Treatment of Hallucinations and Delusions in Parkinson Disease

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Case

A 70-year-old man diagnosed with Parkinson disease (PD) 15 years earlier was brought in by his family for a follow-up visit with his neurologist. The patient's wife was concerned about visual hallucinations in the last few weeks involving seeing unfamiliar people in the house and cats running across the room, particularly at night. On several occasions, he was found to be talking alone in the room when there was no one there. This has greatly bothered his wife, although he did not seem to be frightened. Other than seeing things, he also experienced delusions. He became particularly paranoid when he saw his wife talking to someone on the phone or leaving the house. He was convinced that she was being unfaithful to him without any actual proof. He constantly worried about it and this has caused significant distress for his marriage. He has been sleeping poorly with vivid dreams at night. He denied symptoms of depression. His wife reported mild cognitive decline for the last 5 years prior to onset of hallucinations and delusions. Motorically, he has been doing relatively well on stable doses of levodopa 200 mg three times daily and extended-release ropinirole 12 mg once daily. There were no significant motor fluctuations or dyskinesia. He denied any recent change in his medical health or non-PD medications. He denied any symptoms or signs of infection. Basic laboratory workup including complete blood count (CBC), complete metabolic panel, and urinalysis was within normal range. An attempt was made to slowly taper the dopamine agonist, which made his parkinsonism worse, so the dosage was returned to previous level. His symptoms of hallucinations, paranoia, and sleep disturbance worsened. Quetiapine 25 mg in the evening was initiated to address his psychosis and sleep disturbance and subsequently titrated up to 25 mg twice a day with significant improvement in his psychotic symptoms without deterioration in his parkinsonism.

Discussion

Psychosis is one of the most clinically significant and disruptive behavioral problems in PD. The prevalence of PD psychosis (PDP) ranges from 20% to 50%. It is a common reason for nursing home placement or institutionalization in PD and is associated with increased morbidity and mortality. The characteristic features of PDP include hallucinations, illusions, and delusions. Initially, patients often describe what are called minor hallucinations. These include passage hallucinations which are fleeting shadows in the visual periphery or "sense of presence" hallucination which is a perception that another person is next to or behind the patient. Full-fledged hallucinations are typically visual in nature, usually non-threatening comprised of little children, animals, or relatives who passed away. Occasionally, they can be auditory, tactile, gustatory, or olfactory. Delusions typically are paranoid in nature, best known is the belief of spouse infidelity and abandonment. Because it is almost impossible to convince the patient that delusions are not real and any attempt to reason or argue may cause more agitation, caregivers often become overwhelmed to continue caring for their loved one. The 2007 NINDS/NIMH revised criteria for diagnosis of PDP include the presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations, or delusions. The symptoms of psychosis must occur after the onset of PD and are either recurrent or continuous for at least 1 month. Such symptoms are not better accounted for by other causes of parkinsonism, such as dementia of Lewy body (DLB) or other psychiatric disorders. Level of insight, presence of dementia, and PD treatment are not required in PDP criteria.

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Although dopaminergic medications have been associated with the development of hallucinations in PD, they are not a necessary factor in the development of PDP. The current view in pathogenesis of PDP stems from a complex interaction of extrinsic and intrinsic factors. Age of onset, duration of PD, and cognitive impairment have a strong correlation with PDP. Other medications commonly used for PD patients such as amantadine and anticholinergics may contribute in the development of PDP, as well as visual processing deficits and sleep disturbance. Various scales have been developed to assess psychosis in PD such as Brief Psychiatric Rating Scale, Neuropsychiatric Inventory, and Schedule for Assessment of Positive symptoms, among others. While they may be useful outcome measures in clinical trials assessing new interventions, no individual scale captures the full clinical spectrum of PDP or reflects meaningful clinical change over time in real-life practice.

The principles of PDP management include a search for medical causes of delirium, a thorough review of PD and non-PD medications, and an initiation of psychopharmacologic treatment (Fig. 27.1). Underlying medical conditions such as systemic infections (e.g., urinary tract infection, pneumonia), metabolic and endocrine derangements (e.g., electrolyte imbalance, thyroid disease, liver or kidney dysfunction), cerebral hypoperfusion states, and psychosocial stressors can precipitate psychosis and delirium in PD patients; therefore it is important to assess for them as potential causes of psychosis. Polypharmacy is one of the strong risk factors for PD psychosis, thus it's crucial to perform a thorough review of patient's medication list. Medications such as dopaminergic replacement therapy, opiates, sedatives, anxiolytics, anticholinergics, and antidepressants are implicated in PD psychosis and may need to be reduced or stopped accordingly. Most authorities agree on a gradual tapering strategy for PD medications in the following order: anticholinergics, amantadine, monoamine oxidase B inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitors, and if still needed, levodopa. One needs to be mindful of the development of dopamine agonist withdrawal syndrome and delirium following amantadine withdrawal. The immediate release formulation of levodopa is typically preferred over the controlled-release formulation in the end because of a lower risk of adverse effects with the former. For persistent and problematic psychosis, the next step is to consider adding a psychopharmacologic treatment (Table 27.1).

Pimavanserin is the first and only drug approved by the US Food and Drug Administration, April 2016, for treatment of hallucinations and delusions associated with PDP. It is a 5HT2A inverse agonist that has been shown to significantly reduce hallucinations and delusions without worsening motor symptoms in PD patients at a dose of 40 mg/day. Prior to approval of pimavanserin, clozapine and quetiapine, two atypical antipsychotic drugs, were (and still are) widely prescribed off-label in low doses for PD psychosis. Clozapine, a dibenzodiazepine derivative, selectively binds D1 mesolimbic receptors while sparing striatal D2 receptors and has a greater affinity to 5HT2A/2C receptors. Two landmark studies in 1999 on use of clozapine in PDP demonstrated significant improvement in symptoms of psychosis and improved motor function in some cases. However, clinicians tend to shy away from its use due to the need for frequent absolute neutrophil count monitoring which is weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter, to monitor for the less than 1% chance of developing agranulocytosis. Other adverse effects of clozapine include orthostatic hypotension and sedation. The effective dose of clozapine for PDP is lower than that used for treatment of schizophrenia. The initial dose is 12.5 mg once at night; if necessary, it can be gradually increased as tolerated not to exceed 75–100 mg daily; mean dose in clinical trials was 25 mg daily. Quetiapine is structurally similar to clozapine and has a greater affinity for serotonergic 5HT2 receptors than D2 receptors which confers a favorable motor profile but not as favorable as that of clozapine. There have been some conflicting data on efficacy of quetiapine in PDP, although strong evidence exists that it does not significantly worsen motor function. However, it commonly causes sedation and may worsen orthostatic hypotension. It may be initiated at 25 mg once at night or in divided doses; the dose may be adjusted gradually based on response and tolerability up to 200 mg daily; mean dose in clinical trials was ~91 mg daily. Other atypical antipsychotic medications that have dopamine blockade should be avoided in PDP treatment. Olanzapine causes significant motor function decline with inconsistent benefit in PDP. Aripiprazole has variable efficacy and tolerability in PD with higher risk of motor worsening. There are no large randomized trials examining cholinesterase inhibitors in PDP treatment, although in cognitive clinical trials on patients with dementia with Lewy bodies randomized to cholinesterase inhibitors, incidental improvement in hallucinations have been noted. We have not observed any consistent or clinically meaningful effect in reducing hallucinations in our patients.

Once hallucinations appear, they tend to become a chronic and progressive condition. Continued psychopharmacologic treatment may be necessary to maintain symptom control.

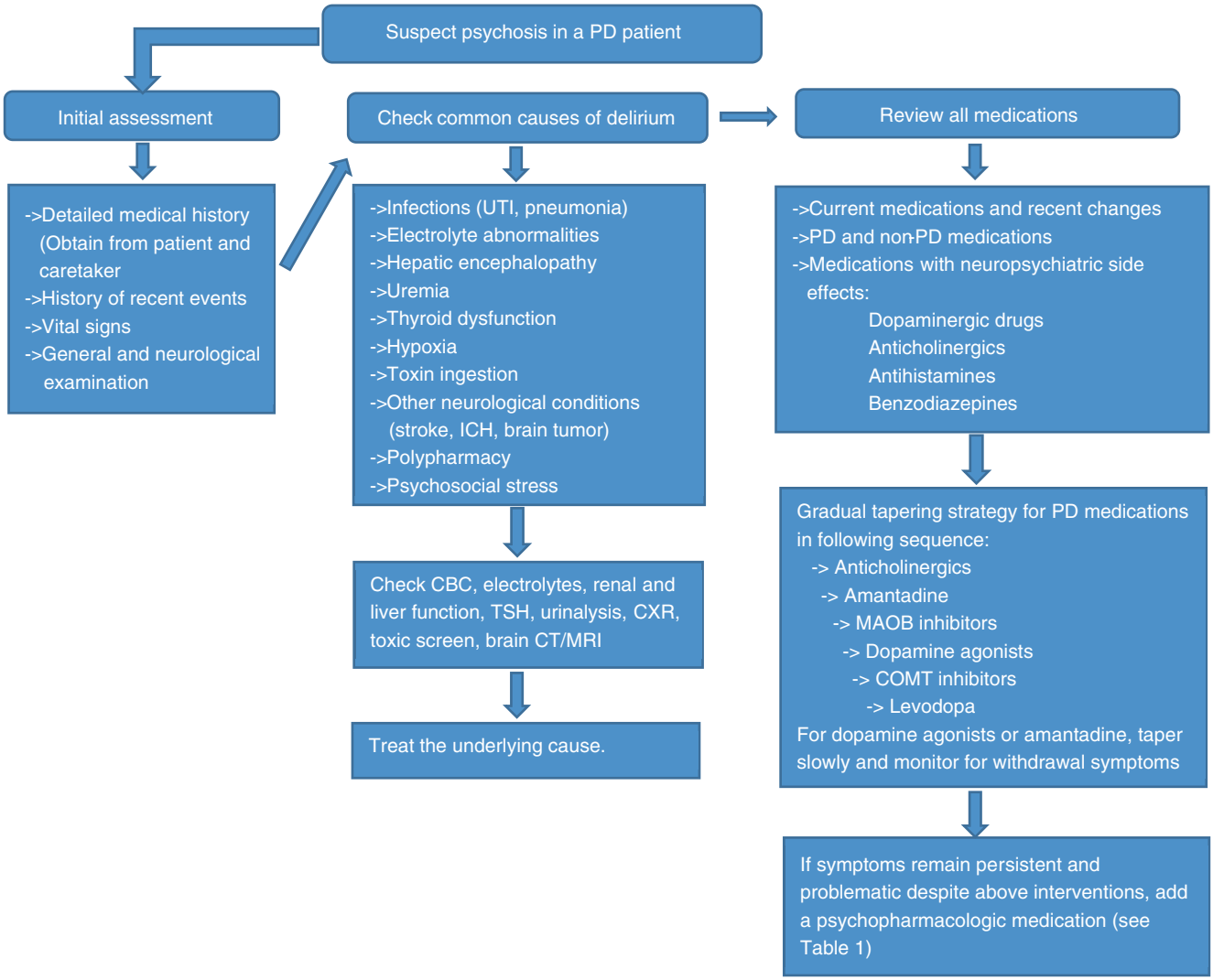

Fig. 27.1 Algorithm of psychosis evaluation in a PD patient

Table 27.1 Medications commonly used for PD psychosis

Medication	Starting dose	Titration	Max dose	Side effects and considerations
Quetiapine	12.5–25 mg at bedtime	Increase by 25 mg every few days as tolerated	200 mg daily	Monitor for worsening parkinsonism, sedation
Clozapine	12.5 mg at bedtime	Increase by 25 mg every few days as tolerated	100 mg daily	Monitor for orthostatic hypotension, agranulocytosis (1% risk) (check weekly CBC for 6 months, followed by biweekly CBCs, then monthly after 1 year)
Pimavanserin	34 mg once daily	None	34 mg once daily	Well tolerated in Phase 3 trial with no significant safety concerns or worsening motor function

Suggested Reading

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