The Practical Management of Non Motor Symptoms in PD

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NON-MOTOR SYMPTOMS OF PD ARE OFTEN THE GREATEST SOURCE OF DISABILITY

- Dysautonomia: Constipation, orthostatic hypotension, sexual dysfunction, bladder dysfunction
- Personality changes: introversion, social viscosity, compulsive behavior (side-effect dopaminergic medications)
- Anxiety – 40%, Apathy – 50%
- Depression in approx 60%
- Bladder/bowel and swallowing disturbances – 50%
- Seborrhoeic dermatitis and excessive sweating > 50%
- Executive cognitive dysfunction & dementia
- Sleep disturbances / daytime somnolence
- Sexual dysfunction > 50%
- Visual changes
- Hyposmia
- Pain
- Fatigue
Non motor symptoms

• Very common
• Very often predate motor symptoms
• 60% of patients > 1 NMS
• 25% of patients > 4 NMS
• Symptoms can be primary complaints
• Lead to a decline in QOL regardless of motor impairment
• Often cause more distress to patients and carers than motor symptoms
An alternative way of thinking..?

- A chronic, progressive, multi-system, neurodegenerative process which has effects on motor and autonomic function, cognitive processing and emotion

- ‘The Quintessential Neuropsychiatric Disorder’

- Allows a realignment of focus and enables recognition of these disabling symptoms
The Evolution of PD: a combination of motor and non-motor features

- **Preclinical PD**
  - Constipation
  - Depression
  - Hyposmia
  - REM sleep

- **Early treated PD (stable)**

- **Advanced PD**
  - Motor complications: wearing off/dyskinesia, gait and balance issues
  - Non-motor complications: cognitive decline, dementia, psychosis, autonomic dysfunction, sleep-wake-dysregulation

Timeline:
- 0 years
- 5 years
- 10 years
- 15 years
Premotor PD

• Strong evidence for:
  – REM behaviour disorder
  – Hyposmia
  – Depression
  – Constipation

• Possible evidence:
  – Anxiety
  – Apathy & fatigue
  – Restless Legs Syndrome
NMS - poorly recognised

- Schulman et al., in >50% consultations clinicians overlooked:
  - Depression
  - Anxiety
  - Fatigue
  - Sleep disturbance
Reasons

• "not aware due to PD"
• "Embarrassed"
• "Motor features were ‘focus’ of consultation"

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,1 Cristina Prieto-Jurcynska, MD,2,3 Yogini Naidu, MSc,4 Tanya Mitra, BSc,5 Belen Frades-Payo, MSc,6 Susanne Thuk, RGN,7 Anne Rueßmann, RGN,5 Per Odin, PhD,8 Greeme Macphee, MD,9 Fabrizio Stocchi, MD,7 William Ondo, MD,10 Kapil Sethi, MD, FRCP11 Anthony H.V. Schapira, MD, DSc,12 Juan Carlos Martinez Castrillo, MD, PhD,13 and Pablo Martinez-Martín, MD, PhD9

TABLE 3. Declared (positive) and nondeclared symptoms analysed according to NMSQuest domains

<table>
<thead>
<tr>
<th>NMS Questionnaire—domains</th>
<th>Positive</th>
<th>Non-declared</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>2.1 ± 1.6</td>
<td>0.9 ± 1.1</td>
<td>43.5</td>
</tr>
<tr>
<td>Urinary</td>
<td>1.3 ± 0.8</td>
<td>0.5 ± 0.8</td>
<td>43.2</td>
</tr>
<tr>
<td>Sexual function</td>
<td>0.7 ± 0.9</td>
<td>0.3 ± 0.7</td>
<td>45.8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.7 ± 0.7</td>
<td>0.3 ± 0.7</td>
<td>45.6</td>
</tr>
<tr>
<td>Apathy/attention/memory</td>
<td>1.4 ± 1.2</td>
<td>0.6 ± 0.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Hallucinations/delusions</td>
<td>0.3 ± 0.6</td>
<td>0.1 ± 0.4</td>
<td>50.0</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>0.9 ± 0.8</td>
<td>0.4 ± 0.6</td>
<td>38.9</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>2.0 ± 1.5</td>
<td>0.9 ± 1.2</td>
<td>45.2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.6 ± 1.1</td>
<td>0.6 ± 0.8</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Mean ± standard deviation.
*Percentage calculated on the number of positive responses.
NMS Distribution in PD Patients

<table>
<thead>
<tr>
<th>Number of NMS/patient</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>25° percentile</th>
<th>75° percentile</th>
<th>Min</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>5.49</td>
<td>2.54</td>
<td>6.00</td>
<td>4.00</td>
<td>7.00</td>
<td>0.00</td>
<td>12.00</td>
</tr>
</tbody>
</table>

Barone et al. Mov Disord 2009
PRIAMO Study: Prevalence of NMS according to PD status

Non-motor symptoms common across all stages of Parkinson’s disease

Patients who have NMS have worse quality of life (PDQ-39 scores) than those without

Adapted from:

N=1072; score range between 0 (best health state) and 100 (worst health state)
NMS correlate with deteriorating quality of life

NMS Scale and PDQ-39

Load of non-motor symptoms shows robust correlation with deteriorating quality of life

Spearman R = 0.70

coeff = 1.7459186, se = .09135449, t = 19.11

Non motor symptoms

• Therapeutically more challenging

• Dopaminergic therapies treat motor symptoms well but may not be so successful with NMS

• Traditional therapies may well ameliorate motor Sx while exacerbating NMS
  – Hallucinations, autonomic Sx etc.
Many patients complain of the occurrence of non-motor symptoms associated with wearing-off

- **Tiredness**
- **Cloudy mind or dullness in thinking**
- **Pain**
- **Panic attacks**
- **Chest discomfort**
- **Abdominal discomfort**
- **Sweating**

- **Restlessness**
- **Slowness in thinking**
- **Bladder problems**
- **Anxiety**
- **Mood changes**
- Abnormal sensations such as:
  - **Hot/cold**
  - **Aching**
  - **Numbness**

Stacy et al. Movement Disorders 2005
How to screen for NMS

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?

1. Delays of saliva during the daytime Yes □ No □
2. Loss or change in your ability to taste or smell Yes □ No □
3. Feeling numb, tingly or ‘flying’ Yes □ No □
4. Difficulty swallowing food or drink or problems with choking Yes □ No □
5. Voriting or feeling of sickness (nausea) Yes □ No □
6. Constipation due to bowel movements being week or having to strain to pass a stool (constipation) Yes □ No □
7. Bowel (rectal) incontinence Yes □ No □
8. Feeling that your bowel movements are incomplete after having used the toilet Yes □ No □
9. A sense of urgency to pass urine makes you rush to the toilet Yes □ No □
10. Urinal retention (urgency to pass urine with difficulty) Yes □ No □
11. Intense, vivid dreams or frightening dreams Yes □ No □
12. Unplanned change in weight (less due to increased appetite) Yes □ No □
13. Problems remembering things that have happened recently or forgetting to do things Yes □ No □
14. Loss of interest in things you used to enjoy doing Yes □ No □
15. Depression Yes □ No □
16. Feeling one is not loved Yes □ No □
17. Feeling one is not understood Yes □ No □
18. Feeling one has been abandoned Yes □ No □
19. Feeling one is not treated properly Yes □ No □
20. Finding that the doctor or nurse does not understand Yes □ No □

All the information you supply through this form will be treated with confidence and will only be used for the purposes 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.


Chaudhuri et al 2006
Martinez Martin et al 2007

International Multicenter Pilot Study of the First Comprehensive Self-Completed Nonmotor Symptoms Questionnaire for Parkinson’s Disease: The NMSQuest Study
Case 1 – Mrs A

- Idiopathic PD for 7 years
- Worsened function
- Describes ‘cognitive numbness’
- ‘Everything takes longer’
- Frequent nausea
- Intermittent headache
- Wearing off at end of dose
- Husband reports that she can no longer keep up and is more vague

- **Current Medication**
  - Cobeneldopa 25/100 @ 7,10, 1, 4 and 7pm
  - Ropinirole XL 10mg od
  - Rasagiline 1 mg od
  - Oxybutynin 2.5mg bd
  - Aspirin 75mg od
  - Omeprazole 20mg od
  - Citalopram 10mg od
Investigations?

• Blood pressure
  – Sat in clinic 156/70
  – Lying in clinic 168/74
  – Stood for 0 mins 162/74
  – Stood for 1 mins 152/78
  – Stood for 3 mins 82/50
Orthostatic hypotension

- 30-58% of patients
- Large impact on QOL
- Responsible for falls and fractures
- Underreported
- Headache, coathanger ache, dizziness
- More common postprandially
- Can be worsened by dopaminergic therapies / amantadine
What to do?

• Check for other contributory medications
  – Antihypertensives, anticholinergics, alpha blockers etc.

• Conservative measures:
  – Increase fluids
  – Avoid large meals/ETOH
  – Avoid situations of sudden head up or straining at stool
  – Compression hosiery
  – Salt & caffeine
  – Quads and calf crunches
Medications?

• Fludrocortisone
  – Dose?
  – Problem... supine hypertension and peripheral oedema

• Midodrine
  – Dose?
  – Times?
  – Problem... supine hypertension and extreme scalp itch
Other medications

• Domperidone
• Venlafaxine
• Erythropoeitin
• Droxidopa
• Pindolol
• Octreotide
• Indomethacin
• Pseudoephedrine
• Desmopressin (DDAVP)
Pyridostigmine

- Still being researched
- Parasympathomimetic
- Reversible cholinesterase inhibitor
- Theory:
  - Enhanced sympathetic ganglionic transmission increases systemic resistance in proportion to orthostatic need
- Dose 15mg od increasing to 60mg tds
- Caution in asthma
Other symptoms of cardiovascular dysautonomia

- Lethargy, fatigue
- ‘Loss of confidence’
- ‘Coat hanger’ ache
- Visual disturbance
- Post prandial hypotension
- Nausea
- Angina – like pain
Case 2 – Mrs B

- 73 years
- IPD 9 years
- Madopar 125 @ 7,10,1,4,7
- Pramipexole 2.1mg MR
- Zydol 200mg MR bd
- Paracetamol 1g qds
- Lisinopril 10mg od
- Simvastatin 40mg nocte
- Aspirin 75mg od

- Recent fall with #Colles 3/52 ago
- Last 2/52 needs help with walking/getting out of bed/assistance with feeding
- O/E in ED
  - GCS E4M1V2
- ‘Courtesy’ call from ED registrar
  - EOLC pathway
Ogilvie’s syndrome...
Constipation

• Very common

• Increased transit time $\rightarrow$ erratic absorption $\rightarrow$ unpredictability

• Can cause gastroparesis, colonic dilatation and pseudo obstruction

• Abdominal bloating, pain and nausea all worsen QOL
Constipation - reasons

- Weak abdominal musculature
- Lower water intake from early life with reduced thirst
- PD patients take less fibre (14g treated, 11g untreated)
- Decreased phasic contraction
- Paradoxical increase in:
  - Puborectalis and anal sphincter activity due to pelvic muscle dystonia
Constipation - treatment

• Decrease off time
• Reduce anticholinergics etc.
• Increase fluid intake
• Encourage exercise
• Stool softener / Macrogol
  – May exacerbate anorectal dysfunction
• Apomorphine for rectal dyssynergia
• BoTox to puborectalis
Delayed gastric emptying

• Occurs in 70% of patients
• Typically experienced as ‘delayed on’ or ‘no on’ with first dose
• May also describe:
  – Early satiety, bloating, regurgitation and nausea

• Treatment strategies include:
  – Madopar dispersible, Apo-Go penject
  – Prokinetics e.g. Domperidone*, Erythromycin
  – Proculapride, Ghrelin, Nizatidine
  – Small and frequent meals
    • Speed: Carbs>Protein>Lipids
Salivary drooling

• Not necessarily synonymous with ‘Sialorrhoea’
• Normal individuals produce 1-1.5 litres of saliva daily
  – Necessary for good oral health
• Worsened by the off state
• Exacerbated by high sugar foods
• 50-80% of PWP have a degree of drooling
• More common in men
• Often associated with runny nose
• Often disturbs sleep
• Worsened by Clozapine
Options for management?

• Conservative
  – Posture training
  – Improved seating
  – Suck sweets / ice cubes
  – Chew gum
  – Frequent drinks
  – SALT intervention
    • Lip seal improvement
    • Tongue awareness
    • Vibrating brooch/badge

• Medical
  – Oral anticholinergics
  – Atropine eye drops per orum
  – Atrovent spray
  – Hyoscine patch
  – Glycoporonnium

• Interventional
  – Salivary Botulinum Toxin
  – Salivary radiotherapy
Case 3 - Mr Z

- 59 year old lawyer
- IPD 6 years
- Ropinirole XL 14mg od (mane)
- Stalevo 125 @ 7,11,3,7 &
- Rasagiline 1mg od
- C/o crawling sensation in both legs from later evening subsides by 8am
- ‘Unable to get relief’
- Associated feelings of tension/panic/anxiety and occasional chest tightness
Ekbom’s???

• Overwhelming desire to move legs

• Burning/itching/crawling/tension feeling

• Movement gives relief (however temporary)

• Diurnal pattern
  – Worsens through the night and improves towards morning
Central pain

• 4 types of pain
  – Musculoskeletal, dystonic, radicular (motor)

• **Central (non motor)**
  • Burning, tingling, stabbing, aching or itching
  • Feelings of tension

• Underrecognized and seldom treated
• Cause of significant distress
• PRIAMO study (Barone et al.)- significant impact upon QOL
• Rarely responsive to dopaminergic therapies
Mechanism of central pain

• Very unclear
• Basal ganglia involved in nociceptive pathways
• Cortical-Basal Ganglia-Thalamic involved in the multisensory integration of pain including:
  – Motor, emotional, autonomic and cognitive response to pain (Borsook et al.)

• Low levels of ‘analgesic’ neurotransmitters
  – Beta endorphin, metenkephalin

• Low heat pain thresholds in PD v controls
  – Lower in ‘painful’ PD than non painful
Management of pain

• Identify likely type by thorough history
• Simple analgesia / physiotherapy
• Optimise dopaminergic treatment – treat dystonia / dyskinesia – Continuous dopaminergic stimulation – eg subcutaneous apomorphine / surgery
• Neuropathic pain – screen for other causes
  – Diabetes
  – B12 deficiency
  – ETOH
Treatment of central pain

• Difficult

• Opioids, Gabapentin, Carbamazepine etc. not particularly effective

• RECOVER study
  – Some improvement in Likert pain scale with Rotigotine compared to placebo
  – Not a primary outcome measure

• Ensure mainainenance of ‘on state’
Thermoregulatory dysfunction

• 64% (vs. 12.5% controls) of PD patients have excessive sweating
• Majority of patients have a fluctuating motor response
• Hypothalamic dopamine deficiency, peripheral Ax dysfunction
• Typically upper trunk and neck with dry extremities
Thermoregulatory disturbance in PD: difficult to treat

- Remember comorbidity e.g. thyrotoxicosis, lymphoma
- Try to achieve CDS & avoid fluctuation
- Aluminium chloride roll on
- Oral glycoporronium (unlicensed)
- Consider BoTox for focal hyperhidrosis
Cautionary tale - Dopamine Agonist Withdrawal

• Without medication patients have very impaired peripheral vasodilation and therefore poor heat dissipation
• Typically in settings of abrupt dopaminergic withdrawal
• Profuse sweating
• Hyperthermia
• Complete failure of thermoregulation
• Can be fatal
Sleep disorders

“To sleep, perchance to dream.
Ay, there’s the rub.”  Hamlet
Vivid dreams/REM sleep disturbance

- Can predate motor symptoms
- Loss of normal atonia
- Very distressing
- Impacts on restful sleep for both patient and carer
- Poor sleep = worsened motor function
Treating RBD

• Reduce late pm doses of dopaminergic therapies
• Consider discontinuing or reducing:
  – Anticholinergics
  – Centrally acting pain medications
  – Anxiolytics
  – Antidepressants
• Clonazepam
  – ‘Start low go slow’
• Non pharmacological measures
  – Improved sleep hygiene for example
Excessive daytime sleepiness

- Neurodegeneration affecting cholinergic, serotenergic and noradrenergic systems
- Can predate motor signs
- May be side effect of Rx
- Impacts greatly on QOL and ability for social interaction
- Contributes to loss of independence
- Ramifications for driving
- SOOS
- No licensed treatments
OSA

• More common in PD
• Typically normal body weight
• PSG studies show 20-50% of PD patients have significant apnoea overnight (Arnulf et al.)
• Jaw thrust and splint devices not efficacious
• CPAP usually required
Urinary problems

• Nocturnal polyuria and urinary urgency are most common
• Incontinence is common reason for NH placement
• Nocturia is a common cause of falls
• Anticholinergics can provide relief but also can exacerbate hallucinations, postural Sx etc.
Bladder control

• Storage – pontine storage centre supported by:
  – Hypothalamus
  – Frontal cortex
  – Basal Ganglia
  – Cerebellum

• Micturition – pontine micturition centre supported by:
  – Prefrontal cortex & Hypothalamus
  – Activates bladder and inhibits sphincter

• Basal Ganglia involved in inhibiting detrusor
Treatment of detrusor hyperreflexia

- Optimise dopaminergic control
  - Helps relaxation of pelvic floor
  - Does not effect detrusor
- Conventional anticholinergic therapy (eg. Oxybutynin, Tolterodine) may worsen:
  - Cognition
  - Constipation
- Side effects:
  - Dry mouth, blurred vision, worsened OH etc.
- Solifenacin and Trospium
  - Do not cross BBB
  - May be better but may worsen PMV*
- Mirabegron (beta 3 agonist) if anticholinergics not tolerated
- Detrusor BoTox
Sexual dysfunction

• >60% report sexual dysfunction
  – Erectile dysfunction
  – Anorgasmia

• Very multifactorial problem
  – Physical disability
  – Stress of living with a progressive illness
  – Drug effects
  – Difficulty in communication
  – Caregiver stress

• All impact on intimacy
Summary
Management of NMS in PD 1

• PD is a systemic (not just a motor) disorder
• NMS are diverse, multiple and common at all stages
  - commoner in older patients
  - dominate the clinical picture as PD progresses
• Intrinsic to disease
• NMS may also be caused by adverse effects of therapy, non motor fluctuations and be common comorbidities in the elderly
Conclusions
Management of NMS in PD 2

• Often poorly recognised by professionals and ‘undeclared’ despite profound impact on QoL

• Screening (NMS QUEST) and further assessment tools will improve holistic care for pwP and their families

• Many NMS can be managed but may be challenging to treat in context multiple NMS

• Urgent need for better treatments particularly for non dopaminergic responsive symptoms
Approach in a busy clinic...?!

- Routine use of the NMS screening questionnaire (Chaudhuri et al.)
- Posted out to patients with appointment or completed in waiting room
- Use of side scales prompted by responses
- If you don’t ask...