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REVIEW

The role of paliperidone extended release for the treatment of bipolar disorder

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Background: Bipolar disorder (BD) is a chronic, relapsing, episodic mental illness associated with other psychiatric comorbidities. There is a substantial economic burden with BD, which makes it challenging to treat. The aim of this review is to evaluate the pharmacology, clinical efficacy, and safety data related to paliperidone extended release (ER) for the treatment of BD.

Methods: A literature search was performed from January 1966 through January 2012 using PreMEDLINE, MEDLINE, EMBASE, IPA, and ClinicalTrials.gov to identify articles in English regarding the pharmacology, clinical efficacy, and safety of paliperidone ER in acute mania or mixed episodes or in the maintenance treatment of BD I.

Results: There are currently three published studies relating to the use of paliperidone ER for the treatment of BD. Two of these evaluated paliperidone ER as monotherapy for acute mania, while the other assessed its role as adjunct with a mood stabilizer.

Conclusion: According to the limited available evidence, paliperidone at higher doses of ER 9–12 mg/day may be a safe and efficacious treatment option for acute episodes of mania in BD. A once-daily dose formulation may improve patient adherence to treatment; however, the cost of paliperidone ER, which is higher than that of generically available second-generation antipsychotics (such as olanzapine and risperidone), and a lack of alternative dosage forms (ie, liquid, intramuscular) compared with other agents may limit its usefulness in the treatment of BD. The role of paliperidone ER as an adjunctive agent or for long-term use requires further investigation.

Keywords: paliperidone ER, bipolar disorder, clinical efficacy, safety

Background

Bipolar disorder (BD) is a chronic, episodic mental illness characterized by periods of mania, depression, and mixed episodes with an estimated lifetime prevalence of approximately 1%.[1] The mean age of onset is 18–20 years, that is, in the late teens to early adulthood.[2] According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR), patients presenting with a manic episode must have an abnormally and persistently elevated or expansive mood for 1 week, or for any duration if the patient is hospitalized.[3] In addition, the patient must have symptoms such as racing thoughts, distractibility, and inflated self-esteem or grandiosity. In severe cases, patients may have psychotic symptoms (eg, auditory hallucinations, delusions). Patients with BD often have other comorbidities, including anxiety and alcohol use as well as other substance abuse disorders, which makes treatment challenging for health care providers.[4,5] Previous evidence has shown that clinical factors such as the presence of anxiety and alcohol use are associated with nonadherence to bipolar medications, and that these factors may also contribute to hypomanic or manic episodes.[6]

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Current consensus guidelines recommend pharmacotherapy as first-line treatment for patients.[7–9] A summary of US Food and Drug Administration (FDA)-approved agents for BD is listed in Table 1. Lithium, valproate, or second-generation antipsychotics (SGAs) represent first-line options, with valproate being preferred over lithium for mixed episodes.[7,8] Combination therapy, consisting of different pharmacologic classes, can be implemented in severe cases. Overall, SGAs are equally, if not more, effective than lithium and valproate for the acute treatment of mania. This was recently confirmed in a meta-analysis that systematically reviewed 68 randomized controlled trials of mood stabilizers and antipsychotics in the treatment of mania.[10] The main outcome of the study was to assess the mean change of the Young Mania Rating Scale (YMRS) over 3 weeks as well as treatment discontinuation rates. Overall, antipsychotics tended to be more efficacious and had fewer discontinuations compared with mood stabilizers.

Although there are several treatment options targeting manic symptoms, reported relapse and recurrence rates range from 39% to 52% per year with varying medication regimens.[11] Nonadherence to medication also has a substantial impact on patient outcome and recovery. A study reported that 10%–60% of patients with mood disorders are nonadherent to treatment, which is possibly related to medication side effects.[12] Conversely, those who are adherent with medications may develop untoward side effects associated with chronic use, including weight gain, metabolic disturbances, and movement disorders.[13] As a result, it is necessary to seek new agents that are well tolerated to improve patient adherence and overall outcomes.

The aim of this review is to evaluate the pharmacology, safety, and efficacy of paliperidone extended release (ER) for the treatment of BD. Paliperidone (9-OH-risperidone) is an SGA currently FDA approved for the treatment of schizophrenia and schizoaffective disorder. Paliperidone has the potential to treat the manic symptoms of BD. It is the major active metabolite of risperidone and it has many similarities with its parent compound that may contribute to potential efficacy in the treatment of manic episodes in BD. Additionally, paliperidone appears to have fewer side effects than risperidone, which may improve patient adherence.

Methods

A literature search was performed from January 1966 to January 2012 using PreMEDLINE, MEDLINE, EMBASE, IPA, and ClinicalTrials.gov databases, to identify articles in English regarding the pharmacology, clinical efficacy, and safety of paliperidone ER in acute mania or mixed episodes, or maintenance treatment of BD I. Full text articles and abstracts were evaluated and included in the review if they were relevant to our topic.

Table 1 Medications FDA approved for bipolar disorder

Pharmacologic class and medication	FDA-approved indications			
	Acute mania	Acute depression	Mixed symptoms	Maintenance treatment
Group 1A alkaline metals				
Lithium	✓[a]			✓[a]
First-generation antipsychotics				
Chlorpromazine	✓[b]			
Second-generation antipsychotics				
Olanzapine	✓[c]		✓	✓
Olanzapine/Fluoxetine combination		✓[a]		
Risperidone	✓[c]		✓[c]	
Risperidone long-acting intramuscular injection				✓[a]
Quetiapine (immediate release and extended release)	✓[c]	✓[a]	✓[c]	✓[d]
Ziprasidone	✓[a]		✓[a]	✓[d]
Aripiprazole	✓[c]		✓[c]	✓[c]
Asenapine	✓[c]		✓[c]	
Antiepileptic medications				
Lamotrigine				✓[a]
Divalproex (immediate release and extended release)	✓[a]		✓[a]	
Carbamazepine extended release	✓[a]		✓[a]	

Notes: [a]FDA approved as a monotherapy; [b]FDA approved to control the manifestations of the manic type of manic-depressive illness; [c]FDA approved as a monotherapy or as an adjunct treatment to lithium or valproate; [d]FDA approved only as an adjunct to lithium or divalproex sodium for maintenance.
Abbreviation: FDA, US Food and Drug Administration.

Chemistry

Paliperidone is the major active metabolite of risperidone. It is a benzisoxazole derivative chemically known as (+/–)-3[2-[4-(6-flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a] pyrimidin-4-one.[14] Insoluble in water, paliperidone has a molecular formula and weight of $C_{23}H_{27}FN_4O_3$, and 426.49, respectively.

Pharmacology

Paliperidone's primary mechanism of action is via potent inhibition of dopamine (D_2) receptors and is a partial serotonergic (5-HT_{2A}) antagonist. It also has an affinity for several additional receptors, including 5-HT_{1D}, 5-HT_{2B}, 5-HT_7, and D_3.[15–17] The K_i values for binding to D_2 and $5HT_{2A}$ receptors are 0.16 and 0.25 nM, respectively.[15,16,18] In vitro studies show a weak affinity for alpha ($\alpha_{1,2}$) adrenergic and histaminic (H_1) receptors while displaying no affinity for cholinergic, muscarinic, or beta ($\beta_{1,2}$) adrenergic receptors.[17] As a result, in vitro data suggest a lower risk of orthostasis, sedation, and weight gain compared with other SGAs (eg, olanzapine). A 6 mg dose of paliperidone in humans provides a striatal D_2 occupancy of 64% and 53% after 22 and 46 hours, respectively.[19] Occupancy for the 5-HT_{2A} receptor is 65% and plasma concentrations range between 5.1 and 6.0 ng/mL over 4 hours.[19] As a result, a 6 mg dose appears to provide sufficient receptor binding in its ability to effectively treat symptoms of mania or psychosis.[20]

Animal data show that paliperidone has protein expression profiles at the neuronal level (ie, synapse) that is most similar to lithium, an agent considered first line in the treatment of BD.[21] Paliperidone appears to inhibit glycogen synthase kinase 3 in the pre-frontal cortex, which may account for its mood stabilizing effects. Additionally, like lithium, paliperidone demonstrates activity on oxidative phosphorylation, electron transport, carbohydrate metabolism, and postsynaptic cytokinesis.[21] As a result, based on in vitro studies, it has been determined that paliperidone may play a role in signaling pathways, energy metabolism, and synaptic plasticity, which may be implicated in BD.

Pharmacokinetics

Absorption and distribution

Overall, the absolute bioavailability of paliperidone is 28%, with a volume of distribution of approximately 490 L. The elimination half-life ($t_{½}$) is 23 hours and time to steady state occurs in approximately 4–5 days. Paliperidone is delivered via Osmotic-controlled Release Oral Delivery System technology, which slowly delivers paliperidone over 24 hours with minimal peak to trough fluctuations.[14,22] Peak plasma concentrations and time to peak plasma concentrations are 11 ng/mL and 24 hours, respectively.[19] Presently, even though the package insert states paliperidone can be taken irrespective of meals, it appears food increases the bioavailability of paliperidone. Unpublished data demonstrate food increases peak plasma concentrations and area under the curve (AUC) by 60% and 54%, respectively.[14] Paliperidone is approximately 74% protein bound and the total volume of distribution is approximately 485 L. The enantiomers of paliperidone interconvert and are equipotent.[23,24]

Metabolism and elimination

Only 32% of paliperidone is recovered as metabolites through cytochrome P450 (CYP) 2D6, and to a lesser extent, CYP 3A4. The pharmacokinetic profile of paliperidone is similar in subjects with normal hepatic function and moderate hepatic impairment.[25] Therefore, dose adjustments are not needed for those with mild to moderate hepatic function. At this time, studies evaluating patients with severe hepatic impairment are lacking, and caution may be warranted in this patient population. Additionally, differences in adverse effects (ie, extrapyramidal symptoms [EPS]) between poor and extensive metabolizers of CYP 2D6 appear to be minimal; therefore, dose adjustments of paliperidone are also not required.[26] Impaired renal function may increase paliperidone concentrations since 60% of the drug is excreted almost unchanged in the urine via the renal tubules.[14,22] As a result, patients with a creatinine clearance rate (CrCl) $\geq$50 mL/min should be initiated at 6 mg daily, while those with CrCl $<$ 50 mL/min should be started at 3 mg daily.[14] The dosing recommendations are based on data that show the total clearance of paliperidone decreases by 32%, 64%, and 71% in those with mild (CrCL 50 to $<$80 mL/min), moderate (CrCl 30 to $<$50 mL/min), and severe (CrCl $<$ 30 mL/min) renal impairment, respectively.[14]

Special populations

Pharmacokinetics have been evaluated in the elderly population (mean age: 71 ± 5.1 years).[27] Data after single and multiple dosing show some differences in the area under the plasma concentration–time curve (ie, $AUC_{0-\infty}$, AUC_t) and $t_{½}$. Additionally, clearance in the geriatric group was 20%–24% lower than in the adult group. Despite these pharmacokinetic differences, paliperidone does not merit any dose adjustment in geriatrics with normal kidney function. The pharmacokinetic profile of paliperidone in 24 children

aged 10–17 years was conducted in a multicenter, open-label study.[28] Plasma concentration gradually peaked after 24 hours from the first dose, and a steady state was achieved at day 4 or 5. The pharmacokinetic profiles of adults and pediatrics appear to be similar.[28]

Drug interactions

Trials evaluating pharmacokinetic drug–drug interactions are limited. One randomized, crossover, open label study in healthy males assessed the drug interaction potential between paliperidone and paroxetine, a potent CYP 2D6 inhibitor.[29] The AUC and $t_{½}$ of paliperidone were minimally increased and not clinically significant. However, it must be noted that low doses of paliperidone (3 mg) and paroxetine (20 mg) were administered during the study. Therefore, it is unknown if normal daily doses of these agents would generate more significant findings. A possible interaction between divalproex sodium and paliperidone may occur. There was a 50% increase in paliperidone (12 mg daily) peak plasma concentrations and AUC concentrations when taken concomitantly with divalproex sodium extended release (1000 mg daily).[14] Additionally, data show that carbamazepine (400 mg daily) can decrease paliperidone (6 mg daily) concentrations by approximately 35%. Therefore, paliperidone dose adjustment is needed when adding or discontinuing divalproex sodium or carbamazepine.

Paliperidone is mostly excreted via the renal tubules through a cation transport system. Other drugs that are also excreted through this mechanism (eg, ketoconazole, lithium) may compete with the transport site. Therefore, concomitant administration may cause a reduction in the clearance and an increase in AUC of any of these agents. In one trial, renal clearance of paliperidone was assessed when taken alone or in combination with trimethoprim (200 mg twice daily).[30] The open-label, randomized, cross-over study showed an insignificant decrease in concentration (ie, $AUC_{0-\infty}$) and a 5-hour decrease in the $t_{½}$ of paliperidone; however, the results did not warrant any dose adjustments. When compared with risperidone, in vitro data appear to demonstrate that paliperidone is a weak inhibitor of P-glycoprotein (P-gp). As a result, lower paliperidone concentrations in cerebrospinal fluid may occur. However, caution interpreting these results is warranted since varying concentrations may affect paliperidone and P-gp interactions.

Paliperidone versus risperidone

Risperidone is FDA approved for the treatment of BD based on clinical data demonstrating efficacy. Since paliperidone is the active metabolite of risperidone, it would seem logical that paliperidone would demonstrate efficacy as well. However, paliperidone and risperidone have some pharmacodynamic differences that could affect efficacy in treatment of BD. First, paliperidone may have more difficulty compared with risperidone in crossing into the central nervous system (eg, blood–brain barrier).[31] Additionally, paliperidone has a greater affinity for D_2 receptors and a lower affinity for $5\text{-}HT_{2a}$ receptors compared with risperidone. As a result, the data suggest paliperidone acts less as an atypical antipsychotic (eg, showing improvements in mood and cognition) compared to risperidone. On the contrary, paliperidone may offer some advantages over risperidone. Studies evaluating receptor affinity suggest that paliperidone may have a lower incidence of orthostatic hypotension and may cause lower weight gain compared with risperidone.[31] Additionally, paliperidone may have a more favorable dosing profile (eg, less titration) and linear kinetics (eg, once-daily dosing); however, risperidone given twice daily would offer lower peak concentrations, which may lead to fewer adverse effects. Comparative studies are needed to confirm whether paliperidone is as equally safe and effective as risperidone in treating patients with BD.

Clinical efficacy studies

Paliperidone ER is not currently FDA labeled for BD; however, to date, there have been three published randomized controlled studies evaluating the efficacy and safety of treating adult patients with BD. Two of these evaluated paliperidone ER as monotherapy and the other assessed adjunctive therapy.[32–34] A summary of these studies is found in Table 2. The primary outcome was change of YMRS from baseline to endpoint in all of the studies. Further, secondary outcomes included changes in Global Assessment of Functioning, as well as response (defined as ≥50% reduction in YMRS total score), remission rates (defined as YMRS score of ≤12 at endpoint), and adverse effects. Of note is that all these published studies were industry-sponsored trials.

Monotherapy

Berwaerts et al conducted a 3-week, double-blind, placebo-controlled, dose–response study in adult patients (n = 443; mean [standard deviation (SD)] age: 39 (10.9); 53% males) with a DSM-IV-TR diagnosis of BD I, most recent episode of mania or mixed mania.[32] The study included a 7-day washout period, followed by 3 weeks of double-blind treatment and a 1-week follow-up for safety assessments. Participants were randomized to receive either paliperidone ER 3, 6, or 12 mg/day or placebo. Patients receiving paliperidone ER

Table 2 Summary of clinical studies with paliperidone extended release in acute mania[32–34]

Study	N	Change in mean (SD) YMRS total score	Difference in LS mean change[a]	
			95% CI	*P* value
Monotherapy				
Berwaerts et al[32]	443			
Paliperidone ER 3 mg	107	−9.1 (11.18)	−1.0 (−1.59, 3.58)	0.79
Paliperidone ER 6 mg	112	−11.4 (9.98)	−1.4 (−3.98, 1.15)	0.57
Paliperidone ER 12 mg	109	−13.8 (9.67)[b]	−3.6 (−6.99, 0.30)	0.025
Placebo	115	−9.8 (10.60)		
Vieta et al[33]	486			
Paliperidone ER 3–12 mg	190	−13.2 (8.68)	−5.5 (−7.57, 3.35)	0.001
Quetiapine 400–800 mg	192	−11.7 (9.28)	−4.2 (6.45, −1.95)	0.001
Placebo	104	−7.4 (10.74)		
Adjunct				
Berwaerts et al[34]	299			
Paliperidone ER plus MS	149	−14.3 (10.01)	−1.36 (−3.27, 0.54)	0.16
MS monotherapy plus placebo	150	−13.2 (10.91)		

Notes: [a]All least square means change versus placebo, except Berwaerts et al adjunctive study: combo vs monotherapy; [b]*P* value = 0.005.
Abbreviations: CI, confidence interval; ER, extended release; LS, least squares; MS, mood stabilizer (lithium or valproate); SD, standard deviation; YMRS, Young Mania Rating Scale.

12 mg had significant improvements in mean (SD) YMRS total score at the endpoint compared with placebo (−13.8 [9.67] vs −9.8 [10.60]; $P < 0.025$) based on last observation carried forward analysis. No other treatment group (3 or 6 mg) showed significant improvements in YMRS total score compared to the placebo. Additionally, there were no statistical improvements in any of the secondary outcome measures compared to the placebo (ie, response, remission rates). According to the study, it appears that paliperidone ER 12 mg is an effective dose for treating acute mania. However, the comparable placebo response may have resulted in a lack of efficacy with the lower doses.

Another study evaluated the efficacy and safety of paliperidone ER in a 12-week randomized, placebo and active control study with quetiapine in adult patients (n = 486; mean [SD] age 39 years [10.9]; 58% males) with a DSM-IV-TR diagnosis of acute manic or mixed episodes of BD.[33] There was a 1-week washout period, followed by a 3-week double-blind phase in which patients received flexible dosing of paliperidone ER, at 3–12 mg/day. A 9-week double-blind maintenance phase was continued, where patients either continued flexible dosing with their active treatment or switched from the placebo to paliperidone ER 6 mg. Paliperidone ER was initiated at 6 mg/day and titrated or tapered in 3 mg increments with a maximum dose of 12 mg/day as clinically necessary. Quetiapine was initiated at 100 mg/day on day 1 and forced titration to 400 mg/day at day 4, with adjustments of 200 mg/day to a maximum of 800 mg/day. Median doses were 9 mg for the paliperidone ER group and 600 mg for the quetiapine group during the 3-week phase.

Based on the last-observation-carried-forward analysis, at the end of 3 weeks, paliperidone ER-treated patients had a significant mean reduction in least square means (LSM) YMRS total score compared with the placebo group (LSM difference from placebo was −5.5; 95% CI −7.57, −3.35; $P < 0.001$). At the end of 12 weeks, LSM for changes in YMRS total score between quetiapine and paliperidone ER was −1.7 (95% CI −0.47, 3.96). The lower limit of 95% CI (−0.47) was greater than the noninferiority margin of −4, so paliperidone ER was considered noninferior to quetiapine in this study. Additionally, mean (SD) change in Global Assessment of Functioning scores was significantly improved in the paliperidone ER group (12.2 [11.1] compared with the placebo (6.7 [13.5] at 3 weeks ($P < 0.001$). There was a higher percentage of remitters in the paliperidone ER-treated group compared with the placebo at 3 weeks (52% [99/190] vs 28% [30/104], $P < 0.001$). As a result, it appears that paliperidone ER 3–12 mg is as effective as quetiapine for the treatment of acute mania; however, the higher doses may be more effective, as the median dose was 9 mg.

Adjunct treatment

A 6-week, randomized, placebo-controlled study evaluating paliperidone ER as adjunct to lithium or valproate was conducted in adult patients (n = 299; mean (SD) age 40 [11] years, 54% males) with acute mania.[34] Inclusion criteria included a DSM-IV-TR diagnosis of BD I, with either a recent episode of mania or mixed mania without psychosis and treatment with lithium or valproate for BD ≥ 2 weeks prior to randomization. The study consisted of a 14-day washout

period, followed by a 6-week double-blind phase, with a 1-week follow-up. Participants were randomized to either continue monotherapy (n = 150) with lithium or valproate, or receive adjunctive paliperidone ER (n = 149) at a flexible dose (3–12 mg/day). Based on the intention-to-treat last-observation-carried-forward analysis, patients who received combination treatment (median dose: 6 mg/day) had no significant differences in mean change in YMRS score from baseline (LSM difference, 95% CI: −1.36 [−3.27, 0.54]; $P = 0.16$). Additionally, there were no differences in Global Assessment of Functioning scores (LSM difference, 95% CI: 2.47 [−0.93, 5.87]; $P = 0.15$). The authors did not report valproate or lithium doses and serum concentrations, and most patients received valproate at baseline (63% [94/150]). Although there were no benefits in adding paliperidone ER to a mood stabilizer for patients with acute mania, caution is warranted when evaluating the results, as these patients may have needed a higher dose for improvement in symptoms.

Safety and tolerability

Tolerability data pertaining to paliperidone ER in patients with BD were obtained from three double-blind clinical trials.[32–34] Adverse events related to paliperidone ER in the bipolar studies are generally consistent with adverse events seen in other populations treated with paliperidone in former clinical studies (eg, schizophrenia, schizoaffective disorder).[35] The treatment-emergent adverse events (TEAEs) associated with paliperidone ER in the three clinical trials are summarized in Table 3.

Paliperidone ER was generally well tolerated in the two 3-week acute monotherapy phase trials.[32,33] Treatment emergent adverse events were similar among paliperidone ER and the placebo in the 3-week fixed-dose trial; however, the frequency of adverse events increased as the dose of paliperidone ER increased. Excluding EPS-related adverse events, the TEAEs most commonly reported (≥5% of all paliperidone ER recipients) were headache, insomnia, somnolence, sedation, dizziness, constipation, nausea, vomiting, dyspepsia, and mania. Mood switches to depression were not significantly different between paliperidone ER groups and the placebo group.[32]

In the monotherapy trial using quetiapine as an active comparator, TEAEs were slightly higher in the quetiapine treatment group (77%) versus the paliperidone ER (65%) and placebo groups (63%) during the 3-week acute treatment phase.[33] Excluding EPS-related adverse events, the TEAEs most commonly reported (≥5% of all paliperidone ER recipients) in the acute phase of treatment were headache, insomnia, somnolence, sedation, dizziness, constipation, dyspepsia, dry mouth, and insomnia. Similar trends were seen in the continuous 9-week maintenance phase, with similar TEAEs occurring in both the placebo/paliperidone ER group (71%) and paliperidone ER group (71%). Slightly higher TEAEs were reported with the quetiapine treatment group (82%) at the end of the maintenance phase. One death was reported in the maintenance phase (quetiapine treatment group) and another death was reported 5 days after withdrawal from the maintenance phase of the

Table 3 Treatment-emergent adverse events (TEAEs) during double-blind controlled trials of paliperidone extended release (ER) for bipolar disorder[32–34]

	Overall TEAEs	Possibly related TEAEs	TEAEs leading to death	1 or more serious TEAEs	TEAEs leading to discontinuation
Monotherapy					
Berwaerts et al[32]					
Placebo (n = 121) n (%)	85 (70)	49 (40)	0	10 (8)	6 (5)
Paliperidone ER 3 mg (n = 112) n (%)	68 (61)	45 (40)	0	4 (4)	1 (1)
Paliperidone ER 6 mg (n = 119) n (%)	89 (75)	64 (54)	0	5 (4)	13 (11)
Paliperidone ER 12 mg (n = 115) n (%)	100 (87)	68 (59)	0	5 (4)	9 (8)
Total (n = 467) n (%)	342 (73)	226 (48)	0	24 (5)	29 (6)
Vieta et al[33]					
Placebo/paliperidone ER (n = 105) n (%)	75 (71)	50 (48)	1 (1)	8 (8)	7 (7)
Paliperidone ER (n = 194) n (%)	136 (70)	113 (58)	0	16 (8)	18 (9)
Quetiapine (n = 192) n (%)	157 (82)	122 (64)	1 (1)	14 (7)	12 (6)
Total (n = 491) n (%)	368 (75)	285 (58)	2 (<1)	38 (8)	37 (8)
Adjunct					
Berwaerts et al[34]					
MS + Placebo (n = 150) n (%)	81 (54)	39 (26)	NR	7 (5)	2 (1)
MS + Paliperidone ER (n = 149) n (%)	104 (70)	62 (42)	NR	7 (5)	12 (8)

Abbreviation: MS, mood stabilizer (lithium or valproate).

study (placebo/paliperidone ER group). Both deaths were considered possibly related to the study drug. A mood switch to depression was not different in any group at the end of the 3-week acute phase. Quetiapine therapy had significantly less ($P = 0.044$) mood switches to depression than paliperidone ER at the end of the maintenance phase.

Treatment with paliperidone ER as an adjunctive agent to lithium and valproate treatment was associated with a higher frequency of TEAEs (70%) compared with patients receiving placebo as an adjunctive agent (54%) during the 6-week study.[34] Excluding EPS-related adverse events, the TEAEs most commonly reported (≥5% of all paliperidone ER recipients) were headache, somnolence, sedation, insomnia, dry mouth, weight gain, and increased appetite. The majority of adverse effects occurred at a higher frequency with paliperidone ER than with mood stabilizer monotherapy (≥3% difference compared with monotherapy), with the exception of insomnia and dry mouth. A higher number of patients switched to depression with mood stabilizer monotherapy (14%) than with combination treatment (7%); however, the difference did not reach statistical significance.

EPS-related adverse events

EPS-related adverse events occurred more frequently in the paliperidone ER treatment groups in all studies. Compared with the placebo group, paliperidone ER treatment groups had higher frequencies (≥3% difference) of hypertonia (3% vs 1%), akathisia (5% vs 2%), and dystonia (4% vs 0%) in the 3-week fixed-monotherapy trial. One patient discontinued treatment secondary to dystonia.[32] In the 12-week maintenance study, EPS-related adverse events that occurred more frequently (≥3% difference) in the paliperidone ER group compared to patients receiving quetiapine included akathisia (10% vs 3%), hypertonia (5% vs 1%), and drooling (6% vs 0%).[33] Compared to mood stabilizer monotherapy, EPS-related adverse events that occurred more frequently with adjunctive paliperidone ER therapy (≥3% difference) included akathisia (8% vs 1%) and extrapyramidal disorder (4% vs 1%). Concurrent anticholinergic therapy for treatment of EPS was higher with combination treatment (10%) than with mood stabilizer monotherapy (3%).[34]

Metabolic and prolactin adverse effects

The mean change in body weight from baseline in the fixed-dose 3-week acute trial was 0.2 and 1.1 kg with placebo and paliperidone ER, respectively. Thirteen patients treated with paliperidone ER as monotherapy experienced ≥7% weight increase from baseline compared to one patient treated with placebo.[32] The mean change in body weight from baseline at the 3-week endpoint in the active comparator trial was 0.6, 1.1, and 1.1 kg with placebo, paliperidone ER, and quetiapine, respectively. At the end of the 12-week maintenance phase, the mean change in body weight from baseline was 1.2, 1.5, and 2.0 kg for placebo/paliperidone ER, paliperidone ER, and quetiapine, respectively. More patients treated with quetiapine (17%) had ≥7% weight increase from baseline compared to the paliperidone ER group (8%) at the end of the maintenance phase.[33] The mean weight change with paliperidone ER adjunctive therapy was higher (1.8 kg) than in mood stabilizer monotherapy (0.7 kg). Fifteen percent of patients treated with the combination therapy had ≥7% weight increase from baseline compared with 5% treated with mood stabilizer monotherapy.[34]

Glucose-related adverse events were rare in the bipolar trials. No treatment-emergent glucose-related adverse events were reported in the fixed-dose monotherapy study and ≤2% occurred in all treatment groups within the adjunctive and maintenance studies. Dose-related increases in prolactin concentrations were associated with paliperidone treatment in all studies. Mean increases in prolactin concentrations ranged from 13.5 to 36.0 ng/mL in men and 59.6 to 103.9 ng/mL in women in the three trials.[32–34] A total of 17 TEAEs with paliperidone ER were identified across all studies, which is possibly related to elevated prolactin elevations, with none leading to study discontinuation.

Cardiac adverse events

With the exception of tachycardia, clinically relevant changes in vital signs or electrocardiography parameters were minimal in the paliperidone ER treatment groups. Twelve percent of patients treated with a combination of a mood stabilizer and paliperidone ER had abnormally high heart rates (≥100 bpm) compared with 5% with mood stabilizer monotherapy.[34] In the maintenance study, abnormally high heart rates were reported in 20% of patients treated with paliperidone ER monotherapy compared to 19% and 10% of patients treated with quetiapine and placebo/paliperidone ER, respectively.[33] With the exception of heart rate, there were no clinically relevant differences in electrocardiography recordings between the placebo and paliperidone treatment groups in all three studies.[32–34]

Summary

Based on the limited amount of available data, paliperidone ER may be an effective agent for the treatment of acute episodes of BD at doses ranging from 9 to 12 mg/day.

The study evaluating lower doses of paliperidone ER (≤6 mg) as adjunctive therapy showed that there was no improvement in efficacy and the addition of paliperidone led to a higher incidence of adverse events (eg, tachycardia). Common adverse effects reported in the acute trials included headache and sedation. A higher incidence of EPS was also reported with paliperidone than with quetiapine. Although more patients gained weight when receiving paliperidone, these effects were comparable to quetiapine. Additionally, tachycardia was reported to occur more frequently in patients receiving a combination of paliperidone and a mood stabilizer and caution is warranted in patients with cardiac comorbidities.

Currently, there are no published results for paliperidone's effects on preventing recurrence of BD and no head-to-head studies comparing paliperidone with other antipsychotic or mood stabilizers. At this time, paliperidone ER does not appear to have benefits additional to those provided by other currently approved SGAs or mood stabilizers for acute mania. Further study is needed, especially regarding mixed or depressed episodes of BD and paliperidone's potential use as a maintenance treatment. A once-daily dose formulation may improve patient adherence to treatment; however, cost, the availability of other approved generic SGAs (ie, olanzapine, risperidone), and a lack of other dosage formulation availability (ie, liquid, intramuscular) compared with other agents, may limit its extended use for the treatment of BD.

Disclosure

The authors declare no conflicts of interest in this work.

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