Pimavanserin Treatment for Psychosis in Patients with Dementia with Lewy Bodies: A Case Series

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Conflict of interest: None declared

Case series
Patients: Male, 71-year-old • Male, 56-year-old • Male, 61-year-old • Male, 74-year-old
Final Diagnosis: Dementia with Lewy bodies
Symptoms: Psychosis
Clinical Procedure: —
Specialty: Geriatrics

Objective: Unusual or unexpected effect of treatment

Background: Many patients with dementia with Lewy bodies (DLB) experience cholinesterase inhibitor- and antipsychotic-resistant psychosis. The new second-generation antipsychotic pimavanserin has been used with some success in the treatment of psychosis in other forms of dementia, including Alzheimer disease and Parkinson disease dementia. It is possible that pimavanserin may also be useful in the treatment of psychosis in DLB. We sought to describe the disease course and treatment of psychosis in 4 patients with DLB who were prescribed pimavanserin after other medications failed to reduce the frequency or severity of hallucinations and delusions.

Case Report: This is a case series of 4 male patients (ages 56 to 74 at the beginning of the reports) who developed DLB and psychosis (eg, visual illusions, visual and olfactory hallucinations, and paranoid delusions). All 4 patients were prescribed cholinesterase inhibitors (eg, donepezil or rivastigmine) prior to pimavanserin, and only 1 patient experienced improved psychosis while on cholinesterase inhibitors. All 3 patients who were prescribed first-generation antipsychotics (eg, haloperidol) or traditional second-generation antipsychotics (eg, olanzapine, risperidone, or quetiapine) experienced initial or lasting side effects with no improvement of psychosis. Conversely, all 4 patients tolerated pimavanserin well, and 3 of the 4 patients experienced significant improvement of psychosis (eg, fewer hallucinations, fewer delusions, reduced paranoia, and/or reduced distress or agitation related to hallucinations and delusions) when prescribed pimavanserin.

Conclusions: This case series suggests that pimavanserin is tolerable in older males with DLB and that it may be useful for the reduction of distressful hallucinations, delusions, and paranoia in patients with DLB.

Keywords: Delusions • Dementia • Hallucinations • Lewy Body Disease • Parkinsonian Disorders • Pimavanserin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/939806
Background

Patients with dementia with Lewy bodies (DLB) are frequently only diagnosed after many clinician visits and years of symptoms [1,2], in part because of the complex clinical manifestations of DLB [3], which can include distressing visual hallucinations [4]. These hallucinations tend to be well formed, occur at night, and are accompanied by delusions in the later stages of the disease [3]. In other psychotic disorders, like schizophrenia, the dopaminergic system appears to be the primary neurochemical system contributing to hallucinations, but in DLB the pathophysiology of psychosis is most likely multifactorial, and this can complicate treatment efforts. To that end, cholinesterase inhibitors (eg, donepezil and rivastigmine) [5-9] and/or second-generation antipsychotics (eg, quetiapine and clozapine) [3,10-13] can reduce symptoms of psychosis in some patients with DLB, but many others continue to experience visual hallucinations or to experience side effects that prevent successful administration of the medications. Novel antipsychotics that have new mechanisms of action and that lack a dopamine receptor's binding property may prove more effective for at least a subset of these cholinesterase inhibitor- or antipsychotic-resistant patients.

Pimavanserin, for example, is a selective serotonin inverse agonist of 5-HT2A receptors; that is, it is a second-generation antipsychotic that does not bind to dopaminergic receptors and may avoid the motor and sedative adverse side effects of other antipsychotics [14]. In a clinical trial of patients with Alzheimer disease (AD) and psychosis, there was a 6-month reduction in psychosis but not a 12-month reduction [15]. The same research team then demonstrated 12-month efficacy for pimavanserin in patients with AD and higher baseline severity of psychotic symptoms [16]. Likewise, in Parkinson disease (PD), treatment with pimavanserin has reduced the number and severity of hallucinations and delusions without worsening parkinsonism [17,18], and it has been approved as a treatment by the Food and Drug Administration (FDA) for PD dementia (PDD)-related psychosis since 2016.

Studies that evaluate pimavanserin as a treatment for psychosis in AD, PD, and other neurodegenerative disorders are valuable, but DLB is the only common neurodegenerative disorder in which visual hallucinations are a core diagnostic criterion and in which around 75% of patients experience psychosis [9]. Yet despite the prominence of psychosis in DLB and the potential of pimavanserin, there are few reports that clearly describe the course of patients with DLB who use pimavanserin to treat psychosis. Therefore, here we share a case series to offer additional context on the potential use of pimavanserin in patients with DLB who present with drug-resistant psychosis.

Case Report

This is a case series in which we report on the use of pimavanserin in 4 older male patients with DLB and psychosis. The case series is based on our direct clinical treatment and follow-up of the 4 patients. We provide detailed descriptions of each case below, a summary of key symptoms in Table 1, a summary of Montreal Cognitive Assessment (MoCA) scores in Table 2, and a summary of the most recently used medications in Table 3.

Patient #1

Early Disease Course

At age 71, this male patient exhibited slower reaction times and was observed acting out his dreams. He was diagnosed by polysomnography with rapid eye movement sleep behavior disorder (RBD). Soon after the RBD diagnosis, he began experiencing increased anxiety and depressed mood. His gait changed, his movements slowed, and he was identified as having orthostatic hypotension. In addition, the patient’s

Table 1. Summary of symptoms and medication responses for patients with DLB.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Dementia</th>
<th>Fluctuating cognition</th>
<th>Parkinsonian motor features</th>
<th>VHs</th>
<th>RBD</th>
<th>VH response to Cholinesterase inhibitors</th>
<th>Pimavanserin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
</tbody>
</table>

+ indicates that the patient experienced the symptom; – indicates that the patient did not experience the symptom. RBD – rapid eye movement sleep behavior disorder; VH – visual hallucination.
Table 2. Trajectory of Montreal Cognitive Assessment (MoCA) scores.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age</th>
<th>Score</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>23/30</td>
<td>Subsequently diagnosed with minor neurocognitive disorder in the course of DLB</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>22/30</td>
<td>Cognitive dysfunction becomes more prominent</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>14/30</td>
<td>At discharge following malignant hyperthermic response to haloperidol</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>20/30</td>
<td>After stabilization on rivastigmine and no cognitive improvement on memantine*</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>20/30</td>
<td>Presented with hallucinations; diagnosis was then changed to DLB</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>22/30</td>
<td>Minimal cognitive improvement on rivastigmine and no cognitive improvement on memantine</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>23/30</td>
<td>Responding well to pimavanserin</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>16/30</td>
<td>At an ER visit at a non-VA facility while on quetiapine and rivastigmine</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>14/30</td>
<td>At another ER visit for worsening agitation, paranoia, and hallucinations when it was determined that quetiapine was no longer beneficial</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>17/30</td>
<td>Following a 6-month trial of pimavanserin, which was discontinued due to persistent psychosis</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>17/30</td>
<td>Following ER visit for visual hallucinations, confusion, and RBD; diagnosed with Lewy body dementia</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>15/30</td>
<td>After a second consecutive admission to a VA hospital due to disruptive visual hallucinations, confusion, and agitation upon waking at night; patient psychiatrically unstable</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>20/30</td>
<td>Six months after discharge continued sleep disturbance with vivid dreams but manageable and stable</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>24/30</td>
<td>For 2 years, pimavanserin was effective in decreasing the patient’s distress related to visual hallucinations and paranoia</td>
</tr>
</tbody>
</table>

* Note that no MoCA scores are available after pimavanserin was prescribed.

Table 3. Most recently used medications and responses.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Medications</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sertraline and melatonin</td>
<td>Improved mood</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine</td>
<td>Improved cognition</td>
</tr>
<tr>
<td></td>
<td>Pimavanserin</td>
<td>Improved psychosis</td>
</tr>
<tr>
<td>2</td>
<td>Clonazepam</td>
<td>Improved sleep induction</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine</td>
<td>Minimally improved cognition</td>
</tr>
<tr>
<td></td>
<td>Carbidopa/levodopa</td>
<td>Improved motor</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>Improved mood</td>
</tr>
<tr>
<td></td>
<td>Pimavanserin</td>
<td>Improved psychosis</td>
</tr>
<tr>
<td>3</td>
<td>Prazosin, quetiapine, and rivastigmine</td>
<td>Somewhat improved cognition and psychosis</td>
</tr>
<tr>
<td>4</td>
<td>Prazosin and melatonin</td>
<td>Improved nightmares</td>
</tr>
<tr>
<td></td>
<td>Donepezil</td>
<td>Mildly improved cognition</td>
</tr>
<tr>
<td></td>
<td>Pimavanserin</td>
<td>Improved psychosis</td>
</tr>
</tbody>
</table>
At that time, the patient scored 20 on the MoCA, an improvement for cognition or the patient’s psychotic symptoms. Hallucinations. A trial of memantine did in the severity and frequency of visual misidentifications and again to 13.3 mg. However, no improvement was observed most noticeable after titration of the dose to 9.4 mg and then received rivastigmine and experienced cognitive improvement, including improved planning, sequencing, and all aspects of the room lacked an ocean or rooftop view. Over time, the patient’s gait slowed, his posture stooped, and he started experiencing more prominent orthostatic symptoms. The patient received levodopa to address parkinsonian symptoms, but it induced more severe episodes of hallucinations, and the medication was discontinued. Well-formed hallucinations continued to reoccur infrequently and without any trigger.

Response to Treatments

The patient underwent hip replacement surgery at age 74. The succinylcholine administered preoperatively caused a malignant hyperthermic response, and 2 doses of haloperidol (1 mg) administered postoperatively induced neuropsychiatric malignant syndrome (fever, muscle rigidity, diaphoresis, tachycardia). The patient was treated in the intensive care unit (with intubation, dantrolene), and his recovery was prolonged. At discharge from the rehabilitation center, his cognitive function had declined significantly, and he scored 14 on the MoCA.

The patient continued experiencing visual illusions, misidentifications, and frank hallucinations. Then, at age 75, he received rivastigmine and experienced cognitive improvement, including improved planning, sequencing, and all aspects of language, including articulation. These improvements were most noticeable after titration of the dose to 9.4 mg and then again to 13.3 mg. However, no improvement was observed in the severity and frequency of visual misidentifications and hallucinations. A trial of memantine did not provide additional benefits for cognition or the patient’s psychotic symptoms. At that time, the patient scored 20 on the MoCA, an improvement that was likely attributable to the rivastigmine.

Response to Pimavanserin

Following the trial of memantine, pimavanserin was started at a dose of 34 mg, and the patient and caregiver reported that he experienced significantly fewer hallucinations. It took 3 months to ensure that the changes were consistently occurring because the patient presented with marked daily fluctuations in cognition and behavior. That said, the patient seemed to better tolerate these fluctuations, and his caregiver opined that the patient now “self-regulates his highs and lows better.” With the exception of 1 episode, when there was a change in mental status due to a urinary tract infection, the caregiver also observed a decrease in the occurrence of delusions. The patient’s cognitive dysfunction remains at the same level.

Patient #2

Early Disease Course

At age 56, this male patient was diagnosed with RBD after he noticed his lower right arm bending up toward his abdomen in a “gun slinger” pose and his wife observed that his sleep appeared restless. The patient began experiencing atypical anxiety with a depressed mood, as well as micrographia, bradykinesia, shuffling gait, hypomimia, and episodes of orthostatic hypotension. He soon struggled to multitask, manage work responsibilities, and perform activities of daily living, including teeth brushing, packing a lunch, remembering his wallet and eyeglasses, and grabbing his keys before driving. He was diagnosed with PD and initially treated with carbidopa/levodopa, paroxetine, rivastigmine, and clonazepam.

Onset of Psychosis

Symptoms of cognitive impairment and psychosis were noticeable and concomitant with the patient’s motor symptoms. At age 57, the patient scored 20 on the MoCA and presented with hallucinations of little girls having tea parties, bugs crawling on the floor, and a bear in the backyard. These symptoms led to a reevaluation and a change in diagnosis to DLB. Nevertheless, the patient continued to work as an investigative reporter and editor, played full-court basketball once a week, and started a basketball tournament to raise money for DLB research. His bradykinesia gradually increased, and he developed more severe anxiety and depression, as well as a decline in executive functioning. His hallucinations and delusions gradually became more pronounced.

Response to Treatments

The patient experienced minimal cognitive improvement after optimization of his rivastigmine dose (ie, he scored 22 on the MoCA), but the addition of memantine had no effect. His cognitive dysfunction remained at the same level.
motor symptoms improved in response to the carbidopa/levodopa, and his depression remitted, partially in response to the paroxetine.

The patient’s caregiver initially sought to address his psychosis nonpharmacologically by minimizing stimulation and teaching him to “send” the scary hallucinations away so that he could feel safe. However, his hallucinations and delusions worsened, his fears progressed to terror, and these symptoms did not respond to trials of quetiapine (increased titration to 150 mg), olanzapine (10 mg), or risperidone (2 mg). Moreover, the antipsychotics appeared to worsen his motor symptoms, and he began experiencing paranoid delusions and visual, auditory, and olfactory hallucinations. The patient was observed listening to trees that he said walked around their yard or talking to people who appeared in his home through a series of imaginary tunnels. These people would morph into cartoons and disappear into walls. Others would morph into fish, and he could smell them in the beds. When he believed these people were trying to harm his family, the patient would attack the bedding and throw it down the stairs. At other times, he believed the coat racks were people who needed help – they were poor and hungry – so the patient would pull food out of the pantry to feed them. He also believed he was starring in a DLB research film and that activities at his house were being recorded for the film. He began pacing around rooms, distrustting his family and friends.

Response to Pimavanserin

A dose of 34 mg pimavanserin was initiated at age 60, 4 years after the patient’s initial symptoms were documented. Within 2 weeks, the patient’s hallucinations dramatically reduced, and the patient’s family reported that he had “come back” out of psychosis. Four weeks after beginning pimavanserin, the patient began writing articles again and communicating with family and friends. One year later, at age 61, the patient was still responding well to treatment with pimavanserin, and his cognition remained at the same level (ie, a MoCA score of 23).

Patient #3

Early Disease Course

This male patient was first diagnosed with DLB at age 71, but it is likely that his symptoms began more than 10 years earlier and were misattributed to posttraumatic stress disorder (PTSD) and depression, for which he received buspirone and fluoxetine, 2 medications that were later discontinued at age 71. At age 61, the patient was seen by a Veterans Affairs (VA) psychiatrist for treatment related to insomnia and self-medicating with alcohol, which he discontinued by age 68 following hospitalization for a pulmonary embolism. From age 63 to 67, he reported increasing anxiety and hypervigilance, including scanning public areas for exits and escape routes, feeling unease when socializing with family members, and switching to a lower-paying job to avoid the stress of working around others. At age 65, he experienced night terrors after falling out of bed, shouting, and responding to violent dreams by placing his hands around his wife’s neck. The patient’s wife reported some minor forgetfulness, word-finding difficulties, mild hand tremors, and slowed movements. At age 68, the patient indicated that he saw someone hiding outside the house, and he remarked that the home seemed crowded. He also became more anxious, and his ability to recall what he heard, engage in conversations, and manage medications declined. By age 69, he had stopped driving due to fluctuations in cognition and a worsening resting tremor in his hands. Finally, at age 71, after the clear onset of hallucinations (see next section), the patient was diagnosed with DLB. The neurological assessment confirmed RBD, loss of olfaction, confusion, forgetfulness, word-finding difficulties, and slow movements with a shuffling gait.

Onset of Psychosis

At age 61, the patient described fire hydrants and other inanimate objects taking on the appearance of humans, and at age 63, he recalled “freaking out” after seeing things move that others did not see. However, the patient and his wife attributed these symptoms to PTSD-related hypervigilance. Then, at an appointment at age 71, the patient was diagnosed with DLB after describing visual hallucinations of humans who were not there and associating his dog with a sign of death. Over time, his paranoid delusions, visual hallucinations, and olfactory hallucinations worsened, and other symptoms included word-finding difficulties, confusion, periods of forgetting names and surroundings, and detailed nightmares that resulted in sleep disturbances.

Response to Treatment

The patient was prescribed 1 mg prazosin at bedtime for night terrors but opted for an herbal remedy and self-medication with alcohol. He was also prescribed selective serotonin reuptake inhibitors (SSRIs) and melatonin for trauma-related symptoms. He also discontinued paroxetine.

After the initial diagnosis of DLB at age 71, the patient was prescribed quetiapine 50 mg 3 times a day and rivastigmine 3 mg at bedtime. During an emergency room (ER) visit at a non-VA facility, the patient scored 16/30 on the MoCA. The quetiapine was thought to cause significant somnolence, but the patient’s wife opted to continue the medication, as she found the psychosis and related agitation more challenging as a caretaker.

The patient’s sleep improved, but the agitation and hallucinations worsened. The patient reported seeing a person crawl...
out of the vacuum cleaner. He also believed his home was his workplace, which caused severe anxiety, so he refused to return home and started living in his car. He was subsequently diagnosed with deep vein thrombosis. Rivastigmine was titrated up to 4.5 mg twice a day, and following optimization of the rivastigmine dose, small improvements were noted in executive functioning (eg, planning and his ability to help with chores), but there was no improvement in the patient’s psychosis. Then, despite increasing doses of quetiapine, the patient experienced worsening physical agitation and vocal outbursts, which led to multiple ER visits.

During an ER visit at age 72 for worsening agitation, paranoia, and hallucinations, it was determined that quetiapine was no longer beneficial. After a consultation with the neurologist, fluoxetine was discontinued, escitalopram and pimavanserin were initiated, and quetiapine was titrated down. At that time, the patient scored 14/30 on the MoCA.

Response to Pimavanserin

Following the ER visit at age 72, the patient was hospitalized for worsening anxiety, agitation, confusion, paranoia, and hallucinations. Pimavanserin 34 mg was added to quetiapine, which initially resulted in some improvement of psychosis. That is, the patient felt that the hallucinations and Capgras delusions were more manageable, but their frequency and intensity did not appear to change.

Following a 6-month trial, pimavanserin was discontinued due to persistent psychosis without response to dose optimization; at that time, the patient scored 17/30 on the MoCA. The patient was then maintained on rivastigmine 4.5 mg twice a day, quetiapine 50 mg 3 times a day, and escitalopram 20 mg per day. Although he continued to have visual hallucinations, they were not bothersome and did not interfere with activities of daily living, and he was considered psychiatrically stable. The patient could help with simple household tasks, such as unloading the dishwasher, but he was unable to perform complex tasks.

Patient #4

Early Disease Course

At age 74, this male patient began screaming, fighting, and jumping from bed following vivid nightmares that occurred 2 to 3 nights per week. After one nightmare, the patient struck his head on a nightstand and experienced headaches that increased in intensity, frequency, and duration over the next 6 days. A subdural hematoma was detected on a computed tomography scan and resolved following a craniotomy. The patient received prazosin 1 mg at bedtime and quetiapine 50 mg for continued nightmares and RBD. Postoperative recovery was unremarkable, and a follow-up bedside cognitive examination revealed intact naming, attention, and long- and short-term memory.

Since that hospitalization, the patient’s daughter reports fluctuations between periods of improved cognition and awareness and periods in which the patient struggles to recognize family members. After getting lost and causing traffic accidents, the patient no longer drives. The family also reported a low mood and anhedonia related to cognitive decline. In addition, the patient’s nightmares resumed; at age 79, his family reported that he would stay awake to avoid violent nightmares. His treatment plan included empathetic listening, reading educational material, and receiving treatment for PTSD.

Onset of Psychosis

At age 80, the patient presented to the ER with the onset of new visual hallucinations, confusion, and disorientation. He began seeing rodents, snakes, and bugs at night and became frustrated that others did not see the creatures. He would stay up late to look for rodent droppings or pull up the covers on the bed when he felt the rodents running across his feet. The patient also cried for no apparent reason and scored 17/30 on the MoCA.

At follow-up visits, the patient’s wife indicated that he frequently became confused, was forgetful in conversations, and would wander and get lost in the grocery store. At that time, his neurological examination exhibited mild cogwheeling of the elbows and wrists (with the right greater than the left); reduced arm swing; slowed, unsteady gait without falls; and impaired heel-to-toe but no visible tremor. He also had significantly disrupted sleep due to RBD.

Response to Treatments

The patient was hospitalized twice at a VA medical center at age 80 for DLB with visual hallucinations that were severely disrupting his ability to function. Prior to the first hospitalization at VA, the patient received the following medications at bedtime: risperidone 0.25 mg, temazepam 7.5 mg, and prazosin 1 mg (for PTSD-related nightmares). Then, at his first hospitalization at the VA, he received sertraline 25 mg in the morning for depressive symptoms, night sweats, and nightmares and clonazepam 0.5 mg to target RBD; the sertraline was later increased to 50 mg with melatonin 3 mg. Risperidone was discontinued, as it was ineffective and exacerbated his anxiety and aggression but with no dystonia side effects. During this ER visit, clonazepam was effective for RBD but discontinued 10 days later due to daytime oversedation, slowed movements, and shuffling gait. Quetiapine 12.5 mg at bedtime was...
then initiated, which resulted in a paradoxical reaction: excessive sedation, screaming at night, incoherence, and an inability to perform activities of daily living the following morning. Quetiapine was discontinued, which resulted in rapid resolution of the medication-related symptoms. One week later, the patient was hospitalized again due to disruptive visual hallucinations, confusion, and agitation upon waking at night.

Later that year, donepezil was initiated. The patient reported muscle spasms during the first week, but the spasms abated and the patient experienced improvements – particularly following dose titration to 5 mg and then 10 mg – in his executive functioning (eg, planning and sequencing and articulating ideas). However, no improvements in hallucinations were noted as a result of the donepezil.

**Response to Pimavanserin**

During the patient’s first psychiatric admission at age 80 (see description above), pimavanserin 10 mg was started given that quetiapine and risperidone were ineffective, and the patient’s cognition improved to close to baseline levels. When he was readmitted less than 1 week later, he scored 15/30 on the MoCA. During this second psychiatric admission, pimavanserin was titrated up to 20 mg daily for visual hallucinations, and he was discharged to a memory care facility. Six months after discharge from the second hospitalization, he continued experiencing sleep disturbances with vivid dreams, but otherwise his symptoms were manageable and stable, and he scored 20/30 on the MoCA. One year later, at age 81, the patient reported having a good mood, appetite, and energy level with decreased concerns related to cognition or hallucinations. He was able to perform some activities of daily living without assistance, and he had improved sleep with vivid dreams but no agitation. Although he continued to experience hallucinations, they no longer bothered him or caused agitation or nighttime behaviors. For 2 years, pimavanserin was effective in decreasing the patient’s distress related to visual hallucinations and paranoia, and his cognition continued to improve (eg, he scored 24/30 on the MoCA). In March 2022, the patient’s hallucinations became more vivid, and pimavanserin was increased to 34 mg with a good response.

**Discussion**

As we have shown, the patients in our case series presented with cholinesterase inhibitor- and antipsychotic-resistant psychosis. Neurochemical analyses of the temporal cortex have found significant differences between patients with DLB who are and are not hallucinating in choline acetyltransferase (CHAT) enzymes, serotonergic receptor binding, dopamine metabolites, and serotonin metabolites, suggesting that an imbalance between monoaminergic and cholinergic transmitters may be involved in hallucinogenesis in DLB and/or that the disruption of serotonin and acetylcholine neurotransmissions may play a role [5,9]. In clinical trials and smaller studies, donepezil [6] and rivastigmine [7] have shown some success in reducing visual hallucinations and/or delusions in DLB [8]. Nevertheless, 2 of the 3 patients who received rivastigmine in our case report experienced cognitive improvement but no reductions in psychosis, whereas the third patient had a more complicated course in which rivastigmine with quetiapine initially led to an increase in hallucinations but later resulted in continued visual hallucinations that did not interfere with activities of daily living or psychiatric stability.

Patients with DLB and severe pharmacotherapy-resistant psychotic symptoms may benefit from somatotherapies like electroconvulsive therapy or transcranial magnetic stimulation [19]. First-generation antipsychotics offer another potential treatment, but they are generally contraindicated in DLB due to increasing parkinsonism, increased mortality risk, and significant deterioration of motor symptoms [20], sedation, and cognitive impairment. Even if they are effective, first-generation antipsychotics should not be used indefinitely [21]. In our case report, 1 patient received haloperidol following a surgery, which induced a neuroleptic malignant syndrome response followed by increased cognitive impairment, anxiety, and aggression.

Second-generation antipsychotics may have a more favorable mechanism of action given that they have less dopaminergic impact. Nevertheless, the potential benefits of second-generation antipsychotics must always be weighed against any increased risks, such as increased risks of cerebrovascular accidents or mortality [22]. Olanzapine, for example, appears to have only limited value in reducing psychiatric symptoms in DLB [23], and risperidone does not appear to be beneficial [20]. Conversely, quetiapine and clozapine may be better tolerated and more useful [3], but no definitive randomized controlled trials clearly support their effectiveness for DLB [10,11], so their expected efficacy is partly based on extrapolation of results from PD studies [12]. Moreover, clozapine includes side effects like drooling, sedation, tremors, constipation, and delirium [13], and due to the risk of agranulocytosis, it requires blood monitoring [12].

In our case study, 1 patient received olanzapine, risperidone, and quetiapine to treat visual hallucinations, which appeared to trigger paranoid delusions and worsening hallucinations and motor symptoms. Another patient received risperidone and quetiapine and experienced increased anxiety and aggression with no change in psychosis, as well as side effects when quetiapine was administered at night. A third patient experienced increased agitation and hallucinations when receiving quetiapine in combination with rivastigmine, but these
symptoms later appeared to recede to baseline levels and become less unsettling. None of the patients experienced a reduction in their visual hallucinations while on these second-generation antipsychotics.

Several of the patients experienced side effects when receiving second-generation antipsychotics, which suggested they may have fared better with an antipsychotic that lacked a dopamine receptor’s binding property, and 3 of the 4 patients experienced a stable decrease in visual hallucinations after receiving pimavanserin (see Table 1). At least 1 of these patients experienced a related decrease in delusions, and at least 2 of these patients were able to return to their regular activities.

We must develop therapies to treat the range of symptoms that are associated with DLB, but few clinical studies have looked specifically at psychosis in elderly cognitively impaired populations, and patients with DLB are typically excluded from drug trials of antipsychotics and psychotropics [24]. This means we have to extrapolate from trials of psychotropic agents in idiopathic psychiatric disorders [24,25]. The extension of these therapies to patients with DLB is thus based on untested assumptions and may lead to efficacy or tolerability issues. For example, while preparing this review, we only found 1 manuscript that specifically focused only on DLB, a case report that described a patient with DLB whose hallucinations responded to pimavanserin but who discontinued it due to financial concerns (ie, the patient had a large copay); that patient subsequently experienced an increase in hallucinations while on clozapine and then returned to his baseline levels of psychosis when clozapine was discontinued and pimavanserin was reinitiated [26]. In addition, 4 retrospective medical record reviews, 1 case report, and 1 clinical trial included patients with DLB alongside other larger cohorts, but these publications did not report clear histories or specific findings on the patients with DLB.

The findings from these past publications seem to generally align with our observations. As part of a series of retrospective chart reviews that included patients with various kinds of dementia, investigators at a movement disorders clinic in Providence, Rhode Island, reported on 15 patients with DLB who experienced psychosis. Although the reviews share few details about the specific cases with DLB or the long-term resolution of their symptoms, it appears that 10 of the 15 patients experienced at least mild or temporary improvement of psychosis when receiving pimavanserin [27-29]. Likewise, Mahajan et al performed a retrospective chart review that included 1 patient with DLB and psychosis who reported more benign hallucinations following monotherapy with pimavanserin [30]. Most significantly, a phase-3, double-blind, randomized, placebo-controlled discontinuation trial that enrolled patients with various forms of dementia found that participants who continued receiving pimavanserin were less likely to relapse into psychosis than patients who discontinued pimavanserin. That study included 38 participants with DLB but did not provide DLB-specific findings and was stopped early due to findings of efficacy; thus, larger studies that encompass a longer trial period and include DLB-specific findings are necessary [31].

Our case report therefore adds important context regarding the application of pimavanserin in patients with DLB. As Hershey et al point out, pimavanserin may fill the gap for patients with DLB psychotic symptoms that do not respond to cholinesterase inhibitors, which are contraindicated in patients with arrhythmias, but caution is needed as pimavanserin may be associated with an increased risk of death for elderly patients [14]. Burstein has countered that pimavanserin has been well tolerated in multiple studies featuring elderly fragile patients [32], and that was our experience in this case series, as pimavanserin appeared tolerable for each of our patients and resulted in long-lasting positive effects for 3 of our 4 patients.

Finally, it is unclear why pimavanserin improved psychosis in Patients 1, 2, and 4 but not Patient 3. In a retrospective cohort study comparing pimavanserin and quetiapine in patients with PD and DLB (without differentiation between the 2 patient groups), Horn et al found that pimavanserin may be more useful than quetiapine for promptly addressing psychosis, and they also note that 5 of the 8 patients who discontinued pimavanserin also took quetiapine concurrently at some point in their care [33]. As we have shown, multiple patients in our case series received quetiapine at some point in their care; however, only the patient who eventually discontinued pimavanserin received pimavanserin and quetiapine concurrently. Although this may suggest that the combination of drugs led to the lack of efficacy for pimavanserin in this patient, additional research is necessary to investigate this point.

**Conclusions**

Given that this is a small case series and not a clinical trial, we cannot definitively remark upon the value of pimavanserin for patients with DLB and psychosis. Nevertheless, this case series is useful in that it includes 4 patients with DLB who presented with a variety of clinical histories, including, for instance, patients with a neuroleptic malignant syndrome or PTSD. The case series also combines the insights of 2 experienced geriatric psychiatrists who directly interacted with the patients and their caretakers. That work shows that for some patients with DLB who experience treatment-resistant psychosis, the new second-generation atypical antipsychotic pimavanserin in may reduce distressful hallucinations and delusions while avoiding the side effects of other second-generation antipsychotics. Additional clinical trial data in patients with DLB and
psychosis would be useful, but in the meantime, our case series suggests that the clinical trial findings observed in other dementia populations may be relevant for patients with DLB and that the risk-versus-benefit ratio for pimavanserin appears likely to be favorable in many patients who suffer from psychosis in this debilitating disorder.

References:

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