

# Additional Reduction of Residual Symptoms with Aripiprazole Augmentation in the Patients with Partially Remitted Major Depressive Disorder

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**Objective:** Many patients with major depressive disorder (MDD) suffer from residual symptoms without achieving remission. However, pharmacologic options for residual symptoms of MDD have been limited. This study aimed to investigate benefit of aripiprazole augmentation in the treatment of residual symptoms in the patients with partially remitted MDD.

**Methods:** We retrospectively analyzed the 8-week medical records of the patients. The enrolled patients did respond to treatment of antidepressant but were not remitted. The range of 17-item Hamilton Depression Rating Scale (HAMD) total score of the subjects were 8 to 15 points. All patients were currently taking antidepressants when they started aripiprazole. The primary endpoint was the mean change of Clinically Useful Depression Outcome Scale (CUDOS). Secondary endpoint measures were HAMD, Clinical Global Impression-severity (CGI-S) scores, Patient Health Questionnaire-15 (PHQ-15), Beck Anxiety Inventory (BAI), Perceived Deficit Questionnaire-depression (PDQ-D), Sheehan Disability Scale (SDS) and General Health Questionnaire/Quality of Life-12 (GHQ/QL-12).

**Results:** A total of 134 medical records were analyzed. The changes of CUDOS, HAMD, CGI-S, BAI, PHQ-15, PDQ-D, SDS and GHQ/QL-12 from baseline to the endpoint were  $-7.93$ ,  $-3.29$ ,  $-0.80$ ,  $-4.02$ ,  $-2.05$ ,  $-4.35$ ,  $-4.77$  and  $-2.82$ , respectively (all  $p < 0.001$ ). At the endpoint, the newly remitted subjects rate by HAMD score criteria were approximately 46%.

**Conclusion:** Our preliminary findings have presented the effectiveness of aripiprazole augmentation for residual symptoms of partially remitted MDD patients in routine practice. This study assures subsequent well-controlled studies of the possibility of generalizing the above promising outcome in the future.

**KEY WORDS:** Residual symptom; Major depressive disorder; Antidepressant; Aripiprazole augmentation.

## INTRODUCTION

Although the primary goal of pharmacotherapy for major depressive disorder (MDD) is the resolution of depressive symptoms, many patients suffer from residual symp-

toms of MDD from incomplete response to treatment. The rate of response to the first antidepressant treatment for MDD is only 55% [1]. The definition of a response to treatment usually refers to the time point when the depression is reduced by more than half of the initial score in the assessment scale [2,3]. Typically, a response is considered effective when the score is reduced by more than 50% on the Hamilton Depression Rating Scale (HAMD) [4]. Even when the score is reduced by more than 50%, patients often suffer from residual symptoms without reaching full remission ( $\text{HAMD} \leq 7$ ) [5]. Among res-

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ponders, these patients are referred to be in partial remission (HAMD 8–15) with residual symptoms [2]. Since the partial remission also result in high rate of relapse and functional impairment [6,7], clinical attention is required but its importance in clinical practice is mostly unknown [8]. Most trials designed to show the efficacy of antidepressant strategies have rarely focused on the patient with partially remitted MDD.

There are many clinical obstacles to treat residual symptoms of MDD. First, side effects can occur if several drugs are combined to treat residual symptoms. Second, switching to a different drug can unexpectedly worsen the depression rather than improve it. Therefore, these strategies may be not adequate therapeutic alternatives. An effective drug for the treatment of residual symptoms has not yet been established, and only a limited number of therapeutic trials have yet been conducted on the treatment of partially remitted MDD with residual symptoms. Most insights on the treatment of residual symptoms refer to the modalities for the adjunctive treatment of MDD showing a partial response. For patients who have residual symptoms with current antidepressants, additional treatment options may include diagnosis reassessment, dose increment, psychotropic augmentation, antidepressant combination, and switching to different antidepressants [9]. However, only few studies have been conducted on patients exhibiting a partial response and suffering from residual symptoms.

Aripiprazole was the first drug approved by the U.S. Food and Drug Administration in 2007 as an augmentation therapy to treat MDD [10,11]. The use of aripiprazole augmentation in MDD has dramatically increased worldwide and continues to be one of the best available augmentation options [12]. The efficacy of aripiprazole augmentation was clearly shown in a number of randomized controlled trials in depressed patients under various clinical conditions. Aripiprazole augmentation of sertraline exhibited superior efficacy to adjunctive placebo with sertraline for the treatment of acute major depressive episode [13]. Aripiprazole augmentation showed the efficacy to treat the MDD patients with partial response (e.g., < 50% reduction of symptoms) to antidepressant monotherapy [11,14]. In the patients with treatment resistant depression, aripiprazole also induced more response and remission through augmentation of antidepressants [15]. However, it is not clear that aripiprazole augmentation is

effective for those MDD patients with partial remission. It is worth investigating the efficacy of aripiprazole augmentation to treat residual symptom for these patients.

The aim of this study is to investigate clinical benefit of aripiprazole augmentation in patients with partially remitted MDD who are treated by current antidepressant, but have residual symptoms. Also, this study tried to determine how the aripiprazole augmented to antidepressant in patients with partially remitted MDD who did not reach remission can induce remission of MDD.

## METHODS

### Study Population

Diagnoses are conducted on clinical assessments by a board-certified psychiatrist. The inclusion criteria for the study subjects are as follows; (1) Patients who were treated by aripiprazole augmentation for more than 8 weeks in general clinical setting to treat residual symptoms of MDD. (2) The patients who were treated by antidepressant monotherapy before aripiprazole augmentation. (3) Antidepressant monotherapy is defined as follows: Escitalopram 10–20 mg/d, fluoxetine 20–40 mg/d, paroxetine controlled release (CR) 12.5–62.5 mg/d or paroxetine 10–40 mg/d, sertraline 50–150 mg/d, bupropion XL (SR) 150–300 mg/d, mirtazapine 15–45 mg/d, venlafaxine immediate or extended release (IR or ER) 75–225 mg/d, duloxetine 30–60 mg/d, tianeptine 12.5–25 mg/d. (4) The patients who had residual symptoms of partially remitted MDD defined as total scores of 8 to 15 on 17-item HAMD before aripiprazole augmentation [2]. (5) Patients are at least 18 years old. The exclusion criteria was as follows: (1) Patients who meet the criteria for a diagnosis of delirium, dementia or other cognitive disorder, bipolar disorder, schizophrenia, other psychotic disorder, eating disorder, obsessive compulsive disorder, posttraumatic stress disorder, mental retardation, or organic mental disorder. (2) Patients who have a history of electroconvulsive therapy to treat the current or previous depressive episode.

### Study Design

This is an 8-weeks, multicenter, retrospective, observational study for investigating the efficacy of aripiprazole augmentation to treat residual symptoms of partially remitted MDD. All information of subjects was obtained from medical records gathered during routine clinical

practice of the psychiatric units at five multi-sites in Korea. Observed subjects were treated for residual symptoms with aripiprazole augmentation although adequate dosage and period of antidepressant monotherapy had been tried. Aripiprazole was augmented on current antidepressant without dose limitation.

The data were collected for the patients who received prescription with aripiprazole augmentation to treat residual symptoms of MDD for more than 8 weeks in routine clinical practice (week 0, baseline; week 8, endpoint). At the baseline and endpoint, we gathered information on routine measurements including Clinically Useful Depression Outcome Scale (CUDOS), Global Impressions Scale-severity (CGI-S), Patient Health Questionnaire-15 (PHQ-15), Beck Anxiety Inventory (BAI), Perceived Deficits Questionnaire-depression (PDQ-D), General Health Questionnaire/Quality of Life-12 (GHQ/QL-12), and Sheehan Disability Scale (SDS) and safety assessment measured by Systematic Assessment for Treatment Emergent Events-Specific Inquiry (SAFTEE-SI).

The primary efficacy was mean change of CUDOS [16] from baseline (week 0) to the endpoint (week 8). The secondary endpoint measures included the changes in the mean scores of CGI-S, PHQ-15, BAI, PDQ-D, GHQ/QL-12, and SDS. Any occurrence of adverse event was assessed by SAFTEE-SI. The percentage of patients with remission (with respect to the entire study population) was defined as the percentage of patients with the HAMD score of 7 or below at point 2 [17].

## Instruments

### CUDOS

CUDOS is a self-administered depressive symptoms assessment developed by Zimmerman *et al.* [16]. The questionnaire consists of 18 items, including 16 items on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV depressive symptoms, 1 item on psychosocial impairment, and 1 item on the quality of life. According to the original study, the cutoff score for the 'minimal depression', 'mild depression', 'moderate depression', and 'severe depression' was suggested as 11, 21, 31, and 46, respectively. In particular, CUDOS has been found to be excellent in assessing residual symptoms of MDD in Korean population samples [18].

### HAMD

The HAMD is a clinician-administered scale for measuring severity of depressive symptoms [19]. The original scale comprises 21 items, though the 4 items for diurnal variation, depersonalization-derealization, paranoid symptoms, and obsessive-compulsive symptoms are not only rare in patients with MDD but were also associated to reduce the internal consistency. The 17-item version, which omits these items, is the most widely used version [20]. We used the well standardized Korean version of the 17-item HAMD [21].

### CGI-S

The CGI-S is a clinician-rating scale for measuring overall severity of patients with mental illnesses [22]. The CGI-S scale is made up of 1 item with 7 gradations of response. The minimum score is 1 and the maximum score is 7.

### PHQ-15

PHQ-15 is a test for measuring subjective somatic symptoms, with a score of 0 to 2 for each item, for a total of 15 items and a total score of 30. The original study suggested that PHQ-15 scores of 5, 10, and 15 represented cutoff points for low, medium, and high somatic symptom severity, respectively [23]. In a standardization study, the Korean version of the PHQ-15 was shown to be a reliable and valid test [24].

### BAI

BAI is a self-report scale consisting of 21 items measuring anxiety symptoms [25]. Each item is scored on a scale of 0 to 3, so the total score ranges from 0 to 63 points. The Korean version of BAI was standardized by Yook and Kim [26] and showed excellent consistency (Cronbach's alpha = 0.91) and a good discriminant validity.

### PDQ-D

PDQ-D is a self-administering test for measuring subjective cognitive impairment. It was originally developed to measure subjective cognitive impairment in multiple sclerosis patients, but has also been found to be effective for depression and is currently being used [27,28]. PDQ-D consists of 20 items in four domains: attention/concentration, retrospective memory, prospective memory, and organization/planning. Each item is scored on a 5-Likert

scale with the total score ranging from 0 to 60. A higher total score indicates that the subject complained more of subjective cognitive impairment. PDQ-D was a reliable and valid instrument in the Korean version of the PDQ-D standardization study conducted in a sample of MDD patients [29].

### GHQ/QL-12

GHQ/QL-12 is a test containing 12 questions on the quality of life from GHQ-60, which measures mental illness [30]. Each item is scored between 0 to 3 on a 4 point-Likert scale, and the total score ranges from 0 to 36 points. A higher score indicates better state for quality of life. The Korean version of the GHQ/QL-12 was translated and validated by Kook and Son [31].

### SDS

SDS is a tool for measuring functional impairment [32]. The subjective level function is scored on a scale of 0 to 10 in 3 domains including work/school, social life, and family life/home responsibilities with the total score ranging from 0 to 30 for the 3 domains. A higher score show more profound functional impairment. The Korean version of the SDS showed excellent internal consistency and test-retest reliability [33].

### Ethics

The study protocol was approved by the Institutional Review Board of the Korea University Ansan Hospital (IRB No. 2015AS0036).

### Statistical Analysis

Nominal data represent the frequency and the ratio, and for continuous data, summarize using frequency, mean, and standard deviation (SD).

In order to verify the efficacy of aripiprazole augmentation for the subjects, it is necessary to compare the changes of residual symptoms before (baseline) and after taking aripiprazole (endpoint). Paired *t* test was performed to test for serial changes in CUDOS scores between baseline and endpoint. Dependent variable is achievement or failure of improvement of residual symptoms. The improvement of residual symptom is defined as total scores of less than below 7 or less on HAMD after aripiprazole augmentation. Remission rates from the above criteria were obtained from all subjects.

Secondary analysis was conducted with CGI-S, PHQ-15, BAI, PDQ-D, GHQ/QL-12, and SDS. 95% confidence interval for the changes of those scales was presented at both sides of visit point (baseline and endpoint). Statistical differences of those scales between baseline and endpoint were tested by paired-*t* test. To determine the factors that may influence remission in the baseline, we examined the difference between demographic variables and rating scales between the remitted group and the non-remitted group at baseline through an ANCOVA test that adjusted age and sex by a confounding factor. All data were analyzed using the SPSS 20.0 for windows (IBM Co., Armonk, NY, USA). Statistical significance was set at  $p < 0.05$ .

## RESULTS

### The Baseline Sociodemographic and Clinical Data

The subjects recruited for this study included 89 females and 45 males with a mean age of  $52.96 \pm 15.81$  years. The mean dose of aripiprazole for week 0 was  $1.72 \pm 0.93$  mg/day, and the mean dose at week 8 was  $2.33 \pm 1.59$  mg/day. The mean duration of the outpatient treatment prior to the aripiprazole augmentation was  $47.06 \pm 73.01$  weeks. The detailed sociodemographic and clinical data are presented in Table 1.

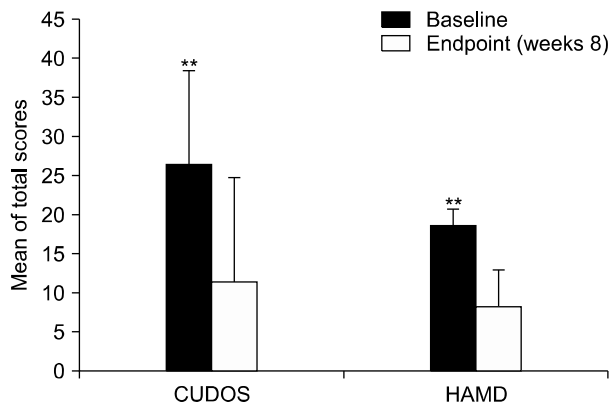
**Table 1.** Baseline sociodemographic and clinical characteristics of the study sample

| Variable                     | Value         |
|------------------------------|---------------|
| Age                          | 52.96 ± 15.81 |
| Age of onset                 | 48.44 ± 15.33 |
| Sex                          |               |
| Male                         | 45 (33.6)     |
| Female                       | 89 (66.4)     |
| Family history of depression |               |
| Yes                          | 118 (88.1)    |
| No                           | 14 (10.4)     |
| Medical comorbidity          |               |
| Yes                          | 70 (52.2)     |
| No                           | 64 (47.8)     |
| Concomitant antidepressant   |               |
| SSRI                         | 74 (55.2)     |
| SNRI                         | 48 (35.8)     |
| NaSSA                        | 5 (3.7)       |
| Tianeptine                   | 7 (4.5)       |
| Trazodone                    | 1 (0.7)       |

Values are presented as mean ± standard deviation or number (%). SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin Norepinephrine Reuptake Inhibitor; NaSSA, Noradrenergic and specific serotonergic antidepressants.

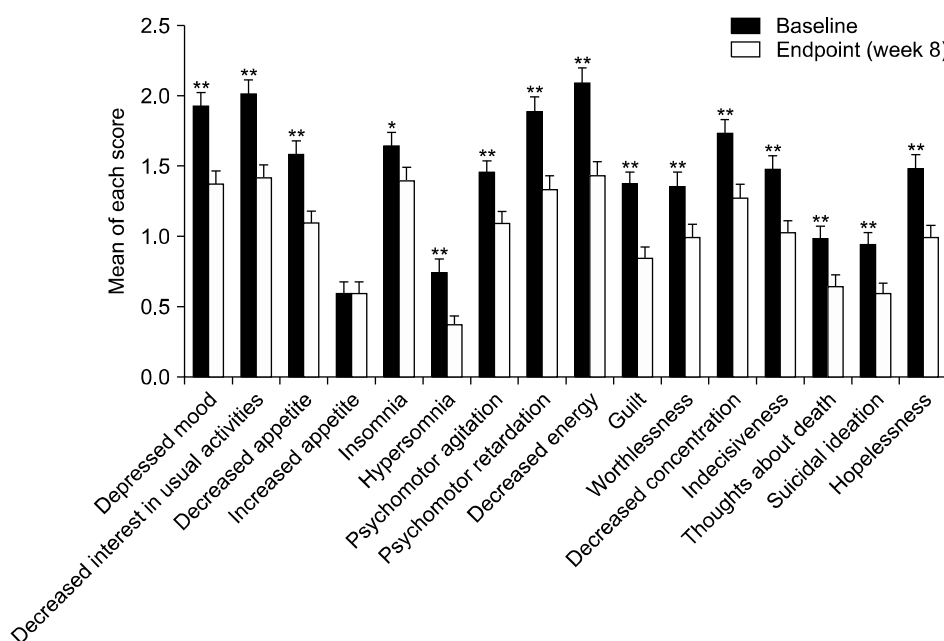
### The Changes of Depressive Symptoms and Clinical Severity

After 8 weeks of the trial, the total score for CUDOS significantly decreased by  $-7.93$  points ( $SD = 11.28$ ), HAMD by  $-3.29$  points ( $SD = 4.40$ ), and CGI-S by  $-0.80$  points ( $SD = 1.02$ ) at the endpoint compared to the baseline (all  $p < 0.001$ ) (Fig. 1). When each CUDOS item was analyzed individually, all items showed a significant overall improvement with the exception of item 4 on 'increased appetite' (Fig. 2). The analysis of each HAMD item showed improved scores but statistical significance was not found for item 5 'initial insomnia', item 6 'mid-phase



**Fig. 1.** Mean changes in the Clinically Useful Depression Outcome Scale (CUDOS) and the 17-item Hamilton Depression Rating Scale (HAMD) between baseline and endpoint (weeks 8).

\*\*Indicates  $p$  value below 0.001. Error bars represent one standard deviation of the mean.



**Fig. 2.** Mean changes of each items of the Clinically Useful Depression Outcome Scale between baseline and endpoint (weeks 8).

\*Indicates  $p$  value below 0.05. \*\*Indicates  $p$  value below 0.001. Error bars represent one standard error of the mean.

insomnia', item 7 'late-phase insomnia', item 15 'hypochondriasis', and item 17 'insight'. The frequency of depression going into remission (HAMD score of 7 or below) was 46.3% (62 subjects in total).

### The Changes of Anxiety, Somatic Symptoms, Subjective Cognitive Function, and Quality of Life

Compared with point 1 and point 2 after treatment with aripiprazole, the total scores of instruments for overall anxiety (BAI), somatic symptoms (PHQ-15), subjective cognitive function (PDQ-D), and quality of life (GHQ/QL-12) were all significantly improved. The mean changes from baseline to endpoint in total BAI, PHQ-15, PDQ-D, SDS, and GHQ/QL-12 score was  $-4.02$  ( $SD = 10.72$ ),  $-2.05$  ( $SD = 4.82$ ),  $-4.35$  ( $SD = 11.06$ ),  $-4.77$  ( $SD = 6.68$ ) and  $2.82$  ( $10.65$ ), respectively ( $p < 0.001$ ).

### The Baseline Difference between Remitted Group and Non-remitted Group

The sociological variables in the remitted group and the non-remitted group did not differ at the baseline before supplement therapy (Table 2). When ANCOVA analysis was conducted at baseline with age and sex as covariates, no difference was found between the remitted group and non-remitted group for BAI, PHQ-15, PDQ-D, GHQ/QL-12, and SDS. The total score for the non-remitted group was significantly higher for HAMD in the aforementioned analysis (Table 3).

**Table 2.** Remission group vs. non-remission group in baseline, demographic and clinical variables

| Variable                     | Remission (n = 62) | Non-remission (n = 72) | Statistics             | p value            |
|------------------------------|--------------------|------------------------|------------------------|--------------------|
| Age                          | 51.19 ± 16.75      | 51.47 ± 15.55          | t = 0.100              | 0.921 <sup>a</sup> |
| Age of onset                 | 43.64 ± 22.66      | 42.44 ± 19.00          | t = -0.332             | 0.741 <sup>a</sup> |
| Sex                          |                    |                        | χ <sup>2</sup> = 0.668 | 0.460 <sup>b</sup> |
| Male                         | 18 (13.6)          | 25 (18.9)              |                        |                    |
| Female                       | 44 (33.3)          | 45 (34.1)              |                        |                    |
| Family history of depression |                    |                        | χ <sup>2</sup> = 2.40  | 0.494 <sup>b</sup> |
| Yes                          | 54 (40.9)          | 64 (48.5)              |                        |                    |
| No                           | 6 (4.5)            | 8 (6.1)                |                        |                    |
| Medical comorbidity          |                    |                        | χ <sup>2</sup> = 3789  | 0.058 <sup>b</sup> |
| No                           | 38 (28.4)          | 32 (23.9)              |                        |                    |
| Yes                          | 24 (17.19)         | 40 (29.9)              |                        |                    |
| Concomitant antidepressant   |                    |                        | —                      | 0.450 <sup>c</sup> |
| SSRI                         | 37 (26.6)          | 37 (27.6)              |                        |                    |
| SNRI                         | 19 (20.7)          | 25 (11.8)              |                        |                    |
| NaSSA                        | 5 (2.4)            | 4 (3.0)                |                        |                    |
| Tianeptine                   | 1 (3.6)            | 5 (0.6)                |                        |                    |
| Trazodone                    | 0 (0.6)            | 1 (0)                  |                        |                    |

Values are presented as mean ± standard deviation or number (%).

SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin Norepinephrine Reuptake Inhibitor; NaSSA, Noradrenergic and specific serotonergic antidepressants.

<sup>a</sup>Student's *t* test. <sup>b</sup>Chi-squared test. <sup>c</sup>Fisher's exact test.

**Table 3.** The baseline difference of rating scores between remitted and non-remitted group

| Scales    | Remission (n = 62) | Non-remission (n = 72) | F    | p value |
|-----------|--------------------|------------------------|------|---------|
| CUDOS     | 25.44 ± 11.34      | 26.61 ± 10.46          | 0.54 | 0.463   |
| HAMD      | 11.05 ± 2.15       | 12.03 ± 1.88           | 7.80 | 0.006*  |
| CGI-S     | 3.61 ± 0.69        | 3.70 ± 0.71            | 0.75 | 0.390   |
| BAI       | 16.45 ± 10.38      | 15.14 ± 10.07          | 0.41 | 0.523   |
| PHQ-15    | 8.35 ± 4.92        | 9.67 ± 5.53            | 2.30 | 0.132   |
| PDQ-D     | 21.82 ± 14.43      | 20.70 ± 13.88          | 0.15 | 0.696   |
| GHQ/QL-12 | 12.63 ± 6.91       | 12.70 ± 6.34           | 0.01 | 0.928   |
| SDS_total | 13.75 ± 6.15       | 13.67 ± 6.14           | 0.01 | 0.944   |

Values are presented as mean ± standard deviation.

HAMD, 17-item Hamilton Depression Rating Scale; CUDOS, Clinically Useful Depression Outcome Scale; CGI-S, Clinical Global Impression-severity Scale; BAI, Beck Anxiety Inventory; PHQ-15, Patient Health Questionnaire-15; PDQ-D, Perceived Deficits Questionnaire-depression; GHQ/QL-12, 12-item General Health Questionnaire/Quality of Life; SDS, Sheehan Disability Scale.

\**p* < 0.005.

### Safety

According to the medical records from the 8-week aripiprazole therapy, the treatment was relatively safe and adverse events were rare. There was no increase in suicidal ideation or completed suicide during the study. Further, there were no deaths or treatment-related severe adverse events. Most adverse events were reports of mild symp-

toms. The most common adverse event was headache in 4 cases (3.0%), followed by dizziness in 2 cases (1.5%). In addition, there occurred new cases of insomnia, abdominal discomfort, and nausea in 1 subject, respectively.

## DISCUSSION

The present study aimed to identify the therapeutic effects of aripiprazole augmentation to existing antidepressant treatment in patients with residual symptoms of MDD who had reached partial remission despite adequate antidepressant treatment. Aripiprazole administration clearly improved the overall clinical condition and most of the residual symptoms. Also, many of the previously partially remitted depressive symptoms in the patients did reach remission. Although various therapeutic strategies such as changing or switching the drug and augmentation may be considered if only a partial response is achieved despite a continuous treatment with antidepressants [34], there are only a handful of therapeutic strategies recommended for patients who show a response that is near remission. These cases are quite common in clinical settings and require active treatment as they are strongly associated with the recurrence of depression, functional impairment, and poor quality of life [35,36]. Judging from our knowledge,

the present study appears to be the first of its kind to report the efficacy of augmentation therapy for this group of patient.

Our study presented that adding a low dose of aripiprazole in routine practice can be a useful treatment strategy for partially remitted MDD with residual symptoms. The anti-depressive effect of aripiprazole for the residual symptoms was shown at a low daily mean dose of  $1.66 \pm 0.86$  mg to  $2.14 \pm 1.47$  mg. This is consistent with previous findings that a low dose of aripiprazole of 2 to 3 mg was superior to an antidepressant monotherapy [13], although previous studies also reported higher dose ranging from 7 to 12 mg of aripiprazole augmentation was needed to treat incomplete responders to antidepressant monotherapy [11,15]. The gap in effective aripiprazole dose between studies is thought to be due to the difference in study population. In the patients with partial or no response, a higher dose was generally required for the treatment of depression than the patients with acute depressive episode.

The low dose of aripiprazole suggests that the potential for side effects may be minimal. The side effects recorded in this study were limited to minor side effects and no severe adverse effects were reported. Considering that aripiprazole can cause side effects such as somnolence and extrapyramidal symptoms in a dose-dependent manner [37], it is encouraging that the treatment efficacy was achieved only with a small quantity of aripiprazole. In addition, a polypharmaceutical approach to patients with residual symptoms or a partial response is necessarily focused on avoiding an increase in adverse effects, but the present study suggests that such concern might be limited to a minimum.

Aripiprazole augmentation therapy improved clinical outcomes including anxiety symptoms, physical symptoms, cognitive function, and the quality of life in our sample. Anxiety is one of the most frequently accompanied symptoms of depression and a significant number of patients who show a significant reduction in depression following treatment still suffer from anxiety [38,39]. Depression and anxiety are similar in that the treatment uses antidepressants but there is no definitive treatment for the residual symptoms after the first treatment. Adson *et al.* [40] have reported using aripiprazole augmentation to relieve anxiety symptoms when the anxiety symptoms remain clinically significant (more than 16 points on the

Hamilton Anxiety Rating Scale) in MDD. The anxiolytic effect of aripiprazole in the present study is in agreement with these results.

Cognitive impairment is another major symptom of MDD, and it affects a significant number of patients as a residual symptom even after reaching remission after treatment [41]. Cognitive impairment as a residual symptom has been a clinical concern as it increases the likelihood of the recurrence of depressive episodes or decreases the function and work capacity [42,43]. Subjective cognitive impairment has also been treated as a persistent residual symptom of depression. A preferred therapy has not yet been established, similar to the absence of a unique treatment for other domains of symptoms. Some families of antidepressants claim to offer better efficacy for cognitive decline [44,45], but complete evidence is lacking. In addition, there is little research into the superior efficacy of a certain specific drug treatments for subjective cognitive decline. Here we show that aripiprazole may be a possible treatment for residual cognitive decline indicated by a significant reduction in PDQ-D.

The physical symptoms measured by PHQ-15 were significantly reduced by the aripiprazole augmentation therapy in the present study. Incomplete remission conditions are commonly associated with somatic anxiety and pain states [46]. Residual symptoms that persist after treatment are considered as a risk factor associated with early relapse [47], and are associated with a severe and chronic course of the disease [48,49]. Of course, according to relieving depression by treatment of antidepressant, somatic symptoms are expected to be reduced. But treatment of residual somatic symptoms in depression may require additional neurotransmitter actions to the antidepressant [50]. Descending dopaminergic modulation by D<sub>2</sub> receptor partial agonism and increased norepinephrine availability by 5-HT<sub>2A</sub> antagonism of aripiprazole may be effective in controlling somatic symptoms [51,52]. Still, little is known about the somatic symptom targeting effects of aripiprazole. Several case reports showed nociceptive effects of aripiprazole [53,54], and a clinical trial reported that aripiprazole augmentation was effective to treat GI symptom related to MDD patients [55].

This study showed that an improvement in the psychiatric symptoms as well as in the quality of life and overall function could be achieved through additional augmentation therapy of residual symptoms. In patients with re-

residual symptoms of depression, a reduction in the overall function and quality of life is an important problem [56], and has been considered to be the true end goal of therapy in recent depression treatment, beyond the general treatment of depressive symptoms [57,58]. Based on the present study, it is advisable to perform an aggressive adjuvant therapy containing aripiprazole if there is clinical evidence of a decreased function or quality of life at any time point with residual symptoms.

In this study, the patients with an HAMD score of 8 or higher and 15 or lower were included. Based on previous studies, the patients who had this range of HAMD score was considered as suffering mild depressive symptoms but did not meet full criteria of major depressive disorder [59,60]. However, after treatment, patients who remain below the HAMD score of 7 or less which is considered as full remission may suffer from residual symptoms or persistent functional impairment due to residual symptoms [39,61] or persistent functional impairment due to residual symptoms [35,36]. It is necessary to investigate whether aripiprazole augmentation has a therapeutic effect in those patients with minimal residual symptoms of MDD.

There are several limitations to this study. First, this study examined the difference in efficacy before and after aripiprazole augmentation therapy in depressed patients. This type of non-controlled study could have been influenced by confounding variables. In order to reach a higher level of evidence for the therapeutic effects of aripiprazole in residual symptoms of depression, a study with a comparative control group would be required. Second, there is a limitation in the validation as no structured interview was used for the diagnosis of depression, and instead, the diagnostic criteria of DSM-5 were applied by an expert clinician. In addition, the HAMD used in this study is a clinician administration scale, but we could not obtain information on inter-rater reliability. However, it was performed by a board-certified psychiatrist or a clinical psychologist at each site. These are basic weaknesses of a naturalistic clinical setting. Nonetheless, such a setting has significant benefits in providing insights into the effectiveness and tolerability of drugs in actual clinical practice.

The mean scores of all scales except HAMD between remitted and non-remitted groups at baseline were not significantly different. Only low HAMD score at baseline

was associated with remission after augmenting aripiprazole. This is to be a natural result that can be expected. Since no psychiatric condition we assessed impact on afterward remission with aripiprazole augmentation, any patient can be recommended to receive aripiprazole augmentation regardless of anxiety, somatic symptoms, cognitive decline, or functional impairment.

Aripiprazole augmentation therapy for antidepressants has improved the residual depressive symptoms, thus remitted many of the subjects' major depressive disorder that were partially remitted. Aripiprazole augmentation may improve not only the depressive symptoms of major depressive disorder patients with some residual symptoms, but also associated anxiety, somatic symptoms, cognitive decline, quality of life, and overall functioning. Although there are several limitations, we suggest that administration of a low-dose of aripiprazole can be a treatment option for the improvement in depressive symptoms and overall functioning in the patients with residual symptoms of partially remitted MDD.

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#### ■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

#### ■ Author Contributions

Conceptualization: Changsu Han, Kyung Phil Kwak, Jong-Woo Kim, and Chi-Un Pae. Data acquisition: Changsu Han, Chi-Un Pae, Kyung Phil Kwak, Hyun-Ghang Jeong, and Jong-Woo Kim. Formal analysis: Sang Won Jeon and Cheolmin Shin. Writing—original draft: Cheolmin Shin. Supervision: Cheolmin Shin, Jong-Woo Kim, and Youn Jung Lee. Writing—review & editing: Changsu Han and Ashwin A. Patkar. All authors contributed significantly to the study, and have approved the final manuscript.

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