Depression in Parkinson's disease: diagnosis and management

Parkinson's disease has a high prevalence of psychiatric comorbidity including depression. This review highlights the epidemiology, aetiology and diagnosis of depression in patients with Parkinson's disease. Recommendations are made on treatment and a closer partnership between neurology and psychiatry.

Parkinson's disease affects about 120 000 people in the UK and about one million individuals in the United States of America. It usually presents in patients over the age of 65 years; some 5% of cases are in patients who are under the age of 40 years at the time of diagnosis. Psychiatric symptoms are not uncommon in patients with neurological conditions such as Parkinson's disease, Huntington's disease, head injury, cerebrovascular disease, epilepsy and multiple sclerosis. The understanding behind neuropsychiatric symptoms in neurological illnesses is growing. Patients with Parkinson's disease develop non-motor symptoms such as depression, psychosis, dementia and anxiety, all of which cause significant morbidity and carer distress (Jankovic, 2008).

This article highlights the important interface between neurology and psychiatry using depression in Parkinson's disease to illustrate how neuropsychiatric conditions often overlap, and the clinical management challenges that arise as a result. Close liaison between neurologists and psychiatrists is recommended in order to optimize treatment.

Pathology of Parkinson's disease

With an annual prevalence of 1% in the UK population, Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's dementia (Mitchel, 2004). The main pathology is the depletion of dopaminergic neurones in the pars compacta of the substantia nigra: symptoms usually appear when such neurones are reduced by 50–80% (Mitchel, 2004). The posterior part of the putamen is most affected. The remaining neurones characteristically show Lewy bodies. Serotonergic and noradrenergic pathways are also affected, with reduced serotonergic binding sites in the frontal cortex and basal ganglia, and neuronal loss in the noradrenergic cells of the locus caeruleus (Paulus and Jellinger, 1991; Soldani and Fornai, 1999).

Clinically the disease is characterized by muscular rigidity, tremor, bradykinesis and postural instability (Lees et al, 2009). Early in the course of the disease many patients show subtle subcortical deficits (Dunne, 1993). The nucleus basalis of Meynert (part of the basal forebrain) is rich in acetylcholine and in Parkinson's disease this nucleus degenerates. The striatum (caudate nucleus and putamen) also contains cholinergic neurones. When cholinergic excitatory discharge exceeds dopamine inhibition in the striatum parkinsonism results, hence the original rationale of using anticholinergic drugs. These are still used in mild cases and very often in combination with neuroleptic drugs.

Epidemiology of depression

Depending on the setting (inpatient or outpatient *vs* community samples) and the methods used for assessing it (rating scales *vs* diagnostic criteria) it is likely that up to 50% of patients with Parkinson's disease suffer from depression (McDonald et al, 2003), but only 20% receive treatment (Frisina et al, 2008). The result is a reduction in quality of life independent of motor symptoms (Frisina et al, 2008; Lemke, 2008). Although suicide attempts are uncommon in Parkinson's disease, suicidal ideation is high (Kummer et al, 2009), being present in a quarter (Kostić et al, 2010) to one third (Nazem et al, 2008) of patients with Parkinson's disease.

Aetiology and risk factors for depression in Parkinson's disease

Mesolimbic and mesocortical dopaminergic pathways that mediate affect, behaviour and cognition contribute to depression in Parkinson's disease (Lieberman, 2006). Depression in Parkinson's disease is related more to catecholinergic than serotonergic system dysfunction (Frisina et al, 2009). Depressive symptoms can precede motor symptoms in Parkinson's disease by an average of 5 years, suggesting that biological factors are prominent in depression associated with Parkinson's disease (Kummer and Teixeira, 2009). Factors strongly correlating with depressive symptoms include stage of

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Parkinson's disease, motor impairment and functional disability (Pankratz et al, 2008).

Depression is the most important predictor of suicidal ideation in Parkinson's disease (McDonald et al, 2003). Completed suicide in Parkinson's disease is associated with male subjects with a recent diagnosis of disease, those residing in rural areas, having multiple physical illnesses, and a past history of suicide attempts (Mainio et al, 2009). Unfortunately, most pharmacological and surgical approaches, e.g. deep brain stimulation used to treat Parkinson's disease, can also contribute to neuropsychiatric syndromes.

A higher suicide risk after deep brain stimulation has been consistently reported in association with postoperative depression and/or altered impulse regulation (Soulas et al, 2008).

How does depression present in patients with Parkinson's disease?

Some symptoms of depression may resemble the clinical features of Parkinson's disease. For example, psychomotor retardation, early morning waking and fatigue are common to both conditions (Lees et al, 2009). The best discriminatory symptoms are pervasive low mood, hopelessness, worthlessness, lack of interest and self-blame (Farabaugh et al, 2009). Because of the overlap, depression may go unrecognized and impact on the management of Parkinson's disease. Furthermore, Parkinson's disease depression increases the risk of deterioration in cognition, general functioning and motor symptoms (Verbaan et al, 2007) and may indicate more advanced neurodegeneration of neurotransmitter pathways (Pålhagen et al, 2008).

Rating scales such as the Geriatric Depression Scale and Hospital Anxiety and Depression Scale can be used for screening and diagnosis because of their high sensitivity, specificity and negative or positive predictive value (Mondolo et al, 2006). The Beck Depression Inventory is considered the gold standard screening tool for depression but is limited by its complexity, so its suitability in Parkinson's disease as a quick and easy screening device is reduced (Schneider et al, 2010). WHO-5 has been proposed as a more useful and brief instrument to screen for depression in Parkinson's disease (Schneider et al, 2010). Rating scales such as the Montgomery–Asberg Depression Rating Scale and the Beck Depression Inventory are also used to measure patients' progress in depression (McDonald et al, 2006). The Movement Disorders Society commissioned a review of a variety of depression rating scales and recommended that scales assessing the severity of motor symptoms, such as the Unified Parkinson's Disease Rating Scale, should be included to account for overlapping motor and non-motor symptoms (Schrag et al, 2007).

Subtle cognitive disturbances which are present from the initial stages of Parkinson's disease progress in many patients to a more severe cognitive impairment and dementia as Parkinson's disease worsens. Failure in the frontal-striatal basal ganglia circuits cause executive defects in planning, initiation, monitoring of goal-directed behaviours and working memory. Cognitive deficits are common in Parkinson's disease and are possibly related to the subcortical nature of the disease, being noticed at an early stage at a time the lesions are thought to be restricted to the substantia nigra. The cognitive changes precede depressive symptoms and may contribute to them when patients become increasingly aware of their physical disability (Dubois and Pillon, 1997).

Management of depression in Parkinson's disease

Treatment should begin with exclusion and treatment of other underlying organic causes for depression, e.g. endocrine, inflammatory, infectious or metabolic conditions. Medication for Parkinson's disease, particularly levodopa, can also contribute to depression. Both Parkinson's disease and hypothyroidism share common symptoms and therefore it is important to assess thyroid function (Munhoz et al, 2004). Anticholinergic side effects may cause other neuropsychiatric symptoms and thus exacerbate depressive symptomatology.

Depression in Parkinson's disease requires a biopsychosocial, multidisciplinary approach with the implementation of pharmacotherapy, education and/or psychotherapy (Frisina et al, 2008).

The most frequently prescribed antidepressants are the selective serotonin-reuptake inhibitors which include citalopram, fluoxetine, paroxetine and sertraline. Some selective serotonin-reuptake inhibitors can be given in liquid form to patients with dysphagia (Marino et al, 2008). Selective serotonin-reuptake inhibitors are generally well tolerated. In one recent double-blind controlled trial evaluating the efficacy of venlafaxine (a serotonin and noradrenaline reuptake inhibitor) *vs* paroxetine (a selective serotonin-reuptake inhibitor), both drugs were effective for treating depression in Parkinson's disease, were well tolerated and did not worsen motor function (Richard et al, 2012). Tricyclic antidepressants, e.g. amitriptyline, have the disadvantage of being poorly tolerated because of their anticholinergic and alpha-adrenergic blocking side effects such as constipation, urinary retention, blurred vision and sedation. However, autonomic symptoms may be the result of Parkinson's disease itself as well as being antidepressant side effects, so differentiation between the two may be difficult. Of particular significance is that tricyclic antidepressants may cause confusion, particularly in older people, which then exacerbates the cognitive impairment seen in Parkinson's disease.

However, there is evidence of the benefits of tricyclic antidepressants over selective serotonin-reuptake inhibitors in Parkinson's disease. For instance, randomized controlled trials have revealed that low-dose amitripty-

line is as effective as sertraline although the latter has been found to significantly benefit quality of life (Antonini et al, 2006). Other studies have found low-dose amitriptyline to be more effective than fluoxetine (Serrano-Duenas, 2002). In a large placebo-controlled trial nortriptyline was found to have better efficacy than paroxetine (Menza et al, 2009). Desipramine, a predominantly noradrenergic tricyclic antidepressant, has also been shown to have a more intense short-term effect compared with citalopram in Parkinson's disease depression (Kummer and Teixeira, 2009). Another reason for choosing a tricyclic antidepressant is that selective serotonin-reuptake inhibitors can worsen motor symptoms although the absolute risk is low (Kulisevsky et al, 2008).

If the above steps are unsuccessful, consider the use of the dopamine agonist pramipexole, which has a direct antidepressant effect (Barone et al, 2010; Fernandez and Merello, 2010), as it can treat both motor deficits and the associated depression (Fernandez and Merello, 2010) in Parkinson's disease. However, pharmacological augmentation strategies have the potential to increase side effects and worsen cognitive and motor symptoms. Another option is reboxetine, a noradrenaline reuptake inhibitor, which may improve quality of life and does not appear to increase Parkinson's disease symptoms (Pintor et al, 2006).

A significant relationship exists between chronic pain (pain for most days for at least a month) and depression, perhaps operating through similar serotonergic and noradrenergic neurotransmitter pathways, and therefore such symptoms should be integrated in the evaluation and management of depression in Parkinson's disease (Ehrt et al, 2009). There is support for the hypothesis that pain begins at the clinical onset or thereafter as a non-motor feature of Parkinson's disease (Defazio et al, 2008). Duloxetine, a serotonin and noradrenaline reuptake inhibitor, is an effective treatment for central pain in Parkinson's disease (Djaldetti et al, 2007).

Enhancing cholinergic function is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Centrally-acting anticholinesterase inhibitors have a place in the treatment of not only Parkinson's disease, but also Parkinson's disease dementia and Lewy body dementia. They may improve mood indirectly through improvement of cognitive symptoms but can also lower mood, and gastrointestinal side effects are common. The classical symptom triad of Lewy body dementia comprises cognitive impairment, Parkinsonism and visual hallucinations. Described by Dr Friedrich Lewy in 1912, Lewy bodies (eosinophilic cytoplasmic spherical protein deposits) occur in all forms of Parkinson's disease.

Fish oils, the main dietary source of omega-3 fatty acids, may, in addition to their nutritional value, have an antidepressant effect in Parkinson's disease (da Silva et al, 2008). Transcranial magnetic stimulation, which causes depolarization of underlying neurones, has been shown to have antidepressant efficacy and may improve motor function and reduce cognitive impairment (Fitzgerald and Daskalakis, 2008). Cognitive behavioural therapy, if modified appropriately, has been shown to be of benefit in Parkinson's disease depression (Dobkin et al, 2006).

Recommendations to neurologists and psychiatrists

Parkinson's disease is a common neurodegenerative condition with a high prevalence of neuropsychiatric complications including affective and psychotic disorders, varying degrees of cognitive impairment, anxiety, sleep disturbances, apathy, emotional lability and loss of impulse control. These neuropsychiatric syndromes have significant negative impact on both patients and carers.

Before introducing treatment for psychiatric complications it is essential to exclude underlying causes such as anti-Parkinson's medication, deep brain stimulation and medical conditions. Deep brain stimulation has been implicated in suicidal ideation, apathy and depression in Parkinson's disease. Once excluded or treated, subsequent management requires a biopsychosocial approach.

Psychotropic pharmacotherapy should involve the combined clinical acumen of neurologists and psychiatrists. A holistic management approach is important whereby the skills and competencies of both are harnessed and combined to ensure the best outcomes for Parkinson's disease patients. Neurologists need to be more aware of psychiatric presentations and psychiatrists likewise ought to possess appropriate skills and knowledge pertaining to neurological conditions such as Parkinson's disease.

The authors recommend that psychiatrists and neurologists become involved in joint case conferences, attend neuropsychiatric academic teaching programmes, and spend time training in each other's specialties. Psychiatrists and neurologists who wish to further develop their special interests in neurology and psychiatry respectively should have the opportunity to do so. Postgraduate diplomas should be introduced for each neurologists and psychiatrists to gain formal qualifications in each other's disciplines. Such programmes could be organized by the appropriate professional governing bodies, boards or Royal colleges. Formal qualifications and training for both neurologists and psychiatrists would improve job satisfaction, clinical skills, and ultimately the care of patients with Parkinson's disease and other chronic debilitating neuropsychiatric disorders. **BJHM**

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KEY POINTS

- Patients with Parkinson's disease have a high prevalence of depression which can contribute to increased morbidity and carer burden.
- Patients should be routinely screened for symptoms of depression that may mimic those of Parkinson's disease.
- Treatment of depression with antidepressants and other drugs can improve the quality of life in patients with Parkinson's disease.
- There should be close liaison between psychiatrists and neurologists for holistic management of patients with Parkinson's disease.

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