Non-Motor Symptoms of Parkinson's Disease:
Quality of Life Beyond Tremor Control

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No Financial Disclosures
Learning Objectives

• To describe common non-motor symptoms (NMS) in Parkinson's disease

• To discuss some non-pharmacologic and pharmacologic approaches to managing NMS

• To recognize the importance of discussing NMS with your neurologist and primary care provider

• To recognize the value of promoting communication between your doctors
Outline

• Non-Motor Symptoms (NMS)

• NMS Timeline

• NMS and Dopamine

• Focus: 3 Common NMS Disturbances

• Take-Home Messages
Parkinson’s Disease

http://www.allaboutparkinsons.com/james-parkinson.html

http://www.sciencemuseum.org.uk/hommedia.ashx?id=91831&size=Small
Parkinson’s Disease: Cardinal Features

- Bradykinesia -- slowness executing movement
  “paucity” of movement

- Muscular Rigidity -- increased tone
  velocity-independent
  cogwheel = rigidity + tremor

- Postural Instability -- primary
  not visual, proprioceptive,
  vestibular, cerebellar

- Rest Tremor -- “pill-rolling,” asymmetric
Cardinal Pathology: Lewy Bodies

Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

Via olfactory bulb
Via vagus nerve

Premotor symptoms
Motor symptoms

Brainstem Lewy body
Cortical Lewy body
Model Timeline of Parkinson’s Disease

Symptoms
- Hyposmia
- Sleep Disorder
- Unilateral Bilateral Balance Falls Chair/Bed
- Constipation
- Obesity
- Tremor, Rigidity, Akinesia
- Cognitive Dementia
- Bladder
- Depression
- Dependence

Lewy Body Pathology
- Enteric Plexus
- Olfactory Bulb CN X
- Coeruleus
- Caudal Raphe
- Magnocel RF
- Sub Nigra
- Amygdala
- PPN
- Temporal Lobe
- TEC, CA2 plx
- Intralam Thal
- Prefrontal Cx
- 3º Sensory Assoc. Areas
- Motor and Sensory Cxs

Braak Stage

Clinical Onset

20-year prodrome
20-year disease stage

Hoehn & Yahr
I II III IV V

Unilateral Bilateral Balance Falls Chair/Bed Tremor, Rigidity, Akinesia

Years
-20 -10 0 +10 +20

Lewy Body Pathology

Braak Stage

Clinical Onset

20-year prodrome
20-year disease stage

Hoehn & Yahr
I II III IV V

Unilateral Bilateral Balance Falls Chair/Bed Tremor, Rigidity, Akinesia

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Braak Stage

Model Timeline of Parkinson’s Disease

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Non-Motor Symptoms
Parkinson’s Disease

Sleep Disturbance
Constipation
Speech Disturbance
Swallow Disturbance
Drooling
Urinary Incontinence
Sleepiness
Mild Confusion

http://www.allaboutparkinsons.com/james-parkinson.html
http://www.scientcemuseum.org.uk/hommedia.ashx?id=91831&size=Small
Model Timeline of Parkinson’s Disease

Clinical Onset

Hoehn & Yahr

I  II  III  IV  V

20-year prodrome

20-year disease stage

Symptoms

Hyposmia
Constipation
Bladder
Sleep Disorder
Obesity
Depression
Unilateral
Bilateral
Balance
Tremor, Rigidity, Akinesia
Falls
Chair/Bed
Dependence

Enteric Plexus
Olfactory Bulb
Coeruleus
Caudal Raphe
Magnocel RF
Sub Nigra
Amygdala
PPN
Temporal Lobe
TEC, CA2 plx
Intralam Thal
Prefrontal Cx
3º Sensory
Assoc. Areas

Lewy Body
Pathology

CN X

Magnocel RF

Temporal Lobe

Prefrontal Cx

2º -> 1º

Motor and Sensory Cxs

Braak Stage

Modified from CH Hawkes, Parkinsonism & Related Disorders 16(2) 79-84 (2010)
NMS: System and Onset

**Sensory Symptoms**
- *Pain*
- **Olfactory disturbance**
- Restless legs syndrome
- *Visual blurring*

**Gastrointestinal Symptoms**
- **Constipation**
  - Dysphagia
  - Drooling
  - *Nausea, Vomiting*

**Sleep Disorders**
- Insomnia
- **REM sleep behavior disorder**
  - Sleep disordered breathing
  - Periodic leg movements
  - Non-REM parasomnias (wandering)
  - Excessive daytime somnolence

**Autonomic Dysfunction**
- Orthostatic hypotension
- Bladder dysfunction (urgency, frequency, nocturia)
- Sexual dysfunction (may be drug-induced)
- Sweating abnormalities (hyperhydrosis)

**Neuropsychiatric Symptoms**
- **Depression**
- Anxiety
- Apathy
- Hallucinations, delusions, illusions
- Delirium (may be drug induced)
- Cognitive Impairment / Dementia

**BLUE = premotor stage of PD.**
“Multisystem involvement develops to varying levels of severity and in a variable sequence in different patients.”
NMS Stages

Prodomal stage
- Hyposmia
- Sleep disruption (e.g. RBD)
- Depression
- Constipation

Early stage–mid stage
- Anxiety
- Hypophonia
- Dysphagia
- Sleep disturbance (e.g. fragmentation)

2–5 years

Early motor stage
- Fatigue
- Pain
- Diplopia

3–6 years

Late stage
- Dementia
- Cognitive dysfunction
- Hallucinations
- Incontinence
- Sexual dysfunction
- Orthostatic hypotension

4–12 years

8 years

## 2006 NMS Questionnaire (NMS-Quest)

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

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>Yes</th>
<th>No</th>
<th></th>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Dribbling of saliva during the daytime</td>
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<td></td>
<td>16</td>
<td>Feeling sad, ‘low’ or ‘blue’</td>
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<tr>
<td>2</td>
<td>Loss or change in your ability to taste or smell</td>
<td></td>
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<td></td>
<td>17</td>
<td>Feeling anxious, frightened or panicky</td>
<td></td>
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<tr>
<td>3</td>
<td>Difficulty swallowing food or drink or problems with choking</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>Feeling less interested in sex or more interested in sex</td>
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<tr>
<td>4</td>
<td>Vomiting or feelings of sickness (nausea)</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>Finding it difficult to have sex when you try</td>
<td></td>
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<tr>
<td>5</td>
<td>Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)</td>
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<td>20</td>
<td>Feeling light headed, dizzy or weak standing from sitting or lying</td>
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<tr>
<td>6</td>
<td>Bowel (fecal) incontinence</td>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>Falling</td>
<td></td>
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<tr>
<td>7</td>
<td>Feeling that your bowel emptied is incomplete after having been to the toilet</td>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td>Finding it difficult to stay awake during activities such as working, driving or eating</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>A sense of urgency to pass urine makes you rush to the toilet</td>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>Difficulty getting to sleep at night or staying asleep at night</td>
<td></td>
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<tr>
<td>9</td>
<td>Getting up regularly at night to pass urine</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
<td>Intense, vivid dreams or frightening dreams</td>
<td></td>
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<tr>
<td>10</td>
<td>Unexplained pains (not due to known conditions such as arthritis)</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td>Talking or moving about in your sleep as if you are ‘acting’ out a dream</td>
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<tr>
<td>11</td>
<td>Unexplained change in weight (not due to change in diet)</td>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td>Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move</td>
<td></td>
</tr>
</tbody>
</table>

NMS and Dopamine
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  "paucity" of movement

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- Rest Tremor -- “pill-rolling,” asymmetric
Parkinson’s Disease: Medication Pathways

Entacapone
Tolcapone

3OMD
COMT

L-DOPA

DDC

Dopamine

Carbidopa

Glia
MAO-A & B

Selegiline
Rasagiline

Pramipexole
Ropinirole
Rotigotine

Blood brain barrier

L-DOPA

DDC

Dopamine

DA

SV

DT

D1

D2

MAO A

AR

Moclobemide

Presynaptic terminal
substantia nigra origin

Postsynaptic terminal
Striatum

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http://www.neurology.org/content/63/7_suppl_2/S32/F2.large.jpg
**Sensory Symptoms**
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- Visual blurring

**Gastrointestinal Symptoms**
- Constipation
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- Sweating abnormalities (hyperhydrosis)

**Neuropsychiatric Symptoms**

*Depression*

*Anxiety*

*Apathy*

*Hallucinations, delusions, illusions*

*Delirium* (may be drug induced)

*Cognitive Impairment / Dementia*

**GREEN = dopaminergic improvement**

**RED = dopaminergic worsening**
Selected Dopaminergic Side Effects

Orthostatic Hypotension (Lightheaded → Falls → Injury)

Cognitive/Behavioral
  - Hallucinations, Delusions
  - Impulse Control Disorders
  - Dopamine Dysregulation Syndrome

Fatigue
Nausea

Narcolepsy-type “sleep attack”
Ankle Swelling
Dyskinesia

*START LOW and GO SLOW…and RE-ASSESS.*
TABLE 3. Percentage of patients reporting each non-motor symptom as measured by the NMSS

<table>
<thead>
<tr>
<th>Items</th>
<th>Patients*</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>1. Light-headedness</td>
<td>167</td>
<td>40.6</td>
</tr>
<tr>
<td>2. Fainting</td>
<td>38</td>
<td>9.2</td>
</tr>
<tr>
<td>3. Daytime sleepiness</td>
<td>195</td>
<td>47.4</td>
</tr>
<tr>
<td>4. Fatigue</td>
<td>271</td>
<td>65.9</td>
</tr>
<tr>
<td>5. Difficulty falling asleep</td>
<td>207</td>
<td>50.4</td>
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<tr>
<td>6. Restless legs</td>
<td>131</td>
<td>31.9</td>
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<tr>
<td>7. Lost interest in surroundings</td>
<td>141</td>
<td>34.3</td>
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<tr>
<td>8. Lack motivation</td>
<td>179</td>
<td>43.6</td>
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<tr>
<td>9. Feel nervous</td>
<td>208</td>
<td>50.6</td>
</tr>
<tr>
<td>10. Seem sad</td>
<td>204</td>
<td>49.6</td>
</tr>
<tr>
<td>11. Flat mood</td>
<td>132</td>
<td>32.1</td>
</tr>
<tr>
<td>12. Difficulty experiencing pleasure</td>
<td>121</td>
<td>29.4</td>
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<tr>
<td>13. Hallucinations</td>
<td>72</td>
<td>17.5</td>
</tr>
<tr>
<td>14. Delusions</td>
<td>40</td>
<td>9.7</td>
</tr>
<tr>
<td>15. Double vision</td>
<td>72</td>
<td>17.5</td>
</tr>
</tbody>
</table>

n = 411
International, Multi-Center Study

Fatigue / Excessive Daytime Sleepiness (EDS)

- Degeneration of Sleep-Wake Cycle Regulators

- Medication Side Effects: Dopamine Agonists, Levodopa, Anti-cholinergics, Amantadine

- Other: Nocturia, Sleep Apnea, Mood Disorders, Medical Conditions, Other Medications
Managing Fatigue / EDS

• Lifestyle
  1. Stimulating environment
  2. Intense light during the day
  3. Exercise (daily, routine)

• Pharmacological
  1. Review Medications
  2. Caffeine (100-200 mg twice daily)
  3. Modafinil (100-400 mg daily)
  4. Others
Drooling

- Cause = bradykinesia: impaired mouth movements and swallowing

- Complications:
  
  Social Embarrassment
  Choking
  Aspiration Pneumonia
Managing Drooling

• Non-pharmacological: Gum, Hard Candy

• Pharmacological

1. Anticholinergics
   Potential side-effects: mouth dryness, blurry vision, constipation, urinary retention, and worsened hallucinations and memory problems
   Uncommon at low doses

2. Botulinum Toxin Injections
   Parotid and/or submandibular glands

3. Dopaminergics
Nocturia / Bladder Dysfunction

- Detrusor Hyperreflexia / Overactive $\Rightarrow$ Nocturia, Urinary Urge, Frequency, and Incontinence

- Bladder dysfunction is due to degeneration of autonomic bladder neurons, motor areas, higher control areas, and substantia nigra

- Consider Urodynamic Studies
Managing Nocturia / Bladder Dysfunction

• Pharmacological

1. Dopaminergics: Levodopa
2. B3 Adrenergic Agonist: Mirabegron (Myrbetriq)
3. Anti-cholinergics
   Oxybutynin (Ditropan), Darifenacin (Enablex),
   Solifenacin (Vesicare), Tolterodine (Detrol),
   Trospium Chloride (Sanctura)

   Side Effects: constipation, memory, hallucinations

3. Detrusor Chemodenervation: Botulinum Toxin A
4. Desmopressin nasal spray
Some Useful Online Resources

http://www.parkinson.ca/resources/educational-publications/

NMS Quest (search pdf)

PD NMS QUESTIONNAIRE

Name: ___________________________ Date: ____________ Age: __________
Centre ID: ________________________  Male □ Female □

NON-MOVEMENT PROBLEMS IN PARKINSON’S
The non-motor 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
problems 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 “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?

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Take-Home Messages

• Non-motor symptoms (NMS) are common.

• NMS-Quest can be a useful tool for you and your doctors.

• Discuss NMS with your neurologist and, when appropriate, other members of your medical team.

• Optimal NMS management may involve pharmacologic and non-pharmacologic approaches.

• The more precisely you report WHEN and WHAT symptoms are most bothersome, the more thoughtfully you and your doctor can develop optimal treatment strategies.

Take your medications on schedule and keep a log.
Thank you!
Additional References


First Comprehensive Evaluation of NMS and QoL

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

Pablo Martinez-Martín, MD, PhD,1,2* Carmen Rodríguez-Blazquez, BS,1 Monica M. Kurtis, MD,3 and K. Ray Chaudhuri, MD, FRCP, DSC,4,5 on behalf of the NMSS Validation Group

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3Movement Disorders Unit, Department of Neurology, Ruber International Hospital, Madrid, Spain
4National Parkinson Foundation Centre of Excellence, Kings College Hospital, London, United Kingdom
5Department of Neurology, University Hospital Lewisham, Kings College, London, United Kingdom

Movement Disorders 26(3): 399-406 (2011)
First Comprehensive Evaluation of NMS and QoL

“The results show that non-motor symptoms have, as a whole, a greater impact on health-related quality of life than motor symptoms...

“...and non-motor symptoms progression contributes importantly to health-related quality of life decline in patients with Parkinson’s disease.”