

Clinical Usefulness of Amisulpride Add-on Therapy in Schizophrenia Patients without Treatment Response to Second-generation Antipsychotics

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Objective: The response to antipsychotics in patients with schizophrenia is still unsatisfactory. Therefore, augmentation with other antipsychotics is common in clinical situations. The purpose of this study was to evaluate the improvement of psychiatric symptoms and side effects after amisulpride add-on therapy.

Methods: Forty patients with schizophrenia or schizoaffective disorder without treatment response to second-generation antipsychotics were included in this study. Psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Korean version of Calgary Depression Scale for Schizophrenia (CDSS) at baseline, 4 weeks, and 8 weeks after the addition of amisulpride.

Results: Among the 29 subjects who completed the 8-week study, 34.5% were responders according to PANSS total score. At week 8, the mean positive ($p < 0.001$), negative ($p < 0.001$), general ($p < 0.001$), and total ($p < 0.001$) PANSS scores and CDSS scores ($p = 0.002$) showed significant improvement compared to baseline. There was no increase in extrapyramidal side effects according to Simpson Angus Scale ($p = 0.379$) and Barnes Akathisia Rating Scale ($p = 0.070$) and no weight gain ($p = 0.308$) after the add-on treatment.

Conclusion: The addition of amisulpride for schizophrenia patients without therapeutic response to second-generation antipsychotics is considered an effective and safe treatment. This study's results suggested that augmentation of second-generation antipsychotics with amisulpride could be a useful option for patients with schizophrenia unresponsive to second-generation antipsychotics. Further studies investigating the efficacy of amisulpride add-on therapy using placebo control are necessary to confirm these results.

KEY WORDS: Antipsychotic agents; Amisulpride; Drug augmentation; Schizophrenia; Treatment efficacy.

INTRODUCTION

Antipsychotics are mainstays in the treatment of schizophrenia and other psychotic disorders. Although many antipsychotics have been developed and the side effects of antipsychotics have decreased considerably, the treatment responses of patients with schizophrenia remain unsatisfactory. Approximately 20–30% of the patients with schizophrenia do not show treatment response to an-

tippsychotics [1]. Treatment resistance of schizophrenia might result in significant sequelae including functional disability at work and in education, social withdrawal, and even suicide. Clozapine is the only effective medication for treatment-resistant schizophrenia [2]. However, it has significant side effects such as agranulocytosis, seizure, sialorrhea, weight gain, and sedation [2].

Therefore, add-on therapies with antipsychotics have been attempted frequently in patients with refractory schizophrenia in clinical situations and many studies have been conducted on this topic [3-5]. Acute patients who did not respond to initial and second antipsychotics showed effective and relatively tolerable response to a third antipsychotic administered as an augmentation therapy [5]. A systematic review of randomized controlled tri-

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als (RCTs) regarding augmentation with aripiprazole in patients with schizophrenia resistant to clozapine suggested trends of aripiprazole augmentation benefits on overall positive and negative symptoms. However, the improvement was not significant [3]. Another meta-analysis on the same topic showed significant improvement in symptoms when the augmentation treatment lasted for more than 10 weeks. However, there was a lack of improvement when the treatment duration was less than 10 weeks [4]. A meta-analysis comparing antipsychotic augmentation therapy and monotherapy showed that augmentation therapy lacked double-blind/high-quality evidence for efficacy, except the reported negative symptom reduction with aripiprazole augmentation [6]. Generally, research results on augmentation therapy have been inconsistent with respect to the combination of augmentation drugs and research design.

Amisulpride is an effective benzamide antipsychotic with high selectivity for D₂ and D₃ dopamine receptors. It has been reported to be as effective as haloperidol [7,8] and olanzapine [9] in treating schizophrenia. In a study comparing amisulpride and haloperidol, amisulpride had a comparable effect on positive symptoms and a superior effect on negative symptoms when compared with haloperidol [8]. In a meta-analysis by Leucht *et al.* [10], amisulpride showed robust efficacy and better tolerability with less discontinuation due to side effects when compared with a placebo. Several studies have reported the efficacy of amisulpride augmentation therapy in patients with schizophrenia who showed partial response to antipsychotics [11-14]. These studies generally reported that augmentation with amisulpride was a useful and safe treatment. However, the number of studies was insufficient to generalize these results and additional studies were recommended since there were no consistent results regarding the side effects [11,14]. Moreover, no research has been done on this subject in Korea.

The present study was designed to determine whether amisulpride augmentation therapy had good efficacy and tolerability in Korean patients with schizophrenia who showed insufficient treatment response to second-generation antipsychotics (SGAs).

METHODS

Subjects

Board-certified psychiatrists interviewed the patients using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria [15]. The inclusion criteria were as follows: 1) men and women aged 18–65 years who were diagnosed with schizophrenia or schizoaffective disorder according to the DSM-5 diagnostic criteria, 2) insufficient treatment response to SGAs for more than 2 months (defined as a score of 4 or higher for both hallucinations and delusions on the Positive and Negative Syndrome Scale (PANSS) [16]), and 3) patients who fully understood the study and provided written consent. The exclusion criteria were as follows: 1) serious medical or neurological diseases other than schizophrenia, 2) subjects who had taken clozapine previously, 3) pregnant or breastfeeding females, and 4) treatment with long-acting injectable antipsychotics during the previous month. All the participants provided written informed consent and the Institutional Review Board of Gil Medical Center approved this study protocols before the commencement of the study (no. GBIRB2014-64). We followed the relevant guidelines and regulations for all experiments throughout the study period.

Amisulpride Treatment and Clinical Assessments

Patients were administered 400 mg of amisulpride orally while maintaining the previous antipsychotic drugs. Generally, if there is a history of extrapyramidal side effects (EPS) or a concern about such side effects, a 200 mg dose may be administered and the increase of dosage to 400 mg should be considered after 2 weeks. In the present study, amisulpride was administered as a fixed dose for 4 weeks. After 4 weeks, it could be changed to a flexible dose depending on the symptoms and the side effects of the drug.

Benzotropine was allowed to be administered when EPS occurred. Same doses of previous antipsychotic drugs, mood stabilizers, sleeping pills, anticholinergic drugs, antidepressants, and anti-anxiety drugs taken during previous 2 weeks were maintained during the study period. No other antipsychotic drugs were allowed during the entire study period.

Psychiatric symptoms and side effects of the antipsychotics were evaluated at baseline, 4 weeks, and 8

weeks. Psychiatric symptoms and their intensity in each participant were evaluated using PANSS [16], Clinical Global Impression Scale (CGI-S) [17], Clinical Global Impression Clinical Benefit Scale (CGI-CB), and the Korean version of Calgary Depression Rating Scale for Schizophrenia (CDSS) [18,19]. Side effects of antipsychotics were evaluated using Barnes Akathisia Rating Scale (BARS) [20] and Simpson Angus Scale (SAS) [21]. Each patient was interviewed and evaluated by the same psychiatrist throughout the study period.

Outcome Measure and Statistical Analysis

The primary goal of the present study was to observe the improvement of psychiatric symptoms according to PANSS scores at 4 weeks and at 8 weeks after the addition of amisulpride to previous SGAs and to investigate the percentage of responders to augmentation.

The secondary goal of the study was to assess the degree of global improvement based on CGI-S scores at 4 and 8 weeks. Depression severity was assessed using CDSS at 4 and 8 weeks. Evaluation of EPS and weight gain was performed using body mass index (BMI), BARS, and SAS.

Treatment response was defined as a decrease in the PANSS total score of more than 50% of the baseline score minus 30 (i.e., minimum possible PANSS total score), as described previously [22].

if x was > 50 , subjects were considered to show a response.

$$x = \frac{(\text{baseline PANSS score minus endpoint PANSS score}) \times 100}{(\text{baseline PANSS score minus 30})}$$

At the start of the clinical study, demographic characteristics (age and sex) and clinical characteristics of all the participants were assessed. The quantitative data were presented as mean \pm standard deviation and the qualitative data were presented as frequency and percentage.

Descriptive statistics, frequency analysis, chi-squared test, independent t test, and paired t test were used for the statistical analyses. All analyses were performed using SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$.

RESULTS

Characteristics of the Participants

Among the 40 subjects included in the study, 29 subjects completed the treatment course and the follow-up evaluation for 8 weeks (Table 1). The mean age of the participants was 45.5 ± 14.0 years, the mean duration of schizophrenia was 13.6 ± 9.9 years, and the mean number of antipsychotic drugs used were 1.2 ± 0.4 . The average PANSS score of the subjects was 81.9 ± 14.3 (81.7 ± 12.5 in completers) and the mean CGI-S score was 4.4 ± 0.9 (4.5 ± 0.9 in completers). Thus, all the participants were in moderately ill to markedly ill state.

Subjects were those who had been taking one or two antipsychotics. The number of subjects who took and dosage of each antipsychotic were as follows: paliperidone ($n = 18$, mean dosage = 10.2 ± 3.9 mg), olanzapine ($n = 5$, mean dosage = 13.5 ± 6.0 mg), risperidone ($n = 5$, mean dosage = 6.2 ± 3.5 mg), blonanserin ($n = 8$, mean dosage = 13.5 ± 6.7 mg), aripiprazole ($n = 5$, mean dosage = 23.0 ± 11.0 mg), quetiapine ($n = 6$, mean dose = 79.2 ± 69.7 mg), and chlorpromazine ($n = 1$, dosage = 100 mg). The average duration of antipsychotics use was 12.5 ± 14.0 months. Eight people had taken two antipsychotics, the majority of whom ($n = 6$) were using quetiapine or chlorpromazine for the purpose of improving sleep. There was no statistically significant relationship between the number of antipsychotic drugs used and the response at 8 weeks ($\chi^2 = 1.06$, $p = 0.303$).

Table 1. Demographic and clinical characteristics of participants at baseline

Variable	All patients (n = 40)	Completers (n = 29)
Age (yr)	45.5 ± 14.0	45.6 ± 13.6
Sex, female	21 (52.5)	14 (48.3)
Duration of schizophrenia (yr)	13.6 ± 9.9	14.5 ± 10.3
Body mass index	25.5 ± 4.5	25.0 ± 3.9
Number of prior antipsychotics	1.2 ± 0.4	1.2 ± 0.4
Starting dose of amisulpride	330.0 ± 96.6	331.0 ± 96.7
PANSS total score	81.9 ± 14.3	81.7 ± 12.5
CGI-S	4.4 ± 0.9	4.5 ± 0.9
SAS	0.9 ± 2.2	1.3 ± 2.5
BARS	1.0 ± 1.3	0.9 ± 1.4

Data are presented as mean \pm standard deviation or number (percentage). PANSS, Positive And Negative Syndrome Scale; CGI-S, Clinical Global Impression Severity Scale; SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale.

Efficacy Evaluation

Among the 29 subjects who completed this study, 34.5% showed symptom improvement of 50% or more according to the PANSS total score (Table 2). Average starting dose of amisulpride was 331.0 ± 96.7 mg in patients who completed the study (Table 3). After 8 weeks, 30% of the patients in the 200 mg starting dose group and 36.7% of the patients in the 400 mg starting dose group responded to the treatment. There was no significant difference in the number of responders between the two groups ($\chi^2 = 0.14$, $p = 0.713$; Table 2).

Pre-treatment and post-treatment (after 8 weeks) PANSS, CDSS, CGI-S, and CGI-CB scores were compared

in subjects who completed the study. PANSS scores in all domains (positive: $t = -10.92$, $p < 0.001$; negative: $t = -7.63$, $p < 0.001$; general: $t = -7.83$, $p < 0.001$) and PANSS total scores ($t = -11.80$, $p < 0.001$) showed significant changes. CDSS ($t = -3.34$, $p = 0.002$), CGI-S ($t = -8.07$, $p < 0.001$), and CGI-CB ($t = -7.41$, $p < 0.001$) scores showed significant improvement (Table 3).

There were no statistically significant differences in demographic characteristics (age and sex), duration of illness, and number of antipsychotic drugs between the 200 mg starting dose group and the 400 mg starting dose group (Table 4). The PANSS and CGI-S scores at baseline and the scores after 8 weeks did not show statistically sig-

Table 2. Response rate and premature withdrawal from the study (n = 40)

Variable	Total (n = 40)	200 mg start group (n = 14)	400 mg start group (n = 26)	Comparison between 200 mg and 400 mg start groups
Responders among completers (n = 29) based on PANSS total score	10/29 (34.5)	3/10 (30.0)	7/19 (36.8)	$\chi^2 = 0.14$, $p = 0.713$
Total withdrawals	11 (27.5)	4 (28.6)	7 (26.9)	$\chi^2 = 0.01$, $p = 0.911$
Reason for withdrawal				$\chi^2 = 8.27$, $p = 0.082$
Lack of efficacy	2 (5)	2 (14.3)	0 (0)	
Adverse reaction	3 (7.5)	2 (14.3)	1 (3.8)	
Lost to follow-up	4 (10)	0 (0)	4 (15.4)	
Other reasons	2 (5)	0 (0)	2 (7.7)	
Time of withdrawal				$\chi^2 = 1.43$, $p = 0.488$
< 4 weeks	9 (22.5)	4 (28.6)	5 (19.2)	
≥ 4 weeks and < 8 weeks	2 (5)	0 (0)	2 (7.7)	

Data are presented as number (percentage).

PANSS, Positive And Negative Syndrome Scale.

χ^2 : chi-squared test was used for statistical comparisons.

Table 3. Comparison of treatment outcomes and adverse reactions in patients with schizophrenia before and after amisulpride add-on therapy

Variable	Baseline	4 weeks	8 weeks	Comparison (baseline vs. 8 weeks)
Dose of amisulpride (mg)	331.0 ± 96.7	358.6 ± 132.3		
PANSS				
Total	81.7 ± 12.5	67.3 ± 12.4	60.0 ± 14.7	$t = -11.80$, $p < 0.001$
Positive	24.0 ± 4.6	17.8 ± 4.7	15.3 ± 4.9	$t = -10.92$, $p < 0.001$
Negative	18.4 ± 3.7	15.7 ± 3.0	14.2 ± 3.4	$t = -7.63$, $p < 0.001$
General	39.7 ± 8.0	33.7 ± 6.7	30.8 ± 7.9	$t = -7.83$, $p < 0.001$
CDSS	3.6 ± 4.5	1.9 ± 3.6	1.9 ± 4.3	$t = -3.34$, $p = 0.002$
CGI-S	4.5 ± 0.9	3.5 ± 0.9	3.1 ± 0.9	$t = -8.07$, $p < 0.001$
CGI-CB	6.8 ± 2.0	4.3 ± 1.9	4.0 ± 1.6	$t = -7.41$, $p < 0.001$
Extrapyramidal side effects				
SAS	1.3 ± 2.5	1.1 ± 2.2	1.0 ± 2.2	$t = -0.89$, $p = 0.379$
BARS	0.9 ± 1.4	0.6 ± 1.1	0.5 ± 1.1	$t = -1.89$, $p = 0.070$
Body weight (kg)	67.6 ± 12.4	67.7 ± 12.5	67.8 ± 12.6	$t = 1.04$, $p = 0.308$
BMI	25.0 ± 3.9	25.0 ± 4.1	25.1 ± 4.1	$t = 1.61$, $p = 0.118$

Data are presented as mean \pm standard deviation.

PANSS, Positive And Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression Scale; CGI-CB, Clinical Global Impression Clinical Benefit Scale; SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale; BMI, Body Mass Index.

Table 4. Comparison of demographics, clinical scales, and treatment outcomes between the two starting dosage groups

Variable	200 mg start group (n = 10)	400 mg start group (n = 19)	Comparison
Age (yr)	48.1 ± 13.5	44.3 ± 13.7	$t = 0.70, p = 0.485$
Sex, female	3 (30.0)	11 (57.9)	$\chi^2 = 2.04, p = 0.153$
Duration of schizophrenia (yr)	15.1 ± 13.7	14.2 ± 8.7	$t = 0.23, p = 0.824$
Number of prior antipsychotics at baseline	1.2 ± 0.4	1.2 ± 0.4	$t = -0.06, p = 0.949$
Average exposure dose ^a of amisulpride (mg/day)	230.0 ± 48.3	405.3 ± 59.8	$t = -7.97, p < 0.001$
BMI (baseline)	24.5 ± 4.8	25.2 ± 3.5	$t = -0.50, p = 0.623$
BMI (change) ^b	0.2 ± 0.4	0.1 ± 0.5	$t = 0.07, p = 0.945$
PANSS total (baseline)	82.4 ± 6.6	81.4 ± 14.9	$t = 0.21, p = 0.838$
PANSS total (change) ^b	-21.3 ± 6.3	-22.0 ± 11.5	$t = -0.16, p = 0.871$
CGI-S (baseline)	4.4 ± 0.7	4.5 ± 1.0	$t = -0.37, p = 0.718$
CGI-S (change) ^b	-1.3 ± 0.5	-1.4 ± 1.1	$t = 0.19, p = 0.849$
SAS (baseline)	2.0 ± 2.8	0.9 ± 2.4	$t = 1.13, p = 0.269$
SAS (change) ^b	0.0 ± 0.0	-0.4 ± 1.8	$t = 0.64, p = 0.527$
BARS (baseline)	0.7 ± 1.3	1.1 ± 1.4	$t = -0.66, p = 0.517$
BARS (change) ^b	-0.3 ± 0.5	-0.5 ± 1.4	$t = 0.37, p = 0.714$

Data are presented as mean ± standard deviation or number (percentage).

BMI, Body Mass Index; PANSS, Positive And Negative Syndrome Scale; CGI-S, Clinical Global Impression Scale; SAS, Simpson Angus Scale; BARS, Barnes Akathisia Rating Scale.

^aAverage daily dosage during 8 weeks. ^bChange is defined as subtraction of the baseline values from the values at week 8.

χ^2 : chi-squared test was used for statistical comparisons.

nificant differences between the two groups (PANSS total change: $t = -0.16, p = 0.871$; CGI-S change: $t = 0.19, p = 0.849$) (Table 4).

Safety Evaluation

A total of 11 subjects did not complete the study; the reason for and time of withdrawal are shown in Table 2. The reasons for withdrawal were: lack of efficacy (n = 2, 5%), adverse reaction (n = 3, 7.5%), lost to follow-up (n = 4, 10%), and other reasons (n = 2, 5%). None of the subjects exhibited significant side effects severe enough to discontinue the medication and none had a causal relationship between drug administration and side effects.

There was no significant difference in sex ($\chi^2 = 0.76, p = 0.385$), age ($t = -0.067, p = 0.945$), duration of illness ($t = -0.903, p = 0.372$), number of prior antipsychotics ($t = -0.173, p = 0.864$), duration of previous antipsychotics ($t = 0.814, p = 0.421$), starting dosage of amisulpride ($t = -0.109, p = 0.914$), and mean exposure dose of amisulpride ($t = 0.016, p = 0.987$) between completer and discontinuation groups.

There was no significant difference in the number of dropouts between the 200 mg starting dose group and the 400 mg starting dose group ($\chi^2 = 0.01, p = 0.911$; Table 2). The severity of EPS based on SAS and BARS scores did not change significantly before and after 8 weeks of treatment

(Table 3). SAS decreased from 1.3 ± 2.5 (baseline) to 1.0 ± 2.2 (at 8 weeks) ($t = -0.89, p = 0.379$) and BARS decreased from 0.9 ± 1.4 (baseline) to 0.5 ± 1.1 (at 8 weeks) ($t = -1.89, p = 0.070$). However, the change was not statistically significant (Table 3). The mean BMI changed from 25.0 ± 3.9 (baseline) to 25.1 ± 4.1 (at 8 weeks). The change was not statistically significant ($t = 1.61, p = 0.118$; Table 3). BMI, SAS scores, and BARS scores at baseline and changes in these scores after 8 weeks did not differ between the groups (BMI: $t = 0.07, p = 0.945$; SAS: $t = 0.19, p = 0.849$; BARS: $t = 0.37, p = 0.714$) (Table 4).

DISCUSSION

The main results of this study revealed that additional administration of amisulpride in patients with schizophrenia without response to SGAs was an effective treatment option, as 34.5% of the completers were responders (response of 50% or more). After amisulpride augmentation, PANSS domain scores and total PANSS scores showed significant improvement and side effects such as EPS and weight gain were not significant.

In this study, augmentation of previous SGAs with amisulpride in patients with schizophrenia lacking treatment response resulted in improvement of positive, negative, depressive, and general symptoms according to PANSS,

CGI-S, CGI-CB, and CDSS scores after 8 weeks. A retrospective study of 15 patients with schizophrenia and schizoaffective disorder resistant to clozapine, olanzapine, risperidone, or ziprasidone reported that add-on therapy with amisulpride was useful in 80% of the patients [13].

An open observational study that used add-on therapy with amisulpride for 3 months in non-responders to risperidone monotherapy showed significant improvement in Brief Psychiatric Rating Scale, CGI-S, and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale scores [11]. In patients who partially responded to olanzapine monotherapy, coadjuvant treatment with amisulpride for 3 months had a high response rate of 75.51% [12]. However, the authors admitted that the dosage of olanzapine was insufficient for some patients [12]. In an RCT involving administration of amisulpride or placebo in 68 patients with insufficient response to clozapine, amisulpride augmentation showed no significant improvement at 6 weeks, but there was greater chance of response and improvement in negative symptoms at the 12-week follow-up [14]. However, amisulpride was associated with a greater side effect burden including cardiac side effects [14]. Previous studies on this topic have shown that in a more well-designed study such as an RCT, the usefulness of augmentation was less pronounced and the response improved with longer treatment periods when compared with an open study.

Previously, antipsychotic monotherapy was recommended in pharmacotherapy guidelines for schizophrenia and polypharmacy was generally avoided if possible [23]. However, a recent study on the association among antipsychotic monotherapy, polypharmacy type, and rehospitalization in patients with schizophrenia revealed that combining aripiprazole with clozapine was associated with the lowest risk of rehospitalization. The authors insisted that correction of treatment guideline is needed in the future [24]. The current revision of the American Psychiatric Association guideline states that augmentation with another antipsychotic can be considered, but recommends that the trial of clozapine should not be delayed due to the augmentation process, since there is established evidence for the better effect of clozapine on treatment resistant schizophrenia [25].

In this study, there was no deterioration of EPS after addition of amisulpride and no change in BMI of the parti-

cipants. Although there was no statistically significant change, BARS scores showed a trend toward decrease at 8 weeks when compared with baseline ($t = -1.89$, $p = 0.070$). In a previous study regarding augmentation of oral or parenteral risperidone with amisulpride, EPS had generally improved at the last visit after the augmentation with amisulpride [11]. Another study regarding augmentation of olanzapine with amisulpride also showed significant decrease in the number of patients suffering from moderate EPS at 12 weeks after treatment [12]. However, an RCT that compared the augmentation of clozapine with amisulpride and placebo showed that the amisulpride augmentation group revealed a greater number of side effects such as weight gain, sexual dysfunction, and aversive subjective experiences according to the Antipsychotic Non-Neurological Side Effects Scale assessments, which was designed to systematically and comprehensively assess the full range of side effects [14].

In the present study, there was no significant difference in the treatment response and side effects between the 200 mg starting dose group and the 400 mg starting dose group (Table 4). There were no significant differences between the two dosage groups in terms of change in BMI as well as in terms of changes in PANSS, CGI-S, SAS, and BARS scores. However, the number of subjects in the 200 mg and the 400 mg groups was rather small and further studies are needed in the future. In a 6-week randomized open-label study of amisulpride in acute exacerbation of schizophrenia, no statistically significant differences were observed in the overall incidence of adverse events between the 400 mg and the 800 mg dose groups [26]. In order to confirm and verify the results of the present study, an RCT comparing various doses of amisulpride and placebo will be needed in the future.

Our study has several limitations. Due to the nature of this being an open-label, prospective study, this study did not have a control group (patients taking SGAs without add-on therapy). The small sample size also makes it difficult to generalize our results. In addition, the possibility that the improvement of symptoms after administration of amisulpride was due to the previous antipsychotics cannot be excluded [27].

In conclusion, the present study suggested that augmentation with amisulpride was effective and safe in patients with schizophrenia who lacked treatment response to SGAs. In clinical practice, this option is expected to be

an effective and safe treatment strategy. Future studies including a greater number of subjects and placebo groups are needed to validate the results of the present study.

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■ Conflicts of Interest

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

■ Author Contributions

Conceptualization: Seong-Jin Cho. Data acquisition: Seung-Gul Kang, Seo-Eun Cho, Kyoung-Sae Na, and Seong-Jin Cho. Formal analysis: Seung-Gul Kang and Kyoung-Sae Na. Funding: Seong-Jin Cho. Supervision: Seong-Jin Cho and Chi-Un Pae. Writing—original draft: Seung-Gul Kang. Writing—review & editing: Seong-Jin Cho.

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