REVIEW ARTICLE

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Paliperidone

A Review of Clinical Trial Data and Clinical Implications

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Abstract

Paliperidone, 9-hydroxy-risperidone, is the major metabolite of the atypical antipsychotic risperidone and is available in an oral extended-release (ER) formulation. Paliperidone ER was approved for treating schizophrenia in 2006, and in 2009 it became the first atypical antipsychotic licensed for treating schizoaffective disorder.

The short-term efficacy, safety and tolerability of paliperidone ER for patients with schizophrenia were demonstrated in three pivotal 6-week, randomized, double-blind, placebo-controlled studies. Data from the long-term trial showed that paliperidone ER is also effective in preventing relapse of schizophrenia. Two randomized, placebo-controlled, short-term studies have documented the efficacy and tolerability of paliperidone ER in the treatment of schizoaffective disorder, but no long-term or maintenance study has been conducted in patients with schizoaffective disorder. Two 3-week, randomized, double-blind, placebo-controlled studies showed that paliperidone ER is significantly superior to placebo for treating patients with bipolar disorder, but the results were driven by certain subpopulations. Limited evidence suggests that paliperidone ER can potentially be superior to quetiapine and risperidone. However, few direct head-to-head comparisons between paliperidone ER and other antipsychotics have been conducted to confirm these results.

The distinctive pharmacological characteristics of paliperidone ER, including smooth fluctuations in plasma drug concentrations, predominantly renal excretion, low risk of causing hepatic impairment and low drug-drug interaction, might provide important clinical advantages compared with risperidone. However, certain side effects require clinical attention. The rate of extrapyramidal side effects was considerably higher than that of a placebo at doses ≥9 mg/day. The risks for orthostatic hypotension, prolongation of the corrected QT interval and hyperprolactinaemia are also concerns.

This review summarizes the currently published data on paliperidone ER for treating patients with schizophrenia, schizoaffective disorder and bipolar disorder, and suggests its appropriate use in clinical practice.

1. Introduction

Schizophrenia is a devastating illness with a chronic impact on psychological, physical, social and economic functioning.[1] Antipsychotics have long been the mainstay of treatment for schizophrenia, and they are generally divided into first-generation (typical) and second-generation (atypical) medications. Typical antipsychotics have therapeutic effects attributable to central dopamine D_2 receptor antagonism, whereas both D_2 and serotonin $5\text{-}HT_{2A}$ receptor antagonism play an important role in the action of atypical antipsychotics.[2] Atypical antipsychotics are widely considered the standard care for treating schizophrenia because these drugs have demonstrated efficacy for a broader spectrum of symptoms with a different adverse event profile compared with typical antipsychotics.[3,4] However, the insufficient efficacy and adverse effects of existing atypical antipsychotics still pose a problem in real-world clinical practice.[5,6] Therefore, additional novel antipsychotic agents are needed to enable clinicians to diversify treatment options to improve symptom control as well as to enhance acceptability and tolerability for long-term treatment.

The recently developed atypical antipsychotic paliperidone is a 9-hydroxy metabolite of its parent compound risperidone.[7] It combines the efficacy of risperidone with an osmotic controlled-release oral delivery system (OROS™) that enables the drug to be released at a controlled rate specific to the properties of 9-hydroxy risperidone. It also allows once-daily dosing and can minimize the

24-hour peak-to-trough variations at a steady-state concentration.[7] Similar to its parent compound, paliperidone was approved by the US Food and Drug Administration (FDA) for treating schizophrenia in 2006. Additionally, because it is the only atypical antipsychotic with FDA approval for treating schizoaffective disorder (2009), it provides an important addition to the range of options available for patients with schizophrenia and schizoaffective disorder.[7] Although its use in bipolar disorder is still not indicated, studies have suggested its potential benefits for treating this condition.[8-10] The results of a study evaluating its effectiveness for delaying the recurrence of symptoms of bipolar disorder are undergoing analysis.[11] This review summarizes the currently available evidence for the use of paliperidone extended release (ER) for treating schizophrenia, schizoaffective disorder and bipolar disorder.

2. Data Search

A search of the studies used the key terms 'paliperidone, 9-hydroxy-risperidone, or Invega' from the databases PubMed and MEDLINE. The studies searched were verified for publication in peer-reviewed journals. We also used reference lists from identified articles and reviews to find additional studies. No date or language constraints were utilized. Proceedings of scientific meetings were also searched for paper and poster presentations. The package label (Ortho-McNeil-Janssen Pharmaceuticals, 2011) was also included in the review.[7] Data search and verification were handled first by one of the authors (S.M.W.) and then independently reassessed by another of the authors (C.U.P.). The style of this paper is a narrative review of the role and clinical implications of paliperidone treatment for the treatment of schizophrenia and schizoaffective disorder, in which all relevant studies meeting the scope of the present review were selected based on consensus among all the authors.

3. Pharmacodynamics

Paliperidone ER is the 9-hydroxy metabolite of risperidone (9-hydroxyrisperidone). Like many other drugs used for patients with schizophrenia, the mechanism of action of paliperidone ER is still not completely understood. It is generally acknowledged that its antagonistic action towards D_2 and serotonin receptors is primarily responsible for its therapeutic effect.[12] Studies have demonstrated that paliperidone ER at a dose of 6 mg/day results in a mean striatal D_2 receptor occupancy of approximately 64%, reflecting a lower risk of causing extrapyramidal symptoms (EPS) at this dosage. The time to 50% dissociation from human cloned D_2 receptors in tissue culture cells is faster for paliperidone (60 seconds) than for risperidone (27 minutes), which may result in reduced risk for EPS.[13] The mean occupancy time of paliperidone ER in the frontal cortex and striatum is estimated to be approximately 12 hours, whereas it is 4–6 hours for risperidone, which is about 3–5 times longer than it is in plasma and in the cerebellum.[14] Paliperidone ER also has an antagonist effect at α_1- and α_2-adrenergic and H_1 histaminergic receptors, which may explain some of its side effects such as orthostatic hypotension, weight gain and sedation.[12] Paliperidone has little or no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors.

4. Pharmacokinetics

The absolute oral bioavailability of paliperidone ER is 28%, and its mean time-to-peak plasma concentration is approximately 24 hours with a terminal elimination half-life of approximately 23 hours. Steady-state plasma levels are achieved after four daily doses.[7,15] The peak-to-trough variation for paliperidone ER is 38%, whereas it is 125% for risperidone.[16] More importantly, the peak-to-trough variation in plasma levels of paliperidone ER 12 mg is much lower than that of risperidone 2 mg. Thus, an initial dosage of 6 mg is suggested without the need for initial dose titration.[17] A comparison of the pharmacokinetic data for oral paliperidone ER in healthy individuals following single and multiple doses of 3 mg and following single doses of 6, 9, 12 and 15 mg is illustrated in table I.

Protein binding of paliperidone ER is lower, averaging 74% in humans, than that of risperidone

(90.0%).[16,18] *In vitro* studies suggest that paliperidone ER does not substantially inhibit cytochrome P450 (CYP) isozymes. Although *in vitro* results suggest CYP2D6 and CYP3A4 may have a potential role in the overall elimination of paliperidone ER, *in vivo* studies indicate that these enzymes play a limited role.[16] In studies with healthy volunteers, both the potent CYP2D6 inhibitor paroxetine and the organic cation transport inhibitor trimethoprim did not show clinically important drug interactions with paliperidone ER.[19,20] However, current clinical data regarding the drug-drug interactions of paliperidone ER with other medications metabolized by CYP isoenzymes such as CYP2D6 and CYP3A4 are still limited.

Paliperidone ER has no enzyme-inducing properties.[20] However, when the once-daily dosage of paliperidone ER 6 mg was co-administered with a twice-daily dosage of carbamazepine 200 mg, the mean steady-state maximum plasma paliperidone concentration (C_{max}) and area under the plasma concentration versus time curve (AUC)[21] of paliperidone ER decreased by approximately 37%. A 35% increase in the renal clearance of paliperidone ER as a result of the induction of renal P-glycoprotein by carbamazepine may be responsible for this effect. Carbamazepine is a potent inducer of hepatic CYP3A4 and 1A2; therefore, it may lead to reduced plasma paliperidone ER concentrations.[22] In contrast, when a single dose of paliperidone 12 mg was co-administered with divalproex sodium ER 1000 mg tablets (two 500 mg tablets once daily), the C_{max} and the AUC of paliperidone ER increased by approximately 50%. Therefore, a dosage reduction of paliperidone ER should be considered when it is co-administered with valproate.[7]

The primary clearance route of paliperidone ER is renal, and hepatic metabolism has a limited role in its excretion.[7] For patients with mild renal impairment, the initial recommended dose is reduced to 3 mg/day, and the maximum recommended dose is 6 mg/day. In individuals with moderate to severe renal impairment, the initial and maximum recommended doses are 1.5 and 3 mg/day, respectively. Paliperidone ER has not been studied in patients with a creatinine clearance <10 mL/min, so use of the drug in these patients is not recommended. Thus, a dose reduction is required in patients with moderate or severe renal impairment. In a study investigating the impact of hepatic impairment on the pharmacokinetics of paliperidone ER, a single oral dose of paliperidone 1 mg was administered to individuals with moderate hepatic impairment.[23] The results showed that the unbound plasma paliperidone concentration and all other pharmacokinetic parameters were comparable to those of healthy subjects. Thus, dose adjustment is not necessary for patients with mild-to-moderate hepatic impairment.

Table I. Pharmacokinetics of oral paliperidone ER following administration of multiple 3 mg doses and single 3, 6, 9, 12 and 15 mg doses

Pharmacokinetic parameter	Dose of paliperidone ER (mg)					
	3[a]	3[b]	6[b]	9[b]	12[b]	15[b]
C_{max} (ng/mL)	10.7	4.85–5.49	10.2	14.8	19.6	26.6
t_{max} (h)	22.7	24.0	24	24	24	24
AUC_{24} (ng • h/mL)	199	67.5	NR	NR	NR	NR
AUC_{∞} (ng • h/mL)	NR	192–211	401	567	778	1014
AUC_{last} (ng • h/mL)	NR	176	368	525	720	938
$t_{½}$ (h)	28.4	20.9–23.5	23.4	22	22.1	22.3
CL/F (mL/min)	270	272–313	292	337	313	294

a Multiple doses of paliperidone ER 3 mg once daily for 7 days.

b Single dose of paliperidone ER.

AUC = area under the plasma paliperidone concentration-time curve; **AUC_{24}** = AUC from time zero to 24 h; **AUC_{∞}** = AUC from time zero to infinity; **AUC_{last}** = AUC from time zero and the last quantifiable plasma concentration measurement; **CL/F** = apparent total oral clearance; **C_{max}** = maximum plasma paliperidone concentration; **ER** = extended release; **NR** = not reported; **$t_{½}$** = terminal elimination half-life; **t_{max}** = time to reach C_{max}.

Table II. Summary of pharmacokinetic properties of paliperidone ER and risperidone

Parameter	Drug	
	Paliperidone ER	Risperidone
t_{max} (h)	24	1
Half-life (h)	23[a]	Extensive metabolizer: 3[b] Poor metabolizer: 20[b]
Presence of food	May increase paliperidone exposure	No effect
Steady-state concentrations (d)	Most: 4–5	Extensive metabolizer: 1 Poor metabolizer: 5
Absolute oral bioavailability (%)	28	70
Plasma protein binding (%)	74	90
Major elimination	Unchanged in urine Limited role for CYP2D6 and CYP3A4	Urine and faeces Extensive role for CYP2D6
Metabolism	Mainly renal	Mainly liver
Peak-to-trough plasma variation (%)	38	125

a Terminal elimination half-life (two-compartmental model).

b Half-life (one- or non-compartmental model).

CYP = cytochrome P450; **ER** = extended release; t_{max} = time to reach maximum plasma paliperidone concentration.

However, the use of paliperidone ER in patients with severe hepatic impairment has not been studied. Table II summarizes the comparative pharmacokinetic properties of paliperidone ER and risperidone.

5. Approved Indications

Paliperidone ER is indicated as monotherapy for the short-term and maintenance treatment of schizophrenia and as an adjunct to mood stabilizers and/or antidepressants for the short-term treatment of schizoaffective disorder. Presently, it is the only antipsychotic approved by the FDA for the treatment of schizoaffective disorder. Despite several studies on the use of paliperidone ER in patients with bipolar disorder, it has not yet been validated for treating any mood disorders.[8-10]

6. Clinical Efficacy

6.1 Schizophrenia

6.1.1 Short-Term Schizophrenia Clinical Trials

Three pivotal 6-week, randomized, double-blind, placebo-controlled, fixed-dose trials using olanzapine as an active internal standard formed the basis of the paliperidone ER efficacy evaluation for acute schizophrenia.[24-26] The primary outcome measure was mean change in total score on the Positive and Negative Syndrome Scale (PANSS) from baseline to treatment endpoint. Secondary outcome measures included the Personal and Social Performance (PSP) scale, Clinical Global Impression-Severity (CGI-S) and PANSS Marder factor scores. Patients received fixed doses of paliperidone ER ranging from 3 to 15 mg/day without titration. Overall, all doses showed significantly superior efficacy to placebo in each of the three trials, and the onset of effects was observed as early as day 4 of treatment.

Kane et al.[24] randomized 630 (intent-to-treat [ITT], n = 628) patients with schizophrenia and compared fixed doses of paliperidone ER 6, 9 and 12 mg/day with placebo. Olanzapine (10 mg/day) was used as an active comparator. The mean total score on the PANSS of patients in the paliperidone-ER group reflected a significantly greater improvement compared with that of members of the placebo group ($p < 0.001$ for all paliperidone-ER doses). Response rate, which was defined as >30% improvement in total PANSS scores from baseline, was also significantly higher in all paliperidone-ER groups than that in the placebo group ($p < 0.001$ for all paliperidone-ER doses). All paliperidone-ER doses were associated with significantly greater improvements in all PANSS Marder subscale and PSP scores from baseline to

endpoint than were those for members of the placebo group ($p < 0.001$ for all paliperidone-ER doses).

The efficacy of paliperidone ER was also noted in studies by Marder et al.,[25] in which 444 (ITT, n = 432) patients with schizophrenia were randomly assigned to either 6 or 12 mg/day of paliperidone ER, 10 mg/day of olanzapine, or placebo. Patients treated with both 6 and 12 mg/day of paliperidone ER showed significantly improved mean total PANSS scores in comparison with those in the placebo group (6 mg/day, $p = 0.006$; 12 mg/day, $p < 0.001$). The paliperidone-ER group also showed significantly higher clinical response rates than did those in the placebo group (6 mg/day, $p = 0.03$; 12 mg/day, $p = 0.012$). The PANSS Marder subscale scores for positive, negative and hostility excitement factors improved significantly in the paliperidone-ER 6 mg/day group relative to the placebo ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively) and 12 mg/day ($p < 0.001$, $p < 0.05$ and $p < 0.05$, respectively) groups. However, scores on the disorganized-thoughts subscale improved significantly only in response to paliperidone-ER 12 mg/day ($p < 0.001$). No significant improvement was observed in either the paliperidone-ER 6 or 12 mg/day groups on the anxiety/depression subscale. PSP scores improved significantly only in the 6 mg/day group ($p = 0.007$).

In another study by Davidson et al.,[26] 618 (ITT, n = 605) patients with schizophrenia were randomized, and fixed doses of paliperidone ER 3, 9 and 15 mg/day were compared with placebo. The mean change in total PANSS scores from baseline to endpoint was significantly greater in all paliperidone-ER groups than that in the placebo group ($p < 0.001$ for all paliperidone-ER doses). Similar trends favouring all doses of paliperidone ER over placebo were noted in the response rates ($p < 0.01$ for all paliperidone-ER doses), all PANSS Marder factors ($p < 0.01$ for all paliperidone-ER doses) and PSP scores ($p < 0.001$ for all paliperidone-ER doses). The outcome measures of these three pivotal studies are summarized in table III.

Table III. Summary of three pivotal randomized, double-blind, placebo-controlled and active-controlled, 6-week clinical trials of paliperidone ER in patients with schizophrenia

Study	Treatment (mg/day)	No. of patients[a]	PANSS total score		Response rate (% of patients)[c]	Mean change in PSP score from baseline to endpoint	Discontinuation because of TAE (% of patients)
			Baseline: mean	Change:[b] mean			
Kane et al.[24]	PAL ER 6	123	94.3	−17.9***	56***	9.1***	7
	PAL ER 9	122	93.2	−17.2***	51***	8.1***	3
	PAL ER 12	129	94.6	−23.3***	61***	11.5***	6
	OZP[d] 10	128	93.0	−19.9	52	10.3	7
	Placebo	126	94.1	−4.1	30	0.5	7
Marder et al.[25]	PAL ER 6	112	92.3	−15.7**	50*	8.8*	7
	PAL ER 12	112	94.1	−17.5***	51*	6.6	5
	OZP[d] 10	110	94.9	−18.4	46	7.6	7
	Placebo	110	93.6	−8.0	34	2.9	5
Davidson et al.[26]	PAL ER 3	123	91.6	−15.0***	40**	8.3***	2
	PAL ER 9	123	93.9	−16.3***	46**	7.6***	5
	PAL ER 15	113	92.4	−19.9***	53**	12.2***	3
	OZP[d] 10	126	93.3	−18.1	NR	NR	4
	Placebo	120	93.9	−2.8	18	−1.5	4

a Total number of intent-to-treat patients.

b Change in PANSS total score from baseline to endpoint (week 6).

c Defined as at least 30% improvement in mean PANSS total score from baseline to endpoint (week 6).

d Olanzapine group was not included in the efficacy analyses.

OZP = olanzapine; **PAL** = paliperidone; **PANSS** = Positive and Negative Syndrome Scale; **PSP** = Personal and Social Performance scale; **TAE** = treatment-related adverse event. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

Canuso et al.[27] investigated the effects of paliperidone ER (3–12 mg/day) in markedly to severely symptomatic patients with schizophrenia (total PANSS score ≥105) in a *post hoc* analysis that included pooled data from three acute-efficacy trials. Patients administered paliperidone ER had a significantly better response on the total PANSS, all PANSS factors and CGI-S ($p < 0.05$) compared with patients receiving placebo. Additionally, scores on the Simpson-Angus Scale did not differ significantly between the groups, suggesting that severely ill patients with schizophrenia also benefit from paliperidone ER with good motor tolerability. A small multicentre trial consisting of 36 patients with schizophrenia-related insomnia suggested that paliperidone ER also improves sleep architecture in patients with schizophrenia.[28] In this 2-week double-blind study, patients were randomized to receive either 9 mg/day paliperidone ER or placebo. Paliperidone ER was superior to placebo in improving total mean sleep time and decreasing latency to sleep onset without producing or worsening daytime sleepiness. Nussbaum et al.[29] reviewed the Cochrane database and calculated the NNT and number needed to harm (NNH) based on an analysis of five studies comparing paliperidone ER with placebo. Paliperidone ER, regardless of dosage, had significantly higher rates of improvement in global state, as indicated by at least 30% improvement in total PNSS scores (n = 1420; four randomized controlled trials [RCTs], NNT = 5). Recurrence rates were also significantly lower in the paliperidone-ER group than those in the placebo group (n = 1638; five RCTs, NNT = 16). *Post hoc* analyses of placebo-controlled trials further suggest that paliperidone ER is efficacious in patients with schizophrenia and prominent affective and negative symptoms.[30,31] Prominent affective symptoms were defined as depressed (PANSS depression score of ≥5) and/or manic (PANSS grandiosity score ≥4 with a score of ≥4 on at least one PANSS item for excitement, hostility, uncooperativeness or poor impulse control) symptoms.[30] Predominant negative symptoms were based on PANSS factor scores and were defined as having a baseline negative factor score ≥40% of the maximum score (score ≥24) plus a positive factor score <40% of the maximum score (score <27).[31]

6.1.2 Relapse Prevention and Long-Term Clinical Trials of Schizophrenia (Maintenance Studies)

Results of a long-term trial established the efficacy of paliperidone ER for preventing a relapse of schizophrenia.[32] In this trial, 530 patients first underwent an 8-week, open-label, run-in phase with flexible paliperidone-ER doses of 3–15 mg/day. Response was defined as either a PANSS total score ≤70, a score ≤4 on predefined PANSS subscales, or a stable fixed dose for the last 2 weeks of the run-in phase. In total, 312 responders entered a 6-week stabilization phase at the dose established during the run-in phase. Of this group, 207 patients were then randomized in a double-blind manner to either continue on paliperidone ER (n = 105) or receive placebo (n = 102) until recurrence of first symptom, study withdrawal or study completion. Recurrence was defined as a significant increase on the PANSS or predefined PANSS subscales, worsening of CGI-S scores, suicidal or homicidal ideation, deliberate self-injurious or aggressive behaviour, or hospitalization. An interim analysis revealed that mean time to symptom recurrence was significantly longer in the paliperidone-ER group ($p = 0.005$), causing the study to finish earlier than scheduled. The recurrence rate for paliperidone-ER recipients was 25% (14/56), whereas 53% (29/55) of patients relapsed on placebo. The mean time to symptom recurrence was 83 days for patients on paliperidone ER and 23 days for patients on the placebo. Results of the final analysis were similar to those of the interim analysis. Furthermore, PANSS total scores over time were significantly lower in paliperidone-treated patients ($p < 0.001$).

An analysis of pooled data from a 52-week open-label extension of three pivotal 6-week, double-blind trials showed that long-term treatment with paliperidone ER not only maintained efficacy but also achieved further improvements in PANSS and PSP scores after the 6-week double-blind phase.[33]

6.2 Schizoaffective Disorder

In July 2009, paliperidone ER became the first antipsychotic to receive FDA approval for treating

schizoaffective disorder. The efficacy of paliperidone ER in patients with schizoaffective disorder was investigated in two 6-week, randomized, double-blind, placebo-controlled trials.[34,35] Subjects in both studies were aged 18–65 years, met diagnostic criteria for schizoaffective disorder and had a PANSS total score ≥60 with prominent mood symptoms (≥16 on the Young Mania Rating Scale [YMRS] or the 21-item Hamilton Rating Scale for Depression [HAM-D-21]). After 6 weeks of treatment, paliperidone ER was associated with significantly improved primary (PANSS total score) and secondary (Clinical Global Impression of Severity for Schizoaffective Disorder-Severity Scale, PANSS factor scores, YMRS and HAM-D-21) outcome measures compared with placebo. These results demonstrate that paliperidone ER, given either alone or together with mood stabilizers and antidepressants, is efficacious in patients with schizoaffective disorder. No long-term or maintenance studies of paliperidone ER have been conducted with respect to treating schizoaffective disorder. Thus, the long-term efficacy of paliperidone ER in patients with schizoaffective disorder has not yet been established. The outcome measures of these two studies are summarized in table IV.

6.3 Bipolar Disorder

In a 3-week, randomized, double-blind, placebo-controlled study, the efficacy and safety of paliperidone ER were investigated in 469 patients with an acute manic or mixed episode defined as a YMRS score ≥20.[8] Subjects were randomly assigned to one of three fixed doses of paliperidone ER (3, 6 or 12 mg/day) or placebo. After 3 weeks of treatment, the mean change in YMRS scores from baseline to endpoint (primary variable) differed significantly in only the 12 mg/day paliperidone-ER ($p=0.025$) group compared with the placebo group. The 6 mg/day ($p=0.57$) and 3 mg/day ($p=0.79$) groups did not differ significantly from the placebo group. Therefore, the authors concluded that paliperidone ER 12 mg/day was superior to placebo for treating acute mania. However, the results were confounded by a significant treatment-by-country interaction ($p=0.0032$). Among patients from US sites, no significant difference in mean change in YMRS scores was observed for the paliperidone-ER and placebo groups. In a subsequent trial, paliperidone ER was also effective in delaying the time to recurrence of any mood symptoms, versus placebo, in patients with bipolar I disorder.[10]

Vieta et al.[9] conducted a study consisting of a 3-week, double-blind, acute-treatment phase (paliperidone ER vs placebo, with quetiapine as a control), and a 9-week double-blind, maintenance phase (paliperidone ER vs quetiapine). In total, 493 patients with YMRS scores ≥20 and a history of at least one manic or mixed episode requiring treatment within 3 years were enrolled in the study. For the acute treatment phase, patients were randomized to a flexible dose of paliperidone ER (3–12 mg/day), quetiapine (400–800 mg/day)

Table IV. Summary of two randomized, double-blind, placebo-controlled, 6-week clinical trials of paliperidone ER in patients with schizoaffective disorder

Study	Treatment (mg/day)	No. of patients[a]	PANSS total score		YMRS score		HAM-D-21 score		Discontinuation because of TAE (% of patients)
			Baseline: mean	Change:[b] mean	Baseline: mean	Change:[b] mean	Baseline: mean	Change:[b] mean	
Canuso et al.[34]	PAL ER 3–15	211	92.3	−20.0***	23.4	−11.4**	20.1	−11.7***	5.1
	Placebo	93	91.7	−10.8	22.6	−6.5	20.4	−7.6	8.4
Canuso et al.[35]	PAL ER 6	105	95.9	−27.7	28.4	−16.2	25.2	−14.3*	9.5
	PAL ER 12	98	92.7	−32.4**	29.9	−20.2**	26.9	−13.9*	4.1
	Placebo	107	91.6	−24.1	28.5	−13.4	24.4	−10.5	6.5

a Total number of intent-to-treat patients.

b Change in total score from baseline to endpoint (week 6).

ER = extended release; **HAM-D-21** = Hamilton Depression Rating Scale 21-item version; **PAL** = paliperidone; **PANSS** = Positive and Negative Syndrome Scale; **TAE** = treatment-related adverse event; **YMRS** = Young Mania Rating Scale. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs placebo.

Table V. Summary of two randomized, double-blind, placebo-controlled clinical trials of paliperidone ER in patients with bipolar I disorder

Study	Treatment (mg/day)	No. of patients[a]	YMRS score (primary measure)		CGI-BP-S score	
			Baseline: mean	Change:[b] mean	Baseline: mean	Change:[b] mean
Vieta et al.[9]	PAL ER 3–12	190	27	−13.2***	4.0	−2.0***
	Placebo	104	27	−7.4	4.0	−0.5
Berwaerts et al.[8]	PAL ER 3	107	28.7	−9.1	4.0	−1.0
	PAL ER 6	112	28.0	−11.4	4.0	−1.0
	PAL ER 12	109	28.2	−13.5**	4.0	−1.0
	Placebo	115	28.7	−10.1	4.0	−1.0

a Total number of intent-to-treat patients.

b Change in total score from baseline to 3-week endpoint.

CGI-BP-S = Clinical Global Impression-Bipolar Disorder-Severity Scale; **ER** = extended release; **PAL** = paliperidone; **YMRS** = Young Mania Rating Scale. ** $p < 0.01$, *** $p < 0.001$ vs placebo.

or placebo. During the maintenance phase, patients assigned to the placebo were switched to paliperidone ER but were not included in the efficacy analysis. Paliperidone ER was superior to placebo for reducing YMRS scores at the 3-week endpoint (primary outcome) and not inferior to quetiapine at the 12-week endpoint. During the 12-week treatment period, the median dose of paliperidone ER was 9 mg/day and that of quetiapine was 600 mg/day. No significant differences in onset of therapeutic effect, responder rate or remission rate were observed between the paliperidone-ER and quetiapine groups. The outcome measures of these two studies are summarized in table V.

7. Efficacy Comparisons with Other Antipsychotics

7.1 Comparisons with Risperidone

To date, no randomized, double-blind studies have been conducted that have been specifically designed to investigate differences in efficacy and tolerability between paliperidone ER and oral risperidone. However, limited evidence suggests that paliperidone ER may be more efficacious and better tolerated than risperidone.

In a 6-week, randomized, blind-initiation study, 201 patients with schizophrenia and a suboptimal response to risperidone (4 or 6 mg/day) were randomized to either immediate switching to paliperidone ER or to a switch after an additional 2 weeks of risperidone.[36] Medication satisfaction in each group was then evaluated and compared. Although the study was not statistically powered to compare the difference in efficacy between paliperidone ER and risperidone, results indicated that a higher proportion of patients reported satisfaction with paliperidone than those who remained on risperidone (67.7% vs 45.3%, $p = 0.002$). In the delayed-switching group, the rate of participants reporting medication satisfaction improved from 45.3% to 70.3% at 4 weeks, 2 weeks after being switched from risperidone to paliperidone ($p = 0.033$). Additionally, a significant improvement in mean total PANSS scores was also observed from baseline to 2 weeks after switching to paliperidone ($p < 0.001$), and significant improvements in akathisia ($p < 0.001$), Parkinsonism ($p = 0.001$) and dyskinesia ($p = 0.010$) were also noted at the study endpoint.

In a *post hoc* analysis of double-blind studies, the efficacy of paliperidone ER (3–12 mg/day) in patients with schizophrenia and acute symptoms previously treated with risperidone was assessed.[37] Paliperidone ER was associated with a significant improvement in symptoms (mean total PANSS scores and CGI-S scores) compared with placebo, suggesting that paliperidone ER may provide additional improvement for patients previously treated with risperidone.

The efficacy and tolerability of paliperidone ER and risperidone were indirectly compared using a propensity score matching analysis.[38] The results revealed that mean total PANSS (mean change in score, −6.7; $p < 0.05$) and CGI-S ($p < 0.001$) scores

improved significantly in patients administered paliperidone ER compared with those taking risperidone 2–4 mg/day. However, although CGI-S scores improved more for patients administered paliperidone ER ($p < 0.05$), changes in mean total PANSS score did not differ between the paliperidone-ER and risperidone treatment groups. The authors suggested that paliperidone ER 6–12 mg/day may be more beneficial than risperidone 2–4 mg/day and at least no less efficacious than risperidone 4–6 mg/day.

Although these studies provide some tentative evidence about the potential efficacy and tolerability advantages of paliperidone ER over risperidone, it must be noted that no prospective comparative clinical trial is available to date. Therefore, all inferences described above must be interpreted with caution.

7.2 Comparison with Quetiapine

In a randomized, double-blind, placebo-controlled study comparing the efficacy of paliperidone ER 9 or 12 mg/day with quetiapine 600 or 800 mg/day in hospitalized patients with schizophrenia and an acute exacerbation of symptoms, paliperidone ER showed significantly superior efficacy over quetiapine and placebo.[39] This study included a 2-week monotherapy phase followed by a 4-week additive-therapy phase. Additional uses of psychotropic drugs such as antipsychotics other than risperidone, paliperidone and quetiapine were allowed in the additive-therapy phase. Improvement in mean total PANSS scores from baseline was reported to be significantly greater for patients administered paliperidone ER than for those administered quetiapine and placebo in the monotherapy phase (primary endpoint), and the improvement was observed from day 5 onwards (−11.4 vs −8.2). In contrast, the improvement in symptoms in patients taking quetiapine was similar to that in those taking a placebo at the 2-week monotherapy phase endpoint. At week 6, the end of the additive phase, paliperidone-ER administration also was associated with greater efficacy than was quetiapine despite the similar use of additional psychotropic drugs in both groups. Additionally, relative to placebo patients, patients taking paliperidone ER received less additional psychotropic medication.

7.3 Comparison with Olanzapine

A 6-month, randomized, open-label, parallel-group, multicentre trial compared the efficacy of paliperidone ER and oral olanzapine.[40] A total of 239 patients were randomized to the paliperidone-ER (6 or 9 mg/day) and 220 to the olanzapine (10 or 15 mg/day) groups. Significant improvements in psychotic symptoms, defined by mean changes from baseline to endpoint in total PANSS and PANSS subscale scores, were seen for both olanzapine and paliperidone ER. In paliperidone-treated patients, mean total PANSS scores decreased 13.5 from baseline to the endpoint; in olanzapine-treated patients, mean total PANSS scores decreased 16.6 from baseline to endpoint (both $p < 0.0001$ vs placebo). This study, which has only been presented on a poster, suggests that the efficacy of paliperidone ER is similar to that of olanzapine.

8. Special Populations

8.1 The Elderly

A 6-week, placebo-controlled study with a 24-week open-label extension phase evaluated the safety and tolerability of paliperidone ER in patients aged >65 years with schizophrenia.[41] The mean paliperidone ER dosage was 8.5 mg/day. The safety and tolerability of paliperidone ER in this older population was fairly consistent with both short-term and extension studies in younger patients. Thus, the recommended daily dose for older individuals with normal renal function is identical to that for younger adult patients, but appropriate adjustment of daily doses according to renal function may be required because renal function decreases with age. Additionally, improvements in the PANSS subscale, CGI-S and PSP scores as well as in the Schizophrenia Quality of Life Scale were also superior to those in the placebo group, and these improvements were maintained throughout the 24-week extension phase. However, results regarding the efficacy of paliperidone ER were not powered to determine

statistical differences because the study was mainly designed to investigate the safety and tolerability of paliperidone ER in elderly individuals. Thus, results regarding efficacy should be interpreted with caution.

8.2 Children and Adolescents

According to a recent patient weight-based, fixed-dose, randomized, double-blind study of paliperidone ER (patients weighing 29 to <51 kg at baseline: 1.5 mg/day [low], 3 mg/day [medium] or 6 mg/day [high]; patients weighing ≥51 kg: 1.5 mg/day [low], 6 mg/day [medium] or 12 mg/day [high]), paliperidone-ER medium-treatment (3–6 mg/day) resulted in a significant improvement in schizophrenia symptoms measured by changes in total PANSS scores; this was also true for those receiving actual doses of 3, 6 and 12 mg/day.[42] Although the total percentages of treatment-emergent adverse events were dose related for the three weight-based treatment groups, paliperidone ER (1.5–12 mg/day) was tolerable, and no new safety concerns were reported in the study. However, few well controlled studies of paliperidone ER in children or adolescents have been conducted. Thus, the efficacy and safety of paliperidone ER for patients aged <18 years are not yet clearly established, and the drug should be prescribed carefully based on an assessment of risks and benefits.[7]

8.3 Pregnancy

No controlled studies regarding the use of paliperidone ER in pregnant women are available. When pregnant rats and rabbits were treated with paliperidone ER, no fetal abnormalities were discovered. Therefore, it has been labeled as category C.[7]

9. Safety and Tolerability

9.1 Metabolic Effects

An analysis of pooled data from three pivotal 6-week, placebo-controlled studies indicates that paliperidone-ER-treated subjects show no clinically significant differences in fasting glucose, triglycerides, lipoproteins or total cholesterol levels compared with those in a placebo group.[43] Weight gain in patients administered paliperidone ER was comparable to that in a placebo group. Although weight gain appeared to be dose related, the overall increase was relatively small for the recommended dosage range of 3–12 mg/day. In another study, the average weight gain was 1.8 kg compared with 0.2 kg for placebo after 24 weeks (average) of treatment.[32] The average weight gain in the three pivotal studies was 1.0 kg, and no clinically significant increases in glucose, total cholesterol, triglycerides or lipoproteins were observed in the paliperidone-ER-treated group compared with the placebo group.[24-26] An additional weight gain of 1.2 kg was observed in patients who continued paliperidone ER in 52-week open-label extension studies of these three trials.[33]

9.2 Cardiovascular Effects

9.2.1 QT Prolongation

In the Marder et al.[25] study, one (1%) patient on placebo, two (2%) patients on paliperidone ER 6 mg/day and one (1%) patient on paliperidone ER 12 mg/day had a prolonged maximum post-baseline QT-corrected linear derived (QT_cLD) assessment. Furthermore, in a subsequent study investigating the cardiac effects of paliperidone ER, high doses of paliperidone ER (12 or 18 mg/day) were also involved with minimal QT corrected (QT_c) prolongation.[44] These results are supported by a 6-month trial in an elderly population and recently conducted meta-analyses.[41,43]

Although one patient receiving paliperidone ER 12 mg/day had a QT_c change of >60 ms in the three pivotal 6-week trials, no clinically significant QT_cLD changes were observed in the paliperidone-ER group compared with those in the placebo group according to pooled data analyses.[24-26,43] A 52-week, open-label extension trial of the three pivotal studies was conducted, and results showed that only one participant had a post-baseline QT_cLD ≥480 msec, and 11 patients had a QT_cLD ≤480 msec but ≥450 msec.[33]

In a study investigating the safety and tolerability of paliperidone ER in elderly patients (age ≥65 years), two patients (n = 76) exhibited post-baseline QT_c ≥500 msec during the 6-week double-blind phase, and both patients were withdrawn

from the trial.[41] One additional post-baseline QT_c ≥500 msec value was reported in the 6-month, open-label continuation phase. Importantly, all three patients had a history of cardiovascular disease including QT_c prolongation, suggesting that the effect of paliperidone ER on the QT_c interval is minimal, including in elderly populations, but that its use in patients with a history of QT abnormalities or cardiac arrhythmias should be avoided.

Because paliperidone ER can cause minor prolongation of the QT_c interval, a combination of paliperidone ER with other drugs known to prolong QT_c should be avoided, although most paliperidone ER trials did not show any significant adverse effects of paliperidone ER on cardiac function, as stated above. These drugs include class 1A or 3 antiarrhythmic agents, antipsychotics, fluoroquinolone antibacterials, or any other agents known to cause QT_c prolongation. Furthermore, use of paliperidone ER in patients with congenital long QT syndrome or in patients with a history of cardiac arrhythmias should also be avoided.[7]

9.2.2 Orthostatic Hypotension

Although paliperidone ER has a lower propensity to block α_1 receptors than does risperidone, it can nevertheless lead to orthostatic hypotension.[45] In a pooled analysis of three pivotal studies, syncope was reported in 0.8% (7/850) of participants receiving paliperidone ER compared with 0.3% (1/355) in the placebo group.[43] The incidence of orthostatic hypotension for paliperidone-ER doses of 3 (2%), 6 (1%) and 9 mg/day (2%) was similar to that of placebo (1%), but the rates were higher among those who received 12 (4%) and 15 mg/day (3%). Postural hypotension in elderly patients receiving paliperidone ER was 4% (3/76), whereas none of the participants receiving placebo experienced hypotension.[41] In a meta-analysis of randomized controlled trials investigating the tolerability of paliperidone ER, no significant difference was observed in the rate of postural hypotension between patients taking paliperidone ER and placebo (3% vs 1%).[46] Furthermore, although it is generally acknowledged that the risk of orthostatic hypotension for patients taking paliperidone ER is relatively low, particularly compared with that of its parent compound risperidone, the manufacturer suggests that paliperidone ER be used with caution in patients with a history of cardiovascular disease, cerebrovascular disease or conditions that may predispose orthostatic hypotension.[7]

9.3 Hyperprolactinaemia

Similar to its parent compound risperidone, paliperidone ER increases plasma prolactin levels. The prolactin elevation caused by paliperidone ER persists during chronic administration.[47,48] A pooled analysis of three pivotal 6-week trials suggested a dose-dependent relationship between paliperidone ER and hyperprolactinaemia-related side effects.[43] The rate of prolactin-related adverse events did not differ from that associated with placebo in patients receiving paliperidone ER at doses of 3–12 mg/day (1–2%), but higher rates were observed for patients administered 15 mg/day (4%). Median plasma prolactin levels were greater in women than in men (81 ng/mL vs 24 ng/mL). In the 52-week extension phase, prolactin-related adverse events dropped to <1%, but this figure does not include reports of amenorrhoea (4%) or irregular menstruation (5%).[33] None of the elderly patients receiving paliperidone ER reported prolactin-related adverse events.[41]

Melkersson et al.[47] investigated the role of risperidone and its active metabolite paliperidone on prolactin elevation and reported that increased serum prolactin levels were positively correlated with serum paliperidone concentrations but not with the serum concentration of its parent compound risperidone.[47] Therefore, this study suggests that paliperidone may be more important than risperidone in contributing to increased serum prolactin levels. Knegtering et al.[49] also reported similar results, suggesting that paliperidone plays a predominant role in prolactin elevation.

9.4 Extrapyramidal Symptoms

According to a pooled analysis, EPS-related adverse event rates for patients on paliperidone ER 3 and 6 mg/day were similar to those receiving placebo (13%, 10% and 11%, respectively).[43] However, the adverse-event rates in the paliperidone-ER

9 and 12 mg/day groups (25% and 26%, respectively) were higher than those in the group taking placebo (11%). The severity of EPS was generally mild to moderate, and only two patients discontinued use due to EPS-related adverse events.[26] A 1-year open-label extension study suggested that no patients experienced worsening of EPS-related adverse events during long-term administration of paliperidone ER, and that EPS-related discontinuation rates are very low (<1%).[33]

A meta-analysis found that the incidence of EPS was 23% in all paliperidone-ER groups, which was higher than that in the placebo group (10%).[46] The relative risk of an EPS event in patients taking paliperidone ER was almost twice as high as that in those taking a placebo. The attributable risk, which is defined as the incidence in the paliperidone-ER group minus the incidence in the placebo group, was significantly higher for hypertonia, tremor, akathisia, dyskinesia, dystonia, dysarthria and musculoskeletal pain.

The incidence of EPS-related side effects is generally low in elderly populations.[41] During the double-blind phase, hypertonia, tremor and akathisia were observed in only two patients (3%) [2/76] in the paliperidone-ER group, whereas none of the patients receiving placebo reported hypertonia or tremor, and only one case of akathisia was observed in the placebo group. Similarly, the incidence of EPS was low throughout the 6-month extension phase and none of the patients discontinued treatment due to EPS-related adverse events.

10. Dosing and Administration

The recommended starting dose of paliperidone for patients with schizophrenia is 6 mg/day, once daily in the morning, and no dosage titration is required.[7] Results from three pivotal studies indicate that efficacy of different doses (3, 6, 9, 12 and 15 mg/day) was largely similar. However, some studies suggest higher doses may provide better results.[24-26] Product labelling suggests dose increments >6 mg/day should be considered only after careful clinical assessment.[7] Furthermore, when a dose increase is planned, no more than 3 mg/day increases with intervals of no fewer than 5 days are recommended. The maximal recommended daily dose of paliperidone for schizophrenia is 12 mg/day. Although clinical trials have shown some different results,[34,35] paliperidone 6–12 mg/day may be the optimal starting dose for schizoaffective disorder. The suggested dose ranges for schizoaffective disorder and schizophrenia are basically identical.[7]

11. Switching to Paliperidone ER

No formal clinical trials have investigated strategies governing switching from risperidone or other antipsychotics to paliperidone ER. However, paliperidone ER showed more benefit for immediate than for delayed switching (2 weeks) for suboptimal responders to risperidone treatment.[36] Slow-down titration reduces the likelihood of adverse effects occurring due to abrupt withdrawal of previous medications; in particular, patients should be more carefully monitored when switching to paliperidone ER from sedating antipsychotics such as olanzapine or quetiapine.

12. Summary

Paliperidone ER may extend the treatment options for patients suffering from schizophrenia, schizoaffective disorder and possibly bipolar disorder. Studies indicate that paliperidone ER may offer some advantages compared with other antipsychotics, including its parent compound risperidone. First, its distinct pharmacodynamics and pharmacokinetic characteristics may provide clinical benefits. The agent's smooth plasma concentration fluctuations might have a profound impact in clinical practice because stable drug plasma concentrations may provide constant therapeutic efficacy and reduced side-effect frequency. Second, unlike its parent compound, it does not require dose titration, which may further contribute to enhanced tolerability. The reduced likelihood that paliperidone ER causes hepatic impairment and CYP2D6/3A4-related drug-drug interactions may be another important advantage, particularly in patients with impaired hepatic metabolism and

those requiring polypharmacy. This may be an important clinical consideration because patients with psychotic disorders appear to have a higher risk of developing medical co-morbidities including liver disease.[50,51] Additionally, paliperidone ER dissociates more rapidly from the D_2 receptor than does risperidone, which could translate into a lower incidence of EPS. Paliperidone ER should not be used in patients taking other medications known to cause QT_c prolongation. Although the α_1 antagonistic propensity of paliperidone ER is lower than that of risperidone, evidence demonstrates that the risk of orthostatic hypotension and syncope remains. Thus, paliperidone ER should be used with extreme caution for patients with a history of cardiovascular disease, cerebrovascular disease or conditions that could predispose orthostatic hypotension. Whether risperidone and paliperidone regulate prolactin release to a different degree remains controversial and needs to be clarified, but the risk must be considered. Finally, most of the rare adverse events occurred in Asian patients, rendering ethnic differences worthy of future investigation and observation in efforts to examine the clinical use of paliperidone ER to treat a variety of psychiatric disorders.[52-54]

13. Future Research

A very limited number of studies have compared the efficacy and safety of paliperidone ER with those of other antipsychotics. Although previous studies have provided some tentative evidence for the potential advantages of paliperidone ER over other antipsychotics such as olanzapine and quetiapine, including risperidone, no well designed randomized controlled trials have directly compared paliperidone ER with risperidone or other new-generation compounds. Clinical trials comparing the efficacy, tolerability and safety of paliperidone ER with those of other antipsychotic agents are needed to further elaborate its risk-benefit profile. Uses for which risperidone has been approved by various registration authorities should also be studied with respect to paliperidone ER. First, risperidone has been approved by the FDA for children with schizophrenia aged 13–17 years.[55] Second, it is not only approved for bipolar disorder in adults but also has FDA approval for bipolar disorder in children aged 10–17 years. Furthermore, paliperidone ER has approval in a number of countries for treating irritability in 5- to 16-year-old children and adolescents with autism. The use of atypical antipsychotics as add-on treatments to antidepressants in depressive disorder increased after aripiprazole and quetiapine received FDA approval for this purpose. Similarly, it is possible that paliperidone ER may possess antidepressant effects, as it has both an α_2 blocking effect and an affinity for $5\text{-}HT_7$ receptors.[56] Hence, investigations of such effects need to be addressed.

14. Conclusion

Paliperidone ER may be another viable treatment option for treatment of schizophrenia and schizoaffective disorder based on results from adequately powered, well controlled, pivotal clinical trials. A long-term clinical trial has also established the efficacy of paliperidone ER for preventing relapses of schizophrenia. Paliperidone ER may also be utilized in the treatment of bipolar disorder with proven efficacy and safety results from placebo-controlled clinical trials, although it has not yet been officially approved by a regulatory agency.

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