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REVIEW

Safety and Efficacy of Paliperidone Extended-Release in Acute and Maintenance Treatment of Schizophrenia

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Abstract: Paliperidone, the major active metabolite of risperidone, is a second-generation antipsychotic that has been developed as an extended-release (ER) tablet formulation that minimizes peak-trough fluctuations in plasma concentrations, allowing once-daily administration and constant drug delivery. Paliperidone ER has demonstrated efficacy in the reduction of acute schizophrenia symptoms in 6-week, placebo-controlled, double-blind trials and clinical benefits were maintained in the longer-term according to extension studies of up to 52 weeks in duration. Compared with quetiapine, paliperidone ER was associated with a more rapid symptom improvement. In addition, it was more effective than placebo in the prevention of symptom recurrence. Paliperidone ER is generally well tolerated with a predictable adverse event profile. Like risperidone, it is associated with a dose-dependent risk of extrapyramidal symptoms and prolactin elevation. Short- and longer-term studies have indicated a low liability for paliperidone ER to cause metabolic (ie, weight gain, hyperglycaemia and lipid dysregulation) or cardiovascular adverse effects. Available safety data from elderly patients appear to be promising. Due to negligible hepatic biotransformation, paliperidone ER is unlikely to be involved in clinically significant metabolic drug-drug interactions. Additional active comparator trials evaluating efficacy, tolerability and cost-effectiveness are required to better define the role of paliperidone ER in the treatment of schizophrenia in relation to other currently available second-generation antipsychotics, particularly risperidone.

Keywords: paliperidone, risperidone, antipsychotics, schizophrenia, efficacy, tolerability, safety

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Introduction

Schizophrenia is a relatively common, severe and debilitating mental illness. Schizophrenia is a heterogeneous disorder characterized by positive and negative symptoms and often associated with cognitive impairment and depressive symptoms. The course of the illness is generally chronic, with relapses in psychotic episodes, cognitive reduction, social decline and poor quality of life. The aims of schizophrenia treatment are rapid symptom elimination, relapse prevention and reduction of illness severity, as well as improving social functioning and relationships. Antipsychotic drugs are the mainstay for the treatment of schizophrenia and include "typical" or "first-generation" and "atypical" or "second-generation" compounds.[1] During the last decade, second-generation antipsychotics have become the treatment of choice due to the perception of a more favourable tolerability profile and a broader spectrum of clinical activity involving not only the positive psychotic symptoms, but also the negative and cognitive aspects of schizophrenia as compared to first-generation agents.[1] Indeed, with respect to safety, newer antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole and amisulpride, have represented clear progress in their low propensity to produce acute extrapyramidal symptoms (EPS) and tardive dyskinesia.[2] On the other hand, the promise of efficacy of newer antipsychotics against negative and cognitive symptoms has not been borne out.[3] Additionally, atypical antipsychotics have been associated with differential risk of metabolic (weight gain, hyperglycaemia and lipid dysregulation) and cardiovascular adverse effects.[2] Two large, non-commercial clinical trials have called into question the degree to which second-generation antipsychotics represent a significant advance in therapeutic effectiveness compared with traditional compounds in schizophrenia.[4,5] In particular, the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study demonstrated that partial and non-adherence is still very common among patients treated with antipsychotics, often leading to high rates of treatment discontinuation.[5] For these reasons, an advance in pharmacological therapy of schizophrenia is required, focusing on novel agents with potential benefits not only in terms of improved tolerability and efficacy, but which may also improve patient compliance.

Paliperidone or 9-hydroxyrisperidone is the most recently available atypical antipsychotic and the primary active metabolite of risperidone, a well-established second-generation antipsychotic.[6–10] Paliperidone has been developed as an extended-release (ER) tablet formulation that uses an osmotic-controlled release oral delivery system (OROS) technology, allowing once-daily administration and constant drug delivery.[11] This formulation consists of an osmotically active trilayer core, composed of two distinct drug layers and an osmotic push layer, surrounded by a subcoat and a semipermeable membrane. Paliperidone ER is approved in the US and EU for the acute and maintenance treatment of schizophrenia in adults. In the US, paliperidone ER is also indicated for the acute treatment of schizoaffective disorder, as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. Paliperidone is also available in the US as a long-acting injectable formulation of paliperidone palmitate which is outside the aim of this review.

Over the past few years, several reviews have been published covering the pharmacological properties, clinical efficacy and tolerability of paliperidone ER in the management of schizophrenia and other related psychotic disorders.[6–10,12–19] This article provides an updated overview on the safety and efficacy profile of paliperidone ER in the acute and maintenance treatment of schizophrenia.

Mechanism of Action

Paliperidone and its parent drug risperidone possess a similar pharmacological profile in vitro. Like risperidone, the therapeutic effects of paliperidone are thought to be mainly related to its antagonism at both dopamine D_2 and serotonin $5HT_{2A}$ receptors, with a higher affinity for $5HT_{2A}$ (Ki 0.22–0.25 nM) than D_2 (Ki 4.6 M).[20,21] Paliperidone is also an antagonist at H_1-histaminergic receptors, α_1- and α_2-adrenergic receptors, which may explain weight gain, orthostatic hypotension or sedative side effects, while it is devoid of significant interaction with cholinergic muscarinic receptors and β_1- and β_2-adrenergic receptors. Paliperidone is a racemic mixture of two enantiomers, ie, (+)- and (−)-paliperidone, which have comparable pharmacological activity in vitro.[22,23]

Brain imaging studies in patients with schizophrenia have suggested that dosages of paliperidone ER

between 9 mg/day provide an estimated level of D_2 receptor occupancy of 70%–80%, a range which is associated with optimal efficacy, with no significant difference between the striatum and the temporal cortex.[24] A study using in vitro models with human cloned D_2 receptors in tissue cultures has documented that the off-rate for dissociation from D_2 receptors is faster for paliperidone (60 sec) as compared to risperidone (27 min).[25] Theoretically, due to the more rapid dissociation from the D_2 receptors, paliperidone should be associated with a reduced risk of EPS than its parent drug.

An in vivo electrophysiological study in rats has documented a differential effect of risperidone and paliperidone on the firing activity of serotonin and noradrenaline neurons.[26] Paliperidone reversed the selective serotonin reuptake inhibitor (SSRI)-induced inhibition of noradrenaline neuronal firing, without interfering with the effect of SSRIs on serotonin neuronal activity, suggesting that paliperidone may be an effective adjunct in SSRI-resistant depression.

Metabolism and Pharmacokinetic Profile

Paliperidone is the major active metabolite of risperidone. In vivo and in vitro studies have shown that the formation of paliperidone from risperidone is catalyzed by CYP2D6 and, to a lesser extent, CYP3A4.[27–29] The pharmacokinetic profile of paliperidone, administered by itself as an immediate- or extended-release formulation, has been investigated in studies in healthy volunteers or patients with schizophrenia.[30] Some of the available information results from abstracts and from the US FDA manufacturer's prescribing information and EU summary of product characteristics.[22,23]

The single-dose pharmacokinetics of three different paliperidone formulations (1 mg paliperidone IR solution, 3 mg paliperidone ER or 1 mg paliperidone intravenous infusion) were initially investigated in a cross-over study in 20 healthy volunteers.[31] The paliperidone ER formulation had a slow ascending concentration-time profile with a time to maximum plasma concentration (t_{max}) reached around 24 hours in contrast to the paliperidone IR formulation for which t_{max} was reached 1–2 hours after dosing. The absolute bioavailability of the ER formulation was 28%, compared with 106% for the IR formulation. The lower bioavailability of the ER formulation was attributed to its release characteristics with reduced absorption in the colon.

The pharmacokinetics of paliperidone ER after single and multiple 3 mg doses and single 6, 9 or 12 mg doses were investigated in healthy volunteers.[32] The plasma concentration-time profile of paliperidone ER after a single dose exhibited a gradual ascending increase in plasma concentrations over a period of 24 hours. Paliperidone was eliminated with a terminal half-life of approximately 24 hours. The pharmacokinetics of paliperidone ER displayed dose-proportionality over the dose range of 3–12 mg/day. After multiple-dose administration, steady-state was achieved after 4 daily doses. Paliperidone ER provided minimal fluctuations in plasma concentrations and the mean steady-state peak-to-trough ratio was 1.7 with a range of 1.2–3.1.

Paliperidone is rapidly distributed in humans with an apparent volume of distribution of 487 L. Racemic paliperidone is 74% bound to plasma protein, primarily to α_1-acid glycoprotein and albumin.[22,23] Due to a hydroxyl group in position 9, paliperidone is less lipophilic than risperidone and crosses the blood-brain barrier less easily the parent drug, as suggested by studies in rats documenting a lower brain-to-plasma ratio for paliperidone over risperidone.[33,34] Experiments in knock-out mice have suggested that the brain entry of both risperidone and paliperidone may be limited by the presence in the blood-brain barrier of the P-glycoprotein, a multidrug efflux transporter, which has a slightly greater affinity for paliperidone than risperidone.[35–37]

Paliperidone undergoes limited hepatic metabolism and is primarily eliminated via renal clearance. In a study of five healthy male subjects, 3 extensive metabolizers (EMs) and 2 poor metabolizers (PMs) of CYP2D6, given a single 1 mg oral dose of radiolabelled paliperidone, approximately 80% of the administered radioactivity was recovered in the urine and approximately 11% in the faeces.[38] About 60% of the dose was excreted unchanged into the urine, while the remainder was eliminated as metabolites formed from dealkylation (4.6%), hydroxylation (3.8%), dehydrogenation (2.7%) and benzisoxazole scission (4.1%) pathways (Fig. 1). Similar pharmacokinetic profiles were observed in EMs and PMs. Preliminary in vitro studies demonstrated some involvement of CYP2D6 and CYP3A4 in the metabolism of paliperidone.[22,23]

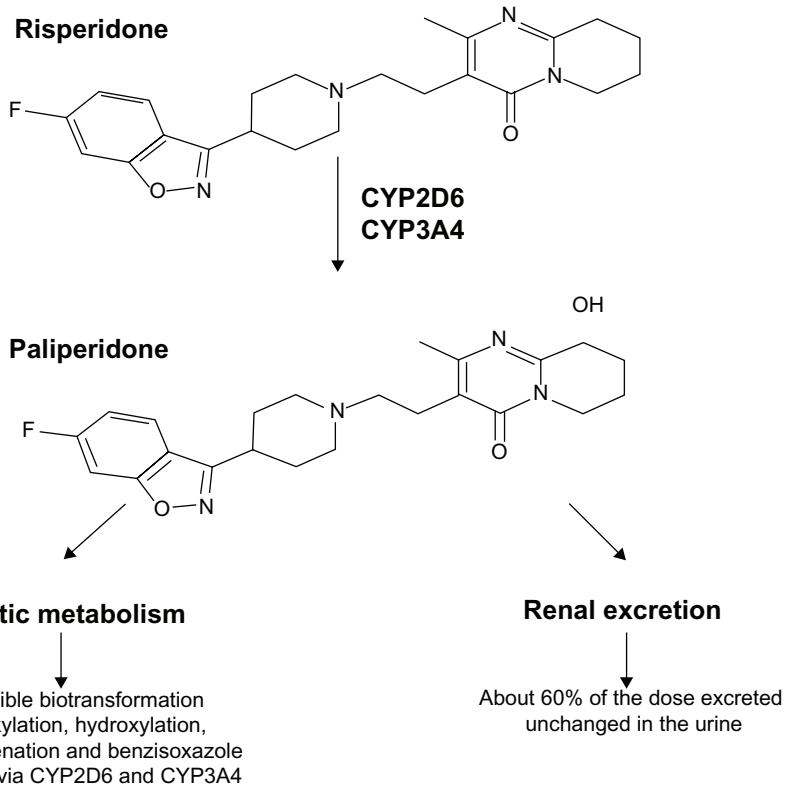

Figure 1. Elimination of risperidone and paliperidone.

The single-dose pharmacokinetics of paliperidone has been investigated in patients with liver or kidney disease. While the pharmacokinetics of paliperidone were not affected by mild-to-moderate hepatic impairment,[39] the total clearance of paliperidone was reduced in the presence of renal impairment.[22,23] In patients with varying degrees of renal impairment, total paliperidone clearance correlated with creatinine clearance decreasing by 32%, 64% and 71% in subjects with mild, moderate and severe impairment as compared to volunteers with normal renal function.[22,23] The pharmacokinetics of paliperidone were not significantly affected by age.[22,23] No dose adjustment of paliperidone ER is needed in the elderly, but is required in elderly patients with renal impairment.

Potential for pharmacokinetic drug interactions

While risperidone is involved in a number of clinically relevant pharmacokinetic drug interactions, this is unlikely to occur with paliperidone.[40] In particular, due to its minimal hepatic metabolism, concomitant administration of inhibitors or inducers of CYP isoforms is not expected to have a significant effect on the biotransformation of paliperidone. Few studies are currently available on metabolic drug interactions with paliperidone ER. A randomized, crossover study has examined the effect of paroxetine, a potent CYP2D6 inhibitor, 20 mg/day, on the pharmacokinetics of a single dose of paliperidone ER 3 mg in 60 healthy male subjects.[41] The mean peak plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) of paliperidone were slightly higher and its clearance was slightly lower following coadministration of paliperidone ER with paroxetine. The increase in total exposure to paliperidone was not considered clinically relevant. Coadministration of carbamazepine, a potent inducer of various CYP isoforms, 200 mg twice daily, was found to decrease the mean steady-state C_{max} and the AUC of paliperidone by approximately 37%, mostly due to a 35% increase in the renal clearance of paliperidone.[22,23] This was likely due to induction of renal P-glycoprotein by carbamazepine. The effect of trimethoprim, a potent organic cation transport

inhibitor, on the pharmacokinetics of paliperidone ER was assessed in a open-label, randomized, two-way crossover study in 30 healthy male volunteers.[42] Coadministration of trimethoprim, 200 mg twice daily, with a single oral dose of 6 mg paliperidone ER did not cause relevant changes on the pharmacokinetic parameters of paliperidone.

Of considerable theoretical interest in terms of pharmacokinetic drug interactions are the findings from in vitro investigations showing that paliperidone is a weaker inhibitor of P-glycoprotein as compared to other antipsychotics including risperidone.[43,44] Therefore, though no human studies exist that address this issue, paliperidone is not expected to interfere with the P-glycoprotein-mediated transport of other drugs in a clinically relevant manner.

Clinical Studies

The body of data regarding efficacy and tolerability of paliperidone ER in patients with acute schizophrenia corresponds up to now to five multicenter, 6-week, randomized, double-blind, parallel-group and placebo-controlled studies.[45–49] One of these trials also included a 24-week, open-label extension phase.[49] Three trials included an olanzapine 10 mg/day treatment arm to confirm trial validity only and were not designed to support statistical comparison of paliperidone ER and olanzapine,[45–48] while one trial included quetiapine 600–800 mg/day as the active comparator.[48] In three studies patients received fixed doses of paliperidone ER 3, 6, 9, 12 and 15 mg/day, differently distributed in the various studies,[45–47] while in the other two trials patients received flexible doses of paliperidone ER.[48,49] Of these trials, four included patients aged between 18 and 65 years,[45–48] and one enrolled only elderly patients aged ≥65 years.[49]

The efficacy of paliperidone ER in the prevention of acute symptom recurrence in patients with schizophrenia was investigated in a randomized, double-blind, placebo-controlled, multicenter study.[50] Long-term efficacy and safety of paliperidone ER (3–12 mg/day) were evaluated in pooled data from the 52-week open-label extension phases of the three 6-week pivotal trials involving 1083 patients with schizophrenia.[51] Table 1 summarizes the study designs and treatment features of the main published studies.

Other clinical studies addressing specific aspects of the efficacy and safety profile of paliperidone ER in patients with schizophrenia will be discussed in the next sections.

Safety

In the pooled tolerability analysis of the three 6-week, randomized, double-blind, placebo-controlled studies,[48,49] treatment-emergent adverse events occurred in 66% to 77% of patients in the paliperidone ER groups and 66% of patients in the placebo group.[52] In general, with the exception of EPS (akathisia, tremor, muscle stiffness), the most frequent adverse events observed in patients treated with paliperidone ER 3–12 mg/day and occurring with an incidence of ≥5% were headache, insomnia, anxiety, tachycardia, somnolence and dizziness. The incidence of the most frequent treatment-emergent adverse events in the pooled data from three 6-weeks, placebo-controlled studies of paliperidone ER is reported in Table 2.

According to pooled data from the open-label extension phases of the three 6-week, double-blind, placebo-controlled trials, paliperidone ER was generally well tolerated over the 52-week treatment duration and there were no unexpected findings.[51] The most common treatment emergent adverse events (occurring with an incidence ≥10%) were insomnia (14%), headache (12%) and akathisia (11%). A total of 76% of patients experienced treatment-emergent adverse events, 16% experienced one or more serious adverse events, 7% had an adverse events leading to study discontinuation and two patients (less than 1%) committed suicide.

A systematic review of the placebo-controlled clinical trials, meta-analyses and unpublished trial data for the tolerability of paliperidone ER was recently conducted.[53] Adverse effects with the greatest incidence in a population of 3779 paliperidone ER-treated patients were EPS (23%), headache (14%), insomnia (11%), somnolence (9%), tachicardia (9%) and weight gain (8%).

From the available data, some aspects need to be covered in detail when evaluating paliperidone ER as a potentially improved safety drug in comparison to risperidone and other second-generation antipsychotics.

Table 1. Main study characteristics of available double blind, placebo-controlled studies with paliperidone ER.

Study	Design	No of patients randomized	Daily dose	Duration
Kane et al[45]	Double-blind, placebo- and active-controlled (olanzapine)	630 – Paliperidone: 375 – Olanzapine: 128 – Placebo: 127	Paliperidone 6 mg Paliperidone 9 mg Paliperidone 12 mg Olanzapine 10 mg	6 weeks
Davidson et al[46]	Double-blind, placebo- and active-controlled (olanzapine)	618 – Paliperidone: 367 – Olanzapine: 128 – Placebo: 123	Paliperidone 3 mg Paliperidone 9 mg Paliperidone 12 mg Olanzapine 10 mg	6 weeks
Marder et al[47]	Double-blind, placebo- and active-controlled (olanzapine)	444 – Paliperidone: 224 – Olanzapine: 110 – Placebo: 110	Paliperidone 6 mg Paliperidone 12 mg Olanzapine 10 mg	6 weeks
Canuso et al[48]	Double-blind, placebo- and active-controlled (quetiapine)	399 – Paliperidone: 160 – Quetiapine: 159 – Placebo: 80	Paliperidone 9 mg Paliperidone 12 mg Quetiapine 600 mg Quetiapine 800 mg	6 weeks (2 weeks monotherapy + 4 weeks additive-therapy)
Tzimos et al[49]	Double-blind + open-label extesion	114 – Paliperidone: 76 – Placebo: 38	Paliperidone 3–12 mg (flexibly dosed)	Double-blind: 6 weeks Open-label extension: 24 weeks
Kramer et al[50]	Open-label run in and stabilization + double-blind, placebo-controlled + follow-up to recurrence	Open-label phase: 530 Double-blind phase: – Paliperidone: 105 – Placebo: 102 – Follow up: 179	Paliperidone 3–15 mg (flexibly dosed)	8 weeks run-in + 6 weeks at stable dose + follow-up up to recurrence
Emsley et al[51]	Open-label extension phase of three 6-week, double-blind, controlled trials	1083 – Placebo/Paliperidone ER: 206 – Paliperidone ER/ Paliperidone ER: 628 – Olanzapine/ Paliperidone ER: 249	Paliperidone: 3–12 mg (flexibly dosed)	52 weeks

Extrapyramidal side effects

The Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS) were used to assess EPS in the pivotal trials of acute treatment.[45–47] According to pooled tolerability data from these three studies, there were no clinically relevant differences in median changes from baseline to endpoint in SAS, BARS and AIMS total scores between any of the paliperidone ER treatment groups and placebo.[52] As shown in Table 2, the proportions of patients who experienced EPS were 13%, 10%, 25%, 26% and 24% for paliperidone ER 3, 6, 9, 12 and 15 mg/day, respectively; the pooled incidence rate was not statistically different from that of placebo (11%). The most frequent events were extrapyramidal disorder, akathisia, tremor, hypertonia and dystonia. With regard to akathisia, the pooled analysis reported similar rates in the paliperidone ER 3 and 6 mg/day and the placebo group (4%, 3% and 4%, respectively), while higher akathisia rates were observed in the paliperidone 9, 12 and 15 mg/day (8%, 10% and 10%, respectively). Across all three studies only one patient was reported to have tardive dyskinesia. In the active comparator trial, EPS ratings on the SAS were significantly ($P < 0.001$) higher in patients treated with paliperidone ER than in those receiving quetiapine at the end of the 2-week monotherapy phase, while there were no significant between-group differences on the BARS or AIMS scores.[48] At the 6-week endpoint, no significant between-group differences were observed for any of these three rating scale scores.

Over the 52-week, open-label extension phases of the three acute treatment trials, EPS-related adverse

Table 2. Incidence (percent of patients) of treatment-emergent adverse events in the pooled data from three 6-weeks, placebo-controlled studies of paliperidone ER (based on ref. 52).

	Paliperidone 3 mg/day (n = 127)	Paliperidone 6 mg/day (n = 235)	Paliperidone 9 mg/day (n = 246)	Paliperidone 12 mg/day (n = 242)	Paliperidone 15 mg/day (n = 113)	Placebo (n = 355)
Total percentage of patients with adverse events	72	66	70	76	77	66
Headache	11	12	14	14	18	12
Somnolence	5	3	7	5	6	3
Dizziness	6	5	4	5	6	4
Insomnia	11	12	14	11	12	14
Anxiety	9	7	6	5	8	8
Extrapyramidal symptoms	13	10	25	26	24	11
– Akathisia	4	3	8	10	10	4
– Parkinsonism	3	3	7	6	6	2
– Tremor	3	3	4	3	3	3
Nausea	6	4	4	4	2	5
Vomiting	2	3	4	5	7	5
Constipation	6	3	3	3	4	6
Tachycardia	11	11	11	14	9	7

events were reported by 25% of patients, but median maximum movement disorder ratings scale scores showed no change in severity.[51] No significant changes were noted in EPS rating scores, assessed by SAS, AIMS and BARS, during continued administration.

In general, paliperidone ER seems to have an extrapyramidal tolerability profile comparable to risperidone, with low risk for EPS at doses of 3–6 mg/day and higher rates of movement disorders, ie, akathisia and parkinsonism, with increasing doses. However, as no direct clinical comparison between paliperidone ER and risperidone is currently available, it is not possible to verify if the lower fluctuations of plasma drug levels and the subsequent more stable D_2-receptor occupancy associated with the innovative formulation may confer to paliperidone ER a reduced EPS liability than oral risperidone. In addition, More carefully designed studies are needed to estimate the true risk for tardive dyskinesia.

Prolactin elevation

Consistent with its pharmacological profile as a dopamine D_2-receptor antagonist, paliperidone ER was found to elevate mean serum prolactin levels to above the normal range in the 6-week trials.[45–47] In general, serum prolactin levels were elevated to a greater extent in female patients than in males, remained elevated throughout treatment, and increased with increasing paliperidone ER dosage. Median increases in prolactin levels were larger in female patients (81 ng/mL) than in male patients (24 ng/mL) when all paliperidone ER doses were combined.[52] Median increases in prolactin levels peaked on day 15 and subsequently decreased slightly, although prolactin concentrations remained above the upper limit of the reference range (1.4–24.2 ng/mL in women and 1.6–18.8 ng/mL in men).[52] During the 52-week open-label extension phase of these trials, at endpoint mean serum prolactin levels still remained outside the normal range in both female and male patients receiving paliperidone ER.[51]

Across the trials of acute treatment, potential prolactin-related adverse events were reported in 1%–2% of paliperidone ER or placebo recipients.[52] They included impotence or other sexual dysfunction, gynaecomastia, galactorrhoea, amenorrhoea or menstrual irregularity, but did not result in treatment discontinuation. During the 52-week open-label extension phases, potentially prolactin-related adverse events were lower than 1% in all treatment subgroups (according to prior double-blind randomization phase) with the exception of amenorrhea (4% of females

in each subgroup), irregular menstruation (5% of female patients in the subgroup initially randomized to receive placebo) and erectile dysfunction (3% of male patients in the subgroup originally randomized to receive olanzapine).[51]

These data clearly indicate that paliperidone ER, like risperidone and amisulpride, may cause hyperprolactinemia. However, the clinical relevance of increased serum prolactin levels is still poorly understood, partly related to methodological limitations of the available paliperidone ER studies. With regard to this, data on prolactin-related adverse events were collected through spontaneous reporting, possibly leading to an under-recognition. Moreover, with the exception of the open-label 52-week trials, the duration of most studies was too short to evaluate more deeply long-term prolactin-related adverse effects such as menstrual irregularities, breast enlargement or decreased bone mineral density/osteoporosis. Direct comparison between paliperidone ER and risperidone in terms of prolactin elevation is still lacking. This may be of interest also in view of the increasing evidence suggesting that paliperidone and not risperidone might be the main contributor to the increased serum levels of prolactin observed in many patients.[54,55] As the potency to stimulate prolactin secretion is comparable between risperidone and its metabolite, this effect has been attributed to the higher plasma levels of paliperidone, to its lower brain-to-plasma ratio (anterior pituitary is located outside the blood-brain barrier) and longer half-life compared to parent drug. In this respect, in a recent double-blind, randomized, parallel-group study, patients with schizophrenia were randomized to receive either paliperidone ER 12 mg/day or risperidone immediate-release 4 mg/day for a period of 6 days.[56] At steady state, the doses administered resulted in a similar exposure to paliperidone and active fraction of risperidone (ie, risperidone + paliperidone) and a similar elevation in serum prolactin concentrations.

Metabolic adverse effects

Evaluation of the metabolic tolerability profile of paliperidone ER is still incomplete due to limited duration of the available double-blind studies. According to pooled analysis of the acute treatment trials, no clinically relevant mean changes from baseline to endpoint in serum glucose were observed in patients treated with paliperidone ER or placebo.[52] Potentially glucose-related adverse events (most commonly increased blood glucose levels) were reported in 1% of paliperidone ER recipients and 1% of placebo recipients. Only two of these events, both occurring in paliperidone ER recipients, were considered serious. Longer-term data from the 52-week open-label extension phases of these trials supported the 6-week findings, with 1% of patients across treatment groups reporting potentially glucose-related adverse events (increased blood glucose, diabetes, glucosuria and hyperglycaemia).[51] With regard to serum lipids, no clinically meaningful changes from baseline to endpoint in low-density lipoprotein, high-density lipoprotein, total cholesterol or triglycerides were observed in any of the paliperidone ER groups and in the placebo in the three pivotal 6-week trials.[52] Consistent with its short-term use, long-term treatment with paliperidone ER over 52 weeks was associated with no clinically relevant changes in serum lipid levels.[51]

In the three short-term trials, mean body weight changes over the 6-week treatment period were <2 kg across all paliperidone ER treatment groups and appeared to be dose-related: +0.6, +0.6, +1.0, +1.1 and +1.9 kg with paliperidone ER 3, 6, 9, 12 and 15 mg/day, respectively (vs. –0.4 kg with placebo and +2.0 kg with olanzapine; statistical analyses not reported).[52] In the 6-week, active comparator trial, at the 2-week monotherapy phase endpoint monotherapy, mean weight gain was significantly higher in quetiapine recipients than in either paliperidone ER ($P \leq 0.028$) or placebo ($P = 0.011$): 0.4, 0.8 and 0.2 kg with paliperidone ER, quetiapine and placebo, respectively.[48] Corresponding values at the 6-week endpoint were 0.4, 1.1 and 0.3 kg. During the 52-week open-label extension phases of three pivotal trials, the mean increase in body weight from the baseline of the extension phase to endpoint was relatively small across all treatment groups (1.1 kg) and 15% of patients had weight increases of $\geq 7\%$.[51] Overall, the effect of paliperidone ER on body weight appears to be lower as compared to clozapine and olanzapine, substantially similar to risperidone and quetiapine, but presumably higher than aripiprazole and ziprasidone.

Cardiovascular adverse effects

As previously mentioned, the pooled analysis of the three pivotal, 6-weeks trials revealed that tachycardia

was the most common cardiovascular adverse event related to paliperidone ER.[52] Concerning other cardiovascular side effects, the incidence of orthostatic hypotension reported for paliperidone ER daily doses of 3 mg (2%), 6 mg (1%) and 9 mg (2%) was similar to that of placebo (1%). Higher incidence rates were reported at paliperidone ER daily doses of 12 mg (4%) and 15 mg (3%). In each of these trials, 12-lead ECGs were obtained for all patients at each study visit. None of the paliperidone ER recipients had a linear-derived (LD) corrected QT (QTc) interval (QTcLD) of ≥480 msec during the double-blind treatment period. No prolongations of QTcLD or the Fridericia-corrected QT interval were observed in paliperidone ER or quetiapine recipients during a 6-week treatment period in one flexible-dose, comparative study.[48] In a recent randomized, double-blind, placebo-controlled investigation, Hough et al[57] evaluated the effect of paliperidone ER and quetiapine on QTc intervals in patients with schizophrenia or schizoaffettive disorder. No differences were observed on the QTc interval between paliperidone ER 12 mg/day (maximum recommended dose), paliperidone ER 18 mg/day (supratherapeutic dose) and quetiapine 800 mg/day.

During the 52-week, open-label extension phases of the acute-treatment trials, 11 (1%) patients had a maximum post-baseline QTcLD assessment ≥450 and <480 msec (8 of these patients had a normal QTcLD and 3 had a maximum QTcLD ≥450 msec at the baseline of the open-label extension phase) and one patient had a maximum post-baseline QTcLD ≥ 480 msec.[51]

These data indicate that treatment with paliperidone ER seems to be associated with a minimal risk of cardiovascular adverse effects, also in the long-term treatment. Tachycardia appeared to be the most frequent side effect, while ECG anomalies were very low, in particular when looking at QTc prolongation events. Orthostatic hypotension was not commonly reported during paliperidone ER, presumably due to slow release of the medication from the ER formulation. In addition, paliperidone is a slightly less potent inhibitor α_1-adrenergic receptors than risperidone.[20,21]

Tolerability in elderly patients

Tzimos et al[49] addressed the problem of safety and tolerability of paliperidone ER in elderly patients, a population more vulnerable to cardiovascular and metabolic side effects and EPS, in particular tardive dyskinesia. They conducted a 6-week, double-blind, randomized, flexible-dose, placebo-controlled, optional 24-week open-label extension study which included 114 patients ≥65 years with schizophrenia, randomized to receive placebo or paliperidone ER (3–12 mg/day, 6-mg starting dose, adjusted in 3-mg dose increments). During the double-blind phase, treatment-emergent adverse events were observed in 67% in the paliperidone ER group and 71% in the placebo group, while study discontinuations due to adverse events occurred in 7% in the paliperidone ER group and 8% of patients in the placebo group. Serious adverse events occurred in three (8%) placebo-treated patients and two (3%) paliperidone ER-treated patients. An age-related increase in the incidence of somnolence was detected (7% of patients aged 65–69 years; 11% of patients aged 70–74 years; 14% of patients >75 years). The incidence of extrapyramidal disorder was 5% for paliperidone ER compared with 11% for placebo, although hypertonia and tremor occurred only with paliperidone ER (3% each). The incidence of akathisia was similar (3%) in the two groups, while there were no reports of tardive dyskinesia. Elevated prolactin levels were observed in approximately one half of patients treated with paliperidone ER during the double-blind phase, but no patient experienced potentially prolactin-related adverse events. There were no notable mean changes from baseline to end point in serum glucose, serum lipids or body weight. Tachycardia was observed only in the paliperidone ER group (16%). A post-baseline prolongation of QTc interval ≥500 msec occurred in 2 of 76 paliperidone ER recipients during the double-blind period (both withdrawn from the study) and a further patient experienced QTc prolongation during the 24-week, open-label extension phase of the study. All three patients had a cardiovascular history that included QTc prolongation. There were no reports of neuroleptic malignant syndrome, orthostatic hypotension, cerebrovascular events, suicidal ideation or depression throughout the study. Safety and tolerability results in the 24-week extension phase were consistent with shorter-term results.

Rare adverse effects

Recently, three case have been reported in the literature regarding the possible occurrence of neuroleptic

malignant syndrome in relation to paliperidone admnistration in patients with schizophrenia.[58–60]

Overdosage

Information on paliperidone ER overdosage is still limited. According to the manifacturer's prescribing information and the summary of product characteristics,[22,23] observed signs and symptoms include extrapyramidal effects, gait unsteadiness, drowsiness, somnolence, tachycardia, hypotension and prolongation of the QTc interval.

Efficacy

Different randomized, double-blind, controlled studies have evaluated the efficacy of paliperidone ER in the acute and maintenance treatment of schizophrenia. Instruments used to measure the efficacy of treatment included, as primary efficacy measure, the Positive and Negative Syndrome scale (PANSS), and, as secondary outcome measures, the Clinical Global Impressions-Severity scale (CGI-S) and the Personal and Social Performance scale (PSP).

Acute treatment

Paliperidone ER was found to be more effective than placebo in the treatment of patients with an acute exacerbation of schizophrenia. Based on a pooled analysis[52] of the three similarly designed 6-week, multicenter, double-blind, randomized, fixed-dose, placebo-controlled studies,[45–47] mean PANSS total and subscale factor scores (positive symptoms, negative symptoms, disorganized thoughts, hostility/excitement, anxiety/depression) improved significantly from baseline to endpoint across all dose of paliperidone ER compared with placebo ($P \leq 0.001$). Significant ($P < 0.05$) improvements in PANSS total scores with paliperidone ER versus placebo were evident within 4–15 days of the beginning of therapy. A significantly greater proportion of patients in the paliperidone ER treatment groups achieved clinical response (paliperidone ER 3 mg/day = 39.8%; paliperidone ER 6 mg/day = 53.2.%; paliperidone ER 9 mg/day = 48.2%; paliperidone ER 12 mg/day = 56.7%; paliperidone ER 15 mg/day = 52.7%) compared to placebo (27.4%) ($P \leq 0.001$). An analysis of dose response for efficacy documented a modestly enhanced efficacy of paliperidone ER at higher doses (eg, 12 and 15 mg/day), with the smallest effect for paliperidone ER 3 mg/day dose. Paliperidone ER was also more effective than placebo in reducing global severity of clinical impairment, assessed by the CGI-S scale and in personal and social functioning, assessed by the PSP scale. With regard to this, results from a separate mediation analysis indicated that the significant effects of paliperidone ER on social functioning were independent of its effects on positive and negative symptoms of schizophrenia.[61]

In a 6-week, double-blind, active comparator study involving 399 patients with recently exacerbated schizophrenia requiring hospitalization, PANSS total scores improved from baseline to a significantly ($P < 0.05$) greater extent with paliperidone ER 9 or 12 mg/day than with quetiapine 600 or 800 mg/day at both 2- and 6-week timepoints.[48]

Canuso et al[62] conducted a post-hoc pooled analysis of patients from the three pivotal paliperidone ER trials of acute treatment who had previously received risperidone but who were experiencing an acute exacerbation. In 198 patients (142 treated with paliperidone ER and 56 with placebo) who met the inclusion criteria for prior risperidone therapy, paliperidone ER significantly improved clinical symptoms, global ratings of illness and functioning compared with placebo.

In a study primarily designed to obtain safety and tolerability data in an elderly population and, therefore, not powered for efficacy, during the 6-week, double-blind, placebo-controlled phase, the PANSS total scores improved from baseline to end point to a significantly ($P = 0.014$) greater extent in elderly patients treated with paliperidone ER than with placebo.[49]

Relapse prevention and long-term treatment

The efficacy of paliperidone ER in the prevention of acute symptom recurrence in patients with schizophrenia was investigated in a randomized, double-blind, placebo-controlled, multicenter study.[50] Hospitalized patients entered an 8-week run-in phase followed by a 6-week stabilization phase, using open-label, flexibly dosed paliperidone ER (3–15 mg/day, starting dose = 9 mg/day). Of the 530 patients enrolled in the run-in phase, 207 were then randomized in a 1:1 ratio to receive double-blind paliperidone ER at the dose

used in the stabilization phase or placebo. During the double-blind treatment phase, the mean dose of paliperidone ER was 10.8 mg/day. The primary efficacy measure was the time to a first recurrence of schizophrenia symptoms which included predefined changes in symptoms scores, psychiatric hospitalization, self-injury, and suicidal or aggressive behaviour during the double-blind phase (paliperidone ER or placebo treatment). Based on positive efficacy, the study was terminated at the prespecified interim analysis consisting of the occurrence of 43 recurrence events. In the intent-to-treat group, 14 patients (25%) in the paliperidone ER group experienced a recurrence event versus 29 patients (53%) in the placebo group. The timepoints at which recurrence occurred in 25% of patients were 83 days with paliperidone ER and 23 days with placebo ($P = 0.005$). Paliperidone ER treatment was also associated with less deterioration in other secondary measures of symptom severity, patient functioning or quality of life as compared to placebo.

Long-term efficacy of paliperidone ER (3–12 mg/day) was evaluated in pooled data from the 52-week open-label extensions of the three 6-week pivotal trials in patients with schizophrenia.[51] Irrespective of treatment assigned in the double-blind phase (paliperidone ER, olanzapine or placebo), during the open-label extension phase all patients received flexibly dosed paliperidone ER 3, 6, 9, 12 or 15 mg/day. Of the 1083 patients enrolled, 507 (47%) completed the 52-week open-label phase. In general, improvements in PANSS and PSP scores observed during the double-blind phase were maintained with longer-term treatment with paliperidone ER. By the end of the open-label phase, a clinical response was achieved by 68% in patients initially randomized to placebo, 69% in patients who continued paliperidone ER and 66% in those treated with olanzapine during the double-blind phase.

Schizoaffective disorder

Two international, 6-week, double-blind, placebo-controlled studies have evaluated the efficacy and tolerability of paliperidone ER in acutely ill patients with schizoaffective disorder.[63,64] Paliperidone ER, either as monotherapy or adjunctive to mood stabilizers and/or antidepressants, significantly improved schizoaffective symptoms compared with placebo.

Patient Preference

The patients' opinions of their treatment are increasingly recognized in psychiatric practice as an important factor which may contribute to the overall success of the therapeutic intervention. Indeed, "patient satisfaction" is now considered a relevant measure of the effectiveness of treatment. According to a recent investigation,[65] patient satisfaction with antipsychotic medication is positively associated with improved adherence, improved clinical outcomes and quality of life. The significance of patient satisfaction is further supported by the results of the CATIE study, which found that the most common reason for discontinuing antipsychotic medication within 18 months by 74% of patients was each patient's own choice.[4]

A recent randomized, 6-week, prospective, blinded-initiation study assessed antipsychotic medication satisfaction as a primary outcome measure in patients with schizophrenia.[66] Participants with suboptimal response to oral risperidone (4 or 6 mg/day) were randomized to receive either paliperidone ER immediate (n = 100) or delayed (week 2) initiation (n = 101). Patients assigned to an immediate initiation arm were given paliperidone ER, flexibly dosed 6 to 12 mg/day, for 6 weeks, while those assigned to a delayed initiation arm received their stable dose of risperidone for 2 weeks and then received paliperidone ER as in the immediate arm for the subsequent 4 weeks. Medication satisfaction was assessed by the Medication Satisfaction Questionnaire (MSQ), a single-item, global, patient-rated scale. In the overall population, MSQ score improved from 2.7 ± 0.8 (very to somewhat dissatisfied) at baseline to 5.1 ± 1.2 (somewhat satisfied) at endpoint ($P < 0.001$). On the basis of dichotomized analysis of the MSQ scale (score 1–4 = dissatisfied, 5–7 satisfied), 82% of participants were satisfied with their medication at endpoint. At the 2-week time point, significantly more participants in the immediate initiation group reported satisfaction (67.7%) compared with those in the delayed initiation group (45.3%) ($P = 0.002$), who were still receiving risperidone at this time. Despite methodological limitations, this preliminary study indicated that schizophrenic patients who were suboptimally responsive to risperidone showed improvement in medication satisfaction when treated with paliperidone ER.

Place in Therapy

The development of paliperdone ER may represent an innovative strategy to improve the pharmacological treatment of schizophrenia. The theoretical advantages of paliperidone ER in terms of efficacy and tolerability in comparison with risperidone and, possibly, other second-generation antipsychotics, are related to its formulation, pharmacokinetic and, to a lesser extent, pharmacodynamic profile.[67] The formulation of paliperidone ER, based on the OROS technology, provides constant drug release over 24-hours and reduce the peak-to-trough fluctuations in paliperidone plasma concentrations at steady-state. Its major advantages should be in terms of improved patient compliance, as it can be administered once daily and without the need for initial dose titration. Moreover, the gradual and continuous paliperidone release should increase the possibility to achieve stable D_2-receptor occupancy. Theoretically, the use of this formulation should ensure an efficacious relapse prevention and should minimize the risk of adverse effects presumably related to peak concentrations, including those occurring in the first few days of treatment with rapidly increasing doses, ie, acute dystonia and postural hypotension. With regard to pharmacokinetic properties, paliperidone is characterized by negligible hepatic metabolism. As a consequence, paliperidone ER should be associated with a lower potential for metabolic drug interactions as compared with risperidone. In addition, this agent should have a reduced liability to cause unexpected over- or under-dosages related to CYP2D6 genetic variability and may be an appropriate choice for patients with hepatic impairment. Although paliperidone and risperidone share many pharmacodynamic properties, some differences have been documented between parent drug and metabolite (ie, off-rate dissociation from D_2 receptors and affinity for P-glycoprotein) whose potential clinical consequences are still unknown. At this time, however, the expected clinical benefits of paliperidone ER when compared to risperidone and other currently available second-generation antipsychotics have been only partially fulfilled.

Randomized, double-blind trials have documented that paliperidone ER is more effective than placebo for the acute treatment of schizophrenia and for the prevention of relapses. Evidence from the open-label extension phases of the short-term trials have indicated that symptom control may be maintained during long-term treatment. Paliperidone ER demonstrated efficacy not only in the control of the core symptoms of schizophrenia (positive and negative symptoms, disorganized thoughts, hostility/excitement, anxiety/depression), but also produced relevant improvement in personal and social functioning, an essential component of optimizing long-term outcomes for patients with schizophrenia. Of note, paliperidone ER is the only antipsychotic agent to date to include functionality assessment throughout the clinical development process. Some aspects of the efficacy profile of paliperidone ER deserve further investigation. To date, few head-to-head comparisons with other second-generation compounds have been performed. Although olanzapine was used as an active comparator in the pivotal trials of acute treatment, no statistical comparisons were conducted between paliperidone ER and olanzapine. When compared with quetiapine in hospitalized patients with a recent hospitalization, paliperidone ER was associated with a more rapid clinical improvement. In addition, no trials have so far evaluated the efficacy of paliperidone ER in patients with treatment-resistant schizophrenia.

Based on short- and longer-term trials, paliperidone ER appears to be a safe and well tolerated agent with a lower liability to acute and chronic side effects in comparison to placebo. Its tolerability profile is very similar to risperidone. As with its parent drug, paliperidone ER may cause EPS and hyperprolactinemia in a dose-dependent manner. Long-term studies are obviously required to establish the incidence of tardive dyskinesia, especially in elderly patients. No evidence of clinically relevant alterations in glucose and lipid metabolism has been documented so far with paliperidone ER, while a dose-related increase in body weight of less than 1 and 2 kg was observed in short- and longer-term studies, respectively. Paliperidone ER appears to carry a low pro-arrhythmic potential. Preliminary data indicate that paliperidone ER has a favourable tolerability and safety profile in elderly patients with schizophrenia. As the available studies investigating the effect of CYP inhibitors or inducers on paliperidone kinetics were consistent with its favorable drug interaction profile, paliperidone ER might

be particularly useful for elderly patients requiring multiple medications for co-morbidities.

A recent pharmacoeconomic analysis has evaluated the clinical and economic consequences of treatment with different oral atypical antipsychotics (aripiprazole, olanzapine, paliperidone ER, quetiapine, risperidone and ziprasidone) in schizophrenia over one-year from a US healthcare system perspective.[68] Despite important methodological limitations, this cost-effectiveness study, using a model that included discontinuation rates, symptom response, relapse, adverse events, resource utilization and unit costs, has indicated that paliperidone ER is associated with better outcomes and lower costs than other antipsychotics in patients with schizophrenia.

Current scientific evidence indicates that paliperidone ER is an effective and well tolerated agent in the acute and maintenance treatment of schizophrenia, without clear advantages over other antipsychotics. Therefore, independent, well-designed, active comparator trials examining efficacy, tolerability and cost-effectiveness are needed in order to accurately place paliperidone ER in relation to other second-generation antipsychotics and, in particular, risperidone.

Conclusions

Paliperidone ER is a second-generation antipsychotic that is administered once daily and without the need for initial dosage titration. The results of randomized, double-blind, placebo-controlled support the efficacy of paliperidone in the treatment of schizophrenia. It has demonstrated efficacy in the reduction of acute schizophrenia symptoms in 6-week, placebo-controlled, double-blind trials and its clinical benefits were maintained in the longer-term according to extension studies of up to 52 weeks in duration. Paliperidone ER appears to be more effective than placebo also for the prevention of acute symptom recurrence. The drug is generally safe and well tolerated with a predictable adverse event profile. Like risperidone, paliperidone ER is associated with a dose-dependent risk of EPS and prolactin elevation. Due to minimal hepatic biotransformation, paliperidone ER has a low potential for metabolic drug interactions. Based on the current scientific evidence, paliperidone ER is a useful option in the management of schizophrenia. However, further independent, head-to-head comparative studies with other newer antipsychotics, in particular risperidone, are needed to determine the role of paliperidone ER in the acute and maintenance treatment of schizophrenia.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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