of patients in the aripiprazole group showed clinically important improvement from baseline in QLS score than with perphenazine treatment (36% vs. 21%); however, this difference approached, but did not reach a statistically significant difference ($p = .052$). Among patients who completed the 6-week treatment period, the difference between the groups did reach statistical significance (38% vs. 23%; $p < .05$). The difference between the treatment groups with this outcome measure was particularly pronounced among patients with worse baseline QLS scores. Given that perphenazine and aripiprazole appear comparable with respect to efficacy, the observed difference between the 2 treatment groups might be attributed to the superior safety and tolerability profile of aripiprazole compared with perphenazine at the doses used in this study. As acknowledged above, use of high doses of perphenazine is likely to increase the risk of EPS-related adverse events compared with lower doses, which could in turn have an impact on patient QoL. It is possible that use of a lower perphenazine dose may have resulted in better QLS score improvements, but could also have resulted in reduced efficacy.

In conclusion, this study has shown that aripiprazole may be of some benefit for patients with treatment-resistant schizophrenia in whom trials of other atypical antipsychotic drugs have failed. Aripiprazole improved the signs and symptoms of schizophrenia in a group of patients who did not respond when treated with the atypical antipsychotic agents risperidone or olanzapine. Although the response rates and improvements in efficacy scores were similar in the aripiprazole and perphenazine treatment groups, the improved safety and tolerability profile, and the improvement in QoL measures seen with aripiprazole therapy, suggest that aripiprazole offers a more attractive option for the management of treatment-resistant patients.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (FazaClo and others), diphenhydramine (Benadryl and others), fluphenazine (Prolixin and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderide and others), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), ziprasidone (Geodon).

Aripiprazole Study Group: W. Abi-Saab (New Haven, Conn.), Adityanjee (Cleveland, Ohio), A. Aleem (Atlanta, Ga.), E. Allan

(Montrose, N.Y.), M. Bari (Chula Vista, Calif.), L. Beckett (Oklahoma City, Okla.), I. Berman (Taunton, Mass.), J. R. Bona (Atlanta, Ga.), J. G. Booker (Shreveport, La.), R. M. Bunt (Atlanta, Ga.), C. Cargile (North Little Rock, Ark.), O. Caro (Cidra, P.R.), F. Centorrino (Belmont, Mass.), J. C. Y. Chou (New York, N.Y.), H. Colohan (Claresholm, Canada), J. E. Cueva (New York, N.Y.), D. G. Daniel (Falls Church, Va.), K. Degen (Middletown, Conn.), R. Douyon (Miami, Fla.), D. D'Souza (New Haven, Conn.), A. Fallu (Sherbrooke, Canada), S. Flynn (Port Coquitlam, Canada), D. L. Garver (Louisville, Ky.), I. D. Glick (Stanford, Calif.), J. W. Goethe (Hartford, Conn.), R. Gopalan (Falls Church, Va.), M. I. Herz (Rochester, N.Y.), R. L. Horne (Las Vegas, Nev.), N. Iqbal (New York, N.Y.), R. Jaffe (Philadelphia, Pa.), P. G. Janicak (Chicago, Ill.), R. Josiassen (Norristown, Pa.), J. Klopper (Smyrna, Ga.), A. Kopelowicz (Mission Hills, Calif.), A. Labelle (Ottawa, Canada), R. Landbloom (St. Paul, Minn.), J. Lauriello (Albuquerque, N.M.), M. Levy (Staten Island, N.Y.), K.-M. Lin (Torrance, Calif.), J.-P. Lindenmayer (New York, N.Y.), R. E. Litman (Rockville, Md.), A. F. Lowry (Washington, D.C.), H. Meltzer (Nashville, Tenn.), M. Miller (Indianapolis, Ind.), R. McCurley (Toronto, Canada), J. P. McEvoy (Butner, N.C.), T. A. Pigott (Washington, D.C.), M. G. Plopper (San Diego, Calif.), S. G. Potkin (Orange, Calif.), D. A. Sack (Cerritos, Calif.), Z. Sharif (New York, N.Y.), S. D. Shillcutt (Macon, Ga.), R. Shiwach (Terrell, Tex.), G. M. Simpson (Los Angeles, Calif.), J. J. Spollen III (North Little Rock, Ark.), R. G. Stern (New Brunswick, N.J.), E. Stip (Montreal, Canada), M. R. Thomas (Denver, Colo.), M. Tremblay (Montreal, Canada), P. Tucker (Oklahoma City, Okla.), T. K. Tran-Johnson (San Diego, Calif.), P. J. Weiden (New York, N.Y.), M. Woodbury (San Juan, P.R.).

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