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Effectiveness of switching to long-acting injectable aripiprazole in patients with recent-onset and chronic schizophrenia

Short running title: Switching to LAI aripiprazole

Abstract

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.

The trial register and clinical trial registration number: (ClinicalTrials.gov) NCT03839251

KEYWORDS: long-acting injection, aripiprazole, switching, schizophrenia, recent-onset

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 several 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, 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 FDA in 2013. Although clinical studies and the manufacture'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 DSM-5 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. All patients gave written informed consent before participating in the study.

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 extrapyramidal symptoms (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 treatment 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 (SPSS, Inc., Chicago, IL, 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 paliperidone 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 paliperidone 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 (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, Figure 1). The post hoc LSD comparisons revealed significant improvements 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, Figure 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 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 deceased 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 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 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 option. 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 × 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 × 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 receiving 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.

References

1. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. *Oral versus depot antipsychotic drugs for schizophrenia--a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 2011;127:83-92.*

2. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, *et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. JAMA Psychiatry 2017;74:686-693.*

3. Kim HO, Seo GH, Lee BC. *Real-world effectiveness of long-acting injections for reducing recurrent hospitalizations in patients with schizophrenia. Ann Gen Psychiatry 2020;19:1.*

4. Lee D, Lee BC, Choi SH, Kang DH, Jon DI, Jung MH. *Effects of Paliperidone Palmitate on Healthcare Utilization and Costs for Patients with Schizophrenia: A Claim-based Mirror-image Study in South Korea. Clin Psychopharmacol Neurosci. 2020;18:303-310.*

5. Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, *et al. Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies. Schizophr Bull 2018;44:603-619.*

6. Pae CU, Wang SM, Han C, Bahk WM, Lee SJ, Patkar AA, *et al. Comparison between long-acting injectable aripiprazole versus paliperidone palmitate in the treatment of schizophrenia: systematic review and indirect treatment comparison. Int Clin Psychopharmacol 2017;32:235-248.*

7. Miller BJ, Claxton A, Du Y, Weiden PJ, Potkin SG. *Switching patients with schizophrenia from paliperidone palmitate to aripiprazole lauroxil: A 6-month, prospective, open-label study. Schizophr Res 2019;208:44-48.*

8. Kim SW, Nelson B, Yang YK, Chung YC. *Editorial: Early Intervention in Psychotic Disorders. Front Psychiatry 2020;11:574532.*

9. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. *A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011;168:603-609.*

10. Kim B, Lee SH, Yang YK, Park JI, Chung YC. *Long-acting injectable antipsychotics for first-episode schizophrenia: the pros and cons. Schizophr Res Treatment 2012;2012:560836.*

11. Stevens GL, Dawson G, Zummo J. *Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Interv Psychiatry 2016;10:365-377.*

12. Abdel-Baki A, Thibault D, Medrano S, Stip E, Ladouceur M, Tahir R, *et al. Long-acting antipsychotic medication as first-line treatment of first-episode psychosis with comorbid substance use disorder. Early Interv Psychiatry 2020;14:69-79.*

13. Shin W, Lee DH, Kim MK, Lee SH, Cho DY, Bang M. *Clinical effectiveness of early treatment with paliperidone palmitate in schizophrenia: A retrospective real-world study in South Korea. Early Interv Psychiatry 2021 (Epub ahead).*

14. Giordano G, Tomassini L, Cuomo I, Amici E, Perrini F, Callovini G, *et al. Aripiprazole Long-Acting Injection During First Episode Schizophrenia-An Exploratory Analysis.*

Front Psychiatry 2020;10:935.

15. Kane JM, Schooler NR, Marcy P, Correll CU, Achtyes ED, Gibbons RD, *et al. Effect of Long-Acting Injectable Antipsychotics vs Usual Care on Time to First Hospitalization in Early-Phase Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry 2020;77(12):1-8.*

16. Kay SR, Fiszbein A, Opler LA. *The Positive and Negative Syndrome Scale for schizophrenia. Schizophr Bull 1987;13:261-276.*

17. Yi JS, Ahn YM, Shin HK, An SK, Joo YH, Kim SH, *et al. Reliability and validity of the Korean version of the Positive and Negative Syndrome Scale. J Korean Neuropsychiatr Assoc 2001;40:1090-1105.*

18. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. *Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr Scand 2000;101:323-329.*

19. Lee JG, Seok JH, Lee JY, Lee KU, Kwak KH, Kwon JS, *et al., A Validation Study of the Korean-Version of the Personal and Social Performance Scale. Korean J Psychopharmacol 2006;17:497-506.*

20. Simpson GM, Angus JWS. *A rating scale for extrapyramidal side effect. Acta Psychiatr Scand 1970;212(suppl):11-19.*

21. Barnes TR. *A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-676.*

22. Guy W. *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-*

338. Washington, DC: US Department of Health, Education, and Welfare, 1976, pp 534–537.

23. Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, *et al. Improvement of schizophrenic patients' subjective wellbeing under atypical antipsychotic drugs. Schizophr Res 2001;50:79-88.*

24. Kim SW, Shin IS, Kim JM, Yoo JA, Ahn YM, Kwon JS, *et al. A validation study of the Korean version of Subjective Well-being Under Neuroleptic Treatment Scale-Short Form. Korean J Psychopharmacol 2007;18:221-230.*

25. Lee SJ. *Development of an emotional awareness test consisting of problem solving tasks. Korean J Soc Pers Psychol 2001;15:65-86.*

26. Guy W. *Clinical Global Impressions Scale (CGI), modified. In: Rush AJ, editor. Handbook of psychiatric measures. Washington, DC: American Psychiatric Association; 2000. pp. 100–102.*

27. McGorry PD. *The recognition and optimal management of early psychosis: an evidence-based reform. World Psychiatry 2002;1:76-83.*

28. Mustafa S, Bougie J, Miguelez M, Clerzius G, Rampakakis E, Proulx J, *et al. Real-life assessment of aripiprazole monthly (Abilify Maintena) in schizophrenia: a Canadian naturalistic non-interventional prospective cohort study. BMC Psychiatry 2019;19:114.*

29. Lieberman JA, Stroup TS. *The NIMH-CATIE Schizophrenia Study: what did we learn? Am J Psychiatry 2011;168:770-775.*

30. Kern RS, Green MF, Cornblatt BA, Owen JR, McQuade RD, Carson WH, *et al. The*

neurocognitive effects of aripiprazole: an open-label comparison with olanzapine. Psychopharmacology 2006;187:312-320.

31. Kim SW, Shin IS, Kim JM, Lee JH, Lee YH, Yang SJ, *et al. Effectiveness of switching to aripiprazole from atypical antipsychotics in patients with schizophrenia. Clin Neuropharmacol 2009;32:243-249.*

32. Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, *et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res 2015;168:498-504.*

33. Kim SW, Shin IS, Kim JM, Bae KY, Yang SJ, Yoon JS. *Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. Clin Neuropharmacol 2010;33:121-125.*

34. Ko YK, Soh MA, Kang SH, Lee JI. *The prevalence of metabolic syndrome in schizophrenic patients using antipsychotics. Clin Psychopharmacol Neurosci 2013;11:80-88*

35. Kim SW, Park WY, Jhon M, Kim M, Lee JY, Kim SY, *et al. Physical health literacy and health-related behaviors in patients with psychosis. Clin Psychopharmacol Neurosci 2019;17:279-287.*

36. Sugawara N, Yasui-Furukori N, Sato Y, Umeda T, Kishida I, Yamashita H, *et al. Prevalence of metabolic syndrome among patients with schizophrenia in Japan. Schizophr Res 2010;123:244-250.*

37. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, *et al. Comparative effects of 18 antipsychotics on metabolic function in patients with*

schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7:64-77.

38. Vázquez-Bourgon J, Ibáñez Alario M, Mayoral-van Son J, Gómez Revuelta M, Ayesa Arriola R, Juncal Ruiz M, *et al. A 3-year prospective study on the metabolic effect of aripiprazole, quetiapine and ziprasidone: A pragmatic clinical trial in first episode psychosis patients. Eur Neuropsychopharmacol 2020; 39:46-55.*

39. Kim SW, Shin IS, Kim JM, Lee SH, Lee YH, Yang SJ, *et al. Effects of switching to long-acting injectable risperidone from oral atypical antipsychotics on cognitive function in patients with schizophrenia. Hum Psychopharmacol 2009;24:565-573.*

40. Kamei H, Homma Y, Takeuchi I, Hajitsu G, Tozawa K, Hatano M, *et al. Acceptance of the Deltoid Muscle Injection of Aripiprazole Long-acting Injectable in the Patients with Schizophrenia. Clin Psychopharmacol Neurosci 2020;18:49-57.*

41. Kim SW, Yoon JS, Kim YS, Ahn YM, Kim CE, Go HJ, *et al. The effect of paliperidone extended release on subjective well-being and responses in patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2012;38:228-235.*

42. Naber D, Baker RA, Eramo A, Forray C, Hansen K, Sapin C, *et al. Long-term effectiveness of aripiprazole once-monthly for schizophrenia is maintained in the QUALIFY extension study. Schizophr Res 2018;192:205-210.*

43. Pae CU, Han C, Bahk WM, Lee SJ, Patkar AA, Masand PS. *Clinical Benefit and Utility of Switching to Aripiprazole Once Monthly in Patients with Antipsychotic Polypharmacy or Long acting Injectable Antipsychotics for Patients with*

Schizophrenia in Routine Practice: A Retrospective, Observation Study. Clin Psychopharmacol Neurosci 2021;19:233-242.

44. Rossi A, Vita A, Tiradritti P, Romeo F. *Assessment of clinical and metabolic status, and subjective well-being, in schizophrenic patients switched from typical and atypical antipsychotics to ziprasidone. Int Clin Psychopharmacol 2008;23:216–222.*

45. Ryu S, Lee H, Lee DK, Nam HJ, Chung YC, Kim SW. *Network Structures of Social Functioning Domains in Schizophrenia and Bipolar Disorder: A Preliminary Study. Clin Psychopharmacol Neurosci 2020;18(4):571-579.*

46. Kampman O, Laippala P, Vaananen J, Koivisto E, Kiviniemi P, Kilkku N, *et al. Indicators of medication compliance in first-episode psychosis. Psychiatry Res 2002;110: 39–48.*

47. Lambert M, Naber D, Schacht A, Wagner T, Huber C, Karow A, *et al. Predicting remission and recovery in 392 never-treated patients with schizophrenia. Acta Psychiatr Scand 2008;118:220–229.*

48. Kim SW, Lee YH, Jang JE, Yoo T, Kim JM, Shin IS, *et al. Comparison of attitudes toward long-acting injectable antipsychotics among psychiatrists and patients. Int Clin Psychopharmacol 2013;28:80-86.*

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

*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 x group interaction: F=3.159, p=0.014

Table 1. Sociodemographic and clinical characteristics of participants

Characteristics	Total (n=82, 100%)	Complete (n=67, 81.7%)	Drop-out (n=15, 18.3%)	p-value
Age, mean (SD), year	33.1 (9.5)	33.1 (9.4)	33.1 (10.1)	0.993
Sex, N (%)				0.356
Female	47 (57.3)	40 (85.1)	7 (14.9)	
Male	35 (42.7)	27 (77.1)	8 (22.9)	
Education, mean (SD), year	14.0 (2.8)	13.7 (3.0)	14.9 (1.7)	0.121
Regular job, N (%)				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, Med (IQR), year	4.6 (2.2-8.9)	4.9 (2.1-11.2)	3.8 (2.5-6.4)	0.299
Onset, N (%)				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, mean (SD)	11.2 (4.7)	11.5 (4.9)	9.7 (3.3)	0.191
Negative, mean (SD)	14.3 (5.7)	14.6 (6.0)	13.1 (4.0)	0.354
General, mean (SD)	26.9 (8.9)	27.7 (9.5)	23.6 (4.5)	0.110
Total, mean (SD)	52.4 (17.8)	53.7 (19.0)	46.4 (8.9)	0.149
PSP, mean (SD)	66.5 (11.6)	65.9 (11.5)	69.2 (12.2)	0.320

Previous antipsychotics, N (%)				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, Med (IQR), mg/day	450 (300-750)	450 (300-800)	300 (200-550)	0.107
Switching to aripiprazole				
Starting dose, 400 mg/day, N (%)	59 (72.0)	49 (83.1)	10 (16.9)	0.751
Final dose, 400 mg/day, N (%)	59 (72.0)	48 (81.4)	11 (18.6)	1.000
Duration of cross-titration, Med (IQR), week	4 (0-14)	4 (0-16)	2 (0-4)	0.098
Duration of oral aripiprazole use, Med (IQR), week	4 (2-4)	4 (2-5)	4 (2-4)	0.261
Combination of oral antipsychotics, N (%)				0.436
Combination	29 (35.4)	25 (86.2)	4 (13.8)	
Monotherapy of LAI	53 (64.6)	42 (79.2)	11 (20.8)	

N, number; SD, standard deviation; Med, median; IQR, interquartile range; LAI, long-acting injectable APs, antipsychotics; PANSS, Positive And Negative Syndrome Scale; PSP, Personal and Social Performance scale;

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

	Baseline	12 weeks	24 weeks	Effect of time		End-point	
	Mean (SD)	Mean (SD)	Mean (SD)	F	P	Mean change (SE)	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

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

SD, standard deviation; SE, standard error; PANSS, Positive And Negative Syndrome Scale; PSP, Personal and Social Performance

scale; SWN, Subjective Well-Being under Neuroleptics

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

	Total			Recent-onset			Chronic		
	Baseline	26 weeks	p-value	Baseline	26 weeks	p-value	Baseline	26 weeks	p-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
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**

SD, standard deviation

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

	Recent-onset (N=45)		Chronic (N=37)		Group x time interactions	
	Baseline Mean (SD)	Mean change (SE)	Baseline Mean (SD)	Mean change (SE)	F	p-value
Age, year	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

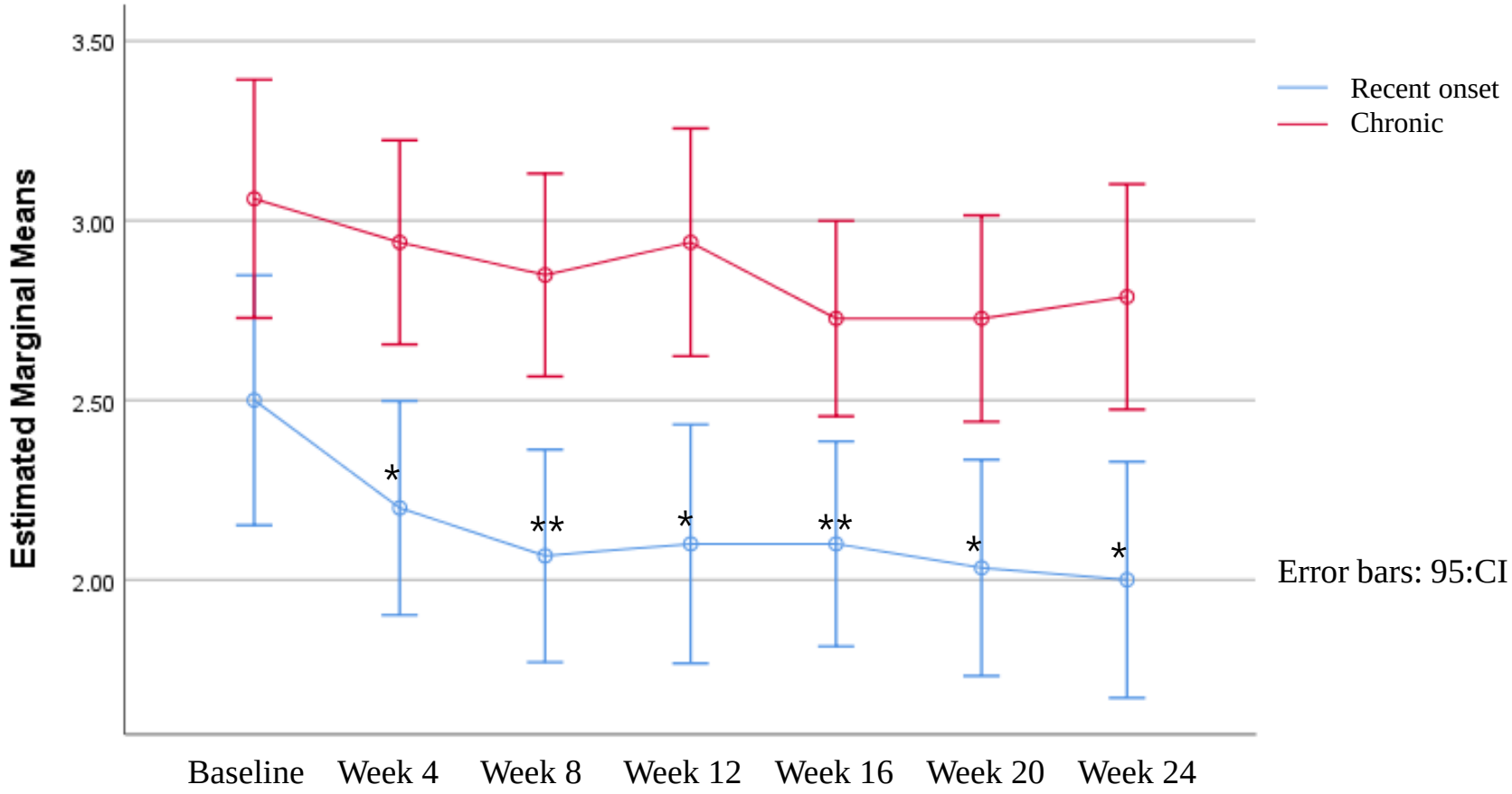
*p<0.05; **p<0.01; ***p<0.001 vs. baseline

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

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

	Baseline	Endpoint	p-value
	N (%)	N (%)	
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

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


Estimated Marginal Means
3.50
3.00
2.50
2.00
Recent onset
Chronic
*
**
*
**
*
*
Error bars: 95:CI
Baseline
Week 4
Week 8
Week 12
Week 16
Week 20
Week 24