ABSTRACT

Objective: This study aimed to examine the degree of clinical and functional improvement after paliperidone long-acting injectable (LAI) administration according to the duration of illness.

Methods: Patients with schizophrenia diagnosed by ICD-10 criteria who were planned to start once-monthly paliperidone LAI were recruited from 2010 to 2017. Clinical and functional changes were measured every 4 weeks using the Clinical Global Impressions–Severity of Illness scale (CGI-S) and Personal and Social Performance scale (PSP), respectively, for 6 months after paliperidone LAI initiation. Improvements after starting paliperidone LAI were compared among patients with duration of illness <3 years, ≥3 and <10 years, and ≥10 years.

Results: A total of 1,166 participants (duration of illness <3 years, n = 240; 3 ≤ duration of illness <10 years, n = 442; duration of illness ≥10 years, n = 484) were enrolled. The total olanzapine-equivalent doses of antipsychotics and the LAI monotherapy proportion at the final visit were significantly different among the 3 duration of illness groups (dose: F2,1165 = 18.41, P < .001; monotherapy: χ2 2,1165 = 17.13, P = .003). The changes in CGI-S score were significantly different according to the duration of illness, and those with duration of illness <3 years showed the best improvement (group × week: χ2 12, 1,165 = 25.33, P = .013). All 3 groups showed significantly improved PSP scores (week: F2,1165 = 29.42, P < .001).

Conclusions: Starting paliperidone LAI significantly improved clinical and functional outcomes in patients with schizophrenia, especially those with shorter duration of illness. These findings suggest that LAI antipsychotic administration may be considered in early-stage schizophrenia for improved outcomes.

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Schizophrenia is a chronic and severe mental illness with psychotic symptoms that affect one’s ability to interpret reality. These symptoms typically appear in young adulthood and may have serious social consequences and even be associated with lifelong disability. Although clinical remission is not rare with adequate antipsychotic treatment, most patients experience recurring psychotic relapses along the disease course that result in clinical deterioration and functional impairments.

Multiple epidemiologic studies have reported that antipsychotic medications effectively prevent psychotic relapses after symptomatic remission. Furthermore, a previous meta-analysis demonstrated that antipsychotic drugs significantly reduce the relapse rates at 1 year of treatment with a number of needed to treat of 3, which indicates relapse prevention in every 3 patients treated with antipsychotic medications. However, given that schizophrenia generally requires long-term maintenance treatment, poor treatment adherence is a serious concern since it increases the psychotic relapse risk.

As a result, long-acting injectable (LAI) antipsychotic drugs, which ameliorate the daily burden of taking oral medication and prevent psychotic relapse from poor adherence, have been introduced. Various benefits of LAI antipsychotics have been reported, especially with respect to psychotic relapse prevention. Studies based on prospective nationwide databases in Sweden have reported an association of LAI antipsychotics with a substantially lower rehospitalization risk compared with equivalent oral formulations. These findings further indicate the superiority of LAI antipsychotics in relapse prevention in patients with schizophrenia. Furthermore, previous studies have reported functional...
improvements in patients with schizophrenia treated with LAI antipsychotics. Specifically, a previous systemic analysis\(^9\) of randomized controlled trials demonstrated the superiority of LAI antipsychotics over oral antipsychotics with respect to functioning and service engagement. Moreover, a prospective study\(^{10}\) reported that treatment with paliperidone LAI improved functioning, as measured using the Personal and Social Performance scale (PSP), in non–acutely ill, symptomatic patients with schizophrenia. Functional improvements after treatment with LAI antipsychotics are significant since they are associated with better prognosis and community adjustment, which are long-term treatment goals in patients with schizophrenia.\(^{11}\)

Despite the aforementioned advantages, LAI antipsychotics have mainly been used to maintain treatment adherence with a focus on psychotic relapse; therefore, compared to oral medication, they have been underutilized in schizophrenia treatment. Specifically, LAI antipsychotics are mostly administered in the later stages of the illness upon identification of nonadherence with psychotic relapses. However, the use of LAI antipsychotics should not be limited to improving treatment adherence by patients in the later stage given the common suboptimal adherence at all illness stages. Suboptimal adherence to oral antipsychotics is associated with stable and nonacute active psychotic symptoms.\(^{12–14}\) Moreover, a strong correlation of persistent active psychotic symptoms with negative symptoms and functional impairments has been reported even after adjustment for the confounding effects of the duration of untreated period.\(^{15,16}\) These findings suggest that LAI antipsychotics could improve the clinical and functional outcomes of patients taking oral antipsychotics at all illness stages. This idea is supported by a previous prospective study\(^{17}\) that reported clinically significant improvements in symptoms, functioning, and treatment satisfaction in stable, non–acutely ill but symptomatic patients on oral antipsychotic monotherapy after switching to paliperidone LAI.

Moreover, there has been increasing evidence for the effectiveness of LAI antipsychotics in the early disease stage\(^{18,19}\) when compared with oral antipsychotics. However, only a few of these studies have compared the effect of LAI antipsychotics among patients with schizophrenia with varying duration of illness.\(^{10,20,21}\) While there have been lines of evidence regarding oral antipsychotics,\(^{22–24}\) a post hoc analysis\(^{20}\) of two multicenter studies reported that paliperidone LAI was more effective in patients with recently diagnosed schizophrenia. Further, a randomized study on patients with a criminal history\(^{21}\) showed that paliperidone LAI had an advantage in reducing treatment failure risk in patients with recent-onset schizophrenia compared to those with more chronic illness. Although these findings suggest that the treatment benefits of LAI antipsychotics are more pronounced in patients with recently diagnosed schizophrenia,\(^{10,20}\) their generalization is limited by the study populations.

Thus, the current study was conducted to examine the differences in the effect of LAI antipsychotics in patients with schizophrenia according to illness stage. Specifically, we aimed to evaluate the degree of clinical and functional improvement after paliperidone LAI administration in patients with schizophrenia with a varying duration of illness by using postmarketing surveillance (PMS) data.

### METHODS

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital, Gyeonggi-do, Korea, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

#### Participants

This study enrolled patients who agreed to be treated with paliperidone LAI and to participate in PMS of paliperidone LAI. Specifically, we enrolled patients who were diagnosed with schizophrenia according to ICD-10\(^{25}\) criteria in 105 hospitals and clinics in South Korea between July 26, 2010, and July 25, 2017. Participants received a full explanation of the study and provided written informed consent.

#### Study Design

Figure 1 presents the study flow diagram. Clinical interviews were used to obtain the patients’ baseline information, including medical history, concomitant medication, and reason for prescribing paliperidone LAI. Subsequently, the patients received their first paliperidone LAI injection (baseline) and a second injection of loading dose after 1 week. The injections were administered intramuscularly at the deltoid or gluteal area. The total study duration was 25 weeks with follow-up scheduled injections at 4-week intervals after the second injection of paliperidone LAI. Information on concomitant medications was collected at every visit during the study period.

#### Assessments

The effectiveness of paliperidone LAI was measured at every visit during the surveillance. The patients’ overall clinical condition was assessed using the Clinical Global Impressions–Severity of Illness scale (CGI-S) (range, 1 [not ill] to 7 [most extremely ill]).\(^{26}\) The functional aspect of the patients was examined using the PSP, which assesses the

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**Clinical Points**

- Despite increasing evidence for the effectiveness of long-acting injectable (LAI) antipsychotics in the early disease stage of schizophrenia, LAI antipsychotics are mostly administered in the later stages of the illness.
- Only a few studies have compared the effect of LAI antipsychotics among patients with schizophrenia with varying duration of illness.
- These study results suggest that the administration of LAI antipsychotics may be considered in the earlier phases of schizophrenia for better outcomes.
domains of personal and social behaviors. The PSP total score ranges from 1 to 100 and is interpreted as follows: ≥71, mild difficulty; 31–70, varying degrees of difficulty; and ≤30, poor level of functioning requiring supervision.11

Throughout the follow-up period, adverse drug reactions were monitored, documented, and classified into the following 3 subcategories: (1) extrapyramidal symptoms (EPS)/movement disorder, (2) sleep disturbance, and (3) prolactinemia/sexual dysfunction.

Statistical Analysis

The per-protocol population, defined as participants who were followed up for over 25 weeks as scheduled with assessments done at every visit, was included for analysis. The eligible participants for the analysis were allocated to the following 3 groups based on their duration of illness: (1) Group I: patients with duration of illness < 3 years; (2) Group II: patients with 3 ≤ duration of illness < 10 years; and (3) Group III: patients with duration of illness ≥ 10 years. One-way analysis of variance and Pearson χ2 tests were used for between-group comparisons of demographic variables. Changes in CGI-S and PSP total scores, the predefined endpoints in the study, were compared between the groups by using generalized linear models and generalized estimating equation for repeated-measures analysis, taking the between-group differences at baseline into account. For an exploratory analysis to investigate the change in antipsychotic dose, the antipsychotic medication dosage was converted to the olanzapine-equivalent dose, and the proportion of the paliperidone LAI dose in the total dose of all prescribed antipsychotic medications was calculated for each patient.27-29 The proportion was analyzed using generalized linear models. All statistical analyses were performed using SAS software version 9.4 (2013; SAS Institute; Cary, North Carolina). Statistical significance was set at P < .05.

RESULTS

Baseline Demographic and Clinical Characteristics of the Participants

Among 1,943 patients who participated in the PMS of paliperidone LAI, 1,166 patients with schizophrenia were included for analysis (Group I, n = 240; Group II, n = 442; Group III, n = 484). Table 1 presents the demographic and clinical characteristics of the participants. The mean ± SD age of the patients was 38.8 ± 12.8 years, while the mean ± SD baseline CGI-S and PSP scores were 4.3 ± 1.0 and 45.2 ± 18.0, respectively. The mean ± SD total olanzapine-equivalent dose of the antipsychotics at baseline was 28.7 ± 18.9 mg.

There were significant between-group differences in age (F2,1163 = 146.95, P < .001) but not in sex (χ21 = 0.19, P = .911). There were significant between-group differences in the olanzapine-equivalent doses of the antipsychotics at baseline (F2,1163 = 4.27, P = .014). There were no significant between-group differences in the percentage of patients taking antipsychotics, antidepressants, or anticholinergics (antipsychotics: χ22 = 0.09, P = .954; antidepressants: χ22 = 0.14, P = .931; anticholinergics: χ22 = 4.05, P = .132). However, there were some between-group differences in the percentage of patients taking mood stabilizers, benzodiazepines, and β-blockers (mood stabilizers: χ22 = 10.33, P = .006; benzodiazepines: χ22 = 8.39, P = .015; β-blockers: χ22 = 12.48, P = .002). There were significant between-group differences in baseline CGI-S and PSP scores as well as in occupation status (CGI-S: F2,1163 = 4.45, P = .012; PSP: F2,1163 = 3.98, P = .019; occupation: χ22 = 15.42, P < .001). There were no significant between-group differences in baseline percentage of hospitalizations (χ22 = 5.76, P = .036).

Information Regarding the Switch to Paliperidone LAI

Table 2 presents information regarding paliperidone LAI. The mean ± SD doses of paliperidone LAI at baseline and last visit (week 25) were 133.1 ± 29.7 mg and 110.2 ± 35.5 mg, respectively. There were significant between-group differences in the mean doses of paliperidone LAI at baseline and last visit (baseline: F2,1163 = 3.53, P < .030; last visit: F2,1163 = 9.05, P < .001). The most common reason for paliperidone LAI prescription was poor adherence to oral antipsychotics (73.0%), followed by an insufficient treatment effect of current antipsychotics (31.2%). There were significant between-group differences in the proportion of patients who reported ineffective current treatment as the reason for paliperidone LAI prescription (poor adherence: χ21 = 0.76, P = .684; ineffective current treatment: χ21 = 13.93, P < .001; side effects: χ21 = 0.63, P = .730; first antipsychotic medication: χ21 = 7.75, P = .005; others: χ21 = 5.39, P = .025).

Among the 1,166 patients, 99 patients (8.5%) exhibited adverse drug reactions after switching to paliperidone LAI; however, there were no significant between-group differences in the frequency of adverse drug reactions. Among the 3 subcategories of adverse drug reactions, only...
### Table 1. Baseline Demographic and Clinical Characteristics of the Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;3 years (n=240)</th>
<th>≥3, &lt;10 years (n=442)</th>
<th>≥10 years (n=484)</th>
<th>Statistics</th>
<th>Total (N=1,166)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>F df P</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Age, y</td>
<td>31.8 12.0</td>
<td>35.3 11.8</td>
<td>45.4 10.7</td>
<td>146.95 2,1163 &lt;.001</td>
<td>38.8 12.8</td>
</tr>
<tr>
<td>Total olanzapine-equivalent dose of antipsychotic treatment, mg</td>
<td>29.7 21.6</td>
<td>26.6 15.4</td>
<td>30.0 20.1</td>
<td>4.27 2,1163 .014b</td>
<td>28.7 18.9</td>
</tr>
<tr>
<td>CGI-S score</td>
<td>4.3 1.1</td>
<td>4.2 1.0</td>
<td>4.4 1.0</td>
<td>4.45 2,1163 .012c</td>
<td>4.3 1.0</td>
</tr>
<tr>
<td>PSP score</td>
<td>47.7 18.0</td>
<td>45.5 17.9</td>
<td>43.8 18.1</td>
<td>3.98 2,1163 .019d</td>
<td>45.2 18.0</td>
</tr>
</tbody>
</table>

|                                                     | n %              | n %                   | n %               | χ² df P     | n %            |
| Sex                                                 |                 |                       |                   |            |                |
| Male                                                | 107 44.6        | 190 43.0              | 213 44.0          | 0.19 2 .911 | 510 43.7      |
| Female                                              | 133 55.4        | 252 57.0              | 271 56.0          | 15.42 2 <.001 | 656 56.3 |
| Occupation                                          |                 |                       |                   |            |                |
| Yes                                                 | 117 48.8        | 175 39.6              | 163 33.7          | 455 39.0   |                |
| No                                                  | 123 51.3        | 267 60.4              | 321 66.3          | 711 61.0   |                |
| Treatment setting                                   |                 |                       |                   |            |                |
| Inpatient                                           | 125 52.1        | 205 46.4              | 262 54.1          | 5.76 2 .056 | 592 50.8      |
| Outpatient                                          | 115 47.9        | 237 53.6              | 222 45.9          | 574 49.2   |                |
| Medications prescribed                              |                 |                       |                   |            |                |
| Antipsychotics                                      | 160 66.7        | 297 67.2              | 328 67.8          | 0.09 2 .954 | 785 67.3      |
| Antidepressants                                     | 29 12.1         | 55 12.4               | 63 13.0           | 0.14 2 .931 | 147 12.6      |
| Mood stabilizers                                    | 19 7.9          | 52 11.8               | 78 16.1           | 10.33 2 .006e | 149 12.8 |
| Benzodiazepines/hypnotics                           | 135 56.3        | 201 45.5              | 254 52.5          | 8.39 2 .015f | 590 50.6 |
| Anticholinergics                                    | 104 43.3        | 157 35.5              | 188 38.8          | 4.05 2 .132 | 449 38.5 |
| β-Blocker                                           | 66 27.5         | 90 20.4               | 79 16.3           | 12.48 2 .002g | 235 20.2 |

*aIncludes olanzapine-equivalent dose of initial paliperidone long-acting injectable.

*bDuration of illness ≥ 3, < 10 years vs duration of illness ≥ 10 years; Tukey honest significant difference, \( P = .014b \).

*cDuration of illness ≥ 3, < 10 years vs duration of illness ≥ 10 years; Tukey honest significant difference, \( P = .0107 \).

*dDuration of illness < 3 years vs duration of illness ≥ 10 years; Tukey honest significant difference, \( P = .0146 \).

*eCochran-Armitage trend test, \( P = .001 \).

*fCochran-Armitage trend test, \( P = .007 \).

*gCochran-Armitage trend test, \( P = .124 \).

**Abbreviations:** CGI-S = Clinical Global Impressions–Severity of Illness scale, PSP=Personal and Social Performance scale.

### Table 2. Information Regarding Switching to Paliperidone Long-Acting Injectable (LAI) by the Duration of Illness

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;3 years (n=240)</th>
<th>≥3, &lt;10 years (n=442)</th>
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<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>F df P</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Paliperidone LAI dose, mg</td>
<td>129.3 32.1</td>
<td>132.7 30.3</td>
<td>135.4 27.7</td>
<td>3.53 2,1163 .030a</td>
<td>133.1 29.7</td>
</tr>
<tr>
<td>Injection at baseline (week 0)</td>
<td>129.3 32.1</td>
<td>132.7 30.3</td>
<td>135.4 27.7</td>
<td>3.53 2,1163 .030a</td>
<td>133.1 29.7</td>
</tr>
<tr>
<td>Injection at last visit (week 25)</td>
<td>102.0 35.8</td>
<td>110.8 35.6</td>
<td>113.8 34.7</td>
<td>9.05 2,1163 &lt;.001b</td>
<td>110.2 35.5</td>
</tr>
</tbody>
</table>

|                                                     | n %              | n %                   | n %               | χ² df P     | n %            |
| Reason for paliperidone LAI prescription             |                 |                       |                   |            |                |
| Poor adherence to oral antipsychotics                | 176 73.3        | 328 74.2              | 437 71.7          | 0.76 2 .684 | 851 73.0      |
| Ineffective current antipsychotic medications       | 55 22.9         | 133 30.1              | 176 36.4          | 13.93 2 .001c | 364 31.2 |
| Side effects of current antipsychotic medications   | 10 4.2          | 20 4.5                | 26 5.4            | 0.63 2 .730 | 56 4.8 |
| Administration as first antipsychotic medication    | 9 3.8           | 8 1.8                 | 4 0.8             | 7.75 2 .021d | 21 1.8 |
| Others                                              | 26 10.8         | 30 6.8                | 6 1.2             | 0.37 2 .833 | 15 1.3 |
| Adverse drug reaction                               | 22 9.2          | 39 8.8                | 38 7.9            | 0.46 2 .795 | 99 8.5 |
| Extrapyramidal symptoms/movement disorder           | 15 6.3          | 26 5.9                | 30 6.2            | 0.05 2 .973 | 71 6.1 |
| Sleep disturbance                                   | 4 1.7           | 5 1.1                 | 6 1.2             | 1.37 2 .025 | 15 1.3 |
| Prolactinemia/sexual dysfunction                    | 4 1.7           | 13 2.9                | 3 0.6             | 0.73 2 .025 | 20 1.7 |

*aDuration of illness ≥ 10 years vs duration of illness < 3 years; Tukey honest significant difference, \( P = .023 \).

*bDuration of illness ≥ 10 years vs duration of illness < 3 years; Tukey honest significant difference, \( P = .0107 \).

*cCochran-Armitage trend test, \( P < .001 \).

*dCochran-Armitage trend test, \( P = .007 \).

*eCochran-Armitage trend test, \( P = .124 \).

**Abbreviation:** LAI=long-acting injectable.
After Switching to Paliperidone LAI

Changes in Antipsychotic Treatment

Differences in the proportion of patients treated with paliperidone LAI monotherapy (χ² = 11.73, P = .003). As shown in Figure 2B, there were significant between-group differences in the proportion of the paliperidone LAI dose in the total dose of all prescribed antipsychotic medications (group: F₁,₁₁₅₅ = 12.17, P < .001; week: F₆,₆₁₅₀ = 52.18, P < .001; group × week: F₁₂,₂₃₀₀₈ = 1.41, P = .153). Group III had the highest total olanzapine-equivalent dose of antipsychotics (21.8 mg/d) and proportion of other antipsychotic drugs (17.9%) and also had the lowest proportion of paliperidone LAI monotherapy (49.0%) at final visit (Figure 2).

Clinical and Functional Outcomes After Switching to Paliperidone LAI

The mean ± SD CGI-S score at final visit was 3.0 ± 0.9, 3.1 ± 1.0, and 3.4 ± 1.0, respectively, for Groups I, II, and III. There were significant between-group differences in the mean ± SD changes in CGI-S score (Group I: −1.2 ± 1.1; Group II: −1.1 ± 1.1; Group III: −1.0 ± 1.0), with Group I showing the greatest decrease in the mean ± SD CGI-S score (group: χ² = 35.26, P < .001; week: χ² = 1,238.17, P < .001; group × week: χ² = 25.33, P = .013) (Figure 3A). The between-group differences in CGI-S score changes were still significant after adjusting for age and PSP total score (group: χ² = 1.02, P = .602; week: χ² = 1,238.17, P < .001; group × week: χ² = 25.33, P = .013). All 3 groups showed a significant mean ± SD increase in PSP scores at the final visit (Group I: 18.8 ± 16.8; Group II: 18.3 ± 16.2; Group III: 16.6 ± 15.7), with Group I showing the greatest increase in PSP score at the final visit (group: F₂,₁₁₆₃ = 20.23, P < .001; group × week: F₁₂,₂₃₁₆ = 1.01, P = .436). The between-group differences in PSP score changes were significant after adjusting for age and CGI-S score as well (group: F₂,₁₁₆₁ = 16.11, P < .001; week: F₆,₆₁₅₆ = 46.06, P < .001; group × week: F₁₂,₂₃₁₂ = 5.94, P < .001). Figure 3B shows changes in the frequency distribution by PSP severity over time in each group. There were significant between-group differences in the proportion of mild or no functional impairment at 9 weeks and after (group: χ² = 13.22, P < .001; week: χ² = 294.2, P < .001; group × week: χ² = 11.77, P = .465). There were significant differences in changes for each PSP domain after paliperidone LAI treatment as well (socially useful activities: group: χ² = 43.24, P < .001; week: χ² = 425.82, P < .001; group × week: χ² = 24.63, P = .017; personal and social relationship: group: χ² = 30.91, P < .001; week: χ² = 433.03, P < .001; group × week: χ² = 18.17, P = .111; self-care: group: χ² = 44.72, P < .001; week: χ² = 381.77, P < .001; group × week: χ² = 44.47,
Figure 3. (A) Change in CGI-S Scores and (B) PSP Score Over Time After Paliperidone LAI Administration by Duration of Illnessa

A.

- Group I (duration of illness < 3 years)
- Group II (3 ≤ duration of illness < 10 years)
- Group III (duration of illness ≥ 10 years)

B.

- Mild difficulty (PSP score > 70)
- Varying degree of difficulty (PSP score 31–70)
- Poor level of functioning requiring supervision (PSP score ≤ 30)

P < .001; disturbing and aggressive behavior: group: $\chi^2 = 32.80$, P < .001; week: $\chi^2 = 339.33$, P < .001; group × week: $\chi^2 = 23.13$, P = .027).

DISCUSSION

To our knowledge, this prospective study is the first on outcome after the administration of paliperidone LAI in patients with schizophrenia with varying duration of illness. We observed clinical and functional improvements after administration of paliperidone LAI in all 3 groups, which is consistent with previous findings on the efficacy of LAI antipsychotics compared to that of oral medications in schizophrenia treatment. Furthermore, patients with shorter duration of illness showed better improvements, with a majority being on paliperidone LAI monotherapy at the final visit. This finding is indicative of the clinical utility of paliperidone LAI in the early phase of schizophrenia treatment.

In our study, patients with schizophrenia showed clinical improvements, as measured by the CGI-S, after 25-week administration of paliperidone LAI. Insufficient adherence to oral antipsychotics was the most common reason for the administration of paliperidone LAI (Table 2); moreover, none of the patients missed injections during the study period. Therefore, the observed clinical improvement could be attributed to the consistent antipsychotic drug delivery allowed by this formulation. Improving adherence is among the major challenges of schizophrenia treatment, and LAI antipsychotics address many of the problems associated with adherence to oral antipsychotics.30–32 Our findings regarding clinical improvements after switching to paliperidone LAI are consistent with previous findings regarding the superior efficacy of LAI antipsychotics compared with that of oral antipsychotics except for clozapine.7,33

Moreover, we observed functional improvements, as indicated by increased PSP scores after switching to paliperidone LAI. Specifically, there was a significant increase in the proportion of patients with mild functional difficulty (Figure 3B). There has been increasing emphasis on the importance of functioning outcomes in patients with schizophrenia with both clinical remission and social function being considered in recovery.34 Functional recovery in patients with schizophrenia is difficult, as demonstrated by a 20-year prospective study35 in which functional impairment in individuals with psychotic disorders was evident at the early illness stage and remained unchanged after illness onset. Therefore, the observed improvement in functional aspects after the administration of paliperidone LAI is an encouraging finding in schizophrenia treatment.

The degree of clinical and functional improvement with paliperidone LAI administration was dependent on duration of illness. Specifically, Group I showed the greatest improvement in CGI-S and PSP scores, although these scores did not differ significantly from those for Group II (Figure 3). This finding suggests that paliperidone LAI administration at an earlier disease stage has a better benefit. Nonadherence to treatment is more prominent in the earlier phase of schizophrenia36 and
related to disease progression. Furthermore, disease progression in patients with schizophrenia has been reported to accompany functional and structural changes in the brain that are associated with antipsychotic responsiveness, which leads to a poor outcome. For example, several imaging studies have reported an association of decreased gray matter volume with psychotic relapse and disease progression in patients with schizophrenia. Moreover, a prospective observational study on the use of paliperidone LAI in patients with schizophrenia reported that individuals with a greater total gray matter volume showed significantly greater psychotic symptom improvement. Taken together, the observed between-group differences in the clinical and functional outcomes after switching to paliperidone LAI may be related to disease progression due to suboptimal adherence and differences in antipsychotic responsiveness.

Therefore, LAI antipsychotics should be considered in early illness stages to improve long-term prognosis in patients with schizophrenia by decreasing treatment nonadherence. Notably, there were significant between-group differences in the total dose of antipsychotic medications, as well as in the dose of paliperidone LAI, at the final visit (Figure 2A). Specifically, Groups I and III presented the lowest and highest doses of total antipsychotic drugs and paliperidone LAI, respectively. This finding indicates that compared with patients with longer duration of illness, those with shorter duration of illness could be treated with a lower dose of antipsychotic drugs. Furthermore, Group I had the highest proportion of paliperidone LAI monotherapy at the final visit (Figure 2A). Most evidence-based guidelines recommend that the lowest effective dose of antipsychotic drugs and monotherapy are the favorable choice for schizophrenia treatment. Contrastingly, polypharmacy is a major contributor to a high total dose and an increased side effect burden; moreover, there is an association of cumulative antipsychotic dose with antipsychotic-associated side effects and mortality. Overall, the between-group differences in the antipsychotic doses and proportion of patients on monotherapy indicate that the benefits of LAI antipsychotics are more pronounced in the early disease phase.

Limitations

This study has several limitations to be considered when interpreting the results. First, we excluded some patients from the final analysis, which limits the generalizability of the results. Among those excluded patients, there might have been some who were nonadherent to paliperidone LAI. A previous retrospective study reported that less than half of patients treated with LAI antipsychotics after psychiatric hospitalization adhered to LAI treatment for over 6 months. Therefore, our findings might not represent the real-world population with respect to the adherence to LAI antipsychotics among patients with schizophrenia. Second, the effect of concurrent use of oral antipsychotics in some patients cannot be ignored. However, the olanzapine-equivalent dose of paliperidone LAI was substantially greater than that of other antipsychotic medications. Moreover, during the follow-up period, there was a decrease in the dose of most of the concurrent oral antipsychotics. These findings suggest that the effect of concurrent antipsychotic medications on clinical and functional outcome may be minimal. In the aspects of study design, a proper control group might have been helpful. Still, the current design seems adequate for the purpose of the study, which was to evaluate the differences in the effect of LAI antipsychotics in schizophrenia with varying illness duration. Lastly, we did not obtain information regarding the duration of the untreated period and the history of antipsychotic treatment before paliperidone LAI administration, which could have affected our results.

CONCLUSION

Starting paliperidone LAI resulted in significantly improved clinical and functional outcomes in patients with schizophrenia, especially in those with shorter duration of illness. These results suggest that the administration of LAI antipsychotics may be considered in the earlier phases of schizophrenia for better outcomes.
Kim et al


