

# Effects of paliperidone extended release on hostility among Thai patients with schizophrenia

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**Objective:** This open-label prospective study investigated the effects of paliperidone extended release (ER) on hostility in Thai patients with schizophrenia.

**Background:** Patients diagnosed with schizophrenia may be hostile or exhibit aggressive behavior, which can occasion their admission to psychiatric hospital. Antipsychotic medications are often used to treat hostility and aggression in such patients. Paliperidone ER is effective and well tolerated in the treatment of schizophrenia. However, there are no data available for paliperidone ER with regard to its efficacy on hostility and aggression among Thai patients. This study was a part of the PERFECT study, a 6-month, open-label, multicenter, multicountry, prospective trial to explore the safety, efficacy, and functionality of paliperidone ER tablets. The current study included only the data obtained from Thai participants.

**Materials and methods:** Flexible dosing of paliperidone ER in a range of 3–12 mg/day was used, allowing investigators to adjust the dosage of each subject individually. The 199 Thai patients had a stable Clinical Global Impression – severity score before enrollment. Demographic data were collected at enrollment, and assessments took place at 1, 2, 3, and 6 months postbaseline. The Positive and Negative Syndrome Scale (PANSS) and Personal and Social Performance (PSP) scale were used to evaluate efficacy. In this analysis, we report the findings for the specific PANSS factor P7 (hostility) and the PSP subscale disturbing and aggressive behavior. Data were analyzed using paired *t*-test method to investigate changes in mean PANSS and PSP total and subscale scores. The significance level was set at  $P < 0.05$ .

**Results:** From a total of 199 Thai patients, 148 patients (74.4%) participated in all visits. There was a significant reduction in mean scores for all total PANSS measures from 1 month onward compared with baseline, as well as ongoing significant reductions in scores from visit to visit. There was a significant reduction in mean hostility score at 2 months ( $P < 0.05$ ), 3 months ( $P < 0.05$ ), and 6 months ( $P < 0.01$ ) ( $n = 148$ ). For the PSP scale, there was a significant across-the-board reduction of mean scores from 3 months onward, including in the disturbing and aggressive behavior subscale ( $P < 0.001$ ) ( $n = 148$ ).

**Conclusion:** Switching from previously unsuccessful antipsychotic treatments to paliperidone ER may be a useful option to reduce hostility and disturbing behavior in patients with schizophrenia. This study in Thai patients is in line with findings in other countries and cultures concerning the management of hostility in patients with schizophrenia.

**Keywords:** schizophrenia, hostility, aggression, disturbing behavior, paliperidone ER

## Background

Antipsychotic medication forms the mainstay of treatment for schizophrenia. Patients diagnosed with schizophrenia are occasionally hostile or may exhibit violent behavior, and such behavior is frequently the reason for their admission to psychiatric units, where they sometimes require seclusion or restraint.<sup>1,2</sup> Various antipsychotic medications, such as clozapine, olanzapine, haloperidol, and risperidone, have been investigated for

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their efficacy in treating hostility and aggression in patients with schizophrenia.<sup>1,3</sup> Paliperidone (9-OH-risperidone) is the major active metabolite of risperidone, and is approved for use as a long-term antipsychotic treatment for schizophrenia.<sup>4</sup> A paliperidone extended-release (ER) formulation has been developed that has been shown to be effective and well tolerated in the treatment of schizophrenia.<sup>5</sup> A number of studies have assessed paliperidone in the context of hostility and aggressive behavior.<sup>6–9</sup> However, there are no data available for paliperidone ER with regard to its efficacy on hostility and aggression among Thai patients.

The socioeconomic, cultural, political, linguistic, health care, and reimbursement systems in Southeast Asian countries are diverse, as well as being different in comparison with other parts of the world.<sup>10</sup> To investigate the efficacy of paliperidone ER in Southeast Asian patients with schizophrenia, the PERFECT study was conducted from June 2007 to April 2009.<sup>11,12</sup> Derived from the PERFECT study, these findings describe the efficacy of paliperidone ER on hostility among Thai patients with schizophrenia who had switched from other antipsychotic medications because of lack of efficacy, poor tolerability, or poor compliance.

## Materials and methods

### Study design and assessments

The PERFECT study was an open-label prospective trial to explore the tolerability, safety, and efficacy of flexibly dosed paliperidone ER in subjects with schizophrenia.<sup>11,12</sup> Flexible dosing of paliperidone ER in a range of 3–12 mg/day was used, allowing investigators to adjust the dosage of each subject individually. The recommended dose of paliperidone is 6 mg once daily in the morning, but may start at higher/lower doses based on clinical judgment. Throughout the study, dose adjustment was done at the investigators' discretion based on clinical response. Demographic data was collected at enrollment together with baseline efficacy data. Efficacy assessments took place at 1, 2, 3, and 6 months postbaseline. Concomitant medications (including benzodiazepines and anticholinergics for treatment of extrapyramidal symptoms, but excluding concomitant antipsychotics) could be administered as long as they were duly documented. Adverse event data were collected throughout the study as the events emerged, and safety assessments were carried out at each scheduled visit. Efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS),<sup>13</sup> Marder score,<sup>14</sup> Personal and Social Performance (PSP) scale,<sup>15</sup> and the Clinical Global Impression – severity (CGI-S) scale.<sup>16</sup> In this analysis, we focus on the findings for the specific PANSS factor P7 (hostility) and the PSP subscale disturbing and

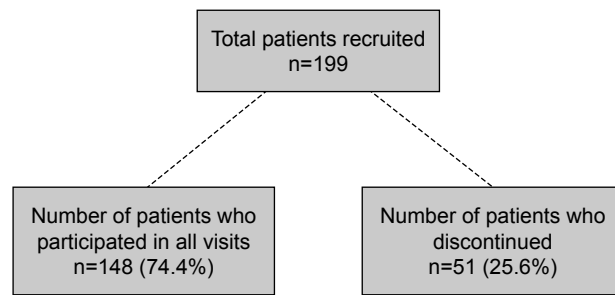
aggressive behavior. PANSS evaluations took place at every scheduled visit, while PSP evaluations were carried out at baseline and after 3 and 6 months.

## Subjects

This study was a part of the PERFECT study, a 6-month, open-label, multicenter, multicountry, prospective trial to explore the safety, efficacy, and functionality of paliperidone ER tablets. The current study included only the data obtained from the 199 Thai participants. In the overall study, 984 patients meeting the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria<sup>17</sup> for schizophrenia who had switched their antipsychotics because of lack of efficacy, tolerability, or compliance were recruited from 61 sites in five countries in Southeast Asia (Philippines, Thailand, Hong Kong, Singapore, and Malaysia). As part of the inclusion criteria, these patients were required to be in a nonacute stage, defined as being established on antipsychotic medication used for the treatment of schizophrenia, and with CGI-S change  $\leq 1$  in the 4 weeks prior to enrollment. Patients had been given an adequate dose of an appropriate oral atypical antipsychotic for an adequate period of time prior to enrollment, but the previous treatment was considered unsuccessful, due to one or more of the following reasons: lack of efficacy, lack of tolerability or safety, lack of compliance, and/or “other”. Subjects who were taking any oral atypical antipsychotic medication were transitioned to an effective dose of paliperidone ER without the need for titration. Subjects were either cross-tapered or directly switched from their previous atypical antipsychotic medication. The switching strategy depended on investigator judgment. The 199 Thai patients whose results are reported here were recruited from 16 sites in Thailand. All patients who volunteered to take part in the study read and signed the written informed consent form for participation before initiation of any trial-related procedures. The study protocol and related materials were reviewed and approved by the Joint Research Ethical Committee (central ethical committee) and each ethical committee participating site: Maharaj Nakorn Chiangmai; Suansaranrom; Khon Kaen Rajanagarindra; Queen Sawang Wadhana Memorial; Rayong; King Chulalongkorn Memorial; Siriraj; Somdejchaophraya Institute of Psychiatry; Suanprung; Ramathibodi; Buddhachinaraj; Srinakarind Khon Kaen University; Prasimahabodi; Prince of Songkhla University; Srithanya; Chachoengsao.

## Data analysis

A paired *t*-test was applied for comparison of the efficacy results at the various time points against the baseline values to investigate statistical significance. For the analyses, the



**Figure 1** Disposition of subjects.

level of significance was set at  $P < 0.05$ . SPSS 18.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical procedures.

## Results

Among the 199 Thai patients who entered the study, 106 (53.3%) were male and 93 (46.7%) female. Of the 199 enrolled patients at the baseline visit, 175 (87.9%) participated in the second visit (after 1 month), 164 (82.4%) participated in the third visit (after 2 months), 155 (77.9%) participated in the fourth visit (after 3 months), and 188 (94.5%) took part in the end-of-study evaluation (after 6 months). The data were analyzed from 148 patients (74.4%) who had recorded P7 in all visits completely, and these patients comprised the group whose results are analyzed here. Stratified by age, 88 patients (59.5%) were aged 20–40 years, 47 patients (31.8%) were 41–60 years old, eight patients (5.4%) were aged over 60 years, and five patients (3.4%) were under 20 years old. Figure 1 shows the disposition of subjects. Table 1 shows patients' demographic and clinical data at baseline for the group who participated in all visits ( $n=148$ ).

## Efficacy

Table 2 shows the effects of paliperidone ER treatment on the positive, negative, and general psychopathology scales of the

**Table 1** Demographic and clinical data at baseline

Characteristic	n=148
Age, years	
Mean $\pm$ SD	37.9 $\pm$ 12.2
Range	18–79
Sex, n (%)	
Male	77 (52)
Female	71 (48)
Baseline PANSS, mean $\pm$ SD	
Overall PANSS score	56.6 $\pm$ 19.9
Hostility (P7)	1.43 $\pm$ 0.88
Baseline PSP scale, mean $\pm$ SD	
Overall PSP score	67.5 $\pm$ 17.7
Disturbing and aggressive behavior	1.68 $\pm$ 0.95
Baseline CGI-S, mean $\pm$ SD	3.37 $\pm$ 1.19

**Abbreviations:** SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance; CGI-S, Clinical Global Impression – severity.

**Table 2** PANSS positive scale, negative scale, general psychopathology scale, and overall score at baseline, 1 month, 2 months, 3 months, and 6 months

	Baseline			1-month visit			2-month visit			3-month visit			6-month visit		
	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
Positive scale	13.03	6.075	0.499	10.99 <sup>v1***</sup>	5.417	0.445	10.85 <sup>v1***</sup>	5.12	0.402	9.81 <sup>v1***v2***v3***</sup>	4.888	0.32	10.22 <sup>v1***</sup>	5.309	0.436
Negative scale	15.22	7.402	0.608	12.34 <sup>v1***</sup>	5.846	0.481	11.51 <sup>v1***v2***</sup>	5.12	0.421	10.82 <sup>v1***v2***v3***</sup>	4.811	0.395	11.06 <sup>v1***v2***</sup>	5.924	0.487
General psychopathology scale	28.3	9.908	0.814	23.64 <sup>v1***</sup>	8.263	0.679	22.3 <sup>v1***v2***</sup>	7.243	0.595	21.63 <sup>v1***v2***v3***</sup>	6.844	0.563	21.78 <sup>v1***v2***</sup>	8.829	0.726
PANSS score	56.55	19.849	1.632	46.97 <sup>v1***</sup>	16.989	1.396	44.66 <sup>v1***v2***</sup>	15.046	1.237	42.26 <sup>v1***v2***v3***</sup>	13.589	1.117	43.06 <sup>v1***v2***</sup>	19.008	1.562

**Notes:** <sup>v1\*\*\*</sup> $P < 0.001$  vs baseline; <sup>v2\*\*\*</sup> $P < 0.01$  vs 1-month visit; <sup>v3\*\*\*</sup> $P < 0.05$  vs 1-month visit; <sup>v4\*\*\*</sup> $P < 0.01$  vs 2-month visit;  $n=148$ .

**Abbreviations:** SD, standard deviation; SEM, standard error of mean; PANSS, Positive and Negative Syndrome Scale.

**Table 3** Positive and Negative Syndrome Scale P7 (hostility) results

Baseline			1-month visit			2-month visit			3-month visit			6-month visit		
Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
1.43	0.881	0.072	1.34	0.923	0.076	1.23 <sup>v1*</sup>	0.64	0.053	1.24 <sup>v1*</sup>	0.587	0.048	1.24 <sup>v1**</sup>	0.706	0.058

Notes: <sup>v1\*\*</sup> $P < 0.01$  vs baseline; <sup>v1\*</sup> $P < 0.05$  vs baseline.  $n = 148$ .

Abbreviations: SD, standard deviation; SEM, standard error of mean.

PANSS, as well as the overall PANSS scores at the various time points of the study. There was a significant reduction in mean scores for all scales from 1 month onward compared with baseline, as well as ongoing significant reductions in scores from visit to visit. The data were also broken down by individual PANSS subscales, and the P7 (hostility) subscale is reported in Table 3. Compared with baseline, the results showed a significant reduction in mean  $\pm$  standard deviation (SD) for the P7 (hostility) score from  $1.43 \pm 0.881$  to  $1.23 \pm 0.64$  after 2 months ( $P < 0.05$ ),  $1.24 \pm 0.587$  after 3 months ( $P < 0.05$ ), and  $1.24 \pm 0.706$  after 6 months ( $P < 0.01$ ) ( $n = 148$ ). Table 4 shows the effects on the various PSP subscales at the different study time points. Again, there was an across-the-board reduction in mean scores from 3 months onward. For the “Disturbing and aggressive behavior” subscale, compared with baseline, mean  $\pm$  SD scores were reduced significantly after 3 months from  $1.68 \pm 0.948$  to  $1.29 \pm 0.538$  ( $P < 0.001$ ), and after 6 months the score had reduced to  $1.22 \pm 0.593$  ( $P < 0.001$ ) ( $n = 148$ ). Table 5 shows the CGI-S scale at different time points. Compared with a mean  $\pm$  SD baseline score of  $3.37 \pm 1.185$ , the scores reduced significantly to  $2.69 \pm 1.234$  after 1 month ( $P < 0.001$ ),  $2.6 \pm 1.217$  after 2 months ( $P < 0.001$ ),  $2.44 \pm 1.089$  after 3 months ( $P < 0.001$ ), and  $2.31 \pm 1.234$  after 6 months ( $P < 0.001$ ) ( $n = 148$ ). There were also significant ongoing reductions in the CGI-S score from visit to visit.

## Discussion

This study examined the efficacy of paliperidone ER on hostility and disturbing/aggressive behavior in patients with schizophrenia using the PANSS and PSP scale. In 148 Thai

patients with schizophrenia who had switched their antipsychotic medication, there was a significant reduction in mean PANSS P7 (hostility) score after 2 months ( $P < 0.05$ ), 3 months ( $P < 0.05$ ), and 6 months ( $P < 0.01$ ) compared with baseline. This goes alongside a significant reduction in mean scores for all PANSS subscales and the CGI-S scale from 1 month onward and PSP subscales (including disturbing and aggressive behavior) from 3 months onward compared with baseline, as well as ongoing significant reductions in scores from visit to visit.

While the efficacy and safety of paliperidone ER have been demonstrated in various international patient groups,<sup>5,6,8,9</sup> there are no data available for Thai patients specifically. Thailand, in common with other Southeast Asian countries, has different socioeconomic, cultural, political, linguistic, health care, and reimbursement systems compared with other parts of the world.<sup>10</sup> These results thus provide a valuable understanding of the role of paliperidone ER in the Thai context.

The results reported here may be compared with those of a 2007 European study,<sup>18</sup> in which 294 patients with schizophrenia were flexibly dosed with oral paliperidone ER 3–12 mg/day in a naturalistic setting. In that study, significant improvements in PANSS factors (including hostility), PSP, and CGI-S were observed. Baseline PANSS for uncontrolled hostility/excitement was  $10.6 \pm 3.7$ . After treatment with paliperidone ER, this reduced to  $7.5 \pm 3.4$  ( $P < 0.0001$ ). In common with many pivotal studies, subjects in the European study were treated for 6 weeks, whereas in the results reported here a 6-month treatment period was applied, which might better provide longer-term data on efficacy and tolerability in Thai

**Table 4** Personal and Social Performance scale results at baseline, 3-month visit, and 6-month visit

Personal and social performance domain	n	Baseline			3-month visit			6-month visit		
		Mean	SD	SEM	Mean	SD	SEM	Mean	SD	SEM
Socially useful activities	148	2.22	1.2	0.099	1.64 <sup>v1***</sup>	0.85	0.07	1.56 <sup>v1***</sup>	0.898	0.074
Personal and social relationships	148	2.28	1.178	0.097	1.67 <sup>v1***</sup>	0.876	0.072	1.534 <sup>v1***,v4*</sup>	0.884	0.073
Self-care	148	1.60	0.975	0.08	1.3 <sup>v1***</sup>	0.687	0.056	1.27 <sup>v1***</sup>	0.706	0.058
Disturbing and aggressive behavior	148	1.68	0.948	0.078	1.29 <sup>v1***</sup>	0.538	0.044	1.22 <sup>v1***</sup>	0.593	0.049
Overall score	148	67.52	17.665	1.452	77.82 <sup>v1***</sup>	14.218	1.169	81.6 <sup>v1***,v4***</sup>	15.499	1.274

Notes: <sup>v1\*\*\*</sup> $P < 0.001$  vs baseline; <sup>v4\*\*\*</sup> $P < 0.001$  vs 3-month visit; <sup>v4\*</sup> $P < 0.05$  vs 3-month visit.

Abbreviations: SD, standard deviation; SEM, standard error of mean.



**Table 5** Clinical Global Impression – severity score at baseline, 1 month, 2 months, 3 months, and 6 months

CGI-S	n	Mean	SD	SEM
Baseline	148	3.37	1.185	0.097
1-month visit	148	2.69 <sup>v1***</sup>	1.234	0.101
2-month visit	148	2.60 <sup>v1***</sup>	1.217	0.1
3-month visit	148	2.44 <sup>v1***,v2**</sup>	1.089	0.09
6-month visit	148	2.31 <sup>v1***,v2***,v3***</sup>	1.234	0.101

**Notes:** <sup>v1\*\*\*</sup> $P < 0.001$  vs visit 1; <sup>v2\*\*\*</sup> $P < 0.001$  vs visit 2; <sup>v2\*\*</sup> $P < 0.01$  vs visit 2; <sup>v3\*\*\*</sup> $P < 0.001$  vs visit 3.

**Abbreviations:** SD, standard deviation; SEM, standard error of mean.

patients. The patients in the European study were experiencing an acute exacerbation of schizophrenia, which may explain their relatively higher baseline PANSS score.

Limitations of this study include firstly its open-label design and lack of a comparator group. However, this reflects more accurately the clinical situation in a real-world setting, and the assessment criteria are objective, detailed, and standard in clinical trials of antipsychotic medication. Furthermore, this study permitted patients to use concomitant medications, which are often disallowed in randomized controlled trials. A second limitation is that validated psychopathological rating scales are often difficult to apply in a naturalistic setting, even though rater training was given.

## Conclusion

In summary, this study in Thai patients with schizophrenia confirms the finding that paliperidone ER is effective in treating hostility and disturbing/aggressive behavior, and as this was an open-label study with flexible dosing, it could reflect the real-life situation in typical clinical practice in Thailand.

Switching from previously unsuccessful antipsychotic treatments to paliperidone ER may be a useful option to reduce hostility and disturbing behavior in patients with schizophrenia. This study in Thai patients is in line with findings in other countries and cultures concerning the management of hostility in patients with schizophrenia.

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## Disclosure

ON is an employee of Janssen-Cilag Thailand. The other authors report no conflicts of interest in this work.

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