Brief Report
https://doi.org/10.9758/cpn.2022.20.3.567 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2022;20(3):567-572

Amisulpride Augmentation in Schizophrenia Patients with Poor Response to Olanzapine: A 4-week, Randomized, Rater-Blind, Controlled, Pilot Study

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Objective: The purpose of this study was to compare the efficacy and tolerability of continued olanzapine (OLA) versus amisulpride (AMI) augmentation in schizophrenic patients with poor response to OLA monotherapy.
Methods: The present 4-week, randomized, rater-blinded study included 25 patients with schizophrenia who were partially or completely unresponsive to treatment with OLA monotherapy. Eligible subjects were randomly assigned at a 1:1 ratio to continuation of OLA monotherapy (OLA group) or OLA with AMI augmentation (AMI group). Efficacy was primarily evaluated using the Positive and Negative Syndrome Scale (PANSS) at baseline and at 1, 2, and 4 weeks.
Results: The changes in PANSS total score and PANSS-positive subscale score were significantly different ($p < 0.05$) between the OLA and AMI groups. The differences between the two groups in PANSS-negative subscale, PANSS-general subscale, Brief Psychiatric Rating Scale, and Clinical Global Impression-Severity (CGI-S) scale scores were not statistically significant.
Conclusion: AMI augmentation could be an effective strategy for patients with schizophrenia who show inadequate early response to OLA monotherapy.

KEY WORDS: Amisulpride; Olanzapine; Schizophrenia; Augmentation; Response.

INTRODUCTION

Antipsychotic combination treatment or polypharmacy has been widely utilized in clinical practice, although concerns regarding safety, tolerability, and cost-effectiveness are widely recognized [1-3]. Furthermore, several recent results supported that a certain proportion of patients can benefit from antipsychotics polypharmacy without further negative consequences [4].

Olanzapine (OLA) is a common first-prescribed antipsychotic and has shown favorable efficacy in acutely exacerbated patients with schizophrenia [5-7]. The mixed receptor activity of OLA and its greater affinity for serotonin 5-HT_{2A} rather than dopamine D_2 receptors are similar to those of clozapine [8,9]. Pharmacokinetically, OLA is metabolized mainly by hepatic cytochrome enzyme P450 1A2 (CYP1A2) [10]. Because risks of antipsychotic polypharmacy include increased drug-drug interactions [11], pharmacokinetic considerations are important for selection of antipsychotics to be combined. Due to its pharmacological characteristics, amisulpride (AMI), another atypical antipsychotic with proven efficacy [6,7,12], is a promising adjuvant agent of special interest. AMI is unlikely to interact with other drugs due to the low plasma protein binding and metabolism and does not affect the activity of the CYP system [13,14]. Furthermore, AMI is highly selective for dopamine D_2/D_3 receptors; has minimal or no affinity for D_1, D_4, or D_5 receptors [15]. Despite the potential benefits of the combination of OLA and AMI, only a few open-label studies have been conducted [16,17], and no randomized clinical trial has been performed to date to examine the efficacy and tolerability of

Received: April 7, 2021 / **Accepted:** April 30, 2021
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the combination. Hence, the goals of this study were to test the hypothesis that AMI augmentation would improve psychotic symptoms and be well tolerated in schizophrenic patients who showed poor response to OLA monotherapy.

METHODS

Study Design and Participants

This open-label, rater-blinded, randomized study was conducted in one university hospital and two psychiatric hospitals in Korea between January 2017 and December 2019. Inpatients or outpatients who met the following criteria were eligible to participate: (1) 19−65 years of age, (2) diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, (3) acute worsening for 3−8 weeks, (4) a Clinical Global Impression-Improvement (CGI-I) score 4 or more (unchanged or worse) despite 1−3 weeks of OLA treatment for the current acute episode, and (5) at least mild severity of symptoms as evidenced by a Positive and Negative Syndrome Scale (PANSS) score of 58 or higher [18]. Subjects were excluded if they had (1) suicidal ideation, (2) comorbid psychiatric disorder other than schizophrenia, (3) unstable comorbid medical conditions, (4) pregnancy or lactation, (5) were prescribed a depot of antipsychotics within 60 days of the study, (6) showed intolerance to OLA or AMI, (7) were prescribed AMI before the study, or (8) showed treatment resistance defined as minimal or no response ($<$ 20% reduction in symptoms) to treatment from at least two adequately dosed ($>$ 600 mg/day of chlorpromazine equivalent) antipsychotic trials over at least 4 weeks [19].

Medication

Eligible subjects were randomly assigned at a 1:1 ratio to continuation of OLA treatment (OLA group) or OLA with AMI augmentation (AMI group) for 4 weeks. For both OLA and AMI groups, subjects continued their OLA doses throughout the study. AMI was initiated at a dose of 400 mg/day, and doses were modified at the discretion of the treating clinical psychiatrist within a range of 400−800 mg/day. Concomitant treatment with ongoing benzodiazepines or anti-Parkinsonian drugs was permitted if the patient had been on a stable dose for at least 2 weeks prior to enrollment, but it was requested that the dose not be changed during the study period. Patients were not given any other antipsychotics, mood stabilizers/anticonvulsants, or antidepressants during the study.

Measures

Psychiatric symptoms were evaluated using the PANSS, Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression-Severity (CGI-S) scale at baseline and at 1, 2, and 4 weeks. The primary efficacy assessment was defined as mean change in PANSS total score from baseline to 4 weeks. Additional efficacy measures included response rates with PANSS and BPRS; mean change in PANSS-positivity or negativity, and general subscale, BPRS, and CGI-S scores. Response was defined as a decrease in PANSS and BPRS total scores $\geq$ 25% [20].

Safety assessments including a physical examination, weight, reported adverse events, the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movements Scale (AIMS) were performed at each visit. All assessors were blinded to patient condition and prescribed medications.

Statistical Analysis

Data were analyzed for an intent-to-treat group, and the last observation carried forward (LOCF) method was applied for endpoint analysis. The data included all patients who underwent baseline and at least one post-baseline data measurement. All subjects who received at least one dose of the study medication were included in the safety analysis. Data for psychiatric symptom measures and adverse effects rating scales were analyzed using repeated measure analysis of variance (RM-ANOVA). The Greenhouse-Geisser correction was used to test for non-sphericity. The chi-square test or Fisher's exact test was used to analyze categorical variables, and Mann–Whitney U test was performed to compare baseline values of continuous variables between the OLA and AMI groups. All statistical tests were two-tailed with a significance level of 0.05.

Ethics

The study protocol, informed consent document, and other study-specific materials were approved by the institutional review committee at Yeouido St. Mary's Hospital (SC14MCSV0018). Written informed consent was obtained from all subjects after an extensive ex-

planation of the nature and procedures of the study.

RESULTS

Patients and Medications

A total of 25 patients was included and randomized to AMI (n = 13) or OLA group (n = 12); 22 (88.0%) participants completed the 4-week treatment. Two subjects from the OLA group (16.7%) and one subject from the AMI group (7.7%) withdrew from the study prematurely; all causes of study incompletion were lack of efficacy. Significant difference was not observed between the two groups in baseline demographic and clinical characteristics (Table 1). The AMI dose at each visit was 400 mg/day at baseline and 550.0 mg/day at week 4.

Efficacy

The changes in PANSS total score and PANSS-positive subscale score were significantly different ($p < 0.05$) between the OLA group and AMI group (Fig. 1). The differences between the two groups in PANSS-negative subscale and PANSS-general subscale were not statistically significant ($p = 0.055$ and $p = 0.096$, respectively); however, a trend toward greater improvement was observed in the AMI group (Fig. 1).

The numbers of responders who showed reduction of 25% or greater in PANSS and BPRS scores at week 4 were 10 (76.9%) and 12 (92.3%) in the AMI group, respectively, and 4 (33.3%) and 7 (58.3%) in the OLA group. The PANSS response rate was significantly higher in the AMI group on week 2 ($p = 0.011$) and week 4 ($p = 0.047$); however, the BPRS response rate was not significantly different between the two groups.

Tolerability and Safety

Two subjects (16.7%) in the OLA group and 5 subjects (38.5%) in AMI group reported adverse events. In the OLA group, akathisia and daytime sedation were reported, and 2 cases of akathisia, 4 cases of extrapyramidal symptoms including rigidity and tremor, 1 case of constipation were

Table 1. Baseline demographic and clinical characteristics

Baseline characteristics	Olanzapine (n = 12)	Olanzapine + Amisulpride (n = 13)	*p* value
Male	6 (50.0)	6 (46.2)	0.848
Age	46.2 ± 14.0	49.0 ± 10.2	0.703
Inpatient	8 (66.7)	8 (61.5)	> 0.999
Married	4 (33.3)	5 (38.5)	> 0.999
Living alone	1 (8.3)	1 (7.7)	> 0.999
Education	13.6 ± 2.9	13.0 ± 2.1	0.424
Employed	2 (16.7)	2 (15.4)	> 0.999
High	0 (0.0)	0 (0.0)	> 0.999
Middle	9 (75.0)	9 (69.2)	
Low	3 (25.0)	4 (30.8)	
Age at onset	35.0 ± 13.7	32.6 ± 7.2	0.870
Duration of illness (mo)	134.0 ± 100.1	196.7 ± 112.6	0.142
Baseline score			
PANSS-Positive	26.7 ± 7.0	29.3 ± 5.1	0.353
PANSS-Negative	23.0 ± 5.3	23.3 ± 6.4	0.913
PANSS-General	52.3 ± 7.7	54.8 ± 10.7	0.723
PANSS total score	102.0 ± 11.8	107.5 ± 19.3	0.446
BPRS	39.8 ± 10.3	42.5 ± 11.8	0.785
CGI-Improvement (comparing the time point of olanzapine initiation)	4.8 ± 0.8	4.8 ± 0.9	0.748
CGI-Severity	5.4 ± 0.8	5.0 ± 1.0	0.194
GAF	32.2 ± 13.0	35.0 ± 11.4	0.393
Medication dose (mg/d)			
Olanzapine	19.6 ± 6.6	16.9 ± 6.6	0.369
Amisulpride		400	

Values are presented as number (%) or mean ± standard deviation.
PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning.

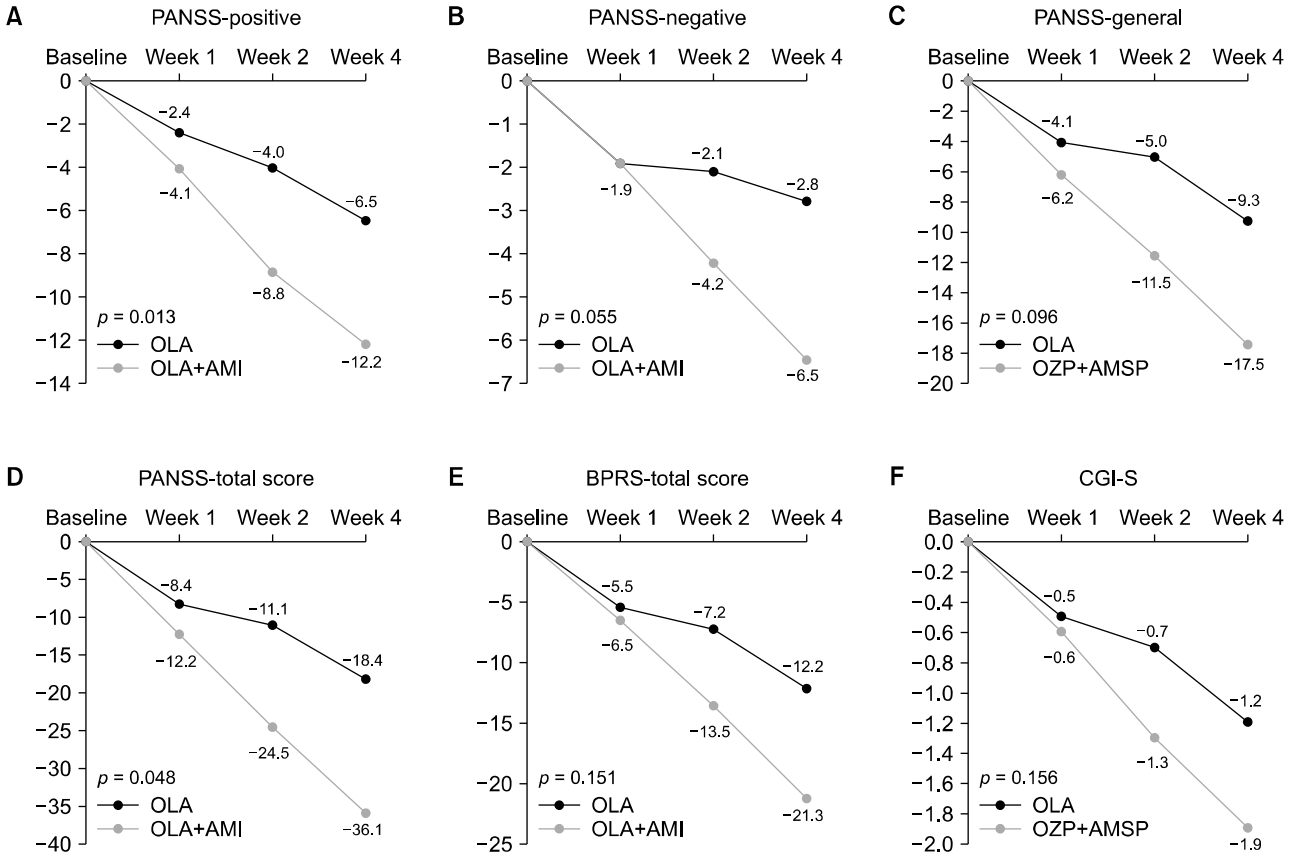

Fig. 1. Changes of Positive and Negative Syndrome Scale (PANSS) scores, Brief Psychiatric Rating Scale (BPRS) total score, and Clinical Global Impression-Severity (CGI-S) score during the study.
OLA, olanzapine; AMI, amisulpride.

reported in the AMI group. The severity of every reported adverse event was mild or moderate.

The RM-ANOVA results showed that the changes in scores on SAS ($p = 0.676$), BARS ($p = 0.129$), and AIMS ($p = 0.370$) during the 4-week study period were not significantly different between the two groups.

DISCUSSION

In this rater-blinded, open-label study, significantly greater reduction in PANSS total score and PANNS-positive subscale score was observed in the AMI group compared with the OLA group. These results correlate with other previous open-label/retrospective chart review studies in which combination of AMI with OLA or other second-generation antipsychotics reportedly induced symptom improvements measured using global assessment of functioning (GAF), CGI, and BPRS scores in treatment-resistant schizophrenic patients without increasing severe neuroleptic-related side effects [16,17,21]. However, unlike previous studies, significant improvements were not observed in BPRS and CGI-S scores. This difference could be due to the difference in number of items scoring negative symptoms in BPRS and PANSS (3 items vs. 7 items); identifying the difference of negative symptoms before and after treatment can be difficult using BPRS [22]. In addition, PANSS might have greater predictive power than BPRS due to its clearly defined scoring system with severity and frequency of psychiatric symptoms; this difference of sensitivity in each scale might have affected our study results [23].

The present study had limitations that should be considered when interpreting the results. Due to the short study period and limited number of recruited patients, the reduction of PANSS score could be insufficient to show difference in CGI-S score between groups [24]. However, greater difference can be expected after a 4-week study period with ongoing medication. In addition, the numer-

ical difference in PANSS general and negative scores between the AMI and OLA groups was not significant, likely also due to the small sample size. Due to the characteristics of an open-label, prospective study, a control group was not included and might have caused bias. Furthermore, due to the small sample size, generalization of the study results is difficult. In addition, due to our sample exclusion criteria, patients with psychiatric diagnosis other than schizophrenia were excluded. Considering that more than half of schizophrenic patients have comorbid psychiatric disorders, it is difficult to generalize the study results [25]. In addition, common side effects such as elevated prolactin and cardiac markers caused by dopamine blockade of AMI were not evaluated and metabolic parameters such as BMI, weight, triglycerides, and fasting glucose were not assessed.

Despite the short study period and lack of assessment of other drug side effects, the present study results indicated that AMI augmentation was effective and tolerable in schizophrenia patients who showed poor response to OLA monotherapy. The study results confirmed antipsychotic polypharmacy as an alternative treatment option for schizophrenic patients showing lack of efficacy with antipsychotic monotherapy.

■ Funding

This work was supported and funded by Handok Pharmaceuticals, Seoul, Korea.

■ Conflicts of Interest

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

■ Author Contributions

Conceptualization: Won-Myong Bahk and Bo-Hyun Yoon. Data acquisition: Young Sup Woo, Sung-Yong Park, Bo-Hyun Yoon, Sheng-Min Wang, and Won-Myong Bahk. Formal analysis: Young Sup Woo, Sung-Yong Park, Sheng-Min Wang, and Won-Seok Choi. Funding: Won-Myong Bahk. Supervision: Won-Myong Bahk. Writing original draft: Young Sup Woo, Sheng-Min Wang, and Won-Seok Choi. Writing review and editing: Sung-Yong Park, Bo-Hyun Yoon, and Won-Myong Bahk.

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