

Paliperidone ER: Reformulated antipsychotic for schizophrenia Tx

Risperidone's metabolite behaves well but differently in once-daily delivery

In the 9 months since paliperidone extended-release was FDA-approved for schizophrenia, the 3 acute pivotal trials supporting its approval have been published.¹⁻³ They join a handful of post hoc analyses of this second-generation antipsychotic (SGA) in schizophrenia subgroups, including patients over age 65, recently diagnosed patients, and those with predominant negative symptoms.

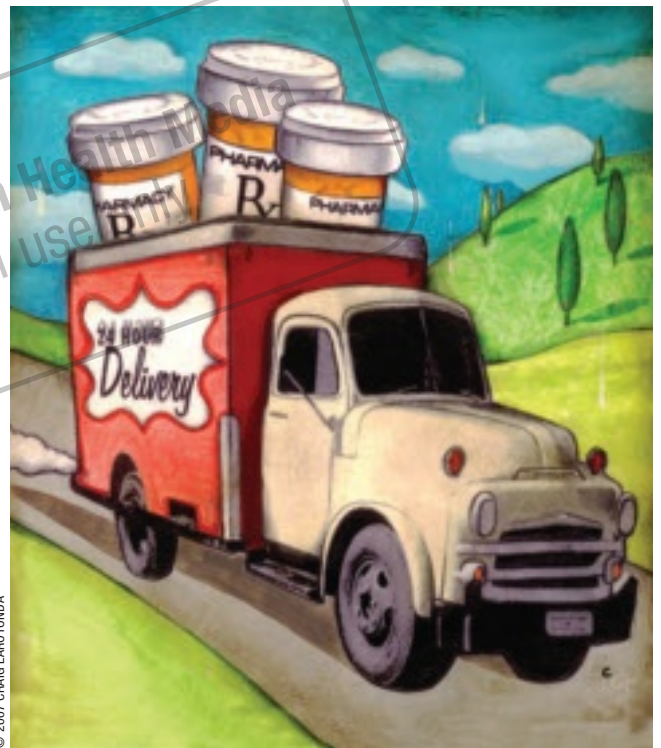
This article discusses the evidence and paliperidone ER's probable clinical benefits and adverse effects, with focus on its:

- pharmacodynamics and pharmacokinetics
- potential efficacy in schizophrenia and for specific patients and symptoms
- safety and tolerability.

How does paliperidone ER work?

Paliperidone ER was approved for schizophrenia treatment in December 2006 based on three 6-week, randomized, placebo-controlled trials. Paliperidone ER is the active metabolite of risperidone (9-OH risperidone) delivered in a once-daily, time-released formulation (Table 1, page 76).

Pharmacodynamics. Similar to risperidone, paliperidone ER has high binding affinity for dopamine (D2) and serotonin (5-HT_{2A}) receptors, with additional affinity for histaminic (H₁) and adrenergic receptors (alpha₁ and alpha₂) but not for muscarinic-cholinergic receptors.



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continued



Paliperidone ER

Clinical Point

Primary renal excretion should minimize the risk of hepatic-related interactions in patients taking multiple medications

Table 1

How paliperidone ER compares with risperidone

Characteristic	Paliperidone ER	Risperidone
Formulation	OROS extended-release	Immediate release
Active moiety	9-OH risperidone	Risperidone plus 9-OH risperidone
Metabolism	Primarily renal	Primarily hepatic
Drug interactions	Minimal	Primarily through cytochrome P-450 enzyme 2D6
Dosing	Start at target dose	Titrate to target dose

OROS: osmotic controlled-release oral delivery system

Pharmacokinetics. After oral administration, the medication is widely and rapidly distributed. The drug's terminal half-life is about 23 hours, and steady-state concentration is reached in 4 to 5 days.^{4,5}

Approximately 60% of the medication is eliminated renally and 11% is eliminated in the feces unchanged, with very limited hepatic metabolism.⁶ As a result, paliperidone ER appears to lack enzyme-inducing or inhibiting properties and does not substantially affect drugs that undergo cytochrome P-450 metabolism in the liver.

Thus paliperidone ER—when compared with risperidone and other antipsychotics that are metabolized primarily in the liver—is less likely to be involved in hepatic drug-drug or drug-disease interactions. However, some drugs that can induce CYP-450 enzymes—such as carbamazepine—may affect paliperidone's metabolism.⁷

Paliperidone has an osmotic controlled-release oral delivery system (OROS[®]) for steady medication delivery across 24 hours⁸ (Table 2).¹⁻³ The tablet consists of an osmotically active tri-layer core surrounded by a semipermeable membrane. When the tablet is swallowed, the membrane controls the rate of water reaching the tablet core, which determines the rate of drug delivery.⁶ The result is less variation between peak and trough drug concentrations, compared with immediate-release formulations.

Clinical use of paliperidone ER

Paliperidone ER offers potential therapeutic benefits in treating schizophrenia

patients, although not without the risk of adverse events such as extrapyramidal symptoms (EPS) (Table 3, page 78).¹⁻³

Patient selection. Because of its slow-release formulation and relatively stable plasma concentrations, paliperidone ER might be useful for patients who are highly sensitive to antipsychotics' side effects. In particular, paliperidone ER might be ideal for patients who respond to but may not tolerate risperidone.

Paliperidone ER appears to be safe in patients with liver disease. Its primary renal excretion should minimize the risk of hepatic-related drug interactions in patients taking multiple medications.

Dosage and titration. For treating schizophrenia, the suggested starting dose of paliperidone ER is 6 mg/d taken in the morning. In the 3 pivotal trials, 6 mg was the lowest dose to show broad efficacy with minimal adverse events.⁹

For many patients, the 6-mg starting dose will be the therapeutic dose. When needed, the dose may be increased in 3-mg increments every 1 to 2 weeks to a maximum 12 mg/d (a 15-mg dose was used in clinical trials, but the adverse effects outweighed the benefits). Lower maximum doses are recommended for patients with renal impairment:

- 6 mg/d for those with creatinine clearance ≥ 50 to <80 mL/min (mild impairment)
- 3 mg/d for those with creatinine clearance 10 to <50 mL/min (moderate to severe impairment).¹⁰

Table 2

Paliperidone ER's clinical characteristics

Second-generation antipsychotic approved for schizophrenia
9-OH active metabolite of risperidone
Osmotic controlled-release system provides steady-state drug delivery over 24 hours
Terminal half-life (time for 50% of drug to be eliminated from the body) ~23 hours
Available in 3-mg, 6-mg, and 9-mg tablets; recommended starting dose is 6 mg/d, and labeled dose range is 3 to 12 mg/d
Excreted primarily by the kidney; maximum recommended dose for patients with moderate to severe renal impairment is 3 mg/d
Source: References 1-3

In the pivotal trials, differences in the terminal elimination half-life between hepatically impaired and healthy patients were minimal (26.5 hours vs 23.6 hours, respectively). Unbound paliperidone levels were slightly lower in patients with hepatic impairment¹¹ but not low enough to recommend dose adjustment.

Safety and tolerability. Pooled data from the 3 trials indicate that adverse events (AEs) occurred during treatment in 66% to 77% of patients receiving paliperidone ER vs 66% in placebo groups. The most common AEs were headache (11% to 18%), insomnia (4% to 12%), and anxiety (6% to 9%).⁹

EPS. Risk of EPS-related AEs (such as akathisia and parkinsonian symptoms) with 3-mg and 6-mg paliperidone ER doses (13% and 10%, respectively) was similar to placebo (11%) but increased with the 9-mg, 12-mg, and 15-mg doses (25%, 26%, and 24%, respectively). Should EPS occur, reduce the paliperidone ER dose or consider adding antiparkinsonian medications.

Lab values. No clinically relevant changes were noted in blood glucose, insulin, or lipids.¹² Similar to risperidone, paliperidone ER elevated prolactin levels.

Weight gain with paliperidone ER is dose-dependent; in the clinical trials, mean body weight change for all doses was ≤ 1.9 kg, which is similar to the weight gain seen with risperidone and in the moderate range compared with other SGAs. When using paliperidone ER, follow the American Diabetes Association/American Psychiatric Association guidelines¹³ for monitoring weight gain and metabolic parameters with antipsychotics. Also monitor patients for clinical symptoms of hyperprolactinemia, and—if intolerable—adjust the dose or switch to another SGA.

Tachycardia. Advise patients that they may experience a rapid heart rate while taking paliperidone ER. In clinical trials, tachycardia occurred in $\leq 14\%$ of patients—twice the rate with placebo—but did not contribute to more serious cardiac rhythm disturbances or to discontinuation. Incidence of prolonged corrected QT interval (QTc) was 3% to 5% in the paliperidone ER group vs 3% in the placebo group.

Cost. Paliperidone ER costs approximately \$12 to \$18 per daily dose, which is similar to risperidone. Cost may be a greater consideration for patients next year, when generic risperidone becomes available (*see Related Resources, page 81*).

Patient education. Because of paliperidone ER's pharmacokinetic properties, counsel patients to:

- take 1 tablet each day in the morning
- not chew, split, or crush the tablets but swallow whole to preserve the controlled-release delivery.

Also inform patients that they may see the tablet's nonabsorbable shell in their stool as undigested residue.

Efficacy trials in schizophrenia

Three 6-week trials¹⁻³ examined paliperidone ER's efficacy in a total of 1,692 patients with chronic schizophrenia who were hospitalized ≥ 14 days with acute exacerbations. The trials were double-blind, randomized, fixed-dose, parallel-group, and placebo- and active-controlled (compared with olanzapine, 10 mg/d). Patients showed no significant differences in demographic or baseline characteristics or in the use of rescue medications.

The primary outcome measure was mean change in Positive and Negative

Clinical Point

12 mg/d is the maximum recommended dose, but the 6-mg starting dose will be the therapeutic dose for many patients



Paliperidone ER

Clinical Point

Counsel patients not to chew, split, or crush the tablets but to swallow whole to preserve controlled-release delivery

Table 3

Paliperidone ER's potential benefits and risks in clinical practice

Potential benefits	Details
Efficacy	Data support acute (6 weeks) and chronic (up to 24 weeks) improvement in schizophrenia symptoms, patient function, and quality of life
Pharmacokinetics	Primarily renal excretion decreases risk of hepatic drug-drug or drug-disease interactions
Long-acting formulation	Once-daily dosing simplifies treatment and may improve adherence
Potential risks	Details
EPS	Risk similar to placebo at 3-mg and 6-mg doses, but increased at higher doses
Weight gain	Similar to risperidone
Hyperprolactinemia	Similar to risperidone
Tachycardia	Occurred in up to 14% of patients in clinical trials (twice the rate of placebo [7%])
QTc prolongation	Increase up to 12 msec on average, with no patients exceeding 500 msec and no clinically adverse events during trials; use paliperidone with caution in patients with arrhythmias or cardiovascular disease or who are taking other medication that can prolong the QT interval

EPS: extrapyramidal symptoms
Source: References 1-3

Syndrome Scale (PANSS) total score, which quantifies positive, negative, and global psychopathologic symptom severity. Secondary outcome measures included:

- PANSS Marder factor scores¹⁴ (derived from PANSS items that reflect positive and negative symptoms, anxiety and depression, hostility, and thought disorganization).
- Clinical Global Impressions-Severity (CGI-S) score, which measures overall illness severity.¹⁵
- Personal and Social Performance (PSP) scores, which rate socially useful activities, relationships, self-care, and disturbing and aggressive behaviors; improvement by 1 category (10 points) reflects a clinically meaningful change.^{16,17}

The first study¹ was conducted at 74 U.S. centers and enrolled 444 subjects (PANSS mean baseline score 94 ± 12). Patients were randomly assigned to fixed doses of paliperidone ER, 6 mg or 12 mg; placebo; or olanzapine, 10 mg/d. The olanzapine arm confirmed assay sensitivity and was not included in the efficacy analyses. Clinical

response was defined as $\geq 30\%$ improvement from baseline in total PANSS score.

A total of 43% of patients completed the study—34% taking placebo; 46% taking paliperidone ER, 6 mg; 48% taking paliperidone ER, 12 mg; and 45% taking olanzapine. Demographic and baseline characteristics of the 432 patients who received ≥ 1 dose were similar across all groups. Approximately 75% of patients in each group used rescue medications—primarily lorazepam—for agitation, restlessness, or insomnia for a mean of 8 days.

Patients taking either paliperidone ER dose showed statistically significant greater improvement in PANSS total score compared with those taking placebo (6 mg, $P = 0.006$; 12 mg, $P < 0.001$).

Clinical response rates were similar with the 6-mg and 12-mg paliperidone ER doses—50% and 51%, respectively—and greater than with placebo (34%). The higher response rates with paliperidone ER were statistically significant compared with placebo (6 mg, $P < 0.03$; 12 mg, $P = 0.013$).

Discontinuation rates for lack of efficacy were lower with paliperidone ER (6

mg, 23%; 12 mg, 14%) than with placebo (35%). A substantially lower percentage of patients taking this agent remained classified as "marked/severe/extremely severe" on the CGI-S score from baseline to endpoint, compared with the placebo group;

- 6 mg paliperidone ER, 58% to 26%
- 12 mg paliperidone ER, 64% to 21%
- placebo, 60% to 45%.

PSP scores improved in both paliperidone ER groups, but the difference compared with placebo was statistically significant only for the 6-mg dose ($P < 0.008$).

The second study² included U.S. and international sites and compared 3 fixed doses of paliperidone ER (6-, 9-, and 12-mg) with placebo. Among the 630 patients enrolled, 66% completed the study. Patients were randomly assigned to 6 mg, 9 mg, or 12 mg of paliperidone ER; 10 mg of olanzapine; or placebo. The number of patients who dropped out because of adverse events was comparable across the groups.

Patient groups assigned to paliperidone ER showed significant improvement when compared with placebo ($P < 0.001$), based on mean change in PANSS total score and PANSS Marder factor scores. The percentage of patients with a >30% reduction in PANSS total score from baseline to endpoint included:

- 6 mg paliperidone ER, 56%
- 9 mg paliperidone ER, 51%
- 12 mg paliperidone ER, 61%
- placebo, 30%.

Discontinuation rates for lack of efficacy also were lower in the paliperidone ER groups vs placebo (6 mg, 16%; 9 mg, 16%; 12 mg, 10%; placebo, 40%). A substantially lower percentage of patients taking the drug remained classified as "marked/severe/extremely severe" by CGI-S score, compared with placebo:

- 6 mg paliperidone ER, 63% at baseline to 22% at endpoint
- 9 mg paliperidone ER, 58% to 23%
- 12 mg paliperidone ER, 64% to 16%
- placebo, 60% to 51%.

PSP scores improved significantly for all 3 paliperidone ER doses vs placebo.

The third study³ was a multicenter international trial that compared 3 fixed doses of paliperidone ER (3, 9, and 15 mg) with placebo. Among the 618 randomized patients, 365 (59%) completed the study: 70 of 127 (55%) on 3-mg paliperidone ER, 78 of 125 (62%) on 9-mg paliperidone ER, 82 of 115

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*Results from a population survey of 500 ADHD adults and 501 gender- and age-matched non-ADHD adults which investigated characteristics of ADHD and its impact on education, employment, socialization, and personal outlook.

Reference: 1. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. *J Clin Psychiatry*. 2006;67:524-540.

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Paliperidone ER

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In clinical trials, weight gain with paliperidone ER was similar to that seen with risperidone and in the moderate range among SGAs

Table 4

Studies of paliperidone ER in schizophrenia subpopulations

Patient population	Study design	Findings
Recently diagnosed	413 patients diagnosed within 5 years of study entry compared with 893 patients who had been ill ≥ 5 years ^{*18,19}	Tolerability was similar, but recently diagnosed patients were more likely to experience movement disorders and somnolence
Age ≥ 65 years	114 schizophrenia patients age ≥ 65 given paliperidone ER, 3 to 12 mg/d, or placebo in 6-week, double-blind, randomized, placebo-controlled trial ²⁰	Rates of cardiovascular, cerebrovascular, neuromotor, and metabolic changes similar to placebo, except for tachycardia (16% with paliperidone vs 0% with placebo)
Severely ill	217 patients with marked to severe symptoms (baseline total PANSS score ≥ 105) ^{*21}	Patients treated with paliperidone showed significantly greater improvement vs placebo in mean total PANSS score (-26.7 vs -5.7) and other measures
Substantial negative symptoms	299 patients with predominant negative symptoms from 3 acute efficacy trials ^{*22}	Patients treated with paliperidone showed significant improvements vs placebo on primary and secondary measures of negative symptoms
Sleep problems	36 patients age 18 to 45 diagnosed with schizophrenia and schizophrenia-related insomnia ^{*23}	In stable patients, paliperidone improved sleep architecture, continuity, and patient-rated sleep quality without producing or worsening daytime sleepiness

* Studies marked with asterisks represent post hoc analyses of data from the 3 clinical trials on which the FDA based its approval of paliperidone ER.

PANSS: Positive and Negative Syndrome Scale

(71%) on 15-mg paliperidone ER, and 47 of 123 (38%) on placebo.

All 3 paliperidone ER doses were associated with statistically significant improvements in PANSS total and Marder factor scores at endpoint compared with placebo ($P < 0.05$). Twice as many patients in each paliperidone group achieved clinical response, compared with placebo:

- 3 mg paliperidone ER, 40%
- 9 mg paliperidone ER, 46%
- 15 mg paliperidone ER, 53%
- placebo, 18% ($P \leq 0.005$).

Discontinuation rates for lack of efficacy were lower in the paliperidone ER groups vs placebo and were dose-related (3 mg, 24%; 9 mg, 18%; 15 mg, 12%; placebo, 44%). Among patients taking olanzapine, 10 mg, 13% discontinued for lack of efficacy. Substantially fewer patients in the active drug groups were classified as "marked/severe/extremely severe" from baseline to endpoint on the CGI-S scale vs the placebo group:

- 3 mg paliperidone ER, 54% to 32%
- 9 mg paliperidone ER, 52% to 23%
- 15 mg paliperidone ER, 57% to 17%
- placebo, 56% to 50%.

Finally, a statistically significant improvement in mean PSP scores from baseline to endpoint was seen for all 3 paliperidone ER doses vs placebo (3 mg, 8.3 ± 17 points; 9 mg, 7.6 ± 14 points; 15 mg, 12 ± 15.7 points; placebo, 1.5 ± 16 points [$P < 0.001$]).

Additional trial evidence

Schizophrenia subpopulations. Post hoc analyses of data reported from the 3 pivotal trials suggest that paliperidone ER may be useful for specific groups of schizophrenia patients, including those who are recently diagnosed, age > 65 , or severely ill or have predominant negative symptoms or sleep problems (Table 4).¹⁸⁻²³

So far, these analyses have been presented as posters at meetings or in sponsored

Related Resources

- Paliperidone extended release. Prescribing information. www.invega.com.
- Johnson & Johnson. U.S. District Court upholds Risperdal® (risperidone) patent (press release). October 16, 2006. www.jnj.com/news/jnj_news. (See page 21).

Drug Brand Names

Carbamazepine • Tegretol
Lorazepam • Ativan
Olanzapine • Zyprexa

Paliperidone ER • Invega
Risperidone • Risperdal

Disclosures

Dr. Rado and Dr. Dowd receive research support from Neuronetics, sanofi-aventis, Janssen Pharmaceutica, and Solvay.

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supplements but have not been published in peer-reviewed publications.

Efficacy in delaying recurrence. Paliperidone ER's efficacy in delaying symptom recurrence was examined in a randomized, double-blind, placebo-controlled study of 207 patients who had been stabilized on open-label, flexible-dosed paliperidone ER.²⁴ Time to first recurrence of schizophrenia symptoms was the primary efficacy measure. Starting dose was 9 mg/d (flexible dose range 3 to 15 mg/d).

The study was halted at a planned interim analysis because time-to-recurrence was significantly longer for patients receiving paliperidone ER compared with placebo ($P < 0.005$). At that point, 43 of 111 patients in the intent-to-treat analysis had experienced a recurrence (14 of 56 [25%] treated with paliperidone ER vs 29 of 55 [53%] with placebo). Time points at which 25% of patients experienced recurrence were 23 days with placebo and 83 days with paliperidone ER.

Final analysis of the 179 patients who completed the study confirmed the interim findings. Ongoing treatment maintained improvement in patients' acute symptoms, functioning, and quality-of-life measures.

References

1. Marder S, Kramer M, Ford L, et al. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry* 2007; Jun 27; Epub ahead of print.
2. Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res* 2007;90(1-3):147-61.
3. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophr Res* 2007;93(1-3):117-30.
4. Rossenu SAC, Rusch S, Janssens L, et al. Extended release formulation of paliperidone shows dose proportional pharmacokinetics. Presented at: Annual Meeting of the American Association of Pharmaceutical Scientists; October 29, 2006; San Antonio, TX.

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*From a retrospective survey assessing the prevalence, comorbidity, and impairment of adult ADHD in 3199 adults, age 18 to 44. Depressive disorder includes major depressive disorder and dysthymia.

Reference 1. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163:716-723.

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Paliperidone ER

Clinical Point

Sleep quality improved without greater daytime sleepiness in stable patients with schizophrenia-related insomnia

5. Vermeir M, Boom S, Naessens I, et al. Absorption, metabolism, and excretion of a single oral dose of 14C-paliperidone 1 mg in healthy subjects. *Eur Neuropsychopharmacol* 2005;15(suppl):S648-9.
6. Conley R, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. *Curr Med Res Opin* 2006;22(10):1879-92.
7. Spina E, Avenoso A, Facciola G, et al. Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit* 2000;22(4):481-5.
8. Paliperidone extended release. Prescribing information. Available at: <http://www.invega.com>. Accessed August 8, 2007.
9. Meltzer H, Kramer M, Gassmann-Mayer C, et al. Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week placebo controlled studies. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S225.
10. Thyssen A, Cleton A, Osselaer NV, et al. Effects of renal impairment on the pharmacokinetic profile of paliperidone extended-release tablets. *Clin Pharmacol Ther* 2007. In press.
11. Thyssen A, Crauwels H, Cleton A, et al. Effects of hepatic impairment on the pharmacokinetics of paliperidone immediate-release. Presented at: 46th Annual Meeting of the New Clinical Drug Evaluation Unit (NCDEU); June 12-15, 2006; Boca Raton, FL.
12. Meyer J, Kramer M, Lane R, et al. Metabolic outcomes in patients with schizophrenia treated with oral paliperidone extended release tablets: pooled analysis of three 6 week placebo-controlled studies. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S282.
13. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *J Clin Psychiatry* 2004;65:267-72.
14. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry* 1997;58:538-46.
15. Guy W. *Clinical Global Impressions Scale. Early clinical drug evaluation unit (ECDEU) assessment manual for psychopharmacology*. Rockville, MD: National Institute of Mental Health, Department of Health, Education, and Welfare; 1976:218-22. ADM publication 76-338.
16. Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000;101:323-9.
17. Patrick D, Adriaenssen I, Morosini P, Rothman M. Reliability, validity and sensitivity to change of the Personal and Social Performance scale in patients with acute schizophrenia. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S287-8.
18. Kostic D, Bossie C, Turkoz I, et al. Paliperidone extended-release tablets in patients recently diagnosed with schizophrenia. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S161.
19. Kostic D, Bossie C, Turkoz I, et al. Paliperidone extended-release tablets in patients recently diagnosed with schizophrenia. Presented at: Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP); July 9-13, 2006; Chicago, IL.
20. Tzimos A, Kramer M, Ford L, et al. A 6-week placebo-controlled study of the safety and tolerability of flexible doses of oral paliperidone extended release tablets in the treatment of schizophrenia in elderly patients. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S155.
21. Canuso C, Youssef E, Dirks B, et al. Paliperidone extended-release in severely-ill patients with schizophrenia. Presented at: 58th Annual Institute on Psychiatric Services; October 5-8, 2006; New York, NY.
22. Dirks B, Eerdeken M, Turkoz I, et al. Efficacy of paliperidone extended-release tablets in patients with schizophrenia and predominant negative symptoms. *Int J Neuropsychopharmacol* 2006;9(suppl 1):S162.
23. Luthringer R, Staner L, Noel N, et al. Sleep assessments in patients with schizophrenia following treatment with paliperidone extended-release tablets. *Eur Neuropsychopharmacol* 2006;16(suppl 4):S224.
24. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized double-blind, placebo-controlled study [published correction appears in *J Clin Psychopharmacol* 2007;27(3):258]. *J Clin Psychopharmacol* 2007;27(1):6-14.

Bottom Line

Paliperidone ER—risperidone's active metabolite in a once-daily, time-released formulation—demonstrates primarily renal excretion and relatively stable plasma concentrations. For many patients, the 6-mg starting dose will be the therapeutic dose. Weight gain and prolactin elevation are similar to risperidone, but paliperidone may be less likely to interact with drugs metabolized in the liver.