Aripiprazole Augmentation in Clozapine-Treated Patients With Refractory Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial

Jae Seung Chang, M.D., Ph.D.; Yong Min Ahn, M.D., Ph.D.; Hye Jean Park, M.D.; Kyu Young Lee, M.D., Ph.D.; Se Hyun Kim, M.D.; Ung Gu Kang, M.D., Ph.D.; and Yong Sik Kim, M.D., Ph.D.

Objective: Inadequate response to clozapine poses a substantial problem in the pharmacotherapy of refractory schizophrenia. This randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia.

Method: Patients with DSM-IV schizophrenia who had a history of treatment failure or partial response to long-term clozapine treatment were recruited. A total of 62 patients with either a baseline Brief Psychiatric Rating Scale (BPRS) score of at least 35 or more than 2 Schedule for Assessment of Negative Symptoms (SANS) global rating item scores of at least 3 were randomly assigned to double-blind augmentation treatment with either aripiprazole (5–30 mg/day) or placebo over 8 weeks. The primary outcome measure was change in BPRS total score from baseline. The study was conducted between December 1, 2005, and December 10, 2006.

Results: There was no significant difference in the primary outcome measure between the 2 groups. In secondary analyses, improvement was significantly greater with aripiprazole treatment than with placebo for negative symptoms assessed by both the BPRS negative symptom subscale and the SANS total score but not for positive symptoms. Prolactin and triglyceride levels were significantly lower in the aripiprazole group than in the placebo group. No significant differences between the 2 groups were observed in adverse effects, including extrapyramidal symptoms and serum glucose levels.

Conclusion: Although aripiprazole augmentation of clozapine did not lead to a significant improvement of total symptom severity in schizophrenia, a favorable change in the negative symptom domain was observed.

Trial Registration: clinicaltrials.gov Identifier: NCT00328367

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Received April 30, 2007; accepted Oct. 1, 2007. *From the Department of Psychiatry, Seoul Municipal Eunpyeong Hospital (Dr. Chang); the Department of Neuropsychiatry (Drs. Ahn, Park, S. H. Kim, Kang, and Y. S. Kim) and the Clinical Research Institute (Drs. Ahn, Lee, Kang, and Y. S. Kim), Seoul National University Hospital; the Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine (Drs. Ahn, Kang, and Y. S. Kim); and the Institute of Human Behavioral Medicine, Seoul National University Medical Research Center (Drs. Ahn, Kang, and Y. S. Kim), Republic of Korea. Dr. Chang is now at the Bipolar Disorders Clinic and Clinical Affective Neuroscience Laboratory, Department of Psychiatry, Seoul National University Bundang Hospital; Dr. Lee is now at the Department of Neuropsychiatry, Eulji University School of Medicine, Eulji General Hospital, Seoul, Republic of Korea.*

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Corresponding author and reprints: Yong Sik Kim, M.D., Ph.D., Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine, 28 Yongon-Dong, Chongno-Gu, Seoul 110-744, Republic of Korea (e-mail: kys@snu.ac.kr).

Given its superior efficacy over other antipsychotic drugs in alleviating treatment-resistant psychotic symptoms, clozapine remains the last resort for the pharmacotherapy of schizophrenia; however, 40% to 70% of patients with treatment-resistant schizophrenia still fail to respond or are only partially responsive to clozapine.[1,2] Clozapine is also associated with several adverse effects, including agranulocytosis, seizures, sedation, tachycardia, and sialorrhea, which may compromise the dose titration of clozapine in managing treatment-resistant symptoms.[3] In addition, a large body of evidence suggests an increased risk of obesity, diabetes, hyperlipidemia, and

cardiovascular diseases following clozapine treatment.[4–6] Both the limited efficacy and adverse effects of clozapine treatment often dictate that clinicians augment clozapine with other antipsychotics, even though antipsychotic polypharmacy itself can be associated with the increased risk of metabolic syndrome.[7]

Clozapine augmentation with other antipsychotics has been attempted in a broad range of clozapine-resistant cases,[8–10] but prospective or controlled trials are sparse.[3,11,12] Sulpiride and risperidone are the only 2 antipsychotics reported to be effective as an adjunct to clozapine therapy in clozapine-resistant patients with schizophrenia in randomized controlled trials,[13,14] suggesting that the changes in functional interaction of the dopamine–serotonin system may further ameliorate positive and negative symptoms.[12] However, negative results have also been reported in some of the randomized controlled trials with risperidone.[15,16] In this regard, it is important to investigate the usefulness of novel antipsychotics with unique dopamine-serotonin receptor–binding profiles in clozapine-resistant schizophrenia.

Aripiprazole is an antipsychotic with partial agonism at several G-protein–coupled receptors (e.g., D_2 and 5-HT_{1A}) and functional antagonism at several serotonin receptors, including 5-$HT_{2A,}$ 5-HT_{2B}, and 5-HT_6.[17,18] Several in vivo studies have suggested a possible role for aripiprazole in the dopamine system on the basis of functional diversity depending on the cellular milieu.[17,19–21] In animal studies, dopaminergic neurotransmission has been selectively increased in the medial prefrontal cortex and hippocampus,[22,23] thereby suggesting the possible effects of aripiprazole on negative symptoms and cognition in schizophrenia. The clinical efficacy and safety of aripiprazole treatment in schizophrenia have been reported through randomized placebo-controlled trials.[24–28] Low risk of extrapyramidal symptoms and metabolic abnormalities has been suggested in aripiprazole-treated patients with psychotic disorders.[29,30] Accumulated data from aripiprazole trials have allowed clinicians to expect additional improvement in clozapine-resistant schizophrenia without increasing the risk of metabolic syndrome.

Although numerous case reports and open-label studies have suggested a therapeutic gain by adding aripiprazole to clozapine in treating clozapine-resistant schizophrenia,[31–37] special consideration should be given to the problems of clozapine resistance, negative symptoms, and metabolic effects before applying these results clinically. First, since the improvement in psychiatric symptoms was reported to reach a plateau after 3 to 6 months of clozapine treatment,[2,38] a decision about suboptimal response to clozapine can only be made conclusively after clozapine treatment of at least 6 months. Second, the negative symptoms of schizophrenia tend to be associated with deteriorating course and poor outcome,[39] but several studies have failed to demonstrate definite efficacy for clozapine in managing negative symptoms.[40,41] Nonetheless, Kane et al.[42] reported a significant improvement in negative symptoms following 4 weeks of aripiprazole treatment compared to placebo, and the additional efficacy of the clozapine-aripiprazole combination in negative symptoms has been suggested by a series of case studies.[34,37] Furthermore, since clozapine has been associated with metabolic side effects, including weight gain, hyperglycemia, hyperlipidemia, and hypertension,[4,5] safety with regard to the metabolic profile should be addressed when augmenting clozapine with other antipsychotics. These findings suggest the necessity for a randomized controlled trial of clozapine-aripiprazole combination therapy.[35]

Both depressive and obsessive-compulsive (OC) symptoms are common in patients with schizophrenia[43,44] and have been associated with clinical outcomes in antipsychotic treatment.[45–48] In addition, it has been reported that clozapine treatment may be associated with the development or exacerbation of both depressive and OC symptoms.[49,50] Since there have been several studies suggesting clinical efficacy for aripiprazole in managing depressive and OC symptoms,[51–54] evaluating the changes in the severity of depressive and OC symptoms may provide additional information about therapeutic gains in clozapine-aripiprazole combination therapy for refractory schizophrenia.

We hypothesized that the addition of aripiprazole might augment the overall antipsychotic activity of clozapine, without increasing the risk of major adverse events, via its unique pharmacologic profile.

METHOD

Subjects

Study participants were selected from the population of patients registered at the Refractory Schizophrenia Clinic of Seoul National University Hospital (Seoul, Republic of Korea), a government-established tertiary hospital for difficult-to-treat cases from all parts of the Republic of Korea. Complete medical or psychiatric histories of all participants were available through paper charts and electronic medical recording systems. Both inpatients and outpatients were eligible. Treatment failure prior to clozapine treatment was defined as persistent psychotic symptoms despite at least 2 different antipsychotic treatments for 6 weeks or longer at a full dose equivalent to 600 mg/day or more of chlorpromazine. The inclusion criteria were a diagnosis of schizophrenia according to DSM-IV criteria; age from 18 through 65 years; documented treatment failure prior to clozapine treatment; clozapine treatment for more than 1 year with at least 8 weeks at a stable daily dose of 400 mg or more, unless compromised by adverse effects; no change in clozapine

daily dose or other concomitant medication for more than 3 months, indicating a plateau of clinical response to clozapine; either a baseline Brief Psychiatric Rating Scale (BPRS)[55] total score of at least 35 or more than 2 Schedule for Assessment of Negative Symptoms (SANS)[56] global rating item scores of at least 3; and fluency in written and spoken Korean. The minimum positive symptom level was also defined as either a positive symptom total score of at least 8 on 4 items of the BPRS or a score of at least 4 on any one of the following items: *hallucinatory behavior*, *conceptual disorganization*, *unusual thought content*, or *suspiciousness*.[57,58] In order to confirm treatment-resistance of positive symptoms prior to clozapine treatment, medical records were reviewed for sustained significant psychosocial disruption to patient's life caused by persistent positive symptoms before starting clozapine treatment.

Patients were excluded when there was any evidence of DSM-IV–defined substance dependence (excluding nicotine and caffeine); mental retardation; pregnancy or lactation; neurologic disorders, including epilepsy, stroke, or severe head trauma; prior history of nonresponse or tolerance to aripiprazole; participation in a clinical trial of another investigational drug within 3 months prior to study entry; treatment with an injectable depot neuroleptic within less than 3 dosing intervals between the last depot neuroleptic injection and baseline; history of electroconvulsive therapy within the previous 3 months; or difficulty in understanding written and spoken Korean.

Sixty-two patients were enrolled after screening for eligibility as described above. All the patients were ethnically identical Koreans. They were fully informed about the details of this study protocol, and then provided with a written informed consent form explicitly affirming for each participant the right to freely terminate study participation at any time without any disadvantage. The study was conducted between December 1, 2005, and December 10, 2006.

Study Design

Participants were randomly assigned to 8 weeks of double-blind treatment with aripiprazole or a placebo of identical appearance. Group allocation through random assignment was achieved by using a random-numbers chart in blocks of 4. The allocation sequence was generated and monitored by faculty members of the Department of Clinical Pharmaceutics at the Clinical Research Institute of Seoul National University Hospital, who were not involved in any part of this study. The investigators were unaware of the block size. All the participants and investigators remained blind throughout the study, and the data analyses were also performed by investigators blind to the identity of the participants. The study medication was administered as 10-mg tablets. The starting dose was 5 mg/day (one-half tablet), and it was increased to 10 mg/day at week 1. The investigators were allowed to increase the dose to a maximum of 30 mg/day over the following 3 weeks. After reaching a daily dose of 10 mg at the end of first week, dose titration ranging from 5 to 30 mg/day was permitted for treatment-emergent adverse effects. In addition to at least 3 months of no change in medication prior to enrollment, the clozapine dose and other concomitant medications remained fixed during the 8-week trial. Clinical assessments were conducted at baseline and weeks 1, 2, 4, and 8 or at the time of discontinuation if that occurred between scheduled visits.

The study was conducted at the Refractory Schizophrenia Clinic of Seoul National University Hospital and was based on the Good Clinical Practices guidelines and conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board, and written informed consent was obtained from each participant before enrollment.

Efficacy and Safety Evaluations

The primary efficacy measure was the mean change in BPRS total score from baseline to 8-week end point. Additional efficacy measures included the mean change in the scores of positive and negative subscales on the BPRS, the SANS, and the Clinical Global Impressions-Severity of Illness scale (CGI-S),[59] the Montgomery-Asberg Depression Rating Scale (MADRS),[60] the Yale-Brown Obsessive Compulsive Scale (YBOCS),[61] and the short form of the Subjective Well-Being Under Neuroleptics (SWN short form).[62] The item structure of SANS gives more consideration to diverse negative symptom constructs than that of other rating scales.[63] The mean changes in MADRS and YBOCS scores were used to evaluate changes in depressive and OC symptoms, respectively. The mean changes in SWN short form score were used to evaluate the impact of antipsychotics on subjective well-being. All the efficacy measures except the SWN short form were assessed at baseline and at weeks 1, 2, 4, and 8. The SWN short form was assessed at baseline and 8-week end point. The investigators were repeatedly trained for high reliability in using all the rating scales of this study with standardized videotaped interviews prior to the initiation of this trial. Interrater reliability for 6 instruments, as determined by intraclass correlations, ranged from 0.81 to 0.92.

Adverse effects were evaluated and recorded at all visits using the 48 items on the Udvalg for Kliniske Undersøgelser (UKU).[64] The details of timing of onset, potential causal relationship with the factors of treatment, and the use of concomitant medication were also described. Drug-induced movement disorders were assessed by the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) combined 9-item rating scale quantifying the severity of drug-induced parkinsonism, akathisia, dystonia, and dyskinesia.[65–68] The serum level of clozapine was

monitored at baseline and weeks 1 and 8. Body weight, waist circumference, vital signs (pulse rate and systolic/diastolic blood pressure), and complete blood cell count with differential were measured at all visits (baseline and weeks 1, 2, 4, and 8). To calculate the body mass index (BMI), height was measured before the initiation of an assigned treatment. Electroencephalography was performed at baseline and weeks 1 and 8. Electrocardiography, liver function tests, measurement of electrolyte levels, urinalysis, and measurement of serum prolactin were carried out at baseline and end point. Because aripiprazole add-on can be helpful in reducing clozapine-associated metabolic disturbances,[33] fasting blood sugar, 2-hour postprandial blood sugar, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured in serum at baseline and end point. Due to the potential inaccuracy of the Friedewald formula in estimating LDL cholesterol level,[69] the non-HDL cholesterol level was calculated by subtracting HDL cholesterol from total cholesterol.

Concomitant Medication

Patients receiving concomitant medications for stable medical conditions were allowed to participate in this study. Concomitant medications including antidepressants, anticholinergics, and benzodiazepines, which had been prescribed prior to study enrollment, were used continually without change in daily dosage during the 8-week study period. No additional medications were allowed. The only permitted coping strategy against adverse effects was dose titration of the assigned study medication.

Statistical Analyses

The primary efficacy measure was the change from baseline to 8-week end point in BPRS total score. In a 10-week, randomized, placebo-controlled trial of sulpiride augmentation in a total of 28 patients with schizophrenia partially responsive to clozapine,[13] the effect sizes—the difference between the mean changes (6.4 in BPRS total score) divided by the pooled standard deviations (7.3 in BPRS total score)—were large for general psychiatric symptoms as measured by BPRS total score (0.9). In this study, a sample size of 30 evaluable patients per treatment group (a total of 60 patients) would provide a statistical power of 85% to detect differential treatment effect sizes of 0.8 with an α level of .05.

The main goal of this trial was to test the hypothesis of therapeutic gain with aripiprazole over placebo. The analyses of efficacy and safety measures were performed on an intent-to-treat basis unless otherwise specified. Paired-sample t tests were used to assess the difference between the baseline and 8-week end point outcome measures within each treatment group. To test the difference between 2 groups (aripiprazole and placebo) in change over time in the primary and additional outcome measures, a mixed-effects model of repeated measurements, which is more flexible for the analysis of repeated-measures data than traditional methods,[70] was used. Under the unstructured covariance structure, this model included terms for treatment group (aripiprazole and placebo), time, and treatment group × time interaction. In this model, the intercept was the baseline BPRS total score, and the statistical significance of the interaction term was tested to compare treatment groups over time. To measure the magnitude of a treatment effect, effect size was provided by using Cohen's d statistic, which gives a measure of the standardized differences in the mean values of changes in scores between medications.[71] For descriptive purposes, the last-observation-carried-forward (LOCF) method was used for any patients who did not complete the 8-week double-blind phase. In addition, observed-case data were also calculated and analyzed for each visit. In the analyses of additional efficacy measures and safety profiles, change in outcome measure from baseline was tested for statistical significance by fixed-effects analysis of covariance, controlling for the effect of baseline score. For categorical variables, the Pearson χ^2 test or Fisher exact test was employed. The Mann-Whitney test was used for nonparametric data. All tests were performed by using 2-tailed probabilities and set at a significance level of .05 unless otherwise specified.

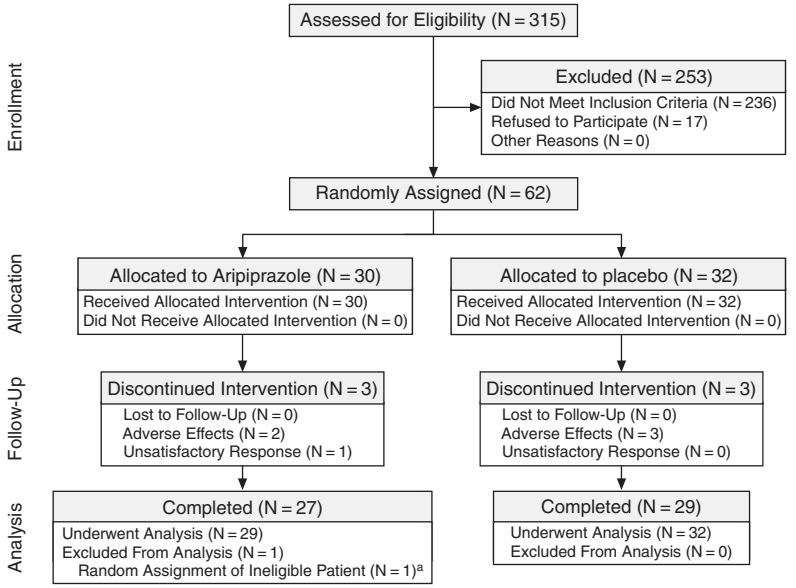
RESULTS

Demographic and Clinical Details

As shown in Figure 1, 315 clozapine-treated patients with psychotic symptoms were assessed for eligibility for the study; 236 (74.9%) did not meet the inclusion criteria, and 17 (5.4%) refused to participate. In total, 62 patients were enrolled, and 56 completed the study (90.3% completion rate). Discontinuation rates were 10.0% for aripiprazole and 9.4% for placebo, with no statistically significant difference in dropouts associated with adverse effects (Fisher exact test, $p > .99$). Among a total of 3 dropouts in the aripiprazole group, 2 patients complained of adverse effects (1 of gastrointestinal discomfort and the other of anxiety with palpitation), and 1 patient withdrew due to a subjectively assessed lack of efficacy. Three discontinuations in the placebo group were all attributed to treatment-emergent adverse effects (1 each due to exacerbation of auditory hallucinations, depressive mood, and tingling sensation). One ineligible patient with arteriovenous malformation was erroneously included in the aripiprazole group and detected through the independent review for data disclosure. Consequently, the data for only 61 patients were analyzed (Figure 1).

The baseline characteristics of 61 patients are detailed in Table 1. At the commencement of the 8-week, double-blind phase, patients had received clozapine treatment

Figure 1. Patient Allocation



[a]One patient with a history of arteriovenous malformation was mistakenly included in the random assignment and was consequently excluded from the intent-to-treat analysis.

Table 1. Baseline Clinical and Demographic Characteristics of 61 Clozapine-Treated Subjects Randomly Assigned to Adjunctive Aripiprazole or Placebo[a]

Characteristic	Clozapine/Aripiprazole (N = 29)	Clozapine/Placebo (N = 32)	Test of Significance
Sex, male/female, N	22/7	26/6	$\chi^2 = -0.26$, p = .76
Age, mean ± SD (range), y	33.2 ± 8.2 (19–51)	31.7 ± 7.4 (18–44)	t = –0.76, df = 59, p = .45
Education, mean ± SD, y	13.7 ± 2.7	13.6 ± 2.3	t = 0.10, df = 59, p = .92
Employment, employed/unemployed, N	7/22	4/28	Fisher exact test, p = .32
Age at onset of symptoms, mean ± SD, y	20.6 ± 4.9	19.1 ± 4.7	t = –1.22, df = 59, p = .23
History of schizophrenia and other psychotic disorders in first-degree relatives	3	5	Fisher exact test, p = .71
Schizophrenia subtype, N			
Paranoid	21	16	$\chi^2 = 3.2$, p = .12
Disorganized	1	1	Fisher exact test, p > .99
Undifferentiated	5	12	Fisher exact test, p = .09
Residual	2	3	Fisher exact test, p > .99
Longitudinal course, N			
Episodic with interepisode residual symptoms	22	23	$\chi^2 = 0.13$, p = .78
Episodic with no interepisode residual symptoms	5	3	Fisher exact test, p = .46
Continuous	2	6	Fisher exact test, p = .26
Duration of clozapine treatment before trial entry, mean ± SD (range), d	740.8 ± 590.7 (369–2461)	744.1 ± 412.7 (382–1852)	t = 0.03, df = 59, p = .98
Daily maintenance dose of clozapine, mean ± SD, mg	304.3 ± 104.8	290.6 ± 101.9	t = –0.52, df = 59, p = .61

[a]Data for 1 ineligible patient mistakenly included in random assignment to aripiprazole are excluded.

for an average of 2 years. None of the patients had been treated with aripiprazole prior to their random assignment. No significant differences were observed between the treatment groups in clinical and demographic variables. The mean ± SD doses (mg/day) at end point were 15.5 ± 7.1 for aripiprazole and 17.0 ± 7.4 for placebo. No significant difference in treatment dose was seen at the end point between the 2 groups (t = –0.8, df = 59, p = .419).

Efficacy Analysis

Results for the efficacy measures within each group are listed in Table 2. Efficacy measure scores did not significantly differ between the aripiprazole and placebo groups at baseline. A significant improvement during the 8-week, double-blind phase was observed in both groups, but BPRS positive symptom subscale scores did not show a statistically significant change in the aripiprazole group.

Table 2. Effects of Treatment on Outcome Measure Scores (LOCF)

	Clozapine/Aripiprazole (N = 29)				Clozapine/Placebo (N = 32)			
Measure	Baseline, Mean (SD)	End Point, Mean (SD)	t Test	p Value	Baseline, Mean (SD)	End Point, Mean (SD)	t Test	p Value
BPRS								
Total	47.6 (9.3)	42.5 (11.0)	–7.0	< .001	48.5 (10.5)	43.8 (10.1)	–5.0	< .001
Positive	11.2 (5.3)	10.8 (5.4)	–1.8	.077	11.4 (5.3)	10.8 (5.0)	–2.6	.016
Negative	9.9 (2.2)	8.3 (2.8)	–5.2	< .001	9.9 (2.6)	9.3 (2.5)	–2.8	.009
SANS	50.7 (15.9)	43.8 (18.0)	–6.6	< .001	51.3 (13.9)	48.1 (13.0)	–3.6	.001
CGI-S	4.2 (0.7)	3.5 (0.9)	–6.0	< .001	4.0 (0.6)	3.7 (0.7)	–3.6	.001
MADRS	14.0 (6.6)	11.8 (7.1)	–3.9	< .001	14.6 (6.7)	13.4 (6.3)	–2.3	.029
YBOCS	14.5 (10.0)	12.0 (9.8)	–3.4	.002	9.6 (11.0)	8.9 (10.5)	–3.2	.003
SWN short form	71.8 (20.4)	78.0 (18.9)	2.9	.008	74.4 (18.2)	76.3 (17.8)	2.3	.030

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, MADRS = Montgomery-Äsberg Depression Rating Scale, SANS = Schedule for the Assessment of Negative Symptoms, SWN short form = short form of Subjective Well-Being Under Neuroleptics scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. Significance of Change During the Study Period and Effect Sizes for Efficacy Measures

Efficacy Measures	Clozapine/Aripiprazole Change, Mean (SD)[a]	Clozapine/Placebo Change, Mean (SD)[a]	p Value[b]	Cohen's d
BPRS				
Total	–5.1 (3.9)	–4.6 (5.2)	.871	0.1
Positive	–0.3 (1.0)	–0.6 (1.3)	.569	0.2
Negative	–1.6 (1.6)	–0.6 (1.2)	.004	0.6
SANS	–6.9 (5.6)	–3.2 (5.0)	.004	0.7
CGI-S	–0.7 (0.6)	–0.3 (0.5)	.035	0.6
MADRS	–2.0 (3.2)	–1.1 (2.8)	.225	0.3
YBOCS	–2.5 (3.9)	–0.7 (1.2)	.013	0.6
SWN short form[c]	1.1 (0.3)	1.0 (0.3)	.578	0.3

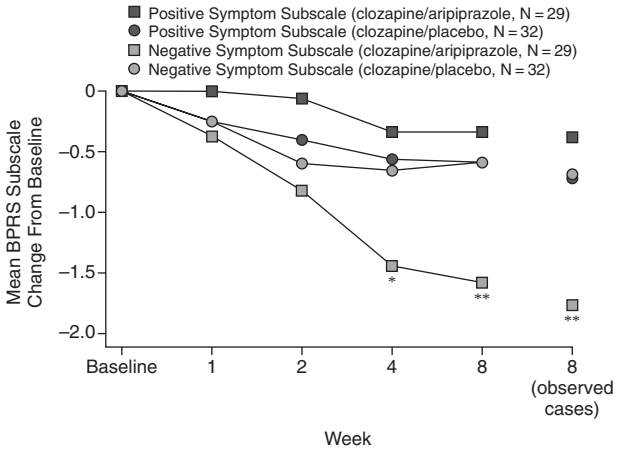
[a]Values for mean (SD) change may vary slightly from values computed from mean (SD) baseline and end point values reported in Table 2 due to rounding.
[b]p Values were based on the treatment group (aripiprazole or placebo)-by-time interaction in the mixed-effects model of repeated measurements.
[c]The logarithmically transformed scores were used for SWN short form to reduce the skewness of data.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, SANS = Schedule for the Assessment of Negative Symptoms, SWN short form = short form of Subjective Well-Being Under Neuroleptics scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3 presents the differences in both the symptom improvement and the magnitude of the treatment effect between the aripiprazole treatment and placebo groups. There was no difference between the 2 groups in the amount of symptom improvement measured by the BPRS total score. In secondary analyses, aripiprazole was significantly associated with greater reduction than placebo in BPRS negative symptom subscale scores (p = .004), SANS scores (p = .004), CGI-S scores (p = .035), and YBOCS scores (p = .013). The effect sizes ranged from 0.6 to 0.7, indicating that the mean score of the aripiprazole group is at the 73rd to 76th percentile of the placebo group. Neither the total BPRS score nor the BPRS positive symptom subscale score showed a statistically significant difference between the aripiprazole and placebo groups.

No significant difference was observed between the aripiprazole and placebo groups in mean change scores of MADRS from baseline to end point. However, after the Bonferroni correction was used to correct for multiple comparisons with a p value of approximately .006 (.05/8), no significant differences were detected between the 2 groups in mean change CGI-S or YBOCS scores from baseline to end point. In the analyses of SANS subscale scores using the Mann-Whitney test, the aripiprazole group did not seem to differ from the placebo group in the mean scores of 5 SANS subscales at baseline (for *affective flattening*, U = 440.0, p = .37; for *alogia*, U = 373.5, p = .10; for *avolition-apathy*, U = 420.5, p = .27; for *anhedonia-asociality*, U = 434.5, p = .34; and for *attention*, U = 415.5, p = .24). At week 8, the aripiprazole group showed significantly lower mean alogia subscale scores than the placebo group (U = 286.0, p = .004, $r_{effect\ size}$ = 0.33). Aripiprazole was also associated with a tendency toward low affective flattening subscale scores at week 8 (U = 360.0, p = .07). The aripiprazole group was not significantly different from the placebo group on the other 3 SANS subscale scores, including avolition-apathy, anhedonia-asociality, and attention (p > .30).

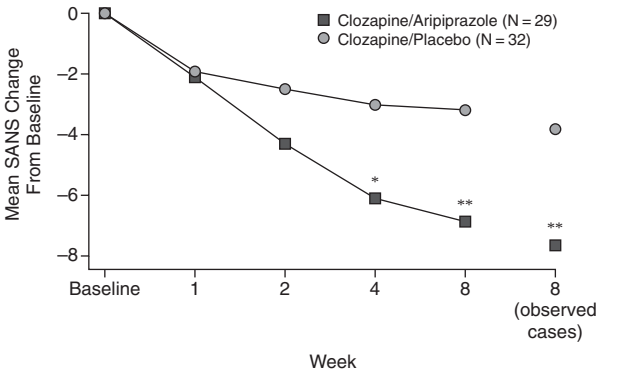
Using a mixed-effects model of repeated measurements, the aripiprazole group showed a greater rate of improvement than the placebo group on BPRS negative symptom subscale scores (t = 3.0, p = .004), SANS scores (t = 3.0, p = .004), CGI-S scores (t = 2.2, p = .035), and

Figure 2. Change in the Brief Psychiatric Rating Scale (BPRS) Positive and Negative Symptom Subscale Scores From Baseline[a,b]



[a]p Values are based on pairwise comparisons using an analysis of covariance method, with treatment as the main effect and baseline score as the covariate.
[b]All values are based on the last observation carried forward unless otherwise specified.
*p < .05.
**p < .01.

Figure 3. Change in the Schedule for the Assessment of Negative Symptoms (SANS) Scores From Baseline[a,b]



[a]p Values are based on pairwise comparisons using an analysis of covariance method, with treatment as the main effect and baseline score as the covariate.
[b]All values are based on the last observation carried forward unless otherwise specified.
*p < .05.
**p < .01.

YBOCS scores (t = 2.6, p = .013). After the Bonferroni correction was performed, the statistical significance of the YBOCS scores disappeared. Group differences in score change over time in all other efficacy measures (p > .1) were statistically nonsignificant. Figures 2 and 3 reveal that aripiprazole treatment showed significantly greater improvement than placebo in negative symptoms as measured by the BPRS negative symptom subscale (F = 5.35, df = 1,58; p = .024 at week 4; F = 7.48, df = 1,58; p = .008 at week 8) and SANS (F = 5.98, df = 1,58; p = .018 at week 4; F = 7.23, df = 1,58; p = .009 at week 8) from week 4 onward (LOCF). This differential treatment effect was reconfirmed by observed-case data from the BPRS negative symptom subscale (F = 4.93, df = 1,53; p = .031 at week 4; F = 7.69, df = 1,52; p = .008 at week 8) and from the SANS (F = 5.67, df = 1,58; p = .021 at week 4; F = 8.12, df = 1,58; p = .006 at week 8).

Safety Analysis

No statistically significant difference was found in the UKU mean change scores from baseline between the aripiprazole and placebo groups (F = 1.88, df = 1,58; p = .176). The severity of all newly developed or aggravated adverse events was mild to moderate (1 or 2 on each item of the UKU). No serious adverse events occurred during the study treatment. No statistically significant differences were seen between the 2 groups in the incidence of adverse effects except in *decreased duration of sleep* (item 1.8) and *orthostatic hypotension* (item 3.9). Aripiprazole was significantly associated with higher frequency of decreased duration of sleep (8/29 vs. 2/32; Fisher exact test, p = .037) and orthostatic hypotension (5/29 vs. 0/32; Fisher exact test, p = .020) than placebo. A total of 10 patients, who reported decreased duration of sleep during the 8-week trial, had been experiencing *increased duration of sleep* (more than 2 hours longer than usual) at baseline.

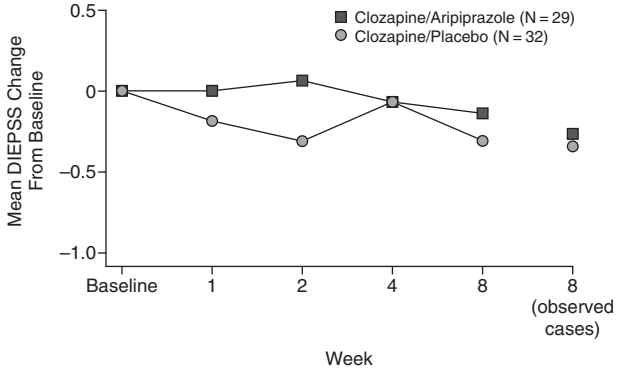
No significant difference between the 2 groups was observed in the DIEPSS mean change score from baseline to end point (Table 4). Figure 4 shows that no statistically significant difference in the DIEPSS total score was seen between the 2 groups during the study treatment (LOCF). No significant difference between the 2 groups was observed in the rate of change in DIEPSS score according to the mixed-effects model with repeated measurements (t = –0.3, p = .795). No statistically significant change in serum clozapine level between baseline and follow-up occurred in either group. Neither group showed significant differences in weight, waist circumference, or BMI. Vital signs did not differ significantly between the 2 groups at any visit. No differences in total white cell or neutrophil counts were observed between the 2 groups, and no patients experienced new-onset neutropenia. Serum prolactin significantly decreased from the baseline level in the aripiprazole group (t = –3.53, df = 28, p = .001) but not in the placebo group (t = 1.10, df = 31, p = .281). After controlling for the effect of the baseline level, aripiprazole was significantly associated with a greater decrease in prolactin level than placebo, and the effect size was large (Cohen's d = 0.95).

Table 4. Changes in Safety Measures

Measure	Clozapine/Aripiprazole (N = 29)			Clozapine/Placebo (N = 32)			p Value[b]
	Baseline, Mean ± SD	End Point, Mean ± SD	Change From Baseline, Mean ± SD[a]	Baseline, Mean ± SD	End Point, Mean ± SD	Change From Baseline, Mean ± SD[a]	
DIEPSS	3.7 ± 2.3	3.6 ± 1.9	–0.1 ± 1.2	3.6 ± 1.4	3.3 ± 1.1	–0.3 ± 0.7	.33
Serum clozapine, ng/mL	332.5 ± 188.6	343.6 ± 290.4	11.0 ± 275.9	328.2 ± 188.2	303.5 ± 184.2	–24.6 ± 193.5	.51
Weight, kg	79.9 ± 15.0	78.7 ± 14.7	–1.2 ± 2.3	77.0 ± 12.5	76.4 ± 12.0	–0.6 ± 1.7	.36
Waist circumference, cm	94.8 ± 11.7	93.6 ± 11.6	–1.3 ± 2.9	92.9 ± 10.6	92.2 ± 9.7	–0.6 ± 3.1	.53
BMI, kg/m^2	27.1 ± 4.1	26.7 ± 4.1	–0.4 ± 0.7	26.4 ± 3.8	26.2 ± 3.7	–0.2 ± 0.5	.35
Pulse, bpm	82.3 ± 9.0	87.1 ± 10.2	4.8 ± 8.7	85.4 ± 9.1	87.2 ± 8.0	1.7 ± 10.6	.55
Systolic blood pressure, mm Hg	125.9 ± 12.1	124.5 ± 14.3	–1.4 ± 11.6	125.6 ± 13.4	120.3 ± 11.5	–5.3 ± 11.6	.14
Diastolic blood pressure, mm Hg	85.7 ± 9.3	81.0 ± 8.6	–4.7 ± 7.3	80.9 ± 10.6	78.1 ± 8.2	–2.8 ± 8.9	.81
QTc interval, ms	438.6 ± 31.6	443.1 ± 19.8	4.5 ± 27.9	439.7 ± 21.5	440.6 ± 23.4	0.9 ± 19.9	.54
WBC count, 10^{-3}/mm^3	7.6 ± 2.8	7.3 ± 2.7	–0.3 ± 2.6	6.8 ± 12.0	6.3 ± 1.7	–0.5 ± 1.8	.23
Neutrophil count, 10^{-3}/mm^3	5.0 ± 2.4	4.8 ± 2.1	–0.2 ± 2.2	4.3 ± 1.7	3.8 ± 1.4	–0.5 ± 1.8	.09
SGOT, IU/L	23.1 ± 10.7	22.2 ± 11.6	–0.8 ± 4.7	22.8 ± 12.0	23.8 ± 13.4	1.1 ± 6.2	.19
SGPT, IU/L	32.4 ± 25.9	30.9 ± 25.5	–1.5 ± 11.4	31.4 ± 21.7	30.9 ± 23.9	–0.5 ± 11.8	.75
Serum prolactin, ng/mL	5.6 ± 5.7	3.3 ± 4.2	–2.3 ± 3.4	6.8 ± 11.5	7.3 ± 11.0	0.5 ± 2.4	< .001
Fasting blood sugar, mg/dL	117.6 ± 58.7	107.4 ± 19.6	–10.2 ± 58.0	99.3 ± 11.8	102.7 ± 17.9	3.4 ± 14.1	.56
2-hour postprandial blood sugar, mg/dL	160.2 ± 128.9	136.2 ± 51.2	–24.0 ± 112.1	131.9 ± 34.7	123.1 ± 35.5	–8.8 ± 29.8	.52
Total cholesterol, mg/dL	188.1 ± 38.9	175.4 ± 37.4	–12.7 ± 23.5	197.2 ± 39.7	192.9 ± 41.9	–4.3 ± 25.6	.11
Triglycerides, mg/dL	180.4 ± 129.8	149.3 ± 85.3	–31.1 ± 106.2	175.7 ± 84.8	200.2 ± 105.2	24.4 ± 60.2	< .01
HDL cholesterol, mg/dL	43.1 ± 11.6	43.9 ± 13.4	0.8 ± 5.4	44.2 ± 10.2	43.7 ± 10.2	–0.6 ± 4.6	.29
LDL cholesterol, mg/dL	112.9 ± 26.1	104.3 ± 27.6	–8.7 ± 14.1	121.8 ± 35.5	117.8 ± 36.5	–3.9 ± 23.8	.22
non-HDL cholesterol, mg/dL	145.0 ± 37.3	131.5 ± 34.4	–13.5 ± 20.7	152.9 ± 42.1	149.2 ± 43.4	–3.7 ± 24.4	.05

[a]Values for mean ± SD change may vary slightly from values computed from mean ± SD baseline and end point values due to rounding.
[b]p Values are based on pairwise comparisons from the analysis of covariance model with treatment as the main effect and baseline as the covariate.
Abbreviations: BMI = body mass index, DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale, HDL = high-density lipoprotein, LDL = low-density lipoprotein, QTc = corrected QT, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, WBC = white blood cell.

Figure 4. Change in Score on the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) From Baseline[a]



[a]All values are based on the last observation carried forward unless otherwise specified.

No statistically significant differences in fasting and 2-hour postprandial blood sugar levels or mean changes from baseline to end point occurred between the 2 groups. Neither group showed statistically significant changes from baseline to end point in the levels of total cholesterol, HDL cholesterol, or LDL cholesterol. However, a significant difference between the 2 groups was detected in the change of triglyceride levels from baseline to end point. Aripiprazole was associated with a tendency toward a greater decrease in the level of non-HDL cholesterol than placebo (p = .052; Table 4).

All the electrocardiograms of participants were independently evaluated for clinical significance by a cardiologist, and no patients showed clinically significant changes in electrocardiographic recordings. Tachycardia was noted in 5 patients in the aripiprazole group and 1 patient in the placebo group. The length of QTc interval did not differ between the aripiprazole and placebo groups at baseline (t = –0.2, df = 59, p = .873) or at end point (t = 0.4, df = 59, p = .658). No significant changes in QTc interval between baseline and end point occurred in either group. No patients experienced clinical seizures or developed definite epileptiform activity on electroencephalographic findings while taking the study medication.

DISCUSSION

In this randomized, placebo-controlled, double-blind trial in 61 patients unresponsive or partially responsive to clozapine therapy, aripiprazole augmentation of clozapine offered no statistically significant advantage over augmentation with placebo for total symptom severity in schizophrenia. This lack of improvement with the addition of aripiprazole compared to the addition of placebo is in line with the similarly negative results

of previous studies of augmentation of clozapine with risperidone.[15,16,72]

The significant improvements on primary and additional efficacy measures between baseline and 8-week end point in both treatment groups suggest a substantial study effect in this sample population. In secondary analyses, aripiprazole augmentation of clozapine was associated with a significant improvement in negative symptoms as compared with augmentation with placebo. The differences in the scores of negative symptom measures occurred by week 4 and widened throughout the latter 4 weeks. Aripiprazole was generally well tolerated across a dose range of 5 to 30 mg/day.

The superiority of aripiprazole over placebo in improving BPRS negative symptom subscale scores and SANS scores strongly supports the preliminary results of numerous open-label studies and case reports.[35,37,73,74] Since negative symptoms are often associated with depressive and parkinsonian symptoms in schizophrenia,[75,76] it is interesting that aripiprazole treatment was associated with an improvement in negative symptoms without changes in depressive symptoms. Among 5 subscales of the SANS, avolition-apathy and anhedonia-asociality are often related to depressive symptoms,[75,77] and alogia may reflect some aspects of cognitive dysfunctions in schizophrenia.[78] Therefore, the association between aripiprazole treatment and negative symptoms shown in this study may be partly mediated by the changes in cognitive functions, which were not assessed in this study. Negative symptoms are now deemed to constitute an independent core deficit with a distinct pathophysiology,[79] but the efficacy of atypical antipsychotics on negative symptoms, especially on primary negative symptoms, is still open to debate.[80] According to the consensus statement on negative symptoms by the National Institute of Mental Health–Measurement and Treatment Research to Improve Cognition in Schizophrenia project,[63] the sharp distinction between primary and secondary negative symptoms is not intrinsic to clinical trials testing the efficacy of therapeutics for negative symptoms, if subjects with persistent negative symptoms are selected and the obvious causes of secondary negative symptoms can be controlled. In clinical practice, it may be ideal to target patients with both primary and secondary negative symptoms.

Though the subtype distribution of schizophrenia did not statistically differ between the aripiprazole and placebo groups at baseline, the predominance of paranoid subtype in the aripiprazole group may offer a clinical advantage to aripiprazole add-on.[81] However, some authors have insisted that the initial schizophrenia subtype is not associated with the frequency of negative social consequences.[82] The slight differences in the pattern of longitudinal course between the 2 groups may also affect the results of this study.

The absence of a statistically significant improvement in overall symptom severity may be fundamentally attributable to the robust actions of clozapine on the positive symptom domain. Clozapine has been demonstrated to show a greater efficacy in positive symptoms than other symptom domains.[40,83] Although a minimum level of positive symptoms was set for the inclusion criteria, it might have been beyond the maximum attainable level of positive symptom improvement in this sample population with aripiprazole treatment. Since there is a possible interplay between positive and negative symptom changes,[84] clozapine treatment may be the most suitable precondition for evaluating the specific efficacy of the therapeutic agent on the negative symptom domain. The absence of a significant difference in MADRS scores between the 2 groups suggests that the improvement in the negative symptoms was not caused by decreased depressive symptoms. In this study, extrapyramidal symptoms were infrequent with aripiprazole treatment, as predicted by the results of previous clinical trials,[25,35,85] and this finding also clarifies the interpretation of negative symptom improvement. Aripiprazole is thought to actively antagonize neuroleptic-induced movement symptoms through 5-HT_{1A}–selective agonism.[17]

No statistically significant difference was found in overall subjective well-being measured by the SWN short-form scale between the aripiprazole and placebo groups. Since anxiety and depression show greater association with quality of life than cognitive and negative symptoms,[86,87] an improvement in negative symptoms that is not accompanied by an improvement in anxiety and depression may be insufficient to bring about short-term improvement in the overall subjective quality of life. By contrast, a poor long-term prognosis, including occupational impairment and impaired interpersonal relationships, has also been strongly correlated with the severity of negative symptoms.[88]

Though there was no statistical improvement of OC symptoms in the aripiprazole group, possible benefits for OC symptoms are intriguing with regard to the risk of clozapine-induced OC symptoms.[50] Balanced dopamine-serotonin neurotransmission may contribute to stabilizing the functional circuit subserving OC symptoms.[89] Aripiprazole treatment significantly decreased serum prolactin levels, as previously reported.[17] Though reducing prolactin levels may improve various treatment-emergent side effects, including amenorrhea, sexual dysfunction, and osteoporosis,[90] decreased prolactin level in patients receiving prolactin-sparing antipsychotics (e.g., clozapine and olanzapine) can also cause serious problems in glucose and lipid metabolism.[91] In the adverse effect profile, a total of 10 patients (8 from the aripiprazole group and 2 from the placebo group), who were rated at least 1 or more on *increased duration of sleep* (item 1.7) of the UKU at baseline, reported *decreased duration of sleep* at

subsequent visits. They subjectively perceived decreased sleep duration as a beneficial effect of treatment rather than treatment-emergent side effect.

Clozapine-associated metabolic disturbances can increase the risk of cardiovascular disease.[5,92] Since a meta-analysis of prospective studies showed an association between hypertriglyceridemia and increased risk of cardiovascular disease regardless of HDL cholesterol level,[93] the decrease in triglyceride levels shown in this study would contribute to the reduction of cardiovascular morbidity in clozapine-treated patients.[94] The aripiprazole group also showed a tendency toward a decrease in serum non-HDL cholesterol level, which is a useful predictor of risk for cardiovascular disease.[95] It is notably better than the LDL cholesterol level in type 2 diabetic patients,[96] because non-HDL cholesterol includes triglyceride-rich remnant lipoproteins, which are excluded in the calculated LDL cholesterol level.[69] Since concern has been growing over the high risk of metabolic syndrome in patients receiving long-term antipsychotic polytherapy,[7] replicating these beneficial effects in the maintenance phase of future trials is desirable.

Preliminary results on interethnic differences supported that Korean patients with refractory schizophrenia would benefit by clozapine treatment, as shown in Caucasian patients.[97] However, there are several studies suggesting interethnic differences in the pharmacokinetic and metabolic characteristics between Asian and Caucasian patients.[98,99] Korean American patients also showed a significantly higher risk of side effects associated with clozapine treatment than Caucasian patients.[97] In this regard, it is possible that a small deviation, downward or upward, in the clozapine daily dose used in this study might offer clinical advantages or, alternatively, cause treatment-emergent side effects not expected from the results of Western studies.

The study design requires that 2 limitations be considered. First, this study protocol did not include a placebo run-in phase to eliminate placebo responders. Although a placebo run-in phase may help to reduce the incidence of false positives,[100] it can also exaggerate the efficacy of an active drug, and a meta-analytic study did not show a statistical difference in the effect size between clinical trials with and without a placebo run-in phase.[101] The absence of a placebo run-in phase may explain the substantial study effects shown by significantly improved psychiatric symptoms in the placebo group. Second, comprehensive interactions with the investigators might have affected the within-group improvement observed in the 2 groups to a certain extent, even though the study participants were not involved in any kind of structured psychoeducation program. This nonspecific effect of treatment is ubiquitous in clinical trials and is a major obstacle to the applicability of study results. Our findings support the role of a prospective, randomized, double-blind, placebo-controlled clinical trial as a definitive tool in evidence-based medicine.[12]

In conclusion, the results of this study indicate that augmentation of clozapine with aripiprazole offers no benefit with regard to the improvement of overall symptom severity in schizophrenia as compared with augmentation with placebo. While not demonstrating a definitive advantage of aripiprazole over placebo, the potential efficacy of aripiprazole augmentation of clozapine for negative symptoms was suggested in clozapine-treated patients with schizophrenia. The favorable changes in metabolic profile with aripiprazole treatment were also highly encouraging, and confirm previous findings from large-scale placebo-controlled studies.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), risperidone (Risperdal).

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