Non-motor Symptoms in Late-stage Parkinson's Disease – Is Continuous Dopaminergic Stimulation Beneficial?

a report by

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Parkinson's disease (PD) was first described by James Parkinson in 1817 and remains one of the most important disabling illnesses of later life. Although the motor symptoms of the disease are easy to identify, the non-motor symptom (NMS) complex frequently goes unrecognised by healthcare professionals, as reported by Shulman and colleagues.[1] This may be because physicians or nurses concentrate more on motor aspects, there is unawareness that NMS are related to PD or the symptoms are not declared to healthcare professionals.[2] Recent work by the Parkinson's Disease Non-motor Group (PD-NMG) has led to the validation of the first comprehensive clinic-based self-completed NMS questionnaire (NMSQuest, see *Table 1*),[3] as well as a scale (the NMS scale) that allows easy identification of NMS by the physician.[3,4]

Patients often find the NMS of PD more disturbing than the motor symptoms. Indeed, NMS dominate the clinical picture of advanced PD and contribute to severe disability, impaired quality of life and shortened life expectancy. In contrast to the dopaminergic (motor) symptoms, for which treatment is available, NMS are often poorly recognised and inadequately treated. Some NMS – including depression, constipation, pain, genito-urinary problems and sleep disorders – can be improved with available treatments. Other NMS can be more refractory and need the introduction of novel non-dopaminergic drugs. The development of treatments that can slow or prevent the progression of PD and its multicentric neurodegeneration provides the best hope of curing NMS.[4]

NMS correlate with advancing age and disease severity, although some NMS – such as olfactory problems, constipation, depression and rapid eye movement (REM) disorder – can occur early in the disease.[2] The prevalence of NMS as a whole is inadequately documented because there are insufficient adequately powered community-based studies on prevalence, effect and treatment efficacy in relation to NMS; there is thus a need for large, well-designed prospective studies. The role and effect of the NMS complex during the disease course has been examined in a prospective study of patients with PD followed up for 15–18 years, which showed that non-levodopa-responsive NMS are the most disabling feature of the disease.[5] A wide spectrum of NMS have been described in PD, as shown in *Table 2*.

Continuous Dopaminergic Stimulation

Continuous dopaminergic stimulation (CDS; see *Table 3*) is a relatively modern concept that has been shown to reduce the severity and incidence of dyskinesias based on the fact that pulsatile delivery of dopamine to the deafferented dopamine receptors in the striatum is likely to be dyskinesogenic.[9] CDS may prevent or reverse motor complications resulting from reduced priming of the basal ganglia for involuntary movements compared with agents that produce pulsatile stimulation.[10]

Table 1: NMSQuest – Parkinson's Disease Non-motor Symptoms Questionnaire

Name:	
Age:	
Date:	
Male/female:	
Centre ID:	

Have you experienced any of the following in the last month?	Yes	No
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (fewer than three bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (faecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or in doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focused	☐	☐
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light-headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting out' a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐

Table 2: Non-motor Symptom Complex of Parkinson's Disease

Neuropsychiatric Symptoms
Depression, apathy, anxiety
Anhedonia
Attention deficit
Hallucinations, illusion, delusions
Dementia
Obsessional behaviour (usually drug-induced), repetitive behaviour
Confusion
Delirium (could be drug-induced)
Panic attacks
Sleep Disorders
Restless legs and periodic limb movements
REM behaviour disorder and REM loss of atonia
Non-REM-sleep-related movement disorders
Excessive daytime somnolence
Vivid dreaming
Insomnia
Sleep-disordered breathing
Autonomic Symptoms
Bladder disturbances:
• urgency
• nocturia
• frequency
Sweating
Orthostatic hypotension:
• falls related to orthostatic hypotension
• 'coat-hanger' pain
Sexual dysfunction:
• hypersexuality (likely to be drug-induced)
• erectile impotence
Dry eyes (xerostomia)
Gastrointestinal Symptoms (Overlaps with Autonomic)
Dribbling of saliva
Ageusia
Dysphagia/choking
Reflux, vomiting
Nausea
Constipation
Unsatisfactory voiding of bowel
Faecal incontinence
Sensory Symptoms
Pain
Paraesthesia
Olfactory disturbance
Other Symptoms
Fatigue
Diplopia
Blurred vision
Seborrhoea
Weight loss
Weight gain (possibly drug-induced)

REM = rapid eye movement.

Table 3: Possible Therapeutic Strategies for Continuous Dopaminergic Stimulation That Can Be Used in a Realistic Clinical Population of Parkinson's Disease Patients

Levodopa-based
CR levodopa; CR levodopa + COMT inhibitor; CR levodopa + MAO inhibitor; frequent small dosing of oral levodopa; levodopa infusion (intraduodenal) (Duodopa)
Non-levodopa-based
Cabergoline once or twice daily; apomorphine (SC) infusion; lisuride (SC) infusion; transcutaneous patch of dopamine agonist (rotigotine, lisuride); CR ropinirole
Surgical
STN stimulation; medial pallidum stimulation

CR = controlled-release; COMT = catechol-O-methyl transferase; MAO = monoamine oxidase; SC = subcutaneous; STN = subthalamic nucleus.

Levodopa-based CDS has been challenging: the lack of solubility of levodopa requires large and cumbersome pump technology and either duodenostomy or Portacath intravenous lines into the subclavian vein, which limited this therapeutic approach to all but a few dedicated research centres. However, the advent of Duodopa has changed this. The novel gel form of Duodopa has allowed levodopa to be infused through percutaneous endoscopic gastrostomy directly into the duodenum. Studies with duodenal infusion of levodopa have shown improved motor fluctuation and reduced disabling dyskinesia, resulting in significant benefit in quality of life.

Apomorphine infusion is the most common non-levodopa-based option; however, the development of skin nodules and needle phobia limit the use of this method. Cabergoline is no longer favoured due to recent evidence that it causes cardiac valvulopathies and fibrosis. However, rotigotine skin patches have been quite useful and provide a novel way of achieving CDS, with the drug absorbed through the skin.

Deep brain stimulation (DBS) is quite an effective means of achieving CDS. However, DBS-related complications include dysarthria, eyelid apraxia and behavioural changes such as cognitive deterioration (40%), depression (8%), hypomania (4%), anxiety (2%) and occasional surgery-related (bleeding, infection) and hardware-related complications (~14%).

However, in clinical practice the question of whether or not CDS is meaningful remains controversial, and some do not accept that CDS is a realistic option in PD. Theoretically, the potential benefits of CDS are many, and may include improvements in aspects of sleep in PD by providing 24-hour cover. Although some would argue that dopaminergic tone is low at night and, as such, PD patients may not need 24-hour dopaminergic stimulation, clinical experience, overnight dopamine agonist infusion (apomorphine) and DBS studies all suggest that dopaminergic nocturnal problems – such as restless legs syndrome, nocturnal akinesia, nocturnal off-related symptoms, early morning dystonia and even nocturia – can benefit from sustained dopaminergic stimulation throughout the night. ■

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