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Efficacy and Tolerability of Paliperidone Extended-release in the Treatment of First-episode Psychosis: An Eight-week, Open-label, Multicenter Trial

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Objective: We investigated the efficacy and tolerability of paliperidone extended-release (ER) tablets in patients with first-episode psychosis (n=75).

Methods: This was an 8-week, open-label, multicenter trial. The primary outcome variable was scores on the Positive and Negative Syndrome Scale (PANSS); secondary measures included the Scale for the Assessment of Negative Symptoms (SANS), the Cognitive Assessment Interview (CAI), and the Global Assessment of Functioning (GAF). To assess safety, we measured drug-related adverse events, weight, lipid-related variables, and prolactin and administered the Simpson-Angus Rating Scale (SARS), the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Scale (BAS), the Arizona Sexual Experiences Scale (ASEX), and the Udvalg for Kliniske Undersogelser side effect rating scale (UKU).

Results: The administration of paliperidone ER resulted in significant improvement in the PANSS, SANS, CAI, and GAF scores ($p<0.001$) over time. This improvement was evident as early as 1 week. The most frequent adverse events were akathisia, somnolence, anxiety, and sedation, which were well tolerated. Modest increases in weight and lipid profiles were also noted. Prolactin levels were substantially increased at the endpoint in both male and female patients.

Conclusion: These results indicate that paliperidone ER is effective and is characterized by good tolerability in the treatment of positive and negative symptoms and cognitive functioning in first-episode psychosis.

KEY WORDS: Paliperidone extended-release; First-episode psychosis; Efficacy; Tolerability.

INTRODUCTION

Successful pharmacological treatment of patients with first-episode psychosis is very important because rapid drug response with good safety can affect drug compliance and maintenance treatment. Generally, first-episode psychosis patients have better therapeutic responses to antipsychotics than chronic, multi-episode patients.[1,2)] Nevertheless, numerous patients with early psychosis or first-episode schizophrenia discontinue their initial medication due to lack of efficacy[3)] or drug side effects.[4,5)] The discontinuation rates due to lack of efficacy range from 9% to 48%.[6)] First-episode patients are more sensitive to drug side effects and have higher rates of symptoms such as extrapyramidal signs (EPSs)[7)] and antipsychotic-induced weight gain.[8,9)] Consequently, experiencing drug side effects during the initial phase of treatment negatively affects future drug compliance.[10,11)] Thus, choosing a first-line antipsychotic drug with superior efficacy and good safety for the patients with first-episode psychosis should be the highest priority for clinicians.

Paliperidone is the major active metabolite of risper-

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idone, a second-generation antipsychotic drug with potent antagonistic properties at serotonin 5-HT_{2A} and dopamine D2 receptors, some affinity towards H1-receptors, α1- and α2-adrenergic receptors, and no effective affinity towards muscarinic receptors or β1- and β2-adrenergic receptors.[12] Paliperidone extended-release (ER) is an atypical antipsychotic with an innovative ER delivery system, Osmotic-Controlled Release Oral Delivery System (OROS) technology. The drug minimizes peak-trough fluctuations and, by obviating dose titration, allows once-daily dosing with a therapeutically active dose from the first day.[13] The low peak-trough fluctuations are reported to be associated with better tolerability such as reduced rates of extrapyramidal symptoms and somnolence.[14] Several randomized, double-blind, placebo-controlled trials have shown that paliperidone ER is an effective, safe, and well-tolerated treatment for schizophrenia[15] and schizoaffective disorders.[16] The pooled data analysis of three 6-week, placebo-controlled studies showed that treatment with paliperidone ER produced a clinical response of at least a 30% improvement in the Positive and Negative Syndrome Scale (PANSS) total score of approximately 50% of patients with acute schizophrenia.[17] However, to the best of our knowledge, there is only one open-label report of the clinical trial with paliperidone ER in patients with first-episode schizophrenia.[18] Considering its unique pharmacokinetic characteristics, we hypothesized that a treatment response would appear earlier and its effects on prolactin levels would be lesser than risperidone. In the present study, we conducted an 8-week, open-label, prospective trial to investigate the efficacy and tolerability of paliperidone ER in acutely ill first-episode inpatients with a primary psychiatric diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder, not otherwise specified.

METHODS

Participants

Patients 18-59 years of age who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for first-episode schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychotic disorder not otherwise specified (NOS), as assessed using the Structured Clinical Interview for DSM-IV Axis I disorders[19] (SCID-I), were eligible to participate in the study. Patients were included if they had symptoms requiring antipsychotic treatment (a score of $\geq$4 [moderate] on at least one of the following: the PANSS[20] positive items: PI, P2, P3, P5, and P6 or Clinical Global Impression [CGI] score $\geq$4) with illness duration of more than 1 month and less than 60 months,[21] and no lifetime history of previous antipsychotic exposure lasting for 2 or more consecutive weeks.[6] Patients were excluded from the trial for any of the following reasons: (i) meeting DSM-IV criteria for another axis I diagnosis, including substance abuse or dependence and mental retardation (IQ $\leq$70); (ii) need for treatment with antidepressants, mood stabilizers, benzodiazepines (except as prescribed for agitation and control of EPSs), anticonvulsants; or (iii) a serious or unstable medical illness. Pregnant or lactating women and women without adequate contraception were also excluded. All enrolled patients provided written informed consent. The trial was approved by the local institutional review boards (approval No., CUH2009-12-141) and registered in ClinicalTrials.gov Protocol Registration and Results System (NCT01157585).

Study Design

An 8-week, open-label, single-arm clinical trial was conducted in 14 university hospitals in Korea between December 2009 and March 2013. The study consisted of screening, baseline, and assessments at 1, 2, 3, 4 and 8 weeks. To achieve reliable assessments of the major rating scales among the centers, approved raters were trained twice at the pre-investigation meetings. Patients concurrently receiving antipsychotics underwent a washout period of at least 3 days. Paliperidone ER was administered once daily in the morning, but it was allowed in the evening in the case of excessive sedation. The initial recommended dose was 3-6 mg/day. Within 2 weeks, the dose could be increased to a maximum of 12 mg/day, depending on the patient's condition. Patients in whom the treatment was considered ineffective were excluded from the study after 3 weeks. Insufficient efficacy was determined based on CGI-Improvement (CGI-I) scores of 3 or more (minimally improved) after at least 1 week of administration of paliperidone ER at a dose of 12 mg/day and after at least a 3-week trial. Patients who were intolerant of the medication's adverse effects at any time were excluded from the study. To control aggressive and threatening behavior during admission, injection of haloperidol plus lorazepam was allowed once only. During the remainder of the study, injection of lorazepam or seclusion was used for behavior control. Concomitant lorazepam (for insomnia or agitation), benztropine (EPS), and β-adrenoceptor antagonists (for akathisia) were allowed if

necessary during the study, but they were not administered prophylactically. Use of antidepressants and mood stabilizers were allowed in patients with schizoaffective disorder or other disorders with significant depression. Adding other antipsychotics was strictly prohibited. Poor drug compliance was defined as not taking more than 1/3 of the medication in a given period between evaluation time points. Patients showing poor compliance over two consecutive periods were excluded from the study.

Efficacy Assessments

The PANSS[20] was used to determine the effect of paliperidone ER on overall psychopathology. Primary efficacy was rated as changes in the PANSS total score between baseline and 1, 2, 3, 4, and 8 weeks. The secondary efficacy variables were the total score (the sum of all 24 items) on the Scale for the Assessment of Negative Symptoms (SANS),[22] Cognitive Assessment Interview (CAI),[23] and the Global Assessment of Functioning (GAF).[24] Discontinuation due to insufficient clinical responses and/or adverse events was recorded. Efficacy variables, with the exception of CAI and GAF, were measured at baseline (day 0) and 1, 2, 3, 4, and 8 weeks. The CAI and GAF were assessed at baseline and 8 weeks.

Safety and Tolerability Assessments

All adverse events reported and observed during the study or within 6 days from the last day of treatment were recorded. The severity, duration, and possible relationship of all adverse events to the study drugs were recorded. The occurrence of parkinsonism, akathisia, and dyskinesia was evaluated at baseline and at every visit or upon early termination using standardized EPS rating scales: Simpson-Angus Rating Scale (SARS),[25] Barnes Akathisia Scale (BAS),[26] and Abnormal Involuntary Movement Scale (AIMS).[27] Arizona Sexual Experiences Scale (ASEX)[28] and sexual side effect items of the Udvalg for Kliniske Undersogelser side-effect rating scale (UKU)[29] were also administered at baseline and at 4 and 8 weeks for the evaluation of sexual adverse events. Weight, body mass index (BMI), and prolactin levels were measured at baseline and at 8 weeks. Electrocardiography and laboratory studies (complete blood cell count, electrolytes, kidney and liver function tests, and fasting lipids, including triglycerides [TG], total cholesterol, high-density lipoprotein [HDL], and low-density lipoprotein [LDL] levels) were conducted at baseline and endpoint (8 weeks).

Statistical Analyses

All efficacy and safety variables were evaluated using an intent-to-treat analysis with the last observation carried forward. Patients were included in the efficacy and tolerability analyses only if baseline measurements and at least one post-baseline measurement or observation after medication were performed. To evaluate changes in symptom scores between different assessment time points, repeated-measures analysis of variance (ANOVA) was used, with the Bonferroni *post hoc* test for multiple comparisons. Effect size was calculated using the following formula: after mean-baseline mean/baseline standard deviation (SD). Analyses of weight and laboratory measures from baseline to endpoint were performed using paired *t*-tests or Wilcoxon's signed-rank tests. In all analyses, a p value < 0.05 was considered to indicate statistical significance.

RESULTS

Demographic and Clinical Characteristics of Patients

Of the 82 eligible patients, 75 (41 males and 34 females) consented to participate in the study. The mean age, educational level, and duration of untreated psychosis (DUP) were 30.8±11.0 years, 12.7±3.0 years, and 15.5±19.5 months, respectively. The diagnoses of participants were as follows: schizophrenia (n=49), schizophreniform disorder (n=16), schizoaffective disorder (n=2), and psychotic disorder NOS (n=8) (Table 1). At the time of enrollment, the numbers of antipsychotic-naïve, -free, and -treated patients were 55, 16, and 4, respectively. Of these 75, 51 patients (68.0 %) were able to complete the 8-week trial (Fig. 1). The reasons for exclusion were loss of follow up (9), withdrawal of consent (5), lack of efficacy (5), intolerable side effects (2), use of prohibited medications

Table 1. Demographic and clinical characteristics of enrolled patients (n=75)

Characteristic	Data
Sex	
Male	41 (54.7)
Female	34 (45.3)
Age (yr)	30.8±11.0
Education (yr)	12.7±3.0
DUP (mo)	15.5±19.5
Diagnosis	
Schizophrenia	49 (65.3)
Schizophreniform disorder	16 (21.3)
Schizoaffective disorder	2 (2.7)
Psychotic disorder NOS	8 (10.7)

Values are presented as number (%) or mean±standard deviation. DUP, duration of untreated psychosis; NOS, not otherwise specified.

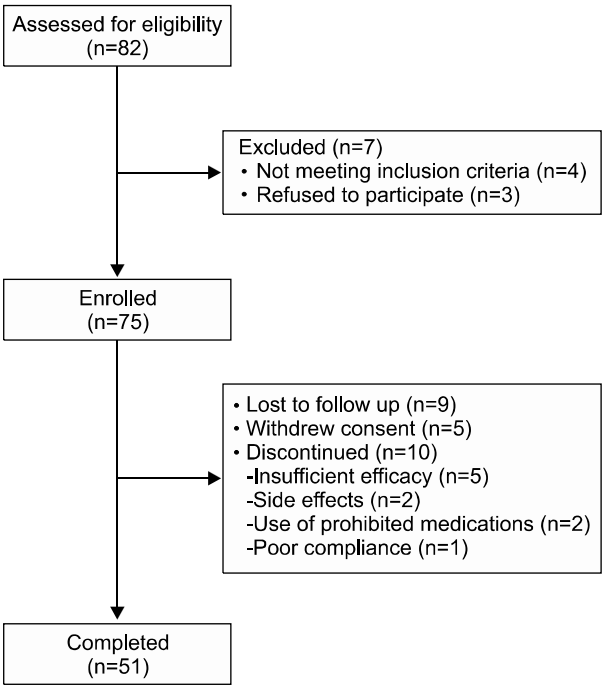

Fig. 1. CONSORT flow of participants through the trial.

(2), and poor drug compliance (1). No differences in demographic or baseline clinical characteristics were found between the patients who completed the study and those who did not (data not shown).

Dosage and Concomitant Medications

The mean total daily doses of paliperidone ER at baseline and endpoint were 4.63±1.67 and 8.74±2.78 mg/day, respectively. There were no significant differences in dosage between males and females across all time points. The percentages of patients who required benztropine, a β-adrenoceptor antagonist, and bgenzodiazepine at any time during the study were 62.7%, 35.3%, and 64.7%, respectively.

Efficacy

Table 2 shows significant reductions in the psychopathology scores (PANSS and SANS) over time, whereas significant increases were observed in the CAI and GAF scores between baseline and endpoint. Significant reductions in the total and subscale scores of the PANSS and SANS were observed as early as 1 week. The largest effect size was observed in the positive PANSS subscale score.

Table 2. Results on primary and secondary outcome measures over time (LOCF) (n=75)

	Baseline	1-Week	2-Week	3-Week	4-Week	8-Week	*p* value	Effect size
PANSS								
Positive total	26.40±5.97	21.57±6.14*	18.89±5.53*,†	17.35±4.86*,†,†	15.91±5.00*,†,†,§	15.09±5.14*,†,†,§,¶	<0.001	1.894
Negative total	22.27±6.15	19.91±5.25*	18.57±5.18*,†	17.84±5.26*,†	16.85±4.82*,†,†,§	16.00±4.97*,†,†,§	<0.001	1.020
General total	50.88±11.78	43.39±12.09*	40.11±11.54*,†	38.49±11.26*,†	36.72±11.05*,†,†,§	34.79±10.59*,†,†,§,¶	<0.001	1.366
Composite total	99.55±20.25	84.87±21.27*	77.57±20.16*,†	73.68±19.69*,†,†	69.48±19.27*,†,†,§	65.88±19.23*,†,†,§,¶	<0.001	1.663
SANS								
Affective blunting	10.52±5.12	8.60±4.59*	7.56±4.55*,†	7.28±4.78*,†	6.87±4.51*,†	6.28±4.38*,†,†,§	<0.001	0.829
Alogia	7.61±4.38	5.71±3.59*	4.77±3.23*,†	4.67±3.33*,†	4.49±3.21*,†	4.19±3.18*,†	<0.001	0.783
Avolition-apathy	6.13±2.63	4.84±2.43*	4.32±2.55*,†	4.04±2.56*,†	3.79±2.61*,†,†	3.41±2.57*,†,†,§	<0.001	1.035
Anhedonia-asociality	9.12±3.85	7.64±3.75*	6.85±3.73*,†	6.41±3.68*,†	5.93±3.64*,†,†,§	5.61±3.66*,†,†,§	<0.001	0.911
Attention	3.95±2.13	3.19±1.78*	2.88±1.80*	2.61±1.79*,†	2.45±1.80*,†,†	2.36±1.83*,†	<0.001	0.745
Total score**	48.09±18.98	21.57±6.14*	18.89±5.53*,†	17.35±4.86*,†	15.91±5.00*,†,†	15.09±5.14*,†,†,§	<0.001	1.739
CAI (n=51)								
Working memory	2.39±1.25	NA	NA	NA	NA	1.70±0.73	<0.001	0.552
Attention vigilance	2.44±1.15	NA	NA	NA	NA	1.76±0.66	<0.001	0.591
Verbal learning and memory	2.57±1.33	NA	NA	NA	NA	1.82±0.81	<0.001	0.564
Reasoning and problem solving	2.23±1.16	NA	NA	NA	NA	1.45±0.55	<0.001	0.672
Speed of processing	2.80±1.43	NA	NA	NA	NA	2.03±0.94	<0.001	0.538
Social cognition	2.78±1.31	NA	NA	NA	NA	1.86±0.86	<0.001	0.702
Global severity score	2.66±1.14	NA	NA	NA	NA	1.92±0.72	<0.001	0.649
GAF (n=51)	54.80±17.46	NA	NA	NA	NA	66.35±9.16	<0.001	0.662

Values are presented as mean±standard deviation.
*,†,†,§,¶Statistically significant difference from the baseline, 1-week, 2-week, 3-week, and 4-week ($p<0.05$) with Bonferroni correction; *p*, one-way repeated measures ANOVA; Effect size=(after mean-baseline mean)/ baseline standard deviation.
**Sum of the item 1-24.
LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; CAI, Cognitive Assessment Interview; GAF, Global Assessment of Functioning; NA, not available.

Safety and Tolerability

Overall, the most frequent adverse events were akathisia, somnolence, anxiety, and sedation (Table 3). Adverse events were observed primarily early during the course of treatment, at 1 or 2 weeks. The incidences of treatment-emergent adverse events (TEAE) over 8 weeks were as follows: akathisia (41.3%), somnolence (24.0%), EPS (22.7%), and sedation (20.0%). However, they were mostly mild and transient. The TEAE of moderate severity reported at two time points by the same patient were

Table 3. Incidence of adverse events observed in patients over the course of treatment

Variable	Baseline (n=75)	After 1-week (n=74)	After 2-week (n=74)	After 3-week (n=67)	After 4-week (n=62)	After 8-week (n=51)	*p* value
Check list							
Headache	10 (13.3)	8 (10.8)	3 (4.1)	5 (7.5)	6 (9.7)	4 (7.8)	
Akathisia	NA	13 (17.6)	19 (25.7)	14 (20.9)	9 (14.5)	7 (13.7)	
Insomnia	12 (16.0)	9 (12.2)	8 (10.8)	7 (10.4)	5 (8.1)	3 (5.9)	
Somnolence	6 (8.0)	17 (23.0)	18 (24.3)	11 (16.4)	11 (17.7)	8 (15.7)	
Sedation	5 (6.7)	7 (9.5)	11 (14.9)	9 (13.4)	11 (17.7)	4 (7.8)	
Dizziness	8 (10.7)	11 (14.9)	4 (5.4)	4 (6.0)	4 (6.5)	2 (3.9)	
Anxiety	23 (30.7)	18 (24.3)	18 (24.3)	12 (17.9)	9 (14.5)	6 (11.8)	
Agitation	12 (16.0)	11 (14.9)	10 (13.5)	8 (11.9)	6 (9.7)	4 (7.8)	
Nausea	2 (2.7)	2 (2.7)	1 (1.4)	2 (3.0)	1 (1.6)	1 (2.0)	
Vomiting	1 (1.3)	1 (1.4)	NA	NA	1 (1.6)	1 (2.0)	
Worsening of psychosis	3 (4.0)	3 (4.1)	2 (2.7)	1 (1.5)	3 (4.8)	NA	
Self report							
Constipation	NA	3 (4.1)	2 (2.7)	4 (6.0)	3 (4.8)	NA	
EPS	NA	3 (4.1)	8 (10.8)	13 (19.4)	10 (16.1)	13 (25.5)	
ASEX							
Total (n=46)	19.28±4.51	NA	NA	NA	20.15±4.50	20.35±3.97	0.096
Male (n=23)	17.61±3.99	NA	NA	NA	18.61±4.16	19.00±3.57	0.194
Female (n=23)	20.96±4.46	NA	NA	NA	21.70±4.37	21.70±3.96	0.475

Values are presented as number (%) or mean±standard deviation.
p, one-way repeated measures ANOVA.
EPS, Extrapyramidal Symptoms; ASEX, Arizona Sexual Experiences Scale; NA, not available.

Table 4. Changes from baseline in metabolism-related measures and prolactin level

Variable		Baseline	8-week	*t*	p^1	p^2
Fasting TG (~200)	Normal/abnormal	59 (93.7)/4 (6.3)	34 (87.2)/5 (12.8)	−2.600	0.014	
	Total/paired	95.46±46.27/96.89±43.78 (n=35)	137.27±85.92/133.06±80.88			<0.001
Fasting TC (≥200)	Normal/abnormal	60 (90.9)/6 (9.1)	30 (73.2)/11 (26.8)	−2.996	0.005	
	Total/paired	158.26±43.22/163.89±40.64 (n=37)	180.18±47.33/180.45±48.09			<0.001
Fasting HDL (40-59)	Normal/abnormal	32 (50.8)/31 (49.2)	21 (52.5)/19 (47.5)	−0.944	0.352	
	Total/paired	48.12±11.70/49.29±10.79 (n=35)	56.06±49.13/57.46±52.35			0.212
Fasting LDL (70-159)	Normal/abnormal	46 (78.0)/13 (22.0)	31 (88.6)/4 (11.4)	−2.791	0.009	
	Total/paired	92.90±27.73/94.82±29.97 (n=33)	110.17±29.77/107.94±27.84			0.010
Fasting glucose (≥100)	Normal/abnormal	51 (77.3)/15 (22.7)	30 (76.9)/9 (23.1)	−1.790	0.082	
	Total/paired	91.34±17.27/93.53±19.87 (n=36)	94.89±9.02/94.36±9.31			0.081
BMI (kg/m^2)						
Total (n=74/51)	Total/paired	22.05±3.22/22.39±3.47	23.63±3.31	−7.647	<0.001	
Male (n=41/26)	Total/paired	21.90±3.25/22.19±3.51	23.50±3.41	−5.130	<0.001	
Female (n=34/25)	Total/paired	22.25±3.23/22.59±3.49	23.77±3.27	−5.774	<0.001	
Prolactin (ng/ml)						
Total	Normal/abnormal	34 (54.8)/28 (45.2)	2 (4.8)/40 (95.2)	−4.885	<0.001	
	Total/paired	23.58±22.66/22.63±21.39 (n=38)	84.93±75.81/81.74±77.75			<0.001
Male (2.5-17)	Normal/abnormal	21 (55.3)/17 (44.7)	1 (4.3)/22 (95.7)	−5.231	<0.001	
	Total/paired	19.37±17.36/19.75±18.23 (n=22)	49.32±27.60/ 48.85±28.16			<0.001
Female (1.9-25)	Normal/abnormal	13 (54.2)/11 (45.8)	1 (5.3)/18 (94.7)	−4.082	0.001	
	Total/paired	30.26±28.30/27.07±25.10 (n=16)	128.03±92.63/126.95±100.17			0.006

Values are presented as number (%) or mean±standard deviation.
p^1, paired *t*-test between baseline and 8-week; p^2, McNemar test between baseline and 8-week.
TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

as follows: akathisia (4.1%), somnolence (2.7%), EPS (2.7%), and sedation (1.4%; data not shown). Only one participant discontinued the medication due to severe akathisia. Assessment of movement disorders using the AIMS, BAS, and SAS revealed no significant changes between baseline and the last observation (data not shown). The ASEX scores did not change significantly over time (Table 3). However, assessed by the UKU at 8 weeks, several sexual side effects were reported: in males, reduced sexual desire (2/34, 5.9%) and erectile dysfunction (2/34, 5.9%) were reported; in females, amenorrhea (5/32, 15.6%) and galactorrhea (1/32, 3.1%) were reported. The fasting TG, total cholesterol, and LDL levels as well as the proportion of abnormal subjects at each level were both increased significantly during the 8-week treatment, but the fasting HDL and glucose levels did not significantly differ between baseline and endpoint (Table 4). The BMI increased significantly over time in both males and females. The mean change in weight between baseline and endpoint was 3.52±3.32 kg and the incidence of a clinically important increase in body weight ($\geq$7% weight gain) was 37.3% (19/51). The prolactin levels and proportion of abnormal subjects increased significantly over time. In particular, prolactin levels increased more in females than in males.

DISCUSSION

This study evaluated the efficacy and safety of paliperidone ER in patients with first-episode psychosis using a single-arm, open-label multicenter trial design. Our results showed that paliperidone ER is effective in improving psychopathology, cognitive impairment, and overall functioning scores and is well tolerated.

The dropout rate in our study was 32.0%, which is slightly higher than the 25.14% observed in a 6-week study of first-episode psychotic patients[30] but much lower compared with the 46.37% and 48.71% observed in 8-week studies of first-episode schizophrenia patients.[31,32] The possible reasons that the nine patients (12.0%) who could not be followed up after discharge from this study may include treatment refusal or visiting other hospitals. This result highlights the difficulty of maintaining continuous treatment after discharge in first-episode psychosis. The 6.7% discontinuation rate due to lack of efficacy in this study is similar to the rates reported for risperidone (4.89%[32] and 9%[33]), olanzapine (6.1%[34]), and haloperidol (8.9%[32] and 12.1%[34]) in 8-12-week trials with patients with first-episode psychosis. However, the rates were much lower than those reported for quetiapine (34.62%), ziprasidone (20.73%), and haloperidol (33.01%) in the European First Episode Schizophrenia Trial.[6] These findings suggest that the efficacy of paliperidone ER in first-episode psychosis is comparable or superior to that of other antipsychotics. However, the issue of the relative efficacy of atypical antipsychotics in first-episode schizophrenia patients should be investigated in future studies using well-designed methodologies and large sample sizes.

A significant improvement in psychopathology (lower PANSS and SANS scores) was observed over time and appeared as early as 1 week after administration of paliperidone ER. The result of this rapid effect is consistent with the previous paliperdione ER studies in which a significant improvement in the mean PANSS total score was evident from day 4.[35,36] This rapid action may result from initiating paliperidone ER at an effective dose due to OROS technology. However, the meta-analysis of 42 double-blind controlled studies showed the mean weekly PANSS or BPRS scores for various antipsychotics differed significantly from that at placebo at the very first week.[37] Furthermore, in previous studies[32,38-42] on the efficacy of risperidone in first-episode psychosis patients, the rapid action of risperidone (as early as 1 week) was never investigated. To clarify whether the rapid action of paliperidone ER is due to the advantage of OROS technology, a comparative study of paliperidone ER and risperidone should be conducted. Interestingly, significant improvement in cognitive functioning was also observed. However, this finding should be interpreted cautiously because it may reflect an indirect effect secondary to the improvement in positive symptoms or general psychopathology. Taken together the results show significant improvements in the positive and negative symptoms and cognitive functioning of patients with first-episode psychosis receiving a mean paliperidone ER dose of 8.74±2.78 mg/day at the endpoint. Mean dosage of paliperidone ER for patients with first-episode of psychosis in this study was almost similar with that in other studies for patients with multiple-episode of psychosis.[43-45]

The most frequently observed adverse events were akathisia, somnolence, and sedation. In particular, akathisia was observed most frequently at 3 weeks. The incidence of treatment-emergent akathisia over 8 weeks was 41.3% which is in contrast with that of previous studies (17.4% and 9.8% with paliperidone ER at 6 and 9 mg/day respectively), which were conducted mostly with multiple-episode patients.[35,46] In previous studies with paliper-

idone ER in Korean patients with schizophrenia, whose mean duration of illness were about 10 years, incidence of akathisia were reported within 10%.[47,48] This discrepancy of akathisia rates among studies suggests that individuals with first-episode psychosis may be more likely to experience akathisia than those with multiple-episode psychosis when administered paliperidone ER. However, given that moderate akathisia persisted in only 4.1% of patients over two consecutive time points suggests that akathisia is usually mild and transient and can be successfully managed by prescribing concomitant medications. Some of the lipid profiles and BMIs increased significantly over time. These results may be due to the low levels of physical activities during admission or the direct effect of paliperidone ER. Regardless of the cause, proper attention should be paid to the occurrence of metabolic syndrome during the initial phase of treatment with paliperidone ER in first-episode psychosis. The incidence of hyperprolactinemia at the endpoint was 95.2% higher than the 74% reported in first-episode psychosis patients treated with risperidone.[33] The endpoint prolactin levels in males (49.32±27.60 ng/mL) and females (128.03±92.63 ng/mL) in the present study were similar to the levels observed in males (45.3±25.4 ng/mL) and females (125.0±65.8 ng/mL) in previous paliperidone ER studies.[17] The incidence of amenorrhea (15.6 %) was higher compared to those in risperidone (12.03% [3] and 9.09%[42]) and other 6-week studies with paliperidone ER.[17] These findings suggest that, contrary to our hypothesis, the effects of paliperidone ER on prolactin levels and related sexual adverse events are greater than those of risperidone. These effects may be related to lower lipophilia and longer half-life of paliperidone and its reduced ability to cross the blood brain barrier because these factors increase the ability of paliperidone to affect the anterior pituitary gland, which is located outside the blood brain barrier.[49,50]

The present study had several limitations. First, this study was open-label in design, which might have biased the findings. However, designing a randomized controlled trial in patients with first-episode psychosis may appear unethical and is very difficult to conduct. The duration of the study was also too short to evaluate the sexual and metabolic side effects of the drug. In conclusion, the present study demonstrated that paliperidone ER is effective in improving the positive and negative symptoms and cognitive functioning of patients with first-episode psychosis. Significant improvement was evident as early as the first week. The most frequent adverse events were akathisia, somnolence, anxiety, and sedation. However, because the adverse events were mild and transient in nature, they were well tolerated. Modest increases in weight and lipid profiles were noted. Although prolactin levels were substantially increased at the endpoint, related sexual side effects were limited.

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