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Stability of psychotic symptoms and safety in switching to aripiprazole once-monthly according to prior oral antipsychotic drugs☆

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ABSTRACT

Long-acting injectable aripiprazole has substantiated safety and efficacy in treating schizophrenia. However, interindividual variability in clinical response to aripiprazole, possibly linked to its D2 partial agonism and D2 upregulation due to prior antipsychotics, has been reported. This study assessed whether there would be symptomatic aggravations or adverse events in clinically stable patients with schizophrenia when switching from oral antipsychotics to aripiprazole once-monthly (AOM), considering prior antipsychotics: oral aripiprazole (Group I) or other D2 antagonists (Group II).

This was a 20-week, prospective, open-label, multicenter trial. Clinically stable patients with schizophrenia were assigned to two groups based on their oral antipsychotic medication and received AOM every 4 weeks. The primary endpoint was a change from baseline in the total Positive and Negative Syndrome Scale (PANSS) score. Treatment-emergent adverse events (TEAEs) were monitored.

Altogether, 100 patients in Group I and 101 in Group II completed the study. The mean changes (±SD) from baseline in PANSS total score after switching to AOM were − 9.43 ± 9.79 in Group I ($p < 0.0001$) and − 4.04 ± 8.72 in Group II ($p = 0.0102$). Compared to Group I, in Group II, more sleep disturbance ($p = 0.0243$) and

☆ LAI aripiprazole and prior oral antipsychotics

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psychotic symptoms ($p = 0.0042$) TEAE emerged after AOM initiation, with both TEAEs resolving during the study. Psychotic symptoms TEAE was associated with faster tapering of the prior oral antipsychotics ($p = 0.0269$).

Initiating AOM did not aggravate symptoms. Furthermore, AOM ameliorated psychotic symptoms without any significant adverse effect, regardless of their prior oral antipsychotics. However, patients previously treated with D2 antagonists may experience transient psychiatric TEAEs that can be minimized with longer cross-titration.

1. Introduction

Schizophrenia is a chronic and debilitating mental illness characterized by psychotic symptoms such as hallucinations and delusions, often accompanied by cognitive and social impairments (Rossler et al., 2005). Schizophrenia typically develops in young adulthood and may lead to lifelong disability. Although antipsychotic treatments are generally effective in alleviating psychotic symptoms and lead to clinical remission (Lally et al., 2017; Solmi et al., 2023), the majority of patients experience psychotic relapses during the course of the illness (Alvarez-Jimenez et al., 2011). The recurring psychotic relapses are associated with clinical and functional deterioration (Wiersma et al., 1998), treatment resistance (Takeuchi et al., 2019), and brain tissue loss (Andreasen et al., 2013).

Many lines of evidence indicate that inadequate adherence and/or antipsychotic discontinuation is the most common risk factor contributing to psychotic relapse (Alvarez-Jimenez et al., 2012; Wunderink et al., 2007). Indeed, diminished adherence to antipsychotic treatment was associated with a higher rate of psychiatric hospitalization (Ascher-Svanum et al., 2009). Even short gaps, ranging from one to ten days in antipsychotic medication coverage, increased the risk of hospitalization in patients with schizophrenia (Weiden et al., 2004). Given the chronic nature of schizophrenia, which conventionally necessitates long-term maintenance treatment (Correll et al., 2018), addressing the issue of poor treatment adherence is imperative, as it holds the potential to trigger psychotic relapse in schizophrenia.

Long-acting injectable antipsychotic drugs (LAIs) have been introduced to enhance adherence and make non-adherence visible (Correll et al., 2016; Kane et al., 2013). LAIs ease the daily burden of adhering to oral medication and mitigate the risk of psychotic relapse resulting from poor adherence. Studies utilizing a nationwide database in Sweden have documented an association of LAI antipsychotic medication with the highest rate of relapse prevention in schizophrenia. Notably, patients treated with LAI antipsychotic drugs exhibited a substantially reduced risk of rehospitalization and mortality compared to equivalent oral formulations (Taipale et al., 2018; Tiihonen et al., 2017). These advantages of LAIs have been substantiated in meta-analysis of relapse prevention (Kishimoto et al., 2021) and mortality risk (Correll et al., 2022b) in patients with schizophrenia. Furthermore, LAIs have shown the potential to enhance functional outcomes in individuals with schizophrenia. For instance, a systematic analysis of randomized controlled trials underscored the efficacy of LAIs in improving functioning, coupled with heightened patient satisfaction and service engagement (Peters et al., 2019). This enhanced focus on functioning assumes paramount importance in the treatment of schizophrenia, as it is closely associated with a more favorable prognosis and better community adaptation (Correll et al., 2022a; Nasrallah et al., 2008).

Aripiprazole, functioning as a D2 receptor partial agonist, has substantiated its safety and efficacy in the treatment of schizophrenia (Kane et al., 2002; Kasper et al., 2003). In particular, aripiprazole has demonstrated effectiveness in treating both positive and negative symptoms in the context of acute intervention or long-term maintenance. It has outperformed placebo treatment and exhibited comparability to conventional D2 receptor antagonists (Kane et al., 2002; Potkin et al., 2003). Furthermore, aripiprazole has a favorable safety and tolerability profile. For example, aripiprazole has shown a low incidence of extrapyramidal symptoms and hyperprolactinemia, even at the highest dose and with D2 receptor occupancy surpassing 80 % (de Bartolomeis et al., 2015). Notably, aripiprazole has been observed to counteract hyperprolactinemia induced by D2 receptor antagonists (Shim et al., 2007), representing an attribute specifically linked to its D2 receptor partial agonism.

With aripiprazole's clinical efficacy comparable to conventional D2 receptor antagonists and more favorable side-effect profiles (Huhn et al., 2019; Kishimoto et al., 2019; Ostuzzi et al., 2022), LAI aripiprazole has been introduced. Reports highlight the clinical advantages of LAI aripiprazole both as an acute intervention and a maintenance treatment for schizophrenia (Kane et al., 2014; Kishi et al., 2022; Naber et al., 2018; Ostuzzi et al., 2021). Indeed, psychotic symptoms improved with LAI aripiprazole in patients with acute schizophrenia (Kane et al., 2014; Kane et al., 2020). Furthermore, functioning and health-related quality of life were enriched, showing the long-term clinical benefit of LAI aripiprazole (Naber et al., 2018). Notably, LAI aripiprazole was better accepted for patients than the equivalent oral formulation (Kishi et al., 2022) or than other LAIs (Ostuzzi et al., 2021).

However, there have been reports of interindividual variability in clinical response to aripiprazole. Several case reports have described worsened psychotic symptoms in patients with schizophrenia following the introduction or transition to aripiprazole (DeQuardo, 2004; Fleischhacker et al., 2010; Newcomer et al., 2008; Raja, 2007; Ramaswamy et al., 2004; Reeves and Mack, 2004; Takeuchi and Remington, 2013). Considering the mechanism of action (Burris et al., 2002), the variability in clinical response to aripiprazole or the worsened psychotic symptoms by aripiprazole might be explained by the supersensitivity psychosis (Russell et al., 2022; Takase et al., 2015) and/or histaminergic and cholinergic rebound (Baumann et al., 2023; Correll, 2010; Hojlund and Correll, 2023). Prior prolonged exposure to D2 receptor antagonists may lead to a compensatory D2 receptor upregulation (Silvestri et al., 2000), and the subsequent addition of D2 receptor partial agonism via aripiprazole could contribute to such variability and exacerbations (Nakata et al., 2017). Such prospect of divergent clinical responses to aripiprazole depending on prior antipsychotic exposure raises concerns, especially for clinicians contemplating the transition from oral antipsychotic drugs to LAI aripiprazole (Hojlund and Correll, 2023).

Thus, we investigated whether there would be symptomatic aggravations or adverse events in clinically stable patients with schizophrenia when switching from oral antipsychotic drugs to aripiprazole once-monthly (AOM), with a specific focus on their prior antipsychotic treatment—either oral aripiprazole or other oral antipsychotic drugs with D2 antagonism.

2. Methods

The present study was a 20-week, prospective, open-label, multicenter trial (NCT03376763). The trial protocol was reviewed and approved by the Institutional Review Boards of each individual recruitment site. The study complied with the International Council on Harmonization guidelines for Good Clinical Practice and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

2.1. Participants

The study group consisted of psychiatrists from 27 hospitals in South Korea who actively participated in this research study. Clinically stable

patients with schizophrenia undergoing treatment at outpatient clinics of participating hospitals were recruited. Prior to enrollment, participants received a comprehensive explanation of the study and provided written informed consent to participate.

The inclusion criteria for eligibility were: (1) male or nonpregnant, nonlactating female patients aged ≥19 and < 65 years; (2) patients who were diagnosed as schizophrenia based on DSM-5 criteria for a minimum of 2 years; (3) patients who had a total score of ≤80 on the Positive and Negative Syndrome Scale (PANSS)(Kay et al., 1987) and scores ≤4 on the four items of the PANSS: P2. Conceptual disorganization, P3. Hallucinatory behavior, P6. Suspiciousness/persecution, G9. Unusual thought content; (4) patients who had a score of ≤4 (i.e., moderate severity) on the Clinical Global Impression-Severity (CGI-S) scale (Busner and Targum, 2007) with no history of hospitalization within 3 months; and (5) patients who were taking oral atypical antipsychotic drugs at the therapeutic effective doses and who were maintained on the current medication for at least 4 weeks.

Patients with a history of intolerance to aripiprazole, other comorbid psychiatric illnesses according to DSM-5 criteria, neurological abnormalities affecting the assessment of the psychotic symptoms, or any significant medical abnormalities were excluded. Patients currently taking two or more antipsychotic drugs at therapeutic doses for psychosis were not enrolled in the study. However, combinations of antipsychotics at doses below the therapeutically effective levels specified in the labeling information were allowed. Patients who were treated with clozapine, electroconvulsive therapy, or other LAI antipsychotic drugs within the past 3 months were also excluded.

Enrollment commenced in November 2017, and the final assessment took place in November 2021.

2.2. Study design

The study included a screening phase of 2 weeks and a treatment phase of 16 weeks. A safety follow-up visit occurred 4 weeks after the treatment phase. Participants were assigned to two groups (Group I and Group II) based on their oral antipsychotic medication at the screening visit. Group I comprised patients with schizophrenia taking oral aripiprazole, while Group II consisted of patients taking oral atypical antipsychotic drugs other than aripiprazole. For Group II, 5 to 10 mg of oral aripiprazole was added to their ongoing medication for at least 2 weeks between the screening (Visit 0) and the baseline (Visit 1) to assess the tolerability to aripiprazole. The dose of oral aripiprazole for Group II were chosen based on the investigators' decision.

At Visit 1, participants in both Group I and Group II received an initial injection of AOM 400 mg. Oral aripiprazole was concurrently prescribed for 2 weeks after the initial AOM injection. Subsequent AOM injections were administered intramuscularly at the deltoid or gluteal area every 4 weeks from Visit 1 for 16 weeks. In Group II, the oral antipsychotic drugs were tapered and discontinued within 6 weeks after Visit 1, and the rate of tapering of the oral antipsychotic drugs was determined based on the investigators' decision. The dose of AOM could be adjusted to 300 mg as needed based on the investigators' decision.

The clinical assessments were carried out at each AOM injection visit and the last visit of the treatment phase; adverse event monitoring was performed at every visit (See Fig. S1 in the supplement).

If necessary, benzodiazepine or non-benzodiazepine sedative hypnotics, beta-adrenergic blockers and anticholinergic antiparkinsonian drugs were permitted based on the investigators' judgement as rescue medications for any reason, including agitation, anxiety and/or insomnia.

2.3. Assessments

The clinical assessments included PANSS, CGI-S, Clinical Global Impression-Improvement (CGI-I) (Busner and Targum, 2007), and Investigator's Assessment Questionnaire (IAQ) (Tandon et al., 2005).

Adverse events emerging during study participation were monitored via spontaneous patient reports and physical examinations, vital signs, laboratory tests, and 12-lead electrocardiograms. Extrapyramidal symptoms were assessed using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), Simpson-Angus Neurologic Rating Scale (SAS) (Simpson and Angus, 1970), and Barnes Akathisia Rating Scale (BARS) (Barnes, 1989).

2.4. Outcomes

The primary endpoint was a change from baseline in PANSS total score at the last treatment visit (Visit 8). The secondary endpoints included changes from baseline in CGI-S score and PANSS subscale scores and mean CGI-I and IAQ scores at the last treatment visit (Visit 8).

Safety was assessed on the basis of the incidence of the treatment-emergent adverse events (TEAEs), defined as any adverse event experienced by a study participant that occurred after the AOM initiation. This encompasses events newly developed after the AOM administration and pre-existing medical issues changing adversely in nature or severity from baseline. TEAEs were documented based on spontaneous patient reports and clinical interviews. Among TEAEs, drug-related adverse events were judged by investigators.

An exploratory analysis was conducted for the relationship between the rate of tapering of prior antipsychotic drugs and the incidence of TEAEs in Group II. The rate of tapering of the prior antipsychotic drugs was defined as (mg of olanzapine-equivalent dose at baseline divided by days of the tapering period). The tapering period was from the AOM start to the end of tapering, and olanzapine-equivalent doses were calculated based on the formula from previous reports (Inada and Inagaki, 2015; Leucht et al., 2016). For the analysis, we divided Group II into Fast group and Slow group based on the median of the rate of tapering.

2.5. Statistical analysis

The primary objective of the study was to examine whether there would be symptomatic aggravation or adverse effects when switching from oral antipsychotic drugs to AOM according to prior oral antipsychotic exposure - either oral aripiprazole or other oral antipsychotic drugs with D2 receptor antagonism. Thus, the present study was designed to determine non-worsening after switching to AOM compared to oral antipsychotic treatment before switching within each group. The statistical hypotheses are as follows:

$$H_0 : \mu - \mu_0 \geq \delta \; vs \; H_1 : \mu - \mu_0 < \delta$$

where μ represents the mean PANSS total score at the last treatment visit (Visit 8), μ_0 is the mean PANSS total score at baseline, and δ is the non-worsening margin.

Based on the previous result by Fleischhacker et al. (2014), the standard deviation (σ) for change from baseline in the PANSS total score at the last treatment visit was estimated and presumed to be 11.5 points. The non-worsening margin was defined as a change of +4 points in the PANSS total score, taking the outcomes from preceding trials (Fleischhacker et al., 2009; Fleischhacker et al., 2014) into consideration.

To determine non-worsening with the test power of 80 % and a one-sided significance level of 2.5 %, the number of necessary participants in each group was calculated as follows:

$$N = \frac{\left(Z_{1-\alpha} + Z_{1-\beta}\right)^2 \bullet \sigma^2}{\left(\mu - \mu_0 - \delta\right)^2}$$

where N denotes the number of necessary participants, $\mu - \mu_0 = 0$, $\sigma = 11.5$, $\delta = 4$, $\alpha = 0.025$, $1 - \beta = 0.8$, $Z_{1-\alpha} = 1.96$, and $Z_{1-\beta} = 0.8416$.

The formula yielded 65 participants per group, and we planned to

recruit 100 participants per group (a total of 200 participants), accounting for a dropout rate of 35 %.

The Full Analysis data Set (FAS) was obtained from the participants who were administered AOM at least once, with PANSS measurements taken after baseline, and were thus evaluable for PANSS total score change from baseline. The Per-Protocol data Set (PPS) was gathered from participants completing the study without major protocol deviations. In the study, combinations of antipsychotics at doses below the therapeutically effective levels were allowed. However, to exclude the effects of oral dopamine antagonists in Group I and oral aripiprazole in Group II before AOM initiation, the modified FAS was collected from participants who were not taking oral dopamine antagonists in Group I and those who were not taking oral aripiprazole in Group II at baseline.

Demographic and clinical characteristics, the incidence of TEAEs, and the relationship between the rate of tapering and TEAEs were examined by using *t*-tests, chi-square tests, and Fischer's exact tests, depending on the data. The primary and secondary endpoints were tested in each group employing mixed-effect models for repeated measures, controlling visit as a repeat factor and baseline as a covariate. In cases of missing values from primary and secondary endpoints, observed data were used without imputation of those missing values.

Comparing the primary and secondary endpoints between the two groups was not the study's primary objective. However, exploratory analyses involved comparing changes in PANSS scores from baseline between the two groups.

Logistic regression analyses were conducted to identify predictors of TEAEs and to conduct sensitivity analysis.

3. Results

3.1. Patient disposition and characteristics

Of 230 patients screened, 100 patients who were taking oral aripiprazole (Group I), and 101 patients taking oral atypical antipsychotic drugs other than aripiprazole (Group II) were enrolled in the present study. The FAS included 92 patients in Group I and 95 in Group II, while the PPS comprised 82 patients in Group I and 71 in Group II (Fig. 1). The number of patients who completed the study was not significantly different between the two groups ($x^2 = 0.514$, df = 1, $p = 0.4735$). Discontinuation of the treatment was the main reason for dropout in

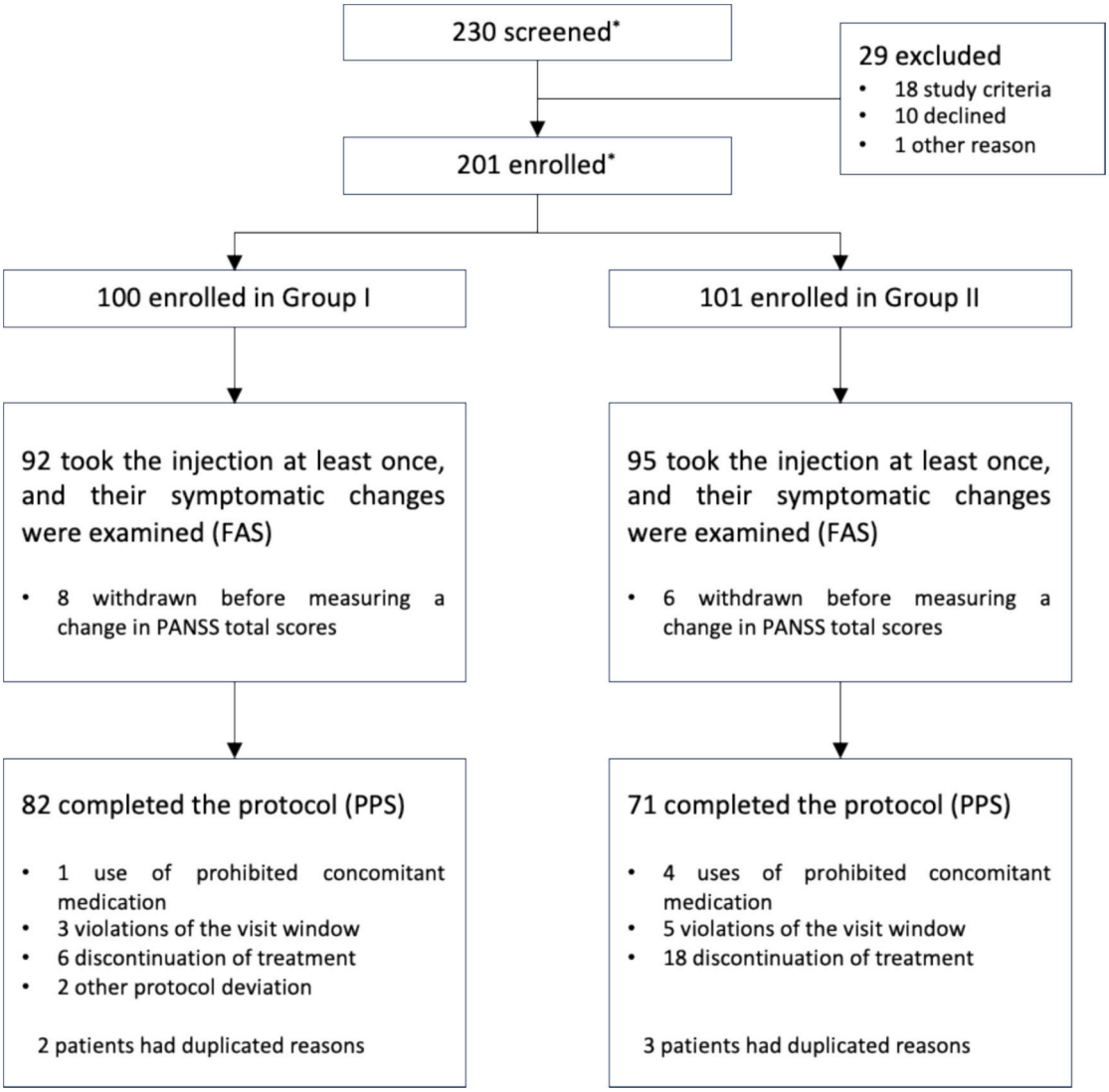


Fig. 1. Study flow diagram
*: Recruited participants were screened for eligibility and allocated to Group I and Group II based on ongoing antipsychotic drugs at the screening visit
Group I: Patients with schizophrenia taking oral aripiprazole prior to aripiprazole once-monthly initiation
Group II: Patients with schizophrenia taking oral atypical antipsychotic drugs other than aripiprazole prior to aripiprazole once-monthly initiation
Abbreviations: FAS, Full Analysis data Set; PPS, Per-Protocol data set.

both groups (Fig. 1). Among the FAS, the rescue medications were prescribed to significantly more patients in Group II (88.4 %) than in Group I (75.0 %) ($x^2 = 5.659$, df = 1, $p = 0.0174$).

Table 1 presents the demographic and clinical characteristics of the FAS. Group I had more female patients compared to Group II ($x^2 = 5.370$, df = 1, $p = 0.0205$). Group I exhibited tendencies of younger age and shorter disease duration compared to Group II (Age: $t = -1.92$, df = 185, $p = 0.0565$; disease duration: $t = -1.97$, df = 175.23, $p = 0.0500$). The baseline symptoms measured by using PANSS, and olanzapine equivalent doses of antipsychotic drugs taken prior to study enrollment did not differ between the two groups (Table 1).

The mean tapering period (±SD) of prior oral antipsychotic drugs in Group II was 36.82 ± 9.76 days. The rate of tapering of prior antipsychotic drugs ranged from 0.04 to 5.00 (median: 0.18) mg/day (Fast group: 0.19 to 5.00 (median: 0.29) mg/day, Slow group: 0.04 to 0.18 (median: 0.12) mg/day).

The doses (±SD) of AOM in Group I and Group II were similar (395.65 ± 15.55 mg vs. 395.26 ± 15.60 mg)($t = 0.17$, df = 185, $p = 0.8646$). However, the average doses of oral aripiprazole prescribed for two weeks after AOM initiation were significantly higher in Group I than Group II (13.85 ± 4.94 mg vs. 6.97 ± 1.76 mg)($t = 12.62$, df = 113, $p < 0.0001$).

3.2. Change in clinical symptoms

Table 2 summarizes the changes in clinical symptoms after switching to AOM. In the FAS, the mean PANSS total scores (±SD) at baseline were 52.32 ± 13.27 in Group I and 54.20 ± 12.83 in Group II. The mean changes from baseline in PANSS total score at the last treatment visit (Visit 8) were − 9.43 ± 9.79 in Group I and − 4.04 ± 8.72 in Group II, which are below the predefined non-worsening margin of +4 in both groups (Group I: LS mean (SE): −9.44 (0.88), p < 0.0001; Group II: LS means (SE): −2.86 (1.09), $p = 0.0102$). The PPS analysis yielded similar results: the mean PANSS total scores (±SD) at baseline were 52.67 ± 13.28 in Group I and 54.90 ± 13.43 in Group II, and the mean changes from baseline at the last treatment visit were − 9.80 ± 9.73 in Group I and − 4.89 ± 7.90 in Group II (Group I: LS mean (SE): −9.80 (0.90), p < 0.0001; Group II: LS means (SE): −4.89 (0.91), p < 0.0001).

Table 2 also demonstrates the changes in PANSS subscales and CGI-S after switching to AOM according to the baseline oral antipsychotic group. Most scores in the scales (except PANSS positive subscale in Group II in the FAS) were significantly reduced after AOM administration in both groups, indicating symptomatic improvement with AOM.

Fig. 2 illustrates changes in PANSS scores over time and comparisons between the two groups in the FAS. The differences in the PANSS scores between baseline and the last treatment visit were greater in Group I than in Group II (PANSS total score: LS mean (SE): −6.78 (1.40), p < 0.0001; Positive scale: −1.86 (0.43), p < 0.0001; Negative scale: −1.50 (0.44), $p = 0.0008$; General psychopathology scale: −3.38 (0.76), p < 0.0001).

Since differential tapering schedules in Group II could affect the results, we conducted another mixed-models sensitivity analysis, including the tapering schedules as covariates. The results remained similar as shown in Table 2 (see Table S1 in the supplement).

3.3. Safety and tolerability

Safety and tolerability analyses were conducted within the FAS. The

Table 1
Baseline demographics and clinical characteristics from Full Analysis data Set.

	Group I (N = 92)		Group II (N = 95)		Statistics		
	Mean	SD	Mean	SD	t	df	p
Age (year)	34.88	10.33	37.79	10.40	−1.92	185.00	0.0565
Disease duration (year)	7.74	5.59	9.62	7.36	−1.97	175.23	0.0500
PANSS total score	52.32	13.27	54.20	12.83	−0.99	185.00	0.3248
Positive scale	11.23	3.89	12.31	3.66	−1.95	185.00	0.0526
Negative scale	14.60	5.00	14.83	4.41	−0.34	185.00	0.7346
General psychopathology scale	26.49	6.64	27.06	6.49	−0.60	185.00	0.5507
CGI-S	2.68	0.95	2.96	0.78	−2.15	185.00	0.0330

	Group I (N = 92)		Group II (N = 95)		Statistics		
	N	%	N	%	x^2	df	p
Sex (male)	32	34.78	49	51.58	5.370	1	0.0205
Disease duration					2.569	2	0.2768
<5 years	36	39.13	32	33.68			
≥5, <10 years	33	35.87	29	30.53			
≥10 years	23	25.00	34	35.79			

	Group I (N = 92)			Group II (N = 95)			Statistics		
	N	Mean	SD	N	Mean	SD	t	df	p
Prior antipsychotic drugs (mg/day)									
Aripiprazole	92	17.86	7.00	22	4.30	1.82			
Paliperidone	0	–	–	33	7.09	2.69			
Risperidone	3	1.00	0.50	22	3.35	1.47			
Amisulpride	0	–	–	17	479.41	244.99			
Olanzapine	7	4.11	2.13	13	11.63	5.76			
Blonanserin	3	4.00	2.00	10	8.80	3.16			
Quetiapine	8	48.44	45.41	15	162.50	141.11			
Ziprasidone	0	–	–	2	40.00	0.00			
Antipsychotic dose in olanzapine equivalent dose (mg/day)	92	12.47	4.79	95	11.38	5.13	1.50	185.00	0.1364

PANSS: Positive and Negative Syndrome Scale. CGI-S: Clinical Global Impression-Severity scale. Group I: Patients who were taking oral aripiprazole prior to aripiprazole once-monthly initiation. Group II: Patients who were taking oral atypical antipsychotic drugs other than aripiprazole prior to aripiprazole once-monthly initiation. Patients currently taking two or more antipsychotic drugs at effective doses were excluded. However, antipsychotic combinations with doses below the therapeutic effective doses specified in the labelling information were allowed. The olanzapine-equivalent dose was calculated based on the formula from previous reports.(Inada and Inagaki, 2015; Leucht et al., 2016).

Table 2
Change in clinical symptoms after switching to aripiprazole once-monthly (AOM).

	Group I								Group II							
	Visit 1		Visit 8		Change		Statistics			Visit 1		Visit 8		Change		Statistics		
	Mean	SD	Mean	SD	Mean	SD	LS Mean	SE	p	Mean	SD	Mean	SD	Mean	SD	LS Mean	SE	p
FAS analysis																		
PANSS total score	52.32	13.27	43.24	11.21	−9.43	9.79	−9.44	0.88	<0.0001	54.20	12.83	50.56	13.76	−4.04	8.72	−2.86	1.09	0.0102
Positive scale	11.23	3.89	9.20	2.98	−2.06	2.70	−2.04	0.22	<0.0001	12.31	3.66	11.55	3.97	−0.79	3.00	−0.41	0.38	0.2807
Negative scale	14.60	5.00	11.90	4.28	−2.91	3.48	−2.94	0.32	<0.0001	14.83	4.41	13.43	4.84	−1.56	2.55	−1.45	0.29	<0.0001
General psychopathology scale	26.49	6.64	22.15	5.65	−4.47	5.60	−4.46	0.50	<0.0001	27.06	6.49	25.58	6.74	−1.69	4.91	−1.21	0.56	0.0332
CGI-S	2.68	0.95	2.29	0.87	−0.44	0.59	−0.44	0.06	<0.0001	2.96	0.78	2.75	0.78	−0.25	0.71	−0.17	0.08	0.0307
CGI-I			3.06	1.10								3.30	0.87					
IAQ			27.60	3.39								27.06	3.12					
PPS analysis																		
PANSS total score	52.67	13.28	42.87	11.08	−9.80	9.73	−9.80	0.90	<0.0001	54.90	13.43	50.01	13.77	−4.89	7.90	−4.89	0.91	<0.0001
Positive scale	11.32	3.99	9.11	2.94	−2.21	2.55	−2.21	0.21	<0.0001	12.42	3.87	11.27	3.92	−1.15	2.57	−1.15	0.29	0.0002
Negative scale	14.68	4.99	11.73	4.14	−2.95	3.54	−2.95	0.33	<0.0001	15.04	4.75	13.45	4.92	−1.59	2.48	−1.59	0.29	<0.0001
General psychopathology scale	26.67	6.65	22.02	5.69	−4.65	5.56	−4.65	0.51	<0.0001	27.44	6.60	25.30	6.61	−2.14	4.58	−2.14	0.52	<0.0001
CGI-S	2.73	0.94	2.28	0.86	−0.45	0.57	−0.45	0.06	<0.0001	3.00	0.81	2.68	0.73	−0.32	0.60	−0.32	0.06	<0.0001
CGI-I			3.01	1.09								3.23	0.83					
IAQ			27.52	3.41								26.94	3.13					

Group I: Patients who were taking oral aripiprazole prior to aripiprazole once-monthly initiation. Group II: Patients who were taking oral atypical antipsychotic drugs other than aripiprazole prior to aripiprazole once-monthly initiation. FAS: Full Analysis data Set. PPS: Per-Protocol data Set. PANSS: Positive and Negative Syndrome Scale. CGI—S: Clinical Global Impression-Severity scale. CGI—I: Clinical Global Impression-Improvement scale. IAQ: Investigator's Assessment Questionnaire.

incidences of TEAEs after switching to AOM and drug-related adverse events were 68.45 % and 49.73 % in the FAS, respectively. These were not significantly different between Group I and Group II (See Table S2 in the supplement).

A total of 85 patients experienced TEAEs of psychiatric symptoms after initiation of AOM, with a significantly higher incidence in Group II (53.68 %) compared to Group I (36.96 %) ($x^2 = 5.275$, df = 1, $p = 0.0216$). Psychiatric TEAEs included sleep disturbance (18.72 %), anxiety (13.37 %), mood disturbance (6.42 %), psychotic symptoms (15.51 %), suicidal ideation (1.07 %), and extrapyramidal symptoms (16.04 %). Group II exhibited a higher incidence of sleep disturbance and psychotic symptoms TEAE than Group I (sleep disturbance: $p = 0.0243$; anxiety: $p > 0.9999$; mood disturbance: $p > 0.9999$; psychotic symptoms: $p = 0.0042$; suicidal ideation: $p = 0.2407$; extrapyramidal symptoms: $p > 0.9999$). However, no significant difference was found in the incidence of psychiatric TEAEs that persisted during the study period (sleep disturbance: $p = 0.2462$; anxiety: $p > 0.9999$; mood disturbance: $p > 0.9999$; psychotic symptoms: $p = 0.2789$; suicidal ideation: $p > 0.9999$; extrapyramidal symptoms: $p = 0.4393$) (Fig. 3). As shown in Table 1, age and disease duration differed marginally between the two groups. Thus, we conducted sensitivity analyses to assess psychotic symptoms and sleep disturbance TEAEs while also accounting for age and disease duration. Logistic regression analyses demonstrated that prior treatment with full dopamine D2 antagonists still predicted the occurrence of psychotic symptoms and sleep disturbance TEAEs following the initiation of AOM, even after adjusting for age (psychotic symptoms: $p = 0.0035$, sleep disturbance: $p = 0.0258$) and disease duration (psychotic symptoms: $p = 0.0086$, sleep disturbance: $p = 0.0401$).

In Group II, the psychotic symptoms TEAE was associated with faster tapering of the prior oral antipsychotic drugs ($p = 0.0269$) while sleep disturbance was not ($p = 0.6320$) (See Fig. S2 in the supplement). Furthermore, the psychotic symptoms TEAE occurred more frequently in patients treated with higher baseline antipsychotic doses (olanzapine-equivalent dose ≥20 mg/day) ($p = 0.0092$). The logistic regression analysis, which included the tapering rate and the type of prior antipsychotic drugs as independent variables, showed that a faster tapering rate predicted psychotic symptoms TEAE (Odds ratio: 3.739, 95 % confidence interval: 1.034 to 13.517), while the type of antipsychotic drugs did not.

Among the psychotic symptoms TEAE, psychotic worsening was defined as a ≥ 20 % increase in PANSS total score after AOM initiation. There were 2 (2.2 %) patients in Group I and 6 (6.3 %) in Group II who showed psychotic worsening, without significant group differences (p = 0.2789).

3.4. Subgroup analysis excluding the combination of dopamine receptor antagonists and aripiprazole

We conducted the same analysis in modified FAS. The modified FAS included 73 patients in each group, respectively. The demographic and clinical characteristics were similar to those of the FAS (Table S3). The mean changes from baseline in PANSS total score at the last treatment visit (Visit 8) were − 9.36 ± 9.22 in Group I and − 4.37 ± 8.76 in Group II, which are also below the predefined non-worsening margin of +4 in both groups (Group I: LS mean (SE): −9.60 (1.09), $p < 0.0001$; Group II: LS means (SE): −2.74 (1.14), $p = 0.0171$) (Table S4). Regarding safety and tolerability, the incidence of TEAEs after switching to AOM did not significantly differ between the two groups ($x^2 = 0.508$, df = 1, $p = 0.4761$). However, Group II exhibited a higher incidence of the psychotic symptoms TEAE during the study period compared to Group I ($p = 0.0031$), and the psychotic symptoms TEAE was related to faster tapering of the prior oral antipsychotic drugs as seen in the result from FAS ($p = 0.0108$).

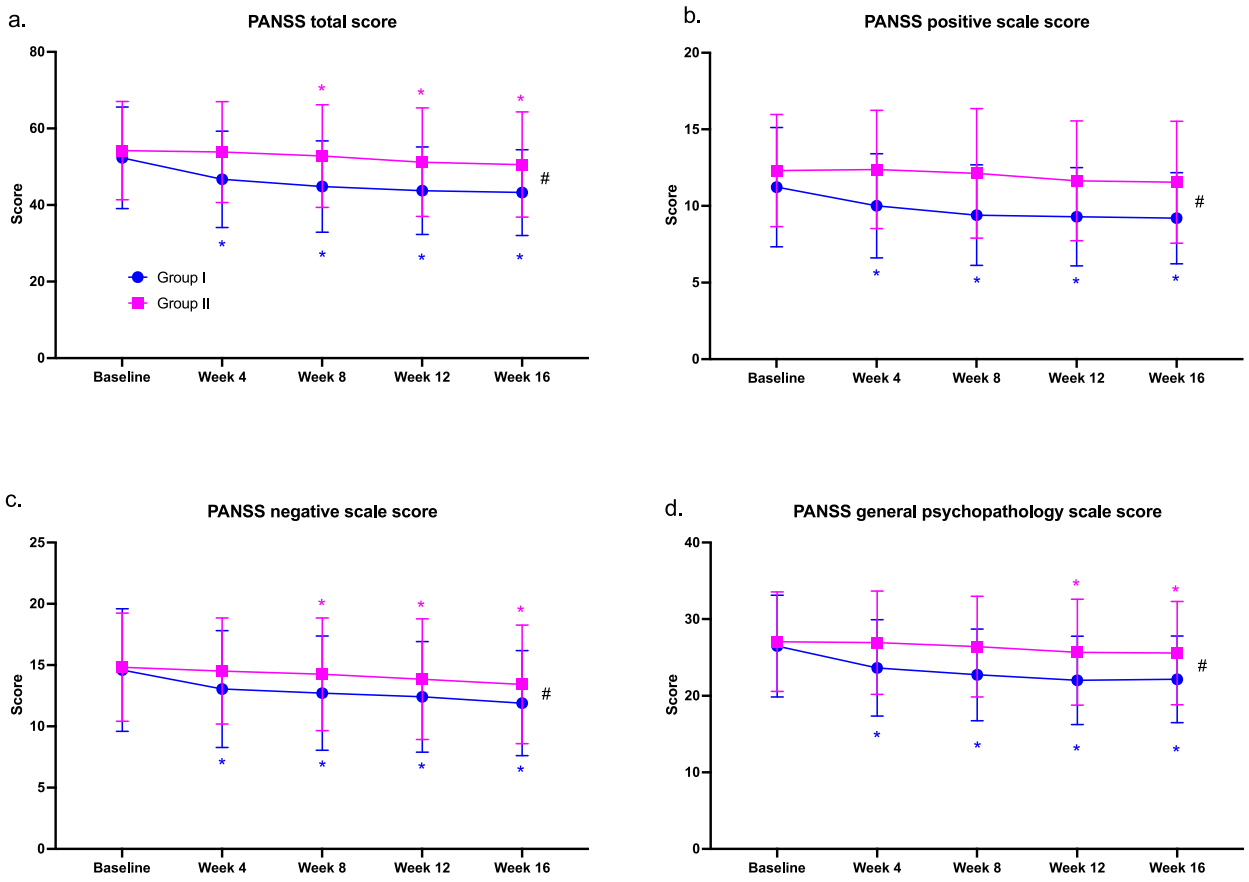


Fig. 2. Change in the Positive and Negative Syndrome Scale (PANSS) scores after switching to aripiprazole once-monthly. The analysis was conducted in Full Analysis data Set. Error bars indicate standard deviation
*: Significantly different from the score measured at baseline ($p < 0.05$)
#: The difference in the score between the baseline and Week 16 was greater in Group I than in Group II ($p < 0.05$)
Group I: Patients with schizophrenia taking oral aripiprazole before aripiprazole once-monthly initiation. ($N = 92$)
Group II: Patients with schizophrenia taking oral atypical antipsychotic drugs other than aripiprazole before aripiprazole once-monthly initiation. ($N = 95$).

4. Discussion

To our knowledge, this is the first prospective study on the stability of psychotic symptoms and safety in switching from oral antipsychotic drugs to AOM according to prior oral antipsychotic drugs. Our study found that clinically stable patients with schizophrenia experienced no worsening of psychiatric symptoms after switching from oral antipsychotic drugs to AOM, regardless of the type of prior oral antipsychotic drugs. They rather exhibited symptomatic improvement following the initiation of AOM. However, patients previously treated with oral antipsychotics with dopamine antagonism displayed a higher incidence of psychiatric TEAEs following the initiation of AOM, compared to patients previously treated with oral aripiprazole, although most of these TEAEs resolved during the study period. Furthermore, the number of patients with psychiatric TEAEs persisting throughout the study was not significantly different between the two groups, which is consistent with a previous meta-analysis showing no significant difference in the risk of psychotic worsening between aripiprazole and other antipsychotic drugs (Takeuchi et al., 2018). These results suggest that switching to AOM can be taken into consideration in the treatment of patients with schizophrenia, regardless of their previous oral antipsychotic drugs. However, consistent with the potential for pharmacodynamic rebound and withdrawal effects (Correll, 2010), these results also highlight that transient adverse events can often occur when transitioning from antipsychotic drugs with dopamine antagonism to the D2 partial agonist AOM with little/no antihistaminergic and anticholinergic effects, warranting clinicians' attention for a successful switching to AOM.

The present study primarily examined non-worsening after the initiation of AOM treatment compared to previous oral antipsychotic treatment. The enrolled patients demonstrated significant symptomatic improvement, rather than just non-worsening, upon initiating AOM. This result aligns with previous findings (Fleischhacker et al., 2014; Kim et al., 2016; Kim et al., 2021; Tiihonen et al., 2017), showing substantial improvement with LAI treatment, even in clinically stable patients previously treated with oral antipsychotic drugs. Moreover, patients treated with oral aripiprazole or oral paliperidone also exhibited improved outcomes after switching to the LAI formulations of the same antipsychotic drugs (Fleischhacker et al., 2014; Kim et al., 2016; Schottle et al., 2018, 2020; Schottle et al., 2023). These better outcomes associated with LAIs may be mediated by improved adherence, as suggested by previous studies regarding suboptimal adherence to oral antipsychotic drugs and its relationship with stable and non-acute active psychotic symptoms (Bernardo et al., 2017; Kane et al., 2013; Steger et al., 2012). The improved adherence with AOM in the present study could ameliorate stable yet active psychotic symptoms in both groups.

Meanwhile, the exploratory analysis indicated differences in PANSS score changes between Group I and Group II (Fig. 2), with Group I showing greater reductions in PANSS scores from the baseline. This finding may be attributed to the pharmacological characteristics of prior antipsychotic drugs used before the initiation of AOM. Although the olanzapine equivalent doses of prior antipsychotic drugs did not differ between the two groups (Table 1), patients in Group I had been treated with oral aripiprazole, a D2 partial agonist, while patients in Group II had received oral antipsychotic drugs with D2 antagonism. As

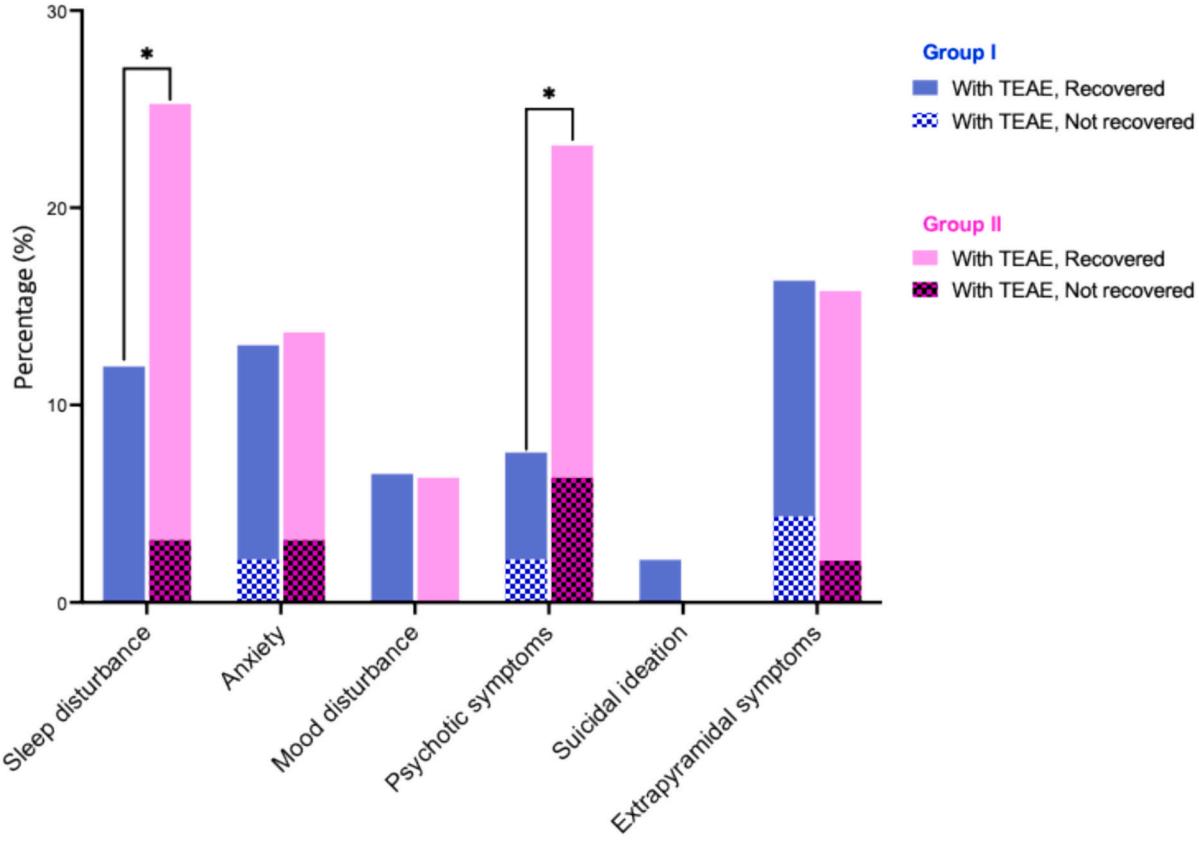


Fig. 3. Psychiatric treatment-emergent adverse effect (TEAE) subgroups and their outcomes.
*: TEAE subgroups showing significantly different incidences between the two groups (Sleep disturbance: $p = 0.0243$; Psychotic symptoms: $p = 0.0042$) but no significant difference (Sleep disturbance: $p = 0.2462$; Psychotic symptoms: $p = 0.2789$) in the aspect of TEAE which was not recovered later.
Group I: Patients with schizophrenia taking oral aripiprazole before aripiprazole once-monthly initiation. (N = 92)
Group II: Patients with schizophrenia taking oral atypical antipsychotic drugs other than aripiprazole before aripiprazole once-monthly initiation. (N = 95).

mentioned in the introduction section, long-term exposure to a D2 antagonist can induce dopamine upregulation (Silvestri et al., 2000), rendering receptors more sensitive to dopaminergic neurotransmission (Nakata et al., 2017). The lesser reductions in PANSS scores in Group II might reflect interindividual variations in clinical response to aripiprazole or a potential psychotic worsening in patients previously exposed to D2 antagonists upon adding or switching to aripiprazole, as described in the previous reports (DeQuardo, 2004; Fleischhacker et al., 2010; Newcomer et al., 2008; Raja, 2007; Ramaswamy et al., 2004; Reeves and Mack, 2004; Takeuchi and Remington, 2013).

Furthermore, the number of patients reporting sleep disturbances and psychotic symptoms after switching to AOM was greater in Group II than in Group I. Rescue medications were also prescribed to significantly more patients in Group II than in Group I. Interestingly, the TEAEs of psychotic symptoms in Group II were observed in the first weeks after discontinuation of previous D2 antagonists, at least some (olanzapine and quetiapine) that also had antihistaminergic/sedating effects (mean days (±SD): 51.31 ± 30.03), with the TEAEs emerging earlier in Group II than in Group I ($t = 1.9$, df = 18, $p = 0.0368$, one-sided test). In addition, the occurrence of psychotic symptoms TEAE in Group II was related to the rate of tapering prior oral antipsychotic drugs with D2 antagonism; the faster tapering prior oral antipsychotic drugs, the higher the incidence of psychotic symptoms TEAE (Fig. S2). A meta-analysis also reported marginally significant differences in tardive dyskinesia and insomnia between immediate and gradual discontinuation of antipsychotic drugs, although no significant differences in clinical outcomes were observed (Takeuchi et al., 2017). These findings could be indicative of dopamine supersensitivity (Nakata et al., 2017) in Group II and the early effects of AOM, which contains a D2 partial agonist.

While the incidences of sleep disturbances and psychotic symptoms following the initiation of AOM were higher in Group II, the TEAEs that did not resolve during the study did not differ between the two groups (Fig. 3). Furthermore, the number of patients experiencing TEAEs leading to study discontinuation or with serious TEAEs was not different between the groups (See Table S2 in the supplement). Regarding psychotic symptoms TEAE, the PANSS scores in Group II were higher than in Group I, though they improved compared to baseline. These findings suggest that the psychiatric TEAEs occurring during the transition from D2 antagonists to AOM may be mild and transient. Therefore, a strategy involving gradual and slow dose reduction of previous D2 antagonists, considering individual responses to AOM, could minimize psychiatric TEAEs, especially in patients with high doses of full D2 dopamine antagonist antipsychotics (Hojlund and Correll, 2023).

This study has several limitations that warrant consideration when interpreting and applying the results. Although we observed differences in responses to AOM based on prior antipsychotic drugs, the study was not primarily designed to test differences between these two groups. Indeed, the disease duration was not matched and differed between the groups. The shorter disease duration in Group I could be associated with better outcomes. Additionally, patients in Group II had been treated with various antipsychotic drugs, though all of them can be categorized as a D2 receptor antagonist. The diversity of prior antipsychotic drugs could have been associated with variations in clinical response to AOM in Group II. As mentioned in the methods section, antipsychotic combinations were allowed in both groups. The antipsychotic combination could have influenced the results, though the combination doses were below the therapeutically effective levels specified in the labeling

information. However, as demonstrated in the subgroup analysis, the results were replicated with modified FAS, where the combinations involving dopamine antagonists in Group I and aripiprazole in Group II were excluded. Therefore, it is unlikely that the antipsychotic combinations biased the outcomes. Our study explored changes in clinical symptoms and safety when switching to AOM based on prior antipsychotic pharmacological characteristics and explained the observed differences between the groups via the supersensitivity psychosis hypothesis and histaminergic/cholinergic rebound. While the hypothesis is plausible for explaining clinical observations related to D2 partial agonists, it lacks biological evidence tested in human brains. Therefore, further biological studies in humans are warranted. Finally, this was not a randomized controlled but a naturalistic study, so that causal inferences cannot be drawn. However, the naturalistic design of this study reflects real-world clinical practice, including the label-based 2-week overlap with oral aripiprazole due to the delayed onset of therapeutic action of AOM after the first injection. As such, these results can provide valuable insights into the transition from oral antipsychotics to AOM. Indeed, naturalistic studies have been recognized for their high ecological validity, which allows for a complementary and more representative assessment of treatment effects compared to randomized controlled trials (Fagiolini et al., 2017).

In conclusion, initiating AOM was effective and safe for patients with schizophrenia, regardless of their prior antipsychotic drugs. However, patients previously treated with D2 antagonists may experience transient psychiatric TEAEs. A strategy involving a slow and gradual dose reduction of prior antipsychotic drugs is suggested when switching from oral D2 antagonists to AOM.

CRediT authorship contribution statement

Euitae Kim: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Seoyoung Kim:** Writing – review & editing, Methodology, Investigation. **Sung-Wan Kim:** Writing – review & editing, Investigation. **Beom-Woo Nam:** Writing – review & editing, Investigation. **Kyoung-Uk Lee:** Writing – review & editing, Investigation. **Bong Ju Lee:** Writing – review & editing, Investigation. **Seung-Hee Won:** Writing – review & editing, Investigation. **Chang Hwa Lee:** Writing – review & editing, Investigation. **Sung Won Jung:** Writing – review & editing, Investigation. **Soo In Kim:** Writing – review & editing, Investigation. **Sung Joon Cho:** Writing – review & editing, Investigation. **Young-Chul Chung:** Writing – review & editing, Investigation. **Tai Kiu Choi:** Writing – review & editing, Investigation. **Eun-Jin Cheon:** Writing – review & editing, Investigation. **Ji Hyun Baek:** Writing – review & editing, Investigation. **Christoph U. Correll:** Writing – review & editing, Formal analysis, Data curation. **Jun Soo Kwon:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Role of the funding source

This study was supported by Otsuka Pharmaceuticals. All authors had full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analysis presented in this publication.

Declaration of competing interest

Euitae Kim has participated in advisory or speaker meetings organized by Janssen Korea, Otsuka Korea, Boehringer Ingelheim, and Bukwang Pharm Company and was the principal investigator of research projects from Otsuka company. Seoyoung Kim has received speakers bureau honoraria from Korea Otsuka Pharmaceutical and Janssen Korea. Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic. Jun Soo Kwon has participated in speaker meetings organized by Otsuka Korea and Dongwha Pharm and received research grants from Boehringer Ingelheim and Whan-In Pharm.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2025.04.033.

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