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Effects of Long-acting Injectable 3-Monthly Paliperidone Palmitate on the Clinical and Social Performance of Patients with Schizophrenia

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Objective: To investigate the effects of long-acting injectable 3-monthly paliperidone palmitate on the clinical and social functioning of patients with schizophrenia.
Methods: This study enrolled patients with schizophrenia receiving long-acting injectable 1-monthly paliperidone palmitate for at least 4 months and who subsequently received 3-monthly paliperidone palmitate. Accordingly, 418 patients were followed up for 24 weeks. Their clinical symptoms and social functioning were measured using the Clinical Global Impression-Severity of Illness and Personal and Social Performance scales.
Results: The Personal and Social Performance total score was significantly higher after 3-monthly paliperidone palmitate treatment than at baseline (baseline vs. week 24: 54.3 ± 18.0 vs. 61.0 ± 14.5 [mean ± standard deviation]; $p < 0.001$; Wilcoxon signed-rank test); the proportion of patients in the mildly ill group (scores 71−100) also increased significantly (baseline vs. week 24: 16.5% vs. 20.6%; $p < 0.001$; McNemar-Bowker test). The mean Clinical Global Impression-Severity of Illness score decreased significantly (baseline vs. week 24: 3.7 ± 1.0 vs. 3.4 ± 0.9; $p < 0.001$; Wilcoxon signed-rank test), as did the proportion of patients in the severely ill group (baseline vs. week 24: 4.1% vs. 2.1%; $p < 0.001$; McNemar-Bowker test).
Conclusion: Continuous 3-monthly paliperidone palmitate treatment significantly enhances the personal and social performance of patients with schizophrenia and reduces the proportion of those with severe illness. These findings suggest that long-acting injectable antipsychotic administration at intervals longer than 1 month might improve the social functioning of and promote return to activities of daily living in patients with schizophrenia.

KEY WORDS: Schizophrenia; Antipsychotics; Paliperidone palmitate; Clinical global impression; Personal and social performance.

INTRODUCTION

Schizophrenia is a severe mental illness that has a complex clinical presentation and biological, social, and genetic causes [1]. Antipsychotics are recommended as the primary treatment in first- and multiple-episode schizophrenia [2] as they have an effect on improving acute symptoms [3] and negative symptoms as well as social functioning [4]. Although antipsychotics are essential to treating acute and chronic symptoms, the duration of antipsychotic treatment in patients with schizophrenia has been controversial [5]. The long-term usage of antipsychotics has been associated with metabolic adverse effects [6] and cognitive dysfunction [7]; however, recent large-scale studies have shown that lifelong antipsychotic treatment may decrease the overall risk of death espe-

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cially from cardiovascular diseases [8,9]. Thus, long-term antipsychotic treatment without discontinuation is recommended for patients with schizophrenia.

As early adherence to and continuation of antipsychotic treatment is known to improve symptoms and lower the mortality rate, the consistent use of antipsychotics is important in schizophrenia. Long-acting injectable (LAI) antipsychotics have been advocated to resolve this issue, as patients require an injection only once every 4 to 12 weeks and it offers more reliable drug delivery than do oral drugs [10]. Although there is a lack of evidence suggesting that LAI antipsychotics are more efficacious than are oral antipsychotics [11], recent studies have shown improved treatment adherence with lower rates of discontinuation and illness relapse in patients receiving LAI antipsychotics than in those receiving classical oral drugs [12]. Moreover, the use of LAI antipsychotics significantly delays the time to first hospitalization in early-phase schizophrenia [13]. Studies have also revealed improved clinical and functional outcomes in patients receiving LAI antipsychotics 6 months after LAI paliperidone treatment initiation [14].

Among the LAI antipsychotics widely used in treating schizophrenia, most have a 2- to 4-week injection interval (risperidone microspheres, 1-monthly paliperidone palmitate [PP1M], risperidone subcutaneous, aripiprazole monohydrate, and olanzapine pamoate) [15]. These account for 20% to 30% of the total antipsychotic prescriptions worldwide [16,17], and the results of efficacy and clinical outcomes of LAI antipsychotic treatment largely depend on their monthly administration interval. The injection interval might also be an important factor in treating patients with schizophrenia, as it is related to the drug concentration in the blood and regular evaluation and management by a psychiatrist. Among the antipsychotics currently available in the market, 3-monthly paliperidone palmitate (Invega Trinza®, PP3M) has the longest injection interval, and it would be a suitable candidate to investigate how longer administration intervals affect the clinical symptoms and performance of patients with schizophrenia. In this study, we examined the effect of LAI PP3M in patients with schizophrenia focusing on their clinical and social improvements during a 24-week treatment period.

METHODS

Study Population

Patients diagnosed with schizophrenia according to the International Classification of Diseases-Tenth Revision [10] criteria were enrolled in this study. Patients were treated with LAI PP1M (Invega Sustenna®) for at least 4 months, and were then administered LAI PP3M (Invega Trinza®). The included patients used the drug within the approved labeling (175 mg to 525 mg as paliperidone). The CONSORT flow diagram of this study is presented in Figure 1.

All patients agreed to the collection of personal information for the post-market surveillance (PMS) and provided written informed consent. The study was approved

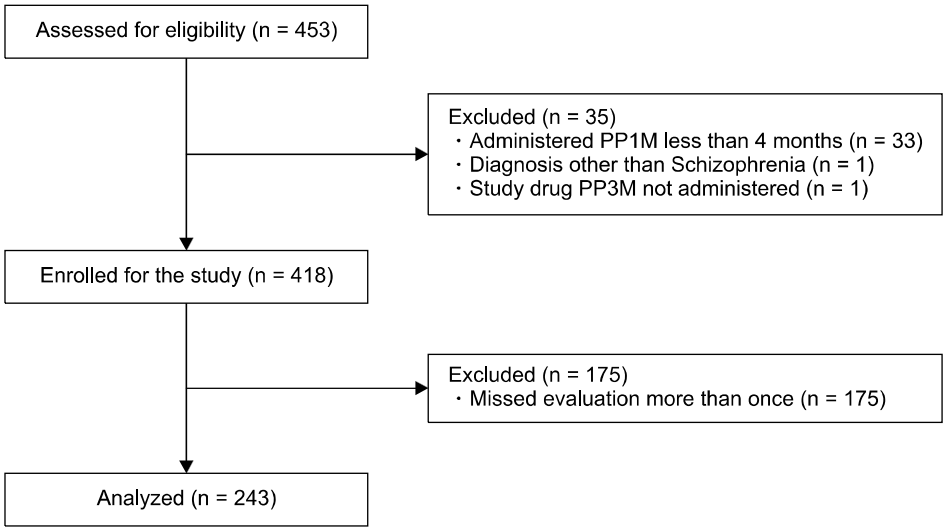

Fig. 1. Flow diagram illustrating the enrollment of patients in the study. PP1M, paliperidone palmitate 1-monthly; PP3M, paliperidone palmitate 3-monthly.

by the Institutional Review Board of the Ethics Committee of each participating clinical center (KC18MDDP0444) (a full list of institutions is presented in Supplementary Table 1; available online).

Study Design and Assessment

The PMS was conducted from March 3, 2018 to March 4, 2020, and 50 hospitals were enrolled in the surveillance. A full list of these hospitals is presented in Supplementary Table 1 (available online). Case-report forms of 453 patients were collected, and the datasets were verified through the issuance and resolution of queries.

The safety assessment targeted 418 patients who received at least one dose of the injectable study drug and who completed the safety assessment once or multiple times. We excluded patients who (1) did not use the study drug, (2) had already used the study drug before signing the contract, (3) had received drug doses outside the range of the approved product labeling, (4) did not meet the safety assessment criteria, and (5) did not complete the final confirmation. Finally, 243 patients were enrolled in the efficacy assessment for 24 weeks. During this period, patients visited the hospital 7 times at 4-week intervals (i.e., at 0, 4, 8, 12, 16, 20, and 24 weeks). The Clinical Global Impression Severity (CGI-S) and Personal and Social Performance (PSP) scales were assessed at weeks 0, 12, and 24. Demographic variables, such as sex, age, employment status, marital status, alcohol drinking, smoking, history of drug abuse, pregnancy, diagnosis (year when first diagnosed), duration of illness, comorbid diseases, weight, and waist circumstance, were recorded and clinical parameters, including blood pressure, pulse rate, and other blood parameters, were measured at the baseline (week 0). At the last visit, clinicians evaluated the overall impression of illness improvement of each patient on the basis of the PSP and CGI-S scores by using a 5-point Likert scale (marked improvement, moderate improvement, mild improvement, no symptom change, and worsening). Based on treatment effectiveness, the patients were further grouped into two groups, namely, the effective treatment (marked improvement, moderate improvement, and mild improvement) and non-effective treatment groups (no symptom change and worsening).

The primary outcomes of this study were the overall CGI-S and PSP scale scores. The CGI-S scale is the standardized assessment tool used to rate the severity of illnesses and assess changes in overall clinical condition over time on a 7-point scale (1 = normal or not ill; 7 = the most extremely ill) [18]. The PSP scale comprises four specific functioning domains and rates the severity of dysfunction on a 6-point scale (1 = absent; 2 = mild; 3 = manifest; 4 = marked; 5 = severe; and 6 = very severe), and a lower score in each domain is interpreted as an improvement. The PSP scale is a reliable tool for measuring social functioning in patients with schizophrenia [19]. Summary of adverse events and adverse drug reactions in participants are presented in Supplementary Table 2 (available online).

Statistical Analysis

The patients were categorized into three groups each according to their total scores of CGI-S (group I, score 1 to 3; group II, score 4 and 5; and group III, score 6 and 7) and PSP (group I, total score 71 to 100; group II, total score 31 to 70; and group III, total score of 30 or below). The McNemar-Bowker test was applied to test the statistical significance between groups over time. The numerical value of the CGI-S and PSP scores were tested using the Wilcoxon signed-rank test. All analyses were defined as significant when the two-sided p value was less than 0.05. Data collection, trimming, and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Figure 1 illustrates the enrollment of patients in the study. A total of 453 patients who received PP3M were assessed for eligibility. Among them, 33 who had received PP1M for less than 4 months were excluded. One patient who had a diagnosis other than schizophrenia and another one who had not adequately received PP3M were also excluded. Among the remaining 418 patients enrolled in the study, 175 were further excluded as they had not undergone evaluations at least once during the 24-week follow-up period (PSP and CGI-S scores of excluded participants are presented in Supplementary Tables 3, 4; available online). Thus, a total of 243 patients with schizophrenia who had received PP3M were further analyzed.

The baseline demographic characteristics and history of medical illnesses are presented in Table 1. The mean age of the patients was 39.9 ± 13.7 years (mean ± stand-

Table 1. Overall effectiveness by demographic and disease characteristics

Variable		Total number of participants (n)	Effective number of participants, number (%)	95% CI	*p* value	Odds ratio (95% CI)[d]
Sex	Male	117	63 (53.85)	44.39−63.10	0.8861[a]	Ref
	Female	126	69 (54.76)	45.65−63.64		1.42 (0.72−2.81)
	Total	243	132 (54.32)			
Age (yr)	< 20	9	7 (77.78)	39.99−97.19	0.7388[b]	Ref
	20−29	62	34 (54.84)	41.68−67.52		0.17 (0.02−1.87)
	30−39	50	28 (56.00)	41.25−70.01		0.19 (0.02−2.32)
	40−49	55	30 (54.55)	40.55−68.03		0.16 (0.01−2.12)
	50−59	44	21 (47.73)	32.46−63.31		0.09 (0.01−1.31)
	60−69	21	11 (52.38)	29.78−74.29		0.11 (0.01−1.95)
	70−79	1	1 (100.00)	2.50−100.00		-
	≥ 80	1	0 (0.00)	0.00−97.50		-
	Total	243	132 (54.32)			
Job status	Yes	107	54 (50.47)	40.63−60.28	0.2848[a]	0.50 (0.25−0.99)
	No	136	78 (57.35)	48.59−65.79		Ref
	Total	243	132 (54.32)			
Marriage status	Married	75	46 (61.33)	49.38−72.36	0.1426[a]	4.28 (1.64−11.20)
	Unmarried	168	86 (51.19)	43.37−58.97		Ref
	Total	243	132 (54.32)			
Alcohol drinking	Yes	67	43 (64.18)	51.53−75.53	0.0570[a]	2.18 (1.02−4.64)
	No	176	89 (50.57)	42.94−58.17		Ref
	Total	243	132 (54.32)			
Smoking	Yes	43	26 (60.47)	44.41−75.02	0.3726[a]	0.94 (0.37−2.38)
	No	200	106 (53.00)	45.83−60.08		Ref
	Total	243	132 (54.32)			
Drug abuse	Yes	1	1 (100.00)	2.50−100.00	1.0000[b]	-
	No	242	131 (54.13)	47.63−60.53		
	Total	243	132 (54.32)			
Diagnosis	Paranoid	190	105 (55.26)	47.90−62.46	0.7534[b]	Ref
	Disorganized	6	3 (50.00)	11.81−88.19		0.96 (0.12−7.51)
	Catatonic	2	1 (50.00)	1.26−98.74		0.22 (0.01−5.39)
	Undifferentiated	38	21 (55.26)	38.30−71.38		0.57 (0.24−1.36)
	Residual	7	2 (28.57)	3.67−70.96		0.15 (0.02−1.03)
	Total	243	132 (54.32)			
Duration of illness (yr)	< 1	8	7 (87.50)	47.35−99.68	0.0073[a]	Ref
	1−3	42	27 (64.29)	48.03−78.45	0.0005[c]	0.42 (0.04−4.95)
	3−5	39	27 (69.23)	52.43−82.98		0.54 (0.05−6.17)
	5−10	52	27 (51.92)	37.63−65.99		0.22 (0.02−2.45)
	≥ 10	102	44 (43.14)	33.37−53.32		0.14 (0.01−1.64)
	Total	243	132 (54.32)			
Status of treatment when registered	Inpatient	36	20 (55.56)	38.10−72.06	0.8720[a]	Ref
	Outpatient	207	112 (54.11)	47.06−61.03		1.25 (0.52−2.98)
	Total	243	132 (54.32)			
Comorbid diseases	Yes	47	32 (68.09)	52.88−80.91	0.0349[a]	4.48 (1.63−12.28)
	No	196	100 (51.02)	43.80−58.21		Ref
	Total	243	132 (54.32)			
Psychiatric medications	Yes	165	92 (55.76)	47.83−63.47	0.5132[a]	1.00 (0.50−2.00)
	No	78	40 (51.28)	39.69−62.77		Ref
	Total	243	132 (54.32)			
PP3M 1st dosage (mg eq.)	175	22	10 (45.45)	24.39−67.79	0.7145[a]	N/A
	263	54	31 (57.41)	43.21−70.77		
	350	70	36 (51.43)	39.17−63.56		
	525	97	55 (56.70)	46.25−66.73		
	Total	243	132 (54.32)			
PP3M maintenance dosage (mg eq.)	175	22	11 (50.00)	28.22−71.78	0.5174[a]	N/A
	263	55	33 (60.00)	45.91−72.98		
	350	69	33 (47.83)	35.65−60.20		
	525	97	55 (56.70)	46.25−66.73		
	Total	243	132 (54.32)			

PP3M, paliperidone palmitate 3-montly; CI, confidence interval; Ref, reference; N/A, not applicable.
[a]Chi-square test. [b]Fisher's exact test. [c]Trend test. [d]Multiple logistic regression.

ard deviation [SD]). Most of the patients had paranoid-type schizophrenia (78%), and 42% had been diagnosed with schizophrenia for more than 10 years. All patients were prescribed PP3M as they had received sufficient treatment with PP1M for 4 months.

When we analyzed the effect of demographic and social variables on the improvement in disease status, the duration of illness ($p < 0.01$, chi-square test) and presence of comorbid diseases ($p < 0.05$, chi-square test) were significantly related to the effectiveness of PP3M. PP3M treatment was 0.14 times less effective in patients who had been diagnosed with schizophrenia for more than 10 years than in those who had been diagnosed with schizophrenia for less than 1 year. Moreover, the efficacy of PP3M was 4.48 times higher in patients with other comorbid diseases than in those without comorbid diseases (Table 1).

Overall Improvement of Illness after PP3M Treatment

We evaluated the overall improvement of illness on the basis of the PSP and CGI-S scores after the 24-week PP3M treatment and categorized all patients into the effective and non-effective groups. Among the demographic and clinical variables, the duration of illness and presence of comorbid diseases showed significant effects. The chi-square test showed a significant difference in illness improvement according to the duration of illness groups, but multiple logistic regression analysis failed to detect any statistical significance between each illness duration group relative to the reference group (< 1 year; Table 1). However, the presence of comorbid diseases affected the overall improvement of illness after PP3M treatment. If patients had comorbid diseases, they were more likely to be in an effective group than were those without comorbid diseases (odds ratio [95% confidence interval], 4.48 [1.63−12.28]; multiple logistic regression analysis). Other variables did not show any significant effects on the overall improvement of illnesses.

PSP Score Improvement during the Treatment Period

During the 24-week follow-up period, we assessed the PSP scores at the baseline (week 0), the fourth visit (week 12), and the last visit (week 24). When the patients were categorized into three groups (mild, moderate, and severe dysfunction), we found that the proportion of each group differed significantly over time ($p < 0.001$; McNemar-Bowker test; Fig. 2A). The proportion of patients who needed intensive supervision (severe group) was 12.3% at the baseline, but it decreased to 3.7% at the last visit. However, the proportion of patients in the mild group was 16.5% at the baseline, and it increased to 20.6% after 24 weeks of treatment with PP3M (Table 2).

The PSP total score also significantly increased after

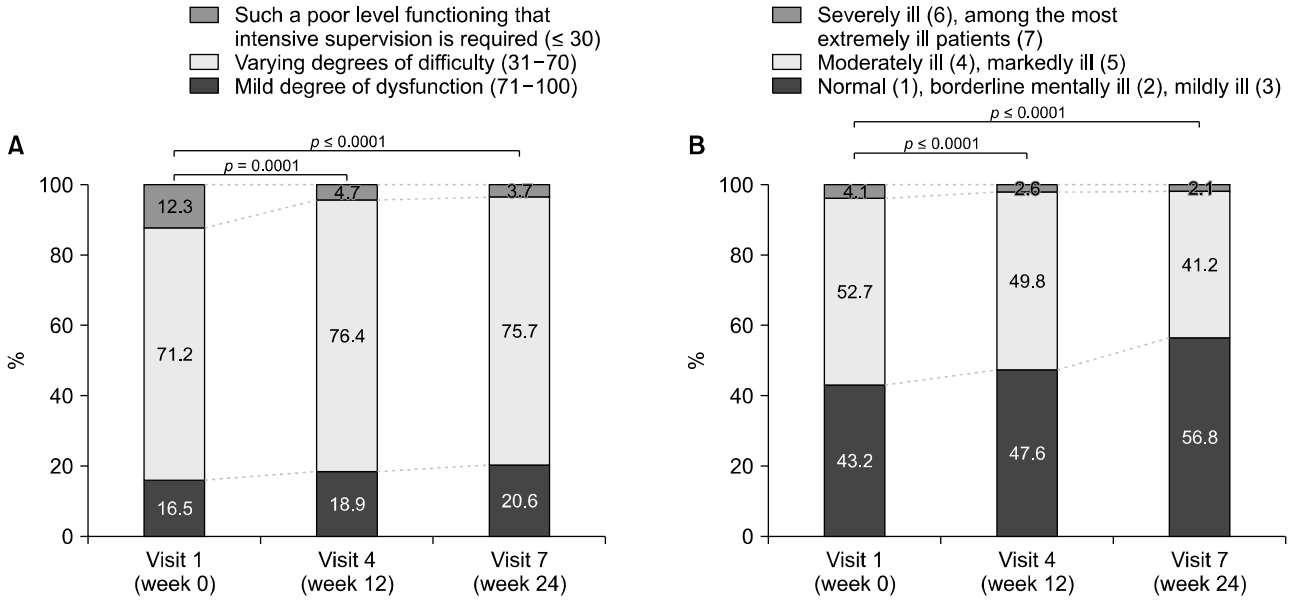

Fig. 2. Changes in the Personal and Social Performance (A) and Clinical Global Impression-Severity of Illness (B) total scores according to the symptom severity groups at each hospital visit.

Table 2. Effectiveness evaluation over time

Criteria	Visit 1 (week 0)		Visit 4 (week 12)		Visit 7 (week 24)	
	Number (%)	p value[a]	Number (%)	p value[a]	Number (%)	p value[a]
PSP total group		N/A		0.0001		< 0.0001
Mild degree of dysfunction (71−100)	40 (16.5)		44 (18.9)		50 (20.6)	
Varying degrees of difficulty (31−70)	173 (71.2)		178 (76.4)		184 (75.7)	
Such a poor level functioning that intensive supervision is required (≤ 30)	30 (12.3)		11 (4.7)		9 (3.7)	
CGI-S group		N/A		< 0.0001		0.0227
Normal, Not ill, Borderline mentally ill, Mildly ill (1−3)	105 (43.2)		111 (47.64)		138 (56.79)	
Moderately ill, Markedly ill (4−5)	128 (52.7)		116 (49.79)		100 (41.15)	
Severely ill, Among the most extremely ill patients (6−7)	10 (4.1)		6 (2.58)		5 (2.06)	

CGI-S, Clinical Global Impression Severity; PSP, Personal and Social Performance; N/A, not applicable.
[a]McNemar-Bowker test, compared to baseline (visit 1).

Table 3. Comparison of effectiveness evaluation before and after PP3M treatment by PSP subscale

PSP subscale	Baseline (week 0)	Week 24	Difference	p value
a) Socially useful activities, including work or academic study				
Number of participants (n)	243	243	243	< 0.0001[a,*]
Mean ± SD	3.24 ± 1.09	2.94 ± 0.94	−0.30 ± 0.56	
Median	3.00	3.00	0.00	
Score range (min−max)	1.00 to 6.00	1.00 to 5.00	−2.00 to 1.00	
b) Personal and social relationships				
Number of participants (n)	243	243	243	< 0.0001[a,*]
Mean ± SD	3.22 ± 1.07	2.90 ± 0.89	−0.32 ± 0.65	
Median	3.00	3.00	0.00	
Score range (min−max)	1.00 to 6.00	1.00 to 5.00	−3.00 to 2.00	
c) Self-care				
Number of participants (n)	243	243	243	< 0.0001[a,*]
Mean ± SD	2.85 ±1.13	2.54 ± 0.96	−0.30 ± 0.71	
Median	3.00	3.00	0.00	
Score range (min−max)	1.00 to 6.00	1.00 to 5.00	−3.00 to 2.00	
d) Disturbing and aggressive behaviors				
Number of participants (n)	243	243	243	< 0.0001[a,*]
Mean ± SD	2.30 ±1.15	2.01 ± 0.92	−0.29 ± 0.68	
Median	2.00	2.00	0.00	
Score range (min−max)	1.00 to 5.00	1.00 to 5.00	−4.00 to 2.00	

PSP, Personal and Social Performance; PP3M, paliperidone palmitate 3-montly; SD, standard deviation.
[a]Wilcoxon signed rank test.
*Statistically significant difference.

PP3M treatment. The PSP total score was 54.3 ± 18.0 (mean ± SD) at the baseline (week 0), and it significantly increased to 57.6 ± 15.9 at week 12 ($p < 0.01$; Wilcoxon signed-rank test) and was 61.0 ± 14.5 at week 24 ($p < 0.001$; Wilcoxon signed-rank test). These results showed that PP3M treatment might improve social performance within 6 months of treatment initiation. Multivariate analysis showed that "job status", "status of treatment when registered", and "psychiatric medications" were significantly related to the PSP total score improvements (Supplementary Table 5; available online).

CGI-S Score Improvement during the Treatment Period

Clinical symptom severity measured using the CGI-S also changed during the PP3M treatment period (Fig. 2B). The proportion of patients in each group (mildly, moderately, and severely ill groups) differed significantly across the baseline, week 12, and week 24 ($p < 0.001$; McNemar-Bowker test). The proportion of severely ill patients was 4.1% at the baseline and it decreased to 2.1% at week 24, but the proportion of mildly ill patients increased from 43.2% at the baseline to 56.8% during the PP3M treatment period (Table 2).

The mean GGI-S score was 3.7 ± 1.0 at the baseline, but it decreased significantly to 3.6 ± 1.0 at week 12 and to 3.4 ± 0.9 at week 24. These results suggested that the psychiatric symptom severity and treatment response of the patients improved during the PP3M treatment period.

Comparison of Effectiveness after the Treatment

To assess how the personal and social performance varied during the PP3M treatment period, the score differences in the four PSP subscales between the last visit (week 24) and baseline (week 0) were measured (Table 3). The results showed that all PSP subscales (i.e., socially useful activities, including work or academic study; personal and social relationships; self-care; and disturbing and aggressive behaviors) had improved after the 6-month PP3M treatment ($p < 0.001$ in all subscales; Wilcoxon singed-rank test). This result suggested that PP3M was effective in improving the overall personal and social performance of patients and not just in improving any one area.

DISCUSSION

In this prospective study, we examined the clinical effectiveness and social performance of patients with schizophrenia receiving LAI antipsychotics at 3-monthly intervals. To the best of our knowledge, this is the first report on a PMS of PP3M, which is widely used in the clinical setting. After the 6-month PP3M treatment, the number of patients who had severe dysfunction significantly decreased and the number of patients in the mildly ill group increased. These clinical and social performance improvements were observed in all subfunctional areas, and the overall effectiveness of PP3M was significantly associated with the presence of comorbid diseases.

Our findings are in line with those of a previous prospective study on PP1M [14]. In that study, Kim *et al.* [14] found that 6-month PP1M treatment significantly improved the clinical and functional outcomes in patients with schizophrenia. Furthermore, the patient group with an illness duration less than 3 years showed the most improvement. Similarly, in our study, patients with schizophrenia who received PP3M treatment showed an improvement in both clinical and social functioning.

Notably, the patients in our study had been treated with PP1M for at least 4 months before enrollment. As PP3M was administered after successful treatment with PP1M, the room for symptom improvement might be small. In fact, during the previous study by Kim *et al.* [14], the proportion of severely ill patients (with PSP scores < 30) was about 20% at the beginning of the study (week 0), but it dropped to around 5% at the end of the study (week 25). The patients enrolled in our study were part of the group that had experienced symptom improvement to some extent as a result of PP1M treatment. However, we found that the number of patients who had a poor level of functioning and required intensive supervision at the time of enrollment to this PP3M study significantly decreased after the 6-month treatment (Fig. 2). Thus, we could infer that continuous PP3M treatment after PP1M treatment is effective in improving the clinical symptoms and increasing personal and social functioning among patients with schizophrenia.

LAI antipsychotics also reduce relapse and rehospitalization rates [20], and 3-monthly dosing intervals may reduce the non-adherence to LAI antipsychotic treatments that are currently available [21]. Our findings of improved clinical global impression and personal and social functioning among patients with schizophrenia receiving PP3M treatment suggest that longer injection intervals of LAI antipsychotics could accelerate these patients' return to society and work. The mild illness group of patients having PSP total scores between 71 and 100 shows no dysfunction or only mild difficulties, and the related symptoms are noticeable only to those familiar with the patients [22]. The increase in the proportion of patients in the mild group from 16.5% (week 0) to 20.6% (week 24) during the PP3M treatment period could suggest that continuous treatment with LAI antipsychotics at longer injection intervals might improve the social functioning of patients with schizophrenia.

Although we examined the contributing demographic and disease characteristics that might be related to the overall improvement in psychiatric illness, we could only find that the presence of comorbid diseases had a significant effect. Patients with comorbid diseases had 4.48 times higher odds for overall improvement of symptoms than did those without comorbid diseases. A previous study reported that approximately half of the patients with schizophrenia have comorbid medical conditions [23]. This high rate of comorbidities is related to the high mortality and morbidity in patients with schizophrenia and has an influence on the patients' quality of life and symp-

tom improvement [24]. As previous studies have shown that a greater number of concurrent medical problems contributes to more severe psychiatric symptoms [25], our results may seem contradictory. However, our study showed that treatment effectiveness in patients with comorbid diseases (68.1% [32 of 47 patients]) was higher than that in patients without comorbid diseases (51.0% [100 of 196 patients]). To investigate which medical condition affected the overall improvement in psychiatric symptoms, we subcategorized the comorbid diseases into four types (i.e., allergies, renal impairment, hepatic impairment, and other diseases), but we could not find any significant relationship between disease category and the improvement in psychiatric symptoms. One possibility is that patients in this study had high adherence and compliance to the psychiatric treatment, because they successfully completed at least a 4-month PP1M treatment. Thus, patients who had a comorbid disease could have higher personal and social performance indicators as they had visited the hospital more frequently than had those without comorbid disease.

Several limitations should be considered when interpreting the results of this prospective study. First, as this study targeted only those patients with schizophrenia who successfully completed PP1M treatment, these results are not representative of the entire population with schizophrenia. Moreover, as most of the enrolled patients had good compliance and adherence to PP1M treatment, the effect of PP3M could be related to the characteristics of the patient group. Second, this study did not measure any quantitative indicators of psychotic symptoms. The most important goal of antipsychotic treatment is the improvement of positive and negative symptoms of psychosis. However, the primary outcomes of this study were the total scores of the CGI-S and PSP scales, which are indirect measurement tools for clinical symptoms. Although a previous study reported that the PSP subscale scores were well correlated with the Positive and Negative Symptoms Scale [26], we did not analyze how the PSP subscales were related to the symptom improvements observed during the study period. Especially, as the degree of baseline psychotic symptoms was not qualitatively measured, how the PP3M affects the positive symptoms of schizophrenia would be uncertain. Third, this study did not compare the effect of other LAI antipsychotics and did not include any control group; hence, we cannot infer whether the improvements in personal/social functioning and overall clinical symptoms were due to the effects of PP3M. Fourth, among 64 hospitals enrolled in this study, a hospital occupied over 18.5% of total participants who were assessed for efficacy. Although there was no upper limit in recruiting participants during the cohort, the uneven distribution might have been related to a selection bias.

Despite these limitations, our study showed that the 6-month treatment with LAI PP3M significantly improved the global impression of clinical symptoms as well as the personal and social performance of patients with schizophrenia. These results suggest that 3-monthly administration of LAI antipsychotics could enhance the adherence to treatment and promote the return to activities of daily living among patients with schizophrenia.

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■ Conflicts of Interest

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

■ Author Contributions

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