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Research Article

# A Flexible-Dose Study of Paliperidone ER in Patients With Nonacute Schizophrenia Previously Treated Unsuccessfully With Oral Olanzapine

MOSHE KOTLER, MD
NESRIN DILBAZ, MD
FERNANDA ROSA, MD✠
PERIKLIS PATERAKIS, MD
VIHRA MILANOVA, MD, PhD
ANATOLY B. SMULEVICH, MD, PhD
MARJOLEIN LAHAYE, MSc
ANDREAS SCHREINER, MD

***Objective:*** **The goal of this study was to explore the tolerability, safety, and treatment response of switching from oral olanzapine to paliperidone extended release (ER).**

***Methods:*** **Adult patients with nonacute schizophrenia who had been treated unsuccessfully with oral olanzapine were switched to flexible doses of paliperidone ER (3 to 12 mg/d). The primary efficacy outcome was a ≥20% improvement in Positive and Negative Syndrome Scale (PANSS) total scores from baseline to endpoint for patients who switched medications because of lack of efficacy with olanzapine and noninferiority versus previous olanzapine treatment (mean endpoint change in PANSS total scores vs. baseline of ≤5 points) for patients who switched for reasons other than lack of efficacy. Safety and tolerability were assessed by monitoring adverse events, extrapyramidal symptoms, and weight change.**

***Results:*** **Of 396 patients, 65.2% were men, mean age was 40.0±12.0 years, and 75.5% had paranoid schizophrenia. Among the patients whose main reason for switching was lack of efficacy, an improvement in the PANSS total score of ≥20% occurred in 57.4% of patients. Noninferiority was confirmed for each subgroup of patients whose main reason for switching was something other than lack of efficacy. Paliperidone ER was generally well tolerated. Extrapyramidal symptoms as measured by total Extrapyramidal Symptom Rating Scale scores showed statistically significant and clinically relevant improvements at endpoint, the average weight decreased by 0.8±5.2 kg at endpoint, and a clinically relevant weight gain of ≥7% occurred in 8.0% of patients.**

***Conclusion:*** **Paliperidone ER flexibly-dosed over 6 months was well tolerated and associated with a meaningful clinical response in patients with nonacute schizophrenia who had previously been unsuccessfully treated with oral olanzapine.**

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KOTLER: Beer Yaakov-Ness Ziona Mental Health Center, Beer Yaakov, Israel; and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; DILBAZ: Üsküdar University Neuropsychiatry Hospital, Istanbul, Turkey; PATERAKIS: Hospital Dromokaiteio Therapeftirio, Chaidari, Athens, Greece; MILANOVA: Department of Psychiatry, Medical University, Sofia, Bulgaria; SMULEVICH: Research Clinical Department of Boundary Conditions and Psychosomatic Disorders, Mental Health Research; and Department of Psychiatry and Psychosomatics, I.M. Sechenov First Moscow Stare Medical University, Moscow, Russia; LAHAYE: Medical Affairs EMEA, Janssen-Cilag BV, Tilburg, The Netherlands; SCHREINER: Medical and Scientific Affairs EMEA, Janssen-Cilag GmbH, Neuss, Germany



Please send correspondence to: Andreas Schreiner, MD, Medical and Scientific Affairs EMEA, Janssen-Cilag GmbH, Johnson & Johnson Platz 5a, Neuss 41470, Germany (e-mail: aschrein@its.jnj.com).

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Extended-release (ER) oral antipsychotic formulations require less frequent dosing and yet produce more consistent plasma levels than immediate-release formulations. They have been recommended for treating patients with schizophrenia to improve adherence and clinical outcomes.[1–4] Two ER oral formulations of atypical antipsychotics are currently available: paliperidone ER and quetiapine XR. Preclinical data in animal models suggested that the use of paliperidone ER is associated with better efficacy and tolerability than administration of risperidone immediate release.[5] These data have been supported by comparative clinical analyses.[6,7] The osmotic controlled-release oral delivery system used for paliperidone ER allows the release of active drug at a controlled rate. As a result, paliperidone ER achieves stable plasma concentrations over a 24-hour period with once-daily dosing, without the peaks and troughs characteristic of immediate-release oral antipsychotic formulations.[1,3,5] Paliperidone ER is approved in the European Union for the treatment of schizophrenia and schizoaffective disorder in adults; its efficacy and safety have been shown in several company-sponsored randomized-controlled clinical trials involving patients with both diseases.[6,8,9]

Several studies have compared paliperidone ER with oral olanzapine in patients with schizophrenia. The 2012 Cochrane review by Nussbaum and Stroup[10] concluded that paliperidone ER at doses of 6 to 12 mg/d had comparable efficacy to olanzapine at a dose of 10 mg/d. Patients receiving lower doses of paliperidone ER (6 to 9 mg/d) were less likely to experience weight gain than those treated with olanzapine (10 mg/d); however, movement disorders were more common with paliperidone ER (9 to 15 mg/d) than with olanzapine (10 mg/d).[10] Another meta-analysis compared the efficacy and tolerability of oral atypical antipsychotics and paliperidone ER using data from randomized-controlled clinical trials.[6] Treatment with paliperidone ER was associated with similar efficacy, as measured by scores on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions of Severity (CGI-S) scale, but it was associated with a lower likelihood of treatment withdrawal for any reason and less somnolence, agitation, and weight gain than oral olanzapine. Another 6-month, prospective, multicenter, randomized, open-label study compared outcomes in adults with schizophrenia treated with flexibly dosed paliperidone ER 6 to 9 mg/d or oral olanzapine 10 to 15 mg/d.[11] Significant improvements in psychiatric symptoms occurred in patients in both groups, with no significant differences between the treatment groups. At the same time, the mean increase in body weight was significantly greater with olanzapine (3.8 vs. 1.2 kg; $P$=0.0013). More importantly, newly diagnosed metabolic syndrome and the development of insulin resistance were significantly more common among patients treated with olanzapine. In a recent 6-week, randomized, double-blind multicenter study, similar efficacy, in terms of symptomatology and illness severity, was shown in patients treated with either paliperidone ER or olanzapine, and safety results were also similar between the treatment groups.[12] Pooled data from three, 6-week, double-blind placebo-controlled studies evaluated the effects of switching from oral olanzapine to fixed doses of paliperidone ER 3 to 12 mg/d or placebo in patients with schizophrenia after experiencing an acute exacerbation.[13] A significant and clinically relevant improvement in symptoms and functioning was observed in patients who switched to paliperidone ER compared with placebo.

Although these comparative data from clinical trials are useful, the applicability of such data to the real-world setting has been questioned because of issues related to volunteer selection bias and unrepresentative exclusion criteria. The study described here was designed to expand on the data from previous studies and meta-analyses[6,10,11,13] by exploring outcomes among a more representative patient population. Real-world studies provide results that can be generalized to a wider range of patients than results from randomized-controlled trials. The design of our study more closely resembled daily clinical practice in which dosing is flexible and individualized on the basis of clinical needs. In clinical practice, patients often have comorbid conditions and/or substance abuse and they often take additional psychotropic or other concomitant medications; these are usually all causes for exclusion from randomized, placebo-controlled clinical trials

conducted for regulatory purposes.[14] The current study explored dosing, treatment response, and tolerability in adult patients with nonacute schizophrenia who had previously been unsuccessfully treated with oral olanzapine and who were switched to flexible doses of paliperidone ER. This study was not designed to directly compare outcomes with paliperidone ER versus olanzapine, but instead to provide clinically useful information on optimal dosing and changes that may occur when switching from oral olanzapine to paliperidone ER.

## METHODS

This report is a subgroup analysis of patients from a previously published 6-month, international, multicenter, open-label, single-arm study using flexible doses of paliperidone ER (3 to 12 mg/d) to treat patients with nonacute schizophrenia who had previously been unsuccessfully treated with other oral antipsychotics.[15] In addition to the full population analysis, several prespecified subgroup analyses were carried out to investigate outcomes in patients with schizophrenia who had previously been treated with olanzapine or risperidone and in patients who were recently diagnosed. All subgroup analyses were considered clinically relevant and included meaningful patient numbers.

This article describes the analysis of data from patients who had previously been unsuccessfully treated with oral olanzapine. The study protocol was approved by Independent Ethics Committees and all potential candidates provided written informed consent before enrollment. A full description of the study methods has been published elsewhere.[15]

### Patients

Adult inpatients or outpatients aged 18 years and older diagnosed with schizophrenia according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[16] on the basis of clinical interviews were included in this study if they were considered to be nonacutely ill but symptomatic and if they had been treated with oral olanzapine for ≥1 month at a dose within the approved label. Schizophrenia was considered to be nonacute (ie, stable but symptomatic) when patients treated with olanzapine experienced a change in their CGI-S score of ≤1 during at least the 4 weeks before enrollment.[17,18] Previous olanzapine treatment could be considered unsuccessful for various reasons, including lack of efficacy, tolerability or safety issues, or lack of adherence, despite patients being treated with an adequate therapeutic dosage for an adequate period of time. Adherence with olanzapine treatment before enrollment was not specifically measured, although lack of adherence was one reason for switching; the remaining patients were considered to be adherent to their oral olanzapine treatment by the investigator. Some patients were not receiving an antipsychotic at baseline (ie, they had discontinued olanzapine before entry into the study). Patients were excluded for any of the following reasons: treatment with clozapine or a long-acting injectable antipsychotic during the preceding 3 months (previous treatment with other antipsychotics, such as paliperidone ER or risperidone, was allowed); significant medical illness interfering with the outcome of the study; tardive dyskinesia; neuroleptic malignant syndrome; high risk for adverse events (AEs) or self-harm; substance dependence (but not substance abuse) over the past 6 months; or known hypersensitivity (eg, previous allergic reaction) to paliperidone ER or risperidone.

### Treatment

Oral paliperidone ER was administered using flexible dosing within the approved dose range of 3 to 12 mg/d; the recommended dose was 6 mg once daily. When possible, paliperidone ER was initiated using an effective dose without titration. Previous olanzapine and, if applicable, any other antipsychotics used for the treatment of schizophrenia at baseline were all discontinued or tapered off. Details of the switching process are described below. Low-potency antipsychotics and other psychotropic medication, such as benzodiazepines (BZDs), administered before enrollment for conditions other than schizophrenia (eg, sleep induction or sedation) could be continued if a stable dose was maintained.

The method of transitioning to paliperidone ER was at the discretion of the investigator. Patients could be switched to an effective dose of paliperidone ER without the need for titration. Patients could be cross-tapered in different ways from olanzapine; a decrease of olanzapine could occur at the time of or

after the initiation of paliperidone ER, and the period of cross-tapering could vary between patients as both the dosing and the timing of the transition depended on individual patient characteristics. Factors that were taken into account included the type and severity of symptoms or side effects, course of previous relapses and rehospitalizations, and the last olanzapine dose. Given the considerable variability in clinical factors among the patients, no randomization or specific transition instructions were used. Anticholinergic medication could be continued for up to 4 weeks and then tapered off at the discretion of the investigator. All oral antipsychotic medications indicated for the treatment of psychotic disorders were stopped at the end of the cross-tapering transition period (ie, the time taken to establish paliperidone ER as antipsychotic monotherapy), which preferably did not exceed 4 weeks. Patients were prospectively treated and followed for up to 6 months or until early discontinuation.

## Outcome Measures

### *Efficacy Assessments*

The primary efficacy outcome was based on the main reason for transitioning to paliperidone ER. For patients whose main reason for switching was lack of efficacy with oral olanzapine, primary efficacy was achieving a ≥20% improvement in PANSS total scores from baseline to endpoint, which was also defined as treatment response. Patients whose main reasons for switching were other than lack of efficacy were evaluated using a primary efficacy measure of noninferiority in efficacy compared with previous oral olanzapine treatment. Noninferiority was defined as a difference of ≤5 points in the mean endpoint change in PANSS total scores versus baseline.

The following additional efficacy measures were assessed at baseline and treatment weeks 4, 8, 13, and 26 (or endpoint): the PANSS subscale and Marder factor scores[19] and the CGI-S score.[20] The PANSS is a 30-item instrument in which each item is scored 1 to 7 (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate to severe, 6=severe, and 7=extreme); it is divided into 3 subscales: positive scale, negative scale, and general psychopathology.[21] Factor analysis of the PANSS has identified 5 factors within which items from the PANSS clustered: (1) negative symptoms; (2) positive symptoms; (3) disorganized thought; (4) uncontrolled hostility/excitement; and (5) anxiety/depression.[19,22] The CGI-S score measures symptom severity on a scale from 0 to 6 (0=normal; 1=borderline ill; 2=mildly ill; 3=moderately ill; 4=markedly ill; 5=severely ill; and 6=extremely ill).[20] Patient functioning was measured using the Personal and Social Performance (PSP) scale at baseline and treatment weeks 13 and 26 (or endpoint). The PSP scale is a 100-point single-item rating scale that is subdivided into 10 equal intervals. Ratings on the PSP scale are based mainly on assessment of the patient's functioning in 4 main domains: (1) socially useful activities; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behaviors.[23] Treatment satisfaction with oral olanzapine was measured at baseline and satisfaction with paliperidone ER was measured at week 26 (or endpoint) using a 5-point categorical scale (5=very poor, 4=poor, 3=moderate, 2=good, and 1=very good). Sleep quality and daytime drowsiness over the previous 7 days were recorded at treatment weeks 4, 8, 13, and 26 (or endpoint) using an 11-point scale for both sleep quality (ranging from "slept very badly" to "slept very well") and daytime drowsiness ("not at all" to "all the time").

PANSS rater training was provided; however, because this was a pragmatic study, intended to explore interventions under the conditions of routine clinical practice, no additional training on the CGI and the PSP was performed.

### *Safety and Tolerability*

Safety and tolerability were assessed by recording the occurrence of treatment-emergent AEs (TEAEs). Extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS)[24] at baseline and at treatment weeks 4, 8, 13, and 26 (or endpoint). Body weight was recorded at baseline and at treatment weeks 13 and 26 (or endpoint). A previously published 6-month study of patients with schizophrenia reported a mean weight increase with olanzapine at endpoint of 3.8 kg;[11] therefore, an analysis was carried out to explore whether patients experienced a change in weight of ≥4 kg after switching from olanzapine to paliperidone ER. Hyperprolactinemia-related TEAEs were not routinely assessed, but were reported as a result of patient and/or clinician concerns. Laboratory testing (including measurement of prolactin levels) was not systematically performed in this study because

prolactin levels were comprehensively measured in earlier controlled, pivotal trials.

### Data Analysis

Efficacy and safety analyses were carried out for all patients who received study medication at least once (intent-to-treat cohort) and who provided at least 1 postbaseline assessment (ie, this was an intent-to-treat analysis with last observation carried forward for endpoint only). Patient demographics, efficacy, treatment satisfaction, and safety parameters were explored using descriptive statistics. Primary efficacy was assessed by comparing the baseline with the endpoint, last observation carried forward. For patients whose main reason for switching was lack of efficacy with olanzapine, 95% confidence intervals (CIs) were estimated for treatment response. For patients whose main reasons for switching were not lack of efficacy, noninferiority was evaluated using Schuirmann's OST/TOST (1-sided test) ($\alpha$=0.025). Within-group changes versus baseline were evaluated using the 2-tailed Wilcoxon signed-rank test ($\alpha$=0.05).

Predictor analyses were carried out using stepwise logistic regression to determine clinical predictors of treatment response and the mode (ie, the most frequently used) dose of paliperidone ER. Treatment response was defined as a decrease in the PANSS total score from baseline to endpoint of ≥20% plus a decrease in CGI-S of ≥1 point.

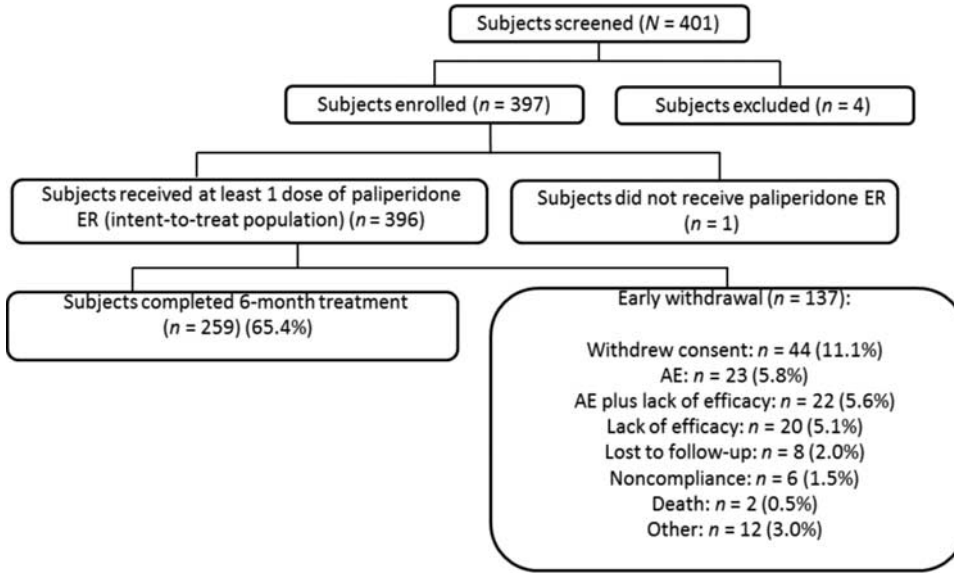
## RESULTS

### Patients

Of the 401 patients who were screened, 397 patients were enrolled and 396 patients received ≥1 dose of paliperidone ER (Fig. 1). These patients constituted 21.9% of the patients enrolled in the primary study, which was carried out from April 24, 2007 to January 15, 2009, in 293 study sites in 23 countries (Belgium, Bulgaria, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom).[15]

A total of 259 patients (65.4%) completed the 6-month study and 137 patients discontinued early (11.1% because of withdrawal of consent, 5.8% because of AEs, 5.6% because of AEs plus a lack of efficacy, 5.1% because of a lack of efficacy, 2.0%

**FIGURE 1. Patient disposition.**




*AE indicates adverse event; ER, extended release.*

**Table 1. Baseline Characteristics**

| *Characteristics* | *N=396* |
|---|---|
| Sex [n (%)] | |
| Male | 258 (65.2) |
| Female | 138 (34.8) |
| Age (mean±SD) (y) | 40.0±12.0 |
| Duration since diagnosis of schizophrenia (mean±SD) (y) | 10.2±9.3 |
| Diagnosis of paranoid schizophrenia [n (%)] | 299 (75.5) |
| Main reason for switching from olanzapine [n (%)] | |
| Lack of efficacy | 210 (53.0) |
| Lack of tolerability | 144 (36.4) |
| Lack of adherence | 16 (4.0) |
| Other | 26 (6.6) |
| Body mass index (mean±SD) (kg/m$^2$) | 27.9±5.4 |

*SD indicates standard deviation.*

were lost to follow-up, 1.5% because of nonadherence, 0.5% died, and 3.0% because of other reasons). Of the 396 patients who entered the study, 16.9% were inpatients at baseline, 43.3% of whom were still hospitalized or had been rehospitalized at endpoint.

Patients were predominantly male and diagnosed with paranoid schizophrenia (Table 1). Most had been enrolled because of lack of efficacy (53.0%) or lack of tolerability (36.4%) with previous oral olanzapine treatment; lack of adherence (4.0%) or other reasons (6.6%) were the main cause for switching in the rest of the patients. In the lack of tolerability subgroup, a total of 179 AEs in 144 patients were cited as the main reason for switching from olanzapine, most commonly: weight increase (n=83); obesity (n=16); somnolence (n=15); sedation (n=13); fatigue (n=10); and overweight, increased appetite, and hypercholesterolemia (n=4 each). The mean, last daily olanzapine dose from which patients were switching was 14.2±7.5 mg/d (range, 2 to 40 mg/d). Among 258 study completers (for 1 patient switching from olanzapine for the main reason of lack of adherence, the daily dose was only available as a range and therefore set to missing), the last daily olanzapine dose from which patients switched was >10 mg/d in 124 patients (48.1%), with 81 (31.4%) receiving ≥20 mg/d (20 mg/d is the maximum approved daily dose of olanzapine). At baseline, 16 of the 396 patients who had previously been unsuccessfully treated with oral olanzapine were no longer taking an antipsychotic.

The mean initial dose of paliperidone ER was 5.3 ±2.0 mg/d, with a mean mode dose (ie, the most frequently used dose during the study per patient) of 7.2±2.9 mg/d at follow-up. Paliperidone ER dosing was comparable in patients whose main reasons for switching were not lack of efficacy or lack of adherence and slightly higher in patients whose main reason for switching was lack of efficacy or lack of adherence [mean mode dose: 7.8±2.9 mg/d (n=210) and 7.5±3.1 mg/d (n=16)]. Among the 396 patients who received at least 1 dose of paliperidone ER, the mean duration of exposure was 141.6 ±63.6 days, with a paliperidone ER dose increase occurring in 235 patients (59.3%) and a decrease occurring in 68 patients (17.2%). Dosages of paliperidone ER administered at each visit are shown in Supplemental Digital Content, http://links.lww.com/JPP/A2. At endpoint, of the 396 patients, 37.9% were treated with paliperidone ER 6 mg/d, 21.8% with 9 mg/d, and 20.5% with 12 mg/d. Dosing was lower among patients whose main reason for switching was lack of tolerability, with 18.6% treated with paliperidone ER 9 mg/d and 12.9% with 12 mg/d at endpoint. Among the treatment completers, the total daily olanzapine dose from which they were switching was higher among those patients who received higher last doses of paliperidone ER (Table 2). The mean daily oral olanzapine dose before transitioning was 8.7±4.1 mg among patients completing the study who received 3 mg/d paliperidone ER as their last dose, 12.0±6.1 mg oral olanzapine for those whose last dose was 6 mg paliperidone ER, 15.8±6.8 mg oral olanzapine for those whose last dose was 9 mg paliperidone ER, and 17.1 ±8.3 mg oral olanzapine for those whose last dose was 12 mg paliperidone ER.

Use of BZDs was somewhat higher in patients who were switched because of lack of efficacy (41.4%) or lack of adherence (43.8%) with previous olanzapine treatment compared with those who switched because of lack of tolerability (33.3%). Over the course of the study, the concomitant use of BZDs decreased from 122 patients (31.7%) to 110 patients (28.6%) at endpoint (in the sample of 385 patients who had an end-of-study visit).

**Table 2. Endpoint Paliperidone ER Dosage Based on Last Oral Olanzapine Dosage in Patients Completing the Study**

| | *Paliperidone ER Daily Endpoint Dosage [n (%)]* | | | |
|---|---|---|---|---|
| ***Last Olanzapine Dosage (mg/d)*** | **3** | **6** | **9** | **12** |
| <10 (n=54) | 14 (25.9) | 30 (55.6) | 5 (9.3) | 5 (9.3) |
| 10 (n=80) | 12 (15.0) | 33 (41.3) | 17 (21.3) | 18 (22.5) |
| 15 (n=40) | 1 (2.5) | 15 (37.5) | 16 (40.0) | 8 (20.0) |
| ≥20 (n=81) | 2 (2.5) | 26 (32.1) | 23 (28.4) | 30 (37.0) |

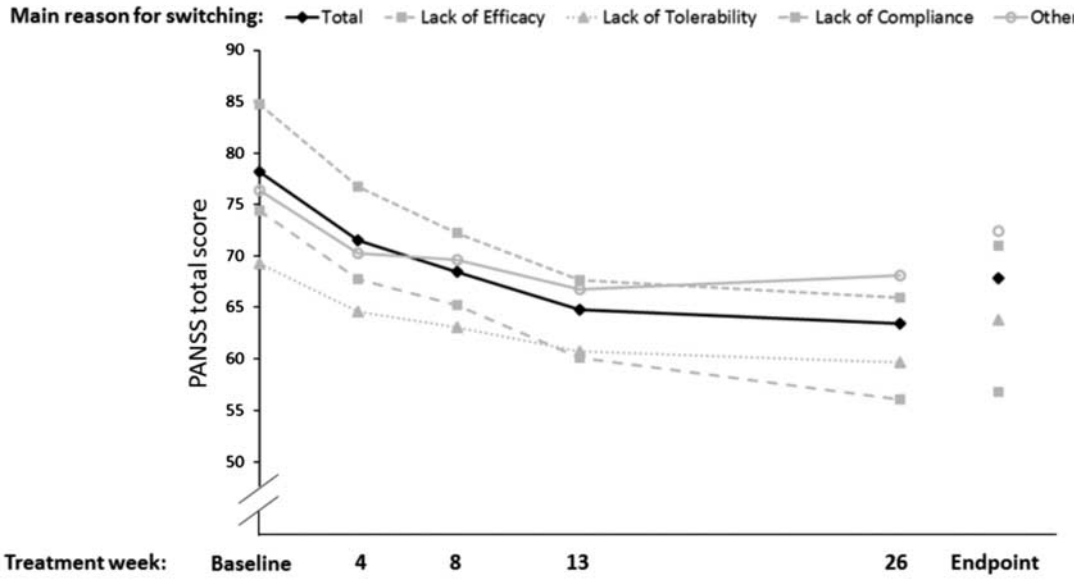
*Note that the last olanzapine dosage of 12.5 mg/d is not included in the table because the number of patients was too small (n=3). ER indicates extended release.*

## Efficacy

Efficacy data were available for 381 patients (96.2%): for 202 patients, the main reason for switching was a lack of efficacy; for the other 179 patients, the main reason for switching was something other than lack of efficacy.

With respect to the primary efficacy outcome for patients whose main reason for switching was a lack of efficacy, 57.4% of 202 patients (95% CI, 50.3–64.3)

**FIGURE 2. PANSS scores over time.**




| Treatment week: | Baseline | 4 | 8 | 13 | 26 | Endpoint |
|---|---|---|---|---|---|---|
| Patients Evaluated, *n*: | | | | | | |
| Total | 380 | 367 | 330 | 311 | 269 | 380 |
| Lack of Efficacy | 202 | 195 | 176 | 166 | 145 | 202 |
| Lack of Tolerability | 138 | 133 | 118 | 112 | 94 | 138 |
| Lack of Adherence | 16 | 16 | 15 | 12 | 12 | 16 |
| Other | 24 | 23 | 21 | 21 | 18 | 24 |

*PANSS, Positive and Negative Syndrome Scale.*

showed an improvement in PANSS total scores of ≥20% from baseline to endpoint. Among patients switching for main reasons other than lack of efficacy, the primary efficacy outcome was mean change in PANSS total score from baseline to endpoint: lack of tolerability (–5.4±20.3) in 138 patients; lack of adherence (–17.7±14.1) in 16 patients; and other reasons (–4.0±22.7) in 24 patients (Fig. 2). Schuirmann's OST/TOST (1-sided test) confirmed noninferiority in efficacy within the specified equivalence bounds for the lack of tolerability and the lack of adherence groups ($P<0.0001$) and for the other-reasons group ($P<0.05$).

Among the total population, clinically relevant and statistically significant improvements from baseline to each visit were observed for PANSS total, PANSS subscale, and Marder factor scores ($P<0.0001$ for each). Changes in PANSS total and subscale scores from baseline to endpoint were statistically significant for subgroups of patients switching for main reasons of lack of efficacy ($P<0.0001$), lack of tolerability ($P\leq0.0289$), and lack of adherence ($P\leq0.0005$), with no significant changes observed for patients switching for other reasons. Changes from baseline to endpoint for Marder factor scores were also statistically significant for patients switching for the main reason of lack of efficacy ($P<0.0001$), lack of tolerability ($P\leq0.0361$; except for the uncontrolled hostility/excitement factor, which was not significant), and lack of adherence ($P\leq0.0039$), with no significant changes observed for patients switching for other reasons.

The percentages of patients in CGI-S categories at baseline and endpoint, respectively, were 26.3% and 45.9% for mildly ill or less, 47.5% and 31.2% for moderately ill, and 26.2% and 22.8% for markedly to most extremely ill. CGI-S category improved for 40.9% of patients, remained the same for 42.8% of patients, and worsened for 16.3% of patients. Among patients who had been classified as markedly to most extremely ill at baseline (n=100), 59.0% improved to a less severe illness category at endpoint. The percentage of patients with "mild degree of difficulty" or less functional impairment (PSP score ≥71) doubled from 16.3% at baseline to 32.2% at endpoint.

Treatment satisfaction with olanzapine at baseline was rated as good to very good for 20.5% of patients, moderate for 46.7%, and poor to very poor for 32.7%. Treatment satisfaction with paliperidone ER at endpoint was good to very good for 65.3% of patients, moderate for 15.1%, and poor to very poor for 19.6%.

Sleep quality and daytime drowsiness over time are presented in Supplemental Digital Content, http://links.lww.com/JPP/A3. There was a statistically significant improvement in sleep quality after switching to paliperidone ER at weeks 8, 13, and 26

**Table 3. Statistically Significant Clinical Predictors Identified Through Stepwise Logistic Regression**

| *Models* | *Odds Ratio* | *95% CI* | $\chi^2$ | *P* |
|---|---|---|---|---|
| Clinical response* | | | | |
| Baseline CGI-S | 1.761 | 1.367–2.267 | 19.2190 | < 0.001 |
| Treated with an antipsychotic at baseline (yes vs. no) | 0.236 | 0.080–0.695 | 6.8661 | < 0.01 |
| Duration since first diagnosis of schizophrenia | 0.972 | 0.946–0.999 | 4.2788 | < 0.05 |
| Mode dose main effect variables | | | | |
| Last daily dose of olanzapine before switching | 1.082 | 1.050–1.115 | 26.0912 | < 0.0001 |
| Sex (male vs. female) | 2.266 | 1.434–3.578 | 12.2986 | 0.0005 |
| Main reason for switching was lack of efficacy (yes vs. no) | 2.009 | 1.282–3.149 | 9.2565 | 0.0023 |
| Total PANSS at baseline | 1.013 | 1.004–1.021 | 8.9777 | 0.0027 |
| Schizophrenia type "undifferentiated" (yes vs. no) | 1.888 | 1.005–3.546 | 3.9020 | 0.0482 |
| Body mass index | 1.040 | 0.998–1.083 | 3.4698 | 0.0625 |

**Clinical response was defined as a decrease in PANSS total score from baseline to endpoint of ≥20% plus a decrease in CGI-S of ≥1 point.*
*CI indicates confidence interval; CGI-S: Clinical Global Impressions of Severity; PANSS: Positive and Negative Syndrome Scale.*

($P$<0.05), with a trend at endpoint ($P$=0.09). Statistically significant reductions in daytime drowsiness were observed from baseline to all visits, with a reduction at endpoint of −1.4±2.9 ($P$<0.0001).

### Predictor Analyses

Statistically significant predictors of clinical response were baseline CGI-S score, being treated with an antipsychotic at baseline, and duration since the first diagnosis of schizophrenia (Table 3). Patients with a higher baseline CGI-S score (ie, more severe symptoms), shorter duration since the first diagnosis of schizophrenia, and who were not being treated with an antipsychotic at baseline were more likely to respond to paliperidone ER. Statistically significant predictors of mode dose of paliperidone ER were sex, lack of efficacy as a main reason for switching to paliperidone ER, PANSS total score at baseline, "undifferentiated" type of schizophrenia, and last daily dose of olanzapine before switching (Table 3). Male patients, patients with a higher last daily dose of olanzapine before transition, patients with the "undifferentiated" type of schizophrenia, patients with a higher baseline PANSS total score, and patients switching for the main reason of lack of efficacy were more likely to receive a higher mode dose of paliperidone ER. A higher body mass index showed a trend toward predicting a higher mode dose of paliperidone ER.

**Table 4. Treatment-emergent Adverse Events**

| *TEAE* | *N=396 [n (%)]* |
|---|---|
| No. patients experiencing any TEAE | 234 (59.1) |
| No. patients experiencing a serious TEAE* | 42 (10.6) |
| No. patients experiencing a TEAE causally related to paliperidone ER | 147 (37.1) |
| No. patients experiencing a TEAE that occurred in ≥5% of patients | |
| Insomnia | 61 (15.4) |
| Anxiety | 31 (7.8) |
| Somnolence | 20 (5.1) |
| Severity of TEAEs† | |
| Mild | 273 (44.5) |
| Moderate | 275 (44.9) |
| Severe | 65 (10.6) |
| Action taken due to TEAE‡ | |
| None | 456 (74.1) |
| Dose adjustment | 84 (13.7) |
| Temporary stop | 1 (0.2) |
| Permanent discontinuation | 74 (12.0) |

**Most commonly, psychotic disorder (3.5%) and anxiety (1.3%).*
*†Based on number of TEAEs with nonmissing severity (n=613).*
*‡Based on number of TEAEs (n=615).*
*ER indicates extended release; TEAE, treatment-emergent adverse event.*

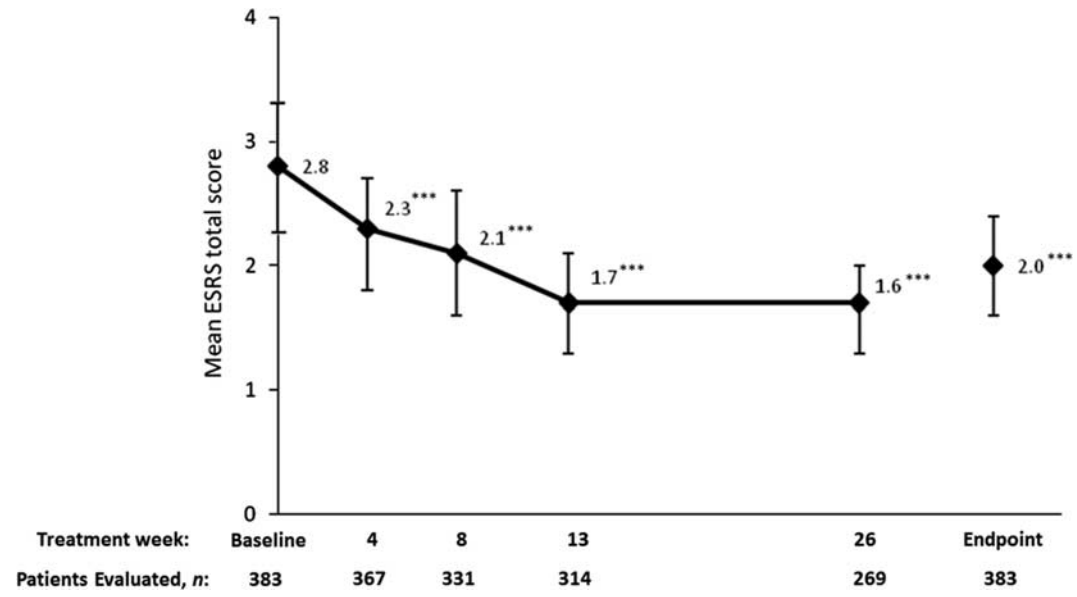
### Safety and Tolerability

Paliperidone ER was generally well tolerated (Table 4). TEAEs were usually mild or moderate in intensity (89.4%). AEs resulting in early discontinuation of paliperidone ER were most commonly psychotic disorder (n=7; 1.8%), delusions (n=5; 1.3%), and insomnia (n=5; 1.3%). There were 2 deaths (acute cardiac failure and death from unknown causes); neither death was considered to be causally related to paliperidone ER.

Fifteen patients (3.8%) reported potentially prolactin-related TEAEs: amenorrhea (n=6); galactorrhea (n=3); sexual dysfunction (n=3); erectile dysfunction (n=2); and abnormal orgasm, decreased libido, breast pain, and oligomenorrhea (n=1 each). Hyperprolactinemia or increased/abnormal serum prolactin levels were reported in 5 patients (1.3%).

Extrapyramidal symptoms as measured by total ESRS scores showed statistically significant and clinically relevant improvements at each assessment and endpoint for the entire population ($P$<0.0001; Fig. 3). Domains within ESRS with the largest change from baseline to endpoint were Parkinsonism (−0.7±2.7; $P$<0.0001), hypokinesia (−0.5±1.9; $P$<0.0001), and Parkinsonism, dystonia, dyskinesia, and akathisia (−0.5±2.2; $P$<0.0001). Changes in total ESRS scores at each assessment and endpoint were statistically significant for subgroups of patients switching for the main reason of lack of efficacy (ranging from −0.7±2.7 to −1.1±3.3; $P$<0.0001) and lack of tolerability (ranging from −0.5±3.2 to −1.1±3.9; $P$≤0.0276). Changes were not statistically significant at any assessment or endpoint for patients switching for the main reason of lack of adherence (ranging from −0.3±1.7 to 1.6±6.0). Among the smallest subgroup of patients who switched because of other reasons, significant changes in ESRS occurred at weeks 4, 8, 13, and 26 (ranging from −1.0±2.2 to −1.4±2.3; $P$≤0.0479),

**FIGURE 3. Mean Extrapyramidal Symptom Rating Scale (ESRS) of the entire cohort.**




****P<0.0001. Total scores (95% confidence intervals shown with error bars) obtained with paliperidone ER. Decreasing ESRS scores reflect an improvement in extrapyramidal symptoms. Improvement versus baseline was statistically significant.*

with change at endpoint (−0.4±2.6) not statistically significant.

Baseline and endpoint body weight were recorded for 361 patients. The mean baseline weight was 83.4 ±16.9 kg. Average weight decreased by −0.5±3.9 kg (95% CI, −1.0 to −0.1 kg) at week 13, −1.0±5.5 kg (95% CI, −1.7 to −0.3 kg) at week 26, and −0.8±5.2 kg (95% CI, −1.4 to −0.3 kg) at endpoint. The mean weight decrease was statistically significant at each assessment ($P \leq 0.0053$). Weight loss of 1 to 4 kg from baseline to endpoint occurred in 100 patients (27.7%), and weight loss >4 kg occurred in 61 patients (16.9%). A total of 38 patients (10.5%) gained >4 kg, and a clinically relevant weight gain (≥7%) from baseline to endpoint was observed in 29 patients (8.0%). Among patient subgroups on the basis of the main reason for switching from oral olanzapine, a statistically significant reduction in weight at weeks 13 and 26 and at endpoint occurred for those switching because of a main reason of lack of tolerability ($P \leq 0.0005$), with no statistically significant weight change observed in subgroups switching for main reasons of lack of efficacy, lack of adherence, or other reasons.

## DISCUSSION

Paliperidone ER was well tolerated and effective in nonacute (ie, stable) but symptomatic patients who had previously been unsuccessfully treated with oral olanzapine. Among patients who were transitioned to paliperidone ER for the main reason of lack of efficacy with previous oral olanzapine, more than half of the patients showed a clinically meaningful improvement in clinical symptoms with a decrease in PANSS total score of ≥20%, an endpoint that has often been used to assess efficacy in clinical trials.[8,25,26] A study that examined pooled data from 7 pivotal, multicenter antipsychotic drug trials in patients with exacerbations of schizophrenia found that at least a 50% reduction from baseline in PANSS score (which corresponded to a CGI-improvement rating of much improved) may be a more appropriate cut-off to define response rather than lower thresholds, although a lower threshold (eg, 25% to 30%) may be appropriate in populations with treatment-resistant illness, in which even a small improvement (corresponding to a CGI-improvement rating of minimally improved) can be important.[27]

Pooled data from patients with an acute exacerbation of schizophrenia who were treated with olanzapine before switching to paliperidone ER showed a mean reduction in total PANSS scores from baseline to the 6-week endpoint of −18.5.[13] In this study, nonacute patients who switched to paliperidone ER because of lack of efficacy of previous olanzapine treatment achieved a mean total PANSS improvement of −13.8 (−21.9% on the basis of the corrected formula), which can be considered clinically meaningful because patients were symptomatically stable. In studies in which patients are switched from a medication to which they have had a suboptimal response to a new treatment, it can be expected that those patients will show clinical improvement; however, what should be explored is the amount of effect observed in patients who are considered stable by their treating psychiatrists. Furthermore, in our study, psychotic symptomatology showed clinically relevant improvements, even among patients whose main reason for switching to paliperidone ER was not lack of efficacy. Improvements were also observed in symptom subdomains, disease severity, and patient personal and social functioning. When tailoring therapy for individual patients, it is important for clinicians to have an understanding of which specific antipsychotics may be better for particular patient subtypes. Our findings suggest that paliperidone ER may provide benefits over olanzapine for some patients with paranoid schizophrenia (positive symptoms) as well as for mood and cognitive symptoms. These findings are in line with other studies of paliperidone ER in patients with schizophrenia that have found improvements in mood symptoms and cognition,[28–31] and they are also consistent with studies that found improvements in patients who had not shown an adequate response to risperidone and were switched to paliperidone ER.[32,33]

Certain disease-related and demographic factors at baseline predicted treatment response and paliperidone ER mode dose, and this information may be useful in making relevant treatment decisions. For example, patients who had a higher baseline CGI-S score, a shorter duration since the first diagnosis of schizophrenia, and who were not being treated with an antipsychotic at baseline were more likely to respond to paliperidone ER. Also, male patients, patients with a higher last daily dose of olanzapine before transition, patients switching for the main reason of lack of efficacy, patients with a higher total PANSS score at baseline, and patients with the "undifferentiated" type of schizophrenia were more likely to need a higher mode dose of paliperidone ER.

Paliperidone ER was generally well tolerated, and switching to paliperidone ER from olanzapine was associated with clinically relevant improvements in extrapyramidal symptoms. On average, patients experienced an average decrease in body weight of almost 1 kg during the study, which was most pronounced in patients who switched for reasons of lack of tolerability. This is consistent with recent randomized-controlled data showing significantly greater weight gain and metabolic changes with olanzapine compared with paliperidone ER,[11] as well as findings from a study in which patients with acute symptoms of schizophrenia were switched from olanzapine to paliperidone ER.[13,34]

In addition to improvements in extrapyramidal symptoms, patients who switched to paliperidone ER showed improvements in functioning and subjective treatment satisfaction. Improvements in functioning in patients with schizophrenia treated with antipsychotic medication are multifactorial, with efficacy in treating positive, negative, depressive, or cognitive symptoms likely to contribute toward improved functional capability. Conversely, side effects, such as sedation, anticholinergic effects, clinically relevant extrapyramidal symptoms, or excessive weight gain, may worsen patient functioning. In our study, clinically relevant improvements in positive, negative, and depressive symptoms were observed, as well as improved sleep quality, less daytime somnolence, and fewer extrapyramidal symptoms. Because all of these parameters have the potential to affect patient functional capabilities, the changes observed in this study may have contributed toward some of the improvements observed in personal and social functioning.

With respect to extrapyramidal symptoms, a recent randomized-controlled study comparing olanzapine and paliperidone ER[11] did not show any relevant differences, with extrapyramidal symptoms reported in <5% of patients in both groups. However, in patients whose symptoms are suboptimally controlled with oral olanzapine who may suffer from extrapyramidal symptoms, there is potential for improvement after the transition to paliperidone ER: first, because switching itself often leads to some improvement; and second, because

the reduction in peak-and-trough fluctuations with paliperidone ER may lead to improved tolerability and reduced extrapyramidal symptoms.[5]

In this subanalysis, switching from olanzapine to paliperidone ER resulted in a significant improvement in sleep quality at 8, 13, and 26 weeks ($P<0.05$) and reduced daytime somnolence ($P<0.0001$). Although olanzapine has shown larger sedative effects than paliperidone ER,[6,35] other factors may contribute toward improved sleep quality. Our results are consistent with a recent randomized trial, which found that paliperidone ER did not exacerbate daytime somnolence, but improved sleep architecture and sleep continuity in patients diagnosed with schizophrenia and concomitant insomnia.[36] These improvements may, in part, be explained by the improvements in positive, negative, depressive, and/or anxiety symptoms observed in this study.[37]

The interpretation of data from this study is limited by the use of open-label treatment and the lack of a comparator group, plus a number of other factors discussed below. This study did not provide the direct head-to-head comparisons between treatment with olanzapine and paliperidone ER that have been provided elsewhere.[8,11,12] However, in this study, patients who had failed to achieve success with olanzapine (because of lack of efficacy, tolerability, adherence, or other reasons) had a meaningful probability of experiencing some clinically relevant improvement when transitioning to paliperidone ER. These results should be viewed with caution as previously published data have shown that doctors often choose to switch medications rather than advance an antipsychotic to a higher dose, which could offer a greater likelihood of success.[38,39] Indeed, in our study, the mean last daily dose of olanzapine from which patients were switching (per investigator judgment) was 14.2±7.5 mg/d, with a wide range of 2 to 40 mg/d. Therefore, it is possible that some of the patients in the current study might have achieved improvement if they had been treated with higher doses of olanzapine rather than switching to paliperidone ER. In our study, 48.1% of patients who completed the study switched from >10 mg olanzapine and 31% switched from maximum approved doses of olanzapine (20 mg/d or higher). It is possible that weight gain, metabolic changes, and sedation may have been factors limiting further olanzapine dose increases. With respect to hyperprolactinemia-related TEAEs and hyperprolactinemia, as these were not routinely assessed for the entire sample, it is possible that these events were underreported.

In summary, flexibly dosed paliperidone ER treatment over 6 months was safe, well tolerated, and associated with meaningful clinical responses in nonacute (ie, stable) but symptomatic patients who had previously been unsuccessfully treated with oral olanzapine. These data expand on previously published clinical trials by showing long-term efficacy in nonacute patients treated with individualized doses of paliperidone ER.[8,9,40] In this study, patients failing to experience successful treatment with oral olanzapine did experience some clinically relevant improvements in symptoms and functioning after switching to paliperidone ER.

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