

Effectiveness of Switching to Long-acting Injectable Aripiprazole in Patients with Recent-onset and Chronic Schizophrenia

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Objective: This study investigated the effectiveness of switching to once-monthly long-acting injectable (LAI) aripiprazole from other second-generation antipsychotics including LAI paliperidone palmitate in both recent-onset and chronic schizophrenia patients.

Methods: This was a 24-week prospective, open-label, flexible dose-switching study in patients with schizophrenia. Scores on the Positive and Negative Syndrome Scale (PANSS), Personal and Social Performance (PSP) scale, Clinical Global Impression (CGI), Subjective Well-being Under Neuroleptics—Short Form (SWN-K), and a computerized emotional recognition test (ERT) were evaluated. Subjects were divided into two groups (recent onset and chronic) based on 5 years' duration of the illness.

Results: Among the 82 patients participating, 67 (81.7%) completed the 24-week study. The discontinuation rate after switching to LAI aripiprazole did not differ according to clinical characteristics including type of previous antipsychotics. Scores on the PANSS, PSP, SWN-K, CGI, and ERT were significantly improved after a switch to LAI aripiprazole without exacerbation of metabolic parameters and bodyweight. The improvements in the PANSS, PSP, and CGI scores were significantly greater in patients with recent-onset than in those with chronic schizophrenia; the improvement in metabolic parameters was significantly greater in the latter group.

Conclusion: High rates of successful switching to LAI aripiprazole from other antipsychotics suggest its good tolerability and effectiveness. Improvements in psychopathology and social functioning were more evident in patients with recent-onset schizophrenia, and improvements in metabolic abnormalities were more prominent in patients with chronic schizophrenia.

KEY WORDS: Antipsychotic agents; Aripiprazole; Long-acting injectable; Recent-onset; Schizophrenia.

INTRODUCTION

Long-acting injectable (LAI) antipsychotics are effective in reducing relapse and rehospitalization compared to oral antipsychotics [1-4]. In addition, the discontinuation rate, an important marker for real-world effectiveness, is reportedly lower in people taking LAI antipsychotics than in those taking oral antipsychotics [2,5]. In the past sev-

eral decades, LAI forms of second-generation antipsychotics (SGAs) such as risperidone, olanzapine, and paliperidone palmitate have been developed. However, studies comparing the effectiveness between second-generation LAI antipsychotics and switching strategies from other LAI antipsychotics are insufficient [6,7].

Major changes in the psychosocial functioning of patients with schizophrenia are often evident within the first 2–5 years after onset, but the decline in functioning tends to plateau thereafter [8]. Therefore, the first 5 years of this disorder have been described as a critical period during which the patient's future course and prognosis are determined. In first-episode schizophrenia, about 42% of patients discontinue treatment within 1 year [9]. Therefore,

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LAI antipsychotics should be actively used in the early phase of schizophrenia [10-13]. However, few prospective clinical trials have investigated the effectiveness of LAI antipsychotics in patients with recent-onset schizophrenia [14,15].

Oral aripiprazole has been widely used due to its effectiveness and favorable adverse effects profile. LAI aripiprazole is the first LAI-type dopamine partial agonist and was approved by the US Food and Drug Administration in 2013. Although clinical studies and the manufacturer's guidance have provided information and a switching strategy, evidence for the effective use of LAI aripiprazole is sparse, particularly for patients with recent-onset schizophrenia and those receiving LAI paliperidone [7,14]. In this study, we aimed to investigate successful changes to once-monthly LAI aripiprazole from other SGAs in both recent-onset and chronic schizophrenia patients. We investigated and compared the improvement profiles after use of LAI aripiprazole in patients with recent-onset and chronic schizophrenia. In addition, we particularly analyzed real-world clinical outcomes after switching to LAI aripiprazole from LAI paliperidone.

METHODS

Subjects

Study participants were selected from patients aged 19–60 years who met the Diagnostic and Statistical Manual of Mental Disorders 5th edition diagnostic criteria for schizophrenia. Subjects were required to be able to complete all measures and to have been receiving a stable dose of oral or LAI SGAs for a minimum of 2 weeks before enrollment. The key exclusion criteria were as follows: presence of any significant or unstable medical disease, pregnancy, or a history of taking clozapine within 60 days. The study was carried out according to the latest version of the Declaration of Helsinki and was approved by the hospitals' Institutional Review Boards (CNUH-2018-104). All patients gave written informed consent before participating in the study. The trial register and clinical trial registration number: (ClinicalTrials.gov) NCT03839251.

Study Procedure

This was a 24-week prospective, open-label, flexible dose-switching study in patients with recent-onset and chronic schizophrenia. Patients were switched to once-

monthly LAI aripiprazole from their previous oral or injectable SGAs because of suboptimal efficacy, tolerability, and/or poor compliance. Switching to LAI aripiprazole was conducted in a naturalistic real-world setting and following the manufacturer's basic guidance. LAI aripiprazole was administered every 4 weeks by the intramuscular route into the gluteal or deltoid muscle. Patients were treated with oral aripiprazole for 14 consecutive days from the date of the first injection to maintain therapeutic plasma levels during the initiation period. Before initiating LA aripiprazole, oral aripiprazole was prescribed for at least 14 days to patients without a history of tolerability and response to the drug. Because there was no manufacturer's guidance on switching from LAI paliperidone to LAI aripiprazole, we made a general rule for this. Considering its long half-life, LAI paliperidone once monthly was directly switched to LAI aripiprazole for a 4-week interval, preferably with pretreatment of oral aripiprazole for at least 2–4 weeks. If patients had received a high dose of LAI paliperidone or had uncontrolled psychotic symptoms, oral paliperidone was prescribed for several weeks.

The starting dose of aripiprazole, the rate of cross titration of previous antipsychotics, and coadministration of concomitant medications including antipsychotics were determined on a case-by-case basis by the treating psychiatrist based on clinical judgment. Concurrent medications, including anticholinergics, propranolol, and benzodiazepines, were permitted for treating extrapyramidal symptoms (EPS) and sleep disturbances. Antidepressants, mood stabilizers, and antipsychotics other than LAI aripiprazole were allowed if they had been administered for more than one month before participating in this study and were needed for control of symptoms according to the treating psychiatrist. This study, conducted from June 2018 to January 2020, involved five university hospitals in the Republic of Korea.

Outcome Measures

The Positive and Negative Syndrome Scale (PANSS) for psychotic symptoms [16,17], Personal and Social Performance (PSP) scale for social functioning [18,19], Simpson–Angus Scale (SAS) for parkinsonism [20], Barnes Akathisia Rating Scale (BAS) for akathisia [21], and Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia (TD) [22] were administered at baseline and at treatment

weeks 12 and 24. Due to the low prevalence of EPS, measures for EPS were analyzed as categorical variables, defined by scores of 2 or higher in the SAS total, BAS global, and AIMS any item. The Subjective Well-being Under Neuroleptics—Short Form (SWN-20) for quality of life [23,24] was administered at the same time points. A computerized emotional recognition test (ERT) for social cognition [25] and laboratory examinations were conducted at baseline and 24 weeks. The Clinical Global Impression (CGI) [26] and adverse events were assessed at every visit. Injection pain was measured using a visual analogue scale (VAS).

Statistical Analyses

First, participants were divided into two groups based on completion of the 24-week study, which indicated a successful switch to LAI aripiprazole. Clinical and demographic characteristics, including duration of illness and type of previous antipsychotics (LAI paliperidone, oral aripiprazole, and other oral antipsychotics), were compared between patients who completed the study and those who did not using the independent *t* test, chi-square test, and Fisher's exact test. Second, patients who completed the study to its last scheduled visit were included in general linear model (GLM) repeated-measure analysis of variance (ANOVA) with a post hoc least significant difference (LSD) test for multiple comparison. In addition, outcome measures were analyzed with end-point analyses using a last observation carried forward approach, that is, the last available assessment after baseline was used as the endpoint. We compared measures at baseline and at the endpoint using paired *t* tests. We calculated the effect size estimate, which was computed as the difference between the endpoint and baseline mean value divided by the standard deviation (Cohen's *d*). Third, subjects were divided into two groups based on illness duration of 5 years, a criterion used in previous studies to define recent-onset schizophrenia [27,28]. Changes in outcome measures from baseline to endpoint were compared with GLM repeated-measures ANOVA for time × group interactions with baseline score adjustment, and comparisons between baseline and endpoint were separately compared in each group. The McNemar test was used to compare the incidence of treatment-emergent EPS during the study with its incidence at baseline and to compare the use of anticholinergic agents and propranolol for the treat-

ment of EPS at the endpoint with that at baseline. All statistical tests were two-tailed with a significance level of $p < 0.05$. The Statistical Package for Social Sciences (SPSS) version 25.0 for Windows (IBM Co., Armonk, NY, USA) was used for statistical analyses.

RESULTS

Eighty-two patients with schizophrenia participated in this study. The mean ± standard deviation age of participants was 33.1 ± 9.5 years, and 57.3% were female. Forty-five (54.9%) of participants were patients with recent-onset schizophrenia, that is, less than 5 years' duration of the illness. The antipsychotics used before switching to LAI aripiprazole were LAI paliperidone in 25 patients (30.5%), oral aripiprazole in 30 patients (36.6%), and other SGA oral antipsychotics in 27 patients (32.9%). The starting and final doses of LAI aripiprazole were 400 mg in 72.0% of participants. The median (interquartile range) duration of cross titration and oral aripiprazole supplementation were 4 (0–14) and 4 (2–4) weeks, respectively. About one-third of patients ($n = 29$) received combined treatment of oral antipsychotics and LAI aripiprazole through the entire study period.

Among the 82 participants, 67 (81.7%) completed the 24-week study. The reasons for patient drop-out were as follows: loss to follow-up ($n = 4$, 4.9%), adverse events ($n = 9$, 11.0%), and withdrawal of consent ($n = 2$, 2.4%). The number of patients who dropped out decreased as the duration of LAI aripiprazole administration increased; 10 (66.7%) of 15 patients who did not finish the entire study dropped out early, within 12 weeks. The drop-out group did not differ significantly from those who completed the study with regard to age, gender, duration of illness, previous antipsychotic dose (chlorpromazine equivalent), starting and final dosage of LAI aripiprazole administered, switching strategy (duration of cross-titration and concomitant aripiprazole use), combination therapy (LAI aripiprazole with other antipsychotics), previous antipsychotic treatment (LAI paliperidone, oral aripiprazole, and other oral antipsychotics), or baseline scores of psychiatric measures (Table 1).

The dosages of paliperidone palmitate previously prescribed were 150 mg ($n = 3$, 12.0%), 100 mg ($n = 10$, 40.0%), 75 mg ($n = 5$, 20.0%), and 50 mg or below ($n = 5$, 20.0%). Two patients had been received 350 mg of a pal-

Table 1. Sociodemographic and clinical characteristics of participants

Characteristics	Total (n = 82, 100%)	Complete (n = 67, 81.7%)	Drop-out (n = 15, 18.3%)	<i>p</i> value
Age (yr)	33.1 ± 9.5	33.1 ± 9.4	33.1 ± 10.1	0.993
Sex				0.356
Female	47 (57.3)	40 (85.1)	7 (14.9)	
Male	35 (42.7)	27 (77.1)	8 (22.9)	
Education (yr)	14.0 ± 2.8	13.7 ± 3.0	14.9 ± 1.7	0.121
Regular job				0.371
Employed or student	34 (43.0)	26 (76.5)	8 (23.5)	
Unemployed	45 (57.0)	38 (84.4)	7 (15.6)	
Duration of illness (yr)	4.6 (2.2–8.9)	4.9 (2.1–11.2)	3.8 (2.5–6.4)	0.299
Onset				0.112
Recent-onset	45 (54.9)	34 (75.6)	11 (13.4)	
Chronic	37 (45.1)	33 (89.2)	4 (10.8)	
PANSS				
Positive	11.2 ± 4.7	11.5 ± 4.9	9.7 ± 3.3	0.191
Negative	14.3 ± 5.7	14.6 ± 6.0	13.1 ± 4.0	0.354
General	26.9 ± 8.9	27.7 ± 9.5	23.6 ± 4.5	0.110
Total	52.4 ± 17.8	53.7 ± 19.0	46.4 ± 8.9	0.149
PSP	66.5 ± 11.6	65.9 ± 11.5	69.2 ± 12.2	0.320
Previous antipsychotics				0.166
LAI	25 (30.5)	20 (80.0)	5 (20.0)	
Oral aripiprazole	30 (36.6)	22 (73.3)	8 (26.7)	
Other oral APs	27 (32.9)	25 (92.6)	2 (7.4)	
Chlorpromazine equivalent dosage (mg/day)	450 (300–750)	450 (300–800)	300 (200–550)	0.107
Switching to aripiprazole				
Starting dose, 400 mg/day	59 (72.0)	49 (83.1)	10 (16.9)	0.751
Final dose, 400 mg/day	59 (72.0)	48 (81.4)	11 (18.6)	1.000
Duration of cross-titration (wk)	4 (0–14)	4 (0–16)	2 (0–4)	0.098
Duration of oral aripiprazole use (wk)	4 (2–4)	4 (2–5)	4 (2–4)	0.261
Combination of oral antipsychotics				0.436
Combination	29 (35.4)	25 (86.2)	4 (13.8)	
Monotherapy of LAI	53 (64.6)	42 (79.2)	11 (20.8)	

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).

LAI, long-acting injectable; APs, antipsychotics; PANSS, Positive And Negative Syndrome Scale; PSP, Personal and Social Performance scale.

iperidone palmitate 3-month formulation (Trinza). Among 25 patients who had been receiving LAI paliperidone, 20 (80.0%), including the Trinza users, were directly switched to LAI aripiprazole over the LAI injection interval (4 or 12 weeks) without oral supplementation of paliperidone. Five participants (25%) dropped out of the study; two did not complete follow-up assessments, and one each dropped out due to psychotic exacerbation, akathisia, and withdrawal of consent. Oral paliperidone was supplemented after administration of LAI aripiprazole in 5 patients (20%) among the LAI paliperidone users. None of the participants with oral paliperidone supplementation dropped out. One participant had received oral paliperidone for 4 weeks after the first injection of LAI aripiprazole was given. Two participants had taken oral paliper-

idone together with LAI aripiprazole until the end point of the study, and 2 had received oral paliperidone at 4 or 5 months into the study for the control of psychotic symptoms. In terms of injection pain, the VAS for injection pain was significantly decreased after switching from LAI paliperidone to aripiprazole (4.8 ± 2.4 vs. 3.2 ± 2.0 , $t = 3.092$, $p = 0.005$).

The dropout rate was higher in participants who had taken oral aripiprazole (26.7%) compared to those who had taken other oral SGAs (7.4%), although the difference was not statistically significant ($p = 0.083$). Among the 8 patients who did not successfully switch from oral to LAI aripiprazole, half patients dropped out due to adverse events. Among the 5 study participants who had previously been administered 5 mg of oral aripiprazole, 3

Table 2. Changes in clinical outcome measures following the switch to long-acting injectable aripiprazole

Clinical measures	Baseline	12 weeks	24 weeks	Effect of time		End-point	
				F	<i>p</i> value	Mean change (standard error)	Effect size
PANSS							
Positive	11.5 ± 4.9	10.6 ± 3.7**	9.9 ± 3.5**	7.75	0.002	-1.42 (0.52)**	0.325
Negative	14.6 ± 6.0	13.3 ± 4.8***	13.2 ± 4.6**	9.32	0.001	-1.18 (0.44)**	0.319
General	27.7 ± 9.5	26.0 ± 8.1**	25.0 ± 6.6***	10.98	< 0.001	-2.41 (0.76)**	0.316
Total	53.7 ± 19.0	49.9 ± 15.1***	48.1 ± 12.7***	10.98	< 0.001	-5.01 (1.54)**	0.385
PSP	65.9 ± 11.5	68.2 ± 10.1**	70.0 ± 11.6***	11.13	< 0.001	3.49 (1.04)**	0.400
SWN							
Total	81.5 ± 18.9	83.9 ± 16.7	86.0 ± 17.5**	4.94	0.009	4.32 (1.49)**	0.352
Mental functioning	16.2 ± 4.3	16.0 ± 4.2	16.7 ± 3.8	1.10	0.335	0.60 (0.38)	0.191
Self-control	16.6 ± 4.2	17.3 ± 3.7*	17.6 ± 3.9**	4.78	0.012	1.09 (0.38)**	0.348
Emotional regulation	16.6 ± 4.1	17.3 ± 3.7	17.1 ± 4.3	1.20	0.304	0.44 (0.49)	0.110
Physical functioning	16.5 ± 4.7	16.6 ± 4.2	17.3 ± 4.6	2.25	0.110	0.76 (0.39)	0.238
Social integration	15.7 ± 3.9	16.5 ± 3.3*	17.0 ± 3.6***	6.45	0.002	1.26 (0.35)***	0.435
Body-weight (kg)	70.2 ± 14.9	70.6 ± 14.7	71.1 ± 14.8	1.61	0.204	0.82 (0.49)	0.190

Values are presented as mean ± standard deviation.

PANSS, Positive And Negative Syndrome Scale; PSP, Personal and Social Performance scale; SWN, Subjective Well-Being under Neuroleptics.

p* < 0.05; *p* < 0.01; ****p* < 0.001 vs. baseline by *post-hoc* comparisons.

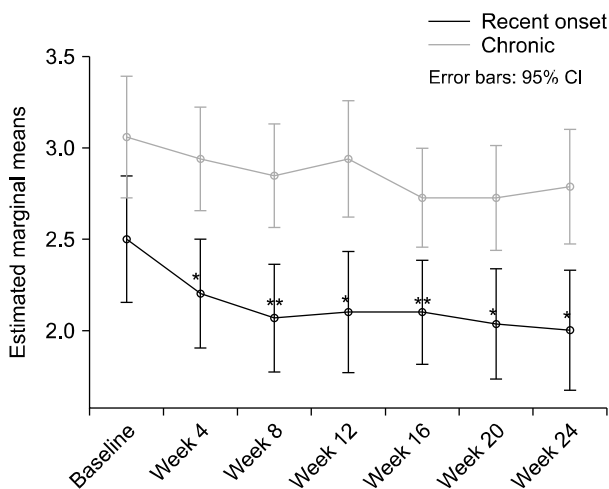


Fig. 1. Changes in clinical global impression scores in patients with recent-onset and chronic schizophrenia.

CI, confidence interval.

p* value < 0.05, *p* value < 0.01 vs. baseline by paired *t* test. General linear model time effect: *F* = 7.067, *p* < 0.001; time × group interaction: *F* = 3.159, *p* = 0.014.

(60%) dropped out within 2 months.

GLM repeated-measures ANOVA revealed significant differences among the measurement times on the CGI, the PANSS total and subscales, the PSP, and the SWN total, self-control, and social integration scales (Table 2, Fig. 1). The *post hoc* LSD comparisons revealed significant im-

provements on the PANSS total and subscales, PSP, and subscales (self-control and social integration) of SWN at both 12 and 24 weeks. Body weight did not significantly differ at these time points. Scores of all ERT variables were significantly improved at 24 weeks. Emotional discrimination and contextual recognition scores were significantly improved in patients with recent-onset schizophrenia, but not in those with chronic schizophrenia (Table 3). Laboratory outcomes did not differ between baseline and the 24-week point except for prolactin, which was significantly decreased after switching to LAI aripiprazole (*p* value = 0.029).

Table 4 shows comparisons of outcomes between baseline and endpoint according to the 5-year cutoff. Significant time × group interactions were observed for scores on the CGI, the PSP, the PANSS positive, general, and total, and the plasma levels of high-density lipoprotein (HDL) and triglyceride (TG). Improvements in the PANSS, PSP, and CGI scores were significant in patients with recent-onset schizophrenia but not in patients with chronic schizophrenia (Table 4, Fig. 1). However, the HDL level was significantly increased, and TG level was significantly decreased, in patients with chronic schizophrenia; changes in these measures were not significant in patients with recent-onset schizophrenia.

Table 5 shows comparison of changes in prevalence of

Table 3. Changes in emotional recognition test results following the switch to long-acting injectable aripiprazole

Emotional recognition test	Total			Recent-onset			Chronic		
	Baseline	26 weeks	<i>p</i> value	Baseline	26 weeks	<i>p</i> value	Baseline	26 weeks	<i>p</i> value
Emotional recognition	16.6 ± 2.8	17.3 ± 2.2	0.017	16.9 ± 2.5	17.5 ± 2.5	0.077	16.1 ± 3.1	17.0 ± 1.9	0.100
Emotional discrimination	9.9 ± 2.8	10.5 ± 2.0	0.012	10.3 ± 2.6	10.9 ± 1.9	0.021	9.2 ± 3.0	10.0 ± 2.1	0.131
Contextual recognition	19.2 ± 4.9	20.2 ± 4.3	0.003	19.9 ± 4.3	21.3 ± 3.5	0.012	18.1 ± 5.5	18.9 ± 4.9	0.120
Emotional capacity	45.2 ± 10.0	48.2 ± 7.8	0.001	47.4 ± 8.5	49.7 ± 7.3	0.007	42.4 ± 11.1	46.1 ± 8.2	0.030

Values are presented as mean ± standard deviation.

Table 4. Comparisons of clinical changes grouped by patients with recent-onset and chronic schizophrenia

Clinical measures	Recent-onset (n = 45)		Chronic (n = 37)		Group × time interactions	
	Baseline	Mean change (standard error)	Baseline	Mean change (standard error)	F	<i>p</i> value
Age (yr)	30.5 ± 8.3		36.2 ± 10.0			0.006
Clinical Global Impression	2.7 ± 1.0	−0.5 (0.1)***	3.0 ± 1.1	−0.1 (0.2)	5.649	0.020
PANSS						
Positive	10.7 ± 3.8	−2.3 (0.5)***	12.2 ± 5.7	−0.6 (0.9)	14.347	<0.001
Negative	14.3 ± 6.7	−1.4 (0.7)	14.7 ± 5.0	−0.9 (0.5)	0.798	0.375
General	26.9 ± 9.4	−3.7 (0.9)***	28.1 ± 9.3	−1.1 (1.2)	8.205	0.006
Total	51.9 ± 18.7	−7.5 (2.0)***	54.9 ± 18.8	−2.6 (2.3)	8.779	0.004
PSP	66.8 ± 11.6	5.6 (1.4)***	48.1 ± 11.08	1.4 (1.5)	5.520	0.022
SWN						
Total	83.8 ± 19.1	5.2 (2.3)*	80.7 ± 18.1	3.4 (1.9)	0.625	0.432
Mental functioning	16.6 ± 4.5	0.6 (0.6)	15.9 ± 4.0	0.6 (0.5)	0.061	0.806
Self-control	17.2 ± 3.9	1.2 (0.6)	16.1 ± 4.4	1.0 (0.5)	0.883	0.351
Emotional regulation	16.4 ± 4.1	0.8 (0.8)	17.0 ± 4.3	0.1 (0.5)	0.258	0.613
Physical functioning	17.5 ± 4.4	1.0 (0.5)	15.9 ± 4.9	0.5 (0.6)	1.366	0.247
Social integration	16.4 ± 4.0	0.9 (0.5)	15.3 ± 3.7	1.7 (0.5)**	0.490	0.486
Body weight (kg)	69.7 ± 16.1	1.5 (0.7)*	71.0 ± 13.3	0.0 (0.7)	2.063	0.155
Waist Circumference (cm)	87.3 ± 14.4	1.5 (1.1)	89.8 ± 10.2	0.3 (1.0)	0.690	0.409
Prolactin (ng/ml)	37.8 ± 45.1	−15.6 (8.5)	31.1 ± 27.0	−7.3 (5.8)	0.140	0.709
Glucose (mg/dl)	98.8 ± 17.7	10.8 (9.0)	100.5 ± 13.7	1.2 (2.1)	0.900	0.346
Total cholesterol (mg/dl)	201.9 ± 43.6	−12.6 (5.3)*	166.1 ± 37.7	10.4 (6.6)	0.484	0.489
HDL (mg/dl)	53.9 ± 13.9	−1.8 (1.4)	48.8 ± 10.8	4.5 (1.3)**	8.271	0.005
LDL (mg/dl)	126.5 ± 33.6	−7.5 (3.9)	100.2 ± 23.9	6.4 (3.0)*	1.128	0.292
Triglyceride (mg/dl)	141.7 ± 110.4	7.8 (12.3)	155.8 ± 122.1	−38.4 (15.8)*	5.578	0.021
ALT (U/L)	33.3 ± 34.0	−5.9 (4.9)	25.2 ± 21.5	4.2 (4.0)	1.012	0.318
AST (U/L)	25.2 ± 13.1	−0.8 (1.8)	25.6 ± 24.4	0.1 (4.4)	0.172	0.680

Values are presented as mean ± standard deviation.

PANSS, Positive And Negative Syndrome Scale; PSP, Personal and Social Performance scale; SWN, Subjective Well-Being under Neuroleptics; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

p* < 0.05; *p* < 0.01; ****p* < 0.001 vs. baseline.

treatment-emergent EPS and adjunctive use of medications for EPS between baseline and at endpoint. The incidences of parkinsonian features, akathisia, and TD were not significantly changed from baseline to endpoint. However, adjunctive use of anticholinergic agents was significantly decreased after switching to LAI aripiprazole. Adjunctive uses of propranolol and benzodiazepine were decreased at endpoint, although the differences were not

statistically significant (both *p* values = 0.064).

Treatment-emergent adverse events associated with the medication (the level of possible causality or above) and occurred in ≥ 2% of participants treated with LAI aripiprazole were as follows: injection pain (n = 12, 14.6%), psychotic exacerbation (n = 9, 11.0%), akathisia (n = 4, 4.9%), EPS (n = 3, 3.7%), fatigue (n = 3, 3.7%), and suicidal ideation (n = 2, 2.4%). In nine patients, adverse events

Table 5. Comparison of changes in prevalence of treatment-emergent extrapyramidal symptoms and adjunctive use of medications between baseline and at endpoint

Variables for extrapyramidal symptoms	Baseline	Endpoint	<i>p</i> value
Parkinsonian feature (≥ 2 of SAS total score)	12 (15.6)	9 (11.7)	0.508
Akathisia (≥ 2 of BAS global score)	4 (5.2)	3 (3.9)	1.000
Tardive dyskinesia (≥ 2 of AIMS any item)	7 (9.1)	4 (5.2)	0.375
Adjunctive use of anticholinergics	61 (76.3)	38 (47.5)	< 0.001
Adjunctive use of propranolol	35 (43.8)	26 (32.5)	0.064
Adjunctive use of benzodiazepine	34 (42.5)	25 (31.3)	0.064

Values are presented as number (%).

SAS, Simpson–Angus Scale; BAS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale.

led patients to drop-out: psychotic exacerbation ($n = 3$), akathisia ($n = 3$), dystonia ($n = 1$), fatigue ($n = 1$), and injection pain ($n = 1$).

DISCUSSION

In this prospective study, most (81.7%) patients with schizophrenia were switched from oral or other LAI SGAs to LAI aripiprazole and continued treatment for more than 24 weeks. Successful switching rates were not significantly different according to previous LAI paliperidone use, recent-onset schizophrenia, or level of psychopathology. In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, the treatment discontinuation rate was high (up to 74%) over the 18-month period of the trial, and the median time until discontinuation of treatment was approximately 6 months [29]. Compared to previous psychopharmacological studies reporting dropout rates > 30% [30–32], including those focused on switching to oral aripiprazole and other LAIs, the dropout rate in our study was low. In addition, most psychiatric measures, including the PANSS, PSP, SWN, and ERT, were significantly improved after switching to LAI aripiprazole without significant exacerbation of metabolic parameters or bodyweight. Thus, our study demonstrated that LAI aripiprazole may be an effective treatment option for patients with schizophrenia who are taking oral or other LAI SGAs.

Official guidance for switching from LAI paliperidone to LAI aripiprazole has not been released. Our study demonstrated that direct switching from LAI paliperidone to aripiprazole may be successful in patients with schizophrenia. However, we should consider that most participants of our study were clinically stable, and most (88%) LAI paliperidone users had received moderate or low

doses (100 mg equivalent or lower) of paliperidone palmitate. In addition, 25% of participants were administered oral paliperidone after discontinuation of LAI paliperidone. Therefore, in patients with severe psychotic symptoms or receiving high doses of LAI paliperidone, oral supplementation of paliperidone for cross titration may be needed to prevent psychotic exacerbation. In terms of injection pain, participants reported decreased pain at the injection site after switching from LAI paliperidone to LAI aripiprazole.

The medication tolerability in patients who have previously taken oral aripiprazole may be better than that in patients who took other antipsychotics. However, the participants who had previously taken oral aripiprazole did not have a higher completion rate than those who had previously taken other oral SGAs. Inappropriate dosage adjustments between oral and LAI aripiprazole may contribute to discontinuation. This is supported by our finding that the main reason for dropping out among participants with previous oral aripiprazole use was adverse events, where most of these participants had received a low dose (5 mg/day) of oral aripiprazole. The dosage range of LAI aripiprazole is narrow because the approved doses were only 300 mg and 400 mg, whereas LAI paliperidone offers five dosage options. Therefore, adverse events should be carefully managed when LAI aripiprazole is administered to patients who had used low doses (5 mg or lower) of oral aripiprazole.

A recent study conducted in patients with early phase schizophrenia showed that the use of LAIs led to a significant and clinically meaningful reduction in the incidence of first hospitalization [15]. LAI aripiprazole was effective in our participants with recent-onset schizophrenia. Significant time \times group interactions were observed in score changes on the CGI, the PANSS, and the

PSP, and in the plasma cholesterol level profiles. LAI aripiprazole was more effective for improving psychotic symptoms and social functioning in patients with a short duration of illness than in those with a long duration. Instead, improvement of metabolic abnormalities (increased HDL and decreased TG) were significant in chronic patients, whereas recent-onset patients did not show significant improvements. This is compatible with our previous study showing different profiles of improvement after the switch to oral aripiprazole between patients with recent onset and those with long illness duration [31]. While no significant time \times group interactions were observed, improvement of social cognition was more evident in patients with recent-onset schizophrenia than in patients with chronic schizophrenia. These findings may be attributable to larger cognitive and functional reserves and greater improvement capacity in patients with a short duration of treatment compared with those with long-duration illness [31].

Metabolic abnormalities have led to serious problems in Asian patients with schizophrenia, as in Western nations [31,33-36]. Although aripiprazole is a well-known and favorable drug in terms of metabolic adverse events [37], it could cause metabolic abnormalities in patients with recent-onset schizophrenia [38]. In addition, increasing adherence to LAI use by patients who had previously had partial adherence to oral medications may cause more drug-related adverse events [39]. However, in this study, changes in metabolic parameters including body weight were not clinically significant in both recent-onset and chronic patients over a 6-month period. Results showing significant improvement in metabolic parameters in the group with long-term illness suggest that LAI aripiprazole may be effective in terms of metabolic parameters in patients with chronic schizophrenia who may already have metabolic abnormalities due to the long duration of treatment.

LAI aripiprazole had a favorable safety profile in the present study. The most common adverse event was injection site pain [40]. But most of them were tolerable. In addition, pain was significantly decreased after switching from LAI paliperidone to LAI aripiprazole. About 10% of participants experienced transient exacerbation of psychotic symptoms after switching to LAI aripiprazole. Considering the dopamine partial agonist profile and the slow increase in the pharmacokinetic level of LAI aripiprazole,

supplementation of oral medication and slow tapering from the previous drug may be needed in some patients with psychotic exacerbation.

While this study was a non-comparable, one-arm study, it showed that objective measures of social functioning and subjective measures of quality of life were significantly improved after switching to LAI aripiprazole. The effect size of improvement on the SWN total score was greater ($d = 0.358$) than those in our previous studies examining switching to other oral antipsychotics for 6 months conducted in Korean patients with schizophrenia ($d = -0.110$ in an oral aripiprazole study, $d = 0.161$ in an oral paliperidone study) [31,41]. This result is compatible with previous studies showing that LAI aripiprazole can effectively improve health-related quality of life and social functioning [32,42,43]. The improvements in the quality of life and social functioning seen in this study are among the most important treatment goals for patients with schizophrenia [41-45]. Moreover, positive subjective experiences are highly correlated with treatment adherence and positive long-term outcomes [46,47]. LAI antipsychotics that improved the subjective well-being of patients can be an effective treatment option for patients with schizophrenia, including those in the early phase of illness [11,48].

Although the observed improvements can be attributed to medication effects, they should be interpreted with caution for the following reasons. First, this was not a controlled study, so practice effects may have resulted from repeated exposure to the cognitive measures and natural clinical improvements with antipsychotic medications. Second, this was an open-label study, which could have allowed bias in ratings by patients. However, significant improvements in subjective measures may have clinical implications. Third, the low dropout rate may be attributable to the characteristics of participants who were clinically stable. Therefore, caution should be taken while applying these results are adjusted to patients with acute symptoms and severe functional impairment. Finally, this prospective clinical study was conducted with a naturalistic switching strategy, and concomitant medications that could contribute to clinical improvement were not strictly controlled. However, in the current situation, with limited evidence for the use of LAI aripiprazole, this study may contribute to our understanding of its effective use in patients with recent-onset schizophrenia and those receiv-

ing LAI paliperidone.

In conclusion, successful switching to LAI aripiprazole from other oral and LAI SGAs in most participants with recent-onset and chronic schizophrenia suggests the drug's good tolerability and effectiveness. Improvements in psychopathology and social functioning were more evident in patients with recent-onset schizophrenia, and improvements in metabolic abnormalities were more prominent in patients with chronic schizophrenia. LAI aripiprazole can be an effective treatment option in various clinical situations for the treatment of schizophrenia.

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■ Conflicts of Interest

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

■ Author Contributions

Conception and design of the study: Sung-Wan Kim, Young-Chul Chung. Acquisition of data: Sung-Wan Kim, Bong-Ju Lee, Eun-Jin Cheon, Seung-Hee Won, Young-Chul Chung. Analysis of data: Sung-Wan Kim, Anna Jo. Drafting the manuscript: Sung-Wan Kim. Making suggestions on the manuscript: Jae-Min Kim, Young-Chul Chung. All authors reviewed the manuscript and approved it for submission.

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