Pimavanserin for psychosis in patients with Parkinson's disease

Jonathan M. Meyer, MD

Pimavanserin is a potent 5-HT2A inverse agonist and 5-HT2C inverse agonist, with 5-fold greater affinity for the 5-HT2A receptor.[1] Although antagonists block agonist actions at the receptor site, inverse agonists reduce the level of baseline constitutive activity seen in many G protein-coupled receptors. This medication is FDA approved for treating hallucinations and delusions associated with Parkinson's disease (PD) psychosis (***Table 1***).[1]

In the pivotal 6-week clinical trial, pimavanserin significantly reduced positive symptoms seen in PD patients with psychosis (effect size = 0.50), with no evident impairment of motor function.[2] Only 2 adverse effects occurred in ≥5% of pimavanserin-treated patients and at ≥2 times the rate of placebo: peripheral edema (7% vs 3% for placebo) and confusion (6% vs 3% for placebo). There was a mean increase in the QTc of 7.3 milliseconds compared with placebo in the pivotal phase III study.

Clinical implications

Despite numerous developments in the pharmacotherapeutics of psychotic disorders, patients with psychosis related to PD previously responded in a robust manner to only 1 antipsychotic, low-dosage clozapine (mean effect size, 0.80),[2] with numerous failed trials for other atypical antipsychotics, including quetiapine.[3,4] The pathophysiology of psychosis in PD patients is not related to dopamine agonist treatment, but is caused by the accumulation of cortical Lewy body burden, which results in loss of serotonergic signaling from dorsal raphe neurons. The net effect is up-regulation of postsynaptic 5-HT2A receptors.[5] Psychosis is the most common cause of nursing home placement among PD patients without dementia.[6]

Table 1

Fast facts about pimavanserin

Brand name: Nuplazid
Class: 5-HT2A inverse agonist
Indication: Hallucinations and delusions associated with Parkinson's disease psychosis
Approval date: April 29, 2016
Availability date: June 1, 2016
Manufacturer: Acadia Pharmaceuticals Inc.
Dosing form: 17-mg tablets
Recommended dosage: 34 mg once daily without titration, and with or without food

Source: Reference 1

Receptor blocking. Based on the finding that clozapine in low dosages acts at 5-HT2A receptors,[7] pimavanserin was designed to be a potent 5-HT2A inverse agonist, with more than 5-fold higher selectivity over 5-HT2C receptors, and no appreciable affinity for other serotonergic, adrenergic, dopaminergic, muscarinic, or histaminergic receptors[8] (***Table 2, page 83***). The concept that 5-HT2A receptor stimulation can cause psychosis with prominent visual hallucinations is known from studies of LSD and

Dr. Meyer is Psychopharmacology Consultant, California Department of State Hospitals, and Assistant Clinical Professor of Psychiatry, University of California, San Diego, San Diego, California. He is also Deputy Editor of Current Psychiatry.

Disclosure

Dr. Meyer is a speaker for Acadia Pharmaceuticals.

In a 6-week clinical trial, pimavanserin reduced positive symptoms with no evident impairment of motor function

other hallucinogenic compounds whose activity is blocked by 5-HT2A antagonists.

As an agent devoid of dopamine D2 antagonism, pimavanserin carries no risk of exacerbating motor symptoms, which was commonly seen with most atypical antipsychotics studied for psychosis in PD patients, except for clozapine and quetiapine.[3] Although quetiapine did not cause motor effects, it proved ineffective in multiple studies (n = 153), likely because of the near absence of potent 5-HT2A binding.[4]

Pimavanserin also lacks:

- the hematologic monitoring requirement of clozapine
- clozapine's risks of sedation, orthostasis, and anticholinergic and metabolic adverse effects.

Pimavanserin is significantly more potent than other non-antipsychotic psychotropics at the 5-HT2A receptor, including doxepin (26 nM), trazodone (36 nM), and mirtazapine (60 nM).

Use in psychosis associated with PD. Recommended dosage is 34 mg once daily without titration (with or without food), based on results from a phase III clinical trial[2] (because of the FDA breakthrough therapy designation for this compound, only 1 phase III trial was required). Pimavanserin produced significant improvement on the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD), a 9-item instrument extracted from the larger SAPS used in schizophrenia research. Specifically, pimavanserin was effective for both the hallucinations and delusions components of the SAPS-PD.

Pharmacologic profile, adverse effects. Pimavanserin lacks affinity for receptors other than 5-HT2A and 5-HT2C, leading to an absence of significant anticholinergic effects, orthostasis, or sedation in clinical trials.[2] In all short-term clinical trials, the only common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were peripheral edema (7% vs 2% placebo) and confusional state (6% vs 3% placebo).[2] More than 300 patients have been treated for >6 months, >270 have been treated for at least 12 months, and >150 have been treated for at least 24 months with no adverse effects other than those seen in the short-term trials.[1]

There is a measurable impact on cardiac conduction seen in phase III data and in the thorough QT study. In the thorough QT study, 252 healthy participants received multiple dosages in a randomized, double-blind manner with positive controls.[1] The maximum mean change from baseline was 13.5 milliseconds at dosages twice the recommended dosage, and the upper limit of the 90% CI was only slightly greater at 16.6 milliseconds. Subsequent kinetic analyses suggested concentration-dependent QTc interval prolongation in the therapeutic range, with a recommendation to halve the daily dosage in patients taking potent cytochrome P450 (CYP) 3A4 inhibitors.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval were in the range of 5 to 8 milliseconds. There were sporadic reports of QTcF values ≥500 milliseconds, or changes from baseline QTc values ≥60 milliseconds in pimavanserin-treated participants, although the incidence generally was the same for pimavanserin and placebo groups. There were no reports of torsades de pointes or any differences from placebo in the incidence of adverse reactions associated with delayed ventricular repolarization.

How it works

The theory behind development of pimavanserin rests in the finding that low-dosage clozapine (6.25 to 50 mg/d) was effective for PD patients with psychosis (effect size 0.80).[8] Although clozapine has high affinity for multiple sites, including histamine H1 receptors (Ki = 1.13 nM), α-1A and a α-2C adrenergic receptors (Ki = 1.62 nM and 6 nM, respectively), 5-HT2A receptors (Ki = 5.35 nM), and muscarinic M1 receptors (Ki = 6 nM), the hypothesized primary

Clinical Point

There is measurable impact on cardiac conduction seen in phase-III data and in the thorough QT study

Discuss this article at www.facebook.com/CurrentPsychiatry

mechanism of clozapine's effectiveness for PD psychosis at low dosages focused on the 5-HT2A receptor. This idea was based on the knowledge that hallucinogens such as mescaline, psilocybin, and LSD are 5-HT2A agonists.[9] This hallucinogenic activity can be blocked with 5-HT2A antagonists. Because of pimavanserin's binding profile, the compound was studied as a treatment for psychosis in PD patients.

Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after a single oral dose as much as 7.5 times the recommended dosage. The pharmacokinetics of pimavanserin were similar in study participants (mean age, 72.4) and healthy controls, and a high-fat meal had no impact on the maximum blood levels (Cmax) or total drug exposure (area under the curve [AUC]).

The mean plasma half-lives for pimavanserin and its metabolite *N*-desmethyl-pimavanserin (AC-279) are 57 hours and 200 hours, respectively. Although the metabolite appears active in *in vitro* assays, it does not cross the blood-brain barrier to any appreciable extent, therefore contributing little to the clinical effect. The median time to maximum concentration (Tmax) of pimavanserin is 6 hours with a range of 4 to 24 hours, while the median Tmax of the primary metabolite AC-279 is 6 hours. The bioavailability of pimavanserin in an oral tablet or solution essentially is identical.

Pimavanserin is primarily metabolized via CYP3A4 to AC-279, and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, indinavir) increase pimavanserin Cmax by 1.5-fold, and AUC by 3-fold. In patients taking strong CYP3A4 inhibitors, the dosage of pimavanserin should be reduced by 50% to 17 mg/d. Conversely, patients on CYP3A4 inducers (eg, rifampin, carbamazepine, phenytoin) should be monitored for lack of efficacy; consider a dosage increase as necessary. Neither pimavanserin nor its metabolite, AC-279, are inhibitors or inducers of major CYP enzymes or drug transporters.

Table 2

Binding affinities of pimavanserin

Receptor	Binding affinity (Ki nM)	Binding profile
5-HT2A	0.087	Inverse agonist
5-HT2C	0.44	Inverse agonist
5-HT2B	>300	
D2	>300	
H1	>300	
M1	>300	
α-1	>300	

Efficacy in PD psychosis

Study 1. This 6-week, fixed dosage, double-blind, placebo-controlled trial was performed in adult PD patients age ≥40 with PD psychosis.[2] Participants had to have (1) a PD diagnosis for at least 1 year and (2) psychotic symptoms that developed after diagnosis. Psychotic symptoms had to be present for at least 1 month, occurring at least weekly in the month before screening, and severe enough to warrant antipsychotic treatment. Baseline Mini-Mental State Examination score had to be ≥21 out of 30, with no evidence of delirium. Patients with dementia preceding or concurrent with the PD diagnosis were excluded. Antipsychotic treatments were not permitted during the trial.

After a 2-week nonpharmacotherapeutic lead-in phase that included a brief, daily psychosocial intervention by a caregiver, 199 patients who still met severity criteria were randomly allocated in a 1:1 manner to pimavanserin (34 mg of active drug, reported in the paper as 40 mg of pimavanserin tartrate) or matched placebo. Based on kinetic modeling and earlier clinical data, lower dosages (ie, 17 mg) were not explored, because they achieved only 50% of the steady state plasma levels thought to be required for efficacy.

continued

Clinical Point

In patients taking a strong CYP3A4 inhibitor, the dosage of pimavanserin should be reduced by 50% to 17 mg/d

Clinical Point

Pimavanserin has no appreciable affinity for dopaminergic receptors, and therefore does not induce motor adverse effects

The primary outcome was assessed by central, independent raters using the PD-adapted SAPS-PD. The efficacy analysis included 95 pimavanserin-treated individuals and 90 taking placebo. Baseline SAPS-PD scores were 14.7 ± 5.55 in the placebo group, and 15.9 ± 6.12 in the pimavanserin arm. Participants had a mean age of 72.4 and 94% white ethnicity across both cohorts; 42% of the placebo group and 33% of the pimavanserin group were female. Antipsychotic exposure in the 21 days prior to study entry were reported in 17% (n = 15) and 19% (n = 18) of the placebo and pimavanserin groups, respectively, with the most common agent being quetiapine (13 of 15, placebo, 16 of 18, pimavanserin). Approximately one-third of all participants were taking a cholinesterase inhibitor throughout the study.

Efficacy outcome. Pimavanserin was associated with a 5.79-point decrease in SAPS-PD scores compared with 2.73-point decrease for placebo (difference −3.06, 95% CI −4.91 to −1.20; P = .001). The effect size for this difference (Cohen's d) was 0.50. The significant effect of pimavanserin vs placebo also was seen in separate analyses of the SAPS-PD subscore for hallucinations and delusions (effect size 0.50), and individually for hallucinations (effect size 0.45) and delusions (effect size 0.33). Separation from placebo appeared after the second week of pimavanserin treatment, and continued through the end of the study. There is unpublished data showing efficacy through week 10, and longer term, uncontrolled data consistent with sustained response. An exploratory analysis of caregiver burden demonstrated an effect size of 0.50.

Tolerability

The discontinuation rate because of adverse events for pimavanserin and placebo-treated patients was 10 patients in the pimavanserin group (4 due to psychotic symptoms within 10 days of starting the study drug) compared with 2 in the placebo group. There was no evidence of motor worsening in either group, demonstrated by the score on part II of the Unified Parkinson's Disease Rating Scale (UPDRS) that captures self-reported activities of daily living, or on UPDRS part III (motor examination). Pimavanserin has no contraindications.

Unique clinical issues

Binding properties. Pimavanserin possesses potent 5-HT2A inverse agonist properties required to manage psychosis in PD patients, but lacks clozapine's affinities for α-1 adrenergic, muscarinic, or histaminergic receptors that contribute to clozapine's poor tolerability. Moreover, pimavanserin has no appreciable affinity for dopaminergic receptors, and therefore does not induce motor adverse effects.

Clozapine aside, all available atypical antipsychotics have proved ineffective for psychosis in PD patients, and most caused significant motor worsening.[3] Although quetiapine does not cause motor effects, it has been shown to be ineffective for psychosis in PD patients in multiple trials.[4]

The effect size for clozapine response is large (0.80) in PD patients with psychosis, but tolerability issues and administrative burdens regarding patient and prescriber registration and routine hematological monitoring pose significant clinical barriers. Clozapine also lacks an FDA indication for this purpose, which may pose a hurdle to its use in certain treatment settings.

Why Rx? The reasons to prescribe pimavanserin for PD patients with psychosis likely include:

- absence of tolerability issues seen with the only other effective agent, clozapine
- lack of motor effects
- lack of administrative and monitoring burden related to clozapine prescribing

continued on page 86

continued from page 84

Related Resources

- Chang A, Fox SH. Psychosis in Parkinson's disease: Epidemiology, pathophysiology, and management. Drugs. 2016;76(11):1093-0118.
- Martinez-Ramirez D, Okun MS, Jaffee MS. Parkinson's disease psychosis: therapy tips and the importance of communication between neurologists and psychiatrists [published online July 13, 2016]. Neurodegener Dis Manag. doi:10.2217/nmt-2016-0009.

Drug Brand Names

Carbamazepine • Tegretol
Clarithromycin • Biaxin
Clozapine • Clozaril
Doxepin • Silenor
Indinavir • Crixivan
Itraconazole • Sporanox
Ketoconazole • Nizoral
Mirtazapine • Remeron
Phenytoin • Dilantin
Pimavanserin • Nuplazid
Quetiapine • Seroquel
Rifampin • Rifadin
Trazodone • Desyrel, Oleptro

Clinical Point

There is no dosage adjustment required in patients with mild or moderate renal impairment

- only agent with FDA approval for hallucinations and delusions in PD patients with psychosis.

Dosing

The recommended dosage of pimavanserin is 34 mg/d administered as a single dose with or without food. There is no need for titration, and none was performed in the pivotal clinical trial. Given the long half-life (57 hours), steady state is not achieved until day 12, therefore initiation with a lower dosage might prolong the time to efficacy. There is no dosage adjustment required in patients with mild or moderate renal impairment, but pimavanserin treatment is not recommended in patients with severe renal impairment. Pimavanserin has not been evaluated in patients with hepatic impairment (using Child-Pugh criteria), and is not recommended for these patients.

Other key aspects of dosing to keep in mind.

- Because pimavanserin is metabolized primarily by CYP3A4, dosage adjustment is required in the presence of a strong CYP3A4 *inhibitor*; the recommended dosage is 17 mg/d when administered concomitantly with a strong CYP3A4 inhibitor.
- Because data are not available regarding concomitant use of pimavanserin with CYP3A4 *inducers*, patients should be monitored for lack of efficacy during concomitant use with a CYP3A4 *inducer*, and consideration given to *a dosage increase*.

Use in pregnancy and lactation. There are no data on the use of pimavanserin in pregnant women, but no developmental effects were seen when the drug was administered orally at 10 or 12 times the maximum recommended human dosage to rats or rabbits during organogenesis. Pimavanserin was not teratogenic in pregnant rats and rabbits. There is no information regarding the presence of pimavanserin in human breast milk.

Geriatric patients. No dosage adjustment is required for older patients. The study population in the pivotal trial was mean age 72.4 years.

Bottom Line

Pimavanserin is the only agent approved to treat psychotic symptoms in Parkinson's disease (PD) patients, and the only medication except for clozapine to demonstrate efficacy in large controlled studies. Pimavanserin is reasonably well tolerated and does not induce motor worsening. The drug's binding profile is marked by high affinity and selectivity for 5-HT2A receptors, a feature that appears to be effective for treating PD psychosis, with no appreciable affinity for adrenergic, dopaminergic, histaminergic, or cholinergic receptors.

Summing up

Before development of pimavanserin, clozapine was the only effective treatment for psychosis in PD patients. Despite clozapine's robust effects across several trials, patients often were given ineffective medications, such as quetiapine, because of the administrative and tolerability barriers posed by clozapine use. Because psychosis is the most common cause of nursing home placement in non-demented PD patients, an agent with demonstrated efficacy and without the adverse effect profile of clozapine or monitoring requirements represents an enormous advance in the treatment of psychosis in PD patients.

References

1. Nuplazid [package insert]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2016.
2. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. [Erratum in Lancet. 2014;384(9937):28]. Lancet. 2014;383(9916): 533-540.
3. Borek LL, Friedman JH. Treating psychosis in movement disorder patients: a review. Expert Opin Pharmacother. 2014;15(11):1553-1564.
4. Desmarais P, Massoud F, Filion J, et al. Quetiapine for psychosis in Parkinson disease and neurodegenerative parkinsonian disorders: a systematic review. J Geriatr Psychiatry Neurol. 2016;29(4):227-236.
5. Ballanger B, Strafella AP, van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. Arch Neurol. 2010;67(4):416-421.
6. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord. 2007;22(8):1061-1068.
7. Nordström AL, Farde L, Nyberg S, et al. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. Am J Psychiatry. 1995;152(10):1444-1449.
8. Hacksell U, Burstein ES, McFarland K, et al. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. Neurochem Res. 2014;39(10):2008-2017.
9. Moreno JL, Holloway T, Albizu L, et al. Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT2A receptor agonists. Neurosci Lett. 2011;493(3):76-79.

Clinical Point

No dosage adjustment is required for older patients; the study population in the pivotal trial was mean age 72.4 years