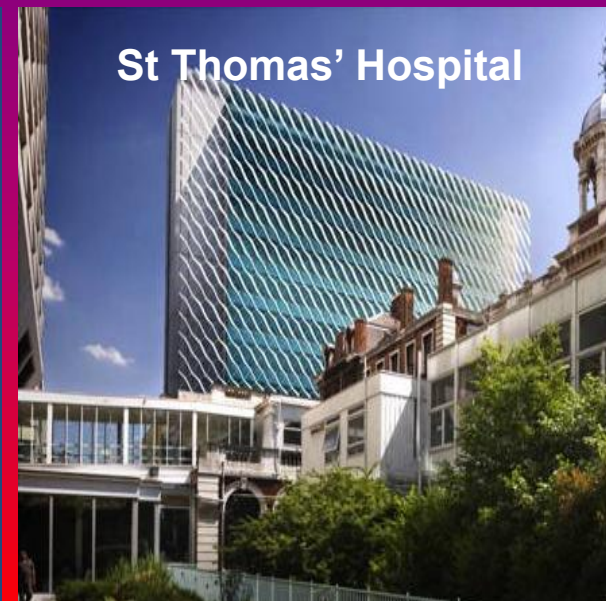


**Centre of excellence  
Parkinson's Care and Research**



**Guy's Hospital**

**Professor  
K Ray Chaudhuri**  
  
National Parkinson  
Foundation International  
Centre of Excellence  
  
and  
  
Kings College/University  
Hospital Lewisham



**St Thomas' Hospital**

**MRC**

Centre for  
Neurodegeneration  
Research

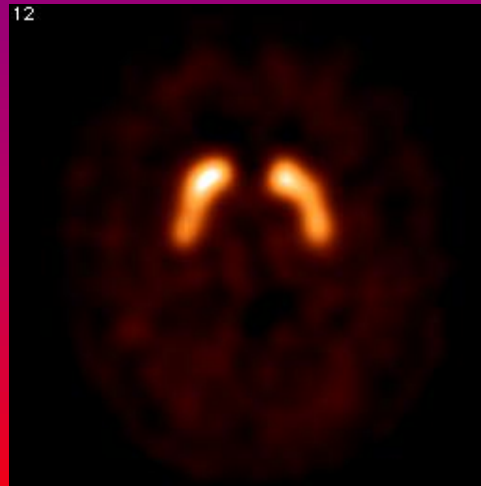
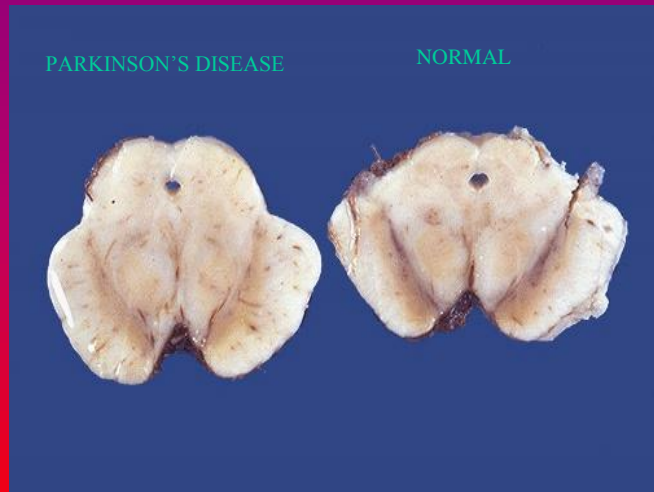
 **KING'S HEALTH PARTNERS**

 **NATIONAL  
PARKINSON  
FOUNDATION**

# What is Parkinson's?

## The traditional view !

- Parkinson's disease is one of the most common neurodegenerative diseases
- First described by James Parkinson in 1817 in *An Essay on the Shaking Palsy*
- The main pathological feature is the degeneration of neuromelanin-containing neurones in the pars compacta of the **substantia nigra**; resulting in depleted levels of **dopamine** within the brain



Images taken from *Fast Facts: Parkinson's Disease* Third Edition 2010;



KING'S HEALTH PARTNERS

N Ray Chaudhuri, C G Clough, K D Sethi

MRC

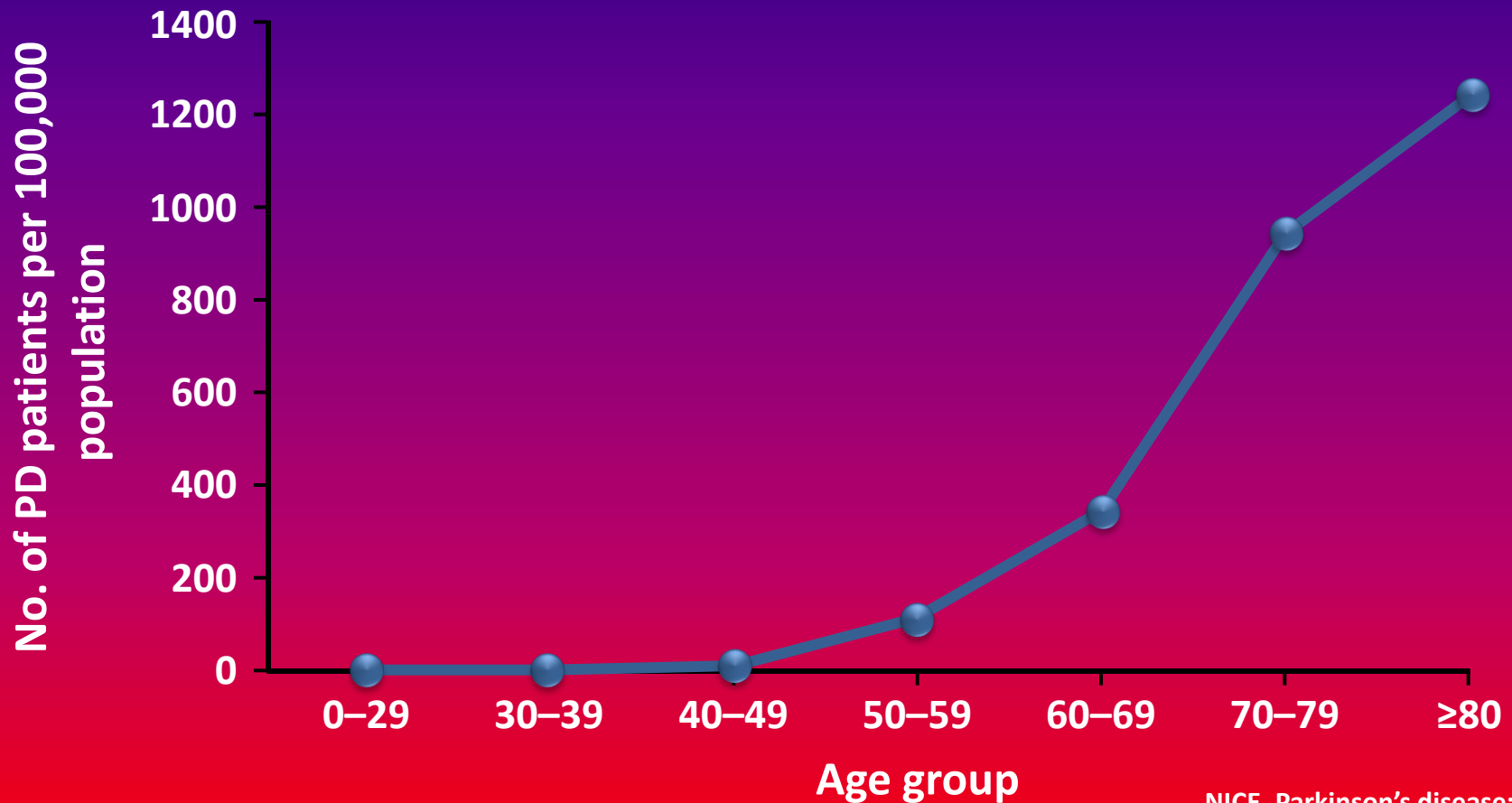
Centre for  
Neurodegeneration  
Research



# Prevalence and the ageing population

- Prevalence of Parkinson's disease is approximately 200 per 100,000 people
- 120,000 – 130,000 diagnosed cases in the UK alone
- 1 in 50 people over the age of 80 years are diagnosed with Parkinson's disease
- Males are 1.5 times more likely than females to develop the condition
- 10% below the age of 40

# Prevalence of Parkinson's disease with advancing age



NICE. Parkinson's disease: diagnosis and management in primary and secondary care, national cost impact report. June 2006

# The Concept of Parkinson's has changed

- Parkinson's is more than a motor disorder
- Dopamine is not the only neurochemical involved
- Non motor symptoms are present in 99% of people with Parkinson's and occur before motor symptoms start
- NMS are the main determinant of QoL of PwP and carer
- Holistic care and assessment are the key to modern treatment but sadly still neglected

# NMS Phenomenology

## Where are we ?

Parkinson's disease (PD), one of the most frequent neurodegenerative disorders, is no longer considered a complex motor disorder characterized by extrapyramidal symptoms, but a progressive multisystem or—more correctly—multiorgan disease with variegated neurological and nonmotor deficiencies.

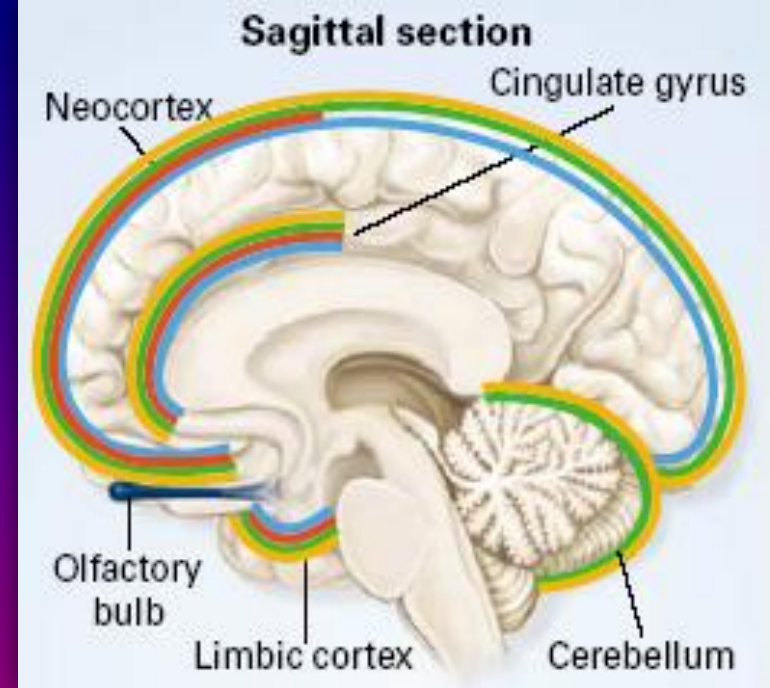
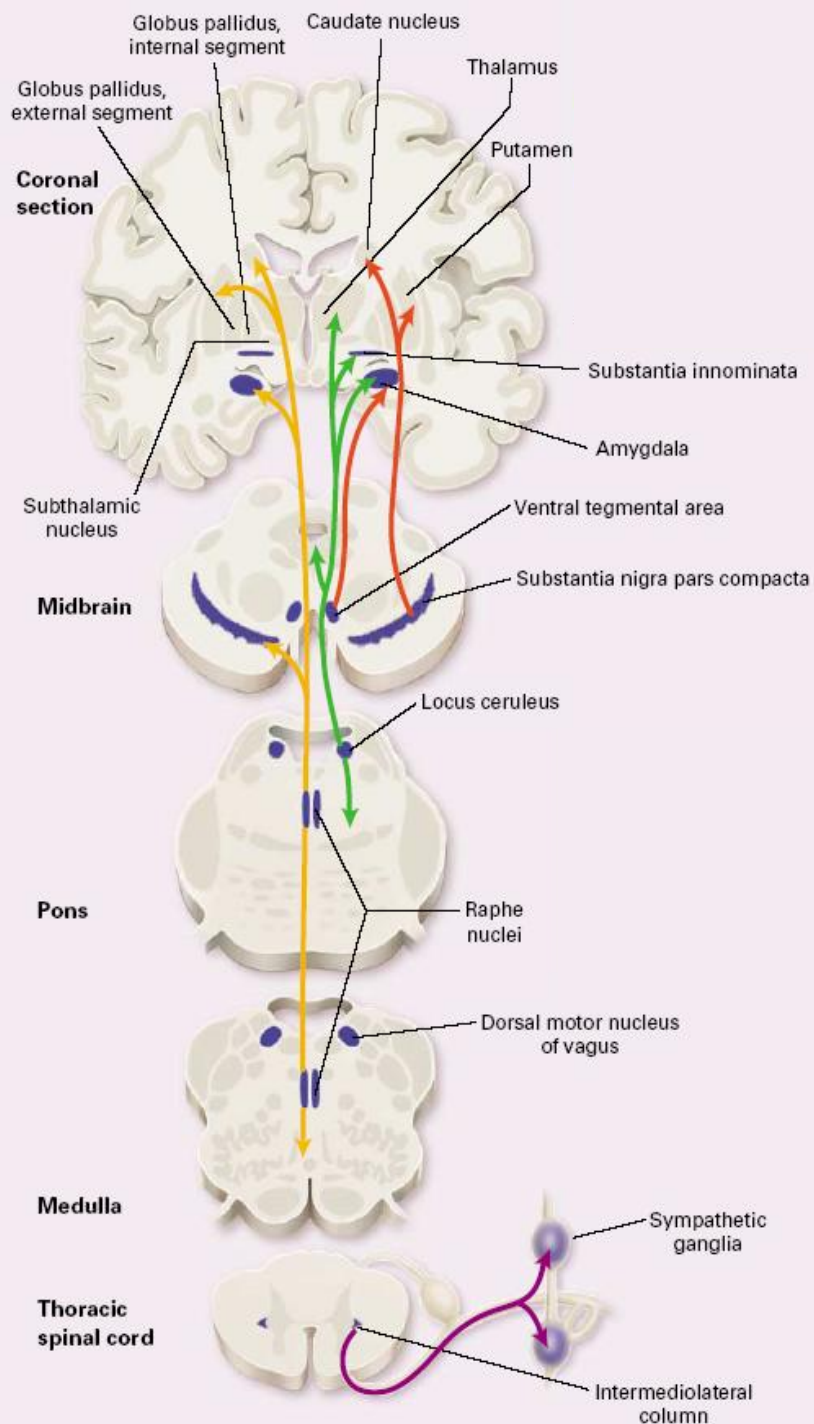
K Jellinger . Mov Disord 2012



Since 1961 treatment focus has been and continues to be “DOPAMINE” based  
Ldopa/Dopamine agonists  
Other DRT (Stem cells, Transplants)

YET

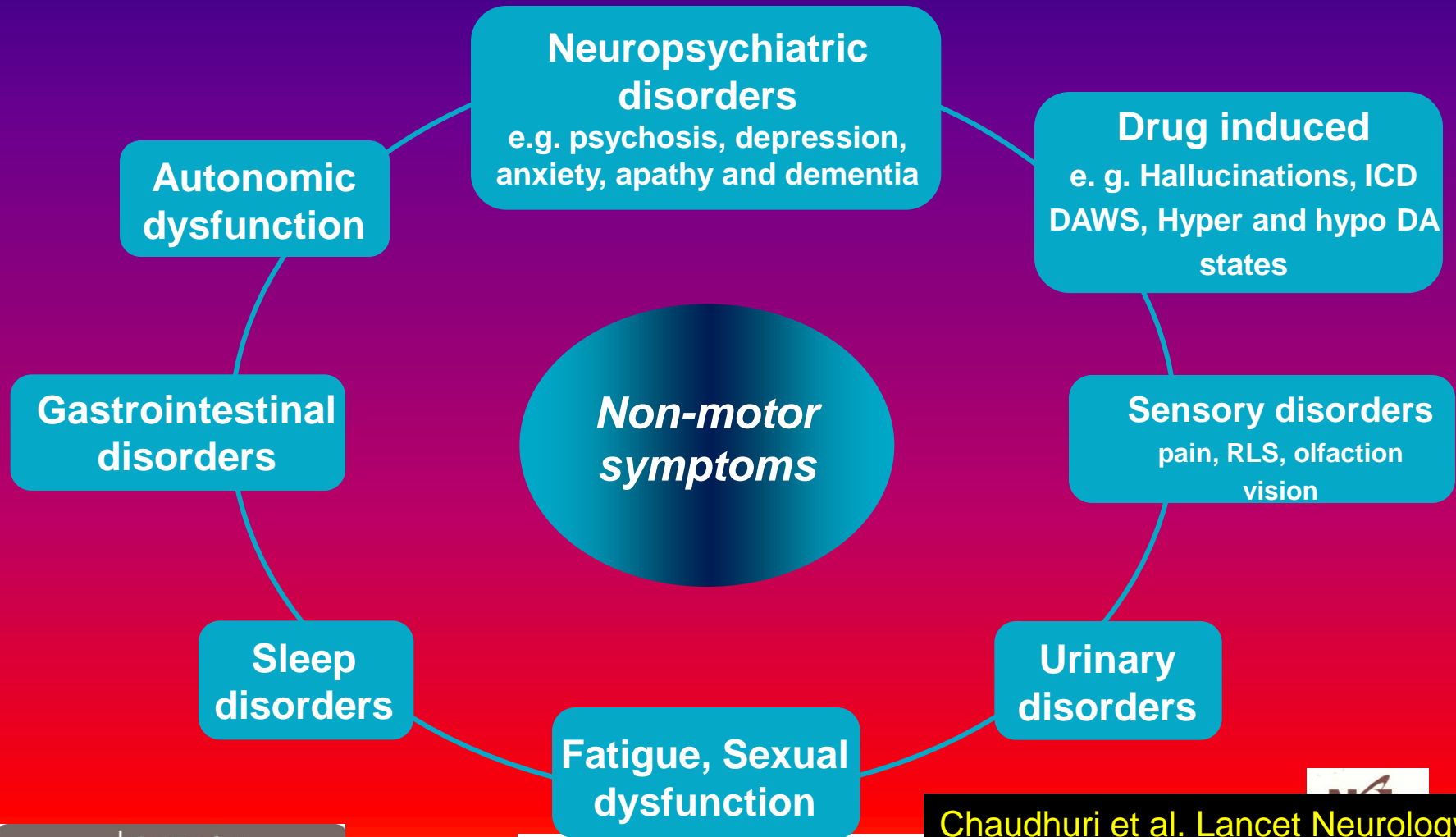




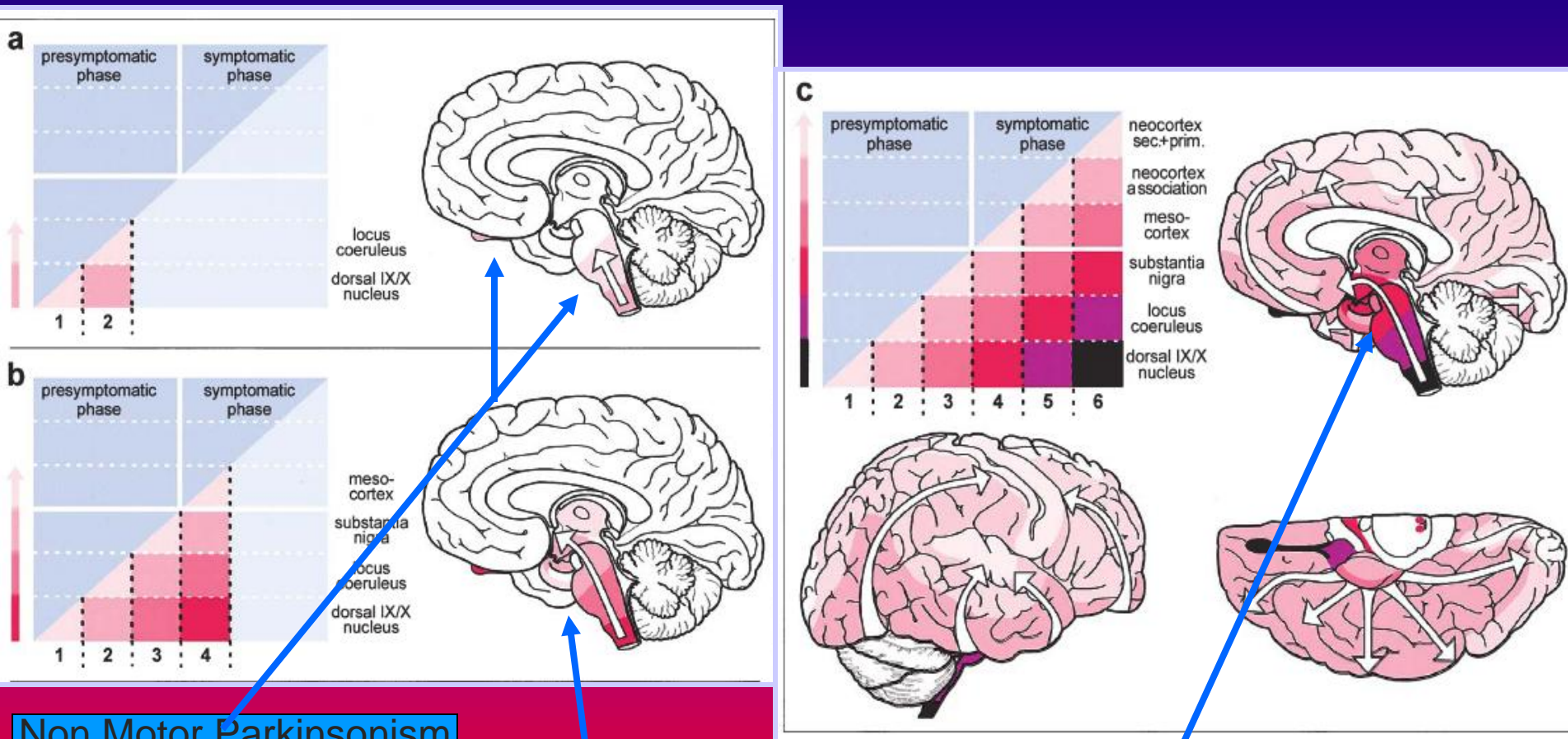
- Sites of neurodegeneration**
- Neurochemical pathways**
- Dopamine
  - Norepinephrine
  - Serotonin
  - Acetylcholine



**Non-motor symptoms of PD cause morbidity, mortality and quadruples cost of care of advanced Parkinson's and are common across all stages of PD**



# Progression of neurodegeneration and NMS



**Non Motor Parkinsonism**  
Hyposmia  
Depresión  
RBD  
Constipación  
AD  
EDS

**Motor Parkinsonism**

**Dementia**  
Apathy  
NMS stages 4  
HY stage 4/5

# VIEWPOINT

## Toward a Redefinition of Parkinson's Disease

Matthew B. Stern, MD,<sup>1\*</sup> Anthony Lang, MD,<sup>2</sup> and Werner Poewe, MD<sup>3</sup>

*Movement Disorders*, Vol. 27, No. 1, 2012

PHASE 1	PRECLINICAL PD	PD-specific pathology assumed to be present, supported by molecular or imaging markers, no clinical signs and symptoms
	PREMOTOR PD	Presence of early non-motor signs and symptoms due to extranigral PD pathology
	MOTOR PD	PD pathology involves substantia nigra leading to nigrostriatal dopamine deficiency sufficient to cause classic motor manifestations followed by later nonmotor features due to extension of the pathology

Hyposmia  
Bowel (constipation)  
Autonomic dysfunction  
RBD/EDS  
Depression  
Pain/Col Vision

Hyposmia: Haehner et al. PRD 2009  
Dresden mice model. (Rotenone) Pan Montojo et al. 2010

## RESEARCH ARTICLE

# The Impact of Non-Motor Symptoms on Health-Related Quality of Life of Patients with Parkinson's Disease

Pablo Martinez-Martin, MD, PhD,<sup>1,2\*</sup> Carmen Rodriguez-Blazquez, BS,<sup>1</sup> Monica M. Kurtis, MD,<sup>3</sup>  
K. Ray Chaudhuri, MD, FRCP, DSC,<sup>4,5</sup> on Behalf of the NMSS Validation Group

<sup>1</sup>Area of Applied Epidemiology, National Centre of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain

<sup>2</sup>Scientific Management, Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain

<sup>3</sup>Movement Disorders Unit, Department of Neurology, University of California, San Francisco, CA, USA

<sup>4</sup>National Parkinson's Centre, London, UK

<sup>5</sup>Department of Neurology, London, UK

**TABLE 6.** Multiple linear regression models of HRQoL scales

	Adjusted $R^2$	Standardized beta	t	Sig.
PDQ-39 SI model	0.59			
(Constant)		(23.76)	5.55	0.000
NMSS total		0.52	13.64	0.000
SCOPA-motor complications		0.20	4.81	0.000

One of 2011 top cited papers in Mov Disord

Premio “Gonzalo Rodríguez Lafora” 2012 Prize

NMSS Domains	Groups of patients (n)	PDQ-39 SI	EQ-5D Index
Cardiovascular	With symptoms (173)	32.45±17.85	0.48±0.37
	No symptoms (238)	24.79±15.66	0.62±0.32
	<b>p*</b>	<0.0001	0.0001
Sleep/fatigue	With symptoms (356)	30.11±16.80	0.52±0.35
	No symptoms (54)	14.48±11.57	0.79±0.20
	<b>p*</b>	<0.0001	<0.0001
Mood/Apathy	With symptoms (310)	31.31±16.87	0.50±0.35
	No symptoms (100)	17.64±13.01	0.74±0.27
	<b>p*</b>	<0.0001	<0.0001
Perceptual problems/ Hallucinations	With symptoms (123)	36.89±17.25	0.38±0.39
	No symptoms (288)	24.22±15.47	0.63±0.30
	<b>p*</b>	<0.0001	<0.0001
Attention/Memory	With symptoms (296)	30.65±16.93	0.52±0.36
	No symptoms (115)	21.27±15.37	0.66±0.30
	<b>p*</b>	<0.0001	0.0005
Gastrointestinal	With symptoms (302)	31.02±17.84	0.49±0.36
	No symptoms (109)	19.76±10.92	0.74±0.23
	<b>p*</b>	<0.0001	<0.0001
Urinary	With symptoms (338)	29.52±17.44	0.54±0.36
	No symptoms (73)	21.12±12.97	0.66±0.28
	<b>p*</b>	0.0002	0.001
Sexual dysfunction	With symptoms (177)	29.71±15.97	0.53±0.34
	No symptoms (234)	26.75±17.71	0.58±0.35
	<b>p*</b>	0.03	0.09
Miscellaneous	With symptoms (99)	30.38±17.36	0.50±0.36
	No symptoms (312)	20.61±13.54	0.73±0.25
	<b>p*</b>	<0.0001	<0.0001

\* Mann-Whitney test. Benajmini-Hochberg adjustment,  $p < 0.026$



# NMS

No holistic assessment tools till 2006

!!

# FIRST MULTIDISCIPLINARY PARKINSON'S DISEASE (PD) NON-MOTOR SYMPTOM (NMS) MEETING FOR DEVISING A NON MOTOR SCALE FOR ASSESSMENT OF PD (Supported by Parkinson's UK, MDS, Industry)

PENNYHILL PARK,  
SURREY, UK  
5,6 FEB 2004



The first validated NMS questionnaire NMSQuest  
Empowering patients across the world to declare NMS to HCP  
Worldwide use  
Chaudhuri et al 2006

**MRC** | Centre for Neurodegeneration Research

 KING'S HEALTH[illegible]

# PD NMS QUESTIONNAIRE

Name: \_\_\_\_\_ Date: \_\_\_\_\_ Age: \_\_\_\_\_

Circle 1/2      Male      Female

**NON-COMMUNICATIVE PATIENTS IN PARADIGM(S)**

The movement symptoms of Parkinson's are well known. However, other symptoms can sometimes occur as well as the movement symptoms or by themselves. It is important that the doctor knows about this, particularly if they are a specialist for problems.

**A sample of problems is listed below. Please tick the box "Yes" if you have experienced it during the past month or during the course of your illness, and "No" if you have not. If you have had the problem for the first time in the past month tick the "Yes" box. You should answer "Yes" 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? \_\_\_\_\_

1. Disturbance of sleep during the daytime	<input type="checkbox"/> Yes	<input type="checkbox"/> No	16. Feeling wet, dry or itchy	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. Loss of energy to make it to work or school	<input type="checkbox"/> Yes	<input type="checkbox"/> No	17. Feeling anxious, fearful or nervous	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Difficulty swallowing food or problems with chewing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	18. Feeling less interested in sex or more interested	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4. Swallowing or feeling of food stuck	<input type="checkbox"/> Yes	<input type="checkbox"/> No	19. Feeling hot or cold when other people say you are not	<input type="checkbox"/> Yes	<input type="checkbox"/> No
5. Difficulty swallowing a liquid or food	<input type="checkbox"/> Yes	<input type="checkbox"/> No	20. Feeling light-headed, dizzy or like you are spinning	<input type="checkbox"/> Yes	<input type="checkbox"/> No
6. Feeling like you are having a hard time to get your arms to move	<input type="checkbox"/> Yes	<input type="checkbox"/> No	21. Fainting	<input type="checkbox"/> Yes	<input type="checkbox"/> No
7. Feeling food's inconsistency	<input type="checkbox"/> Yes	<input type="checkbox"/> No	22. Feeling if effort is easy to make during activities	<input type="checkbox"/> Yes	<input type="checkbox"/> No
8. Feeling like you are not getting a complete meal	<input type="checkbox"/> Yes	<input type="checkbox"/> No	23. Feeling if effort is easy to make during activities	<input type="checkbox"/> Yes	<input type="checkbox"/> No
9. A sense of urgency to pass urine makes you rush to the toilet	<input type="checkbox"/> Yes	<input type="checkbox"/> No	24. Difficulty getting to sleep or not sleeping enough at night	<input type="checkbox"/> Yes	<input type="checkbox"/> No
10. Getting to urinate at night makes you wake up	<input type="checkbox"/> Yes	<input type="checkbox"/> No	25. Incessant, loud drooling or drooling during sleep	<input type="checkbox"/> Yes	<input type="checkbox"/> No
11. Involuntary pants that do not become comfortable (as in activities)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	26. Taking or missing doing a step of time if you are "out of sync" or out of time	<input type="checkbox"/> Yes	<input type="checkbox"/> No
12. Unpleasant change in voice that has to change	<input type="checkbox"/> Yes	<input type="checkbox"/> No	27. Unpleasant sensations in the legs or of walking, and a feeling that you need to move	<input type="checkbox"/> Yes	<input type="checkbox"/> No
13. Problems remembering things just after doing them	<input type="checkbox"/> Yes	<input type="checkbox"/> No	28. Sweating of your face	<input type="checkbox"/> Yes	<input type="checkbox"/> No
14. Loss of interest in what is happening around you in a social setting	<input type="checkbox"/> Yes	<input type="checkbox"/> No	29. Excessive sweating	<input type="checkbox"/> Yes	<input type="checkbox"/> No
15. Sweating during a social setting	<input type="checkbox"/> Yes	<input type="checkbox"/> No	30. Drooling vision	<input type="checkbox"/> Yes	<input type="checkbox"/> No
16. Sweating during a social setting	<input type="checkbox"/> Yes	<input type="checkbox"/> No	31. Believing things are happening to you that other people are not	<input type="checkbox"/> Yes	<input type="checkbox"/> No
17. Difficulty concentrating or staying focused	<input type="checkbox"/> Yes	<input type="checkbox"/> No			

[illegible]

# International Multicenter Pilot Study of the First Comprehensive Self-Completed Nonmotor Symptoms Questionnaire for Parkinson's Disease: The NMSQuest Study

Kallol Ray Chaudhuri,<sup>1\*</sup> Pablo Martinez-Martin,<sup>2</sup> Anthony H.V. Schapira,<sup>3</sup> Fabrizio Stocchi,<sup>4</sup> Kapil Sethi,<sup>5</sup> Per Odin,<sup>6</sup> Richard G. Brown,<sup>7</sup> William Koller,<sup>8†</sup> Paolo Barone,<sup>9</sup> Graeme MacPhee,<sup>10</sup> Linda Kelly,<sup>11</sup> Martin Rabey,<sup>12</sup> Doug MacMahon,<sup>13</sup> Sue Thomas,<sup>14</sup> William Ondo,<sup>15</sup> David Rye,<sup>16</sup> Alison Forbes,<sup>17</sup> Susanne Tluk,<sup>17</sup> Vandana Dhawan,<sup>17,18</sup> Annette Bowron,<sup>19</sup> Adrian J. Williams,<sup>20</sup> and Charles W. Olanow<sup>21</sup>



Now used worldwide  
Translated to 14 languages  
Recommended by  
MDS  
Parkinson's UK  
DH UK  
EPDA

**TABLE 2.** Domains included in the NMSQuest

Number	Domain	Number of items
1	Gastrointestinal tract	8
2	Urinary tract	2
3	Sexual function	2
4	Cardiovascular	2
5	Apathy/attention/memory	3
6	Hallucinations/delusions	2
7	Depression/anxiety/anhedonia	2
8	Sleep/fatigue	5
9	Pain (unrelated to other causes)	1
10	Miscellaneous (e.g., diplopia, weight loss)	3

## PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

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 .....	<input type="checkbox"/>	<input type="checkbox"/>	16. Feeling sad, 'low' or 'blue' .....	<input type="checkbox"/>	<input type="checkbox"/>
2. Loss or change in your ability to taste or smell .....	<input type="checkbox"/>	<input type="checkbox"/>	17. Feeling anxious, frightened or panicky .....	<input type="checkbox"/>	<input type="checkbox"/>
3. Difficulty swallowing food or drink or problems with drinking .....	<input type="checkbox"/>	<input type="checkbox"/>	18. Feeling less interested in sex or more interested in sex .....	<input type="checkbox"/>	<input type="checkbox"/>
4. Nausea or feelings of sickness (nausea) .....	<input type="checkbox"/>	<input type="checkbox"/>	19. Finding it difficult to have sex when you try .....	<input type="checkbox"/>	<input type="checkbox"/>
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces) .....	<input type="checkbox"/>	<input type="checkbox"/>	20. Feeling light headed, dizzy or weak standing from sitting or lying .....	<input type="checkbox"/>	<input type="checkbox"/>
6. (fecal) incontinence .....	<input type="checkbox"/>	<input type="checkbox"/>	21. Falling .....	<input type="checkbox"/>	<input type="checkbox"/>
7. Feeling that your bowel emptying is incomplete or having been to the toilet .....	<input type="checkbox"/>	<input type="checkbox"/>	22. Finding it difficult to stay awake during activities such as working, driving or eating .....	<input type="checkbox"/>	<input type="checkbox"/>
8. A sense of urgency to pass urine makes you rush to the toilet .....	<input type="checkbox"/>	<input type="checkbox"/>	23. Difficulty getting to sleep at night or staying asleep at night .....	<input type="checkbox"/>	<input type="checkbox"/>
9. Waking up regularly at night to pass urine .....	<input type="checkbox"/>	<input type="checkbox"/>	24. Intense, vivid dreams or frightening dreams .....	<input type="checkbox"/>	<input type="checkbox"/>
10. Joint pains (not due to known conditions such as arthritis) .....	<input 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 type="checkbox"/>
11. Unexplained change in weight (not due to illness or in diet) .....	<input type="checkbox"/>	<input 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 type="checkbox"/>
12. Problems remembering things that have happened recently or forgetting to do things .....	<input type="checkbox"/>	<input type="checkbox"/>	27. Swelling of your legs .....	<input type="checkbox"/>	<input type="checkbox"/>
13. Loss of interest in what is happening around you or doing things .....	<input type="checkbox"/>	<input type="checkbox"/>	28. Excessive sweating .....	<input type="checkbox"/>	<input type="checkbox"/>
14. Seeing or hearing things that you know or are told are not there .....	<input type="checkbox"/>	<input type="checkbox"/>	29. Double vision .....	<input type="checkbox"/>	<input type="checkbox"/>
15. Difficulty concentrating or staying focussed .....	<input type="checkbox"/>	<input type="checkbox"/>	30. Believing things are happening to you that other people say are not true .....	<input type="checkbox"/>	<input type="checkbox"/>



# NMSS: a grade rating scale

1. Chaudhuri KR *et al.* The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. *Mov Disord* 2007;22:1901–11; 2. Martinez-Martin P *et al.* International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease. *Neurology* 2009;10;73:1584–91.

**Non-Motor Symptom assessment scale for Parkinson's Disease**

Patient ID No: \_\_\_\_\_ Initials: \_\_\_\_\_ Age: \_\_\_\_\_

Symptoms assessed over the last month. Each symptom scored with respect to:  
Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.  
Frequency: 1 = Rarely (<1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time)

Domains will be weighed differentially. Yes/No answers are not included in final frequency x severity calculation.  
(Bracketed text in questions within the scale is included as an explanatory aid).

Domain	Severity	Frequency	Frequency x Severity
<b>Domain 1: Cardiovascular including falls</b>			
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Does the patient fall because of fainting or blacking out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>SCORE:</b>			<input type="text"/>
<b>Domain 2: Sleep/fatigue</b>			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Does the patient have difficulties falling or staying asleep?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Is the patient aware or has he/she been told about talking during sleep or moving about as if acting-out a dream?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>SCORE:</b>			<input type="text"/>
<b>Domain 3: Mood /Cognition</b>			
8. Has the patient lost interest in his/her surroundings?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Has the patient lost interest in doing things or lack motivation to start new activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Does the patient look dazed or unaware of what is going on? (Not just when drowsy or falling asleep?)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Does the patient feel nervous, worried or frightened for no apparent reason?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Does the patient seem sad or depressed or has he/she reported such feelings?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Does the patient have flat moods without the normal "highs" and "lows"?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>SCORE:</b>			<input type="text"/>
<b>Domain 4: Perceptual problems/hallucinations</b>			
15. Does the patient indicate that he/she sees things that are not there?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Does the patient experience double vision? (2 separate real objects and not blurred vision)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>SCORE:</b>			<input type="text"/>
<b>TOTAL SCORE:</b>			<input type="text"/>

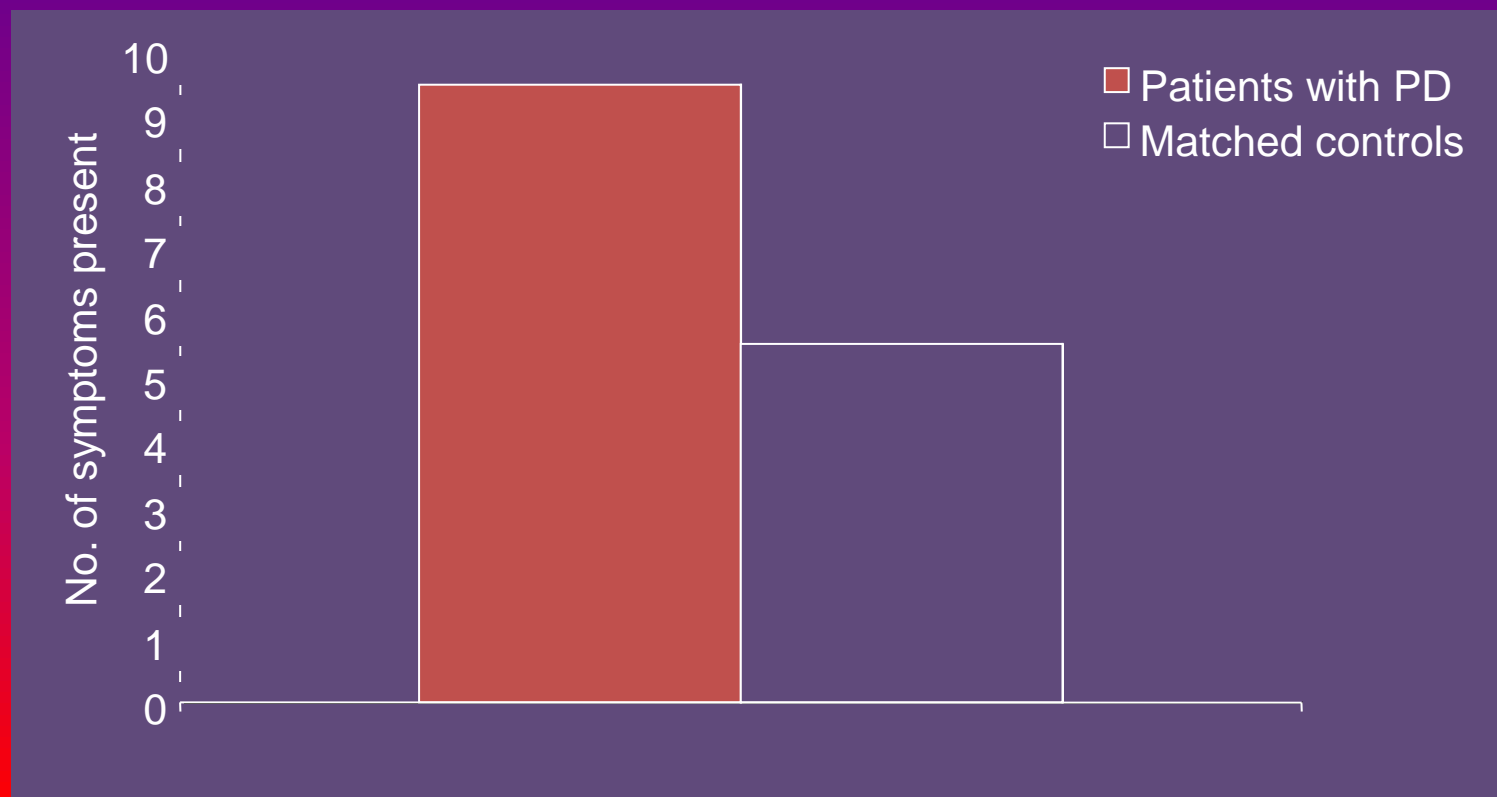
Developed by the International  
Contact: ray.chaudhuri@uh

- The first comprehensive grade rating scale for PD
  - Addresses 9 domains and 30 questions
  - Complementary to NMSQuest
  - To be administered by healthcare professional
  - Good clinimetrics in two international studies and validated in over 600 patients<sup>1,2</sup>
  - Sensitive to change in clinical trials

# Highly significantly more non-motor symptoms present in PD

Chaudhuri et al, 2006

$p=0.0000$



## Prevalence of Nonmotor Symptoms in Parkinson's Disease in an International Setting; Study Using Nonmotor Symptoms Questionnaire in 545 Patients

Pablo Martinez-Martin, PhD, MD,<sup>1</sup> Anthony H.V. Schapira, FRCP, MD, DSc, FmedSci,<sup>2</sup> Fabrizio Stocchi, MD,<sup>3</sup> Kapil Sethi, MD, FRCP,<sup>4</sup> Per Odin, MD,<sup>5</sup> Graeme MacPhee, FRCP,<sup>6</sup> Richard G. Brown, PhD,<sup>7</sup> Yogini Naidu, BSc, RGN,<sup>8</sup> Lisa Clayton, BSc,<sup>9</sup> Kazuo Abe, MD,<sup>10</sup> Yoshio Tsuboi, MD,<sup>11</sup> Dough MacMahon, FRCP,<sup>12</sup> Paolo Barone, MD,<sup>13</sup> Martin Rabey, MD,<sup>14</sup> Ubaldo Bonuccelli, MD,<sup>15</sup> Alison Forbes, RGN,<sup>16</sup> Kieran Breen, MRCP,<sup>17</sup> Susanne Tluk, RGN,<sup>8</sup> C. Warren Olanow, MD,<sup>18</sup> Sue Thomas, RGN,<sup>19</sup> David Rye, MD,<sup>20</sup> Annette Hand, RGN, MSc,<sup>21</sup> Adrian J. Williams, FRCP,<sup>22</sup> William Ondo, MD,<sup>23</sup> and K. Ray Chaudhuri, MD, FRCP, DSc<sup>24\*</sup>

PDNMG  
International  
2007

## The Priamo Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease

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PRIAMO  
Italian  
2009

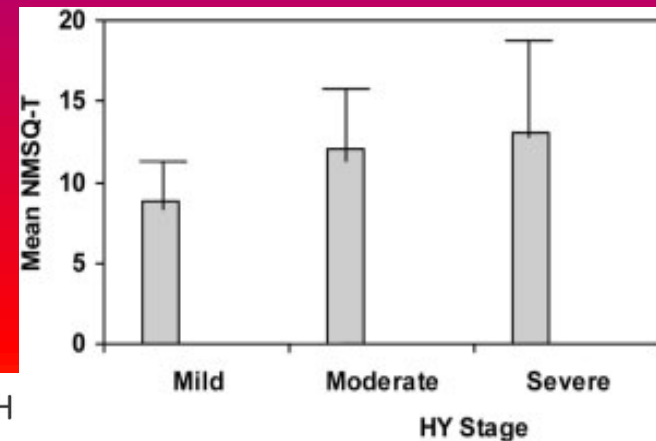
PDNMG  
International  
2010

## The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

K. Ray Chaudhuri, MD, DSc,<sup>1\*</sup> Cristina Prieto-Jurcynska, MD,<sup>2,3</sup> Yogini Naidu, MSc,<sup>4</sup> Tanya Mitra, BSc,<sup>5</sup> Belen Frades-Payo, MSc,<sup>6</sup> Susanne Tluk, RGN,<sup>4</sup> Anne Ruessmann, RGN,<sup>7</sup> Per Odin, PhD,<sup>7</sup> Graeme MacPhee, MD,<sup>8</sup> Fabrizio Stocchi, MD,<sup>9</sup> William Ondo, MD,<sup>10</sup> Kapil Sethi, MD, FRCP,<sup>11</sup> Anthony H.V. Schapira, MD, DSc,<sup>12</sup> Juan Carlos Martinez Castrillo, MD, PhD,<sup>13</sup> and Pablo Martinez-Martin, MD, PhD<sup>6</sup>

Prevalence of Nonmotor Symptoms in Parkinson's Disease in an  
International Setting; Study Using Nonmotor Symptoms  
Questionnaire in 545 Patients

Hoehn & Yahr	Mean	SD	Patients %
1	8.9	5.1	20.5
2	8.8	4.8	36.8
3	12.0	5.2	33.9
4	13.1	5.4	6.7
5	12.8	6.2	2.2



# The Priamo Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease

P. Barone et al.

Frequency of NMS increased along with the disease severity

**TABLE 3.** *Prevalence of NMS domains and disease stage*

NMS domains	All N = 1,072 (%)	Disease Stage (Hoehn and Yahr scale)			
		1 N = 167 (%)	1.5–2 N = 515 (%)	2.5–3 N = 325 (%)	4–5 N = 49 (%)
Gastrointestinal	654 (61.0)	76 (45.5)	280 (54.4)	250 (76.9)	36 (73.5)
Pain	653 (60.9)	85 (50.9)	302 (58.6)	218 (67.1)	39 (79.6)
Urinary	614 (57.3)	72 (43.1)	266 (51.7)	222 (68.3)	44 (89.8)
Cardiovascular	158 (14.7)	22 (13.2)	70 (13.6)	53 (16.3)	11 (22.5)
Sleep	687 (64.1)	80 (47.9)	312 (60.6)	245 (75.4)	40 (81.6)
Fatigue	623 (58.1)	63 (37.7)	291 (56.5)	224 (68.9)	40 (81.6)
Apathy	328 (30.6)	41 (24.6)	138 (26.8)	119 (36.6)	24 (49.0)
Attention/memory	479 (44.7)	63 (37.7)	208 (40.4)	168 (51.7)	32 (65.3)
Skin	260 (24.3)	24 (14.4)	102 (19.8)	112 (34.5)	16 (32.7)
Psychiatric	716 (66.8)	102 (61.1)	326 (63.3)	238 (73.2)	41 (83.7)
Respiratory	191 (17.8)	16 (9.6)	80 (15.5)	74 (22.8)	15 (30.6)
Miscellaneous	515 (48.0)	62 (37.1)	247 (48.0)	168 (51.7)	29 (59.2)

Cochran-Armitage trend test  $<0.0045$  (with Bonferroni's correction) for all NMS except cardiovascular symptoms ( $P = 0.0774$ ).





## Review

Parkinson's disease: The non-motor issues<sup>☆</sup>K. Ray Chaudhuri<sup>a,\*</sup>, Per Odin<sup>b,c</sup>, Angelo Antonini<sup>d</sup>, Pablo Martinez-Martin<sup>e</sup><sup>a</sup> National Parkinson Foundation Centre of Excellence, King's College Hospital, Kings College, 9th Floor Ruskin Wing, Denmark Hill, London SE5 9RS, UK<sup>b</sup> Department of Neurology, Central Hospital, Bremerhaven, Germany<sup>c</sup> Department of Neurology, University Hospital, Lund, Sweden<sup>d</sup> IRCCS San Camillo, Venice and University of Padua, Italy<sup>e</sup> AD Research Unit and CIBERNED, CIEN-Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, SpainChaudhuri KR et al. *Parkinsonism Relat Disord* 2011;

Table 2

A comparative tabulation of NMS prevalence data from holistic international studies (NMSQuest) and Italian study (PRIAMO).

Studies	Urinary	Depression	Sleep	Fatigue	Gastrointestinal	Sexual fn	Cognitive	Miscellaneous
Percentages								
NMSQuest N = 545	Urgency 55.8% Nocturia 61.9%	Sadness/blues 50.1% Anxiety 45.3%	EDS 31.1% Insomnia 45.7% RBD 35.6%	31.1%	Dribbling saliva 41.5% Swallowing 28.3% Constipation 52.4%	34%	Memory 44.8% Concentration 45.7% Apathy 34.6%	Pain 28.7%
NMSQuest N = 242	Urgency 59.9% Nocturia 64.9%	Sadness/blues 48.8% Anxiety 41.7%	EDS 34.7% Insomnia 47.3% RBD 38.7%	35%	Dribbling saliva 41.7% Swallowing 27% Constipation 47%	37.3%	Memory 51.2% Concentration 45.7% Apathy	Pain 45.9%
PRIAMO N = 1072	Urgency 35 % Nocturia 34.6%	Sadness 22.5% Anxiety 55.8%	EDS 21.2% Insomnia 36.9% RBD 29.6%	58.1%	Dribbling saliva 31.1% Swallowing 16.1% Constipation 27.5%	19.6%	Memory 25.1% Concentration 31.4% Apathy 21%	Pain 20.8%



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## Parkinsonism and Related Disorders

journal homepage: [www.elsevier.com/locate/parkreldis](http://www.elsevier.com/locate/parkreldis)



Review

### Non-motor symptoms of Parkinson's disease in China: A review of the literature

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**Table 1**

Comparison of essential items of non-motor symptoms from NMSQuest assessment between China and Western countries.

Battery	Sources	1.Urinary	2.Gastrointestinal	3.Cardiovascular	4.Sexual	5.Cognitive	6.Sleep	7.Depression	8.Miscellaneous
NMSQuest	China [11,12] ( n = 200 )	Urgency 56.5% Nocturia 65.4%	Dribbling 46.3% Swallowing 30.3% Constipation 71.7%	Dizziness 38.5%	Sex difficulty 57.5%	Memory 62.5% Concentration 31.5%	EDS 32.5% Insomnia 52.5% RBD 33.5% RLS 41%	Sadness 56% Anxiety 47.5%	Pain 38.8%
	Original study [6] ( n = 123 )	Urgency 61.0% Nocturia 66.7%	Dribbling 35.0% Swallowing 23.6% Constipation 46.7%	Dizziness 39.8%	Sex difficulty 26.8%	Memory 43.9% Concentration 37.4%	EDS 28.4% Insomnia 40.6% RBD 32.5% RLS 37.4%	Sadness 44.7% Anxiety 39.9%	Pain 27.6%
	PRIAMO study [9] ( n = 1072 )	Urgency 35.0% Nocturia 34.6%	Dribbling 31.1% Swallowing 16.1% Constipation 27.5%	Dizziness 14.2%	Sex difficulty 19.6%	Memory 25.1% Concentration 31.4%	EDS 21.2% Insomnia 36.9% RBD 29.6% RLS 15.2%	Sadness 22.5% Anxiety 55.8%	Pain 27.6%

Notes: NMSQuest, non-motor symptoms questionnaire; EDS, excessive daytime sleepiness; RBD, Rapid eye movement sleep behavior disorders; RLS, Restless leg syndrome.

J Neurol (2012) 259:1639–1647  
DOI 10.1007/s00415-011-6392-3

ORIGINAL COMMUNICATION

# Gender-related differences in the burden of non-motor symptoms in Parkinson's disease

Pablo Martinez-Martin • Cristian Falup Pecurariu • Per Odin • Jacobus J. van Hilten •  
Angelo Antonini • Jose M. Rojo-Abuin • Vanderci Borges • Claudia Trenkwalder •  
Dag Aarsland • David J. Brooks • Kallol Ray Chaudhuri

# Gender related differences in burden of Non-motor symptoms in Parkinson's disease

Pablo Martinez-Martin<sup>1\*</sup>; Cristian Falup Pecurariu<sup>2</sup>; Per Odin<sup>3</sup>; Jacobus J. van Hilten<sup>4</sup>; Angelo Antonini<sup>5</sup>; Jose M. Rojo-Abuin<sup>6</sup>; Vanderci Borges,<sup>7</sup> Claudia Trenkwalder<sup>8</sup>; Dag Aarsland<sup>9</sup>; David J. Brooks<sup>10</sup>; K Ray Chaudhuri<sup>11</sup>.

J Neurol 2012;259:1639-1647 N = 951

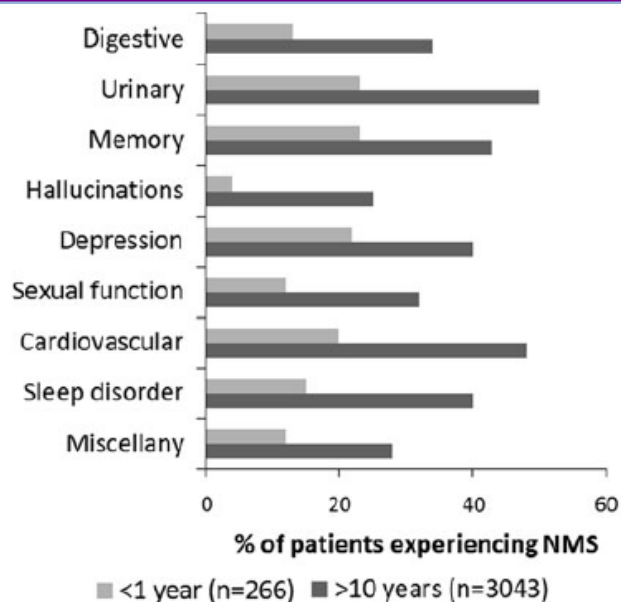
Number of NMSS domains affected	Total sample	Men	Women
0	0.53	0.84	-
1	1.06	1.68	0.42
2	1.59	2.21	0.95
3	2.12	2.74	1.48
4	2.65	3.27	2.01
5	3.18	3.80	2.54
6	3.71	4.33	3.07
7	4.24	4.86	3.60
8	4.77	5.39	4.13
9	5.30	5.92	4.66

Fatigue, feelings of nervousness, feelings of sadness, constipation, restless legs, and pain were more common and severe in women.  
On the contrary, daytime sleepiness, dribbling saliva, interest in sex, and problems having sex were more prevalent and severe in men.

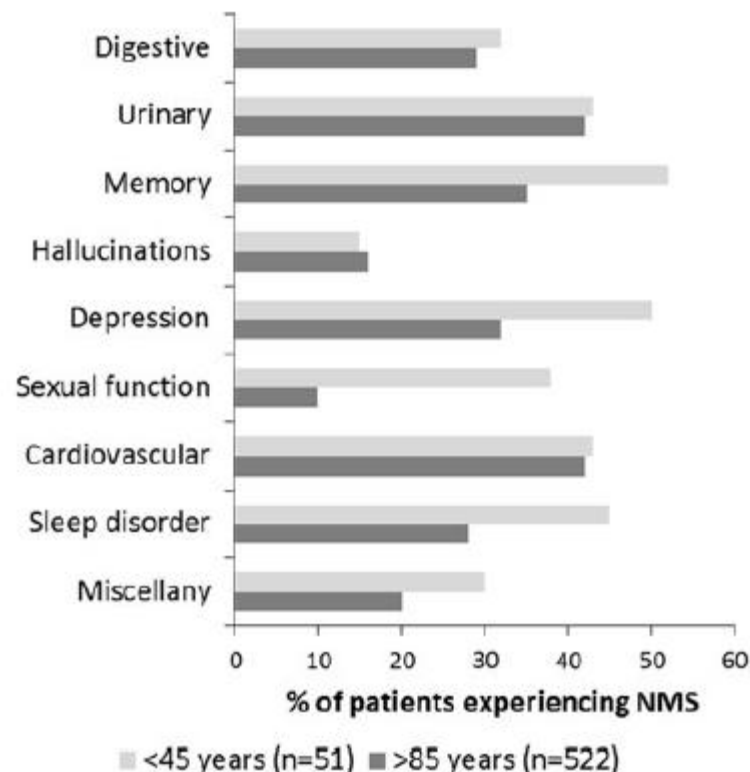


## Non-motor symptoms of Parkinson's disease: the patient's perspective

Kieran C. Breen · Gerda Drutytė



**Fig. 1** The percentage of survey participants, either diagnosed within 1 year prior to completing the survey or diagnosed more than 10 years previously who have experienced non-motor symptoms since their diagnosis

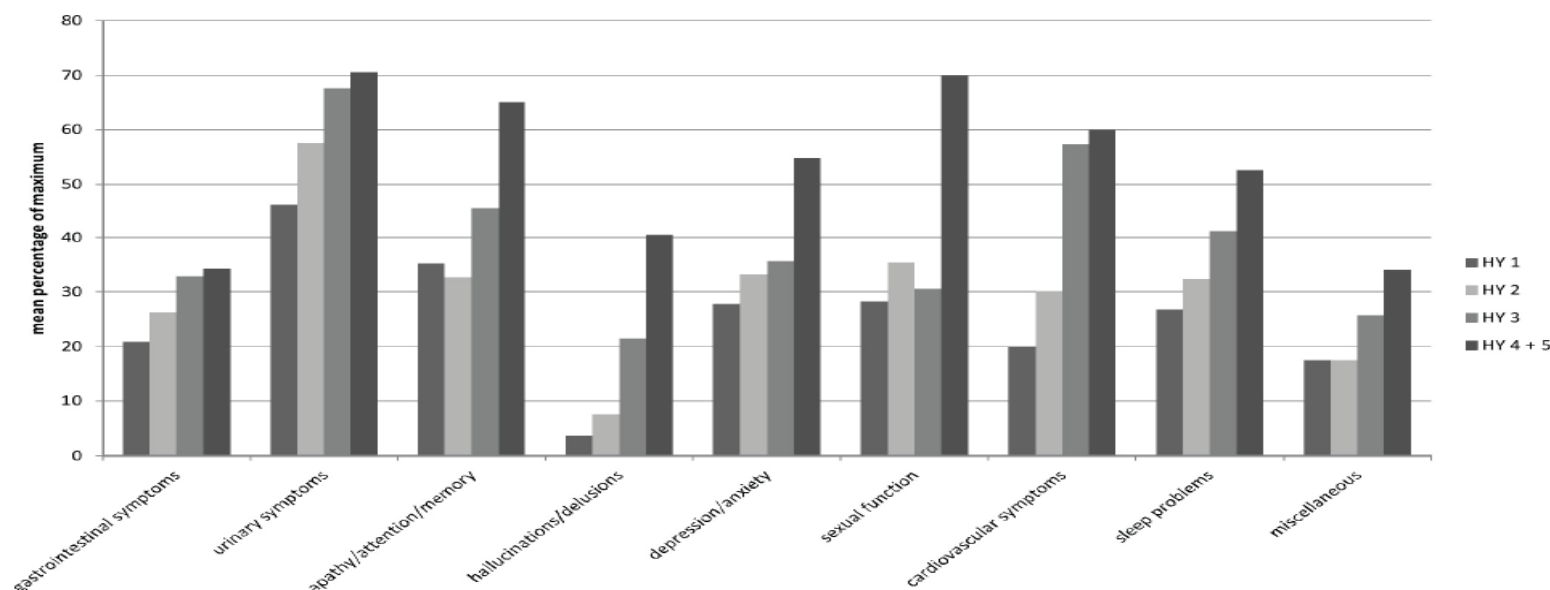


**Fig. 2** The percentage of survey participants, either under the age of 45 prior to completing the survey or over the age of 85, experiencing non-motor symptoms since their diagnosis

## Original Article

# Non-motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire

David Crosiers<sup>1,2,3</sup>, Barbara Pickut<sup>1</sup>, Jessie Theuns<sup>2,4</sup>, Peter Paul De Deyn<sup>5,6,7</sup>, Christine Van Broeckhoven<sup>2,4</sup>, Pablo Martinez-Martin<sup>8</sup>, K Ray Chaudhuri<sup>9</sup>, Patrick Cras<sup>1,3</sup>



**Figure 2.** Subdomains of NMSQuest across different Hoehn and Yahr stages. The mean percentage of positive answers on all questions of a subdomain of the NMSQuest is shown across different Hoehn and Yahr stages. Abbreviations: HY 1: Hoehn and Yahr stage 1; HY 2: Hoehn and Yahr stage 2; HY 3: Hoehn and Yahr stage 3; HY 4 + 5: Hoehn and Yahr stage 4 and 5. The respective p-values of the Kruskal-Wallis test for each domain are: gastrointestinal symptoms: 0.014; urinary symptoms: 0.039; apathy/attention/memory: 0.006; hallucinations/delusions: <0.001; depression/anxiety: 0.054; sexual function: <0.028; cardiovascular symptoms: <0.001; sleep problems: 0.003; miscellaneous: <0.016.

## Non-recognition of depression and other non-motor symptoms in Parkinson's disease

L.M. Shulman\*, R.L. Taback, A.A. Rabinstein, W.J. Weiner

Detection of NMS is useless if we do not recognize the problem

*Movement Disorders*  
Vol. 25, No. 6, 2010, pp. 704–709  
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## The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

K. Ray Chaudhuri, MD, DSc,<sup>1\*</sup> Cristina Prieto-Jurcynska, MD,<sup>2,3</sup> Yogini Naidu, MSc,<sup>4</sup> Tanya Mitra, BSc,<sup>5</sup> Belen Frades-Payo, MSc,<sup>6</sup> Susanne Tluk, RGN,<sup>4</sup> Anne Ruessmann, RGN,<sup>7</sup> Per Odin, PhD,<sup>7</sup> Graeme Macphee, MD,<sup>8</sup> Fabrizio Stocchi, MD,<sup>9</sup> William Ondo, MD,<sup>10</sup> Kapil Sethi, MD, FRCP,<sup>11</sup> Anthony H.V. Schapira, MD, DSc,<sup>12</sup> Juan Carlos Martinez Castrillo, MD, PhD,<sup>13</sup> and Pablo Martinez-Martin, MD, PhD<sup>6</sup>

The non declaration of non motor symptoms of Parkinson's disease to health care professionals. An international study using the non motor symptoms questionnaire

K Ray Chaudhuri, C Prieto-Jurcynska, Y Naidu, T Mitra, B Frades- Payo, S Tluk, A Ruessmann, P Odin, G Macphee, F Stocchi, W Ondo, K Sethi, AHV Schapira, P Martinez- Martin

- Mean of total NMS =  $10.9 \pm 5.6$
- Mean of undeclared NMS =  $4.6 \pm 4.1$

42.8% of the positive symptoms

\* Calculated on the number of positive NMS

		Positive		Non-declared	
Items		N	%	n	% *
1	Dribbling	101	41.7	46	45.5
2	Taste/ Smelling	103	42.9	41	39.8
3	Swallowing	65	27.0	24	36.9
4	Vomiting	38	15.8	16	42.1
5	Constipation	115	47.5	53	46.1
6	Bowel incontinence	15	6.3	5	33.3
7	Bowel emptying incomplete	65	27.0	31	47.7
8	Urgency	145	59.9	61	42.1
9	Nocturia	157	64.9	69	43.9
10	Pains	111	45.9	45	40.5
11	Weight	55	22.7	21	38.2
12	Remembering	124	51.2	55	44.4
13	Loss of interest	82	33.9	35	42.7
14	Hallucinations	41	17.0	17	41.5
15	Concentrating	121	50.0	46	38.0
16	Sad, Blues	118	48.8	45	38.1
17	Anxiety	101	41.7	40	39.6
18	Sex_drive	90	37.3	41	45.6
19	Sex_difficulty	82	34.3	37	45.1
20	Dizzy	94	38.8	47	50.0
21	Falling	70	29.3	28	40.0
22	Daytime sleepiness	84	34.7	44	52.4
23	Insomnia	114	47.3	50	43.9
24	Intense, vivid dreams	84	34.7	44	52.4
25	Acting_out during dreams	93	38.7	41	44.1
26	Restless Legs	99	41.1	36	36.4
27	Swelling	91	37.6	33	36.3
28	Sweating	74	30.6	25	33.8
29	Diplopia	44	18.2	14	31.8
30	Delusions	23	9.5	15	65.2

Table 3: Potentially treatable NMS of PD undeclared to health care professionals across several European centres.

NMS	% Undeclared	Potentially Treatable
Dribbling saliva	45.5	BTx, Atrovent , oral atropine, swallow timer
Vomiting	42.1	Domperidone
Constipation	46.1	Macrogol
Hallucinations	41.5	Drug modifications/neuroleptic
Anxiety	39.6	Anxiolytics
EDS	52.4	Modafinil, sleep hygiene, caffeine
RBD	44.1	Clonazepam, melatonin
Insomnia	43.9	Hypnotics, nighttime CDD

**None of these symptoms were treated prior to NMSQuest use even in major PD centres**



NMSQ score 5/30

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

	Yes	No		Yes	No
1. Drobbing of saliva during the daytime	<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 (fecal) 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"/>

5/30

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998.

NMSQ score 19/30, untreated, HY 2

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

	Yes	No		Yes	No
1. Drobbing of saliva during the daytime	<input type="checkbox"/>	<input checked="" type="checkbox"/>	16. Feeling sad, 'low' or 'blue'	<input checked="" type="checkbox"/>	<input 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 checked="" type="checkbox"/>	<input type="checkbox"/>
3. Difficulty swallowing food or drink or problems with choking	<input checked="" type="checkbox"/>	<input type="checkbox"/>	18. Feeling less interested in sex or more interested in sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4. Vomiting or feelings of sickness (nausea)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	19. Finding it difficult to have sex when you try	<input checked="" type="checkbox"/>	<input type="checkbox"/>
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	20. Feeling light headed, dizzy or weak standing from sitting or lying	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6. Bowel (fecal) incontinence	<input type="checkbox"/>	<input checked="" type="checkbox"/>	21. Falling	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
7. Feeling that your bowel emptying is incomplete after having been to the toilet	<input checked="" type="checkbox"/>	<input type="checkbox"/>	22. Finding it difficult to stay awake during activities such as working, driving or eating	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8. A sense of urgency to pass urine makes you rush to the toilet	<input type="checkbox"/>	<input checked="" type="checkbox"/>	23. Difficulty getting to sleep at night or staying asleep at night	<input checked="" type="checkbox"/>	<input type="checkbox"/>
9. Getting up regularly at night to pass urine	<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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	25. Talking or moving about in your sleep as if you are 'acting' out a dream	<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"/>
12. Problems remembering things that have happened recently or forgetting to do things	<input checked="" type="checkbox"/>	<input type="checkbox"/>	27. Swelling of your legs	<input type="checkbox"/>	<input checked="" 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"/>

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# A Proposal for a Comprehensive Grading of Parkinson's Disease Severity Combining Motor and Non-Motor Assessments: Meeting an Unmet Need

Kallol Ray Chaudhuri<sup>1</sup>, Jose Manuel Rojo<sup>2</sup>, Anthony H. V. Schapira<sup>3</sup>, David J. Brooks<sup>4</sup>, Fabrizio Stocchi<sup>5</sup>, Per Odin<sup>6</sup>, Angelo Antonini<sup>7</sup>, Richard J. Brown<sup>8</sup>, Pablo Martinez-Martin<sup>9\*</sup>

Grading the Parkinson's Disease Non-motor Burden

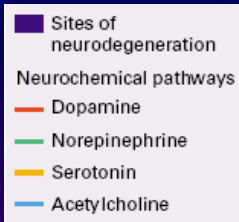
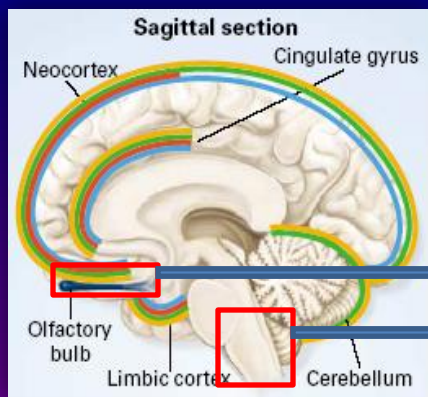
**Table 3.** Variables in the study broken down by the NMS burden levels and Hoehn and Yahr staging\*.

	Non-Motor Symptoms Burden Levels				
	No	Mild	Moderate	Severe	Very severe
Level	0	1	2	3	4
<b>NMSS score</b>	0	1–20	21–40	41–70	≥71
<b>n (935)</b>	5	244	233	218	235
<b>PD Duration</b>	2.80±2.49	5.88±4.68	7.64±4.99	8.38±5.21	10.16±7.12
<b>SCOPA-Motor</b>					
A. Examination	4.00±1.87	9.54±5.16	10.35±5.56	12.16±6.11	14.89±7.94
B. ADL	0.00±0.00	4.70±3.11	5.93±3.12	7.33±3.72	9.65±4.72
C. Complications	0.40±0.89	1.43±2.27	2.28±2.55	3.07±2.80	4.11±3.57
Total score	4.40±2.07	15.68±8.85	18.55±9.04	22.56±10.68	28.57±14.35
<b>CISI-PD Total</b>	1.80±1.10	5.52±3.19	7.19±3.55	9.02±4.04	11.55±5.04
<b>EQ-5D Index</b>	1.00±0.00	0.78±0.23	0.68±0.28	0.60±0.29	0.36±0.38
<b>EQ-VAS</b>	75.80±37.43	66.73±22.65	65.08±20.86	63.11±20.86	54.35±21.62
<b>PDQ-8 Index</b>	6.25±10.60	19.88±17.85	25.80±15.89	31.51±16.87	45.70±19.05

# NM Endophenotypes

Chaudhuri et al. PLOS One. 2013

- Park Cognitive
- Park Depression/Anxiety
- Park Sleep
- Park Pain
- Park Fatigue
- Park Autonomic



**Brainstem phenotype**

**Park Sleep**

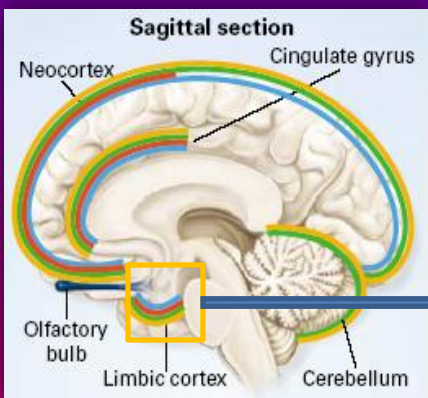
EDS

RBD

Insomnia

Autonomic/  
GIT/GUT

**Park Autonomic**



**Limbic phenotype**

**Park Depression  
Anxiety**

Anxiety  
Anx-Depression

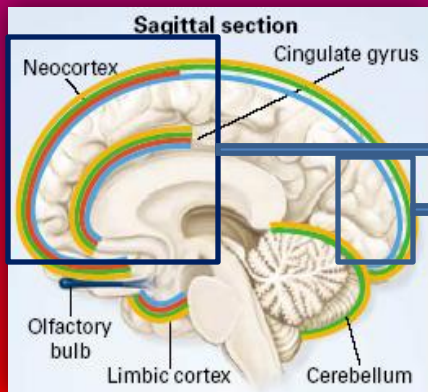
Major Depression

**Park Fatigue**

Central  
Fatigue

**Park Pain**

Central  
Pain



**Cortical phenotype**

**Park  
Cognitive**

Dementia

Amnesic  
MCI



Apathy

MRC

Centre for  
Neurodegeneration  
Research



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# Fatigue an independent NMS of PD

## Fatigue in PD can occur

- Independent of Depression
- Independent of Excessive daytime sleepiness
- Independent of DA intake





# Fatigue in levodopa-naïve subjects with Parkinson disease

G. Schifitto, MD  
J.H. Friedman, MD  
D. Oakes, PhD  
L. Shulman, MD  
C.L. Comella, MD  
K. Marek, MD  
S. Fahn, MD  
The Parkinson Study  
Group ELLDOPA  
Investigators\*

## ABSTRACT

**Background:** Fatigue is a common complaint in Parkinson disease (PD). We investigated fatigue in a cohort of previously untreated patients with early PD enrolled in the Earlier vs Later Levodopa (ELLDOPA) clinical trial.

**Methods:** A total of 361 patients were enrolled in the randomized, double-blind, placebo-controlled ELLDOPA trial and assigned to receive placebo or carbidopa-levodopa 37.5/150 mg, 75/300 mg, or 150/600 mg daily for 40 weeks, followed by a 2-week medication washout period. Subjects who scored >4 on the Fatigue Severity Scale were classified as fatigued. PD severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn-Yahr scale, and Schwab-England Activities of Daily Living Scale. A subgroup of subjects underwent [ $^{123}$ I]- $\beta$ -CIT SPECT to measure striatal dopamine transporter density.

Neurology 2008;71:481-485

Elldopa study: 37% fatigue in untreated non depressed PD

# Fatigue Vs Sleep

- The word “tired” is used interchangeably with sleepiness.
- Symptoms of fatigue and sleep dysfunction overlap sufficiently to potentially confound studies of fatigue
- Several studies suggest that fatigue is an independent symptom in PD, unrelated to the degree of sleepiness or to nocturnal sleep disturbance.
- Distinct clinical phenotypes:
- EDS: Older age, male > Female, cognitive issues, unrelated to depression
- Fatigue: No link with age, gender, cognitive issues, and ? increased with depression

Brain Advance Access published September 30, 2010

doi:10.1093/brain/awq268

Brain 2010; Page 1 of 10 | 1

**BRAIN**

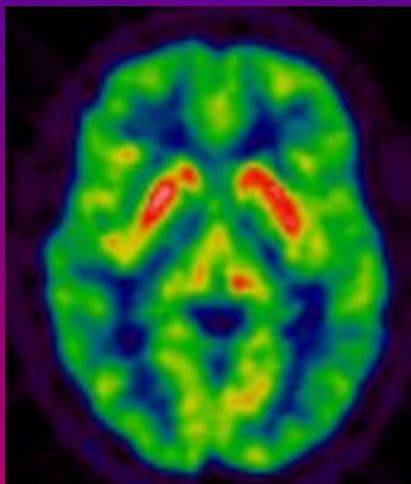
A JOURNAL OF NEUROLOGY

# Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction

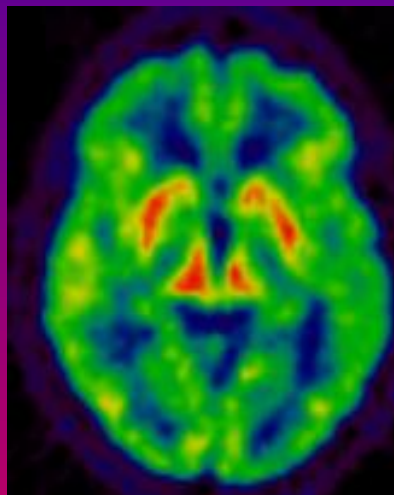
Nicola Pavese,<sup>1</sup> Vinod Metta,<sup>2</sup> Subrata K. Bose,<sup>1</sup> Kallol Ray Chaudhuri<sup>2</sup> and David J. Brooks<sup>1</sup>

# *$^{11}\text{C}$ -DASB binding in PD*

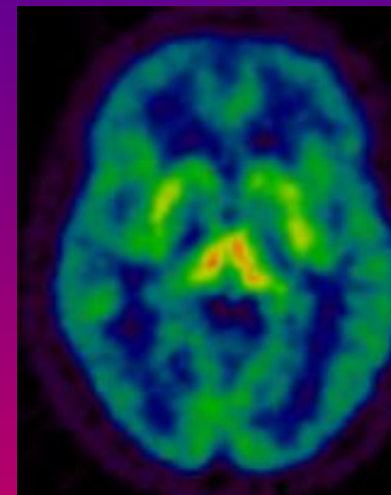
R



Healthy  
volunteer



PD without fatigue  
PFS-16 = 2



PD with fatigue  
PFS-16 = 15

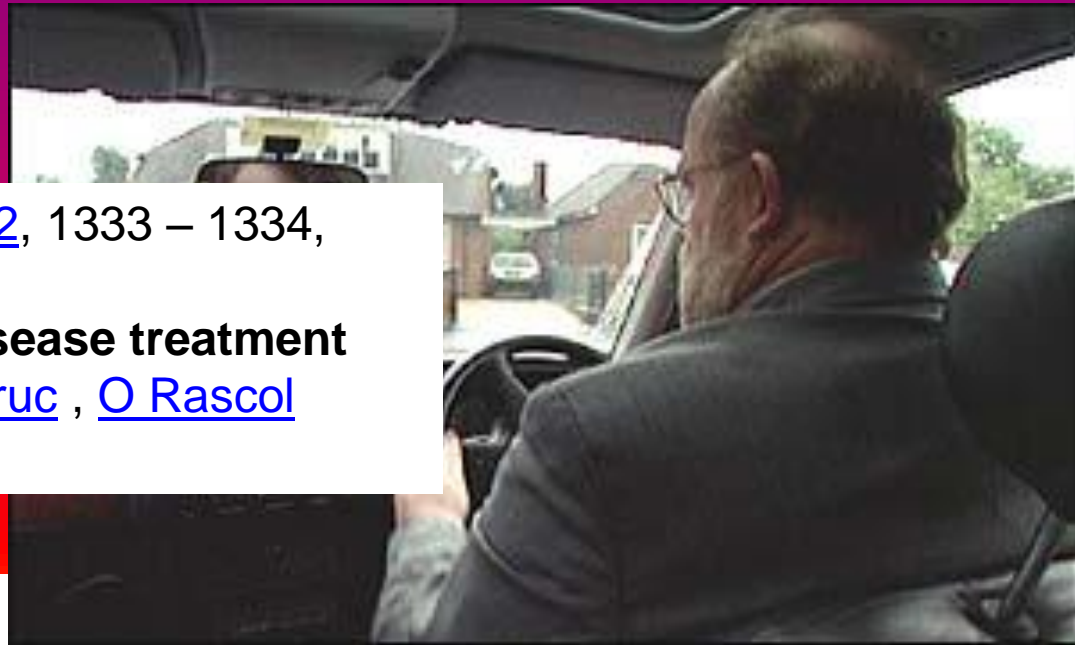


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- **Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole**

S. Frucht, J. D. Rogers P. E. Greene, M. F. Gordon, S. Fahn, Neurology 1999

The authors report a new side effect of the dopamine agonists pramipexole and ropinirole: sudden irresistible attacks of sleep. Eight PD patients taking pramipexole and one taking ropinirole fell asleep while driving, causing accidents. Five experienced no warning before falling asleep. The attacks ceased when the drugs were stopped. Neurologists who prescribe these drugs and patients who take them should be aware of this possible side effect.

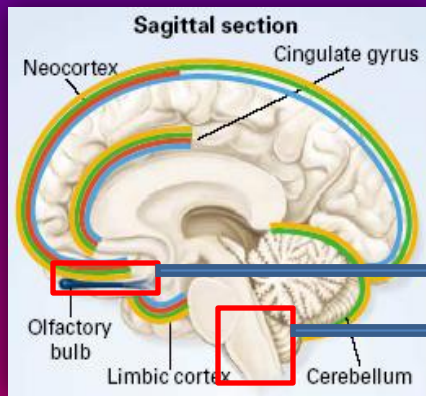
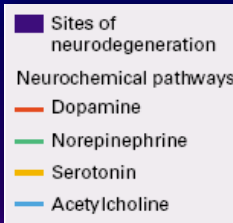


The Lancet, [Volume 355, Issue 9212](#), 1333 – 1334, 2000

**Sleep attacks and Parkinson's disease treatment**

[JJ Ferreira](#), [M Galitzky](#), [JL Montastruc](#), [O Rascol](#)





**Brainstem phenotype**

**Park Sleep**

**EDS**

**RBD**

**Insomnia**

**Park Autonomic**

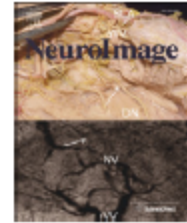
**Autonomic/  
GIT/GUT**



Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: [www.elsevier.com/locate/ynimg](http://www.elsevier.com/locate/ynimg)



[ $^{18}\text{F}$ ]FDOPA uptake in the raphe nuclei complex reflects serotonin transporter availability. A combined [ $^{18}\text{F}$ ]FDOPA and [ $^{11}\text{C}$ ]DASB PET study in Parkinson's disease

N. Pavese <sup>a,\*</sup>, B.S. Simpson <sup>a</sup>, V. Metta <sup>b</sup>, A. Ramlackhansingh <sup>a</sup>, K. Ray Chaudhuri <sup>b</sup>, D.J. Brooks <sup>a</sup>

# Sleep regulatory centres dysfunction in Parkinson's disease patients with excessive daytime sleepiness.

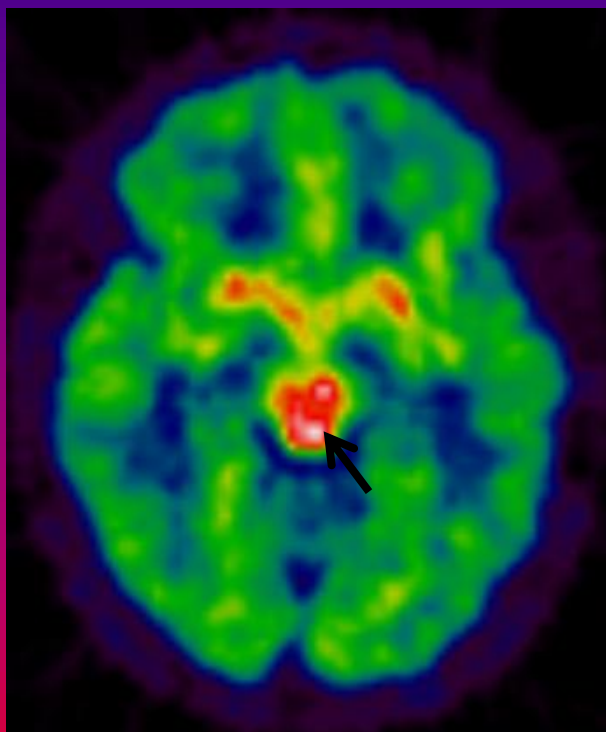
## An in vivo PET study

Nicola Pavese<sup>1</sup>, Vinod Metta<sup>2</sup>, Benjamin S Simpson<sup>1</sup>, Tytus A Murphy<sup>1</sup>,  
A Ramlackhansingh<sup>1</sup>, K Ray Chaudhuri<sup>2</sup>, and David J Brooks<sup>1</sup>

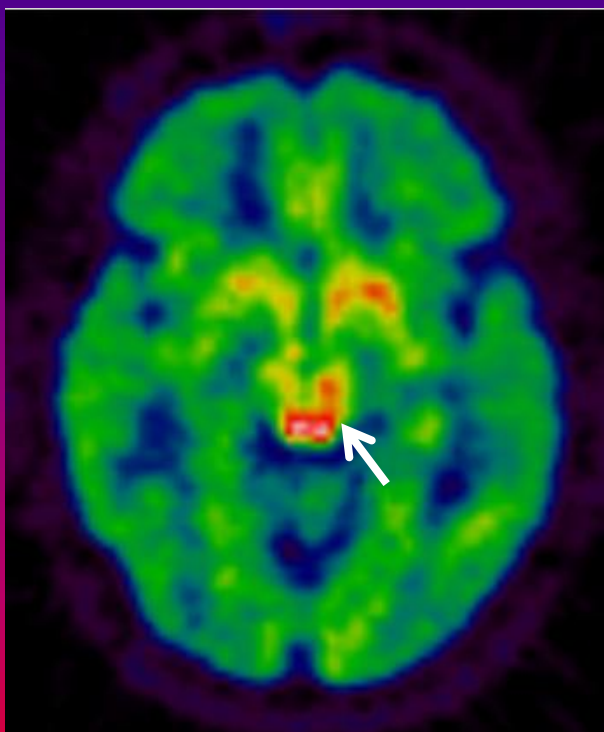
<sup>1</sup> Centre for Neuroscience, Faculty of Medicine, Hammersmith Hospital, Imperial College, London, UK;

<sup>2</sup> Kings College and Lewisham Hospitals, Kings College, London, UK

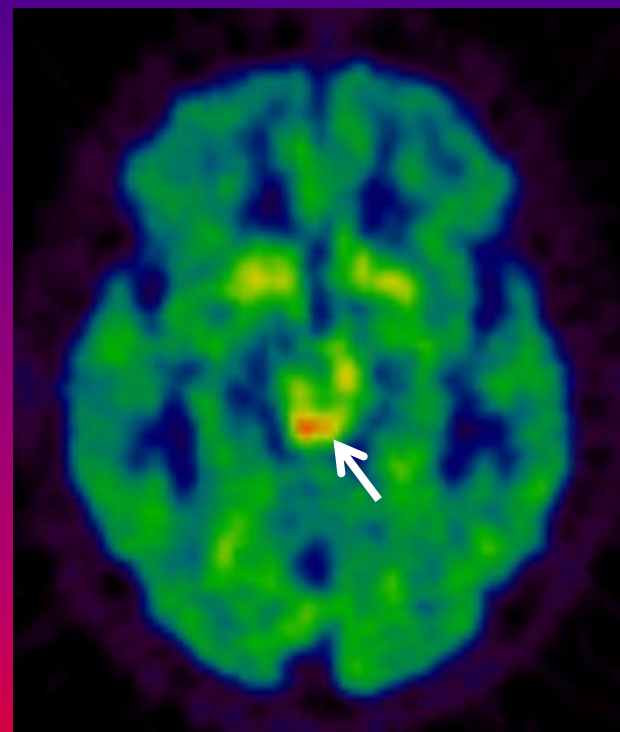
# $^{11}\text{C}$ -DASB – Rostral Raphe



Control



PD without excessive  
daytime somnolence  
ESS < 10

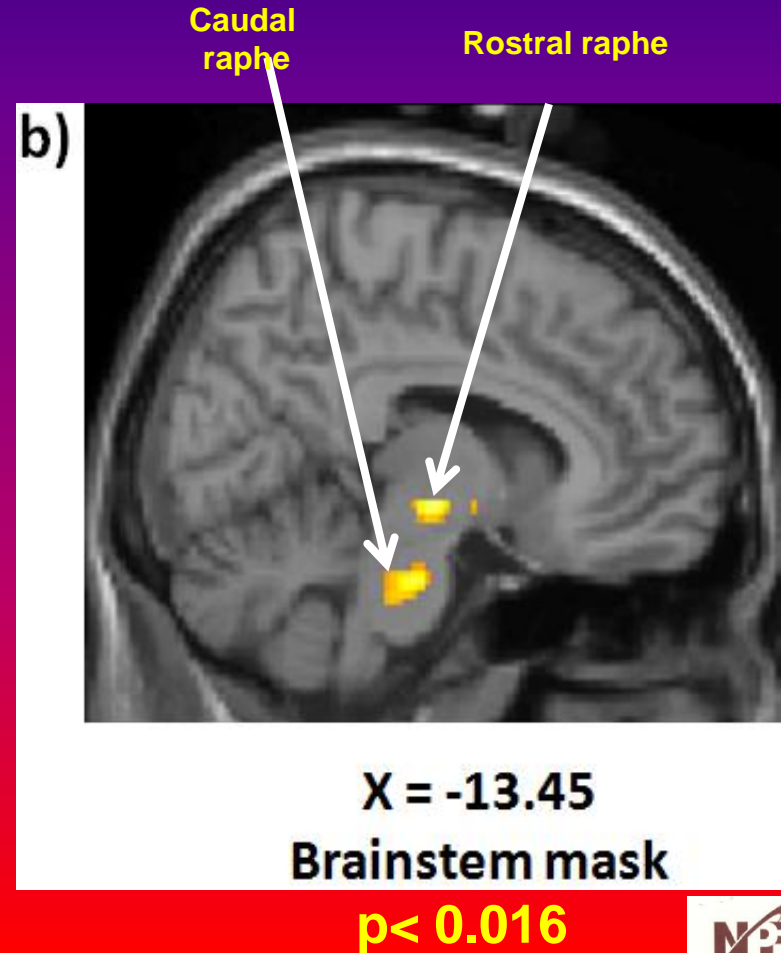
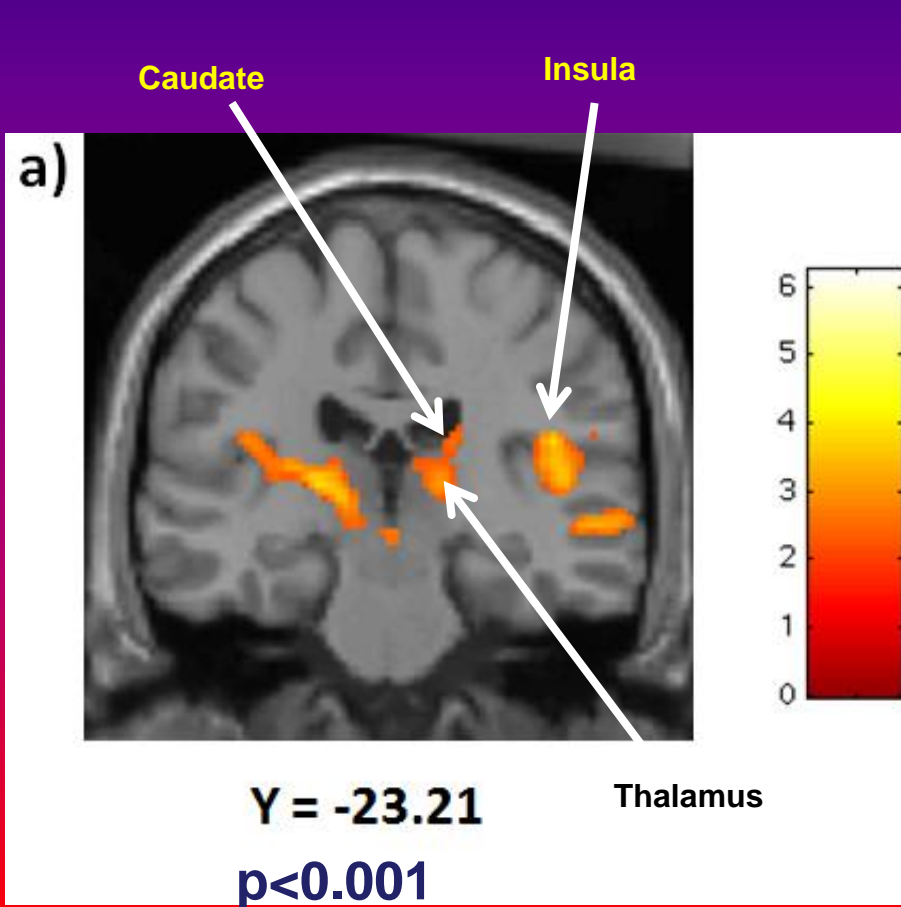


PD with excessive  
daytime somnolence  
ESS > 10



# $^{11}\text{C}$ -DASB PET

## Statistical parametric maps



# Treatment of EDS in PD

B. Knie, T. Mitra, K. Logishetty, K. Ray Chaudhuri. *CNS Drugs* 2011;25(3):1-10.

## Therapy of EDS in Parkinson's disease

- **Stimulants** (methylphenidate/ amphetamines):  
effective, but side effects; no studies on PD yet
- **Caffeine**: clinically useful
  - Espresso coffee (n-of-one trial). Ferreira et al 2012
- **Modafinil**: better tolerated
- **CDD: ? Rotigotine patch**
- **Bupropion** (indirect dopaminergic agonist):  
proven only in non-human primate model, no data on PD

## Currently researched:

- **Tiprolisant** (selective inverse histamine H<sub>3</sub> receptor agonist)
- **Sodium oxybate** (nocturnal): improves subjective night-time and daytime sleep problems and daytime fatigue in PD
- **A2a receptor antagonists**

## AAN recommendation:

- **Modafinil**:  
subjective improvement of EDS, not in objective tests

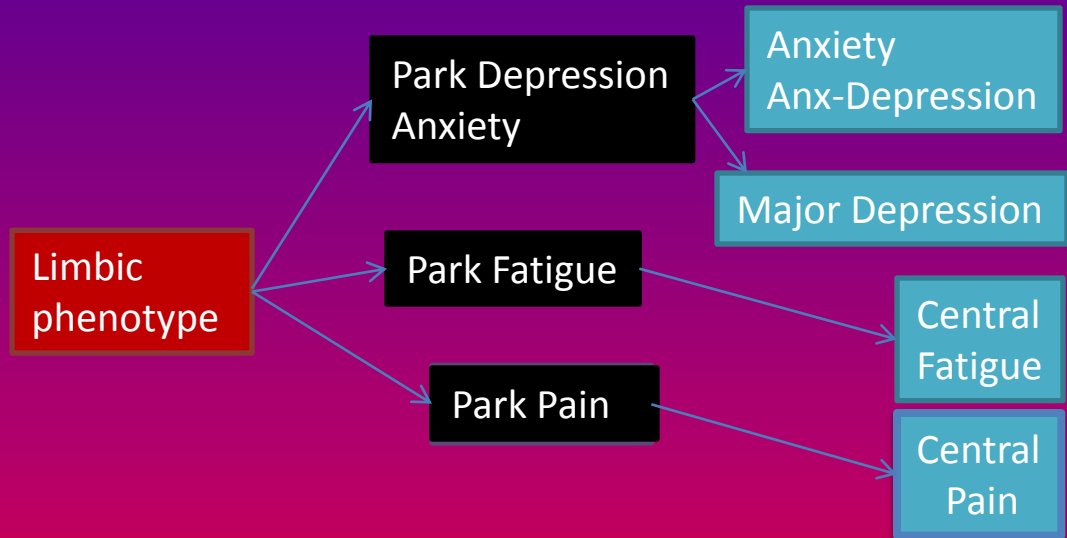
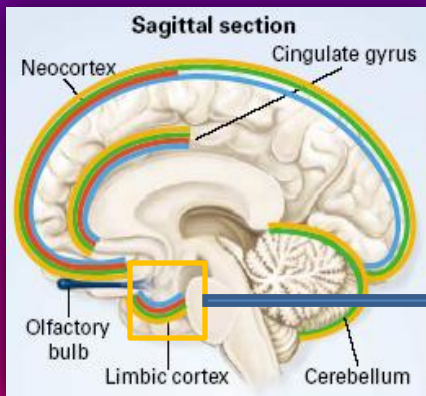


# Caffeine in Parkinson's Disease: A Pilot Open-Label, Dose-Escalation Study

Robert D. Altman, MD,<sup>1</sup> Anthony E. Lang, MD,<sup>2</sup>  
and Ronald B. Postuma, MD, MSc<sup>1\*</sup>



3.0,  $P = 0.015$ ). **Conclusion:** Maximum dose tolerability for caffeine in PD appears to be 100 to 200 mg BID. We found pilot preliminary evidence that caffeine may improve some motor and nonmotor aspects of PD, which must be confirmed in longer term, placebo-controlled, clinical trials. © 2011 *Movement Disorder Society*



Depression and pain often co-exist in PD

# Pains in Parkinson disease—many syndromes under one umbrella

**Gunnar Wasner & Günther Deuschl**

*Nature Reviews Neurology* **8**, 284-294 (May 2012) | doi:10.1038/nrneurol.2012.54

## Measuring pain in Parkinson's

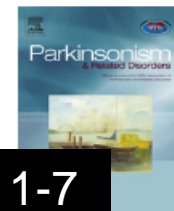
**K Ray Chaudhuri**

**S Pal**

**P Martinez-Martin**

### How the research will help people with Parkinson's

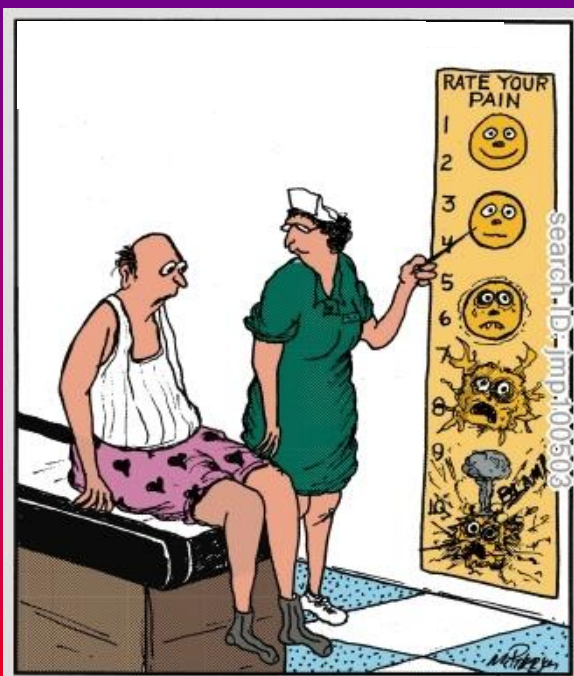
Measuring pain in Parkinson's is the first step towards understanding what causes it. And a reliable scale will play a vital role in measuring the effectiveness of new treatments as they are tested in clinical trials.



## Review

## Parkinson's disease: The non-motor issues☆

K. Ray Chaudhuri<sup>a,\*</sup>, Per Odin<sup>b,c</sup>, Angelo Antonini<sup>d</sup>, Pablo Martinez-Martin<sup>e</sup>



**Table 1B**

The Chaudhuri–Schapira classification of pain in Parkinson's disease. Adapted from reference [11]. RLS = restless legs syndrome, PLM = periodic limb movement. TMJ = temporo-mandibular joint.

**Musculoskeletal pain** (including indirectly aggravated pain)

**PD related chronic pain** (may respond to dopaminergic therapy)

Central pain

Visceral pain

**Fluctuation related pain** (dopaminergic therapy responsive)

Dyskinetic pain

Off period dystonia related pain

Off period generalized pain

**Nocturnal pain** (usually dopaminergic therapy responsive)

RLS/PLM related

Nocturnal akinesia linked

Coat Hanger pain (rare in PD and linked to postural hypotension)

**Oro-facial pain**

TMJ pain

Bruxism related pain

Burning mouth syndrome (maybe levodopa responsive)

**Peripheral limb/abdominal pain**

Drug-induced

Peripheral oedema linked

Lower bowel pain related to retroperitoneal fibrosis



## PD PAIN SCALE

Patient ID No: \_\_\_\_\_ Initials: \_\_\_\_\_ DOB: \_\_\_\_\_

This scale is designed to define and accurately describe the different types and the pattern of pain that your patient may have experienced **during the last month** due to his/her Parkinson's disease or related medication.

Each symptom should be scored with respect to

**Severity:** 0 = None,  
1 = Mild (symptoms present but causes little distress or disturbance to patient),  
2 = moderate (some distress or disturbance to patient),  
3 = Severe (major source of distress or disturbance to patient).

**Frequency:** 0 = Never,  
1 = Rarely (<1/wk),  
2 = Often (1/wk),  
3 = Frequent (several times per week),  
4 = Very Frequent (daily or all the time).

	<u>Severity</u> (0 – 3)	<u>Frequency</u> (0 – 4)	<u>Frequency</u> <u>x Severity</u>
<b>Domain 1: Musculoskeletal Pain</b>			
1. Does the patient experience pain around their joints? (including arthritic pain)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 1 TOTAL SCORE:</b>			<input type="checkbox"/>
<b>Domain 2: Chronic Pain</b>			
2. Does the patient experience pain deep within the body? (A generalised constant, dull, aching pain – <i>central pain</i> )	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Does the patient experience pain related to an internal organ? (For example, pain around the liver, stomach or bowels – visceral pain)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 2 TOTAL SCORE:</b>			<input type="checkbox"/>
<b>Domain 3: Fluctuation-related Pain</b>			
4. Does the patient experience dyskinetic pain? (pain related to abnormal involuntary movements)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Does the patient experience “off” period dystonia in a specific region? (in the area of dystonia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Does the patient experience generalised “off” period pain? (pain in whole body or areas distant to dystonia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Domain 3 TOTAL SCORE:</b>			<input type="checkbox"/>

## PD PAIN SCALE

### Domain 4: Nocturnal Pain

7. Does the patient experience pain related to jerking leg movements during the night (PLM) or an unpleasant burning sensation in the legs which improves with movement (RLS)?

☐ ☐ ☐

8. Does the patient experience pain related to difficulty turning in bed at night?

☐ ☐ ☐

Domain 4 TOTAL SCORE:

### Domain 5: Oro-facial Pain

9. Does the patient experience pain when chewing?

☐ ☐ ☐

10. Does the patient have pain due to grinding their teeth during the night?

☐ ☐ ☐

11. Does the patient have burning mouth syndrome?

☐ ☐ ☐

Domain 5 TOTAL SCORE:

### Domain 6: Discolouration; Oedema/swelling

12. Does the patient experience a burning pain in their limbs? (often associated with swelling or dopaminergic treatment)

☐ ☐ ☐

13. Does the patient experience generalised lower abdominal pain?

☐ ☐ ☐

Domain 6 TOTAL SCORE:

### Domain 7: Radicular Pain

14. Does the patient experience a shooting pain/pins and needles down the limbs?

☐ ☐ ☐

Domain 7 TOTAL SCORE:

TOTAL SCORE (all domains):

Comments:



- **International Multicentre, double-blind, randomised, placebo controlled study**
- **Primary:** To demonstrate **superiority of Oxycodone/Naloxone Prolonged Release tablets** compared to **placebo** with respect to analgesic efficacy in subjects with **chronic severe pain** associated with **Parkinson's disease**
- **Secondary:** Assessment of impact upon other motor and non-motor symptoms of PD
- 210 subjects, 16 week double-blind phase, 4 week open label treatment phase
- C-S classification for pain

102 patients currently recruited

# Unexplored and under-reported NMS

- Fatigue
- Pain
- EDS
- Dribbling Saliva
- Sexual disturbances
  - Loss of libido
  - Hypersexuality
- Visual disturbances
- Apathy
- Autonomic problems

Now used worldwide  
Translated to 14 languages  
Recommended by  
MDS  
Parkinson's UK  
DH UK  
EPDA

**TABLE 2.** Domains included in the NMSQuest

Number	Domain	Number of items
1	Gastrointestinal tract	8
2	Urinary tract	2
3	Sexual function	2
4	Cardiovascular	2
5	Apathy/attention/memory	3
6	Hallucinations/delusions	2
7	Depression/anxiety/anhedonia	2
8	Sleep/fatigue	5
9	Pain (unrelated to other causes)	1
10	Miscellaneous (e.g., diplopia, weight loss)	3

## PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

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 .....	<input type="checkbox"/>	<input type="checkbox"/>	16. Feeling sad, 'low' or 'blue' .....	<input type="checkbox"/>	<input type="checkbox"/>
2. Loss or change in your ability to taste or smell .....	<input type="checkbox"/>	<input type="checkbox"/>	17. Feeling anxious, frightened or panicky .....	<input type="checkbox"/>	<input type="checkbox"/>
3. Difficulty swallowing food or drink or problems .....	<input type="checkbox"/>	<input type="checkbox"/>	18. Feeling less interested in sex or more .....	<input type="checkbox"/>	<input type="checkbox"/>
4. Drooling .....	<input type="checkbox"/>	<input type="checkbox"/>	18. Feeling less interested in sex or more .....	<input type="checkbox"/>	<input type="checkbox"/>
5. Nausea or feelings of sickness (nausea) .....	<input type="checkbox"/>	<input type="checkbox"/>	19. Finding it difficult to have sex when you try .....	<input type="checkbox"/>	<input type="checkbox"/>
6. Constipation (less than 3 bowel movements a .....	<input type="checkbox"/>	<input type="checkbox"/>	20. Feeling light headed, dizzy or weak standing .....	<input type="checkbox"/>	<input type="checkbox"/>
7. Difficulty or having to strain to pass a stool (faeces) .....	<input type="checkbox"/>	<input type="checkbox"/>	20. Feeling light headed, dizzy or weak standing .....	<input type="checkbox"/>	<input type="checkbox"/>
8. (fecal) incontinence .....	<input type="checkbox"/>	<input type="checkbox"/>	21. Falling .....	<input type="checkbox"/>	<input type="checkbox"/>
9. Feeling that your bowel emptying is incomplete .....	<input type="checkbox"/>	<input type="checkbox"/>	22. Finding it difficult to stay awake during activities .....	<input type="checkbox"/>	<input type="checkbox"/>
10. Having been to the toilet .....	<input type="checkbox"/>	<input type="checkbox"/>	22. Finding it difficult to stay awake during activities .....	<input type="checkbox"/>	<input type="checkbox"/>
11. A sense of urgency to pass urine makes you .....	<input type="checkbox"/>	<input type="checkbox"/>	23. Difficulty getting to sleep at night or staying .....	<input type="checkbox"/>	<input type="checkbox"/>
11. A sense of urgency to pass urine makes you .....	<input type="checkbox"/>	<input type="checkbox"/>	23. Difficulty getting to sleep at night or staying .....	<input type="checkbox"/>	<input type="checkbox"/>
12. Waking up regularly at night to pass urine .....	<input type="checkbox"/>	<input type="checkbox"/>	24. Intense, vivid dreams or frightening dreams .....	<input type="checkbox"/>	<input type="checkbox"/>
13. Joint pains (not due to known conditions .....	<input type="checkbox"/>	<input type="checkbox"/>	25. Talking or moving about in your sleep as if you .....	<input type="checkbox"/>	<input type="checkbox"/>
13. Joint pains (not due to known conditions .....	<input type="checkbox"/>	<input type="checkbox"/>	25. Talking or moving about in your sleep as if you .....	<input type="checkbox"/>	<input type="checkbox"/>
14. Unexplained change in weight (not due to .....	<input type="checkbox"/>	<input type="checkbox"/>	26. Unpleasant sensations in your legs at night or .....	<input type="checkbox"/>	<input type="checkbox"/>
14. Unexplained change in weight (not due to .....	<input type="checkbox"/>	<input type="checkbox"/>	26. Unpleasant sensations in your legs at night or .....	<input type="checkbox"/>	<input type="checkbox"/>
15. Problems remembering things that have .....	<input type="checkbox"/>	<input type="checkbox"/>	27. Swelling of your legs .....	<input type="checkbox"/>	<input type="checkbox"/>
15. Problems remembering things that have .....	<input type="checkbox"/>	<input type="checkbox"/>	27. Swelling of your legs .....	<input type="checkbox"/>	<input type="checkbox"/>
16. Loss of interest in what is happening around .....	<input type="checkbox"/>	<input type="checkbox"/>	28. Excessive sweating .....	<input type="checkbox"/>	<input type="checkbox"/>
16. Loss of interest in what is happening around .....	<input type="checkbox"/>	<input type="checkbox"/>	28. Excessive sweating .....	<input type="checkbox"/>	<input type="checkbox"/>
17. Seeing or hearing things that you know or are .....	<input type="checkbox"/>	<input type="checkbox"/>	29. Double vision .....	<input type="checkbox"/>	<input type="checkbox"/>
17. Seeing or hearing things that you know or are .....	<input type="checkbox"/>	<input type="checkbox"/>	29. Double vision .....	<input type="checkbox"/>	<input type="checkbox"/>
18. Difficulty concentrating or staying focussed .....	<input type="checkbox"/>	<input type="checkbox"/>	30. Believing things are happening to you that other .....	<input type="checkbox"/>	<input type="checkbox"/>
18. Difficulty concentrating or staying focussed .....	<input type="checkbox"/>	<input type="checkbox"/>	30. Believing things are happening to you that other .....	<input type="checkbox"/>	<input type="checkbox"/>



## Suggested discrete clinical pattern of diplopia in Parkinson's (Sauerbier et al. 2013)

Type 1	Fleeting transient diplopia described often as “word’s jumping during reading”
Type 2	A relatively constant pattern of diplopia often related to convergence dysfunction
Type 3	Diplopia linked to motor response fluctuations (on-off and dyskinesia)
Type 4	Diplopia linked to visual hallucinations (perceptory diplopia)
Type 5	Drug induced diplopia



## Mucuna Pruriens Benefits:

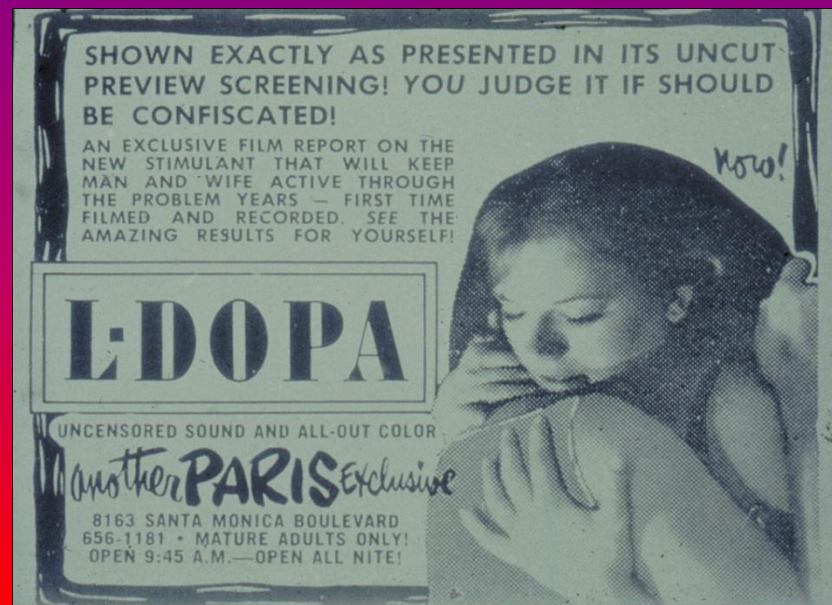
### L-Dopa to Boost Testosterone, Libido, Improve Mood and More!

**Mucuna Pruriens provides a neurotransmitter pre-cursor called L-Dopa.** L-Dopa is the amino acid compound from which your body makes Dopamine. As a regular part of the diet, Mucuna Pruriens provides many benefits. Among the long list are: enhancing libido and sexual capacity, optimizing testosterone production and improved mood and energy.

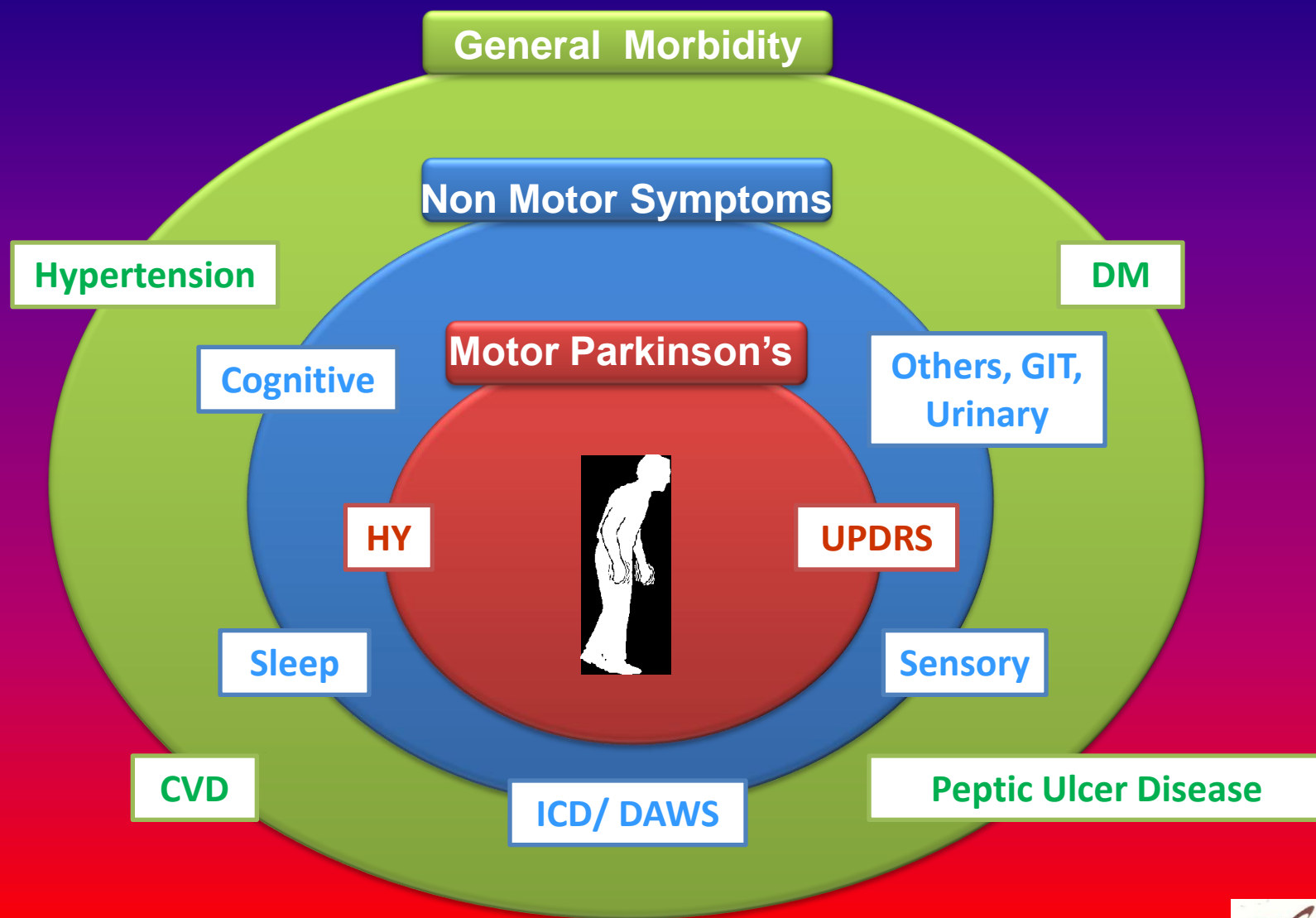
Mucuna Pruriens common names include Velvet Bean, Cow-Itch (because the red hairs on the outside of the pods can cause a cow's tongue to itch) and Buffalo Bean. It is a vine that grows up to 50 feet or more.



[www.peak-health-now.com](http://www.peak-health-now.com)

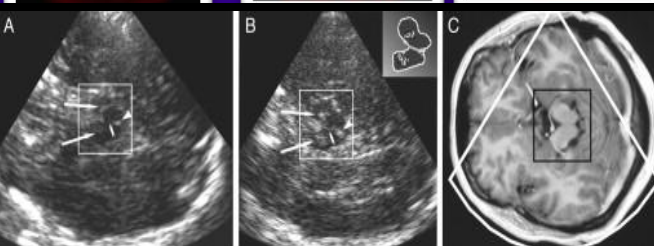
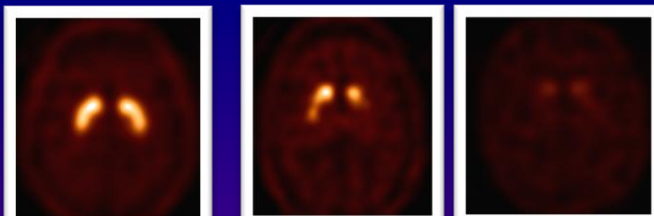


# The Multi-Morbid PD



# The Modern Concept of Assessing people with Parkinson's in Clinic

- Analysis and assessment based on motor assessment alone is inadequate and old fashioned
- Assessment must take into account NMS, direct and indirect and comorbidity
- Staging can be done by validated motor systems (HY stage) and the new NMSB system
- NM Endophentotypes
  - Emerging Biomarkers
    - PET/SPECT
    - Neuropeptides ?
- Endophenotype specific treatment packages
  - Quality of life
  - Addressing NMS that are often ignored



Disorders xxx (2011) 1–7

Available at ScienceDirect



## Parkinsonism and Related Disorders

journal homepage: [www.elsevier.com/locate/parkreldis](http://www.elsevier.com/locate/parkreldis)

Review

### Parkinson's disease: The non-motor issues<sup>☆</sup>

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**Instability & falls**

**Motor complications  
& dyskinesias**

**Bilateral**

**Unilateral**



**Table 3**

A suggested scheme of clinical assessment of patients using non-motor tool ensuring that holistic evaluation is undertaken. NMSQuest = non-motor questionnaire. NMSS = non-motor symptoms scale.

