

# Neuropsychiatric features of Parkinson's disease

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**ABSTRACT** Parkinson's disease is a chronic, progressive, neurodegenerative condition that damages central nervous system pathways. In addition to the well-recognised motor features of the disease, patients commonly experience non-motor symptoms including neuropsychiatric complications. These symptoms may precede motor symptoms and have a very significant impact on quality of life for patients and their carers.

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## DEPRESSION

Depression is common in Parkinson's disease (PD), affecting around 35% of patients during the course of their disease, and may predate motor symptoms. Diagnosis of mild depression in PD can be challenging as clinical features may overlap with motor features.<sup>1,2</sup> (See also R Smyth, Depression in physical illness, p. 337.)

Cohort studies have demonstrated that the Beck Depression Inventory and the Hamilton Depression Rating Scale are useful screening tools for depression in PD.<sup>2</sup>

Treatment for depression in PD is controversial, with only limited evidence from small trials available for all treatment modalities. NICE guidelines published in 2006 state that there is insufficient data to confirm the efficacy or safety of any intervention for depression in PD, with only small underpowered trials published to date. Since the publication of these guidelines no conclusive randomised controlled trial (RCT) has been published, with the largest RCT to date (52 patients) suggesting that nortriptyline may be superior to both paroxetine and placebo. This trial has also suggested that tricyclic antidepressants may be better tolerated than previously thought.<sup>3</sup>

Electroconvulsive therapy can be considered in severe depression and may improve both depressive and motor features; however, intratreatment delirium may occur.<sup>4</sup>

In the absence of conclusive data from RCTs the choice of antidepressant should be made on an individualised basis, considering the drug's pharmacological profile, patient's co-morbidities, symptoms and potential drug interactions.

## ANXIETY

Anxiety is common in PD and affects up to 40% of patients.<sup>5</sup> The aetiology of anxiety in PD is poorly understood. Panic attacks are commonly associated. Anxiety may present prior to the motor features of the disease and is also associated with the neurotransmitter deficits seen in PD.<sup>5</sup>

Given this, it is unlikely that anxiety is a purely reactive phenomenon following diagnosis. Severe anxiety may accompany 'off' periods in advanced disease, but this is not a consistent finding.<sup>5</sup> There is no good trial evidence to suggest which treatments are effective for anxiety in PD.<sup>1,5</sup> In those with anxiety associated with 'off' periods dopaminergic medications should be optimised. A trial of anxiolytic agents such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants may be attempted. Short courses of benzodiazepines may relieve symptoms but are associated with sedation and falls. Psychological treatments may be used; again, little evidence exists to support this strategy.<sup>5</sup>

## PSYCHOSIS

Psychosis is a frequent problem in patients with PD, affecting up to 40% at some point in the disease.<sup>6</sup> Visual hallucinations are the most common psychotic symptom seen, with both minor (presence and passage hallucinations) and major formed hallucinations being common.<sup>6</sup> Auditory hallucinations and delusions (commonly paranoid or persecutory) occur less frequently.<sup>1,6</sup> Psychosis may occur at any stage of the disease. The pathophysiology is complex and multi-factorial,<sup>1,6</sup> with severe cognitive impairment, daytime somnolence and increasing duration of disease being strongly predictive of its development.<sup>6</sup> Other associations include dopaminergic medications, depression and visual problems.<sup>6</sup> At present there is no validated screening tool for psychosis in PD; the Parkinson Psychosis Rating Scale may be helpful but has not yet been validated.<sup>2</sup>

New onset of psychosis in PD should prompt a search for a precipitant such as intercurrent infection or the addition of new medications. Medications that are more likely to cause psychosis, such as dopamine agonists and anticholinergics, should be reduced or withdrawn where possible. Levodopa is the agent least likely to cause psychosis.<sup>1</sup> Patients should undergo cognitive assessment as PD dementia may present with psychosis. Where psychotic symptoms are severe or poorly tolerated, antipsychotic drug therapy may be considered. The older

typical antipsychotics (phenothiazines and butyrophenones) exacerbate the motor features of PD and should not be used. The atypical antipsychotic clozapine has been shown in randomised trials to reduce the psychotic symptoms of PD without worsening motor features, and is the treatment of choice.<sup>1,2</sup> However, the use of clozapine is limited due to the risk of potentially fatal agranulocytosis requiring mandatory registration with the clozapine patient monitoring scheme and stringent blood count monitoring.<sup>1</sup> Quetiapine does not require monitoring and as such is used by many physicians prior to clozapine; however, the evidence for its effectiveness is less robust.<sup>1,2</sup>

The limited evidence available suggests that olanzapine does not improve psychosis, worsens the motor features of PD<sup>1,2</sup> and should be avoided. In the context of PD dementia, cholinesterase inhibitors are effective in treating psychotic symptoms (see below).<sup>7</sup>

## DEMENTIA

Dementia is common in PD, with 20–50% of patients developing cognitive impairment during the course of the condition.<sup>8</sup> The pathogenesis of Parkinson's disease dementia (PDD) is not fully understood, with deficits in multiple neurotransmitter systems, including dopaminergic, cholinergic, serotonergic and noradrenergic transmitters. In addition, cortical Lewy bodies have been implicated.<sup>8</sup> Psychotic features, especially visual hallucinations, often accompany PDD, with PDD being strongly predictive for the development of psychosis.<sup>6</sup>

Diagnostic criteria for PDD have been suggested but await validation. Currently, generic criteria such as the American Psychiatric Association DSM-IV 'dementia due to other general medical conditions' criteria are used for research purposes but, again, are not validated.

The Mini Mental State Examination (MMSE) and the Cambridge Cognitive Examination (CAMCog) are useful screening tools for PDD. Both display similar sensitivity (98% and 95% respectively) in identifying dementia as defined by the DSM-IV criteria.<sup>2</sup> The CAMCog also includes additional domains of cognition.<sup>2</sup> The executive clock drawing task CLOX-I may be a more sensitive test of subcortical dementia seen in PD.

Management should initially involve investigation for reversible causes of cognitive decline and the cessation of medications known to have deleterious effects on cognition, such as anticholinergic agents.

The dual cholinesterase inhibitor rivastigmine has been shown in a RCT of 541 PDD patients to produce moderate improvements in cognition across a number of outcome measures when compared with placebo. Rivastigmine also significantly improved non-cognitive neuropsychiatric parameters, including delusions and

hallucinations. Adverse effects were not uncommon with significant increases in nausea (29%), vomiting (16.6%) and tremor (10.2%) in the rivastigmine group.<sup>7</sup> Current guidelines support the use of rivastigmine in PDD.<sup>1,2</sup>

## SLEEP DISORDERS

Some form of sleep disorder affects almost all PD patients. Advice regarding good sleep hygiene should be given to all PD patients with sleep disorders.<sup>1</sup> Rapid eye movement behaviour disorder (RBD) affects up to 33% of PD patients. It may precede the onset of motor symptoms and is associated with an increased risk of developing PD.<sup>9</sup> Rapid eye movement behaviour disorder is characterised by the loss of skeletal muscle atonia during rapid eye movement (REM) sleep. During REM sleep, patients act out their dreams with abnormal vocalisations and movements, including flailing of limbs and combative gestures. No RCTs investigating the treatment of RBD have been published. The patient's sleeping environment should be made as safe as possible. Two large case series have shown clonazepam to be effective in approximately 90% of cases, with good tolerability.<sup>10</sup> Smaller case studies have suggested that melatonin may be a therapeutic option in patients with contraindications (cognitive impairment, sleep apnoea, increased falls risk), or in those who develop tolerance, to clonazepam.<sup>10</sup>

Several studies have shown daytime hypersomnolence to be common in PD.<sup>11</sup> A combination of the neurodegeneration seen in PD, poor nocturnal sleep, depression and dopaminergic medications are likely causes.<sup>11</sup> Initial treatment should include good sleep hygiene and the withdrawal or reduction (if possible) of offending medications. Depression should be screened for and treated. Small RCTs have suggested that the centrally acting agent modafinil may be useful in treating hypersomnolence in PD.<sup>11</sup> Where hypersomnolence is secondary to dopamine agonists, the use of modafinil may allow continuation of the agonist.<sup>11</sup>

Sudden onset of sleep has been described in PD patients and has controversially been attributed as the cause of road accidents. Initially, dopamine agonists were incriminated as the cause. However, it is now thought that all dopaminergic PD medications can cause sudden onset of sleep.<sup>1</sup> All patients should be warned about falling asleep while driving, particularly those undergoing up-titration with dopamine agonists.<sup>1</sup>

## IMPULSE CONTROL DISORDERS

The dopaminergic system (particularly D2 receptors and the mesolimbic pathway) is implicated in numerous addictions and impulse control disorders. Dopamine deficiency and replacement in PD may result in a predisposition to develop addictive behaviour. Severe dopamine addiction (dopamine dysregulation syndrome

– DDS) in PD is well described and may affect up to 4% of patients.<sup>12</sup> Dopamine dysregulation syndrome consists of excessive levodopa seeking, hoarding and self-medication associated with pathological changes in mood and behaviour. These changes include pathological gambling, punding (a compulsive fascination with and performance of repetitive, mechanical tasks), hypersexuality, aggression and social isolation.<sup>12</sup> Dopamine depletion in PD may disrupt pathways between the striatum and the prefrontal cortex, altering reward and decision-making systems, thereby predisposing to DDS.<sup>12</sup> Treatment involves gradual withdrawal of dopaminergic medications to acceptable levels and the avoidance of rapid-acting preparations such as dispersible levodopa.<sup>12</sup>

Pathological gambling affects around 3.4% of patients with PD, increasing to 7.2% of patients taking dopamine agonists, compared with an incidence of 1% in the general population.<sup>13</sup> All dopamine agonists have been implicated, with cases also being reported in patients taking levodopa.<sup>13</sup> Many PD patients are secretive concerning their gambling habits and incur large debts before the condition is identified.<sup>13</sup> Patients commencing dopamine agonists should be warned of the risks of pathological gambling and should be tactfully monitored for the development of the condition.

Hypersexuality and sexual deviation can complicate the use of dopamine agonists, often in patients without a previous history of psychiatric or cognitive problems.<sup>14</sup> If possible, the dopamine agonist should be withdrawn.

## CONCLUSION

Neuropsychiatric complications are common in Parkinson's disease and are often less well recognised than the motor features of the disease. Neuropsychiatric

complications have major implications for the quality of life of both patients and carers. Several neurotransmitter deficits are implicated in the development of these complications. Dopaminergic medications may worsen the symptoms of psychosis, sleep disorders and impulse control disorders. Depression is common; however, the evidence to support the use of any particular class of antidepressant is limited. Psychosis occurs most frequently in the form of visual hallucinations; clozapine is the pharmacological treatment of choice. Sleep disorders are almost universal and may precede motor symptoms. Further research is required to establish the most effective treatments for many of these common complications.

## KEY POINTS

- Neuropsychiatric problems are common in Parkinson's disease and have major implications for patients' and carers' quality of life.
- Deficits in numerous neurotransmitter systems are implicated in the aetiology of neuropsychiatric features.
- Dopaminergic medications may precipitate psychosis, sleep and impulse control disorders.
- Depression is common, and the evidence for antidepressant treatment is limited.
- Psychosis (especially visual hallucinations) occurs frequently. Clozapine is the pharmacological agent of choice; quetiapine is also widely used.
- Cognitive impairment occurs in up to 80% of patients with Parkinson's disease.
- The cholinesterase inhibitor rivastigmine can improve cognitive and non-cognitive features of Parkinson's disease dementia.
- Sleep disorders are almost universal at some point during the course of the condition.

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