Dopaminergic treatment of non-motor problems in Parkinson’s Disease

K. Ray Chaudhuri
London, UK
Not all PD symptoms are due to dopamine degeneration

STN: subthalamic nucleus; GPi: globus pallidus interna; GPe: external segment; SNc: substantia nigra pars compacta; VTA: ventral tegmental area

Non-motor symptoms of Parkinson’s disease: dopaminergic pathophysiology and treatment

K Roy Chaudhuri, Anthony H V Schapira

Several studies, including work from the Parkinson’s disease (PD) non-motor group and others, have established that the non-motor symptoms of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of quality of life. Research suggests that the non-motor symptoms of the disease are frequently unrecognised by clinicians and remain untreated. Even when identified, there is a common perception that many of these symptoms are untreatable. The role of dopaminergic drugs in treating the various non-motor problems of PD, although clinically recognised, has received little attention. In this Review, we investigate the dopaminergic basis of the range of non-motor symptoms that occur in PD such as depression, apathy, sleep disorders (including rapid-eye movement behaviour disorder), and erectile dysfunction. We discuss the evidence that these symptoms are treatable, at least in part, with various dopaminergic strategies and, where relevant, we also refer to the use of deep-brain stimulation of appropriate targets in the brain. This Review provides a comprehensive overview of the management of this challenging aspect of PD.

Non-motor symptoms of Parkinson’s disease: diagnosis and management

K Roy Chaudhuri, Daniel G Hardy, Anthony H V Schapira

The clinical diagnosis of Parkinson’s disease rests on the identification of the characteristics related to dopamine...
NMS of PD that are in part driven by dopaminergic mechanisms

• Sleep related
  – RLS, PLM, Akathisia, Akinesia, Nocturia, RBD
• Cognitive
  – Depression, Anxiety, Apathy, Anhedonia, ?MCI
• Pain
  – Central, Wearing off
• Bowel Dysfunction
  – Constipation, unsatisfactory voiding
• Bladder
  – DO, Nocturia
• Sexual & General
  – ED, Fatigue
• Vision
  – Contrast sensitivity
• Fluctuation Related NMS

Dopamine and depression

- $^{11}$C-RTI-32 PET – *in vivo* marker of dopamine and NA transporter binding
- Depressed PD ↓ $^{11}$C-RTI-32 PET binding vs non depressed (AC, amygdala, Vent Str)
- Anxiety severity ↓ $^{11}$C-RTI-32 PET binding
- Apathy severity ↓ $^{11}$C-RTI-32 PET binding in Vent Str
- ↓ $^{11}$C-RTI-32 PET binding LC and thalamus (NA)$^1$
- DA and NA pathways targeting limbic system$^2$

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Effect of pramipexole in major depressive disorder (MDD)

Weeks

0 1 2 3 4 5 6 7 8 9

HAMD17 score

Mean decrease from baseline

-15 -12 -9 -6 -3 0

Placebo
Pramipexole 0.26 mg
Pramipexole 0.70 mg
Pramipexole 3.50 mg
Fluoxetine 20 mg

* p < 0.05 vs placebo

Washout

Effect of pramipexole on depression in patients with Parkinson’s disease (PD)

Prospective observational cohort study (n=657)

Baseline vs After 9 weeks on pramipexole
Mean dose 1.05 mg/day

Depression (SPES*)

*SPES: Short Parkinson’s Evaluation Scale

Reichmann et al. CNS Drugs 2003;17:965–73.
Both pramipexole and sertraline improved depressive symptoms

- Baseline
- 12 Weeks

HAM-17 = 17-item Hamilton Depression Rating Scale

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**Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: An in vivo(11)C-Raclopride PET study.**

Politis M, Piccini P, Pavesi N, Koh SB, Brooks DJ.

Division of Neuroscience and MRC Clinical Sciences Centre, Faculty of Medicine, Cyclotron Building, Hammersmith Hospital, Imperial College London, DuCane Road W12 0NN, London, UK.

<table>
<thead>
<tr>
<th>11C-Raclopride BP</th>
<th>PD</th>
<th>Normals</th>
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<td>0.06</td>
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*Fig. 3. Coronal section of statistical parametric map (SPM). Yellow-red areas represent voxel clusters with significant decreases in 11C-raclopride (RAC) binding within the hypothalamic region mask in PD patients (n=14) compared with the group of normal volunteers (n=9). The color stripe indicates z values.*
**Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial.**

*Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, Rupp M, Boroojerdi B; SP 515 Investigators.*

Department of Neurology, Innsbruck Medical University, Innsbruck, Austria. werner.poewe@i-med.ac.at

<table>
<thead>
<tr>
<th>PDQ-39 total score</th>
<th>-5.1 (10.1)</th>
<th>-4.7 (9.2)</th>
<th>-13 (9.4)</th>
<th>0.0030</th>
<th>0.0011</th>
<th>0.7175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>-10.0 (16.8)</td>
<td>-8.8 (15.1)</td>
<td>-2.0 (15.9)</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>0.6869</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>-9.9 (17.3)</td>
<td>-10.2 (16.3)</td>
<td>-1.6 (15.5)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.9070</td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>-6.5 (15.2)</td>
<td>-7.1 (15.0)</td>
<td>-1.3 (13.6)</td>
<td>0.0006</td>
<td>0.0033</td>
<td>0.5256</td>
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<td>Stigma</td>
<td>-6.4 (17.9)</td>
<td>-5.1 (17.7)</td>
<td>-5.4 (20.4)</td>
<td>0.8860</td>
<td>0.6109</td>
<td>0.4156</td>
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<tr>
<td>Bodily discomfort</td>
<td>-5.9 (18.2)</td>
<td>-3.3 (17.5)</td>
<td>-0.6 (20.6)</td>
<td>0.2439</td>
<td>0.0101</td>
<td>0.0771</td>
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</tbody>
</table>

Parkinson's disease sleep scale (cm): 4.9 (19.3) 4.3 (21.1) -2.8 (21.6) 0.0129 0.0006 0.2030

Data are mean (SD) or % (SD). UPDRS=Unified Parkinson's disease rating scale.
Effect of rotigotine, pramipexole, ropinirole on PDSS in PD

![Graph showing the effect of drugs on PDSS in PD](image)

- Ropinirole (24 hr)
  - n=201
  - P = 0.0196
- Placebo
  - n= 190
  - P = 0.2

- Pramipexole
  - n=204
  - P=0.0129
- Rotigotine
  - n=101
  - P=0.0006


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Insomnia in PD

• **Onset/Initiation**
  – Adjustment of anti PD Rx
  – Sleep hygiene
  – Hypnotics

• **Maintenance**
  – Cabergoline (CBG)(po) (Ergot)
  – Apomorphine (Apo)(sc)
    – Apo infusion over 24 hours
  – Rotigotine patch
  – Ropinirole XP
  – STN/Pallidal stimulation
  – Duodopa

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Non-motor symptoms of Parkinson’s disease: dopaminergic pathophysiology and treatment

Several studies, including work from the Parkinson’s disease (PD) non-motor group and others, have established that the non-motor symptoms of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of quality of life. Research suggests that the non-motor symptoms of the disease are frequently unrecognised by clinicians and remain untreated. Even when identified, there is a common perception that many of these symptoms are untreatable. The role of dopaminergic drugs in treating the various non-motor problems of PD, although clinically recognised, has received little attention. In this Review, we investigate the dopaminergic basis of the range of non-motor symptoms that occur in PD such as depression, apathy, sleep disorders (including rapid-eye-movement behaviour disorder), and erectile dysfunction. We discuss the evidence that these symptoms are treatable at least in part, with various dopaminergic strategies and, where relevant, we also refer to the use of deep-brain stimulation of appropriate targets in the brain. This Review provides a comprehensive overview of the management of this challenging aspect of PD.

Intrajejunal levodopa infusion in Parkinson’s disease: A pilot multicenter study of effects on nonmotor symptoms and quality of life.


Department of Neurology, Central Hospital, Brønshøj, Denmark.

Switching from oral medications to continuous infusion of levodopa/carbidopa gel reduces motor complications in advanced Parkinson’s disease (PD), but effects on nonmotor symptoms (NMSs) are unknown. In this prospective open-label observational study, we report the effects of intrajejunal levodopa/carbidopa gel infusion on NMS in PD based on standard assessments utilizing the nonmotor symptoms scale (NMSS) along with the Unified Parkinson’s disease rating scale (UPDRS 3 motor and 4 complications) and quality of life (QoL) using the Parkinson’s disease questionnaire (PDQ-8). Twenty-two advanced PD patients (mean age 58.6 years, duration of disease 15.8 years) were followed for 6 months. A statistically significant beneficial effect was shown in six of the nine domains of the NMSS: cardiovascular, sleep/fatigue, attention/memory, gastrointestinal, urinary, and miscellaneous (including pain and itching) and for the total score of this scale (NMSS) paralleling improvement of motor symptoms (UPDRS 3 motor and 4 complications in “best on” state) and dyskinesias/motor fluctuations. In addition, significant improvements were found using the Parkinson’s disease sleep scale (PDSS) and the PDQ-8 (QoL). The improvement in PDQ-8 scores correlated highly significantly with the changes in NMSS, whereas a moderately strong correlation was observed with UPDRS changes. This is the first demonstration that a levodopa-based continuous dopaminergic stimulation is beneficial for NMS and health-related quality of life in PD in addition to the reduction of motor fluctuations and dyskinesias. (c) 2009 Movement Disorder Society.

PMID 19425079 [PubMed - as supplied by publisher]
Changes in sleep assessment following duodopa

Honig et al. Mov Disord 2009;24:1468–74.
Proposed pathophysiology of REM sleep behaviour disorder in humans

Lesions in sublaterodorsal nucleus + Sufficient locomotor drive = REM sleep behaviour disorder

Boeve et al. Brain 2007
# RBD treatment: no controlled trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Ringman <em>et al.</em> <em>Neurology</em> 2000; 55:870–1</td>
</tr>
<tr>
<td>?Quetiapine</td>
<td></td>
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<tr>
<td>?Carbamazepine</td>
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<td>Worsening</td>
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</table>
Fatigue in PD

- Feeling of constant tiredness (either mental or physical or both)
- No fatigability during sustained muscular contraction
- Not related to: disease severity disease duration treatment
Central fatigue = failure in the integration of the limbic input and the motor function within the basal ganglia circuitry
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Fatigue

• Dopaminergic basis
• Improved by
  – Levodopa
    • Oral
    • I J infusion
  – Apomorphine
PD and pain
(Chaudhuri, Schapira classification)

- Musculoskeletal pain
- PD related chronic pain
  - Central pain
  - Indirectly aggravated pain
  - Visceral pain
- Fluctuation related pain (WO)
  - Dystonic
  - Central
- Dyskinesia related pain (Beginning dose, peak dose, end of dose. Diphasic)
- Nocturnal pain
  - RLS/PLM related
  - Noct akinesia
- Coat Hanger pain
- Oro-facial pain
  - TMJ pain
  - Bruxism related pain
  - Burning mouth syndrome
- Peripheral limb pain
  - Drug induced

Dopamine and pain

• Pain threshold to cold significantly lower in PD withdrawn from Rx vs Control
• Normalisation after levodopa in PD but not Control
• Off Rx activation of AC, Insula and Rt PFC
• On Insular activation
• Pain threshold to cold are DA dependent

Dopamine and pain

- Primary central pain (no obvious cause):
  - 9 PD + PCP, 9 PD – pain, 9 central pain
    - Hyperalgesia
    - Lack of habituation of sympathetic sudomotor response to repetitive pain
    - More marked on affected side
    - Abnormalities improved by levodopa 100 mg
- Dysfunction of DA dependent autonomic centres regulating AF and inhibitory modulation of pain input

In PD pain responded to dopaminergic treatment changes in night-time pain and spasm scores before and after apomorphine (Apo)/placebo infusion in Parkinsonian RLS.

Intrajejunal levodopa infusion in Parkinson’s disease: A pilot multicenter study of effects on nonmotor symptoms and quality of life.


Department of Neurology, Central Hospital, Bremenhaven, Germany.

Switching from oral medications to continuous infusion of levodopa/carbidopa gel reduces motor complications in advanced Parkinson’s disease (PD), but effects on nonmotor symptoms (NMSs) are unknown. In this prospective open-label observational study, we report the effects of intrajejunal levodopa/carbidopa gel infusion on NMS in PD based on standard assessments utilizing the nonmotor symptoms scale (NMSST) along with the unified Parkinson’s disease rating scale (UPDRS 3 motor and 4 complications) and quality of life (QoL) using the Parkinson’s disease questionnaire (PDQ-8). Twenty-two advanced PD patients (mean age 53.6 years, duration of disease 15.3 years) were followed for 6 months. A statistically significant beneficial effect was seen in six of the nine domains of the NMSST: cardiovascular, sleep/tetraparesis, attention/memory, gastrointestinal, urinary, and miscellaneous (including pain and dribbling) and for the total score of this scale (NMSST) paralleling improvement of motor symptoms (UPDRS 3 motor and 4 complications in “best on” state) and dyskinesias/motor fluctuations. In addition, significant improvements were found using the Parkinson’s disease sleep scale (PDSS) and the PDQ-8 QoL. The improvement in PDQ-8 scores correlated highly significantly with the changes in NMSST, whereas a moderately strong correlation was observed with UPDRS changes. This is the first demonstration that a levodopa-based continuous dopaminergic stimulation is beneficial for NMS and health-related quality of life in PD in addition to the reduction of motor fluctuations and dyskinesias. (c) 2009 Movement Disorder Society.

PMID: 19426070 [PubMed - as supplied by publisher]
Effect size of duodenal levodopa on non-motor symptoms

< 0.2 = negligible; 0.2–0.49 = small; 0.5–0.79 = moderate; > 0.8 = large

CVS: cardiovascular symptoms

(Kazis et al. Med Care 1989; 27:S178–89)

Honig et al. Mov Disord 2009; 24:1468–74.
Swallowing problems

- Can lead to mortality and may cause
  - Asphyxiation / choking
  - Pulmonary aspiration/ Chest infections
  - Malnutrition
  - Dehydration
  - Drooling
- Can have a tremendous impact on quality of life
- Problems swallowing PD medications
Silent aspiration

- 40% of patients with PD shown to be aspirating during video fluoroscopic examination were unaware and showed no external signs
- May be helped by DA therapy

Logemann 1995.
Potential indications of a ‘non-oral’ or once-a-day therapy in PD


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Duodopa study

NMS Gastrointestinal (GIT) domain

- Does the patient dribble saliva during the day?
- Does the patient have difficulty swallowing?
- Does the patient suffer from constipation? (Bowel action less than three times weekly)

Changes in GIT domain

<table>
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<th>% change</th>
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<td>50</td>
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<tr>
<td>60</td>
<td>0</td>
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<tr>
<td>70</td>
<td>62%</td>
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</tbody>
</table>

P=0.0003

Honig et al. Mov Disord 2009;24:1468–74.
Visual symptoms in PD

- **Diplopia**
  - Fleeting
  - Fluctuation related
  - Selective diplopia
- **Ocular motility related**
  - Low or reduced blink rate
  - Cogwheel pursuit movement
  - Impaired remembered saccades (hypometria of saccades)
  - Impaired upgaze
  - Convergence insufficiency
  - Square wave jerks
- **Pupillary**
  - Impaired response to light and pain
- **Visual hallucinations**
  - Charles Bonnet
    - Korczyn 2007
Dopaminergic cell bodies are located within the layer of amacrine cells, at the border of inner nuclear and inner plexiform layers.
Dopamine and vision: Non-motor fluctuations

- PD-patients describe blurred vision especially at lower luminosity during ‘OFF’ phases
- The pathophysiological correlate is likely a degeneration of foveal retinal dopaminergic neurons (referenced group A17) which physiologically enhance visual contrast

DA drugs may also have unwanted effects

Parkinson's drugs 'made me gambler, thief and gay sex fiend'

Sunday Observer, Dec 2007
**Brief Communications**

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

  S. Frucht, MD, J. D. Rogers, MD, P. E. Greene, MD, M. F. Gordon, MD and S. Fahn, MD

From the Columbia-Presbyterian Medical Center (Drs. Frucht, Greene, and Fahn) and Beth Israel Medical Center (Dr. Rogers), New York, NY; and the Long Island Jewish Medical Center (Dr. Gordon), New Hyde Park, NY.

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.

Cerebrospinal fluid-orexin levels and sleep attacks in four patients with Parkinson's disease.


Department of Neurology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan. asaihozon@yahoo.co.jp

OBJECTIVES: Sleep attacks (SAs) in Parkinson's disease (PD) are rare, but clinically important because they significantly impair the daily lives of patients. Causes of SAs include long-term activation of dopaminergic (especially D3) receptors. Recent studies suggest that SAs in PD may be related to impairment of hypothalamic orexin neurons, similar to narcolepsy. Whether orexin is associated with long-term activation of dopaminergic receptors remains uncertain. PATIENTS AND METHODS: We measured levels of orexin in samples of spinal cerebrospinal fluid (CSF) from 25 patients with PD, including 9 with excessive daytime sleepiness and 4 with SAs. Furthermore, in the four patients with SAs, the selective dopamine D1/D2 agonist pergolide was substituted for the causative drugs with D3 stimulatory activity, and CSF-orexin levels were measured before and after switching treatment. RESULTS: In the 25 patients with PD, including the 4 patients with SAs, lower CSF-orexin levels were associated with a longer disease duration, which has been linked to a higher incidence of SAs. Switching treatment to pergolide significantly increased CSF-orexin levels and completely resolved SAs in the four patients with PD. CONCLUSION: Despite the small number of patients studied, our results suggest that orexin transmission is most likely involved in SAs in PD and that abrogation of D3 receptor stimulation may increase orexin and thereby inhibit SAs.

PMID: 19097685 [PubMed - indexed for MEDLINE]
Impact of dopaminergic drugs

Motor symptoms

Non-motor symptoms

Sleep disability

Activities of daily living
- Handwriting
- Preparing food
- Walking
- Speech

Disruption to daily life
- Pain
- Depression
- Non motor off
- GIT, Bladder
Non-motor Symptoms of Parkinson’s Disease

Edited by:
K. Ray Chaudhuri
Eduardo Tolosa
Anthony Schapira
Werner Poewe

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