Neuropsychiatric symptoms in Parkinson’s disease

Neuropsychiatric symptoms in Parkinson’s disease are now known to be very prevalent and greatly impact on patients’ quality of life

PARKINSON’S DISEASE (PD) is one of the most common neurodegenerative diseases, the motor symptoms of which are well recognised.1 Even as recently as 1986, it was considered to affect mainly the motor system,2 and it was these symptoms that all treatments had been aimed to address. It is characterised by low mood and anhedonia, but may be accompanied by loss of appetite, loss of libido, psychomotor retardation and impaired concentration, memory loss, fatigue and difficulty sleeping; many of these features, however, are associated with PD in their own right and therefore diagnosis of depression in a PD setting can be tricky.1,5

Non-motor symptoms, however (occurring in up to 88% of patients with PD3), have now been well documented, and it has also been shown that these symptoms may go under-recognised and, as a result, under-treated.2 These include autonomic and sensory dysfunction and neuropsychiatric symptoms. The impact that these symptoms can have on a patient’s quality of life is now increasingly appreciated.

The presence of neuropsychiatric symptoms can make it more difficult for a carer to look after a patient with PD: in particular apathy, depression and impulsive compulsive behaviours (ICBs), as they tend to need more support.4 Examined here are the neuropsychiatric aspects of PD, such as depression, anxiety, apathy, fatigue, hallucinations, cognitive impairment, sleep disturbances and ICBs. Prevalence of these symptoms in PD and possible management options are looked at as the identification and management of these form an important part of overall treatment of PD.

Depression

Depression is one of the most common neuropsychiatric symptoms experienced by PD patients. It has been estimated that symptoms of depression affect 30-40% of patients with PD,3 and that it may even be present in as many as 76% of patients.1 The fact that there is an increased prevalence of depression in PD compared with other populations with chronic disease, has led to the theory that there may be additional endogenous causes connected to the disease process, rather than solely a reactive depression, i.e. a responsive reaction to having a chronic condition.1,2

Depression is associated with a significant negative impact on health-related quality of life in patients with PD and with greater disability.6,7 It is characterised by low mood and anhedonia, but may be accompanied by loss of appetite, low libido, psychomotor retardation and impaired concentration, memory loss, fatigue and difficulty sleeping; many of these features, however, are associated with PD in their own right and therefore diagnosis of depression in a PD setting can be tricky.1,5

Depression may pre-date the motor symptoms of PD.7,8 Depletion of dopamine has been linked to the early changes in mood and in cognition, as well as to the motor symptoms.9 It can be difficult to distinguish which symptoms are related to depression, and which are features of the PD.1 Furthermore, depression in a patient with PD may have different features to idiopathic depression: PD patients may experience fewer feelings of guilt, failure and worthlessness but may have heightened anxiety or pessimism, for example.1,5

When assessing a PD patient for depression, the patient’s family or caregiver should be involved, as in some cases the patient themselves won’t realise they are depressed or don’t report symptoms of depression.8 It is also important to establish if the symptoms of depression or anxiety are occurring in ‘off’ periods, where the effects of the patient’s dopamine replacement therapy are wearing off: if this is the case then an adjustment of their dopaminergic medication may improve the symptoms.5 If this is not the case, the severity of the depression or anxiety should be assessed and treated, either with non-pharmacological interventions in the case of mild depression, such as counselling or cognitive behavioural therapy, or pharmacological treatment may need to be considered.5

In terms of medications, the selective serotonin reuptake inhibitors (SSRIs) are the most commonly used to treat depression in PD, despite the fact that there has generally been insufficient evidence to support the use of citalopram, sertraline, fluoxetine or fluvoxamine.6,10 They are, however, known to be the best tolerated.7 Other options include the tricyclic antidepressants (TCAs), where there is some evidence supporting nortriptyline and desipramine,10 but their use tends to be limited due to their anticholinergic side-effects, which can worsen cognitive function or orthostatic hypotension.1,7

A small amount of data has been published suggesting that the dopamine agonist pramipexole may be useful,10 and possibly also ropinirole.1 These are both used to treat motor symptoms but may also exert an antidepressant action.8 Trazodone (a sedating tricyclic-related antidepressant), venlafaxine (a serotonin-noradrenaline reuptake inhibitor; SNRI) and mirtazapine (sedating pre-synaptic α2-receptor antagonist) have also been used.3 These, as well as duloxetine or bupropion, may be options where the patient doesn’t respond, or achieved only a partial response, to an SSRI.7

Apathy

Although commonly a feature of depression, apathy can also occur in its absence. The patient typically will have reduced motivation and display indifference and lack of...
initiative and therefore tend to be withdrawn and lacking in the ability to engage or participate in normal daily activities, which can often be misinterpreted by others as laziness. It can be very difficult to discern between depression and apathy and PD patients with apathy can also be over-diagnosed with depression. Methylphenidate may be an option for treatment of apathy but, again, robust evidence is lacking. Fatigue

Fatigue is also reported by up to a third of PD patients, and its impact is often under-rated, apart from by the patient themselves. Although it may be a symptom related to depression, and it can therefore be virtually impossible to distinguish fatigue in its own right from being a feature of a different pathology, it is also commonly reported in PD patients who are not depressed. It is characterised by either a mental or physical tiredness or lack of energy. Again, it can even be an issue prior to the patient having a diagnosis of PD and management of fatigue can be extremely challenging, as generally it doesn’t respond well to dopamine therapies. Both methylphenidate and modafinil have been investigated for the treatment of the fatigue associated with PD in very small trials, but both (particularly methylphenidate) have the potential to induce psychiatric side-effects.

Anxiety

Anxiety is thought to affect up to 40% of patients with PD, either in the form of panic attacks (which can be associated with “off” periods), generalised anxiety disorder, phobias or obsessive compulsive disorders. Anxiety, as well as depression, can in fact occur several years in advance of the motor symptoms. It is recommended that patients with PD be screened for anxiety disorders.

Despite the fact that supportive evidence is lacking, SSRIs are often used for the management of anxiety disorders in PD as benzodiazepines are known to increase the risk of falls, cause drowsiness and fatigue, and have adverse effects on cognitive and autonomic function. SSRIs that are used for anxiety in the general population include paroxetine, escitalopram and venlafaxine, and their use is being extended to PD patients. Due to their side-effects, benzodiazepines should be reserved for more severe cases of anxiety.

Cognitive impairment

Risk factors for cognitive impairment in PD include advancing age, male sex, hallucinations, trouble with speech and swallowing, as well as gastrointestinal or urinary problems. In the long-term, dementia affects approximately 75-80% of PD patients and, of those who do not have dementia, 25% may have some degree of cognitive impairment, even at diagnosis. This may be so slight as to go unnoticed by their families, doctors or even the patients themselves but these patients with mild cognitive impairment have a higher risk of going on to develop dementia, and even mild cognitive impairment has a negative impact on quality of life. The presence of visual hallucinations, apathy and depression are associated with rapid cognitive decline and dementia in PD. The main cause appears to be Lewy body disease, although some have been found to have Alzheimer-type changes. They may have difficulty with planning, decision-making and attention, for example, as well as memory impairment, difficulties with visio-spatial processing and psychomotor speed. Language, however, appears less affected.

Evidence for treatment options in the PD population is again lacking. The first step is to discount other causes of cognitive impairment, such as depression, infection or dehydration, for example. Anticholinergic medications and amantadine used to treat PD can cause confusion and a decline in cognition. If possible without losing control of motor symptoms, doses of anti-Parkinson medications should be decreased or the offending medication eliminated if there is a decline in cognition, starting with anticholinergic medications but including amantadine, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors and monoamine oxidase type B (MAO-B) inhibitors, in that order.

The anticholinesterase inhibitor rivastigmine has been shown to be beneficial, and is licensed for treatment of dementia in PD, but there is not enough evidence base to recommend donepezil or galantamine, though they may be used. Side-effects associated with the anticholinesterases, such as nausea, constipation, exacerbation of tremor and urinary frequency, can be problematic and limit their use; there is conflicting evidence surrounding the use of memantine.

Psychosis

Prior to the introduction of dopamine replacement therapy, psychosis was apparently relatively uncommon in PD, affecting < 10% of patients. However, now it is thought that psychosis may affect up to 50% of the PD population at some stage. Psychotic symptoms include visual hallucinations as the most commonly reported, but there may also be paranoid delusions and thought disorder as well as auditory, tactile and olfactory hallucinations.

Management of such symptoms usually involves discontinuing or reducing dosage of medications and, although it is not evidence-based, a commonly followed procedure is to discontinue or reduce in the following order: anticholinergics first, followed by selegiline, amantadine, dopamine agonists, COMT inhibitors and lastly to reduce levodopa dosage.

The challenge is to avoid loss of control of motor symptoms. This approach is often enough to achieve resolution of psychotic symptoms but occasionally antipsychotics are used, though again they are limited by side-effects and can worsen motor symptoms. Clozapine is the only antipsychotic that has been shown to be effective but requires stringent monitoring of blood count and it is probably for this reason that quetiapine is more frequently prescribed.

The risk of exacerbating motor symptoms with olanzapine or risperidone, for example, is considered too great to justify use in PD.

The main side-effects reported with quetiapine were sedation and hypotension, but all antipsychotics are nonetheless associated with increased mortality and risk of cardiovascular events in elderly patients with dementia. Anticholinesterases may also be beneficial, particularly in dementia or if the psychosis is mild, but onset of action is delayed.

Sleep disorders

Sleep disorders are a huge issue in PD and a common
problem, having been reported in as many as 60% of patients with PD, which is a significantly higher proportion than is associated with other chronic diseases such as diabetes, or when compared to a healthy elderly population. Frequent problems in the elderly population, including difficulty getting to sleep, waking often during the night and early wakening, are even more common in the PD population. Other studies have reported sleep disorder occurring in 40-90% of PD patients and even have been reported as affecting 98% of patients. Sleep disorders may also pre-date the motor symptoms or diagnosis of PD. In some cases, particularly where early morning wakening is the issue, this can be attributed to other symptoms of their PD: for example nocturia, as well as stiffness, ‘off’ dyskinesias, depression, restless leg syndrome and cramps that may disturb sleep. Other features of sleep disturbance in PD include insomnia, terrors, nightmares and REM sleep behaviour disorder, and they are also thought to have more sleep apnoea than the general population. Up to a third of patients rated their sleep disorder as being moderate or severe, with early morning wakening and sleep fragmentation as the most commonly reported problems. Difficulty in the onset of sleep may in some cases be caused either by depression or by RLS, and insomnia in PD is associated with longer disease duration and depression, as well as female sex. Where an underlying cause is identifiable, or indeed the insomnia is the result of an adverse effect of a medication, it should be treated or the offending medication withdrawn as appropriate. Offending medication could include, for example, selective serotonin reuptake inhibitors, which has a stimulant effect. Often dopaminergic medication may need to be adjusted: either a reduction may be helpful where there are dyskinesias or an increase, for example in the setting of RLS or nocturnal akinesia. Use of long-acting dopaminergic therapy may be beneficial if the difficulty sleeping is being caused by loss of control of motor symptoms overnight. Increasing physical activity can aid sleep. Many patients, however, will require further treatment and pharmacological treatments that have been shown to be effective in insomnia in PD include tricyclic antidepressants, which are sedating, or short-term treatment with benzodiazepines – although neither option is limited to the short term as they can exacerbate the motor symptoms of PD, as previously mentioned. Treatment of depression or anxiety can improve sleep. Clonazepam has been used to treat REM sleep behaviour disorder, and melatonin may help to reduce sleep disturbances.

**Impulsive compulsive behaviours (ICBs)**

ICBs in PD include pathological gambling, hypersexuality, compulsive shopping and binge eating, punding and dopamine dysregulation syndrome. Punding is characterised by obsessive collecting or sorting of items, and is often linked to the patient’s occupation. The behavioural changes can be in the setting of compulsive drug-taking, where some patients keep increasing their dopaminergic medications beyond what they need to control their motor symptoms. Such behaviour disorders are associated with dopamine agonist therapy but are also thought to occur in 6% of PD patients not taking dopamine agonists. The prevalence rises to 17% in the population of PD patients that are treated with dopamine agonists (such as pramipexole, ropinirole or rotigotine), although it is thought that these behaviours may go under-reported as people may either not associate them with treatment or be embarrassed to disclose them. Another study reported a correlation between the dose of dopamine agonist prescribed and the development of the pathological compulsive behaviours: a frequency as high as 30% reported in patients taking what they defined as ‘mid-to-high therapeutic doses’ and 24% on ‘at least therapeutic doses’. Although the dopamine agonists are more closely associated with these behavioural disorders, dopamine replacement therapy (DRT) with levodopa is also a risk factor for their development. Other risk factors include younger onset of PD, alcohol addiction, illicit drug use or a family history of addictive behaviour. The association with younger age, however, could be explained by the fact that dopamine agonists are more commonly prescribed for younger patients.

While dopamine replacement therapy with levodopa is thought to act on D1, D2 and D3 receptors, the dopamine agonists, in contrast, have a much stronger affinity for the D3 receptor, which is located largely in the limbic system and so thought to be involved with reward behaviours: the behaviours implicated here are known to be rewarding in moderate amounts but become excessive and pathological in these patients. Another theory is that the mesocorticolimbic pathways in the brain are more preserved in early PD. Dopamine transmission on these pathways is associated with risk-taking behaviour and so pharmacological treatment to increase dopaminergic transmission may cause over-activation here. Furthermore, it is the D3 and D2 receptors that are expressed here. Patients and their families should be warned of the risk of ICBs prior to commencing treatment with dopamine agonists, not least so that family members can be vigilant for any behavioural changes. In the event of ICBs occurring, the dopamine agonist should be withdrawn, and in many cases this results in resolution of the symptoms. Withdrawal effects, however, such as panic attacks or dysphoria, are common. If antipsychotics are used, they should be limited to the short term as they can exacerbate the motor symptoms of PD, as previously mentioned.

**Conclusion**

Neuropsychiatric symptoms in PD, though previously largely unrecognised, are now known to be very prevalent and considered to be a huge factor contributing to the significant impact on patients’ quality of life. Unfortunately, these symptoms can often be difficult to recognise, as there is much overlap between aspects of the disease, and treatment can be even more of a challenge. Medications used offer up their own difficulties and in many cases a convincing evidence base for the treatments widely accepted for use is lacking. It is clear that the population of patients with PD would benefit from further investigation of whether conventionally used treatments in the general population can truly be effectively and safely used in PD.

Pamela Goodbody is a medical student, Patrick Browne is a clinical nurse specialist and Timothy Counihan is a consultant neurologist at University Hospital Galway.