

Expert Opinion

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Pimavanserin tartrate: a 5-HT_{2A} inverse agonist with potential for treating various neuropsychiatric disorders

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Background: Pimavanserin tartrate is the first 5-HT_{2A} inverse agonist to enter clinical trials as a treatment for L-dopa-induced psychosis in Parkinson's disease and for augmentation of low-dose risperidone treatment in schizophrenia. Pimavanserin is also being evaluated as a possible anti-insomnia drug. **Objective:** To discuss the potential of pimavanserin to fill multiple therapeutic needs. **Methods:** The problems with currently approved antipsychotics and sleep agents are explored to highlight how pimavanserin might address some longstanding issues in the treatment of psychosis and insomnia. **Results/conclusions:** In Phase II clinical trials, pimavanserin seemed to be safe, well-tolerated and efficacious in treating L-dopa-induced psychosis without worsening motor symptoms. Pimavanserin also potentiated the therapeutic effects of low-dose risperidone, reduced haloperidol-induced akathisia, and increased slow-wave sleep in older individuals.

Keywords: 5-HT_{2A}, 5-HT_{2A}, antipsychotic, inverse agonist, Parkinson's Disease, pimavanserin, psychosis, schizophrenia

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1. Introduction

Pimavanserin tartrate (ACP-103, Acadia Pharmaceuticals, Sorrento Valley, CA) is a 5-HT_{2A} inverse agonist in clinical trials for the treatment of psychosis in Parkinson's disease (PD) and as adjunct therapy in the treatment of schizophrenia.

2. Schizophrenia

The disease most often associated with psychosis is schizophrenia, a debilitating psychiatric illness whose etiology remains largely unknown, though some form of glutamatergic dysfunction is thought to underlie the disease [1]. Schizophrenia has been estimated to have an annual incidence of between 2 and 4 per 10,000, with a prevalence 10 times that rate [2]. Schizophrenia is characterized by deficits in three symptom domains: positive, negative, and cognitive (see reference [3] for more details). To date, all approved drug therapies are most effective in treating positive symptoms, with moderate efficacy in treating negative and cognitive symptoms [3]. This relative lack of efficacy for treating negative and cognitive symptoms of schizophrenia is unfortunate, as the severity of negative symptoms is the best predictor of quality of life, and severity of cognitive dysfunction is positively correlated with functional outcome in patients with schizophrenia [3].

The economic impact of schizophrenia is large and growing rapidly – from an estimated \$32.5 billion in 1990 [2] to \$63 billion just 12 years later [4]. A

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substantial portion of the cost of schizophrenia is due to indirect costs – resulting from increased mortality and morbidity, criminal behavior, use of social welfare programs, and family caregiving costs [5]. By some estimates, these indirect costs represent half or more of the economic cost of schizophrenia, with direct costs – money spent on drug treatment and hospitalizations, for example – accounting for the other half [2,5].

The pharmacotherapy of schizophrenia began more than 50 years ago with the discovery of chlorpromazine, the first antipsychotic used to treat the disease [3]. The earlier generations of antipsychotics were effective in treating the more salient symptoms exhibited by schizophrenic patients such as hallucinations and delusions [6]. These first generation antipsychotics are now referred to as typical antipsychotics and are characterized primarily by high affinity for D2 dopamine receptors and a number of class-specific side effects [6]. The class-specific side effects include extrapyramidal symptoms (EPS), which refer to the various movement disorders that can result from typical antipsychotic treatment – tardive dyskinesia, akathisia and dystonia. Other class-specific side effects include elevation of serum prolactin and neuroleptic malignant syndrome (NLS) [6].

Decades after its initial discovery in 1958, clozapine was shown to be characterized by a low affinity for D2 receptors and a high affinity for 5-HT_{2A} receptors [7-9]; a complex pharmacological profile [6,8,10,11]; a lack of EPS [12,13]; and an inability to elevate serum prolactin [3]. The discovery of clozapine inspired the development of the next generation of antipsychotics, the atypical antipsychotics, which are considered ‘atypical’ owing to their reduced EPS and serum prolactin elevation liabilities. Many, but not all [14], atypical antipsychotic drugs are characterized by a relatively low D2 occupancy at therapeutic doses [15], and this seems to distinguish them from many typical antipsychotic drugs. Unfortunately, some, but not all, atypical antipsychotics carry their own unique side-effect profile, including weight gain and metabolic syndrome [3,16]. Furthermore, with the exception of clozapine, atypical antipsychotics are not superior to the typicals in their efficacy in most schizophrenic populations [17], although clozapine has demonstrated utility in diminishing suicidality [18] and in treatment-resistant schizophrenia [19,20].

It has been proposed that schizophrenia should be subdivided into the different symptom domains of which it is composed, and it follows that the different symptom domains probably correspond to different therapeutic targets that may have to be treated separately. This may explain why developing a rapid onset agent with efficacy in treating the positive, negative, and cognitive symptoms of schizophrenia has proved so elusive. Novel approaches aimed at developing effective therapies for schizophrenia have moved away from the predominant paradigm of designing selective drugs – ‘magic bullets’ – which appear to be effective only in treating select symptom domains. Instead, it has been proposed that selectively non-selective drugs – ‘magic shotguns’ – may be

more useful in treating unrelated symptom domains of one illness [6]. Alternatively, polypharmacy using more selective agents aimed at treating the different symptom domains individually could achieve similar results [3].

A major issue in the treatment of schizophrenia is the fact that the antipsychotic treatments are characterized by high rates of patient non-compliance. A survey of 24 different studies of varying sample sizes estimated patient compliance in taking antipsychotic medications as prescribed to range from 24 to 90%, with an average of 58% [21]. In the most rigorous studies, in which urine tests were accompanied by pill counts, the average rate of compliance was 60% [21]. The economic cost of non-compliance is likely to represent a significant portion of the societal cost of schizophrenia. For example, rehospitalization costs due to non-compliance with prescribed medication regimens by Medicaid patients alone were estimated to be almost \$1.5 billion, and possibly higher [4]. Increased mortality and morbidity in non-compliant patients, along with an increased burden on community resources and family caregivers, are likely to increase the economic cost to many billions of dollars per year.

One of the major sources of non-compliance is the highly unpleasant side-effect profile of both typical and atypical antipsychotics [22,23]. As might be expected, drugs with different side-effect profiles have different rates of non-compliance and associated direct costs [22]. EPS are unpleasant for obvious reasons, and elevation of serum prolactin can lead to numerous sexual side effects, which can be among the most unpleasant side effects of antipsychotic treatment [24,25]. It was hoped that the newer generation atypical antipsychotics would improve patient compliance, but most studies that compare typicals and atypicals with respect to patient compliance did not detect any difference [17,23]. This is probably due to their own unique side effects – for example, the vast majority of patients experiencing weight gain, a side effect of many of the atypicals, reported that to be problematic [16,26]. Clearly, new treatments that accelerate symptom reduction, treat multiple symptom domains or improve the side-effect profile of approved agents may increase patient compliance (and thus long-term effectiveness of treatment) and improve quality of life.

3. Psychosis in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with a prevalence of 0.3% in industrialized nations and an incidence of 4 – 20 per 100,000 [27]. Like schizophrenia, the economic burden of PD is high – a study comparing 20,000 PD patients to controls produced an estimated cost of \$23 billion annually using data from 2002 [28]. Another study showed that PD is associated with large direct economic costs to society [29].

First-line PD drugs are aimed at alleviating movement dysfunction. However, psychotic symptoms are a very

commonly seen side effect in L-dopa-treated PD patients [30]. Visual hallucinations, occurring in 30% of PD patients, are the most common, and are associated with auditory or tactile hallucinations in roughly 10% of patients [30]. Most patients experiencing PD-related hallucinations exhibit intact reality testing but some 5 – 10% of PD patients have frank delusions and hallucinations without insight [31]. PD patients exhibiting psychotic symptoms have been estimated to be 15-fold more likely to be in a nursing home, suggesting a dramatically increased caregiver burden in this subset of PD sufferers [32]. Furthermore, all currently available anti-PD agents have been implicated in the development of hallucinations [30].

The earliest treatments for PD psychosis involved either reducing the anti-PD dosage or prescribing a typical antipsychotic – both strategies that tend to worsen PD symptoms [31]. Presently, the most efficacious and best studied treatment is low dose clozapine, for which there is strong evidence of an ability to ameliorate psychotic symptoms with no concomitant worsening of PD symptoms [31]. The main drawback to clozapine is the dose-independent occurrence of agranulocytosis, which requires frequent blood monitoring of patients taking the drug. Clozapine has further unpleasant side effects that limit its use, including hypersalivation, hypotension, constipation, and severe weight gain [33]. A number of other atypical antipsychotics have been used and studied in the treatment of PD psychosis. Risperidone and olanzapine both seem to be effective in reducing psychotic symptoms in double-blind, placebo-controlled trials, but motor symptoms were worsened in a large percentage of patients [31,32]. Low-dose quetiapine, on the other hand, has been reported in a number of open-label trials to reduce psychotic symptoms without worsening motor function [31,32]. Furthermore, quetiapine has an advantage over clozapine in that blood monitoring is not required. Thus, many PD experts consider quetiapine to be first-line treatment for PD psychosis [31]. It should be stressed, however, that quetiapine has not been shown to be effective without worsening motor symptoms in any double-blind, placebo-controlled trials. New, proven treatments for PD-related psychosis that do not worsen motor symptoms or have serious side effects are not available at present and would fill an important and growing need.

4. 5-HT_{2A} antagonists/inverse agonists and sleep

The incidence of insomnia is 10 – 30%, with about 50% of those patients complaining of significant effects on daytime functioning [34]. The most commonly prescribed treatments are benzodiazepenes that target GABA_A receptors to produce sedation, but with major limitations including tolerance and abuse potential, ataxia, memory loss and other cognitive impairments, and next-day sedation, which impairs functioning [34]. There is evidence that stage 3 and stage 4

sleep – slow-wave sleep (SWS) – are especially important for sleep maintenance [35]. There is an increasing appreciation that 5-HT_{2A} antagonists may be particularly useful therapy for insomnia without many of the less desirable side effects of benzodiazepines [34]. Numerous immediate-early genes that are misregulated after sleep deprivation are also regulated by 5-HT_{2A} agonists [34,36,37]. Studies in rodents and humans have shown a robust increase of SWS by 5-HT_{2A} antagonists [38,39]. At present, there are three 5-HT_{2A} antagonists in Phase III trials for treating insomnia (eplivanserin, volinanserin, pruvanserin), and two inverse agonists in Phase II insomnia trials (APD125 and HY10275) [34].

5. Chemistry

Pimavanserin tartrate is the United States Adopted Names (USAN) Council designation for ACP-103, or (1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-[[4-(2-methylpropoxy)phenyl]methyl]urea) (see Figure 1A and B) [40]. Pimavanserin tartrate (C₅₄H₇₄F₂N₆O₁₀) contains two molecules of pimavanserin per molecule of tartrate, for a total molecular weight of 1005.12 g/mol (428.56 g/mol for each molecule of pimavanserin, C₂₅H₃₅N₃O₂⁺). Numerous lab-scale and large-scale syntheses have been described (see international patent application PCT/US2007/011720 US60/854,665 for details and list of related patent applications).

6. Pharmacodynamics

A study published in 2008 examines the pharmacodynamics of pimavanserin [41]. In that study, 5-HT_{2A} receptor occupancy was measured in four patients by PET imaging using the ligand [¹¹C]N-methylspiperone (NMSP). Two patients received 1-, 5- and 20-mg doses orally at 2-week intervals followed by PET imaging after 6 h to measure 5-HT_{2A} occupancy, although this ligand also has high affinity for other biogenic amine receptors. Two other patients received 2-, 10- and 100-mg doses orally but otherwise underwent the same studies. The lower limit of cortical receptor occupancy ranged from 20% at the lowest dose in one patient to saturation at almost 80% occupancy at doses of 10 mg or more. The inability to reach 100% inhibition is probably due to the fact that [¹¹C]NMSP also binds cortical α₁ adrenergic and D_{2/3/4}-dopaminergic receptors for which pimavanserin has minimal affinity.

7. Pharmacokinetics

To date, two research articles have been published that contain detailed measurements of pharmacokinetic parameters in humans, representing data from two single-center, randomized, double-blind, placebo-controlled, escalating dose studies [42,43]. In the first article, 25 patients were divided into six groups for single-dose treatments: placebo, 20, 50, 100, 200 and

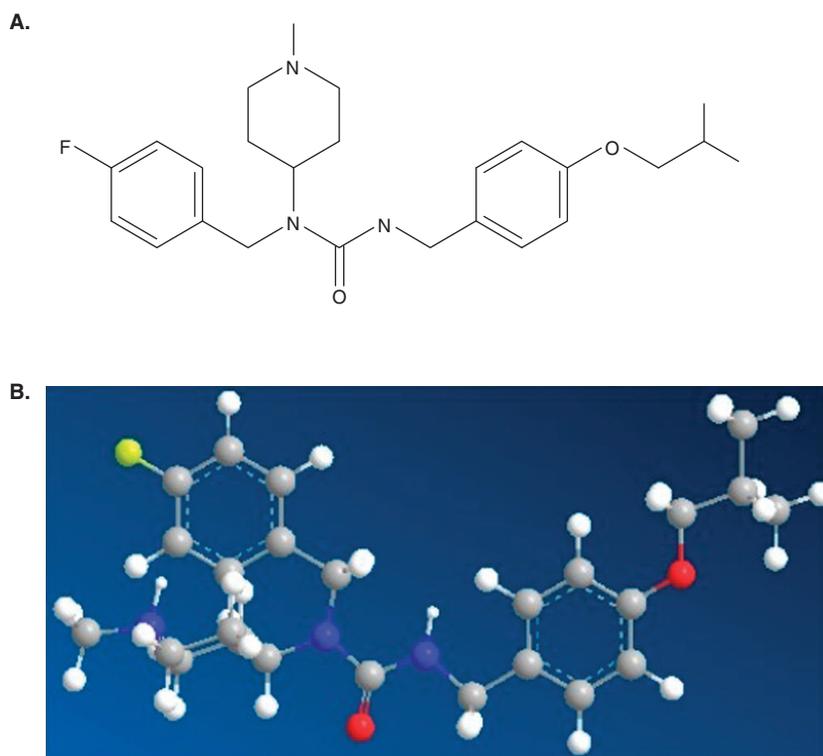


Figure 1. Chemical structure (A) and 3-D model (B) of pimavanserin.

300 mg. The following pharmacokinetic parameters were then measured: C_{max} , T_{max} , AUC, $t_{1/2}$, and CL/F [42]. Another group of 24 patients received once-daily doses of placebo, 50, 100 or 150 mg for 2 weeks. The aforementioned pharmacokinetic parameters were measured in this group as well, both after the first dose and at steady-state. Accumulation and C_{max} ratios were also calculated. For the single-dose measurements, C_{max} and AUC were dose-proportional, ranging from 9 ng/ml and 700 h·ng/ml at the 20-mg dose to 152 ng/ml and 10,800 h·ng/ml at the 300-mg dose. T_{max} was roughly 6 h, $t_{1/2}$ approximately 55 h, and oral clearance between 23 and 33 L/h. Subjects showed low inter-subject variability. Pimavanserin was highly protein bound in plasma (~ 95%). For the multiple-dose study, the accumulation and C_{max} ratios were approximately 5 at the two lower doses and 3.5 at the higher dose.

In the second study, a third group consisting of eight patients had their pharmacokinetic parameters measured after ingesting pimavanserin solution on a 10-h fast, pimavanserin tablets on a 10-h fast, and pimavanserin tablets immediately after a high-fat meal [43]. Each drug treatment was separated by at least 2 weeks. Pharmacokinetic parameters did not differ between the various treatments. Together, the data indicate that pimavanserin has desirable pharmacokinetic parameters that are conducive to once-daily administration.

8. Clinical efficacy (see Table 1 for concise summary)

8.1 Phase II studies related to schizophrenia

In one double-blind, placebo-controlled study, 18 healthy volunteers were given 7.5 mg of haloperidol, with 11 of the subjects developing measurable akathisia as measured by the Barnes Subjective-Distress Rating Scale (BSDRS) [44]. Haloperidol treatment also induced a threefold increase in prolactin levels. A single 100-mg dose of pimavanserin reduced akathisia in most cases, with complete disappearance in four subjects. Furthermore, pimavanserin significantly reduced ($p < 0.001$, paired t-test) prolactin secretion by approximately 33%. The pharmacokinetic parameters of neither drug were affected by co-administration, and no serious adverse events were reported.

In another double-blind, randomized, placebo-controlled study, 34 patients with a clinical diagnosis of schizophrenia or schizoaffective disorder who also experienced haloperidol-induced akathisia were split into two groups, one receiving once-daily 60-mg doses of pimavanserin for 5 days and the other receiving placebo [45]. The Barnes Akathisia Scale (BAS) was used to measure antipsychotic side effects. Pimavanserin significantly reduced objective akathisia on day 5 ($p = 0.04$) and significantly reduced subjective awareness of restlessness ($p = 0.02$) and the BAS total ($p = 0.03$) on day 3. There were no significant effects of pimavanserin on

Table 1. Summary of pimavanserin tartrate clinical trial data.

Phase	Indication	Summary	Date of completion/publication
Phase I	–	Drug-like pharmacokinetics Safe and well-tolerated	June 2007
Phase I	–	Pharmacokinetic parameters unaffected by food	July 2007
Phase I	–	High receptor occupancy easily achieved at therapeutic doses	Mar 2008
Phase II	Schizophrenia co-therapy	Reduced haloperidol-induced akathisia as assessed by BSDRS Reduced prolactin secretion No serious TRAEs reported	Sept 2004
Phase II	Schizophrenia co-therapy	Significantly reduced haloperidol-induced akathisia as measured by BAS No effect on haloperidol-induced EPS or elevation of serum prolactin	Dec 2005
Phase II	Schizophrenia co-therapy	Potentiated low dose risperidone to efficacy comparable to high dose risperidone, as measured PANSS Faster onset of action No effect on haloperidol efficacy or onset of action No serious TRAEs	Mar 2007
Phase Ib/IIa	PD treatment-induced psychosis	Did not worsen motor symptoms No serious TRAEs reported	June 2004 ⁺
Phase II	PD treatment-induced psychosis	Did not worsen motor symptoms as assessed by UPDRS Parts II and III Improved psychotic symptoms as assessed by UPDRS Part I	Mar 2006
Phase II	Sleep maintenance insomnia	Increased time spent in slow wave sleep Decreased the number of awakenings Did not impair daytime functioning as assessed by the CPT	Apr 2006
Phase III	PD treatment-induced psychosis	240 subjects, 6 weeks 3 study arms: placebo, pimavanserin 10 mg, pimavanserin 20 mg	Dec 2009
Phase III	PD treatment-induced psychosis	240 subjects, 6 weeks 3 study arms: placebo, pimavanserin 10 mg, pimavanserin 40 mg	Dec 2009
Phase III	PD treatment-induced psychosis	500 subjects Open-label study lasting as long as pimavanserin is tolerated and beneficial Will assess longer term safety	Dec 2009

other EPS side effects or on plasma prolactin. There were also no significant effects on the positive or negative symptoms of schizophrenia, probably owing to the short treatment duration.

In a third, multi-center, double-blind, placebo-controlled study, 423 patients were enrolled and assigned to one of five study arms: pimavanserin (20 mg) plus risperidone low dose (LD) (2 mg); risperidone LD plus placebo; risperidone high dose (HD) (6 mg) plus placebo; pimavanserin plus haloperidol (2 mg); and placebo plus haloperidol [46]. Pimavanserin and risperidone LD co-therapy resulted in

a 27.4% improvement as measured by the Positive and Negative Syndrome Scale (PANSS) at day 42 ($p < 0.001$). Pimavanserin plus risperidone LD demonstrated enhanced antipsychotic efficacy compared with risperidone LD alone ($p = 0.01$), and this enhancement was observed for both positive and negative symptoms. Pimavanserin co-therapy with risperidone LD achieved comparable efficacy to risperidone HD. Pimavanserin co-therapy with risperidone LD provided significantly faster onset of action, with 50% more patients in the co-therapy arm responding after 2 weeks of treatment ($p < 0.008$) compared with the other two risperidone-

Pimavanserin tartrate

treated groups. Pimavanserin co-therapy with haloperidol did not lead to increased efficacy or a faster onset of action.

8.2 Phase II studies related to Parkinson's disease psychosis

In one multi-center, double-blind, placebo-controlled study, 60 PD patients suffering from treatment-induced psychosis were enrolled at multiple sites, receiving either placebo or 20 mg of pimavanserin once-daily for 28 days [47]. The study design allowed for escalation of the pimavanserin dose to 40 mg and then 60 mg at two scheduled time points. Motoric tolerability was measured by the Unified Parkinson's Disease Rating Scale (UPDRS). It was found that pimavanserin did not worsen motor symptoms as measured by the UPDRS Parts II and III ($p = 0.22$). Furthermore, pimavanserin-treated patients showed significant improvement in the UPDRS Part I, which measures mental impairment, and the improvement was attributable to effects on hallucinations and delusions.

8.3 Clinical study related to sleep maintenance insomnia

Forty-five healthy volunteers ranging in age from 40 to 64 years were enrolled in a double-blind, placebo-controlled study and randomly assigned to one of five treatment arms corresponding to subjects receiving placebo or one of four doses of pimavanserin (1, 2.5, 5 or 20 mg) once-daily for 14 days [48]. Subjects underwent a 2-night baseline polysomnography (PSG) assessment and PSG measurements were taken on days 1 and 13. They also completed a Continuous Performance Test (CPT) to measure potential impact on daytime functioning. Pimavanserin dose-dependently increased time spent in slow-wave sleep both acutely and chronically. The effect of pimavanserin on slow-wave sleep was highly significant ($> 50\%$) after treatment with 5- or 20-mg doses ($p < 0.001$ at days 1 and 13 for both doses). Pimavanserin also significantly decreased the number of awakenings ($p = 0.4$) and did not impair daytime functioning.

8.4 Phase III trials

Three Phase III trials are underway to study the safety, efficacy and tolerability of pimavanserin in the treatment of PD psychosis. One primary end point will be the scale for the assessment of positive symptoms (SAPS), which should assess pimavanserin's efficacy better than the UPDRS part I used in the Phase II trials. The estimated completion date for these studies is December 2009.

9. Safety and tolerability

The powdered capsule form of pimavanserin was well tolerated at all doses, and there were no serious treatment-related adverse events (TRAE) at any dose [42,43]. The most common TRAEs reported by patients were drowsiness

and postural dizziness, which were reported in about 50% of patients [42,43].

10. Conclusions

The data so far indicate that pimavanserin, a 5-HT_{2A} inverse agonist, is safe and well-tolerated, with good drug-like pharmacokinetic and pharmacodynamic properties. Clinical trials until now have shown pimavanserin to potentiate low-dose risperidone efficacy and reduce akathisia when taken in conjunction with haloperidol. Pimavanserin as stand-alone therapy seems to be effective in treating PD psychosis without worsening motor symptoms. Finally, initial clinical data indicate that pimavanserin increases slow-wave sleep, suggesting the possibility for its use as an anti-insomnia agent.

11. Expert opinion

The antipsychotic drugs available at present have a number of limitations. Typical antipsychotic drugs are relatively ineffective in treating the negative and cognitive symptoms of schizophrenia, while atypical antipsychotic drugs have only modest actions on cognition and negative symptoms [49,50]. The typical antipsychotics are effective in treating positive symptoms but they have a number of very serious side effects including EPS, serum prolactin elevation and NLS. Many, but not all, of the atypical antipsychotic drugs cause significant weight gain and are associated with a metabolic syndrome. The side-effect profile of many antipsychotics is a major source of non-compliance and negatively affects the quality of life of patients undergoing therapy. Clozapine is superior with respect to all other antipsychotics with regard to efficacy, EPS liability and a number of other characteristics of treatment quality and effectiveness [51] but can cause severe weight gain and dose-independent agranulocytosis. Furthermore, clozapine is the only antipsychotic that has been convincingly shown to be effective in treating PD psychosis without exacerbating motor symptoms but has the aforementioned serious limitations that have historically militated against its use. 5-HT_{2A} antagonists alone have been shown in clinical studies to be efficacious in treating schizophrenia as assessed by the total PANSS score but are not as efficacious as the comparator, haloperidol [52]. 5-HT_{2A} antagonists also compare favorably to other approved antipsychotics in treatment discontinuation rates and are not associated with weight-gain liability [51,52].

5-HT_{2A} inverse agonist and antagonists have two distinct advantages with respect to currently approved antipsychotics that argue in favor of pursuing their development more aggressively. First, their side-effect profile appears to be very favorable. Given the fact that the side effects of most antipsychotics severely impair quality of life (and can even be fatal) and often lead to non-compliance/treatment discontinuation, consideration of side-effect burden represents an underemphasized consideration in the treatment of

psychosis. Second, owing to the D2 antagonistic effects of available antipsychotics, these drugs have been largely ineffective at treating PD psychosis without exacerbating motor symptoms, with clozapine and perhaps quetiapine being exceptions. Since pimavanserin does not antagonize D2 receptors, this represents another major advantage with respect to treating PD psychosis.

Preliminary clinical data indicating that pimavanserin might reduce antipsychotic side-effect liability opens another avenue of promise – the use of 5-HT_{2A} inverse agonists and antagonists to reduce the side-effect burden of currently approved drugs – which would improve compliance (and therefore long-term efficacy of treatment) and quality of life for sufferers of schizophrenia. The initial data suggest that pimavanserin significantly reduces haloperidol-induced akathisia. Furthermore, pimavanserin co-therapy enhances the efficacy of low-dose risperidone to a level similar to much higher dosages of risperidone. This, in turn, may lead to a reduction in the side-effect burden with respect to EPS, serum prolactin elevation, and weight gain, as there is some evidence that these actions are dose dependent [53]. To convince the medical community of the usefulness of pimavanserin as co-therapy with first-line antipsychotics, it will be important to establish that pimavanserin causes a robust decrease in the side-effect burden of its partner antipsychotic, with a concomitant increase in patient compliance or decrease in treatment discontinuation rates. It would also be desirable to see a potentiating effect of pimavanserin in conjunction with multiple first-line antipsychotics. There are no Phase III studies concerning pimavanserin co-therapy that

have been announced publicly, so it is difficult at this point to assess what the status of pimavanserin as antipsychotic co-therapy will be in the near future.

It is widely agreed that the drugs available at present for treating PD psychosis are inadequate. Pimavanserin represents a new, safe, well-tolerated treatment that appears to decrease psychotic symptoms in individuals with PD without aggravating motor symptoms. The results of Phase III trials in late 2009 to early 2010 will be very important with regards to establishing the usefulness of pimavanserin as standalone therapy in treating PD psychosis. The Phase II data indicate that pimavanserin may prove to be a safe, well-tolerated, efficacious drug in this patient population. Pimavanserin could become a first-line treatment for PD psychosis, and this is most likely the first indication for which it will be approved if the results of the Phase III studies continue to be promising.

As far as the use of pimavanserin for the treatment of insomnia is concerned, testing is still in Phase II. Furthermore, there are three 5-HT_{2A} antagonists in Phase III clinical trials and two 5-HT_{2A} inverse agonists in Phase II [34]. Thus, if 5-HT_{2A} antagonists are ever approved for the treatment of insomnia, which appears more likely than not, pimavanserin will probably not be the first on the market for this indication.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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