Managing the major non-motor symptoms of Parkinson's disease

Non-motor symptoms such as depression, sleep disturbances or hallucinations are common in Parkinson's disease (PD), but often these are under-recognised and poorly treated. The frequency of non-motor symptoms usually increases with severity of disease and thus are more likely to affect older patients, many of whom may have had PD for 15 years or more. In this article, **Drs Doug MacMahon and Simon McIntosh** discuss the major non-motor symptoms.

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Parkinson's disease (PD) has traditionally been characterised by motor symptoms such as tremor, rigidity, bradykinesia and gait disturbance. In addition to these classical features, patients may experience non-motor problems related to the disease such as depression, sleep disturbance or hallucinations. These symptoms may present before the PD diagnosis is made and will often increasingly emerge as the disease progresses, and may ultimately dominate the clinical picture[1,2].

Diagnosis of non-motor symptoms in PD

Studies have demonstrated that clinicians fail to identify these non motor symptoms — the presence of depression, anxiety and fatigue is missed in more than 50 per cent and sleep disturbance in 40 per cent of PD patients[3]. The importance of these non-motor symptoms is both clinical and economic since dementia, psychosis and hallucinations are a major reason for admission to expensive care homes[4].

In contrast to the numerous scales for motor symptoms in PD, a screening tool has only recently become available to quantify non-motor symptoms. The Non-Motor Symptoms Questionnaire (NMSQuest) has been developed and piloted to specifically target these areas[1]. It is comprised of 30 questions covering 10 domains. The major findings of its validation study are shown in *Table 1*. In a pilot study of the questionnaire, an average of 10 non-motor symptoms were identified for each patient. The number of symptoms increased with disease severity (eight for mild disease, 12.7 for severe). Furthermore, it is becoming increasingly recognised that several non-motor symptoms such as anosmia (the absence of a sense of smell), rapid eye movement (REM), sleep behaviour disorder, excessive daytime somnolence and constipation may even predate the diagnosis of PD[5]. These indicators are shown in *Table 2* (*overleaf*).

Table 1. Proportion of affected PD patients

Nocturia	59.5%
Urinary urgency	53.6
Constipation	50.2
Blues/depression	48.2
Insomnia	44.3
Concentration	44.0
Anxiety	43.4
Memory	43.1
Restless legs	40.3
Dribbling	40.1

One theory why certain non-motor symptoms may precede diagnosis is that neurodegeneration starts in the olfactory bulb and progresses to the

Table 2. Non-motor symptoms suggested as preclinical (motor) characteristics in PD

Strong evidence
- Constipation
- Olfactory deficit
- REM sleep behaviour disorder
- Depression

Suggested links (weaker evidence base)
- Restless legs syndrome
- Apathy
- Fatigue
- Anxiety

(Table adapted from Chaudhuri *et al*, 2006[6])

lower brainstem causing problems of anosmia, sleep homeostasis and autonomic function. It is only as the disease progresses to involve the substantia nigra and other basal ganglia that typical motor symptoms appear[7]. In addition to inadequate recognition and diagnosis, a survey from the Parkinson's Disease Society (PDS) suggested these symptoms are poorly managed, yet we have a range of validated treatments this article will further explore.

Major non-motor symptoms of PD

Depression

Depression is one of the most common non-motor symptoms of PD, affecting over 40 per cent of patients[3]. Depression is difficult to pick up in the clinic as it overlaps with many of the signs and symptoms of PD itself. When severe, it may dominate the clinical picture and cause major interference with quality of life, but often will be less severe and have more subtle features for which the clinician should be alert. A multidisciplinary approach to treatment of depression in PD should be employed. Carer support, PD nurse specialists and psychiatric liaison services (offering cognitive behavioural therapy and counselling) have important roles in identifying and managing the condition. There is insufficient evidence from randomised controlled trials of the safety and efficacy of treatment for depression in PD[8]. However, clearly non-motor symptoms need optimal control and studies comparing the dopamine agonist pramipexole to the antidepressant sertraline have shown comparable results[9]. Although there is little specific trial evidence, selective serotonin reuptake inhibitors (SSRIs) are the mainstay of drug treatment and are generally safe and well tolerated, although care is needed to ensure the patient is not taking a monoamine oxidase inhibitor (selegiline or rasagiline) due to the small risk of serotonin syndrome — albeit exceedingly rare in normal doses[10]. Finally, there is evidence of the value of electroconvulsive therapy (ECT) in refractory cases, and this treatment will also additionally benefit the motor aspects of PD[11,12]. This therapy can be extremely useful in hospitalised patients in whom nutrition, mobility and well-being are compromised by the combined motor and non-motor disturbances.

Dementia

PD patients have a sixfold increased risk of developing dementia compared with healthy individuals and it usually manifests later on in the disease[13]. Mortality increases with deteriorating cognition and often leads to the breakdown of support networks and admission to institutional care. Dementia is the largest predictor of quality of life in PD[6]. Dementia in PD is linked to Lewy body pathology in the cortex/neocortex of the fronto-temporal lobes, resulting in a cholinergic deficit as seen also in Alzheimer's disease[14]. Having confirmed a cognitive deficit, reversible causes should be excluded or treated. The first step in managing cognitive impairment is a careful medication review as many dopaminergics are implicated in confusion or poor memory. After simplification or reduction of drugs, effective management requires a pragmatic approach including home care, carer respite and support groups. Ultimately, if community care becomes unsustainable, a smooth transition into institutional care will need to be facilitated. Conventional cognitive enhancers can be used, although rivastigmine is currently the only cholinesterase inhibitor licensed for the treatment of dementia in PD[15]. Referral to old age (or liaison) psychiatry for difficult behaviour or complicated cases should be considered.

Constipation

Constipation is a common non-motor symptom of PD and may precede the disease. In addition to reduced mobility, Lewy bodies in the myenteric plexus of the colon result in colonic dysmotility and reduced transit time. Patients complain of excessive straining, pain or a sense of incomplete evacuation. Some patients find that they need to be 'on' in order to evacuate their rectum, and occasionally

Table 3. Order of withdrawal in drug-induced psychosis

First:
- Anticholinergics
- Tricyclics
- Selegiline
- Amantadine
- SSRIs
- Dopamine agonists
- Catechol O-methyltransferase (COMT) inhibitors
- Apomorphine

Last:
- Levodopa

adjustment of levodopa or apomorphine may help. However, in general, despite the loss of colonic dopaminergic neurones, constipation does not respond well to treatment with levodopa or dopamine agonists. Patients should be encouraged to increase their fluid and fibre intake and use stool softeners or osmotic laxatives as directed. There is also evidence from a small trial of the effectiveness of macrogol 3350 and electrolytes for constipation in PD[16].

Sexual dysfunction

It is difficult to quantify the extent of sexual problems in PD. Some older patients may not have a partner and be sexually inactive, while others may feel uncomfortable discussing this aspect of their lives in a busy clinic. This is reflected in the NMSQuest pilot study results — the question regarding sex received the largest number of non-responders. Symptoms range from a loss of libido to hypersexuality and aberrant sexual behaviour as part of the dopamine dysregulation syndrome in susceptible individuals. A careful history is required as sexual problems may be a symptom of relationship difficulties, apathy or cognitive decline. Erectile dysfunction can be treated with sildenafil after a full discussion with the partner, and a number of pharmacological and non-pharmacological treatments are available for women.

Hallucinations and psychosis

Hallucinations are a common occurrence with up to 40 per cent patients experiencing a range of symptoms including vivid dreams, a sense of presence, formed images and frightening psychosis. Duration of disease, daytime somnolence and cognitive impairment increase the risk of hallucinations[8]. Anti-parkinsonian medications are often implicated, although abnormal perceptions may occur without treatment. The management depends upon whether the patient and/or carer are distressed by the hallucinations. Unthreatening visual images with preserved insight may simply require observation. The treatment of drug-induced psychosis involves step-wise withdrawal of medications. It is usually advisable to withdraw or reduce the last drug prescribed to a patient and then those with the higher risk of adverse effects, as shown in *Table 3*. Psychosis secondary to delirium or toxic confusional state must be investigated and treated in the usual way, searching for infection, a metabolic upset or dehydration. Typical antipsychotics should not be used because of extra-pyramidal side effects and the danger of precipitating a major crisis in Lewy body disease. Atypical antipsychotics such as quetiapine have been shown to be effective[17] although one trial found it to be no better than placebo[18]. Clozapine is probably more effective, but its use is limited by mandatory weekly blood tests due to the risk of agranulocytosis. Hospital admission is to be avoided if possible as it increases confusion and disorientation.

Pain

Pain often precedes the diagnosis of PD and can later occur with the motor fluctuation stages of the disease. A study by Guiffrida[19] of 388 patients with PD found 67 per cent complained of painful stimuli, the vast majority being muscular in origin followed by joint pain. Paraesthesia was relatively less common. Most pain is intermittent and interestingly does not seem to increase with duration of disease, severity, depression or dopaminergic therapy. Pain may be either directly related to PD (eg, dystonia when 'off') or secondary to increased muscular tone and rigidity, or unrelated to PD (eg, osteoarthritis or neuropathic pain).

Management involves taking a careful history to determine any pattern to the on/off fluctuations or timing of medication. Pain due to motor fluctuations responds to increasing dopaminergic therapy or adjunct therapy such as COMT inhibitors to smooth out motor fluctuations. Pain unrelated to PD should be investigated and treated on its own merit. Physiotherapists, occupational therapists and pain teams all have a useful role. Early referral and discussion between primary care, mental health teams, and specialist PD teams should help to avert admission.

Sialorrhea

Excessive salivation and drooling are common complaints in PD patients; approximately 75 per

cent will experience it at some stage. It is often the patients' carers who perceive this to cause a major stigma as well as a practical problem. It is advisable to engage the assistance of a speech and language therapist and physiotherapist to improve posture and work on behavioural solutions, lip seal and swallow exercises. A sublingual one per cent atropine solution has been advocated and in refractory cases salivary glands can be injected with botulinum toxin[8].

Sleep disturbances

Most patients have disrupted sleep that may be apparent prior to the development of PD[20]. A number of different sleep problems are recognised.

Excessive daytime somnolence (EDS)

EDS usually occurs early in the disease. Daytime sleepiness becomes excessive when the patient is overwhelmed by tiredness or unintended sleep adversely affects the patient, carer or their safety. Dopaminergic drugs and fragmented sleep compound the problem. Indeed, eight cases of sudden onset of sleep while driving were identified in patients taking dopamine agonists (seven taking pramipexole, one ropinirole) resulting in road traffic accidents[21].

REM sleep behaviour disorder

REM sleep behaviour disorder is characterised by loss of muscle atonia allowing patients to physically act out their dreams. Injury to patient or bed partner is not unknown. As with constipation, depression and anosmia, REM sleep behaviour disorder is considered a preclinical marker of PD[20].

Restless legs syndrome (RLS)

RLS occurs in around a fifth of patients with PD. Patients complain of an irresistible urge to move their legs, symptoms that are worse at rest or at night, and relief on moving around or massaging the legs. A good sleep history noting the initiation, maintenance and awakening phases of sleep helps to clarify the diagnosis. The Epworth sleepiness scale is a simple assessment tool that can be used in the clinic setting. Insomnia may improve with simple sleep hygiene measures such as avoidance of caffeine and daytime naps. Pharmacological treatment of sleep disorders includes a review of all medications to identify drugs that may promote wakefulness at night and sleepiness during the day. Modafinil is a wake promoting therapy that can be used in EDS although the evidence is sparse[22]. Dopamine agonists (in low dose) have also been shown to be useful in RLS[23].

Key points

- Non-motor symptoms in PD are common, under-recognised and poorly treated.
- There are a number of non-motor rating scales available for use.
- The Non-Motor Symptoms Questionnaire (NMSQuest) has been developed and piloted to specifically target non-motor symptoms.
- The NMSQuest results show that the frequency of non-motor symptoms increases with severity of disease.
- Depression is one of the most common non-motor symptoms of PD, affecting over 40 per cent of patients.

Non-motor symptoms management tools

There are a number of non-motor rating scales available for use. However, these tend to concentrate on individual symptoms such as sleep (SCOPA-sleep, Epworth sleepiness scale), fatigue (fatigue severity scale, PF-16) and cognitive function (Beck depression inventory, Hamilton depression rating scale), some of which are not specific to PD. The NMSQuest is the first comprehensive assessment of non-motor symptoms in PD.

The elderly

Elderly patients are more prone to the non-motor symptoms of PD. The NMSQuest results show that the frequency of non-motor symptoms increases with severity of disease and thus are more likely to affect older patients, many of whom may have had PD for 15 years or more. Carer support and respite should be available — and the involvement of PD nurse specialists and other members of the multidisciplinary team utilised at an early stage. A palliative care approach, with involvement of specialist teams on occasions may be invaluable in the late stages of disease when specific problems such as pain or nausea are encountered.

Conclusion

Non-motor symptoms in PD are common, under-recognised and poorly treated. The NMSQuest is a comprehensive screening tool that will help the busy clinician identify these problems at an early stage. Specific treatment strategies and a multidisciplinary approach to non-motor symptoms management may then be used to improve the care of patients with PD.

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