Psychosis in Parkinson’s disease

Parkinson’s Disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s Disease. Most of the earlier breakthroughs in treating the illness focused on the motor manifestations but in recent years, there has been an increasing awareness of the non-motor complications of the disease. Psychotic phenomena are common and their presence leads to significant morbidity. The onset of psychosis is usually in advanced disease, indicates a poorer prognosis and places a great deal of burden on carers and patients alike. PD psychosis (PDPsy) is a complex clinical entity, with many potential hazards in its management, but it is possible to achieve positive clinical outcomes.

Dr Brett Metelerkamp* Associate Specialist in Old Age Psychiatry, Sevenoaks Older People’s Mental Health Services, Sevenoaks, Kent TN13 3PG
Dr David Tang FT2 Trainee Sevenoaks Older People’s Mental Health Services, Sevenoaks, Kent TN13 3PG
*email brett.metelerkamp@kmpt.nhs.uk

Parkinson’s Disease (PD) is no longer considered a pure motor disorder, as more attention is being paid to the neuropsychiatric manifestations of the illness. While the three cardinal motor symptoms of PD (resting tremor, bradykinesia and rigidity) dominate the clinical picture, there are a variety of cognitive, behavioural, emotional and autonomic features that can cause significant morbidity.

Psychosis is common in PD affecting nearly one third of patients, particularly in its later stages.1 Its presence indicates a poorer prognosis.2 Symptoms of psychosis in PD are a strong predictor of whether or not the patient will be placed in a nursing home3 and also represent a greater stressor than physical symptoms do for carers.4

PD psychosis (PDPsy) has unique clinical features, namely that it arises within a context of a clear sensorium and retained insight, there is relative prominence of visual hallucinations, and progression occurs over time. The psychotic symptoms range from comparatively minor illusions, vivid dreams, and occasional, non-disturbing visual hallucinations to frank psychosis with disturbing visual (and rarely, auditory and tactile) hallucinations, and paranoid delusions that can be distressing and lead to significant behavioural disturbances.

PDPsy poses a management challenge because of potentially catastrophic consequences for the patient and carers, lack of universally effective and safe drugs, and the progressive nature of this complication.3 In this article, we review the condition.

**Parkinsonism**

The term parkinsonism is used for symptoms of tremor, stiffness, and slowing of movement caused by loss of dopamine. PD is the synonym of “primary parkinsonism”, i.e., isolated parkinsonism due to a neurodegenerative process without any secondary systemic cause. It is possible for a patient to be initially diagnosed with PD but then to develop additional features, requiring revision of the diagnosis.

PD is, therefore, one of the conditions under the umbrella term of parkinsonism. Other causes of parkinsonism include disorders that are called Parkinson-plus diseases (such as multiple system atrophy or progressive supranuclear palsy).

There are less common causes of parkinsonism including genetic, toxins, head trauma, cerebral anoxia, and drug-induced Parkinson’s disease that are often referred to as secondary parkinsonism.

The relationship between PD, Parkinson’s disease with dementia (PDD), and dementia with lewy bodies (DLB) might be most accurately conceptualised as a spectrum, with a discrete area of overlap between each of the three disorders. It is particularly important to consider DLB as a cause of parkinsonism as these patients can have a catastrophic reaction to antipsychotics.
The complex pathophysiology of PDPsy is known to involve an interaction between extrinsic, drug-related and intrinsic, disease-related components. PDPsy has a well-characterised temporal and clinical profile of hallucinations and delusions, which is different from the pattern seen in other psychotic disorders such as substance induced psychosis or schizophrenia. Medications used to treat PD certainly contribute to PDPsy but may not be the only factors. There is some debate as to whether psychosis is present at the pre-treatment stage. PDPsy is associated with Lewy Body pathology, imbalances of monoaminergic neurotransmitters, and visuospatial processing deficits. These findings suggest that PDPsy may result from progression of the disease process underlying PD, rather than a comorbid psychiatric disorder or drug intoxication.6

Old age, cognitive impairment, history of depression, and sleep disorders are also important risk factors for the development of PDPsy.7 The most important extrinsic factor is use of dopaminergic medication, which plays a prominent role. Dopamine is known to play a key role in the development of hallucinations in other conditions such as schizophrenia, where hyperactivity in the dopaminergic neurons of the limbic system and cortical system is thought to lead to psychosis. The two front line dopaminergic medications used to treat PD, L-Dopa and dopamine agonists, have both been associated with psychosis.8 Randomised controlled trials has revealed that psychosis occurs more commonly with dopamine agonists than with L-Dopa.9

Research has demonstrated that cholinergic neurons show significant breakdown in PD.10 In both PD with dementia and DLB, there is a lack of cholinergic neurons as well as Lewy Body pathology. One study combines this association with the occurrence of psychosis in both of these conditions.11 This could explain the sometimes dramatic improvement in symptoms when treatment is initiated with an acetylcholinesterase inhibitor.

Serotonin too has been posited to potentially play a part in the development of psychosis. The alleviation of psychotic symptoms in patients treated with ondansetron (a 5-HT3 antagonist) and atypical antipsychotics (with their mixed block on serotonin and dopamine receptors) adds weight to this belief.12 The balance of serotonin and dopamine too has been thought to play a role in the development of psychosis.13-15

Presentation of psychosis

Patients with psychotic disorders associated with parkinsonism fall into two groups. One group typically experiences mild visual perceptual changes (eg, sensation of a presence or a sideways passage) or visual illusions or visual hallucinations only, although auditory hallucinations and, more rarely, olfactory and tactile hallucinations can also occur.16 Visual hallucinations are typically well-formed animal or human figures and are stereotyped for each patient. PD patients with this type of psychosis typically retain insight into the hallucinations, do not find them troubling (and sometimes do not even report the symptoms), and may not require treatment (ie, “benign hallucinosis”).

The other group, typically PD patients with dementia and the majority of DLB patients, experience complex psychotic symptoms, including both hallucinations and systematised persecutory delusions in the context of dementia, sometimes complicated by delirium.17 In a comparative study of PD with dementia and DLB,18 the most common delusions in both disorders were of persecution and theft, phantom boarders, television characters in the room, and spousal infidelity; only patients with DLB experienced Capgras’ syndrome (delusional misidentification syndrome). These patients typically do not have insight into their psychosis, often find their hallucinations frightening, may display behavioural changes (including “sundowning” and other forms of agitation), and typically require treatment.

The timing of the onset of the psychotic symptoms is important in deciding whether or not the patient is suffering from true idiopathic PDPsy. Drug induced hallucinations usually occur after several months or years into the treatment process. If hallucinations become apparent shortly after the initiation of dopaminergic medication, then conditions other than idiopathic PD need to be considered, with DLB high on the list of differentials. Distinguishing DLB from PDPsy may be important because of potential differences in prognosis and treatment planning.
**Hallucinations**

Common hallucinations in PD include:

- **Visual-complex**: usually vivid well-formed figures in full-colour, often of people, animals, or objects, sometimes in groups and possibly moving about; may be normal in size or miniaturised; figures may be familiar or strangers. Visions are usually silent and non-threatening, but not always; patients may have affiliated secondary delusions (examples are children standing at the foot of the bed, men chopping trees in the yard, or a deceased pet lying on the sofa).
- **Presence**: vivid sensation or perception of a person or animal somewhere in the room, including behind the patient, but when they turn, “nothing is there”
- ** Passage**: brief visions of a person, animal, or shadow that passes sideways in the peripheral visual fields
- **Illusions**: sensory distortions or transformations of actual objects (and, thus, not technically hallucinations). A stick looks like a snake, or a bush looks like a lurking person
- **Auditory**: can involve voices talking, commands, hearing one’s name called, music, or indistinguishable whispering; may or may not be related to visual hallucinations.

**Delusions**

Delusions in PD are usually of a paranoid nature. Paranoid ideation can be non-specific, especially when dementia is severe. More frequently, patients have well-systematised ideas that focus on a single theme. Patients describe delusions of jealousy or spousal infidelity, fears of being poisoned, elaborate schemes about people (sometimes including their physicians) who conspire against them, somatic delusions, and delusions of control that others commit actions that aggravate their motor symptoms.

**Treatment**

Initial treatment should be a review of antiparkinsonian medication, with a reduction in medication if possible. Failing that, several atypical antipsychotic agents (eg, clozapine, olanzapine) have been shown to be efficacious in reducing psychotic symptoms in PD. If an antipsychotic is necessary, then care should be taken in selecting the most appropriate therapy.

The general strategies in the management of psychosis in PD are:

- At the onset of hallucinations, a thorough screen for causes of delirium, medication overdose, electrolyte imbalance or other physical illness, should be performed
- Consider a reduction in the antiparkinsonian medication. Initially try a reduction of the most recently added medication. A suggested order of removing/reducing medications is:
  1. Stop drug most recently started
  2. Reduce and stop anticholinergics
  3. Reduce and stop dopamine agonists
  4. Reduce and stop COMT inhibitors
  5. Reduce and stop MAOB inhibitors
  6. Reduce L-dopa

This can be a slow process as patients need to be carefully monitored for worsening motor symptoms.
- Reducing the sensory input of the patient yet at the same time not causing any sensory deprivation. The patient should be nursed in a quiet side room and the room should feature furniture that is not excessively patterned.
- Encourage a multidisciplinary team approach in the ongoing management of the patient. Involving the patient, next of kin, carer(s), physician, liaison psychiatrist and social worker is key in optimising patients’ outcome
- Treatment of psychiatric comorbidities (ie, depression and anxiety) may reduce morbidity to patients, carers and next of kin
- As previously mentioned, visual hallucinations where the patient retains insight need not be treated.

**Antipsychotics**

Antipsychotics are indicated when other efforts to treat psychosis or agitation have failed, or if antiparkinsonian medications cannot be reduced without sacrificing motor function. Apart from the usual precautions when prescribing antipsychotics, Neuroleptic Malignant Syndrome (NMS) is an important complication to consider. The usual signs of NMS, rigidity, altered consciousness, elevated creatine kinase, hyperpyrexia, and autonomic instability, can be difficult to identify in PD patients with psychosis and acute agitation, who have some of these symptoms at baseline, especially if there is an intercurrent infection.
Typical antipsychotics are not recommended for the treatment of PDPs due to their significant side-effects.

Clozapine is currently the gold standard of antipsychotic agents in PD given its demonstrated safety and efficacy in controlled trials without worsening parkinsonian symptoms.\textsuperscript{21-23}

It is classed as an atypical antipsychotic medication as it binds to serotonergic as well as dopaminergic receptors. It is licensed for the treatment of psychosis in PD, but registration with a mandatory monitoring scheme is required. It is recognised that few specialists caring for people with PD have experience with clozapine.\textsuperscript{24}

In two randomised, double-blinded studies, clozapine was shown to be significantly superior to placebo in the treatment of psychosis in patients with PD. In one study,\textsuperscript{22} clozapine did not worsen motor function and actually decreased tremor. In the other,\textsuperscript{21} one third of the trial patients benefited from increases of levodopa or dopamine agonists, without concomitant increases in clozapine doses. Other studies show clozapine to outperform placebo in reducing the positive symptoms of psychosis.\textsuperscript{22,25}

One paper,\textsuperscript{26} however, suggested the worsening of motor functioning as the dose of clozapine increased; this was the first double blind trial and its authors “treated the patients as if they were young schizophrenic patients, beginning with clozapine 25 mg a day and increasing by 25 mg a day.”\textsuperscript{27} The results of this study were greatly increased sedation, manifested as worsening parkinsonism. This suggests that patients should be started on low doses (eg, 625 mg), with gradual increments. Evidence also exists for clozapine having additional benefits in patients who develop dyskinesias as a complication of PD.\textsuperscript{28}

Agranulocytosis is a well documented, life-threatening side effect of clozapine. This side effect is dose independent, which means that the effect can be triggered by the smallest to the highest doses. To date, there have been no deaths attributable to agranulocytosis in any of the trials involving clozapine treatment in patients with PD psychosis.\textsuperscript{27}

One retrospective analysis of 39 parkinsonian patients on clozapine for a mean duration of 60 months showed 85% with continued partial/good response and 13% with complete resolution of psychosis on clozapine.\textsuperscript{29} Thirteen of the 39 patients (33%) were eventually admitted to nursing homes. Six of them (46%) died over a period of five years—a significant improvement over previously reported two-year mortality rates approaching 100% among nursing home residents with PD and psychosis.\textsuperscript{30} The overall five-year mortality rate in this cohort was 44% (17/39).

Olanzapine is an atypical antipsychotic that is chemically related to clozapine. Initial reports showed that olanzapine was able to treat psychosis in non-demented patients without any worsening in motor function.\textsuperscript{31} Unfortunately meta-analysis of several further studies into the use of olanzapine in such a setting did in fact show motor worsening in 40% of patients.\textsuperscript{32}

In addition to that, a 15-patient double-blinded study comparing low dose clozapine to low dose, olanzapine needed to be stopped due to six of the seven olanzapine treated patients developing motor dysfunction while no worsening was noted in the clozapine group.\textsuperscript{33} In another study that involved non-psychotic patients, olanzapine was shown to exacerbate pre-existent dyskinesias as caused by dopaminergic medication.\textsuperscript{34}

Risperidone is another atypical antipsychotic that is known to cause dose related problems, such as acute dystonia and hyperprolactinaemia. The majority of studies that include risperidone are open label. 33% of patients in an 82-patient meta-analysis were shown to report worsening of their motor symptoms while taking risperidone.\textsuperscript{35} The one double blinded study to compare low dose risperidone to low dose clozapine showed that in a population of 12 patients, three (two clozapine and one risperidone) patients dropped out and that parkinsonism worsened in one clozapine patient in comparison with three risperidone patients. The data available suggests that risperidone is more likely to induce motor side effects than clozapine as well having an indifferent effect on the psychosis.\textsuperscript{36}

Quetiapine is another drug in the same class that is also the closest structurally to clozapine, yet without inducing the agranulocytic side effect of clozapine. The amount of data concerning its use in PD patients exhibiting psychotic symptoms is less flattering, with only one unpublished double blinded study of 30 patients showing little to no difference to placebo.\textsuperscript{37} One large (106 patient) long-term study at a single centre did, however, show that 82% of patients showed partial or total resolution of their psychotic symptoms. 32% patients reported motor worsening,
but not to the degree that the study was in danger of being stopped. It was also reported that it was the more demented patients that tended to display symptoms of motor worsening. In comparison to clozapine then, quetiapine may lead to mild motor worsening; in comparison to olanzapine and risperidone, any motor worsening that did occur was to a lesser extent — no trials needed to be stopped in light of patient safety and psychosis responded better. Quetiapine is thought to be relatively safe and does not require haematological monitoring. As a result, quetiapine has been widely used in PD psychosis.

Both ziprasidone and aripiprazole have been shown to be superior to placebo in terms of reducing psychotic features. However, they do have an increased incidence of unwanted side effects, which generally restricts their use.38

Acetylcholinesterase inhibitors
These are agents used primarily in the treatment of dementing conditions, such as Alzheimer’s and PD Dementia. There is some evidence to suggest they may have a role in PD psychosis without dementia.

Donepezil has been trialled in several small studies. An open label study with eight non-dementing patients experiencing hallucinations with or without delusions demonstrated a significant decrease in psychotic symptoms.39 Two of the eight patients experienced worsening of their motor function. In a different study,40 five of six patients with PD psychosis demonstrated a moderate improvement in symptoms with no motor worsening. Two placebo-controlled studies with donepezil have been published, demonstrating either no difference on effects on psychosis or differences that are not statistically significant.41,42

Evidence for the use of rivastigmine in PD psychosis arrived in 2006 when a double blind placebo study that involved 188 hallucinating and 348 non-hallucinating patients with PD dementia was published.43 Patients experiencing hallucinations improved significantly overall as well as experiencing a greater therapeutic benefit than non-hallucinating patients.

ECT
It appears that ECT may be useful in reducing psychotic symptoms in PD, particularly when there is concurrent depression and/or pharmacological therapies have been unsuccessful. It should be used with caution due to the possible negative effects on cognition.38

Conclusion
In the treatment of PD, it is important to identify the cause of the movement disorder to begin with, as this will prompt optimal treatment. Once idiopathic PD has been identified, prolonged treatment with dopaminomimetic or dopamine agonist medication may lead to patients reporting symptoms of psychosis. However, psychosis may also be a part of the disease process inherent in PD. It is necessary to detail the natural history of the hallucinations and to trial the withdrawal of medication in order to uncover the cause of those symptoms. In patients with ongoing psychotic symptoms, clozapine has been shown to be both efficacious and safe to use under monitored conditions, as well as performing better against both placebo and other medications in its class. Agranulocytosis, the recognised and potentially life threatening side effect of Clozapine, has not been noted in any of the literature regarding its use in PDPsy.

Conflict of interest: none declared

References
9. Parkinson Study Group: Pramipexole vs levodopa as initial treatment for Parkinson disease: a
randomized controlled trial. *JAMA* 2000; 284: 1931–38