Place in therapy review

Paliperidone: the evidence of its therapeutic value in schizophrenia

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Abstract

Introduction: Paliperidone, the 9-hydroxy metabolite of risperidone, is a second-generation antipsychotic that was recently approved for the treatment of schizophrenia. It is marketed as an improvement over risperidone, but is likely to be considerably more costly when risperidone is no longer protected by patent.

Aims: To review the evidence for the clinical impact of paliperidone in the treatment of patients with schizophrenia, particularly in contrast to risperidone.

Evidence review: Paliperidone is primarily metabolized and excreted renally, and thus may be of particular utility for patients with hepatic impairment. There is clear evidence that paliperidone is more efficacious than placebo in reducing the positive and negative symptoms of schizophrenia. In patients with schizophrenia, paliperidone has been shown to stabilize acute psychotic symptoms. There is some evidence that it can prevent relapse in stabilized patients. Studies on the cost effectiveness of paliperidone are needed. Most importantly, there are no trials comparing paliperidone directly with other second-generation antipsychotics.

Place in therapy: Until direct efficacy and cost effectiveness comparisons are made with risperidone, it is difficult to justify paliperidone use over risperidone. It will become even harder to justify when risperidone becomes available as a less expensive generic medication.

Core Evidence. 2008;2(4):261–271

Key words: paliperidone, clinical impact, evidence, schizophrenia, cost effectiveness

Core evidence place in therapy summary for paliperidone in schizophrenia

Outcome measure	Evidence	Implications
Patient-oriented outcomes		
Reduction in positive and negative symptoms of schizophrenia	Clear	Clearly improves symptoms compared with placebo; comparisons with other second-generation antipsychotics needed
Reduction in mood symptoms of schizophrenia	Moderate	Improves mood based on PANSS factor scores. More specific measures of mood needed
Prevention of relapse in stabilized patients	Moderate	May be useful, although more robust evidence required
Adherence with treatment	Clear	Fewer patients may discontinue treatment; comparisons with other second-generation antipsychotics needed
Extrapyramidal symptoms	Clear	Fewer extrapyramidal symptoms than first-generation antipsychotics, similar to other second-generation antipsychotics; appears to be similar to risperidone
Weight gain or metabolic disorders	Clear	Appears to be similar to risperidone
Improves quality of life	Moderate	Improves ability to function in daily life; comparisons with other second-generation antipsychotics needed
Effective in treatment-resistant schizophrenia	None	Evidence needed
Economic evidence		
Cost effectiveness	None	Likely to be more expensive than generic risperidone

PANSS, Positive and Negative Symptom Scale.

Scope, aims, and objectives

Paliperidone, the 9-hydroxy metabolite of risperidone, is a second-generation antipsychotic that was approved on December 20, 2006 by the US Food and Drug Administration (FDA) for the treatment of schizophrenia. Risperidone is extensively used, and has received regulatory approvals for the treatment of schizophrenia, bipolar mania, and, more recently, irritability associated with autistic disorder in children and adolescents. Paliperidone (Invega®, Janssen Pharmaceuticals) is being promoted as having a distinct treatment profile with an innovative pharmacologic delivery system, being effective when given once daily, able to be initiated at a potentially therapeutic dose, and being less likely to interfere with other medications that are metabolized by the liver. As a metabolite of risperidone, however, it is probable that paliperidone has a similar efficacy and side effect profile to risperidone. This is a particularly relevant issue given the pending availability of inexpensive generic formulations of risperidone.

The objective of this review is to assess the impact of paliperidone on the treatment and clinical management of schizophrenia. Specific attention is given to evidence for potential advantages/disadvantages when compared with risperidone.

Methods

Clinical trial information was accessed by English language searches conducted on September 5, 2007 using PubMed (http://www.ncbi.nlm.gov/entrez) with the search terms: "paliperidone" or "9-hydroxy-risperidone."

Clinical trials of paliperidone and clinically relevant publications of paliperidone pharmacokinetics, side effects, and drug–drug interactions were included in this review. Review articles, duplicate publications, and articles not directly related to the clinical use of paliperidone in schizophrenia were excluded. Posters presented at national and international meetings were specifically excluded from our synthesis and analysis because posters are not ordinarily subject to peer review and their content can be subject to change prior to publication. A request was made to Ortho-McNeil Janssen Scientific Affairs, LLC of Titusville, NJ, USA for copies of any original research of paliperidone already accepted for publication and still in press as of September 29, 2007, but this did not generate any additional publications for review. A Cochrane Collaboration review of paliperidone is currently in progress (Nussbaum & Stroup 2007). The evidence base included in the review is shown in Table 1.

Table 1 | Evidence base included in the review

Category	Number of records
Initial search	131
records excluded	95
records included	36
Additional studies identified	2
Level 1 clinical evidence (systematic review, meta analysis)	0
Level 2 clinical evidence (RCT)	5
Level ≥3 clinical evidence	31
relevant laboratory	31
studies in humans	0
Economic evidence	0

For definitions of levels of evidence, see Editorial Information on inside back cover or on *Core Evidence* website (http://www.coremedicalpublishing.com).
RCT, randomized controlled trial.

Disease overview

Characteristics of schizophrenia

Schizophrenia is a complex condition, increasingly recognized as a neurodevelopmental disorder. DSM IV-TR (American Psychiatric Association 2000) criteria include having at least two of the following five symptoms: 1) delusions, 2) hallucinations, 3) grossly disorganized behavior, 4) catatonic behavior, or 5) negative symptoms. Having only bizarre delusions, or hallucinations that affect behavior, or hallucinations of conversing voices would also meet the criteria. Additionally, symptoms must last at least six months, be associated with marked impairment in functioning, and not be better explained by another condition.

While the most striking symptoms of schizophrenia are the positive symptoms (easy-to-spot behaviors not typically seen in healthy people that usually involve a loss of contact with reality, i.e. delusions or hallucinations), it is often the less obvious symptoms that are more associated with poor functioning (Siegel et al. 2006). Negative symptoms (Stahl & Buckley 2007), or reductions in normal emotional and behavioral states, are often associated with disability. Additionally, schizophrenia often occurs with significant impairment in cognition (Green et al. 2000; Keefe et al. 2006), and a substantial decline from premorbid IQ (Reichenberg et al. 2005). Impaired performance on measures of neurocognition is closely linked to community outcome (Green et al. 2000). Substance abuse is common in patients with schizophrenia, with some studies reporting up to 50% comorbidity (Green et al. 2007), and association with more severe symptoms and a poorer outcome.

Schizophrenia is also correlated with poor physical health, including higher rates of obesity, diabetes, hypertension, metabolic syndrome, and cardiovascular disease (Mitchell & Malone 2006). This risk is multifactorial, involving shared vulnerability, genetic factors, and unhealthy lifestyle, as well as the potential impact of antipsychotics.

Prevalence of schizophrenia

The prevalence of schizophrenia is commonly reported as 1% of the adult population worldwide, although some report lower percentages (Goldner et al. 2002). Typical onset is during adolescence, with peak ages of diagnosis of 20–28 years for men and 26–32 years for women (Castle et al. 1991). The disease is often subdivided into several phases (Häfner & an der Heiden 1999): premorbid (pre-illness), prodromal (attenuated symptoms),

psychotic (full presence of symptoms), and residual (between prodromal and active psychosis, with a lack of a return to baseline). Often, patients shift between periods of active psychotic exacerbations and residual phases.

Pathophysiology

Clear cause and effect relationships for schizophrenia are unknown, but advances have been made recently. Since the 1960s, the dopamine hypothesis has been prominent (i.e. schizophrenia is caused by excess dopamine in the brain), and although this explains part of the process, the pathophysiology is substantially more complex. Although a full survey is beyond the scope of this review, the ultimate etiology of schizophrenia may be related to disturbances in regulation of trophic genes such as neuregulin or dysbindin (Norton et al. 2006), neurochemical alterations (Boks et al. 2007), or adverse environmental events (Byrne et al. 2007; Muller & Schwarz 2006). However, disturbances of specific neurotransmitter systems, particularly dopamine (Di Forti et al. 2007), glutamate (Javitt 2004), and gamma-aminobutyric acid (GABA) (Vacher et al. 2006) may be the proximate cause of symptoms and neurocognitive deficits.

Other, not mutually exclusive, theories include a deficit in myelin or white matter (Davis et al. 2003), aberrant synaptic pruning (Hoffman & McGlashan 1997), and an association with adolescent cannabis (Moore et al. 2007). Genetic evidence is sometimes conflicting, but several putative susceptibility genes (including COMT, DISC1, RGS4, GRM3, and G72) have been identified (Harrison & Weinberger 2005).

Post-mortem studies have identified localized alterations of specific neuronal, synaptic, and glial populations in the hippocampus, dorsolateral prefrontal cortex, and dorsal thalamus (Harrison et al. 2005). Inhibitory interneurons are particularly affected, as demonstrated by a decrease in their number, diminished expression of synthesizing enzyme, diminished expression of neuropeptides, and decreased migration of neurons into the cortex from the underlying white matter (Akbarian et al. 1996; Benes et al. 1998; Woo et al. 1998). The total number of neurons is diminished in certain areas of the brain (Jeste & Lohr 1989), and, moreover, magnetic resonance imaging (MRI) demonstrates corresponding enlarged ventricles and diminished volume in the hippocampus and the superior temporal cortex (Kubicki et al. 2002).

Epidemiology

Schizophrenia is associated with a high burden of illness, in large part because of its onset during adolescence and the subsequent loss of the prime working years. Only a minority of patients ever achieve gainful employment, and less than 50% of patients in the United States raise families (Javitt & Coyle 2004). Approximately 15% spend many years in mental health facilities, and another 15% are incarcerated for petty crimes and vagrancy; 60% live in poverty, with a 5–15% prevalence of homelessness (Folsom et al. 2005; Javitt et al. 2004). Furthermore, 10% of patients attempt suicide, often by violent means (Hunt et al. 2006).

Current therapy options

Antipsychotics are the mainstay of treatment for schizophrenia and, although psychotherapy and psychosocial treatments have an important role, this review will focus on the pharmacologic management of schizophrenia. Although antipsychotics with novel mechanisms of action are on the horizon (Heresco-Levy et al. 2005; Patil et al. 2007), at present all marketed antipsychotics share in common a blockade of the dopamine type 2 (D_2) receptor (Di Forti et al. 2007), and primarily are only effective on positive symptoms (Lieberman et al. 2005). There is evidence that all available antipsychotics, with the exception of clozapine and possibly olanzapine, have approximately equivalent efficacy (Lieberman et al. 2005; Jones et al. 2006; McEvoy et al. 2006). Others have found advantages for clozapine, olanzapine, amisulpride, and risperidone in a systematic review (Davis et al. 2003).

Conventional, or first-generation, antipsychotics are primarily D_2 blockers, and can be divided into three groups: high, medium, and low potency. High potency is generally associated with a higher rate of extrapyramidal symptoms (EPS), namely acute dystonia, parkinsonism or akathisia; haloperidol is a representative example. Low potency is generally associated with higher sedation and anticholinergic side effects; chlorpromazine is a representative example. Medium potency is generally somewhere in between, with perphenazine a representative example.

Atypical, or second-generation, antipsychotics bind primarily to different degrees to both the D_2 receptor and the serotonin$_{2A}$ (5-HT_{2A}) receptor. In addition, all demonstrate some antagonism at other dopamine and serotonin receptors. All are distinguished from the first-generation antipsychotics by a lower propensity for causing EPS. In addition to paliperidone and risperidone, the second-generation agents currently marketed in the United States are clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole.

Adverse effects are a significant issue for all antipsychotics, and to a certain extent distinguish the various medications, particularly the second-generation antipsychotics, from each other. Although more common with the first-generation antipsychotics, all have the potential to cause EPS. Tardive dyskinesia is a disfiguring, potentially disabling, and potentially permanent movement disorder associated with antipsychotics that may be more common with first-generation drugs (Correll et al. 2004), although this is debated (Jones et al. 2006; Rosenheck 2007). Second-generation antipsychotics also have a higher propensity for weight gain, with this effect being less for risperidone and quetiapine compared with clozapine and olanzapine, and least frequent with aripiprazole and ziprasidone (Citrome 2007). Other potential side effects of both first- and second-generation antipsychotics include hyperprolactinemia, orthostatic hypotension, blood dyscrasias, gastrointestinal distress, and neuroleptic malignant syndrome. Often, an individual drug's side effect profile must be matched with the individual patient.

The economic burden of schizophrenia is large, including psychosocial disability costs (unemployment, disability payments), hospitalization costs, and outpatient clinical and social rehabilitation costs. The acquisition costs of the newer antipsychotic medications also play a role in this large economic burden. The cost effectiveness of the second-generation antipsychotics has been questioned, with recent studies raising serious doubts. The cost effectiveness component of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found that average monthly healthcare costs were $US300–$US500 greater with the newer second-generation medications than with perphenazine, with no significant advantage in symptom control or quality of life (Rosenheck et al. 2006). Other studies and systematic reviews have come to similar conclusions (Jones et al. 2006; Polsky et al. 2006).

Nevertheless, there is a need for improvement in the pharmacologic treatment of schizophrenia. The ideal antipsychotic would achieve rapid stabilization of positive, negative, and cognitive symptoms in all patients with schizophrenia. It would also not be associated with extrapyramidal, endocrine, metabolic, or cardiovascular side effects, and not cause weight gain or excessive sedation. Improvements in social functioning would also be highly desirable. Falling short of these goals, future agents should offer clear advantages over current agents.

Development of paliperidone

Before reviewing the clinical efficacy of paliperidone and its potential to add to our current treatment armamentarium, we will summarize the mechanism of action and metabolism of risperidone and paliperidone. Although a full discussion of the pharmacology of these medications is beyond the scope of this review, we have tried to highlight the most clinically relevant preclinical studies, and examine some of the purported advantages of paliperidone.

Risperidone received regulatory approval in the United States in 1993, making it the next second-generation antipsychotic to be marketed after clozapine. It is the precursor of 9-hydroxy-risperidone (paliperidone). As noted above, it might be more effective than first-generation antipsychotics, and in low to moderate doses (under 6 mg) has a favorable side effect profile (Davis & Chen 2004). At higher doses, EPS is common and risperidone is the second-generation antipsychotic most likely to cause EPS (Weiden 2007). Risperidone is associated with moderate weight gain and is the most likely second-generation agent to elevate prolactin (Lieberman et al. 2005), although, as explained below, paliperidone may have an even greater propensity to cause hyperprolactinemia, a speculation supported by the clinical data.

Other potential side effects include somnolence (Anon. 2007c) and urinary incontinence (Kantrowitz et al. 2006). Proposed mechanisms for this side effect include adrenergic blockade via alfa$_1$ receptors or blockage of pudendal reflexes via antagonism of 5-HT$_2$ or 5-HT$_3$ (Vera et al. 2001).

Paliperidone, the subject of this review, has a similar pharmacologic profile to risperidone (van Beijsterveldt et al. 1994). Like most second-generation antipsychotics, it is an antagonist at the dopamine D$_2$ and serotonin 5-HT$_{2A}$ receptors. There is evidence that paliperidone binds to D$_2$ receptors less tightly (Seeman 2005), suggesting that paliperidone might cause fewer extrapyramidal side effects, although, as seen below, this speculation is not supported by the clinical data. Like risperidone, paliperidone is an antagonist at alfa$_1$ and alfa$_2$ adrenergic receptors and at histaminergic H$_1$ receptors, which could lead to weight gain, orthostatic hypotension, or sedative side effects (Shayegan & Stahl 2004; Anon 2007a). Neither risperidone nor paliperidone are antagonists of muscarinic receptors, predicting a low rate of anticholinergic side effects, including cognitive dysfunction and gastrointestinal disturbances (Shayegan & Stahl al. 2004).

Animal studies using oral risperidone have shown that the cerebral distribution of its metabolite paliperidone was more limited than that of risperidone, with mean residence times in the frontal cortex and striatum of 4–6 hours for risperidone, compared with approximately 12 hours for paliperidone (van Beijsterveldt et al. 1994). These mean residence times were 3–5 times longer than those observed in plasma and in the cerebellum (van Beijsterveldt et al. 1994), although the clinical significance of this is unclear.

Paliperidone is primarily metabolized and excreted renally (Anon. 2007a), and thus may be of particular utility for patients with mild to moderate hepatic impairment. This is in contrast to risperidone, which is metabolized to paliperidone by the liver. Paliperidone is recommended to be given at lower doses in patients with renal impairment.

A large number of studies have been performed with oral risperidone and thus, by default, its metabolite paliperidone. No correlation has been found between plasma levels of risperidone or its metabolite paliperidone on antipsychotic response measured by the Positive and Negative Symptom Scale (PANSS), but higher concentrations in plasma were associated with patients who developed clinically significant parkinsonian symptoms (Spina et al. 2001). There is *in-vitro* evidence that oral risperidone might inhibit the metabolism of its metabolite paliperidone in the brain (Zhu et al. 2007), theoretically resulting in a lower central nervous system (CNS) concentration when oral paliperidone is used. In other words, this would predict a lower potency for oral paliperidone, a speculation supported by the lower end of the effective dose for paliperidone (6 mg) being higher than the corresponding dose for risperidone (3 mg).

In contrast to risperidone, paliperidone is available in an oral extended-release formulation, using a patented technology called osmotic controlled-release oral delivery system (OROS) (Conley et al. 2006). The extended-release formulation of paliperidone consists of an osmotically active trilayer core, composed of two drug layers and a push layer (Conley et al. 2006), and can be administered once daily. It is thought that by reducing the amplitude of the peaks and troughs, which are seen with immediate-release oral therapies in general, the risk of adverse

effects may be reduced. This speculation has not been tested in a head-to-head comparison with risperidone and, as seen below, is not well supported by the clinical data.

Although of unclear clinical significance, past studies of risperidone and its metabolite concentrations reported that the serum concentration of paliperidone can differ with both the formulation used and the age of the patient. The paliperidone to risperidone ratio has been found to be comparatively lower in patients receiving the long-acting injectable formulation of risperidone than in those receiving oral risperidone (Nesvåg et al. 2006), a potential consideration when switching from paliperidone to long-acting injectable risperidone. After controlling for dose, higher serum concentrations are seen in patients older than 42 years, but there are no significant sex-related differences in the average plasma concentrations (Aichhorn et al. 2005b). In addition, the paliperidone to risperidone ratio can be highly variable, with some patients receiving risperidone having risperidone plasma levels that were nondetectable and relatively high plasma levels of paliperidone (Aravagiri et al. 2003). Similar to other second-generation agents (Eberhard-Gran et al. 2006), paliperidone is detectable in breast milk (Aichhorn et al. 2005a).

Several potential drug–drug interactions have been reported for oral risperidone. Antidepressants, such as paroxetine (Saito et al. 2005), sertraline (Spina et al. 2004), and fluoxetine (Bondolfi et al. 2002), can increase the concentration of risperidone and its metabolite paliperidone, but this is not the case for valproic acid (Ravindran et al. 2004; Yoshimura et al. 2007), topirimate (Migliardi et al. 2007), lamotrigine (Spina et al. 2006), mirtazapine (Loonen et al. 1999), and venlafaxine (Amchin et al. 1999). Carbamazapine can decrease the concentration of the metabolite paliperidone in patients receiving risperidone (Spina et al. 2000). The clinical significance of these observations with oral risperidone is unknown, and it is likely that many will not be relevant with orally prescribed paliperidone because of its minimal hepatic metabolism—a potential advantage for paliperidone.

Clinical evidence with paliperidone

Efficacy

As of September 5, 2007, 27 clinical trials of paliperidone were listed on www.clinicaltrials.gov, a repository operated by the US National Institutes of Health and the National Library of Medicine. Of these, 20 were primarily in patients with schizophrenia.

At the time of writing, three efficacy trials of paliperidone have been published (Davidson et al. 2007; Kane et al. 2007; Marder et al. 2007). All three were similar 6-week, randomized, placebo-controlled trials in patients with schizophrenia, with an additional active comparator arm (olanzapine 10 mg). On the basis of these three trials, paliperidone 6 mg to 12 mg daily was approved for the treatment of acute schizophrenia. The three trials are summarized in Table 2. Response rates and adverse events to the various dosages across the three trials have been combined, except for EPS, for which the package inserts were used. To aid clarity, results for the nonefficacious dose of paliperidone 3 mg are not included.

Table 2 | Summary of the efficacy of paliperidone 6 to 15 mg/day in patients with schizophrenia (Anon. 2007a; Davidson et al. 2007; Kane et al. 2007; Marder et al. 2007)

Treatment and dose	Placebo	Paliperidone				Olanzapine
		6 mg	9 mg	12 mg	15 mg	
Number of patients	356	235	245	242	113	364
Completion rate after 6 weeks (%)	39.4	55.7	66.6	64	71.3	62.4
Response rate (%)[a]	26.6	53.2	48.6	56.7	53	50.5
NNT for response vs placebo	NA	3	4	3	3	4
EPS (%)	NA	10.2	25.2	26	Not reported	25
Somnolence (%)	7	8.5	9.8	4	8.8	16.4
Insomnia (%)	14.6	12.8	15.5	6.6	15.9	11.8

All data, except EPS, are pooled from the three efficacy trials of paliperidone. Data to pool EPS data were not reported, necessitating use of the paliperdone and olanzapine package inserts, which do not report data for placebo or the unapproved 15 mg dose.
[a]Response rate is improvement by 30% on the PANSS.
EPS, extrapyramidal symptoms; NNT, number needed to treat, calculated as the reciprocal of the difference in response rates for medication vs placebo; PANSS, Positive and Negative Symptom Scale.

Using similar designs and inclusion criteria, these three studies tested the efficacy and safety of paliperidone extended-release over a 6-week period by comparing fixed doses of 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg administered once daily versus placebo. Not all doses were tested in every study, but olanzapine 10 mg administered once daily was used as an active control in all three trials. The primary efficacy outcome measure was change in PANSS total score from baseline to endpoint.

In total, 1555 patients with an acute episode of schizophrenia were randomized at multiple sites worldwide. The patients' mean ages ranged from 36.8 to 41.6 years, and they were generally male and Caucasian. The mean age at diagnosis was 25 to 27 years and between 25% and 42% had been hospitalized at least four times (specific proportions varied in the three studies). Mean baseline PANSS score was approximately 94.

As seen in Table 2, paliperidone is efficacious, and begins to separate from placebo as early as day 4. It clearly performs better than placebo, and while these studies were not powered to directly compare with olanzapine, it appears that they are at least as efficacious as a starting dose of olanzapine. There is evidence that the near maximal effective dose of olanzapine is >16 mg (Davis et al. 2004). A comparison with a more typical therapeutic dose of olanzapine, as well as with risperidone, would be useful to assess differential response.

As noted above, paliperidone is approved at a daily dosage of 6 mg to 12 mg, and although the manufacturer states that the starting dose of 6 mg is generally therapeutic, this may not be appropriate for all patients. Response rates appear to be generally equivalent, with the highest rate of 56.7% achieved with the 12 mg dose, the 6 mg and 15 mg being nearly identical at 53%, and the lowest rate of 48.6% with 9 mg. The completion rates (confidence intervals in parentheses), however, which range from 55.7% (0.4935–0.6195) at 6 mg, 66.6% (0.6040–0.7215) at 9mg, 64% (0.5782–0.6984) at 12 mg, and 71.3% (0.6274–0.7920) at 15 mg, appear to show an increased likelihood for patients assigned to the higher doses to complete the trial, although the modified Wald confidence intervals overlap. It should be noted that the 15 mg data are based only on one trial (Davidson et al. 2007). The tendency to have greater completion rates with larger doses despite an increased likelihood of side effects in higher doses (see below), combined with a tendency for psychiatrists to prescribe doses greater than 6 mg in flexible dose trials (see below), can be interpreted as evidence for a dose response, although alternative interpretations are possible since completion rates represent the proportion of patients who have not dropped out for whatever reason (e.g. lack of efficacy, withdrawal of consent, adverse effects). As seen in the table, the number needed to treat appears to be equivalent between the dosages. Longer follow-up trials are needed to determine whether the majority of patients will have their symptoms sufficiently controlled by 6 mg.

The mean decreases in PANSS total scores range from 2.9 to 8 for placebo, and 15.7 to 17.9, 16.3 to 17.2, 17.5 to 23.3, and 19.9 for paliperidone 6 mg, 9 mg, 12 mg and 15 mg, respectively, and 18.1 to 19.9 for olanzapine. Paliperidone showed statistically significant improvements over placebo at all doses tested. This was also the case for the PANSS scores examining positive symptoms, negative symptoms, depression/anxiety, uncontrolled hostility/excitement, and disorganization.

Improvements in personal and social functioning, assessed using the single item Personal and Social Performance Scale (PSP) (Morosini et al. 2000), were greater for paliperidone compared with placebo. Based on these findings, paliperidone is the only antipsychotic that can be marketed as improving social functioning. This claim of uniqueness, however, is tempered by a comparable improvement found in the starting dose olanzapine group, and the CATIE report of significant within-group improvements in overall quality of life for olanzapine and risperidone, and no between group differences between antipsychotics (Swartz et al. 2007).

Safety and tolerability

The completion rates indicate good tolerability for paliperidone, although direct comparisons with risperidone are not available. Of note, while the initial efficacy trials report short-term completion rates for the 6 mg dose of risperidone of >70% (Chouinard et al. 1993), the 18-month CATIE trial offers a more pessimistic 26%.

Tachycardia was the most common adverse event and led to a 2% discontinuation rate for the 12 mg dose in one of the trials (Kane et al. 2007). Tachycardia occurred in 7% of those randomized to placebo, 12%, 12%, and 14% of those randomized to paliperidone 6 mg, 9 mg, and 12 mg, respectively, and 9% of those randomized to olanzapine. Tachycardia is not commonly associated with risperidone: it is reported at 2% at commonly accepted dose ranges (Anon. 2007c). A prolonged QTc interval was noted with paliperidone in 3% to 5% of patients among the three trials (Anon. 2007a), although this is unlikely to be clinically important unless the drug is used in the presence of other risk factors for QTc prolongation.

Despite speculation that the extended-release formulation would lead to a reduced risk of adverse effects, paliperidone appears to cause a somewhat higher rate of parkinsonism and EPS than risperidone, especially at dosages of 9 mg and 12 mg (Anon. 2007a). The rates reported for paliperidone 6 mg (10.2%) appear to be slightly lower than for usually therapeutic dosages of risperidone (Anon. 2007c), in which EPS rates of 11% and 17% were reported for 4 mg and 6 mg, respectively.

Although the data necessary for pooling were not reported, statistically higher scores were seen on the Barnes Akathisia Rating Scale and the Simpson–Angus Rating Scale for paliperidone 9 mg and 12 mg compared with placebo in one trial (Kane et al. 2007); on the Barnes Akathisia Rating Scale for paliperidone 6 mg in the second trial (Marder et al. 2007); and for the 9 mg dose in the Simpson–Angus Rating Scale in the third (Davidson et al. 2007).

As noted earlier, risperidone has the highest propensity of all the second-generation agents to cause hyperprolactinemia, with the potential to cause oligomenorrhea or amenorrhea in women, erectile dysfunction in men, and loss of libido and infertility in both sexes (Molitch 2005) and potentially osteoporosis (Howes et al. 2005). There is evidence that prolactin elevation is more closely related to paliperidone concentration, rather than risperidone concentration (Knegtering et al. 2005; Melkersson 2006). This could lead to higher prolactin elevations with paliperidone than with risperidone.

In the three short-term trials, paliperidone appears to lead to a dose-dependent elevation in prolactin, although symptomatic hyperprolactemia (including galactorrhea, gynecomastia, amenorrhea, anorgasmia, and abnormal sexual function) was low (eight patients overall). Data necessary to pool data and evaluate the likelihood of developing hyperprolactinemia were not reported. Larger increases were noted in females, and minimal increases, if any, were noted in the olanzapine and placebo groups.

Across the individual efficacy trials, the mean increases in prolactin from baseline for men were 15.4 ng/mL for 3 mg (Davidson et al. 2007), 22.8 ng/mL for 6 mg (Marder et al. 2007), 29.2 ng/mL for 9 mg (Davidson et al. 2007), 24.3 ng/mL for 12 mg (Marder et al. 2007) and 35.2 ng/mL for 15 mg (Davidson et al. 2007). For women, the mean increases were 62 ng/mL for

3 mg (Davidson et al. 2007), 81.1 ng/mL for 6 mg (Marder et al. 2007), 79.9 ng/mL for 9 mg (Davidson et al. 2007), 76.4 ng/mL for 12 mg (Marder et al. 2007) and 106.9 ng/mL for 15 mg (Davidson et al. 2007). In the study by Kane et al. (2007), only the across-dose mean is presented: 27.9 ng/mL for men and 86 ng/mL for women.

Although it was a longer trial, the CATIE study (Lieberman et al. 2005) reported smaller cross-gender mean increases (15.4 ng/dL) in patients treated with a moderate dose of risperidone (mean 3.9 mg). Another recent publication (Potkin et al. 2006) reported a cross-gender mean increase of 18 ng/mL. Longer follow-up for treatment-emergent prolactin-related adverse events is needed, but the clinical data thus far support the preclinical evidence for a greater prolactin increase with paliperidone than risperidone.

Only a few glucose-related adverse events were seen in trials with paliperidone, and minimal changes were noted in metabolic parameters. The percent of patients with a gain of ≥7% of bodyweight was similar for the paliperidone 3 mg and 6 mg (7% and 6%, respectively) and placebo (5%) groups, but there was a higher incidence of weight gain at higher doses. Specifically, rates for the 9 mg, 12 mg, and 15 mg dosages were 9%, 9%, and 18%, respectively. In contrast, 17.5% of patients on olanzapine experienced ≥7% weight gain. There were no clinically relevant changes in mean fasting serum glucose, insulin or serum lipid levels (low density lipoprotein, high density lipoprotein, and triglycerides) or in renal function. This is consistent with risperidone's metabolic profile, although the incidence of ≥7% weight gain is comparatively lower than that reported for commonly prescribed doses of risperidone (18%) (Anon. 2007c).

Insomnia and somnolence

In the three efficacy trials, rates of somnolence and insomnia were 4% to 9.8%, and 12.8% to 15.9%, respectively, for the various doses of paliperidone. As seen in Table 2, there is evidence for a U-shaped dose response for paliperidone in treating sleep disorders, with rates decreasing with escalating doses until 12 mg, and then increasing rates of sleep-related adverse events at 15 mg. This finding is notable because of the increasing understanding of the intrinsic connections between subjective and objective sleep deficits in schizophrenia. For example, in the CATIE study, residual insomnia occurred in 16–30% of patients across treatment arms (Lieberman et al. 2005), and has been related to reduced quality of life and poor coping skills (Ritsner et al. 2004; Hofstetter et al. 2005). Objective polysomnographic measurements of sleep have been correlated with PANSS scores (Yang & Winkelman 2006) and various neurocognitive tests (Göder et al. 2004). It is possible, although speculative, that a correction of subjective and objective sleep deficits in schizophrenia would lead to clinical improvement.

The objective and subjective effects of paliperidone on sleep in schizophrenia were tested in a 2-week double-blind study (Luthringer et al. 2007). In this study, 36 patients with stable schizophrenia and insomnia related to schizophrenia underwent a 2-week antipsychotic taper and then were randomized to 2 weeks of paliperidone 9 mg or placebo. Patients were given the Leeds Sleep Evaluation Questionnaire (LSEQ) (Parrott & Hindmarch 1980) and underwent polysomnographic evaluations at the beginning and the end of the study. Although the groups were randomized, it is unclear if there were any significant baseline differences between the two groups in sleep architecture variables, as the paper makes no claim about the statistical similarity at baseline, although it does state that they were "generally well matched." The study reports several significant changes between baseline and endpoint in the paliperidone group compared with the changes observed in the placebo group. Most notable were improvements in total sleep, sleep continuity, and in stage II sleep, although these results are limited by the misleading setting of alfa at the 0.1 level in the paper. It also should be noted that paliperidone was associated with decreased slow-wave sleep, although this was not statistically significant. This study is commendable as data on the long-term effects of antipsychotics on sleep architecture are scarce. In a shorter study, risperidone has also been associated with improved subjective sleep (Dursun et al. 1999).

Prevention of recurrence

The effectiveness of paliperidone in preventing relapse was tested in a three-phase trial (Kramer et al. 2007). The methodology of this study is similar to other relapse prevention studies with other psychotropic drugs. A total of 530 patients with a baseline PANSS score of 70–120 and no documented treatment failure with risperidone were enrolled and began phase 1, an 8-week open-label run-in phase where they received a starting daily dose of paliperidone 9 mg, with increases/decreases of 3 mg per week to a maximum allowable dose of 15 mg daily. Phase 2 followed; a 6-week stabilization phase where the dose established in the run-in phase was continued. Response criteria necessary to enter phase 2 were not specified, other than patients being deemed stable for 2 weeks. The modal daily dose in phase 2 was 9 mg (45%), with 47% of patients needing increases to doses of 12–15 mg, and only 8% controlled by doses of 6 mg or less.

In the trial, 312 patients entered phase 2, and 207 patients subsequently entered phase 3, a double-blind phase where they were randomized to receive placebo or paliperidone at the dose they were receiving in the stabilization phase. Again, response criteria for patients to be eligible to enter the double-blind phase were not specified. During the double-blind treatment phase, the most frequently reported adverse effects were insomnia (5% for paliperidone, 6% for placebo), tachycardia (15% paliperidone, 8% placebo), and orthostatic hypotension (5% paliperidone, 2% placebo). Extrapyramidal symptoms were observed in 7% of patients taking paliperidone (compared with 3% taking placebo). Similar to the efficacy trials, prolactin levels were increased in patients taking paliperidone compared with placebo, with a 4% incidence of prolactin-related adverse events (e.g. breast enlargement in men, amenorrhea, and galactorrhea). Overall, the mean weight gain was 1.8 kg for paliperidone and 0.2 kg for placebo, with no significant changes in serum insulin, glucose, or lipids. It should be noted that these reports are only for the

patients in the double-blind phase, i.e. those who had tolerated paliperidone through the first two phases, and that reports of adverse events were considerably higher in the first two phases.

The duration of the double-blind phase was variable, and would continue until the patient experienced a recurrence (defined as hospitalization, specified increase in PANSS, specified dangerous behavior, or specified worsening on the Clinical Global Impressions—Severity of Illness scale), or until study termination. Details about the conversion to placebo, including rapidity of conversion, were not reported. A planned interim analysis was performed after 43 recurrence events, and the study was terminated early on the basis of significant efficacy results, which showed that 25% of the placebo group experienced a predefined recurrence at 23 days, versus 68 days in the paliperidone group ($P<0.001$). Overall, recurrence occurred in 52% and 22% of the placebo and paliperidone groups, respectively (NNT 4).

Several methodologic issues of this study bear further discussion. Firstly, 323 patients were not randomized to the double-blind stage (phase 3). Furthermore, 91 of these patients had not completed phase 1 or 2 when the study was prematurely stopped, so the total number of dropouts was 232 (52%). Listed reasons for dropouts are vague. For immediately before and during phase 2, 124 subjects (53%) dropped out because of "criteria not met" or "subject choice." An additional 33 subjects (14%) were lost to follow-up. Moreover, the majority of the dropouts in the double-blind phase were for similar reasons. Dropouts are not considered recurrences, but all of the listed reasons could potentially be referring to treatment failure, especially given the lack of detail reported of the response criteria necessary to proceed to the next phase. Second, the rapidity of conversion to placebo is not reported, and it is possible that the results are more descriptive of the rate of recurrence with antipsychotic withdrawal. An active comparator arm would have been informative. Third, the large majority of patients (92%) required a paliperidone dose greater than 6 mg to control their symptoms. Although the starting dose of 9 mg is a potential confounding variable, this is evidence against the starting dose of 6 mg being therapeutic for the majority of patients.

A more conservative conclusion to this study is that patients responsive to, and able to tolerate, paliperidone are more likely to have a recurrence when their paliperidone is stopped in comparison to continued treatment. Of note is the evidence that risperidone has been shown to be effective in maintenance treatment of schizophrenia, equivalent to haloperidol in one study (Marder et al. 2003), and superior in another (Csernansky & Schuchart 2002; Marder et al. 2003).

Economic evidence and resource utilization

As noted above, the economic burden of schizophrenia is large for many reasons, only partly because of the acquisition costs of brand name medications. No formal economic analysis has been published for paliperidone. However, the costs of paliperidone and risperidone are likely to be substantially different when risperidone is no longer governed by patent protection in June 2008. At the time of writing, the cost of a paliperidone 3 mg or 6 mg tablet is $US9.54, and that for a 9 mg tablet is $US14.31 (Rockland Psychiatric Center Pharmacy, Orangeburg, NY, USA, October 1, 2007). Risperidone 4 mg, meanwhile, costs $US9.75 (ibid). In Canada, however, where risperidone has been available as a generic medication since July 2006, the generic 4 mg tablet is now available for 43% of the cost of branded risperidone, at $Can1.92 compared with $Can4.40 for the branded product (Anon. 2007b).

Assuming that both the price of paliperidone 6 mg will remain constant and that generic and branded risperidone will have an equivalent price ratio in the United States as it does in Canada, using generic risperidone 4 mg over paliperidone 6 mg would lead to an annual saving of approximately $US2000 per patient. However, potential savings in hospital costs could make up this difference if paliperidone leads to a quicker response or improved social functioning. Significant separation from placebo is seen as early as day 4 in the three efficacy trials, although a similar analysis of data was not done for olanzapine. Moreover, the long-term relapse prevention trial in which titration of medication was allowable resulted in mean doses of paliperidone greater than 6 mg. While paliperidone did improve functioning on the PSP, similar results are reported for olanzapine and risperidone in the three efficacy trials and CATIE trial, respectively.

To repeat, a direct comparison with other antipsychotics is needed before definitive recommendations about these potential benefits can be made. It can, however, be said with confidence that paliperidone is likely to cost considerably more than generic risperidone. A trial of economic outcomes for patients treated with paliperidone is currently recruiting patients, as listed at www.clinicaltrials.gov/ct2/show/NCT00488891?term=paliperidone&rank=32.

Patient group/population

Paliperidone is effective compared with placebo in the acute treatment of schizophrenia in adults. The once-a-day dosing is helpful. Given its lack of hepatic metabolism, it may be particularly useful in patients with liver disease. No trials have been performed in other disease classifications, in contrast to risperidone, which has regulatory approval to treat bipolar mania and irritability associated with autistic disorder in children and adolescents. Several ongoing/planned trials for paliperidone in other diagnostic groups are listed on www.clinicaltrials.gov.

Dosage, administration, and formulations

Paliperidone (Invega) is available as 3, 6, and 9 mg tablets. At present, only the extended-release oral formulation is available. The recommended starting dose is 6 mg once daily, administered in the morning. Initial dose titration is not recommended in the product labeling, which also recommends that dose increases generally should occur at intervals of more than 5 days in increments of 3 mg/day if considered necessary. The maximum recommended dose is 12 mg/day. For patients with mild renal impairment (creatinine clearance ≥50 to <80 mL/min), the

maximum recommended dose is 6 mg/day. For patients with moderate to severe renal impairment (creatinine clearance 10 to <50 mL/min), the maximum recommended dose is 3 mg/day. Paliperidone must be swallowed whole and should not be chewed, divided, or crushed. The tablet shell, along with insoluble core components, is eliminated from the body in the stool.

Place in therapy

Schizophrenia is a severe, chronic, and disabling illness. Although many different antipsychotic drugs are available, their overall effectiveness is less than optimal. Some patients have no response to available drugs. Other patients have residual symptoms despite adequate drug treatment. Many patients respond to treatment, but have noxious or intolerable side effects that often contribute to poor medication adherence. For these reasons, new drug therapies are always needed, and the purpose of this review was to evaluate the place of paliperidone in the treatment of schizophrenia.

Paliperidone has a significantly different hepatic enzyme and metabolic profile compared with risperidone and several other atypical antipsychotic drugs, and is more effective than placebo in treating schizophrenia. It appears to be equivalent in efficacy to a relatively low dose of olanzapine. It remains to be seen whether it should be used in place of risperidone; the only clear advantage of paliperidone is the minimal hepatic metabolism, which may be important with respect to drug interaction potential. Although the extended-release formulation allows for once-daily administration, risperidone is also approved for this dosage frequency. A claim that paliperidone can be initiated at a therapeutic dose and has unique benefits in improving social functioning is only minimally supported by the limited evidence currently available (Kramer et al. 2007). Additionally, there is preliminary evidence that paliperidone may lead to greater EPS (at doses greater than 6 mg/day) and prolactin elevations than risperidone.

A controlled clinical trial directly comparing paliperidone and risperidone is highly desirable in order to contrast and compare these two agents. Until such a trial is performed, despite its effectiveness over placebo and theoretical advantages, it is difficult to justify first-line paliperidone use over risperidone, and it will become even harder to justify when risperidone becomes available as a less expensive generic medication.

Acknowledgments

Leslie Citrome, MD, MPH, is a consultant for, has received honoraria from, or has conducted clinical research supported by the following: Abbott Laboratories, AstraZeneca Pharmaceuticals, Avanir Pharmaceuticals, Azur Pharmaceuticals, Barr Laboratories, Bristol-Myers Squibb, Eli Lilly and Company, Forest Research Institute, GlaxoSmithKline, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Pfizer Inc, and Vanda Pharmaceuticals.

Joshua Kantrowitz, MD, has conducted clinical research supported by Jazz Pharmaceuticals.

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