Management of psychotic symptoms in Parkinson's disease

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Practice Points

- Psychotic symptoms affect more than one third of drug-treated people with Parkinson's disease, primarily visual hallucinations and a feeling of someone being present, but out of sight.
- The visual hallucinations are generally benign, usually being nonthreatening people or animals but hallucinations carry a poor prognosis, with an increased risk of paranoid delusions and dementia.
- The only medication proven effective and safe in double-blind, placebo-controlled trials is clozapine, used at doses of one hundredth to one tenth of those used in schizophrenia.
- Quetiapine has been evaluated in double-blind, placebo-controlled trials and found to be safe but not effective. All other atypicals for which information has been published have demonstrated the potential for worsening motor problems and are generally avoided.
- The American Academy of Neuorlogy guidelines for treating psychotic symptoms in Parkinson's disease recommend that only clozapine and quetiapine be considered.
- This author recommends a trial of low-dose quetiapine first, with low-dose clozapine used as the second line.

SUMMARY Parkinson's disease psychosis is a major problem complicating the drug treatment of the motor symptoms of the disease. It is one of the leading causes for nursing home placement, exceeding that of motor dysfunction, and is also a greater stressor for caregivers than motor dysfunction. While there is no approved treatment for this problem, it is important to first exclude medical contributions, such as occult infections, then to reduce psychoactive medications, including the medications for motor symptoms, followed by use of low-dose quetiapine or clozapine, giving the bulk of the dose at bedtime.



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Parkinson's disease (PD) is the second most common neurodegenerative disorder in the western world, affecting more than 1% of people over the age of 60 years, with increasing incidence with age [1]. While PD is classified as a movement disorder, it is a neurobehavioral disorder defined by its motor signs and symptoms [2]. It causes or is associated with dementia, depression, apathy, anxiety, impulse control disorders and possibly psychotic symptoms, as a direct result of the neuropathology, or by indirect and iatrogenic effects [3].

Psychotic symptoms in PD are primarily hallucinations, with visual being the most common type, affecting about 20-30% of drug-treated patients [4-11]. These hallucinations have fairly stereotypic features, generally occurring in a low stimulus environment, with patients often alone, reading or watching television, suddenly noticing that there are others in the room. These may be normal appearing adults, oddly dressed or in shadows, often children [12]. The hallucinated figures usually do not interact with the patient. Unlike the hallucinations of primary psychotic disorders, these usually have no emotional content [4-12]. The hallucinations tend to be the same each time, so that one patient sees soldiers marching on parade on his lawn every day, another sees three girls in tutus doing ballet in her driveway when she does the evening dishes.

Visual hallucinations are usually well tolerated but may become bothersome [4]. For one thing they affect the perception of reality. The patient often needs to wonder whether what he's seeing is real or not. Sometimes the hallucinations become mildly threatening. The patient, often someone with physical disabilities, may be bothered by having strange people in the house. And finally, the visions may become overtly threatening. One of my patients saw friendly nuns, wearing habits, working outside his house. Another saw nuns with fangs, dripping blood.

We used to label the visual hallucinations as 'benign hallucinations', using the term to describe the benign nature of the visions. Some patients even enjoy the distraction and would prefer to not give them up. Most do not. Unfortunately, the presence of hallucinations is often the herald symptom of incipient dementia, so that the term 'benign hallucinations' has fallen into disfavor [7].

Auditory hallucinations occur in about half of the patients who have visual hallucinations [13].

These tend to occur in two major categories. They may be part of the visual hallucinatory experience, with the hallucinated people carrying on conversations, usually with the patient, or they may occur completely unconnected to the visual hallucination. Common auditory hallucinations are radio sounds, music, indistinct voices coming from another part of the house, or outdoors. Unlike the schizophrenic voices, which usually discuss the patient in a derogatory fashion, these voices are usually not well heard so that the content is unclear. Other hallucinations are distinctly uncommon in PD [13].

Since hallucinations are, by definition, a perception of a stimulus that is not present, they may affect any of the five basic senses: hearing, smell, taste, vision and tactile. However, in addition to the 'usual' hallucinations that may involve one or more of the five senses, a peculiar sensation that many PD patients describe, currently called 'presence hallucination' is that someone or something is either next to or behind them. Patients will report that they feel a strong sense of 'presence', so that although they know there is no one else in the room they will turn around to look anyway. It is uncommon for patients to be particularly bothered by this. A second type of hallucination, called 'passage hallucinations', are fleeting images, seen peripherally, of shapes, people or small animals, which disappear on looking in that direction. These passage hallucinations and perceptions of presence are lumped together as 'minor' hallucinations [14].

The second type of psychotic symptom that occurs in PD are delusions. A delusion is a false, irrational belief. These tend to be paranoid, with jealous delusions of spousal infidelity being very common [13].

Psychotic symptoms may emerge without any changes in medication, even when they have not changed in years [4].

The following cases were all screened for toxic/metabolic problems that might have contributed to their psychotic symptoms.

Case A

Mr A was an 80-year-old man with a 5-year history of PD. He could walk without assistance but usually used a cane as he had fallen twice in the previous year. He reported increasing problems connecting faces with names, and losing track of his thoughts in mid-sentence. He was fully oriented and could recall news events of the last few months. He rarely acted out his dreams. He admitted to mild depression despite taking sertraline 50 mg q.d. He was also taking carbidopa/levodopa (C-L) 25/100 1.5 t.i.d. as his only PD medication, lorazeapam 0.5 mg once daily and darifenacin for overactive bladder. He had begun seeing shadows of people in his peripheral field several-times daily, and also admitted to having the sensation that there was someone behind him so that he would turn around to look. These hallucinations did not bother him.

Management

The history of memory impairment was new, and although not clearly a manifestation of dementia, might also have been due to depression. His mini-mental state examination (MMSE) result was 24. Anticholinergic agents often cause memory impairment and may induce hallucinations. Although darifenacin is an anticholinergic, it does not significantly cross the blood-brain barrier and has been found to be free of memory and cognitive impairment in double-blind studies. I chose to ignore the hallucinations and treat the depression by increasing the dose of sertraline, warning the patient about the possibility of increased hallucinations. This produced a mild improvement in depression but no change in memory complaints or hallucinations. Rivastigmine was then added. It is approved in the USA for dementia in PD, and the cholinesterase inhibitors, in general, have level III evidence to support their use in reducing hallucinations in demented PD patients (see discussion below). After approximately 6 weeks the passage and presence hallucinations became considerably less frequent, although still occurring from time to time.

Case B

Ms B was a 68-year-old woman with a 12-year history of PD, living in a nursing home. She had clinical fluctuations and could walk with a walker when 'on' but was in the wheelchair most of the day. She was moderately demented (MMSE 20). Her medications were: C-L 25/100 1.5 four times daily (q.i.d.); entacapone 200 mg q.i.d.; amantadine 100 mg t.i.d. She reported that the nursing home staff were killing patients and ran a crematorium in the basement, selling body parts when they could. They also sold drugs in the stairwells. Some of the staff in the crematorium were Nazis, so she attended every Christian service on Sundays, hoping she would fool them into believing she was not Jewish. The staff reported that she was particularly agitated at nighttime and slept little.

Management

Since amantadine is cleared by the kidneys, any decline in renal function can induce amantadine toxicity. Her renal function was normal so her amantadine was stopped rather than reduced. It is clearly less potent than the L-Dopa for treating motor symptoms and is probably more likely to cause mental side effects. Entacapone primarily acts by altering the pharmacokinetics of L-Dopa peripherally, and little enters the brain. Reducing entacapone is, therefore, equivalent to simply reducing the L-Dopa. Since her mobility was very impaired, this was not done. Quetiapine was started at 25 mg before bedtime (qhs), both to help her psychosis and to help her sleep. She did not sleep much better on the first two doses so it was increased to 50 mg, which did help both the sleeping and the psychotic symptoms. It was increased to 75 mg, which induced a complete remission of the psychotic symptoms, but with some mild daytime somnolence.

Case C

Mr C was a 64-year-old man with a 26-year history of PD. He had done extraordinarily and unusually well for having had the illness for so long and must therefore be considered an atypical case of PD; however, management approaches for his psychosis are identical to patients with more typical histories. He was not demented. He had moderate dyskinesias when 'on' and was 'off' for only brief periods each day, never significantly affecting his gait. He had had the persistent belief that his wife was having affairs and that the men were sometimes spraying him with scent. He had spied on her but had never seen any of the men. Nevertheless he had followed cars he believed were driven by one of the lovers. He had been taking L-Dopa and pramipexole when the problem began, and eliminating the pramipexole did not help. His L-Dopa, 1000 mg/day could not be reduced. He did not improve on quetiapine 400 mg /day. His white blood cell count dropped on cloazapine. He tried melperone, an atypical antipsychotic free of motor side effects, from Europe, without benefit and refused electroconvulsive therapy



(ECT). He continued to have this fixed, isolated delusion and moved out of his house.

Management

Delusions of jealousy are not uncommon in Parkinson's disease psychosis (PDP). In one study they were the single most common delusion and in another, they were second [4]. PDP delusions are typically paranoid, and therefore very upsetting, both to the patient, who is often dependent on the very person who is the delusion's focus, as well as to the caregiver, who feels that the reward for heroic sacrifice is an unjust accusation. This is one major reason that the single most common cause for nursing home care for PD patients is psychosis [15,16].

This patient had his medication lowered to the lowest level he would tolerate. He tried the only antipsychotic drugs known to not worsen motor function. If he had been demented a trial of a cholinesterase inhibitor should have been considered, but there are no case reports of their use in nondemented patients with PDP. In extremis, failure to respond to any drugs, electroconvulsive therapy should be offered. There are several case reports of the benefits of the ECT in this situation, even in patients who are not depressed. He refused. The next option is to try antipsychotic drugs with the least likelihood of worsening motor function, which I believe is aripiprazole, although published data does not support this [17].

Case D

Mr D was a 78-year-old man who was diagnosed with PD at age 65. At age 77, because of clinical fluctuations with mild dyskinesias, amantadine was added to his C-L 25/100 q.i.d. and pramipexole 0.75 mg t.i.d., which caused pedal edema and visual hallucinations. The amantadine was stopped, with resolution of the hallucinations, until about a year later, when he first began feeling things on his skin. He was a retired engineer, who owned his own manufacturing company and was quite successful. He thought he had a memory problem, but his family thought that his cognitive function was almost normal, and probably better than his peers'. He scored 25 on the MMSE. His speech was minimally hypophonic. He was fully oriented and his mood, attention and ability to provide history was above normal. He reported having hallucinations daily. He felt "little creatures" that felt like insects crawling on his skin. Sometimes he saw them crawling under his shirt although he noted that his family didn't see this even when he did. He mostly experienced these when he was alone, and they were most frequently present when he went to bed at night. No matter how suddenly he rolled over or slapped them, they were never found. On one occasion he moved as quickly as he could from his house to his car in order to be free of them, but they appeared in the car as well. On another occasion he took a hot shower, and, staying naked to keep the creatures from being carried in his clothing, ran to his bedroom to escape them, but this did not work either. After several weeks he started seeing some of them in addition to feeling them. One of them, who he described as "the leader of the pack" was a gray "fuzzy chicken", which evidently moved extremely quickly so that it was difficult to see, "like the Road Runner cartoon character." He had no other delusions or hallucinations.

Management

Mr D had visual and tactile hallucinations. In addition he intermittently believed the hallucinations were real, a phenomenon that is considered a 'secondary delusion'. He could explain why he knew the hallucinations were not real, such as crushing them but never finding their bodies; no one else seeing his shirt move when he did. However at times he did think them real.

Mr D was not clinically demented, although his MMSE suggested that he suffered from a mild cognitive deficit. Reducing his anti-PD medications did not improve the psychotic symptoms so an antipsychotic was introduced. Although quetiapine has not been proven to be helpful, it has been proven to not worsen motor function. The American Academy of Neurology task force on the treatment of PD suggested that clozapine and quetiapine should be considered for this use, although acknowledging the absence of double-blind data to support quetiapine's use [18]. Quetiapine was added, starting with 12.5 mg qhs; this did not help and it was increased every few days, depending on his response. At 37.5 mg qhs, he was groggy in the morning, although he slept through the night. He became confused and the hallucinations had not resolved. Quetiapine was stopped and clozapine was begun, with 6.25 mg qhs. At

12.5 mg qhs he was sleeping through the night and only occasionally felt the "creatures".

Discussion

The psychotic symptoms that occur in PD are very different to those that appear in primary psychiatric disorders, such as schizophrenia or depression with psychotic features [19]. In these disorders the hallucinations are almost always auditory, whereas in PD they are predominantly visual. In the primary psychiatric disorders the symptoms are 'ego-syntonic', meaning that the emotions conveyed by the hallucinations are consistent with the patient's emotional state [19]. The patient feels worthless and the voices confirm this by telling the patient how worthless he is, that everyone hates him, that he is ugly, stupid, etc. When the patient is sad the voices suggest suicide. Only occasionally do the voices 'command' some behavior. In PD patients, as in neurological disorders in which hallucinations occur, the hallucinations tend to be visual and nonemotional. PDP patients do not have delusions of grandeur [12].

PDP is an important problem in PD because of its severe impact on quality of life, and because it is a common precipitant for nursing home placement [15,16]. It is also a herald feature or possibly even an overt manifestation of dementia. The phenomenology of psychosis in PD is exactly the same as that seen in dementia with Lewy bodies [20-22].

In approaching treatment one should take into account whether the psychosis developed with the introduction of a new medication or an increase in an old one. The approach then would be to reverse the recent medication increase. A second issue to consider is whether or not the patient has insight into the psychosis, understanding that the problem is drug related. These patients, and those who are not demented generally have a much better prognosis.

The general approach to its treatment is to reduce contributing factors, if they can be found: infection, metabolic derangements, non-PD-related psychoactive medications, environmental changes [18]. Then the PD medications are reduced, if possible, starting with anticholinergics, amantadine, MAO-b inhibitors, dopamine agonists and then L-Dopa [18]. This order has not been studied and there are no data to support this order of preference. My own recommendation is to eliminate as many medications as possible, rather than maintaining several at lower levels. I believe that polypharmacy at low doses is less tolerable than fewer drugs, albeit at higher doses. This in an opinion and there is no data to support this recommendation.

Once the decision has been made to treat the psychosis, the American Academy of Neurology task force only suggests considering use of quetiapine or clozapine. Clozapine's use is supported by two double-blind, placebocontrolled, multicenter trials demonstrating that it is safe and very effective [23,24]. Longterm follow-up also supports the usefulness of clozapine for PDP [25]. Unfortunately the low doses required, starting at 6.25 mg once daily (in contrast to the doses in schizophrenia of 200-900 mg/day) may still cause agranulocytosis so that weekly monitoring of the white blood cell count is still required for the first 6 months [26]. The data on quetipine are difficult to understand. Three double-blind, placebo-controlled trials found the drug to be safe but ineffective [27] but several open-label studies reported it both safe and effective [28].

The symptoms of PDP are identical to the psychotic symptoms experienced by patients with dementia with Lewy bodies [29] suggesting that they might be treated with cholinesterase inhibitors. The problem with this approach is that there is no data other than case report material to support it, and that the benefits, if they occur, may take 6–8 weeks to occur whereas the antipsychotics usually take effect within days [30-35].

Not all patients respond to antipsychotics [36], as was true for Mr C and many cannot tolerate their sedative or orthostatic hypotensive side effects. Cholinesterase inhibitors may be tried on these patients, and, if the problem is intolerable, ECT may be offered. ECT has been used to great effect in severely depressed PD patients, as well as in occasional patients with PDP [37-39]. Many physicians are unaware that ECT frequently produces a dramatic improvement in motor function, in addition to its effects on psychiatric problems. This improvement may last days to weeks, and although it is never long lasting, its benefits in the short run can be very gratifying, helping to get the patient and family over the recent decline in quality of life associated with the psychotic episode.

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