Depression in patients with Parkinson's disease: identification and treatment

Recognizing depression in Parkinson's disease can be problematic but since it has such a significant impact on the quality of life in these patients and is easily treatable the value of therapeutic intervention should not be underestimated.

In 1817, James Parkinson described the malady which now bears his name as 'involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured' (Parkinson, 1817). The description emphasizes the motor features of the disease and still holds good with the cardinal features considered to be tremor, bradykinesia, rigidity and loss of righting reflexes.

Recently, the non-motor aspects of Parkinson's disease have become increasingly recognized as an important cause of morbidity. Such symptoms may become more apparent with disease severity, but some occur early in the disease and with advancing life expectancy become increasingly important. In a study of patients followed up for 15 years the non-levodopa-responsive non-motor symptoms were found to be most disabling (Hely et al, 2005).

Motor and non-motor symptoms

The wide spectrum of non-motor symptoms ranges from neuropsychiatric, sleep disorders, autonomic problems, gastrointestinal complaints and sensory symptoms to others including fatigue, double vision, blurred vision, seborrhoea and weight changes. Some non-motor symptoms, including constipation, olfactory impairment and rapid eye movement sleep behaviour disorder, might be preclinical markers for Parkinson's disease.

Of the neuropsychiatric symptoms, which include anxiety and apathy, depression is one of the most common and more importantly ranks ahead of the motor problems as impacting on the quality of life in these patients, worsening disability and increasing the rate of institutionalization with obvious effects on health economics (Aarsland et al, 2000; Global Parkinson's Disease Survey Steering Committee, 2002).

In addition, depression and dementia in Parkinson's disease rather than the motor problems are associated with increased mortality (Hughes et al, 2004).

Symptoms of depression in Parkinson's disease

Depression is more common in patients with Parkinson's disease than in the general population and there is also some evidence that premorbid depression is significantly more common in Parkinson's disease patients than in those without Parkinson's disease (Ishihara and Brayne, 2006). Similarly, premorbid anxiety may also be associated with Parkinson's disease (Ishihara and Brayne, 2006).

Estimates of the frequency of depression in Parkinson's disease vary widely between 4 and 70% but the true prevalence is likely to be 40–50% (Veazey et al, 2005). However, the accuracy of such estimates remains questionable since making the diagnosis of depression in patients with Parkinson's disease can be difficult as the two conditions share similar symptoms, including reduced facial expression, impoverished voice, sleeping problems, cognitive difficulties and lack of energy.

To make it more difficult it is now proposed that apathy, being common, may be a core feature of Parkinson's disease and may be present in the absence of depression in the disease (Kirsch-Darrow et al, 2006). Apathy is a mental state characterized by loss of interest, motivation and effortful behaviour and, crucially, differs from depression in that it is not a mood disorder, the mood being neutral in apathy but negative in depression.

Recognizing the difficulty of applying the strict criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994) to the Parkinsonian patient, a working group (Marsh et al, 2006) has recommended using the DSM-IV criteria together with an inclusive approach. Practically this involves two initial questions. First, are you depressed or sad and second do you not enjoy things as much as you used to? If either of these is true for more than 2 weeks, then other symptoms of depression should be enquired about, regardless of whether they might be Parkinsonian in origin. These are weight loss or gain, insomnia or hypersomnia, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness or guilt, decreased concentration, indecisiveness and suicidal ideation. The symptoms need to have been present for a 2-week period and represent a change from previous functioning. Major depression is diagnosed if four symptoms are present and one symptom is sufficient for the diagnosis of minor

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depression. This approach includes symptoms that might be attributable to Parkinson's disease itself such as psychomotor slowing, fatigue or insomnia but is still considered valid. Although provisional and likely to require further definition and validation this is a promising starting point for research of Parkinson's disease-associated depression.

As loss of interest rather than pleasure and psychomotor retardation are symptoms of apathy it follows that an apathetic Parkinsonian patient might be misdiagnosed with depression on the basis of DSM-IV criteria. Treating apathy is more difficult than treating depression although there are reports that acetylcholinesterase inhibitors may be useful as well as dopamine agonists and amphetamines because of their dopaminergic properties. Treating apathy may be important in relieving caregiver burden.

A similar situation may occur with anhedonia in which there is reduced capacity to experience pleasure. There are very few data on this psychopathological feature in Parkinson's disease but one study assessed and quantified it using the Snaith-Hamilton pleasure scale (Lemke et al, 2005). The authors found anhedonic patients to have more severe motor deficits and reduction in activities of daily living. The frequency of anhedonia and depression was significantly reduced during treatment with pramipexole, suggesting a role for dopamine agonists in this symptom complex. If anhedonia is part of the depression complex, however, it may respond to antidepressants.

The clinical features of depression in Parkinson's disease range from a mild mood disorder or dysthymia, present for only short periods during the day, to severe as a major affective disorder. Patients experience typical symptoms of guilt, worthlessness, hopelessness and losing interest, initiative and self-esteem. Curiously, although they may have suicidal ideas, successful suicide attempts are unusual (Myslobodsky et al, 2001).

Subsyndromal depression is a recognized problem in Parkinson's disease and may be clinically relevant. There are no uniformly accepted criteria but Judd et al's (1994) approach has been widely cited. It involves the presence of two or more symptoms at subthreshold levels, i.e. not present most of the day, nearly every day. It is important as these patients may be at risk of developing major depression and have increased morbidity.

Depression in the Parkinsonian patient is under-recognized and consequently under-treated even in centres with particular interest in the condition. One third patients from a specialist clinic were depressed but, of these, nearly two thirds were not being treated for depression (Weintraub et al, 2003).

Pathophysiology

The mechanisms underlying depression in Parkinson's disease are not fully understood but the cause is likely to be biological with the life events which commonly beset patients at their stage in life as secondary causes.

Although loss of dopaminergic innervation to the limbic system from the midbrain is likely to be important in the development of depressive symptoms it is unlikely that dopamine deficiency alone is the explanation. Hence L-dopa alone is not usually an effective treatment for depression in a majority of patients. Serotonergic transmission is reduced in the disease which might account for the good response of depressive symptoms to selective serotonin-reuptake inhibitors (SSRIs) (McCance-Katz et al, 1992).

Impact of depression on patients and carers

The motor aspects of Parkinson's disease inevitably affect quality of life including relationships, work, travel and leisure but depression also has a psychosocial impact. In a community-based study (Kuopio et al, 2000) measuring various aspects of health status, depression was found to be the factor associated most significantly with quality of life. Only the clinical stage was more significantly associated with physical functioning than depression. It follows that recognizing and treating depression successfully may be one of the most important factors in enhancing the quality of life in these patients.

It is not only the patient who is affected by these symptoms but also the carer(s). Depression in Parkinson's disease has been shown to increase the caregiver burden (Caap-Ahlgren and Dehlin, 2002).

Identifying the symptoms

It is unusual for a Parkinsonian patient to present primarily with symptoms of depression; more often the alert clinician uncovers the condition. Thus a specific enquiry for fatigue, loss of energy, depressed mood, lack of enjoyment, disturbed sleep, poor appetite, difficulty concentrating, indecision, emotional lability and memory problems (pseudodementia) may be rewarding. A change in the patient's behaviour over time, especially in his/her interests, social interactions and skills, may be an early clue.

The interaction between affective, cognitive and motor features and their lack of specificity affects interpretation of symptoms and can either lead to under- or over-diagnosis of depression.

Leentjens et al (2003) found that non-somatic core symptoms of depression were most predictive of the presence of a depressive disorder whereas most somatic symptoms, with the exception of reduced appetite and early morning wakening, were not discriminatory. Somatic and cognitive symptoms are a prominent feature of depressive disorders and feature heavily in DSM-IV criteria. However, there does not appear to be any consistent profile of somatic symptoms that is more suggestive of a diagnosis of depression in Parkinson's disease. It may be that the current diagnostic systems for depression do not capture the heterogeneous nature of the disorder and in particular a simple symptom count may be an unreliable way of assessing depression in Parkinson's disease.

Assessment tools

Attempts have been made to resolve the diagnostic dilemma by the use of assessment tools.

The Geriatric Depression Scale (GDS) and the Beck Depression Inventory (BDI) are common tools, easily scored and helpful in evaluating follow up and response to treatment. The GDS is a straightforward self-reporting scale which is easy to administer in the outpatient setting. The BDI, also a self-reporting scale, may be more difficult for patients to complete and includes questions which they may be unwilling to answer such as interest in sex. It may, however, be able to screen out those who are apathetic but not depressed.

Alternatives are the observer-rated scales of which the Hamilton Depression Rating Scale (HAM-D) is the most widely used and the Montgomery Asberg Depression Rating Scale (MADRS) is the easiest to use having only ten questions. The latter is a tool to assess the effects of therapy rather than to make a diagnosis.

For the busy clinician the best combination seems to be the GDS for diagnosis and the MADRS for follow up. If the GDS is five or greater or clinical symptoms of depression are evident then the inclusive approach should be applied and, if appropriate, treatment instituted.

Treatment

Failure to diagnose is the most important barrier to treatment. Even those with mild depressive symptoms need to be considered for antidepressant treatment (Marsh et al, 2006). A stepwise approach to treatment is recommended, as outlined in *Table 1*.

Before using pharmacological agents to treat depression, attention should first be given to lifestyle. Minimizing stress, addressing relevant psychological and social factors, tackling loneliness and providing household aids are all simple manipulations with psychological benefits. The patient's best interests are served via a multidisciplinary approach to assessment and management.

The patient should be on optimal treatment for Parkinson's disease including the use of dopamine agonists. Pramipexole is effective in treating depression both in patients with Parkinson's disease and those without (Corrigan et al, 2000) comparable to fluoxetine. In a trial comparing pramipexole with sertraline in patients without motor complications the agonist produced much higher recovery of 61% *vs* 27% based on the HAM-D score (Barone et al, 2006). It implies that dopamine agonists should not only be introduced early to manage motor symptoms but as an alternative to antidepressants.

More specific therapy may be selected depending on the individual need of the patient since the efficacy of most of the available agents is broadly similar.

Tricyclic antidepressants are commonly used to treat depression in Parkinson's disease but the anticholinergic side effects, especially dry mouth, blurred vision, urinary difficulties, cognitive problems and tachycardia, may make them less attractive as well as the adrenergic effect of orthostatic hypotension and histaminergic effect of sedation. The latter may be useful, however, for agitation and in improving sleep and the anticholinergic effect may improve tremor. Nortriptyline may have the least troublesome side-effect profile. In an assessment of the effect of sertraline or amitriptyline on depression and quality of life, both drugs were found to improve depression but amitriptyline did not change the quality of life (Antonini et al, 2006). However, the dose of amitriptyline (25 mg) was at the lowest end of the range for treatment.

SSRIs are generally well tolerated with fewer anticholinergic side effects but may cause unacceptable weight gain and sexual dysfunction. They include fluoxetine, paroxetine (which may also help symptoms of panic and anxiety common in Parkinson's disease), sertraline (which has dopaminergic properties) and citalopram. However, agitated depression may worsen with SSRIs and there are occasional reports of movement disorders associated with their use too. Although on theoretical grounds, the introduction of SSRIs to patients already taking the monoamine oxidase B inhibitor selegiline may cause serotonin syndrome, in practice this is unlikely.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor with only mild anticholinergic properties. Although it may be useful in patients with postural hypotension because it causes increased blood pressure as a side effect it should be used with caution if there is preexisting heart disease.

Mirtazepine is a tetracyclic antidepressant increasing noradrenaline release. It reduces anxiety, lessens nausea and improves sleep. It may sedate and also improve tremor. It might be the better option in patients troubled with sexual dysfunction caused by other antidepressants.

Trazodone is a 5HT2 receptor blocker as well as a weak SSRI. It causes sedation but when combined with an SSRI is a good treatment for insomnia in the depressed patient. Unfortunately it may contribute to falls and cognitive problems and has to be used cautiously in patients who have orthostatic hypotension or ventricular arrhythmias.

Coexistent bipolar disorder should probably be treated with agents other than lithium salts since there are reports that these drugs may induce or exacerbate Parkinsonism. This also needs to be borne in mind when patients on long-term lithium therapy become Parkinsonian and also that the toxic effects of lithium salts include instability and clumsiness. However, the risks of relapse on stopping lithium should be weighed against this.

In an evidence-based review examining effective treatments for depression and psychosis in Parkinson's disease,

Table 1. A stepwise approach to treating the depressed patient with Parkinson's disease

Address lifestyle issues
Optimize dopamine agonists: pramipexole or ropinirole
Use a selective serotonin-reuptake inhibitor: sertraline, paroxetine, fluoxetine or citalopram
Consider other drugs: nortriptyline or amitriptyline, venlafaxine, mirtazepine or trazodone
Consider other approaches: electroconvulsive therapy or cognitive behavioural therapy

only six studies provided class I, II or III evidence. The interventions included amitriptyline, nortriptyline, citalopram, fluoxetine, sertraline, pergolide and pramipexole. Apart from amitriptyline there was insufficient evidence to support or refute the efficacy of the other antidepressants. Insufficient published evidence of clear efficacy is not the same as absence of efficacy (Miyasaki et al, 2006).

Most patients with Parkinson's disease are followed up routinely but the Old Age Depression Interest Group (1993) suggests that medication prescribed for the treatment of depression should be continued for 2 or more years after recovery, at least in elderly subjects.

Cole and Vaughan (2005) have reviewed the literature on cognitive behavioural therapy (CBT) as a treatment for depression associated with PD. They conclude that whether CBT works in depressed Parkinsonian patients is still an open question, suggesting further quality studies and modifications to the traditional model for CBT in depression are needed. DeFronzo Dobkin et al (2006) subsequently described a modified CBT package for depression in Parkinson's disease making novel use of caregivers in the therapy. Although only minimal improvements in anxiety were noted, the therapy was not primarily directed at these symptoms. Large studies are needed but CBT may yet present an effective treatment option.

Electroconvulsive therapy is an effective treatment for severe disease unresponsive to medication, and may transiently improve motor symptoms of Parkinson's disease.

Conclusions

Depression in Parkinson's disease is common yet poorly recognized and consequently under-treated. Treatment is important because depression causes significant morbidity both for the patient and the carer affecting especially quality of life. DSM-IV criteria have not been validated for depression in Parkinson's disease and there is a need to determine the best screening tools in terms of both accuracy and ease of administration.

Addressing issues of lifestyle and consideration of dopamine agonist therapy are important considerations in the first instance in the management of the Parkinson's disease patient with symptoms of depression.

There is little published evidence to guide use of antidepressant medication or other therapies such as CBT and properly conducted studies of sufficient size and duration are required. **BJHM**

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KEY POINTS

- Depression in Parkinson's disease is poorly recognized.
- Depression in Parkinson's disease causes significant morbidity.
- Recognizing depression in Parkinson's disease can be difficult.
- Treatment of depression in Parkinson's disease is usually easy.

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