Brief Report

ARIPIPRAZOLE AUGMENTATION FOR TREATMENT OF PATIENTS WITH INADEQUATE ANTIDEPRESSANTS RESPONSE

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This study evaluated whether or not augmentation with aripiprazole is beneficial and tolerable to patients with an inadequate response to antidepressants (ADs). Thirteen patients with nonpsychotic major depression, who had failed to respond to an adequate trial of at least one AD, were prescribed aripiprazole (dose, 5–30 mg) for 8 weeks. The dose of their preexisting ADs was not changed. The treatment response was defined as the mean changes in the scores of the Hamilton Depression Rating Scale (HAM-D) from the baseline to the end of treatment. Eleven (84.6%) patients returned for at least one follow-up visit, and 7 (53.8%) patients completed the study. The HAM-D and Clinical Global Impression—Severity (CGI-S) scores decreased significantly from the baseline to the end of treatment by 53.8% and 56.0%, respectively ($Z = -2.937$, $P = .003$; $Z = -2.961$, $P = .003$). Seven (63.6%) patients showed a $\geq 50\%$ reduction in the HAM-D score at the end of treatment. Three (27.3%) patients met the remission criteria at the end of treatment. There were no serious side effects. Despite the high dropout rate in this open study, aripiprazole appears to be reasonably effective and tolerated as an augmentation strategy in conjunction with conventional ADs treatment in patients with an inadequate AD response. These results highlight the potential benefits of aripiprazole for these patients. However, adequately powered, randomized, controlled trials are needed to confirm these results. Depression and Anxiety 24:522–526, 2007.

Key words: *aripiprazole; depression; inadequate antidepressant response; augmentation; atypical astipsychotic*

INTRODUCTION

Aripiprazole has been characterized as being a partial agonist at the D_2 (dopamine) and 5-HT_{1a} (serotonin) receptors, and an antagonist at the 5-HT_{2a} receptors, as well as producing a high 5-HT_2:D_2 ratio, which is related to the reduced development of extrapyramidal symptoms [EPS; Fernandez et al., 2004; Jordan et al., 2002].

Among the favorable receptor profiles of aripiprazole, the 5-HT_{1a} receptors may contribute to its overall effectiveness in the treatment of depressive symptoms, as well as anxiety and negative symptoms. Aripiprazole has also been reported to restore the cognitive function of patients with schizophrenia, even

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though the mechanism of its action on the cognitive functions is unclear;aripiprazole treatment is less likely to result in EPS, weight gain, and prolactin abnormalities [Lieberman et al., 2005].

A previous study reported that 29–46% of depressed patients showed no response or only a partial response to the appropriate antidepressants [ADs; Fava and Davidson, 1996]. Atypical antipsychotics have been reported to be effective and tolerable in the treatment of refractory patients with major depressive disorder (MDD) without psychotic symptoms, as evidenced by many controlled and open clinical studies [Corya et al., 2003; Papakostas et al., 2004; Viner et al., 2003]. Regarding aripiprazole, there have been some retrospective studies [Barbee et al., 2004; Worthington et al., 2005], a case report [Hellerstein, 2004], and small, prospective, open-label studies [Papakostas et al., 2005; Simon and Nemeroff, 2005]. Some controlled trials [Gupta and Masand, 2004; Kane et al., 2002; Potkin et al., 2003] indicated that aripiprazole has potential roles in treating depression in patients with schizophrenia. However, there is a paucity of data related to Asians in this field. Therefore, as a pilot study, we evaluated the effectiveness and tolerability of aripiprazole augmentation for the treatment of patients with MDD with inadequate responses to ADs in a Korean sample.

SUBJECTS AND METHODS

Thirteen individuals with DSM-IV [American Psychiatric Association, 1994] recurrent MDD without psychotic symptoms participated in this study. The diagnosis was made by the two board-certified psychiatrists (C. Lee and I.-H. Paik) using the Korean version of the Structured Clinical Interview for DSM-IV Axis I Disorders [Hahn et al., 2000]. Additional inclusion criteria were as follows:

1. Patients who scored ≥ 15 on the 17-item, Korean version of the Hamilton Depression rating Scale [HAM-D; Yi et al., 2005] and a Clinical Global Impression—Severity score [CGI-S; Guy, 1976] ranging from marked to extremely severe despite treatment with one or more ADs [selective serotonin reuptake inhibitors (SSRIs), venlafaxine XR (extended release), bupropion, and mirtazapine] for at least 8 weeks at an acceptable dose [a daily dose ≥ 20 mg of fluoxetine, paroxetine or citalopram; 225 mg of venlafaxine XR; 300 mg of bupropion; 30 mg of mirtazapine as a monotherapy or combination therapy with each AD (e.g., 30 mg/day of paroxetine plus 15 mg/day of mirtazapine)].
2. Patients ages 18 to 65 years.
3. Patients who were not taking any antipsychotic medication at the time of the study.
4. Patients for whom written informed consent has been obtained.

The exclusion criteria were as follows:

1. Patients treated with depot antipsychotic medications within one dosing cycle prior to day 1.
2. Pregnant or breast-feeding women, or potentially childbearing women without proper contraception.
3. Any other current occurrence or prior history of Axis I disorders other than MDD.
4. Any significant medical conditions.
5. Prior treatments with antipsychotics.
6. Patients with known arrhythmia or QTc >450 ms.

The study protocol was critically reviewed and approved by the Institutional Review Board. Thirteen patients participated in this 8-week study.

Medications: The existing ADs and other psychotropics at the time of enrollment (day 1) were maintained during the study without alteration. Aripiprazole was combined with patients' current medications, with a starting dose of 5–10 mg once daily, which was adjusted up to 30 mg/day based on the clinicians' assessment of the clinical response and the patients' tolerance. No new psychotropics other than aripiprazole were permitted as an augmentation during the study periods, with the exception of zolpidem for sleep disturbances, lorazepam for anxiety, and benztropine for EPS.

Effectiveness measures: The effectiveness was measured using the HAM-D score, which was assessed at days 1, 7, 14, 28, and 56. The primary measure of effectiveness was the mean changes from days 1 to 56, and the secondary measures of effectiveness included $\geq 50\%$ reduction in the HAM-D score and remission criteria defined as a HAM-D score ≤ 7 (at day 56). The other measure was the CGI-S score, which was completed at each visit. All adverse events were recorded after the first dose of aripiprazole.

Tolerability measures: Vital signs (blood pressure in the sitting and standing position, body temperature, and heart rate) were collected at each visit. The laboratory tests included the complete blood count (CBC) and blood chemistry at days 1 and 56. We assessed the EPS using the Barnes Akathisia Rating Scale [BARS; Barnes, 1989] and the Simpson–Angus Rating Scale [SARS; Simpson and Angus, 1970] at each visit.

Data analysis: Statistical analysis was performed with SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL). The data were run on an intent-to-treat (ITT) basis, with the last observation carried forward (LOCF) for end-of-treatment analysis. Nonparametric analyses were performed because of the small sample size, even though data had a normal distribution, as confirmed by a Kolmogorov–Smirnov test. Where appropriate, we obtained 95% confidence intervals (CIs). The descriptive statistics and Wilcoxon signed-rank test were performed where appropriate, and statistical significance was determined at $P<.05$. Under a two-tailed α value of .05, the power of our sample to detect an effect size ($f = 0.85$) was 80%, which corresponds to

a difference in the 17-item HAM-D of approximately 8 points.

RESULTS

Demographic data: The mean age of patients was 43.3 ± 11.9 years and 5 patients were male. The mean age at onset was 32.9 ± 8.4 years and mean number of previous hospitalizations was 2.6 ± 1.7. Six (46.2%) patients terminated the study early as a result of adverse events ($n = 2$, 15.4%), withdrawal of consent ($n = 2$, 23.1%), loss to follow-up ($n = 1$, 7.7%) and lack of effectiveness ($n = 1$, 7.7%). Table 1 shows the clinical and demographic data of the original 13 participants. Although only 7 (53.8%) patients completed the full 8-week trial, 11 (84.6%) patients returned for at least one post–follow-up visit.

Medications: The daily mean dose and exit dose of aripiprazole was 10.8 ± 2.4 mg/day and 10.0 ± 3.8 mg/day throughout the study, respectively. The mean first dose of aripiprazole was 5.5 ± 1.0 mg/day, and the mean period of aripiprazole administration was 43.3 ± 19.0 days. Table 1 lists the pre-existing medications, which were maintained at the same doses at the time of study entry in accordance with the study protocol.

Effectiveness: The HAM-D and CGI-S scores decreased significantly from the baseline to the end of treatment by 53.8% and 56.0%, respectively ($Z = -2.937$, $P = .003$; $Z = -2.961$, $P = .003$), as shown in Figure 1. Compared with the baseline, 7 of the 11 ITT patients (63.6%) showed a ≥50% reduction in the HAM-D score at the end of treatment. Three (27.3%) patients met the remission criteria at the end of treatment. There was also a significant decrease in the HAM-D and CGI-S scores from baseline to the end of treatment, by 59.4% and 66.0%, respectively, according to completer analysis ($Z = -2.371$, $P = .018$; $Z = -2.401$, $P = .016$, respectively). Among study completers, 6 (85.7%) patients showed a ≥50% reduction in the HAM-D score, and 4 (57.1%) patients achieved the remission state at the end of treatment.

Tolerability: Nine patients (81.8%) reported at least one adverse event. There was little evidence of significant EPS according to BARS and SARS scores throughout the study period. Three patients scored on either BARS or SARS scores at certain times during the study. The reasons for scoring were mild hand tremor ($n = 2$, scored 1 point, 95% CI = 0.0228–0.5178) for the SARS score and mild akathisia ($n = 1$, scored 2 points in the global clinical assessment item, 95% CI = 0.0023–0.4128) for the BARS score. The mild hand tremor and akathisia appeared within 1 week and 10 days after administering aripiprazole, respectively. However, these side effects were resolved with benztropine. The most common side effects were headache and nausea ($n = 3$, 95% CI = 0.0602–0.6097; $n = 3$, 95% CI = 0.0602–0.6097, respectively). Other side effects were sedation, constipation, insomnia, and

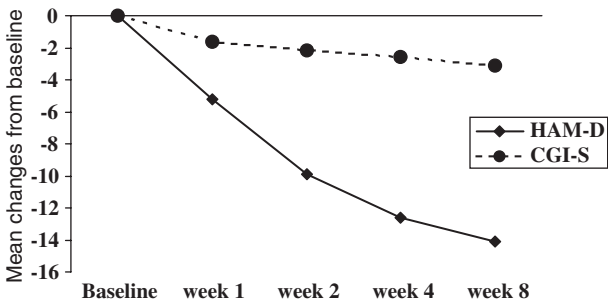

Figure 1. Mean changes on the HAM-D and CGI-S scores from baseline to the end of treatment [ITT samples with the LOCF for the end-of-treatment analysis ($n = 11$)].

TABLE 1. Baseline characteristics of the patients during the study (n=13)

Patients	Age (years)	Sex	Duration of illness (years)	Number of past admission	Existing psychotropics (mg/day)	Outcome	Response	Reason of DO
1	31	Female	4	1	P 40 plus LZP 3	DO at day 14	NR	Adverse event
2	32	Female	2	1	P 30 plus M 15 and LZP 2	DO at day 56	R	Lost to follow-up
3	66	Female	27	4	V 225 and LZP 3	Completion	R	—
4	49	Female	30	5	P 30 plus M 15 and LZP3	Completion	R	—
5	29	Male	2	2	P 20 plus M 15	Completion	R	—
6	52	Female	10	3	V 225 and LZP 3	Completion	NR	—
7	45	Female	4	1	C 40 plus LZP 3	DO at day 1	NA	Consent withdrawal
8	26	Male	2	1	P 20 plus M 30 and LZP2	Completion	R	—
9	47	Male	12	2	V 150 puls P 20 and LZP 3	Completion	R	—
10	37	Female	15	6	P 40 plus LZP 3	DO at day 1	NA	Consent withdrawal
11	44	Female	12	4	V 225puls P 20 and LZP 1.5	DO at day 56	NR	Lack of effectiveness
12	58	Male	18	3	V 225 plus LZP 1.5 and PPL	Completion	R	—
13	47	Male	2	1	P 40 plus M 15 and LZP 3	DO at day 28	NR	Adverse event

Abbreviations: P, paroxetine; V, venlafaxine XR; C, citalopram; M, mirtazapine; LZP, loeazepam; PPL, propranolol; DO, dropout; NR, nonresponse; R, response; NA, not applicable.

dizziness ($n = 2$, 95% CI = 0.0228–0.5178; $n = 2$, 95% CI = 0.0228–0.5178; $n = 1$, 95% CI = 0.0023–0.4128; and $n = 1$, 95% CI = 0.0023–0.4128, respectively). The mean change in weight was 1.7 ± 1.1 kg ($Z = -2.687$, $P = .007$). Electrocardiogram (ECG) and laboratory data showed no significant change at the end of the study. No serious adverse events attributable to aripiprazole were observed.

DISCUSSION

A plausible mechanism for aripiprazole augmentation to ADs might be its partial agonistic activity on the dopamine D_2 receptor, resulting in an increase in the release of dopamine in the hippocampus and prefrontal cortex [Li et al., 2004]. This is in line with the fact that the augmentation of dopamine agonists to ADs enhances the therapeutic response and outcome in the treatment of depressed patients [Thase et al., 2006]. In addition, partial agonism on the 5-HT_{1a} receptor, which is essential for neurogenesis in the hippocampus, can also account for its effects on depressive symptoms [Santarelli et al., 2003].

The overall efficacy of aripiprazole has been reported to range from 50% to 60% in terms of the CGI score [Barbee et al., 2004; Worthinton et al., 2005], which is in line with our findings. In particular, those who completed the study with $\geq 50\%$ reduction in the HAM-D score showed a better response than the ITT samples (85.7% vs. 63.6%), which is comparable to previous reports [67.0% vs. 59.0%, Worthington et al., 2005; 55.6% vs. 58.3%, Papakostas et al., 2005; 100.0% vs. 93.3%, Simon and Nemeroff, 2005]. The magnitude of the improvement observed with aripiprazole is comparable to that seen in augmentation studies with risperidone, olanzapine, and ziprasidone [Corya et al., 2003; Papakostas et al., 2004; Viner et al., 2003]. It is believed that the release of dopamine in the prefrontal cortex may play a role in the early response observed when second-generation antipsychotics are used as augmentation agents in those patients showing an inadequate response to ADs [Viner et al., 2003].

The dose findings of this study suggest that the aripiprazole dose needed to augment ADs would be less than that needed for patients with schizophrenia, which was derived from controlled studies [Kane et al., 2002; Potkin et al., 2003]. However, a similar dose has been suggested [Barbee et al., 2004; Papakostas et al., 2005; Simon and Nemeroff, 2005]. One study indicated that the starting dose should be between 2.5 and 7.5 mg/day, which is likely to be tolerable. The starting dose in our study was 5.5 mg/day. The average dose in this study was approximately 11.0 mg/day, which is less than that reported in a previous study [17.0 mg/day; Barbee et al., 2004]. It appears that the dose of aripiprazole for patients with an inadequate response to ADs should be less than that for patients with schizophrenia. In this context, the doses of risperidone, olanzapine, and ziprasidone in augmentation studies in depressed patients have generally been lower than the recommended therapeutic doses for schizophrenia [Corya et al., 2003; Papakostas et al., 2004; Viner et al., 2003]. This study did not evaluate whether an even lower starting dose (5 mg/day) would be effective in patients with an inadequate response to ADs. This issue clearly merits further investigation.

Eighty-two percent of patients suffered at least one adverse effect and 27.3% reported EPS. However, none of adverse events was serious. This reported rate of EPS is similar to the results (27–32%) from an acute and maintenance controlled trial for schizophrenia [Kane et al., 2002; Kasper et al., 2003; Potkin et al., 2003]. EPS were detected within 2 weeks of the aripiprazole treatment, which suggests a need for titration. In previous studies, the incidence of akathisia was 16.7% and 20% of 12 and 15 patients, respectively [Papakostas et al., 2005; Simon and Nemeroff, 2005], which was lower than that observed in this study. These differences might be due to patient characteristics, including ethnicity, and study method. Simon and Nemeroff reported that the rates of EPS in patients given low doses were less than rates for those on a high dose. Therefore, aripiprazole augmentation with ADs needs to be carefully monitored. Indeed, a recent large study with 1,493 patients with schizophrenia, recruited from 57 U.S. centers, compared a first-generation antipsychotic, perphenazine, with atypical antipsychotics in a double-blind design and failed to find any significant difference in the incidence of EPS between atypical antipsychotics and perphenazine [Lieberman et al., 2005].

The mean change in weight was similar to those in placebo-controlled studies of patients with schizophrenia [Kane et al., 2002; Potkin et al., 2003]. No patient in this study showed a more than 7% increase in weight compared with baseline. There were no major tolerability issues found with the combination of aripiprazole and the therapeutic doses of ADs.

This study has several shortcomings. It was not a randomized, double-blind, placebo-controlled method, which might lead to potential selection bias. The sample size was small, allowing the possibility of false-positive findings. The pharmacokinetics of the drug was not monitored. Finally, the follow-up period was relatively short. Hence, the period over which the effect was maintained could not be determined.

In conclusion, aripiprazole as an augmentation strategy in conjunction with conventional AD treatment was effective, well tolerated, and produced clinical improvement in patients with an inadequate response to ADs. These results highlight the potential benefit of aripiprazole for these patients. However, adequately powered, randomized, controlled trials are needed to confirm these results.

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