Update on the treatment of Parkinson’s disease psychosis: role of pimavanserin

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Abstract: Parkinson’s disease (PD) has a prevalence of nearly 1 million people in the USA, with increasing incidence in the elderly population. Generally, the age of presentation is between 55 and 65 years, with the likelihood of diagnosis increasing as patients reach the age of 80 years or above. Some of the common treatments for PD increase dopamine levels in the brain. Dopaminergic therapy helps to improve motor and non-motor symptoms, but it is not without risks. Dopaminergic therapy can cause confusion, delirium, and psychotic-like behavior. It is recommended that these agents are used cautiously in patients with a history of psychosis due to the risk of exacerbation. It is unclear whether Parkinson’s disease psychosis (PDP) is due to the disease itself, the treatment, or a combination of both, but it is clear that a safe, effective treatment is necessary. Second-generation (atypical) antipsychotics are the current choice of therapy for PDP. All of these agents have a black box warning from the US Food and Drug Administration (FDA) for elevated risk of mortality in elderly patients with dementia-related psychosis. Pimavanserin (Nuplazid®) received its novel drug approval by the FDA on April 29, 2016, to treat hallucinations and delusions associated with psychosis experienced by some people with PD. We review in this article the new research that led to this approval as well as its potential place in therapy.

Keywords: pimavanserin, Parkinson’s disease psychosis, Parkinson’s disease

Introduction
Parkinson’s disease (PD) is a chronic, neurodegenerative disorder. Dopamine-producing cells in the brain start to diminish, and thus the concentration of dopamine in the brain diminishes. The loss of dopamine results in motor dysfunction, changes in behavior, and other burdensome effects to patients and caregivers. Very little is known about the cause of PD, and there is no cure or way to prevent progression. Current treatment focuses on alleviating motor symptoms, with very few options for treating non-motor symptoms such as psychosis.1

Pimavanserin, manufactured by Acadia Pharmaceuticals, Inc., was the first atypical antipsychotic drug approved by the Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis (PDP). Pimavanserin was approved after several successful preclinical studies on April 29, 2016, after being granted breakthrough status in 2014.2 As per the FDA, a breakthrough drug is one that treats a serious or life-threatening condition and demonstrates substantial improvement over current therapies for that condition. The FDA usually expedites development and review of the drug, leading to a faster approval.3

Before the approval of pimavanserin, PDP was treated with the same medications indicated to treat schizophrenia and bipolar disorder. Clozapine and quetiapine are the second-generation antipsychotics (SGAs) usually utilized for PDP, but quetiapine...
has not been shown in placebo-controlled studies to be efficacious.\textsuperscript{4} Clozapine has been shown to be effective, but it also has additional monitoring requirements that can be burdensome on patients and caregivers. In addition, all SGAs have a black box warning from the US FDA. This states that all patients with dementia-related psychosis treated with SGAs are at an increased risk of death. This is a class-wide distinction for all SGAs, and not all drugs in this class have been proven to have this effect. In several studies, it was found that the death rates of those taking SGAs versus placebo were 4.5\% compared to 2.6\%.\textsuperscript{5} This means that physicians must do a more thorough evaluation of their patients prior to prescribing any antipsychotics, especially in those with a history of cardiac or metabolic disorders.

This limitation has been influential in the search for novel drugs that may be safer in this population. In a study to identify mortality risk factors in PD, psychosis at baseline was also found to lead to a higher incidence of death. This shows that the disease itself has a mortality risk, and the risk is not solely due to addition of dopaminergic therapy.

In addition to psychosis at baseline, higher age, male sex, and decreased cognitive function led to worse prognosis in patients presenting with PD.\textsuperscript{6}

In a 12-year, prospective longitudinal cohort study from Norway, researchers found that 59.5\% of the patients had developed PDP at some time during the course of the disease. It was also noted that 41.9\% of the patients without a history of PDP had an incidence of PDP.\textsuperscript{7} Advancing age is often a risk factor for PD, and the world’s elderly population is increasing. 8.5\% of the total population was considered elderly in 2015. It is hypothesized that this will increase to 16.7\% in 2050.\textsuperscript{8} It seems necessary that new drugs to treat this prevalent disease state be approved, given that the likelihood of PD will increase.

Many SGAs are hypothesized to work at least partially by blocking dopamine D2 receptors in the limbic system. This can lead to aggravation of motor symptoms in PD patients. Even at doses used to treat PDP (3\%–10\% of the usual dose used in schizophrenia), D2 receptors are blocked enough to cause some motor symptoms. Since the D2 receptors are only partially blocked, but the psychosis did subside, it is hypothesized that blocking the D2 receptors in PDP may not be the reason for the therapeutic effect seen with SGAs. Since clozapine is effective at low doses, and quetiapine has not been proven to be, other receptors that may cause PDP were examined. This led to the hypothesis that the serotonin (5-HT)\textsubscript{2A} receptor was implicated in PDP, rather than the D2 receptor. This reasoning led researchers to investigate pinavanserin, a selective serotonin\textsubscript{2A} receptor inverse agonist, which was subsequently shown to treat PDP without adversely effecting motor functions.\textsuperscript{4} Due to its novel drug status and quick approval, more post-marketing clinical trials are warranted to prove long-term safety and efficacy.\textsuperscript{2} This drug will allow clinicians to have more therapeutic options when it comes to treating PDP.

**Background**

PD occurs most commonly in the elderly population. The etiology of the disease is still not known, but now it is considered to be a mixture of environmental and genetic factors. Though many chemicals have been tested, such as pesticides, metals, and neurotoxins, a single causative chemical has not been observed. It is noted that patients who smoke cigarettes may be at a decreased risk of PD. In addition, patients who drink coffee or tea may also be at a decreased risk.

It is very difficult to find a reproducible study on the prevalence and incidence of PD. According to a multinational study from the *Tzu Chi Medical Journal*, the burden of diseases such as PD is greatly underestimated. The prevalence of PD in Europe is estimated to be between 65.6 and 12,500 per 100,000 patients. The incidence is between 5 and 346 per 100,000 patients. They hypothesized that this variance could merely be differences in research methodologies though. It is noted that the prevalence is lower in Asian countries, although it was not determined if this was due to genetic or environmental factors or both.\textsuperscript{9}

It is also estimated that over 1 million USA citizens have PD. It is said to affect approximately 1\% of people over 65 years old and 2.5\% of people over 80 years old. The general age range of diagnosis is between 55 and 65 years old.\textsuperscript{10} It is considered the second-most prevalent and burdensome age-related neurodegenerative disorder behind Alzheimer’s disease.\textsuperscript{11}

PD has historically been diagnosed by motor symptoms. James Parkinson first described these clinical indicators in 1817, and since then no cure has been found. Therapy has predominantly focused on maintaining quality of life and reduction of symptoms. Patients often present with bradykinesia, muscular rigidity, resting tremor, postural instability, or a combination of these symptoms. Diagnosis is sometimes very difficult because symptoms will present differently and at varying times in patients. Practitioners will diagnose a patient with PD if they present with bradykinesia or asymmetry prominence and also respond to dopaminergic therapy.\textsuperscript{10}

The etiology and pathology of PD are not completely understood, but numerous advances over the past 100 years
have shown some insight. It was discovered that a loss of neurons in the substantia nigra could be the cause for the symptoms experienced by patients.\(^\text{12}\) During the 1950s, additional data about the depletion of dopamine from the basal ganglia helped create a theory of the pathophysiology of the disease.\(^\text{13}\) It has been shown that the number of neurons in the substantia nigra, both pigmented and non-pigmented, decreases by 66% and 24%, respectively, in patients with PD.\(^\text{12}\) Many hypotheses have been generated from this information, but it is clear that further studies must be done in order to truly understand the pathogenesis of this disease.

It is known that the world’s percentage of elderly persons is increasing, which may result in diseases that generally affect the elderly population becoming more prevalent with time. Analysis of the 2015 global census data leads to estimates that the percentage of adults over 65 will increase from 8.5% to 16.7% by 2050. Also, the number of persons over 80 is likely to triple (126.5 million to 446.6 million), and in some countries quadruple by 2050.\(^\text{8}\) Although there is no evidence that any risk factor is more likely to lead to a PD diagnosis than another, it is likely that global incidence will increase with advancing age. PD affects people globally, with differences in prevalence likely due to multiple factors such as genetics, average life expectancy in certain countries, and availability of health care. This shows that PD, and potentially PDP, is a global concern that is likely to increase. In addition to increasing prevalence, patients who currently have the disease are living longer, which means that they are exposed to the disease and therapeutic agents longer.\(^\text{14}\) Health care providers and researchers should be informed about current and future treatments for these chronic and debilitating diseases, and they should be prepared to see increasing number of patients with the disease and long-term effects of therapy.

As the number of cases of PD increases, it is also being observed that the treatment of motor symptoms is no longer sufficient. Non-motor symptoms, such as depression, dementia, and psychosis, are reported to be more burdensome than motor symptoms in patients with PD. These symptoms often result in a more disabling disease with worse outcomes.\(^\text{15}\) These symptoms put further strain on patients and their caregivers, and they are the primary reason that PD patients are admitted to nursing homes.\(^\text{16}\)

PDP, like Parkinson’s disease, is not fully understood. Questions remain as to whether it is a symptom of the disease, a response to dopaminergic therapy given to alleviate motor symptoms, or a completely independent pathology. It is also unclear what role dopamine plays in PDP. The PDP in drug-treated patients presents in a similar fashion to schizophrenia (hallucinations and delusions), but the manifestation of the hallucinations is often starkly different. Most commonly, PDP patients present with visual hallucinations, with a lifetime prevalence of visual hallucinations being 50% or higher.\(^\text{17}\) Possibly, one-third of individuals with PD experience visual hallucinations; however, up to 75% of patients will develop such phenomena over a 20-year period.\(^\text{18}\) These hallucinations have been reported to often involve children or animals, or they can be simpler visual disturbances, such as a quick flashing light.\(^\text{19}\) It has been observed that these visual hallucinations often occur during the evening or when lighting is dim.\(^\text{18}\) In schizophrenia, auditory hallucinations are most common.\(^\text{17}\) These auditory hallucinations, which occur in 60%–80% of schizophrenic patients, are commonly voices (either internal or external).\(^\text{20}\) These auditory hallucinations are perceived by the patient as clearly as actual perceptions.\(^\text{21}\) Delusions also present differently in both disease states. They are not as common in PDP, and they may present as delusions of abandonment or infidelity.\(^\text{19}\) Schizophrenic delusions can present in many ways; they can be grandiose, persecutory, nihilistic, somatic, or any combination of these. They could also present as bizarre, where the hallucination is completely implausible or referential.\(^\text{21}\)

Schizophrenia has historically been considered a disease in which there is an excess of dopaminergic signaling, and it has been treated with drugs that reduce this signaling.\(^\text{17}\) Since most of the therapies used in PD increase dopaminergic transmission in the brain, these therapies have been implicated in causing psychosis in PD patients. Other studies have implicated anticholinergic drugs and amantadine in causing psychosis. Contrary to these studies, some patients on dopaminergic therapy never experience psychosis.\(^\text{15}\) It is now hypothesized that medications are not the only factor that determines whether a PD patient experiences hallucinations. In numerous studies, there has been no correlation between dose of levodopa and whether or not patients experienced psychosis. Also, high-dose levodopa given intravenously has not been proven to induce visual hallucinations. It is currently not possible to predict which patients will experience PDP, but it is likely that most patients will experience visual hallucinations at least once over the course of their disease.\(^\text{18}\) It is essential that clinicians have therapeutic options for the treatment of psychosis with high efficacy and minimal intolerability.

Since a decrease in dopamine is implicated as the cause of the disease, current therapies for PD center around
increasing dopaminergic signaling in the brain. There are several mechanisms by which this can be done, such as supplementation with a drug that produces dopamine in the body (levodopa), inhibiting the enzymes that break down dopamine (monoamine oxidase B inhibitors [MAO-B inhibitors]), and directly stimulating the receptors in the brain (dopamine agonists [DAs]). Levodopa is considered the most effective drug for relieving symptoms such as bradykinesia. It is often used in combination with carbidopa (or benserazide in Canada and Europe), which helps increase efficacy and reduce side effects (which are primarily gastrointestinal). MAO-B inhibitors such as selegiline and rasagiline have side effects similar to levodopa, which include nausea, headache, and difficulty falling asleep. They also have a specific drug interaction with certain antidepressants that may cause dangerous increases in blood pressure. DAs such as pramipexole and ropinirole are used in younger patients to conserve the most effective treatment for later in the progression of the disease. Typically, all patients will progress to levodopa therapy. DAs can be used to postpone levodopa therapy, which prolongs the time until patients will experience levodopa-associated motor complications. DAs have other undesirable side effects, including sedation, swallowing of lower extremities, and decreased impulse control. Both levodopa and DAs cause an increase in dopaminergic transmission, and there is the potential for them to cause psychosis, hallucinations, and delusions.

Another class of drugs helps mainly by increasing the effectiveness of dopaminergic drugs. Catechol-O-methyl transferase inhibitors, such as tolcapone and entacapone, help enhance levodopa effects and are used to treat “wearing off” periods. Side effects can include nausea, orthostatic hypotension, and orange discoloration of urine. Tolcapone has been shown to increase liver enzymes, so it is not commonly used in practice. Anticholinergic drugs such as benztrapine and trihexyphenidyl are often beneficial in younger patients whose primary symptom is tremor. Decrease in secretions and tachycardia are their most common side effects. Amantadine, originally an antiviral drug, has also shown efficacy in treating mild dyskinesias. Purple discoloration of the skin and ankle swelling are possible side effects. Though these drugs work primarily through other mechanisms, not dopamine or its receptors, they all have potential side effects of confusion and hallucination.

It is known that all of these medications can lead to psychosis in PD patients, with DAs being the most commonly implicated. It appears that medications may be a risk factor for developing PDP, but it is not an absolute risk. There are some patients on therapy who will never experience psychosis, and some patients will develop psychosis before PD medications are initiated. Drug therapy is not the only risk factor to consider in PDP. Other observations correlated with psychosis include changes in visual processing, increased sleep disturbances, and abnormalities in other neurotransmitters such as serotonin and acetylcholine. These can occur in the elderly population and may also be causes for perceived psychosis.

Prior to April 2016, there was no FDA-approved treatment for PDP. SGAs (atypical antipsychotics) have often been used off-label by clinicians to reduce the symptoms of these patients. Of these current agents, there are few medications that have been proven to be both effective and safe in this population through clinical trials.

The most commonly used agent, clozapine, has been shown to be effective for PDP, requiring doses ~10% of the normal dose used in schizophrenia to reduce psychosis symptoms without causing a relapse in motor symptoms. New research has shown that the indication-specific target plasma concentration for clozapine is between 15 and 141 ng/mL. SGAs, such as clozapine, are thought to treat hallucinations by blocking dopamine D₄ receptors in the brain. At 10% of the dose typically administered in schizophrenia, clozapine shows selectivity for serotonin 5-HT₂A and histamine H₁ receptors. Since antagonizing H₁ receptors results in drowsiness, but not clinical efficacy, it has been hypothesized that blocking 5-HT₂A is the actual mechanism by which PDP is ameliorated using clozapine. This raises questions regarding whether the psychosis is actually due to excess dopamine-mediated signaling in the brain, or if there is some other mechanism causing these symptoms in PDP.

One of the biggest issues clinicians have with clozapine is its safety profile. It has the potential to cause rare, but life-threatening, agranulocytosis. It is likely that clozapine is underutilized due to its many rare side effects and required blood monitoring. This monitoring for agranulocytosis (an absolute neutrophil count below 500/mm³) was initiated after a study in 1975. In this study, 17 of 2,660 (0.7%) patients were diagnosed with agranulocytosis, and 8 of these patients died from infection after diagnosis. It has been shown that agranulocytosis may occur at any dose; therefore, patients taking even the smaller doses used in PDP must be closely monitored. During the first 6 months of therapy, patients are required to have blood drawn weekly to check for neutrophil count, and without these results, pharmacies in the USA cannot dispense the medication. As can be expected, this creates a huge burden for both the patient and the caregiver.
For this reason, although it is the only antipsychotic with proven efficacy in multiple clinical trials, many doctors will not prescribe it for their patients or continue it when a patient is admitted to a nursing home.

Quetiapine has a mechanism similar to clozapine; therefore, a number of clinicians have moved to using this antipsychotic instead. Although its safety profile is preferable to clozapine, it has not had many clinical trials confirming its efficacy. Clinicians typically use doses that are far below the normal dosing for schizophrenia, and quetiapine does have safety concerns of its own, most specifically metabolic syndromes.

Typical antipsychotics (first-generation antipsychotics) should not be used since trials showing their efficacy are lacking, while multiple studies have shown side effects, including an increase in motor symptoms, risk of stroke, cognitive decline, and death. Typically, no other atypical antipsychotics are used besides clozapine and quetiapine. Risperidone and olanzapine often result in worsening motor symptoms, in addition to multiple metabolic and cerebrovascular risks. Aripiprazole, an atypical antipsychotic that acts on serotonergic and dopaminergic receptors, has been shown to be effective in psychosis. It may also result in decreased movement and function, so is unlikely to be beneficial in PD patients.

Search methodology
The recent approval of pimavanserin could be a vitally important development needed by clinicians and patients, but more data are required. Several searches were conducted to find the most up-to-date information on pimavanserin. The PubMed and UpToDate databases were used extensively. We have also included some of the data used by Acadia Pharmaceuticals in support of its New Drug Application. The Centers for Disease Control and Prevention (CDC), the US FDA, and the World Health Organization (WHO) also provided excellent starting ground in order to learn more about the prevalence of disease and current therapy difficulties.

Results
The approval of pimavanserin by the FDA was supported by 21 completed studies and 4 ongoing studies. Of the 1,237 subjects estimated to have taken pimavanserin (as of January 2016), 616 had been diagnosed with PDP. Original data showed that healthy volunteers could tolerate up to 85 mg doses. Tolerability declined at higher doses due to nausea and vomiting. There were four placebo-controlled studies confirming safety and efficacy that led to the approval of pimavanserin. All of these were multicenter, randomized, double-blind, placebo-controlled studies. In the Concept Phase 2 Study (Study 006), 60 subjects were followed for 4 weeks, and they were allowed a flexible titration of 17, 34, or 51 mg. Phase 2b/3 studies (Studies 012 and 016) increased the study time to 6 weeks and attempted to see if lower doses (8.5 mg) were effective in addition to previous strengths used. The Pivotal Phase 3 trial (Study 020) was also 6 weeks but focused on the eventually approved dose of 34 mg versus placebo. In the monograph by Hunter et al, the authors review studies 006 and 020. Two Phase 2b/3 trials (studies 012 and 014) were not published as full manuscripts. They are accessible from the manufacturer and have been presented at conferences. It is from the data of these studies that the Phase 3 trial was developed and designed.

Study 012 followed 298 patients between June 2007 and July 2009. These patients were randomly assigned in a 1:1:1 manner to receive either pimavanserin 8.5 mg, pimavanserin 34 mg, or placebo every day for 6 weeks. These patients were spread over 72 sites in the USA, India, and Europe. To be included in the study, the patients had to be at least 40 years old, be diagnosed with PD for a minimum of 1 year, and have had hallucinations or delusions within the 4 weeks before screening. Patients were not enrolled if they had previous psychotic disorders prior to or at diagnosis of PD. This study had a high placebo response, which researchers think may have confounded results. Because no results could be determined from this study, they reevaluated their methods that led to the first improvement in the Phase 3 trial design.

The primary endpoint was an improvement in Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions (SAPS-H+D) score from baseline. Secondary endpoints were changes in Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression – Severity (CGI-S) scores. It was noted during this trial that pimavanserin 34 mg patients had higher improvement in SAPS-H+D scores in the USA, but not in the other countries. Interestingly, it was also observed that placebo patients had higher improvement in SAPS-H+D scores in India and Europe. It was hypothesized that the high rate of response in the placebo group may have shadowed statistically significant clinical effects in the pimavanserin group, but this conclusion cannot be proven with the current data. Secondary endpoints were numerically higher in the pimavanserin 34 mg patients, but these results were not statistically significant. Although the outcomes of the study were not encouraging, it did lead to a better design for the Phase 3 trial. This study did show that pimavanserin...
does not negatively influence motor function in PD. This was accessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) II + III composite score.28

Study 014 was structurally similar to Study 012. The only exception was that the doses of pimavanserin were lower. Researchers concluded that they had similar study design problems as the previous trial, so it was stopped early and only enrolled 123 of the anticipated 280 patients. Using the data collected from the shortened trial, the primary endpoint was not found to be statistically significant. Similar to the previous trial, this trial showed no negative influence on the motor symptoms of PD caused by pimavanserin. Of note, one secondary outcome did yield viable data. The 17-mg pimavanserin patients improved in CGI-I scores more than placebo patients (−0.66; 95% CI −1.21 to −0.11; \(P=0.020\)).28

Although these trials did not prove efficacy, they did lead to the improvement of the Phase 3 trial. First of all, the data did show some positive trends, so the researchers were able to determine which doses may be successful. Also, they did show that pimavanserin did not have a negative impact on motor symptoms in PD diagnosed patients. The Phase 3 trial added a 2-week placebo lead-in focused on Psychosocial Therapy. This was included in order to help improve the validity of the study by removing patients who were not candidates for drug therapy based on their positive response to non-pharmacological therapy alone. The scale used to assess the primary endpoint was improved to make it more specific to the PDP population. Instead of using the SAPS-H+D scale, which is commonly used for schizophrenia, the scale was shortened to focus solely on the primary symptoms associated with PDP. This new scale is called the Scale for the Assessment of Positive Symptoms – Parkinson’s disease-adopted (SAPS-PD). The SAPS-PD is a rating scale of 9 items, decreased from the 20-item form used in schizophrenia (SAPS-H+D). It assesses if the patient has positive psychotic symptoms, specifically hallucinations and delusions specific to PDP. The new scale removed items most commonly associated with schizophrenia, not PDP.28 The hallucination items removed were voices commenting and olfactory hallucinations. The delusion items removed were delusions of guilt or sin, grandiose delusions, religious delusions, somatic delusions, delusions of being controlled, delusions of mind reading, thought broadcasting, thought insertion, and thought withdrawal.28 The removal of these items allowed the new scale to appropriately access only the most commonly associated symptoms of PDP.

The Phase 3 trial did significantly show an improvement in this score while using the 34 mg dose (equivalent to 40 mg pimavanserin tartrate) versus placebo. A decrease in score by at least 2.33 points on the SAPS-PD scale was deemed clinically significant. In this trial, patients taking pimavanserin had a mean reduction in score over placebo by 3.06 points (CI −4.91, −1.20). This reduction was shown in 65.3% of pimavanserin-treated patients versus 42.2% of patients receiving placebo. Also, complete remission was seen in 13.7% of the pimavanserin group, compared to 1.1% in the placebo group.28 This study also confirmed that pimavanserin is not associated with negative motor function capabilities in PD patients.

In addition to short-term efficacy and safety studies, studies have also been done to show the long-term safety of pimavanserin. Most of these studies included patients taking 34 mg pimavanserin once daily. Long-term studies include over 300 patients taking the drug for at least 6 months, over 270 patients taking the drug for at least a year, and over 150 patients taking the drug for at least 2 years. The most common adverse drug events found over placebo were peripheral edema (7% versus 2%) and confusional state (6% versus 3%).

Another long-term safety study showed the major adverse drug events to be fall, urinary tract infections, and hallucinations. Risk factors for these adverse drug events include increased age and time participated in the study. In previous studies, different adverse drug events were reported, so further clarification of true adverse drug effects versus worsening of PDP is needed. No drug interactions were found between pimavanserin and carbidopa/levodopa. Since levodopa is considered the best drug available to treat PD, most patients either currently take it or will take it as their disease progresses. Since there is no drug interaction, clinicians can feel safe prescribing both medications concomitantly if necessary. Pimavanserin is also not known to be either a cytochrome P450 (CYP 450) inhibitor or inducer. CYP 450 is a family of enzymes that aid in the metabolism of drugs through the liver. Pharmacokinetic data show that dose adjustments should be made if pimavanserin will be used with drugs that are considered CYP 450 inhibitors or inducers. When given concomitantly with a CYP 450 inhibitor, it is recommended to reduce the dose by 50%. When given with a CYP 450 inducer, clinicians are encouraged to watch for decreased efficacy and consider a dose increase if necessary.30

QT prolongation (the elongation of the space between the Q and T sections on an electrocardiogram) was seen in trials, but the largest observed mean for the 34 mg dose was 9.6 milliseconds.30 A QT interval of 500 ms is usually
associated with fatal arrhythmias, such as torsades de pointes, but there are little data on how much the interval can prolong from normal to induce these arrhythmias.\textsuperscript{31} Generally, in order to prevent complications, clinicians are encouraged to avoid multiple drugs that can cause QT prolongation together. The \textit{American Journal of Health-System Pharmacists} recommends not to use pimavanserin in patients who are currently on drugs that increase the QT interval, have preexisting QT prolongation, or have a history of cardiac arrhythmia.\textsuperscript{32} The only other statistically significant event was orthostatic hypotension. The placebo group had a higher percentage of patients experiencing this side effect compared to the pimavanserin group (5.2\% versus 1.0\%). There were no reports of cerebrovascular events. There was no significant change in sedation-related events, metabolic syndrome, or blood dyscrasias. Urinary tract infection (13\%), fall (11\%), peripheral edema (7\%), hallucination (7\%), and confused state (6\%) were reported side effects in the group that took at least one dose of pimavanserin. Nausea was reported equally between both groups (6\%), and headache was reported more in the placebo group (5\% versus 2\%) than in the pimavanserin group.\textsuperscript{30}

**Conclusion**

After review of the literature, the approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP seems appropriate. According to the package insert, prescribers are encouraged to use two 17 mg tablets (34 mg total) per day, which was the dose most effectively used in the clinical trials.\textsuperscript{33} Special dosing requirements are necessary when there are strong CYP P450 interactions, but not with mild-to-moderate renal impairment. No studies were done in patients with severe renal or hepatic impairment, so currently this drug is not recommended in these populations.

Like all other antipsychotic drugs, pimavanserin has a black box warning on its package labeling in the USA, which is mandated by the FDA for other drugs in this class for increasing mortality in elderly patients with dementia-related psychosis. Since this is a class-wide warning, it is likely to be precautionary only. The labeling also precautions practitioners against using this drug in combination with others that potentially cause QT prolongation. There was evidence for this occurrence in clinical trials. Pimavanserin showed several side effects in its clinical trials, but it showed no negative effect on motor symptoms in patients with PDP.

While the New Drug Application for pimavanserin was approved on April 29, 2016, there are still multiple post-market trials taking place.\textsuperscript{34} Post-marketing commitments still required are a randomized withdrawal trial comparing pimavanserin to placebo, at least one randomized placebo-controlled trial with predominantly frail and elderly subjects that exposes at least 500 patients to pimavanserin 34 mg daily for a minimum of 8 weeks, an in vivo drug–drug interaction study measuring the effect of strong CYP P450 inducers and recommending a maximum dose with this combination, and a microscopic reevaluation of lung tissue samples to detect collagen from data collected in the 2-year rat study.\textsuperscript{35} Assuming positive results from each of these additional studies, pimavanserin may replace current antipsychotic therapy (clozapine and quetiapine) for the treatment of patients diagnosed with PDP.

**Disclosure**

The authors report no conflicts of interest in this work.

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