Neuroleptic Sensitivity in Dementia with Lewy Body and Use of Pimavanserin in an Inpatient Setting: A Case Report

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Patient: Male, 75-year-old
Final Diagnosis: Dementia with Lewy bodies
Symptoms: Parkinsonism
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Unusual clinical course

Background: Antidopaminergic medications, including antipsychotics, are known to worsen motor and neuropsychiatric symptoms, including cognition and psychosis, in patients with dementia with Lewy body (DLB). The intensity of worsened clinical symptoms may vary and can result in mortality in certain situations. There have been some reports supporting clozapine, quetiapine and pimavanserin use in psychosis control in this population.

Case Report: We describe the case of 75-year-old man with diagnosis of DLB and the post-treatment outcome with olanzapine for psychosis during hospitalization. He experienced worsened cognitive and motor functions. Discontinuation of olanzapine resulted in resolution of the clinical worsening. Further, re-initiation of Pimavanserin helped treat his hallucinations. He returned back to his baseline during a follow-up visit in the clinic at 1 month after discharge. Further, we incorporated the use of Best Practice Alert (BPA) as a part of the electronic health record (EHR) system to help providers identify patients prone to neuroleptic sensitivity and help select appropriate medications to treat psychosis in this patient population.

Conclusions: Administration of antipsychotics in patients with parkinsonism, especially DLB, requires close clinical monitoring and judicious use. Awareness of morbidity and mortality associated with such use is of importance, especially during hospitalization. From our experience, we incorporated use of BPA, which can help providers make judicious choices while treating this patient population. Pimavanserin, which is FDA-approved for psychosis in Parkinson’s disease, could be a potential safe and effective treatment option in this patient population.

Keywords: Neuroleptic Receptor • Lewy Body Disease • Psychotic Disorders

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Background

Parkinsonism is an clinical term used to define the symptoms of resting tremor, bradykinesia, rigidity, and postural instability exhibited by individuals with idiopathic Parkinson’s disease (PD) [1]. Parkinsonism may also include conditions other than PD, such as drug-induced parkinsonism, dementia with Lewy body (DLB), corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), vascular parkinsonism (VP), and multiple system atrophy (MSA). Drug-induced parkinsonism caused by neuroleptic medications that block dopamine receptors, is the most common form of parkinsonism after idiopathic PD [2]. These drugs have an increased potential to exacerbate pre-existing parkinsonian symptoms secondary to such patients’ pre-existing nigrostriatal dopaminergic deficiencies [3]. Such medications can worsen tremor, rigidity, gait instability, cognition, and hallucinations, and even cause psychosis. Patients are also predisposed to neuroleptic malignant syndrome characterized by muscle rigidity, fever, and altered mental status, which can be life-threatening [4]. Other considerations when using this class of drugs include cardiac risk factors such as QTc prolongation, myocarditis, cardiomyopathy, torsades de pointes, and sudden cardiac death [5]. Despite these potential adverse effects, the use of this class of medications may be unavoidable when treating psychosis in parkinsonian patients.

An estimated 80% of DLB patients experience severe hallucinations requiring pharmacological intervention [6]. It is estimated that 30-50% of DLB patients experience severe sensitivity reactions when given even a nominal dose of an antipsychotic drug for treatment of hallucinations and/or other symptom(s) of psychosis [7,8]. Providers may prescribe antipsychotics, often to alleviate a patient’s psychosis, despite the well-documented increased risks of mortality, cerebrovascular events, and adverse events, including worsening psychosis [9]. At least 1 study found that since the US Food and Drug Administration (FDA) issued warnings of mortality associated with antipsychotics in PD patients, there was a dramatic decline in antipsychotic use in this population over the years [10]. This shows the impact of highlighting adverse effects and the potential for practice change.

There has been some evidence supporting use of clozapine, quetiapine, and pimavanserin in psychosis control in patients with parkinsonism [11-13]. In contrast to other anti-dopamine antipsychotics, pimavanserin is a selective serotonin 5-HT2A inverse agonist with no appreciable effect on dopaminergic or muscarinic receptors [14]. After some studies and clinical trials showed its efficacy and safety in improving psychotic symptoms among PD patients, the FDA approved pimavanserin for Parkinson disease psychosis (PDP) [15].

We present the case of a patient with DLB who had a rapid decline in motor function and mental condition after receiving antidopaminergic medications during hospitalization, and discuss the clinical outcome. Such incidents have further compelled us to start an inpatient Best Practice Alert (BPA), which is a part of the electronic health record (EHR) system and includes a pop-up when a provider works on a patient [16]. We created a BPA alert that notified providers about contraindications and potential adverse effects with use of neuroleptics in patients with Parkinson disease. This alert is triggered any time a provider orders a neuroleptic medication, and suggests use of alternative medications for the same indication.

Case Report

A 75-year-old man with a diagnosis of DLB presented to our institution for falls secondary to orthostatic symptoms in the context of worsening visual hallucinations.

Preadmission History

He started to experience visual hallucinations, which included seeing nonexistent children in the room, for about 2 years prior to presentation. He reported rapid eye movement (REM) behavioral disorder with acting out of his dreams. In addition to autonomic problems such as constipation and orthostatic symptoms, he also had cognitive problems, including short-term memory troubles such as difficulty handling finances when shopping and forgetting parts of daily conversations. On a clinical exam 2 months prior to admission, he was noted to have stooped posture along with grade 1 bradykinesia (per Unified Parkinson Disease Rating Scale (UPDRS) [17]) on finger tap on the upper extremities and alternating hand movements. There was no evidence of cogwheel rigidity or resting tremor on clinical exam. He had 16 years of official education. His cognitive testing demonstrated deficits in visuospatial and executive functioning (set-shifting and copying cube) and difficulty with clock drawing. Immediate object recall was 4/5 and 5-min delayed recall was 3/5. He was diagnosed as having probable DLB per diagnostic criteria [6].

The hallucinations were initially well managed by pimavanserin, a 5HT2A receptor antagonist, but he later stopped taking it due to an expensive copay. He was then placed on clozapine 12.5 mg daily with gradual up-titration to 50 mg daily. Other medications at admission included donepezil 10 mg daily.

Post Admission Clinical Course

At the time of admission, his wife reported he was having worsened hallucinations since pimavanserin had been stopped for 10 days despite treatment with 50 mg of clozapine. During admission, he was oriented to person and place but not to time. He was afebrile on presentation. Sepsis workup including white blood cell...
count, urine analysis, and chest X-ray were normal. Computed tomography of the head did not reveal any acute intracranial processes. He became agitated overnight and was treated with repeated doses of olanzapine 2.5 mg, along with bilateral soft restraints, escalated to 4-point restraints less than 2 h later. He was started on valproic acid 500 mg twice a day to de-escalate restraints use as soon as possible. In less than 12 h, his mental status had worsened, being only oriented to self and remaining combative with staff. Cognition continued to wax and wane over the course of 2 days, expressing agitation and responding to internal stimuli, while receiving olanzapine for agitation.

By day 3 of hospital stay, he received a cumulative dose of 25 mg of olanzapine and was placed in either 2-point or 4-point restraints multiple times. Mental status continued to worsen, including not recognizing his wife. Psychiatry consult team recommended discontinuation of olanzapine and titration of clozapine to 50 mg twice a day, and use of lorazepam as needed for agitation, along with admission to the psychiatric Intensive Care Unit (ICU) for further medication management.

On the day of admission in to the psychiatric ICU, a neurological exam displayed obtunded mentation, lack of comprehension or any verbal responses, and significant rigidity (grade 2 per UPDRS). He was not independently mobile and required assistance walking. The remainder of the neurological exam could not be performed due to mental status and difficulty with cooperation.

Because of the rapid change and concern of adverse effects, clozapine and valproic acid were discontinued. The use for lorazepam for agitation was also restricted to life-threatening psychiatric emergency only. On day 3, improvement in the mental status was observed when he was able to answer questions and walk mostly on his own rather than being confined to bed. Over the next 2 days, he reported having less visual disturbance and his orientation and thought processes continued to improve. Upon collaboration with the outpatient neurologist, he was enrolled in a grant that would continue to cover the cost of pimavanserin. Thus, by day 6 of psychiatric ICU admission, he was restarted on pimavanserin. He continued to make progress, with no falls or visual hallucinations. After 8 days of psychiatric ICU treatment, he was deemed appropriate for discharge to the care of his wife.

**Post-Discharge Follow-Up**

An outpatient visit 1 month after hospitalization revealed improved cognition, which was his baseline, and return to daily activities without limitations of motor abilities. Clinical exam findings were the same as before admission. Of note, he was on pimavanserin 34 mg daily, along with donepezil 15 mg daily and memantine 5 mg daily.

**Discussion**

Treatment of psychosis in DLB can be difficult and requires a stepwise approach. This starts with eliminating agents that can provoke or worsen psychosis, including anticholinergics, opioids, and benzodiazepines. Clozapine and pimavanserin have been proven to be effective in treating psychosis without worsening motor symptoms and are currently the recommended medications to treat psychosis in parkinsonian patients [11,18]. This is likely because clozapine has very little affinity to D2 receptors [19], which is implicated in worsening of parkinsonian symptoms, while pimavanserin acts through 5HT2A receptor antagonistic activity.

Our case displays the deleterious effects of neuroleptic medications in DLB patients. During this patient’s hospitalization, the use of olanzapine led to significant worsening of neuropsychiatric and motor symptoms.

At the apex of the patient’s decline, he had received a cumulative dose of 25 mg of olanzapine over 3 days. In addition to olanzapine, on day 3, he was also receiving 1000 mg of valproic acid, 10 mg of donepezil, and 100 mg daily dose of clozapine. After having all the medications held and being admitted to the psychiatric ICU secondary to worsening symptoms, including developing postural rigidity, the patient returned almost entirely to his baseline by day 3 of psychiatric ICU admission (day 6 of total hospital stay). Worsened motor symptoms point to sensitivity to olanzapine as being the probable etiology rather than clinical worsening from clozapine up titration, which is less likely to affect motor function.

Improvement after discontinuation of neuroleptic medications has been documented in other DLB patients with a similar presentation. Teng et al reported the case of a 45-year-old woman with DLB admitted for worsening altered mental status, rigidity, shuffling gait, tachycardia, diaphoresis, and a temperature of 38.2°C, among many other symptoms, shortly after being prescribed olanzapine [4]. She was eventually diagnosed with neuroleptic malignant syndrome (NMS), a central nervous system infection, endocrine problems, and other drug-related problems during her admission. Like our patient, she was prescribed olanzapine before admission and was titrated to 10 mg daily due to worsening symptoms. After stopping her olanzapine, she quickly recovered, causing the clinicians involved in the case to implicate olanzapine due to its “temporal relation between the occurrence of NMS and the initiation of olanzapine” [4]. Her condition and olanzapine dose were inversely correlated. While a post hoc analysis of DLB patients experiencing psychosis that were treated with olanzapine suggested that olanzapine reduced psychosis in DLB patients while not worsening parkinsonism symptoms [20], other studies have found that olanzapine is no better than other conventional...
neuroleptics and should be used sparingly in those with DLB due to potential neuroleptic sensitivities [21]. A 2005 comparative study found that severe neuroleptic reactions in DLB patients were most prevalent in those prescribed olanzapine [3]. Another study on the relation between olanzapine and PD patients demonstrated worsened motor function in those taking olanzapine [22]. Additionally, a retrospective case-control study of antipsychotic use in dementia patients demonstrated the highest 6-month absolute mortality risk occurred with haloperidol (3.9%; 95% confidence interval [CI], 1.0-6.6%) and the lowest risk with quetiapine (2.0%; 95% CI 0.7-3.3%). The absolute mortality risk with risperidone was 3.7% (95% CI, 2.2-5.3%) and the mortality risk with olanzapine was 2.5% (95% CI, 0.3-4.7%) [23].

Cholinesterase inhibitors such as rivastigmine in 6-12 mg doses have also produced statistically and clinically relevant improvements in behavior in patients with DLB [24]. The utility of memantine, an NMDA receptor antagonist, in treating hallucinations is unclear as both improvement and worsening have been reported in the literature [25]. These are just a few potential alternative options to olanzapine, which appear to have fewer adverse effects. Use of medications with 5HT2A receptor antagonist activity provides good control of hallucinations, as they do not block dopamine receptors and hence prevent worsening of parkinsonism. Use of pimavanserin has not been extensively studied in patients with DLB. Further studies, including randomized controlled trials, may help establish its efficacy, as in our present case. To increase awareness of and attention to neuroleptic sensitivity, we incorporated use of BPA to prevent such clinical instances for parkinsonian patients within an inpatient setting where several providers are involved in patient care and may not know the implications of using neuroleptics in this patient population.

We recommend a stepwise approach to treating inpatient delirium or psychosis in DLB patients. This begins by treating precipitating factors such as sepsis, then eliminating medications with anticholinergic burden (eg, antispasmodics, antiallergy medications, tricyclic antidepressants) and considering the total anticholinergic burden [26]. Benzodiazepine and opioids should also be eliminated in such scenarios as these can worsen hallucinations and confusion. Attention may be given to PD medications and providers may attempt weaning off dopamine agonists such as pramipexole, ropinirole, and rotigotine, as well as amantadine, which can contribute to worsening hallucinations and cognition [27]. Interventions could include a trial of donepezil or rivastigmine as mentioned previously. It is only after all these interventions have been tried that providers may consider antipsychotic medications, including quetiapine, clozapine, and pimavanserin.

Conclusions

Our case report demonstrates neuroleptic sensitivity syndrome in a DLB patient and elucidates the delicate nature of this syndrome and the need to monitor such patients closely. This instigated incorporation of a BPA alert system, which helps providers make decisions in unfamiliar clinical scenarios. Other factors that led to worsened outcome included discontinuation of pimavanserin, which previously helped relieve the patient’s symptoms. More randomized control trials are required, which may help in the process FDA approval for the use of this medication in DLB. There is a need for better insurance coverage of appropriate medications in vulnerable populations to avoid increasing the health care burden associated with hospitalization and neuroleptic sensitivity seen in such clinical scenarios.

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