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Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected

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ABSTRACT

Non-motor symptoms are a key component of Parkinson's disease, possibly representing a clinical biomarker of its premotor phase. The burden of non-motor symptoms can define a patient's health-related quality of life. Non-motor symptoms substantially increase the cost of care—requiring increased hospitalisation and treatment—and pose a major challenge to healthcare professionals. However, clinicians often regard non-motor symptoms and their management as peripheral to that of the motor symptoms. Here, we address the clinical issues and unmet needs of non-motor symptoms in Parkinson's disease.

INTRODUCTION

I have Parkinson's. I would like you to address the following symptoms that bother me the most: sleep, pain and then my movement disorder.

A patient with Parkinson's disease,
10 October 2013

James Parkinson recognised the implications and importance of motor Parkinson's disease (PD) in 1817 and highlighted key non-motor symptoms, such as sleep dysfunction, dysautonomia, cognitive and neuropsychiatric issues. However, it was almost 150 years before the importance of the burden of non-motor symptoms on the lives of the people with Parkinson's and the carers became apparent. Many studies have addressed cognition, dementia, sleep disorders and depression in PD. More recently, holistic tools, such as the self-rated Non-Motor Symptoms Questionnaire (NMSQuest)¹ and the Non-Motor Symptoms Scale (NMSS)^{2–3} have allowed clinicians to quantify the overall burden of these additional symptoms in PD and their impact on quality of life.

THE PROBLEMS

Clinicians frequently overlook non-motor symptoms and do not discuss important symptoms like depression, anxiety, fatigue and sleep disturbance.⁴ The UK's National Institute for Health and Care Excellence—a non-departmental public body of the Department of Health—has recognised non-motor symptoms and their management as an important area of unmet need in PD.⁵ However, despite their 2006 guidance, an international survey in 2010 showed that up to 62% of PD patients do not declare symptoms such as apathy, pain, sexual difficulty, bowel incontinence or sleep disorder, either through embarrassment or being unaware that their symptoms link to PD.⁶ Furthermore, clinicians themselves may not realise that these symptoms need addressing. Non-motor symptoms are common even at first presentation. In 2013, a German study assessed them (by the NMSQuest) in untreated PD patients at presentation: these symptoms presented a significant burden—even at this early untreated stage—compared with age-matched controls.⁷ A UK-based study reported similar findings, highlighting the important need for an awareness of non-motor symptoms right at the onset of 'motor' PD.⁸ Their under-reporting has important therapeutic and societal implications as most are treatable. Left untreated, non-motor symptoms detrimentally affect quality of life and frequently cause hospitalisation and institutionalisation,^{9–10} increasing the cost of PD care by fourfold.⁶

INITIATIVES TO ADDRESS MANAGEMENT OF NON-MOTOR SYMPTOMS

Parkinson's UK—the major UK-based patient charity—commissions an annual

audit of Parkinson services. The 2011 report showed non-motor symptoms recorded in only 21% of elderly care and 9% of neurology services in the UK. This deficiency mainly relates to lack of time during consultation and also to not using self-declaration tools, which would allow patients to 'flag' symptoms. This outcome led to a national policy for data collection (motor and non-motor) of patients being referred to hospital.¹¹

THE NEUROPATHOLOGICAL BASIS OF NON-MOTOR PARKINSON'S

For the nigrostriatal dopaminergic disorder of PD, one pathological process clearly does not fit all! Jellinger stated that Parkinson's can no longer be considered a complex motor disorder characterised by extrapyramidal symptoms, but as a progressive multi-system disease—or more correctly, multiorgan disease—with variegated neurological and non-motor deficiencies.¹²

The traditional concept that the first neuropathological insult leading to PD is the degeneration of neuromelanin-containing neurones in the pars compacta of the *substantia nigra* (resulting in depleted levels of the *dopamine*) has been challenged. Many studies, spearheaded by the Braak theory, suggest that a non-dopaminergic process is key to the non-motor symptoms of PD, many of which start well before the motor Parkinson's features emerge.^{12–14} Interestingly, Friedrich Lewy (1913) first described Lewy bodies in the dorsal motor nucleus of the vagus, a site implicated in Braak stage 2.¹⁵

Table 1 summarises the growing evidence that in PD the degeneration of non-dopaminergic neurones occurs well before dopaminergic motor symptoms start. There is also clear evidence of differential neuronal degeneration involving several neuropeptide pathways in the brain in PD.^{13–14} Furthermore, there is neuropathological heterogeneity between early-onset and late-onset PD,¹³ which manifests clinically as subtypes within both motor PD and (more recently recognised) non-motor PD.¹⁶

Animal models addressing non-motor symptoms of PD are important. We discuss these in online supplementary material, and box 1 shows a snapshot of existing animal models.

WHAT ARE THE NON-MOTOR SYMPTOMS OF PD?

James Parkinson referred to sleep disturbance, constipation, dysarthria, dysphonia, dysphagia, sialorrhoea, urinary incontinence and 'at the last, constant sleepiness with slight delirium' in his essay.²⁸ The widespread neuropathology of PD gives a wide range of symptoms from gastrointestinal to sleep disorders, from cognitive to apathy and depression. In addition, some symptoms relate to drug therapy. It is thus difficult to 'lump' non-motor symptoms into a single category, and we suggest the following classification:

Box 1 Parkinsonian animal models with possible expression of non-motor symptoms and exploration of pathophysiology

6-OHDA lesioned rodents²⁴

- ▶ Sensorimotor
- ▶ Olfaction
- ▶ Sensory/pain threshold
- ▶ Sleep/wakefulness
- ▶ Circadian rhythms
- ▶ Cognitive function
- ▶ Also possible to study:
 - ▶ Altered cardiovascular function
 - ▶ Bladder hyperactivity
 - ▶ Altered motility of gastro-intestinal tract

α -Synuclein overexpressor (ASO=Thy1-aSYN) mice²⁵

- ▶ Olfaction
- ▶ Autonomic
- ▶ Constipation
- ▶ Sleep
- ▶ Cognition

MPTP-treated primates²⁴

- ▶ Bladder hyper-reflexia
- ▶ Constipation
- ▶ Drooling
- ▶ Altered cardiovascular function
- ▶ Sleep disturbance
- ▶ Cognitive disturbance

Mice model of intragastric rotenone administration²⁶

- ▶ α -Synuclein accumulation in dorsal vagal nucleus
- ▶ Potential for investigating autonomic symptoms such as constipation

Göttingen minipigs (Ellegaard Minipigs ApS)²⁷

- ▶ Cognition/sleep
- OHDA, hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

- ▶ Related to the disease process or pathophysiology
 - Dopaminergic origin
 - Non-dopaminergic origin
- ▶ Related to a partial non-motor origin (usually brainstem autonomic impairment with motor end result, such as constipation or diplopia)
- ▶ Related to non-motor fluctuations (cognitive, autonomic and sensory subtypes)
 - Fluctuating
 - Constant
- ▶ Related to PD drug therapy
 - Specific symptoms (eg, hallucinations, delirium)
 - Syndromes—impulse control disorders, dopamine agonist withdrawal syndrome, Parkinson's hyperpyrexia syndrome (thermoregulatory failure, delirium)
- ▶ Possibly genetically determined
 - Dementia in cases with glucocerebrosidase mutation
 - Depression and sleep disorders in cases with leucine-rich repeat kinase-2 mutation

Table 1 Non-dopaminergic involvement in PD

Evidence of non-dopaminergic involvement in PD	Implications on stage of PD	Author/year
Lewy bodies first described in non-dopaminergic neurones	Premotor and early motor	Forno, 1996 ¹⁷
Neuronal loss in dorsal motor nucleus of the vagus is as marked as in the substantia nigra	Premotor and early motor	Jellinger, 1987 ¹⁸ Hirsch, 1987 ¹⁹ Halliday, 1990 ¹³
Cholinergic pediculopontine nucleus neurones and substance P-containing neurones suffer 77% loss in dorsal motor nucleus of the vagus while tyrosine hydroxylase-immunoreactive neurones appear spared (<5% loss)	Premotor and early motor	Jellinger, 1987 ¹⁸ Hirsch, 1987 ¹⁹ Halliday, 1990 ¹³
Complete sparing of medullary dopaminergic neurones reported	Premotor and early motor	Saper, 1991 ²⁰
Lewy body degeneration is prominent in the non-dopaminergic anterior olfactory nucleus	Premotor and early motor	Wakabayashi, 1997 ²¹
Non catecholaminergic neurones severely depleted in PD in the autonomic system: spinal intermediolateral nucleus 30–40% loss of preganglionic autonomic neurones	Premotor and early motor	Wakabayashi, 1997 ²¹
Lewy bodies are frequent in the vasoactive intestinal peptide neurones of the enteric nervous system but rare in catecholaminergic cells	Premotor and early motor	Wakabayashi, 1997 ²¹
Lewy bodies present in both tyrosine hydroxylase+and tyrosine hydroxylase—cells in the cardiac plexus	Premotor and early motor	Wakabayashi, 1997 ²¹ Iwanaga, 1999 ²²
Lewy body degeneration developing in lower brainstem neurones well before the substantia nigra	Premotor and early motor	Braak, 2003 ¹⁵
Incidental Lewy bodies identified within pontomedullary neurones in the absence of substantia nigra pathology, but not vice versa	Premotor and early motor	Braak, 2004 ²³

PD, Parkinson's disease.

Some symptoms may overlap: for instance, hallucination as part of the advancing disease, or non-motor fluctuations in PD.

While some non-motor symptoms dominate in the early or even in the 'premotor' phase of PD, others complicate the clinical picture throughout the disease (pain, fatigue) and especially in its advanced stages (dementia, apathy, dysautonomia), as shown in the Sydney multicentre study report at 20 years.²⁹ The 'Parkinson's at risk syndrome' study tries to identify the premotor non-motor risk factors for developing the motor syndrome of PD. There is now also an attempt to redefine PD, moving away from the typical brain bank-defined motor diagnostic criteria.^{30–32}

PD can be divided into a preclinical phase (supported by molecular or imaging markers), a premotor phase (with non-motor symptoms, table 2) and the motor phase, the 'tip of the iceberg'. The key is to

develop robust biomarkers and also to define the specific predictive value of the premotor non-motor symptoms. Table 2 shows examples of non-motor symptoms reported in the premotor stage.

EPIDEMIOLOGY

The NMSQuest and the NMSS each assesses their global burden in PD. Table 3 lists the studies that have used them to assess non-motor symptoms in unselected PD populations across the world and shows the importance of these symptoms in PD irrespective of cultural background, racial origin and hospital settings. Three controlled studies compared NMSQuest data in PD with age-matched healthy controls: all show that while some symptoms, such as insomnia, urinary difficulties and memory issues, are common in 'normal' subjects, the severity and frequency of these non-motor symptoms are more severe in PD.

Table 2 Non-motor symptoms in the premotor PD

<i>Commonly associated—with reasonable evidence base</i>	
Hyposmia (usually of late onset and idiopathic)	10 times increase in risk of developing PD; +abnormal DATScan—43% develop motor PD in 4 years ³³
Rapid eye movement sleep behaviour disorder	25–40% risk of developing a synucleinopathy at 5 years; 40–65% risk of developing a synucleinopathy at 10 years ³⁴
Constipation	2.7–4.5 times increased risk of PD ³⁵
Depression	2.4 times increased risk of developing PD ³⁶
<i>Described associations</i>	
Excessive daytime sleepiness	3.3 times increased risk of PD ³⁷
Fatigue (a sense of exhaustion as opposed to sleepiness)	In 45%—a premotor symptom ³⁸
Pain (often unilateral and in affected limb)	34% increased risk of PD ³⁹
Erectile dysfunction	3.8 times increased risk of PD ⁴⁰

PD, Parkinson's disease.

Table 3 Prevalence of non-motor symptoms from published studies using NMSQuest^{1 6–8 41–44}

Non-motor symptoms	Mean (%)	Range (%)
Cognitive		
Memory	45.8	37.9–62.5
Concentration	38.7	29.6–50.0
Depression		
Sadness	42.5	22.5–56.0
Anxiety	43.4	30.7–55.8
Sleep		
Excessive daytime somnolence	30.5	21.2–37.1
Insomnia	40.9	17.6–52.5
REM sleep behaviour disorder	34.2	29.6–38.7
Restless legs syndrome	35.8	27.7–41.1
Fatigue	41.5	31.1–58.1
Pain	31.1	18.2–45.9
Gastrointestinal		
Swallowing	25.4	16.1–30.3
Constipation	46.5	27.5–71.7
Urinary		
Urgency	53.4	35–61
Nocturia	53.8	26.4–66.7
Global comparison		
NMSQ-PD	8.3	4–19
NMSQ-C	3.5	2–12

Data taken from studies by Chaudhuri *et al.*¹ Chaudhuri *et al.*⁶ Mollenhauer *et al.*⁷ Khoo *et al.*⁸ Martinez-Martin *et al.*⁴¹ Barone *et al.*⁴² Crosiers *et al.*⁴³ Chen *et al.*⁴⁴ and expresses mean values of non-motor symptoms.

PD, Parkinson's disease; NMSQ-PD, Non-Motor Symptoms Questionnaire in PD patients; NMSQ-C, NMSQ—in controls.

Furthermore, some symptoms, such as fatigue, dribbling of saliva and excessive daytime sleepiness, are highly significantly more common in PD.^{1 7 8}

BIOMARKERS

There are several suggested biomarkers, both tissue and imaging, but all remain investigational. A controlled study from Germany comparing untreated PD with age-matched controls suggested that clinical tools such as the NMSQuest and a validated bedside autonomic scale (SCOPA-autonomic), combined with laboratory tests such as the smell-identification test, reach the sensitivity and specificity (>0.9) for a biological marker of PD at presentation.⁷ Table 4 lists other possible biomarkers in PD.

SOME PROBABLE BIOMARKER TESTS AND KITS

See figures 1A,B and 2.

THE CLINICAL SCENARIO: A POSSIBLE SOLUTION TO THE NEGLECT OF NON-MOTOR SYMPTOMS IN CLINIC

First, tools such as NMSQuest do not consume clinical interactions; the patient completes them and they help direct the consultation with nurse specialist or

Table 4 Some reported possible biomarkers in the early diagnosis of PD

Biochemical/histopathology markers	
Rectal/colonic biopsy	Phosphorylated α -synuclein-positive Lewy neurites; α -synuclein-positive nerve fibres (figure 1)
Skin biopsy	α -Synuclein accumulation
Gastric biopsy	Phosphorylated α -synuclein-positive Lewy neurites
Low uric acid	Proposed
Low-density lipoprotein/serum cholesterol	Proposed
Genetic markers	
Leucine-rich repeat kinase 2 mutation (G2019S)	
Glucocerebrosidase mutation	
Imaging markers	
Transcranial sonography	
DAT scan	
<i>The above two can be used in conjunction with clinical symptoms such as hyposmia or REM sleep behaviour disorder</i>	
Clinical markers combined with imaging	
NMSQuest, SCOPA AUT, smell-identification test (figure 2) and transcranial sonography—can be used as marker with 95.8% sensitivity in PD ⁷	

PD, Parkinson's disease; NMSQ, Non-Motor Symptoms Questionnaire; SCOPA AUT, SCOPA autonomic scale.

consultant. The clinician can then grade the non-motor symptoms burden numerically (box 2). Patients are then usually asked to flag the most bothersome symptoms. These are then addressed either through pharmacological, allied health specialist therapies, neuropsychological or neuropsychiatric input (figure 3). A yearly documentation of non-motor symptoms score helps to chart the progress of these symptoms. Pharmaceutical companies have developed and distributed alternative self-completed tools—such as the Parkinson well-being map—but have not been validated in PD. Figure 4 shows the importance of using such tools in the clinic. Two newly diagnosed patients, untreated and with similar motor disability, completed NMSQuests (figure 4A,B). The first patient reports only five non-motor symptoms: mainly problems with dribbling of saliva at night, urgency to pass urine, unexplained pain and dizziness. The second patient reports a wider range of non-motor symptoms (19/30): problems related to sleep, dribbling of saliva and other autonomic symptoms. Each of them needs a different management plan for their non-motor symptoms, as well as the treatment of the motor symptoms. These observations have been confirmed by two recent studies in untreated PD⁷ and early PD⁸ (compared with controls).

A simple grading using patient-completed NMSQuest has stages of severity burden of non-motor symptoms ranging between levels 1 and 4 (proposed as the Kings-ISCI grading).⁴⁶ This classification has been validated using the NMSS, the latter being particularly aimed towards research-based studies. NMSQ

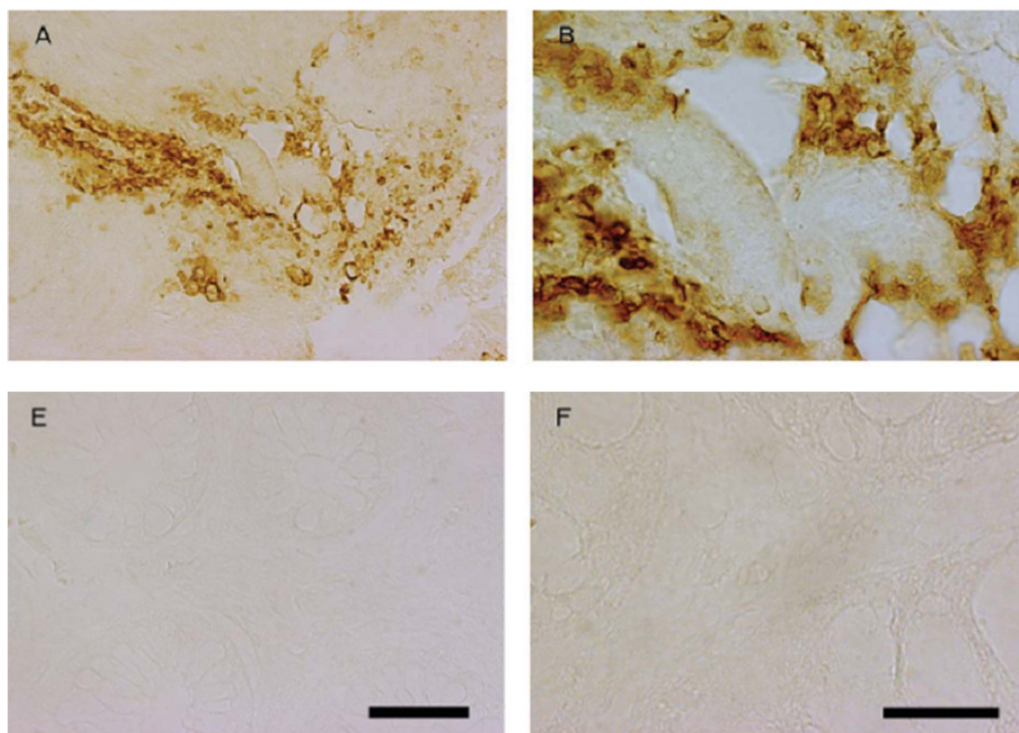


Figure 1 (A) Showing 10 untreated Parkinson patients; all positive for α -synuclein and 3-nitro-tyrosin (a marker for mitochondrial stress) on sigmoidoscopy and rectal biopsy (A,B). From Shannon *et al.*⁴⁵ Copyright 2011 Movement Disorder Society. Reproduced with permission from John Wiley and Sons, Inc. (B) Controls show no relevant staining (E,F). From Shannon *et al.*⁴⁵ Copyright 2011 Movement Disorder Society. Reproduced with permission from John Wiley and Sons, Inc.

grading of the burden can influence treatment and screening in primary care is particularly recommended. For instance, for the patient cited in figure 4B, Hoehn and Yahr stage 1 would have NMSQ grade 4 and should be referred for treatment more promptly than the patient cited in figure 4A. Both NMSQ and NMSS burden grades have highly significant inverse correlations with HRQoL of patients.⁴⁷

NON-MOTOR CLASSIFICATION AND SUBTYPES

The classification based on NMSS has also given rise to the growing concept of non-motor dominant

subtypes within PD. Just as in multiple sclerosis and motor neurone disease, clinical subtyping in PD is important (although some argue against this). Subtyping helps give a clearer definition of the clinical symptoms of PD as well as helping with inclusion criteria of patients for clinical trials. It also makes sense

Box 2 Non-motor Parkinson's disease burden grading using Non-Motor Symptoms Scale (NMSS) and Non-Motor Symptoms Questionnaire (NMSQ) (Kings ISCIII grading)

Kings-ISCIII grading by NMSQuest (can be performed by healthcare professional and based on patient responses using NMSQ)⁴⁶

Stage 0 NMSQ—0 no non-motor symptoms

Stage 1 NMSQ—1–5 mild

Stage 2 NMSQ—6–12 moderate

Stage 3 NMSQ—13–20 severe

Stage 4 NMSQ—21–30 very severe

Grading by NMSS (to be used for clinical and research based studies)⁴⁷

Non-motor symptoms burden level 0 NMSS—0

Non-motor symptoms burden level 1 NMSS—1–20

Non-motor symptoms burden level 2 NMSS—21–40

Non-motor symptoms burden level 3 NMSS—41–70

Non-motor symptoms burden level 4 NMSS— ≥ 71



Figure 2 University of Pennsylvania smell-identification test for testing olfaction in the clinic.

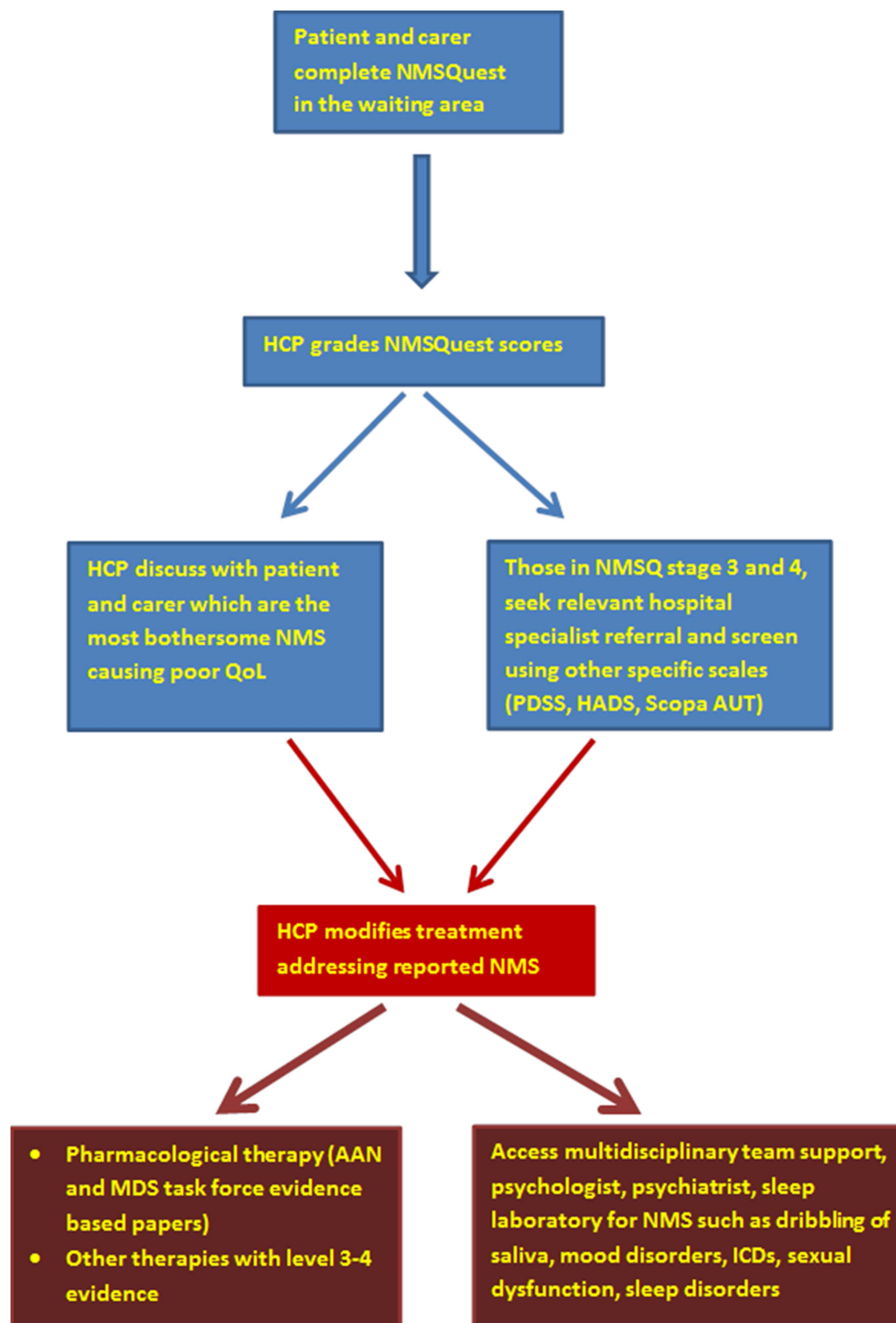


Figure 3 Suggested algorithm of addressing non-motor symptoms in clinic (modified from Chaudhuri *et al*).⁴⁸ HCP, healthcare professional; QoL, quality of life; PDSS, Parkinson's Disease Sleep Scale; HADS, Hospital Anxiety and Depression Scale; Scopa AUT, Scales for Outcomes in Parkinson's disease—Autonomic; ICD, impulse control disorders.

given the heterogeneity of neuropathological process underlying PD.

The groups of motor subtypes of PD include

- ▶ tremor dominant
- ▶ akinetic dominant
- ▶ postural instability and gait disturbances
- ▶ mixed.

Based on the dichotomy between non-motor symptom scores and motor scores in PD, non-motor classification of PD has been proposed, with five levels of non-motor symptoms burden⁴⁷ (box 2), as well as non-motor subtyping.⁴⁷ A recent study identified four distinct clusters within PD: two were non-motor-dominant and benign mixed

(a)

Centre ID: _____ Male ☐ Female ☒

NON-MOVEMENT PROBLEMS IN PARKINSON'S
 The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

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

4/30

Figure 4 (A) Non-motor symptoms (NMS) Quest, drug-naïve patient, H&Y 1, 5/30.

motor/non-motor (with prominent clinical expression of non-motor symptoms); the other two groups were motor-dominant and benign pure motor.¹⁶ We have proposed specific PD subtypes based on the predominance of key symptoms relevant to the early stage of PD; in the advanced stages, many of these subtypes may merge, as with motor subtypes.⁴⁷ However, the natural history of these proposed subtypes at the moment remains unknown.

EVIDENCE THAT NON-MOTOR SYMPTOMS ARE A KEY DETERMINANT OF QUALITY OF LIFE

Several studies have shown that the non-motor symptoms burden is a key determinant of quality of life of PD and carers.^{42–49} Patient-related questionnaires also show a growing awareness that these symptoms need addressing since they may adversely affect the lives of patient and carer. Improvement in non-motor symptoms, particularly the dopaminergic therapy-responsive symptoms, translates to robust improvements in quality of life.^{50–51}

(b)

Centre ID: _____ Male ☒ Female ☐

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6. Bowel (fecal) incontinence	<input type="checkbox"/>	<input checked="" type="checkbox"/>	21. Falling	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
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9. Getting up regularly at night to pass urine <i>x 1</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	24. Intense, vivid dreams or frightening dreams	<input checked="" type="checkbox"/>	<input type="checkbox"/>
10. Unexplained pains (not due to known conditions such as arthritis) <i>++</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	25. Talking or moving about in your sleep as if you are 'acting' out a dream <i>RM</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
11. Unexplained change in weight (not due to change in diet)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move ...	<input checked="" type="checkbox"/>	<input type="checkbox"/>
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14. Seeing or hearing things that you know or are told are not there	<input type="checkbox"/>	<input checked="" type="checkbox"/>	29. Double vision	<input type="checkbox"/>	<input checked="" type="checkbox"/>
15. Difficulty concentrating or staying focussed	<input type="checkbox"/>	<input checked="" type="checkbox"/>	30. Believing things are happening to you that other people say are not true	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Figure 4 (B) NMS Quest, drug-naïve patient, H&Y 1, 19/30.

NON-MOTOR FLUCTUATION IN PD

Apart from motor fluctuation, patients with PD also experience 'non-motor fluctuations',^{52 53} which often develop in tandem with motor fluctuations. Some non-motor symptoms are accentuated during 'off' periods while others occur only in 'off' periods (below).

NON-MOTOR SYMPTOMS THAT WORSEN DURING 'OFF' PERIODS

- ▶ fatigue
- ▶ depression
- ▶ anxiety
- ▶ inner restlessness
- ▶ impaired concentration/attention.

NON-MOTOR SYMPTOMS OCCURRING ONLY/ EXCLUSIVELY DURING 'OFF' PERIODS

- ▶ fatigue
- ▶ depression
- ▶ anxiety
- ▶ impaired concentration
- ▶ inner restlessness.

Anxiety, depression, fatigue and pain had a negative impact on health-related quality of life.⁵²

TREATMENT

There are diverse treatments to address non-motor symptoms in PD. Both the American Academy of Neurology and the Movement Disorders Society have

Table 5 Treatment suggestions for some non-motor symptoms

Non-motor symptoms	Commonly used strategies (where possible based on randomised controlled studies)	Investigational or reported treatment options (based on open label or observational reports)
Sleep disorders		
Excessive daytime sleepiness	Sleep hygiene (regular daytime exercise, avoiding stimulants at bedtime, regular hours of sleep at night) Modafinil (subjective improvement)	Caffeine intake (contradictory data and tablets may be used) Sodium oxybate—taken at night, only under specialist supervision (potential for abuse) Selective histamine H3 receptor inverse agonist ► Pitolisant (in trial) Adenosine receptor antagonists—Istradefylline, Tozadenant (in setup)
Insomnia	Sleep hygiene Short-acting benzodiazepines Non-benzodiazepine hypnotics ► Zopiclone Tricyclic antidepressants ► Amitriptyline	Night-time apomorphine infusion or Rotigotine patch (may help in cases of insomnia due to severe nighttime rigidity, restless legs syndrome and 'off' periods)
REM sleep behaviour disorder	Sleep in a safe environment while in bed, (remove all sharp and breakable objects) Clonazepam (usually used first line) Melatonin Pramipexole in combination with Clonazepam (one successful trial reported)	Long-acting melatonin (use being investigated)
Mood disorders		
Depression	► Pramipexole—recommended by Movement Disorders Society ► Selective serotonin reuptake inhibitor – Paroxetine – Citalopram ► Serotonin and norepinephrine reuptake inhibitor – Venlafaxine XR ► Tricyclic antidepressants—recommended by Movement Disorders Society – Nortriptyline – Desipramine Awareness of non-motor fluctuation related mood disorders	If as part of non-motor fluctuations ► Trial of long acting dopamine agonists ► Infusional therapies – Apomorphine infusion – Intrajejunal levodopa infusion
Fatigue	Methylphenidate—recommended by American Academy of Neurology, although considerable side effect profile	Modafinil (weak evidence base)
Pain	No specific recommendations apart from analgesics and dopaminergic drugs for non motor fluctuation related pain such as off related dystonic pain Baclofen (muscular pain aggravated by rigidity, anecdotal evidence) Opiates (Tramadol)	Central pain: Oxycodone with naloxone (PANDA study, randomised placebo-controlled study completed)
Cognitive dysfunction		
Dementia	► Rivastigmine—recommended by the Movement Disorders Society (oral or transdermal patch) ► Donepezil	Memantine Galantamine
Psychosis (hallucinations/delusions)	► Quetiapine (often used first line, based on clinical experience, despite of unconvincing trial data) ► Clozapine (needs specialised monitoring of blood count to monitor for agranulocytosis)—recommended by the Movement Disorders Society ► Exclusion of concomitant systemic infection or illness which may precipitate psychosis	Pimavanserin (serotonin 2A receptor inverse agonist)—in clinical trial
Autonomic dysfunction		
Dribbling of saliva	► Oral atropine drops—2–3 times/day ► Botulinum toxin A and B—parotid and submandibular injections (under specialist supervision in centres with experience in technique)—recommended by the American Academy of Neurology and the Movement Disorders Society	► Glycopyrrolate for short-term treatment—recommended by the Movement Disorders Society ► Ipratropium bromide spray (Atrovent)—1–2 doses per day sublingually
Constipation	► Diet and lifestyle advise: – Fibre-rich diet	

Continued

Table 5 Continued

Non-motor symptoms	Commonly used strategies (where possible based on randomised controlled studies)	Investigational or reported treatment options (based on open label or observational reports)
	<ul style="list-style-type: none"> – Ensure adequate fluid intake to avoid dehydration 	Lubiprostone (Amitiza)—in clinical trial
Bladder dysfunction—urgency, nocturia	<ul style="list-style-type: none"> ► Medications: <ul style="list-style-type: none"> – Macrolog (Movicol in the UK)—recommended by the American Academy of Neurology and the Movement Disorders Society – Lactulose (Duphalac) – Senna (Senokot) – Avoid constipating opiates for pain ► Anticholinergic agents (use with caution in patients with hallucinations and cognitive decline) <ul style="list-style-type: none"> – Oxybutynin – Tolterodine XL ► Desmopressin spray for troublesome nocturia (beware of nocturnal hypertension) 	<ul style="list-style-type: none"> ► If during off state—adjust PD medications ► Exercise-based behavioural therapy
Erectile dysfunction	Phosphodiesterase-5 inhibitors (use with caution in patients with postural hypotension) <ul style="list-style-type: none"> ► Sildenafil—recommended by the American Academy of Neurology ► Tadalafil (Cialis) 	Apomorphine injection may be tried
Orthostatic hypotension	Non-pharmacological therapies <ul style="list-style-type: none"> ► Increased salt and water intake ► Waist-high support stockings ► Physical counter manoeuvres ► Avoid volume depleting drugs (diuretics, antihypertensives) Pharmacological therapy <ul style="list-style-type: none"> ► Fludrocortisone ► Ephedrine ► Midodrine 	Pharmacological therapies <ul style="list-style-type: none"> ► Domperidone in addition to fludrocortisone ► L-threo-3,4-dihydroxyphenylserine for refractory orthostatic hypotension

PD, Parkinson's disease.

issued task force documents for managing non-motor symptoms in PD.^{54–55} Also, several open-label or comparative studies have addressed the effect of advanced therapies in PD on non-motor symptoms (apomorphine, intrajejunal levodopa infusion and rotigotine transdermal patch).^{56–58} However, the evidence base is poor, with few level 1 studies supporting any specific therapy. However, there was a recent randomised double-blind controlled study providing class I evidence that paroxetine and venlafaxine XR treat depression effectively in PD.⁵⁹ A few randomised clinical trials have addressed key non-motor symptoms in PD, such as pain (oxycodone with naloxone: the PANDA study) and excessive daytime sleepiness (caffeine, pitolisant, adenosine receptor antagonists). Several novel non-dopaminergic targets using non-dopaminergic agents have been described for managing some motor (mainly dyskinesias) and non-motor (excessive daytime sleepiness, pain, constipation, depression and cognition) symptoms (table 5). At present, these remain investigational.⁶⁰ We still await robust evidence for treatment of non-motor symptoms in PD; this remains a key unmet need.

For some non-motor symptoms, such as anxiety, depression, pain and fatigue, clinicians must ascertain as far as possible whether these are part of non-motor fluctuations. If so, and if they are exclusively present in the 'off' period, then treatment

may need to focus on alleviation of motor 'off' period with relevant anti-parkinsonian medication, rather than using antidepressants or antianxiety medications.

MULTIDISCIPLINARY SUPPORT

For symptoms such as dribbling of saliva, pain, sexual dysfunction, impulse control disorders and cognitive impairment, it is important and ideal to have the participation of a multidisciplinary team comprising PD nurse specialist, speech and language therapist, physiotherapist, occupational therapist, clinical psychologist and neuropsychiatrist. Speech and language therapy input in cases with disabling or severe dribbling of saliva is essential, for advice on swallow timers and head positioning. Experienced input from psychology and neuropsychiatry and a PD nurse specialist are essential in cases for managing severe depression, anxiety disorders and impulse control disorders. We also recommend, where possible, joint working with a member of the care of the elderly team with a special interest in PD with good access to multidisciplinary team support.

There is also increasing evidence suggesting that treating comorbidities, such as hypertension, diabetes mellitus, peptic ulcer disease, small intestinal bacterial overgrowth and osteoporosis, can ensure a complete treatment package for PD, in addition to monitoring

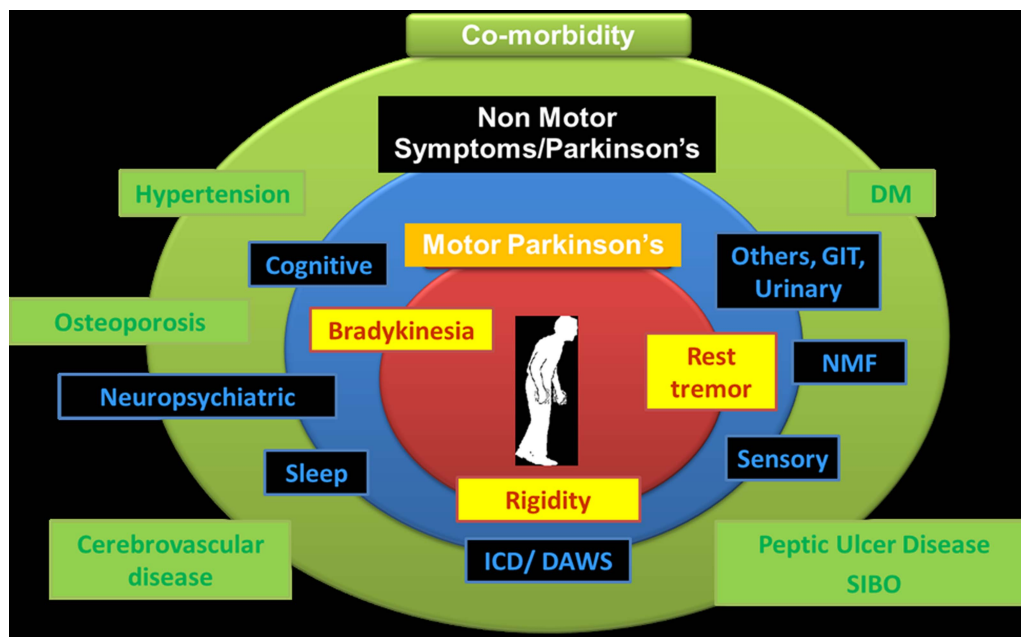


Figure 5 The spectrum of the multimorbid Parkinson's disease. GIT, gastrointestinal; NMF, non-motor fluctuation; DM, diabetes mellitus; SIBO, small intestinal bacterial overgrowth; ICD, impulse control disorders; DAWS, dopamine agonist withdrawal syndrome.

for and managing drug-induced non-motor symptoms and non-motor syndromes (figure 5).

THE FUTURE AND CONCLUSIONS

Non-motor symptoms represent a huge challenge to the treating physicians and allied health colleagues and continue to be a key determinant of patients' and carers' quality of life at huge societal costs. Their diversity, their differential effects on quality of life and their possible progression patterns pose additional challenges. We need much more research to recognise and manage non-motor symptoms effectively in clinical practice.

Future biomarkers will probably define the premotor stages of PD as well as the clinical patterns of PD into specific endophenotypes. Classifications have hitherto focused on motor subtypes but will include specific non-motor subtypes with the potential for specific treatments. Extension of non-motor symptoms-based studies will also address hitherto unaddressed issues, such as the influence of ethnicity, and poorly explored issues, such as influence of genetics.

Greater awareness of non-motor PD symptoms and the development of validated rating scales have led to major advances in understanding their evolution and progression; experimental models to explore their pathogenesis and potential treatments have lagged behind. There are now opportunities using existing dopaminergic animal models, some of which are now gathering momentum but others, such as the investigation of dopamine dysregulation syndromes/compulsive behaviours and dopamine agonist withdrawal syndromes, are in their infancy. What would really help is a major push to solve the role of non-dopaminergic degenerative changes in the evolution

of non-motor symptoms in PD. This is perfectly feasible as there are well-established tools to do this (eg, lesioning, toxin treatment), but so far there is no momentum for this.

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