Research Article

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Flexible-dose oral paliperidone ER in non-acute schizophrenia previously unsuccessfully treated with oral risperidone

Practice points

- In patients with non-acute schizophrenia unsuccessfully treated with oral risperidone, clinically relevant and statistically significant improvements were observed for PANSS total, PANSS subscale, and Marder factor scores after switching to paliperidone ER ($p < 0.0001$).
- Baseline symptom severity, lack of compliance as main reason for switching, diagnosis of residual schizophrenia, and diagnosis of disorganized schizophrenia were significant predictors of treatment response.
- Age, baseline BMI, last daily dose of oral risperidone before switching, diagnosis of disorganized schizophrenia, and baseline PANSS total score were statistically significant predictors of mode dose.
- Extrapyramidal symptoms improved significantly at each assessment and end point ($p < 0.0001$).
- There was a statistically significant but not clinically relevant weight increase at end point (0.4 ± 4.3 kg; $p = 0.0071$).
- Flexibly dosed paliperidone ER treatment over 6 months was well tolerated and associated with meaningful clinical responses in patients with non-acute schizophrenia who had been previously unsuccessfully treated with oral risperidone.
- These data expand on previously published literature by demonstrating efficacy in non-acute patients treated with flexible doses of paliperidone ER in a more naturalistic and real-world setting.

Aims: Assessment of oral paliperidone ER therapy. **Methods:** A subgroup analysis of patients with schizophrenia switched from unsuccessful oral risperidone therapy in a 6-month, open-label, multicenter study investigating flexibly dosed paliperidone ER. **Results:** 694 patients were analyzed (59.2% male; mean age: 40.0 years). Mean change in PANSS total score from baseline to end point was -14.4 ± 20.2 in patients switching due to lack of efficacy (n = 359). Mean change in PANSS total score for patients switching for other reasons (n = 319) was: -7.6 ± 17.0 (lack of tolerability, n = 175), -19.6 ± 20.3 (lack of compliance, n = 76), and -12.0 ± 16.8 (other, n = 68). **Conclusion:** In patients with schizophrenia previously unsuccessfully treated with oral risperidone, paliperidone ER was well tolerated and associated with a meaningful treatment response.

Keywords: flexible dosing • paliperidone • risperidone • schizophrenia • switching

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Introduction

Extended-release (ER) oral formulations of antipsychotics that require less frequent dosing and/or produce more consistent plasma levels have been recommended for treating schizophrenia to enhance adherence and improve patient outcomes [1–4]. Oral paliperidone is available in the EU as an ER formulation for the treatment of schizophrenia in adults and adolescents ≥15 years and manic or psychotic symptoms of schizoaffective disorder in adults. An indirect comparison of placebo-controlled randomized clinical trials exploring the efficacy of pali-

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peridone ER and oral risperidone in patients with acute schizophrenia has reported better improvement in Positive and Negative Syndrome Scale (PANSS) total scores with paliperidone ER 6–12 mg/day than risperidone 2–4 mg/day (difference in mean change score: -6.7; $p < 0.05$) and comparable response to risperidone 4–6 mg/day (0.2; $p = 0.927$) [5]. Placebo-adjusted adverse event (AE) profiles generally favored paliperidone ER over oral risperidone, with more somnolence, restlessness, nausea, anxiety, salivary hypersecretion, akathisia, dizziness, and nasal congestion reported with risperidone [5]. Extrapyramidal symptoms have also been reported to be less frequent with paliperidone ER [3]. Weight gain has been reported to be both less with paliperidone ER [3,6] and similar with paliperidone ER and risperidone [5]. Risperidone and paliperidone ER potentially have a differential prolactin-elevating profile, with the recommended dose of risperidone (4 mg/day) causing comparable prolactin elevation to the highest approved dose of paliperidone ER (12 mg/day) [7]. Benefit has been shown in patients switching to paliperidone ER who had previously not achieved satisfactory outcomes with oral risperidone [8–10].

Randomized clinical trials have demonstrated clinically meaningful and statistically significant improvements in psychiatric symptoms, overall disease severity, and personal and social functioning in patients with acute schizophrenia treated with fixed doses of paliperidone ER [11]. Open-label, long-term extension studies of these randomized controlled clinical trials have reported good maintenance of symptom control and patient functioning, with generally good tolerability [12].

As switching between oral antipsychotics is the rule rather than the exception in routine practice [13] and healthcare professionals need information from real-world patient populations that cannot be provided by randomized, placebo-controlled trials, a study was conducted to provide important information about dosing, treatment response, tolerability, safety, and the effects of switching antipsychotics on outcomes in patients with non-acute but symptomatic schizophrenia who were previously unsuccessfully treated with other oral antipsychotics before switching to flexibly dosed paliperidone ER [14]. In contrast to clinical trials used for regulatory purposes, this study used a less restrictive patient population by enrolling patients with common comorbidities including substance abuse and patients concomitantly treated with additional relevant psychotropic and somatic medications. In addition, paliperidone ER dosing was individualized, as determined by the treating physicians, to provide important information about optimal dosing in clinical practice. The findings from the entire study population have been reported elsewhere [14]. The current report is an analysis of the largest and clinically important subgroup of this study population, that is, the group in whom prior oral risperidone therapy was unsuccessful. Risperidone is currently the most frequently prescribed second-generation oral antipsychotic worldwide, often as first-line treatment; however, a substantial number of patients will not achieve optimal symptom control or acceptable safety and tolerability outcomes or sufficient adherence with oral risperidone. The objective of this analysis, therefore, was to investigate the treatment response, tolerability, and safety in adult patients with non-acute schizophrenia who did not achieve optimal symptom control, safety, tolerability, or sufficient adherence with oral risperidone, and who were switched to flexible doses of paliperidone ER. This was not a head-to-head comparison of paliperidone ER with any other oral antipsychotic. Since patients often improve when being switched from an immediate-release to an ER or long-acting antipsychotic [15–18], the question is less if, but to what extent, patients improve after switching and if improvement can be considered to be clinically meaningful.

Patients & methods

This multicenter, international, open-label, single-arm, 6-month study treated patients with non-acute schizophrenia who had been unsuccessfully treated with oral risperidone with flexible doses of paliperidone ER (3–12 mg/day). Previous treatment could be considered unsuccessful for various reasons, including, but not limited to, incomplete therapeutic response despite adequate dosage of oral risperidone for an adequate period of time, lack of tolerability or safety, or lack of compliance. This study was conducted in 291 sites in 23 countries in Europe and the Middle East from April 2007 to January 2009. The study was performed in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice, and the study protocol was approved by Independent Ethics Committees. Prior to study enrollment, all potential candidates gave written informed consent. Full details of study methodology have recently been published [14].

Patients

Adult inpatients or outpatients aged ≥18 years with schizophrenia (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; DSM-IV [19]) were included in this analysis if they had been treated with an adequate therapeutic dose of oral risperidone for an adequate period of time, as determined by the investigator.

Patients were required to have been diagnosed with non-acute schizophrenia, defined as a change in Clinical Global Impression Severity (CGI-S) score of ≤1 during at least the 4 weeks before enrollment while being treated with oral risperidone. Patients were excluded if they had: been treated with clozapine or a long-acting injectable antipsychotic during the preceding 3 months; significant medical illness; tardive dyskinesia; neuroleptic malignant syndrome; high risk for AEs or self-harm; substance dependence over the past 6 months; or known hypersensitivity to paliperidone ER or risperidone.

Treatment

Paliperidone ER was administered as flexible dosing from 3 to 12 mg/day, with a recommended dose of 6 mg/day. Paliperidone ER was initiated using an effective dose without titration when possible. Patients were prospectively treated and followed for up to 6 months or until early discontinuation. All previous antipsychotics used for the treatment of schizophrenia were to be discontinued or tapered off. Antipsychotics (e.g., low potency) and other psychotropic medication administered prior to enrollment for conditions other than schizophrenia, for example sleep induction or sedation, could be continued if the medication was maintained at a stable dose.

Outcome measures

Efficacy assessments

The primary efficacy outcome was based on the main reason for transitioning to paliperidone ER. Among patients switching for the main reason of lack of efficacy with oral risperidone, the primary efficacy outcome was defined as ≥20% improvement in PANSS total score from baseline to end point, as specified in the study protocol. Patients switching for main reasons other than lack of efficacy had a primary efficacy outcome of non-inferiority compared with previous risperidone treatment. Non-inferiority was defined by a difference of ≤5 points in mean end point change in PANSS total score versus baseline, as specified in the study protocol. Additional efficacy measures were assessed at baseline and at treatment week 26 (or end point), including: PANSS total, subscale, and Marder factor scores; CGI-S score; and Personal and Social Performance (PSP) score. Patient satisfaction with previous treatment with risperidone at baseline and with paliperidone ER was assessed using a categorical 5-point scale: very poor (1); poor (2); moderate (3); good (4); or very good (5). Sleep quality and daytime drowsiness over the previous 7 days were recorded at each assessment using an 11-point categorical scale (sleep: 0 = "very badly" to 10 = "very well"; daytime drowsiness: 0 = "not at all" to 10 = "all the time").

Safety & tolerability

Treatment-emergent AEs (TEAEs) were recorded throughout the study. Extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS), with measurements obtained at baseline and at treatment weeks 4, 8, 13, and 26 (or end point). Body weight was recorded at baseline and at treatment weeks 13 and 26 (or end point).

Data analysis

Efficacy and safety analyses were conducted on all patients who received at least one dose of study medication (intent-to-treat population) with at least one post-baseline efficacy or safety measurement (intent-to-treat population for efficacy or for safety). Patient demographics, efficacy, treatment satisfaction, and safety parameters were evaluated using descriptive statistics. The primary efficacy outcome was assessed by comparing baseline to end point, last observation carried forward. For patients switching for the main reason of lack of efficacy with oral risperidone, 95% CIs were estimated for treatment response. For patients switching for other reasons, non-inferiority was evaluated using the Schuirmann 1-sided test ($\alpha = 0.025$) [20]. Within-group changes versus baseline were evaluated using the 2-tailed Wilcoxon signed-rank test ($\alpha = 0.05$). Predictor analyses were performed to determine predictors for treatment response and mode paliperidone ER dose, using a stepwise logistic regression evaluating clinical variables. The end point for the predictor analysis was prespecified and more stringent than the primary and secondary clinical end points used in the study, in line with data presented, for example, by Leucht *et al.* [21]. The clinical end points used represent the ones most frequently described in the literature, which allows the data to be put into perspective. Treatment response was defined as a decrease of ≥20% in PANSS total score from baseline to end point [22–24], with an additional CGI-S score improvement of at least 1 to reflect at least minimum improvement in disease severity of 1 point [25].

Results

Patients

A total of 709 patients were screened, with 694 patients enrolled and treated with paliperidone ER (Figure 1), of whom 25.9% discontinued early while 74.1% completed the trial. The number of patients per site and country is detailed in an online Supplementary File (please see online at http://www.futuremedicine.com). Patients were predominantly male, with paranoid schizophrenia. Most had been enrolled because of a main reason of lack of efficacy (52.7%) or lack of tolerability (25.6%) with prior oral risperidone treatment

(Table 1). Among patients switching due to a main reason of lack of tolerability, the most commonly cited AEs with oral risperidone resulting in switching to paliperidone ER were weight increase (n = 32), extrapyramidal disorder (n = 24), somnolence (n = 18), fatigue (n = 14), and akathisia (n = 12). Mean last risperidone daily dose before enrollment was 4.3 ± 2.3 mg, with a wide range of 1–20 mg/day. Mean last risperidone dose at baseline was lowest among patients switching for a main reason of lack of compliance (3.9 ± 1.7 mg/day) and highest for patients switching due to lack of efficacy (4.6 ± 2.5 mg/day). Last risperidone dose for patients completing the 6-month study was ≥4 mg/day in 315 patients (61.3%), and 55 patients (10.7%) were taking at least 8 mg/day. A minority of patients (n = 12) had discontinued previous risperidone prior to enrollment and were using no antipsychotic medication at baseline.

The mean initial paliperidone ER dose was 5.3 ± 2.1 mg/day, with a mean mode dose of 7.1 ± 2.9 mg/day. Change in dose over time is shown in Figure 2. At end point, 42.4% of patients were taking paliperidone ER 9–12 mg/day. Paliperidone ER dosing was comparable for patients switching for reasons other than lack of efficacy but somewhat higher for patients switching for the reason of lack of efficacy. For example, among patients who had switched due to a main reason of lack of efficacy, 49.4% were treated with 9–12 mg paliperidone ER daily at end point, which was only 32.0% for those switching for a main reason of lack of tolerability. Paliperidone ER last dose was higher among those patients being treated with higher doses of risperidone before enrollment. Among study completers, mean risperidone daily dose before enrollment was 2.8 ± 1.2 mg for patients treated with paliperidone ER 3 mg as their last dose, 3.9 ± 2.0 mg risperidone for 6 mg paliperidone ER last dose, 4.6 ± 1.9 mg risperidone for 9 mg paliperidone ER, and 6.2 ± 2.7 mg risperidone for 12 mg paliperidone ER. Of completers receiving ≤3 mg/day of risperidone before enrollment, end point paliperidone ER dose was 3 mg/day for 32.8%, 6 mg/day for 43.9%, 9 mg/day for 19.2%, and 12 mg/day for 4.0%. For completers treated with risperidone >3 mg/day before enrollment, end point paliperidone ER dose was 3 mg/day for 9.5%, 6 mg/day for 35.4%, 9 mg/day for 29.4%, and 12 mg/day for 25.6%. Mean duration of paliperidone ER exposure was 154.2 ± 55.2 days, with an increase in dosing during the trial occurring for 395 patients (56.9%) and a decrease for 113 patients (16.3%).

Efficacy

The numbers of patients at baseline, week 4, week 8, week 13, week 26, and end point were 694, 669, 625, 590, 538, and 679, respectively. Efficacy data were available for 678 patients: 359 of the 366 patients switching due to a main reason of lack of efficacy, and 319 of the

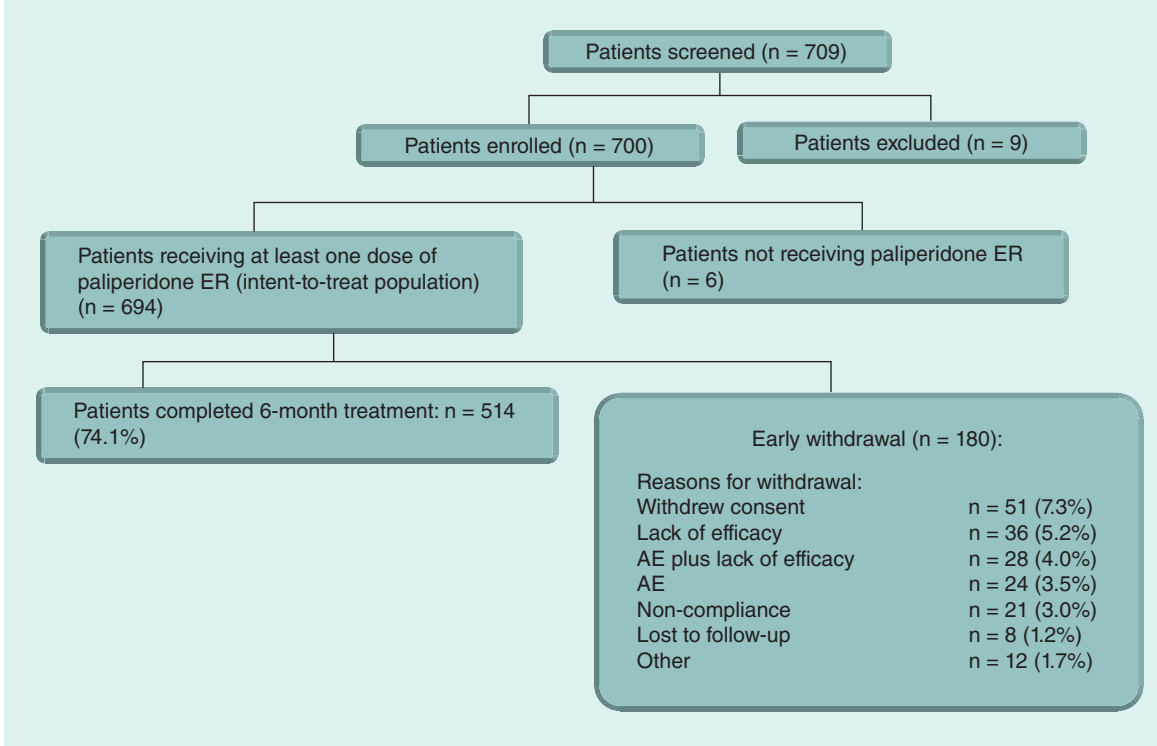

Figure 1. Patient disposition.
AE: Adverse event; ER: Extended release.

Table 1. Baseline characteristics (n = 694).	
Characteristics	
Sex, n (%):	
– Male	411 (59.2)
– Female	283 (40.8)
Age, years, mean ± SD	40.0 ± 12.8
Duration since diagnosis of schizophrenia, years, mean ± SD	9.4 ± 9.5
Schizophrenia diagnosis, n (%):	
– Paranoid	519 (74.8)
– Undifferentiated	78 (11.2)
– Residual	55 (7.9)
– Disorganized	36 (5.2)
– Catatonic/other	6 (0.9)
Main reason for switching from risperidone, n (%):	
– Lack of efficacy	366 (52.7)
– Lack of tolerability	178 (25.6)
– Lack of compliance	82 (11.8)
– Other	68 (9.8)
BMI, kg/m^2, mean ± SD	27.5 ± 5.5

BMI: Body mass index; SD: Standard deviation.

328 patients switching for main reasons other than lack of efficacy. For the primary efficacy outcome for patients transitioned due to the main reason of lack of efficacy (n = 359), 61.8% of patients (95% CI: 56.6–66.9%) showed an improvement in PANSS total score ≥20% from baseline to end point. The mean change

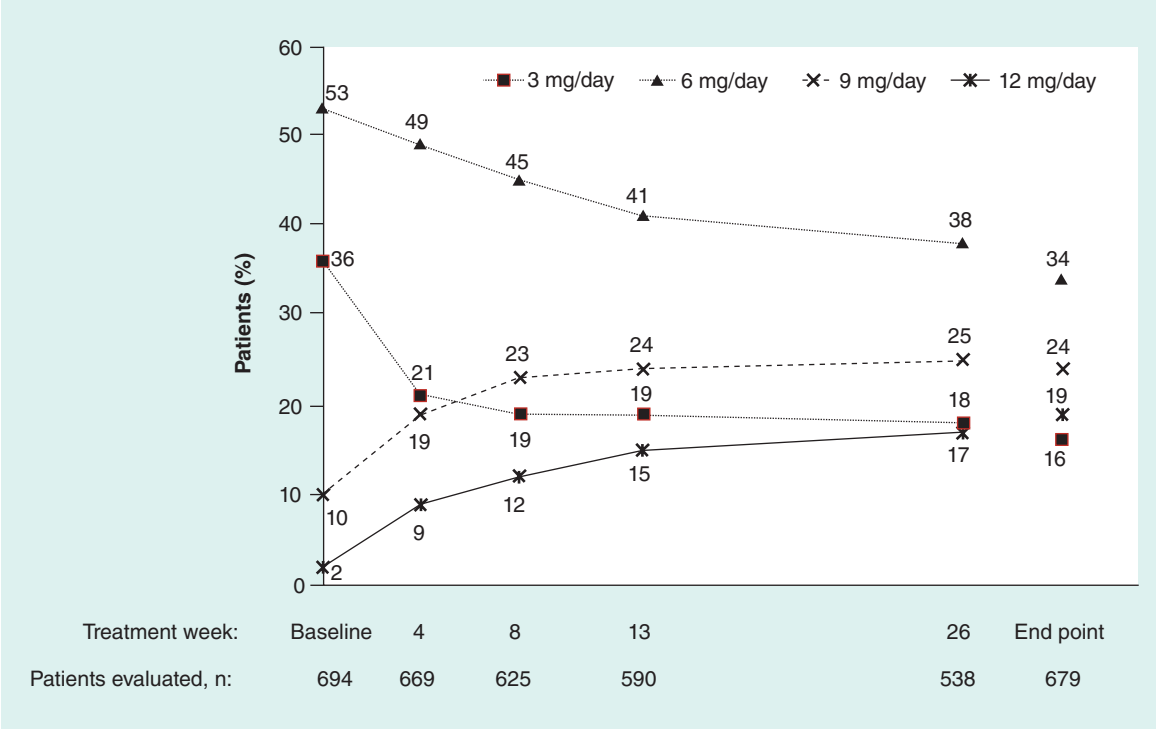

Figure 2. Paliperidone extended-release (ER) dose over time. The x-axis reflects the different between-visit time intervals.

in PANSS total score was -14.4 ± 20.2 for the lack of efficacy group. Among patients switching for main reasons other than lack of efficacy, the primary efficacy outcome of mean change in PANSS total score at end point was: lack of tolerability (n = 175): -7.6 ± 17.0; lack of compliance (n = 76): -19.6 ± 20.3; and other (n = 68): -12.0 ± 16.8. Schuirmann's 1-sided test confirmed non-inferiority to within the specified equivalence bounds for each group ($p < 0.0001$). Even more, the negative values of the changes in PANSS total score for each subgroup of patients switched for reasons other than lack of efficacy (lack of tolerability, lack of compliance, and other) indicate that patients improved from baseline to end point. These improvements were statistically significant within each subgroup (all subgroups $p < 0.0001$, Wilcoxon signed-rank test), as was the case for the subgroup of patients that switched for the main reason of lack of efficacy (-14.4 [20.2]; $p < 0.0001$).

Overall, across all patients, clinically relevant and statistically significant improvements were observed for PANSS total, PANSS subscale, and Marder factor scores (Table 2; $p < 0.0001$). The percentage of patients in CGI-S categories at baseline and end point, respectively, were 28.3 and 52.5% for mildly ill or less, 45.3 and 28.5% for moderately ill, and 26.4 and 19.0% for markedly to most extremely ill. CGI-S category improved for 47.9% of patients, remained the same for 38.6% of patients, and worsened for 13.4% of patients. Among patients who had been classified as markedly to most severely ill at baseline (n = 179), 62.6% improved to a less severe illness category at end point. The percentage of patients with PSP-defined mild functional impairment more than doubled from baseline to end point (16.5% to 36.6%, respectively).

With previous oral risperidone, treatment satisfaction was rated "good to very good" for 24.1% of patients, "moderate" for 51.4%, and "poor to very poor" for 24.5%. Treatment satisfaction with paliperidone ER at end point was rated "good to very good" for 71.2% of patients, "moderate" for 16.0%, and "poor to very poor" for 12.7%.

Statistically significant and clinically relevant improvements were seen from baseline to end point, respectively, for sleep quality (0.5 ± 2.8; $p < 0.0001$) and daytime drowsiness (-1.2 ± 3.0; $p < 0.0001$).

Predictor analyses

Using the response definition of a decrease in PANSS total score from baseline to end point of ≥20% plus a decrease in CGI-S of ≥1 point, 274 of the 678 patients with evaluable data were considered to be treatment responders (40.4%). Statistically significant predictors of response (Table 3) were baseline CGI-S score, lack of compliance as main reason for switching, diagnosis of residual schizophrenia, and diagnosis of disorganized schizophrenia. Patients with a higher baseline CGI-S score, lack of compliance as main reason for switching, diagnosis other than residual schizophrenia, and diagnosis of disorganized schizophrenia were more likely to respond.

Statistically significant predictors of paliperidone ER mode dose (Table 3) were age, baseline body mass index (BMI), last daily dose of oral risperidone before switching, diagnosis of disorganized schizophrenia, and baseline PANSS total score. Patients with a lower age, a higher BMI, a higher last daily dose of oral risperidone, a diagnosis other than disorganized schizophrenia, and a higher baseline PANSS total score at baseline were more likely to have a higher paliperidone ER mode dose.

Safety & tolerability

Paliperidone ER was generally well tolerated (Table 4). TEAEs were usually mild or moderate in intensity (88.7%). AEs most commonly cited for resulting in early treatment discontinuation were psychotic disorder symptoms (n = 9; 1.3% of patients), schizophrenia symptoms (n = 6; 0.9%), and agitation (n = 4; 0.6%). Extrapyramidal symptoms improved significantly at each assessment and end point ($p < 0.0001$; Figure 3). Changes in ESRS subscale scores from baseline to end point were most substantial for Parkinsonism (-1.3 ± 3.3; $p < 0.0001$) and hypokinesia (-0.9 ± 2.4; $p < 0.0001$).

Baseline and end point body weight were recorded for 644 patients. Mean baseline weight was 80.7 ± 17.7 kg. Weight increased by 0.1 ± 3.6 kg (95% CI: -0.2 to 0.4 kg) at week 13, 0.5 ± 4.5 kg (95% CI: 0.2–0.9 kg) at week 26, and 0.4 ± 4.3 kg (95% CI: 0.1–0.7 kg) at end point. Increases were statistically significant at week 26 ($p = 0.0012$) and end point ($p = 0.0071$), although neither change was considered clinically relevant. A clinically relevant weight increase from baseline (≥7%) occurred in 58 patients (9.0%).

At baseline, a total of 38 potentially prolactin-related AEs were reported in 36 (5.2%) patients: amenorrhea (n = 13); sexual dysfunction (n = 8); erectile dysfunction (n = 7); galactorrhea (n = 3); decreased libido/loss of libido (n = 3); ejaculation failure (n = 2); dysmenorrhea (n = 1); gynecomastia (n = 1). Hyperprolactineamia or increased blood serum prolactin levels were reported in 17 patients (2.4%) at baseline.

During the study, a total of 34 potentially prolactin-related TEAEs were reported in 30 patients (4.3%): amenorrhea, galactorrhea, and erectile dysfunction (n = 7 each); libido disorder/decreased libido/anorgasmia (n = 6); and sexual dysfunction and irregular menstruation/menstrual disorder (n = 2 each). In 16

Table 2. Mean PANSS scores at baseline and end point (n = 678).

PANSS score ± SD	Baseline	End point
Total	78.6 ± 20.5	65.6 ± 22.5
Subscale:		
– Positive	16.9 ± 6.1	14.0 ± 6.3
– Negative	22.2 ± 6.4	18.4 ± 6.7
– General psychopathology	39.5 ± 11.1	33.2 ± 11.7
Marder factors:		
– Positive	21.3 ± 7.1	17.6 ± 7.3
– Negative	21.5 ± 6.3	17.5 ± 6.4
– Disorganized thoughts	17.9 ± 5.4	15.1 ± 5.5
– Uncontrolled hostility/excitement	7.6 ± 3.4	7.0 ± 3.6
– Anxiety/depression	10.3 ± 3.8	8.4 ± 3.6

All improvements were statistically significant: $p < 0.0001$.
PANSS: Positive and Negative Syndrome Scale; SD: Standard deviation.

patients (2.3%), elevated serum prolactin levels were reported. Anti-Parkinson medication was received by 114 patients (16.4%) at baseline and 81 patients (11.9%) at end point.

Discussion

Paliperidone ER is well tolerated and effective in patients with non-acute schizophrenia previously unsuccessfully treated with oral risperidone. Among patients transitioned to paliperidone ER for the main reason of lack of efficacy with oral risperidone treatment, more than half of the patients showed a clinically relevant improvement in clinical symptoms. Previous reports have shown significant improvements in patients with acute schizophrenia treated with paliperidone ER. For example, data pooled from three 6-week studies showed more improvement in PANSS total scores among patients treated with paliperidone ER when compared with patients who received placebo [11]. The magnitude of the improvement observed for the entire population of patients in the current study was comparable to previously published studies [11,12]. The current data expand upon these earlier reports by showing clinically meaningful and statistically significant reductions in clinical symptoms among patients with non-acute but symptomatic schizophrenia treated

Table 3. Statistically significant clinical predictors identified through stepwise logistic regression†.

Model	Odds ratio	95% CI	χ^2	p-value
Treatment response‡:				
– Baseline CGI-S	1.845	1.445–2.355	24.1838	<0.001
– Main reason for switching was lack of compliance, yes vs no	2.460	1.420–4.262	10.3102	<0.01
– Residual schizophrenia diagnosis vs other diagnoses, yes vs no	0.360	0.174–0.742	7.6639	<0.01
– Disorganized schizophrenia diagnosis vs other diagnoses, yes vs no	2.448	1.140–5.254	5.2770	<0.05
Paliperidone ER mode dose:				
– Age	0.972	0.960–0.984	19.6066	<0.0001
– Last daily oral risperidone dose before switching	1.527	1.405–1.659	99.8437	<0.0001
– BMI	1.051	1.022–1.081	12.0431	0.0005
– Baseline PANSS total score	1.013	1.004–1.021	8.9777	0.0027
– Disorganized schizophrenia diagnosis, yes vs no	0.465	0.242–0.894	5.2813	0.0216

†Correction for country effect only took place for treatment response model.
‡Decrease from baseline to end point of ≥20% PANSS total score and ≥1 point CGI-S.
BMI: Body mass index; CGI-S: Clinical Global Impression Severity score; ER: Extended release; PANSS: Positive and Negative Syndrome Scale.

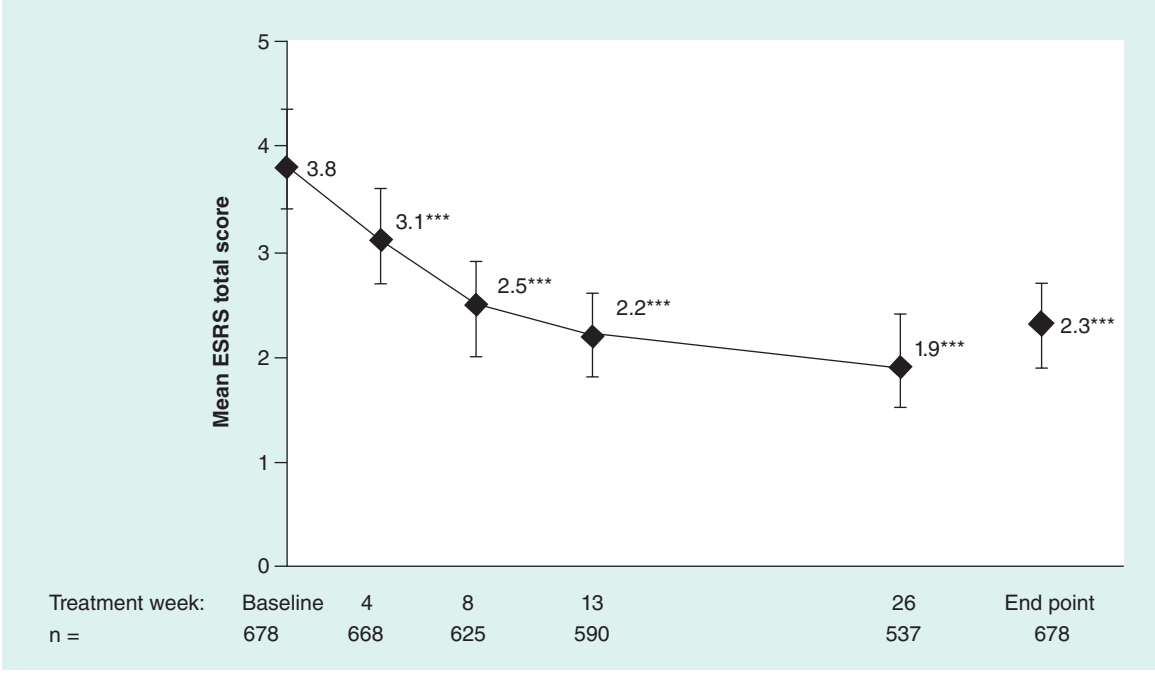

Figure 3. Mean ESRS total scores. Decreasing ESRS scores reflect improvement in extrapyramidal symptoms. The x-axis reflects the different between-visit time intervals. Improvement versus baseline was statistically significant from week 4 onwards.
***$p < 0.0001$.
ESRS: Extrapyramidal Symptom Rating Scale.

with paliperidone ER, even among patients switching to paliperidone ER for main reasons other than lack of efficacy with previous oral risperidone. Relevant improvements were also seen for disease severity and patient personal and social functioning. These data additionally support those from a small study by Caval-

Table 4. Treatment-emergent adverse events (n = 694).

TEAE	n (%)
Any TEAE	391 (56.3)
Serious TEAEs[†]	68 (9.8)
TEAEs causally related to paliperidone ER	239 (34.4)
TEAEs occurring in ≥5% of patients:	
– Insomnia	61 (8.8)
– Anxiety	51 (7.3)
Severity of TEAEs[‡]:	
– Mild	446 (48.1)
– Moderate	377 (40.6)
– Severe	105 (11.3)
Action taken due to TEAE[‡]:	
– None	715 (77.0)
– Dose adjustment	138 (14.9)
– Temporary stop	5 (0.5)
– Permanent discontinuation	70 (7.5)

[†]Most commonly, psychotic disorder (2.6%) and schizophrenia (2.0%).
[‡]Based on number of TEAEs (n = 928).
ER: Extended release; TEAE: Treatment-emergent adverse event.

laro *et al.*, in which 31 patients with schizophrenia who were poor responders to oral risperidone (average dose 5.7 mg/day) were switched to paliperidone ER (average dose 9.1 mg/day) and prospectively treated for 12 weeks [10]. At end point, 27% of previous risperidone non-responders were rated as much improved using the CGI-Schizophrenia scale, a reliable measure of symptom severity and treatment response in schizophrenia [26]. The clinical significance of the improvement in efficacy (mean change in PANSS score) for the patients switched due to other reasons was of particular interest, given that these patients already had achieved a meaningful response with previous oral risperidone. The improvement observed among patients switched due to lack of efficacy could be due to other factors (e.g., regression to the mean) that are less likely in the other reasons group.

Patients with a higher baseline CGI-S score, lack of compliance as main reason for switching, diagnosis other than residual schizophrenia, and diagnosis of disorganized schizophrenia were more likely to respond to treatment. Patients with a lower age, a higher BMI, a higher last daily dose of oral risperidone prior to switching, a diagnosis other than disorganized schizophrenia, and a higher baseline PANSS total score were more likely to have a higher paliperidone ER mode dose.

Switching to paliperidone ER was generally well tolerated and associated with clinically relevant improvements in extrapyramidal symptoms, sleep quality, and daytime drowsiness. Mean body weight change from baseline to end point was small (0.4 ± 4.3 kg). Previous studies have shown that body weight increased with risperidone treatment [27] and that weight change with risperidone was more likely to occur among people who are initially underweight or of normal weight [28]. Consequently, if patients in the current study had already gained weight with previous risperidone treatment, they may have been less likely to subsequently gain weight after switching to paliperidone ER. A comparison among short-term clinical trials and a meta-analysis showed similar or numerically lower weight gain with paliperidone ER compared with oral risperidone [5,6].

A number of limitations should be kept in mind when considering the findings of this analysis. A relevant limitation of this study is that it is an uncontrolled, single-arm study in patients in whom oral risperidone failed, who improved when switched to paliperidone ER. The possibility cannot be ruled out that the complementary trial (i.e., patients in whom paliperidone ER failed, who switched to oral risperidone) would also show improvement. This study was not a direct head-to-head comparison of treatment with risperidone and paliperidone ER and was not designed to provide information about the comparative efficacy of oral risperidone (or any other antipsychotic) and paliperidone ER; hence, it provides no evidence that paliperidone ER is equivalent or superior to other drugs that could be considered. However, the findings of this analysis do suggest that paliperidone ER might be an appropriate choice in patients who do not respond to or tolerate oral risperidone. Previously published data have shown that, for different reasons, doctors choose to switch medications rather than advance an antipsychotic to a higher dose [29,30]. However, in the current study, previous oral risperidone doses were relatively high, with 61% of patients receiving >4 mg/day and 11% receiving ≥8 mg/day; thus, the likelihood of successfully increasing the risperidone dose may have been limited, particularly since tolerability may have become a relevant factor. With regard to methodology, in a multicenter approach such as the one used in this study, there is a chance that study management is different across centers, particularly regarding patient recruitment, patient management, and scoring. However, many large pragmatic studies (e.g., Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE] [13], European First Episode Schizophrenia Trial [EUFEST] [31]) and regulatory studies are conducted in multiple sites, countries, and even continents, so all are subject to similar limitations.

Conclusion

Flexibly dosed paliperidone ER treatment over 6 months was well tolerated and associated with meaningful clinical response in patients with non-acute schizophrenia who had been previously unsuccessfully treated with oral risperidone. These data expand on previously published randomized controlled clinical trials showing short- and long-term benefits with paliperidone ER [11,12,32] by demonstrating efficacy in non-acute patients treated with flexible doses of paliperidone ER in a more naturalistic and real-world setting.

Future perspective

Within the next 5–10 years, new treatments for schizophrenia are expected, in particular for negative and cognitive symptoms, presumably as adjunctive treatment to established antipsychotics. A better understanding of the differences between antipsychotics, including benefits and downsides of switching patients from one medication to another, taking into consideration both pharmacokinetic and pharmacodynamic properties, will help to further individualize and optimize the pharmacological treatment of patients with schizophrenia.

Financial & competing interests disclosure

This study was funded by Janssen Pharmaceutical Companies of Johnson & Johnson in EMEA. D Naber has participated in advisory boards of AstraZeneca, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, and Servier. He received speaker fees from AstraZeneca,

Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka. J Peuskens has received speaker's honoraria and research support from and was part of advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer, and Sanofi Synthélabo. B Millet consulted for AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Medtronics, and Syneika. He received grants from AstraZeneca, Lilly, Medtronics, and Servier. He has also received speaker fees from AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Lundbeck, Medtronics, Otsuka, and Servier. He is a shareholder of Syneika. R Cavallaro has received fees for consultancy, for participation on advisory boards from Janssen, and as a speaker from Janssen and Pfizer. MA Franco has received speaker fees from Janssen, Lilly, Bristol-Myers Squibb, Otsuka, and Servier. He has been involved in clinical trials promoted by Janssen, Lilly, AstraZeneca, Servier, Lundbeck, Pfizer, Organon, Novartis, Roche, Otsuka, and Bristol-Myers Squibb. M Lahaye is a member of the Medical Affairs EMEA and is employed by Janssen-Cilag BV, The Netherlands. A Schreiner is a full-time employee of Janssen-Cilag, Germany, and a shareholder of Johnson & Johnson. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing and editorial support was provided by Pim Dekker, PhD, from Excerpta Medica, which was funded by Janssen Pharmaceutical Companies of Johnson & Johnson in EMEA.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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