Hypersomnia (with emphasis in PD and other MD)

L. Ferini-Strambi
Università Vita-Salute
San Raffaele, Milan, Italy

HISTORICAL ASPECTS IN PARKINSON’S DISEASE

• “SLEEP BECOMES MUCH DISTURBED” and terminal stages of disease is associated with “CONSTANT SLEEPINESS…”

J Parkinson, 1817
CNS primary changes
- Dopaminergic and serotonergic impairments
- Hypocretin? 
- MLT?

SLEEP FRAGMENTATION

Specific disorders:
- Sleep Apnea
- PMLs
- Depression

EDS in Parkinson

Dopaminergic drugs
+ Drugs used for co-morbidities

Original Communication

Parkinsonism with excessive daytime sleepiness
A narcolepsy-like disorder?

In conclusion, our clinical, neurophysiological and CSF data do not support the hypothesis of a “final common pathway” in the pathophysiology of narcolepsy and Parkinsonism with EDS, not even when associated with hallucinations and REM sleep behavior. Sleep apnea and PLMS may play a so-far underestimated role in the pathogenesis of EDS in Parkinsonian disorders.
Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole

S Frucht et al
Neurology, 1999; 52: 1908-1910

The authors report a new side effect of dopamine agonists pramipexole and ropinirole: sudden attacks of sleep. Eight PD patients taking pramipexole and one taking ropinirole fell asleep while driving, causing accidents.
### Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study (RECOVER)

Claudia Trevisanov, MD,1,2 Bryan Kao, PhD,3 Giuseppe Rutigliano, MD,4 Jennifer Pfe, MD,1,2,4,5
Jonas Kall, MD,1,2 Massimo Rizzolatti, MD,4 Peter Grossarth, MD,5 Dennis C. Janzen, MD,1,2

### Table 1. Baseline demographic and clinical characteristics (safety population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo n=190</th>
<th>Rotigotine n=195</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>114 (60.0%)</td>
<td>107 (54.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>76 (40.0%)</td>
<td>88 (45.3%)</td>
</tr>
<tr>
<td>Age, mean (SD), range</td>
<td>64.5 (12.0), 24-92</td>
<td>68.4 (11.3), 27-91</td>
</tr>
<tr>
<td>Height, mean (SD), range</td>
<td>163.5 (6.6), 147-179</td>
<td>163.5 (6.6), 148-179</td>
</tr>
<tr>
<td>Weight, mean (SD), range</td>
<td>75.8 (18.1), 39.5-116</td>
<td>75.9 (18.1), 39.5-116</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>126 (66.3%)</td>
<td>128 (65.3%)</td>
</tr>
<tr>
<td>African American</td>
<td>25 (13.2%)</td>
<td>24 (12.4%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (10.5%)</td>
<td>22 (11.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (13.2%)</td>
<td>21 (10.8%)</td>
</tr>
<tr>
<td>Time from first diagnosis, mean (SD), range</td>
<td>4.3 (4.3), 0-9.6</td>
<td>4.1 (4.3), 0-9.6</td>
</tr>
</tbody>
</table>

### Graphs

- **Graph A**: UPSRS Part III
  - Placebo vs. Rotigotine: Comparison
  - Placebo: Mean reduction in score
  - Rotigotine: Mean reduction in score

- **Graph B**: PDSS-2 Total
  - Placebo vs. Rotigotine: Comparison
  - Placebo: Mean reduction in score
  - Rotigotine: Mean reduction in score
Obstructive sleep apnea

Sleep disordered breathing in Parkinson’s disease: A critical appraisal

Pereira F da Silva-Jonnet1,2, , Gilmar T do Prado3, , Nilton R. Barreira4, , Sergio Toledo Silva M. Tagliaro
Sleep Medicine Reviews, 18 (2014) 281-296

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Normal controls</th>
<th>Normal controls</th>
<th>Parkinson’s patients</th>
<th>Parkinson’s patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velez-Flórez et al., 2005 (6a)</td>
<td>26 64.5±15.68</td>
<td>15 83±16.78</td>
<td>15 84±16.78</td>
<td>27 1±27</td>
<td>Not stated</td>
<td></td>
</tr>
<tr>
<td>Myllylä et al., 2008 (7a)</td>
<td>15 83±12.23</td>
<td>15 89±12.23</td>
<td>27 1±27</td>
<td>&lt;0.01 difference vs. placebo, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bredow et al., 2005 (8a)</td>
<td>40 65±12.9 ± 16.5</td>
<td>40 64±12.9 ± 16.5</td>
<td>25±5</td>
<td>&lt;0.05 flow decrease vs. placebo, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han et al., 1999 (9a)</td>
<td>40 62±12.9 ± 16.5</td>
<td>40 62±12.9 ± 16.5</td>
<td>25±5</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Chill et al., 2005 (10a)</td>
<td>100 62±12.9 ± 16.5</td>
<td>100 62±12.9 ± 16.5</td>
<td>25±5</td>
<td>&lt;0.05 flow decrease vs. placebo, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testa and Restie, 2014 (11)</td>
<td>50 45±12.9 ± 16.5</td>
<td>50 45±12.9 ± 16.5</td>
<td>25±5</td>
<td>&lt;0.05 flow decrease vs. placebo, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fadiga et al., 2011 (12)</td>
<td>50 38±12.9 ± 16.5</td>
<td>50 38±12.9 ± 16.5</td>
<td>25±5</td>
<td>Not stated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<0.05 = p<0.05 in 10% of patients; Normal values shown in parentheses; Group differences in mean values calculated by independent Student t test. 1 = 1 month study; 2 = 3 month study; 3 = 6 month study; 4 = 12 month study; n.s. = not significant.
CPAP improves sleep and daytime sleepiness in patients with PD and sleep apnea

Neikrug AB et al., Sleep 37: 177-85, 2014

- Randomized placebo-controlled, cross over study
- 38 PD patients, treated for 6 weeks
- CPAP treated patients showed significantly decrease in AHI and Arousal index, and increase in N3 stage %
- CPAP also reduced daytime sleepiness, measured by MSLT

Continuous Positive Airway Pressure Improves Sleep and Daytime Sleepiness in Patients with Parkinson Disease and Sleep Apnea

The associations between fatigue, apathy, and depression in Parkinson's disease

Moore et al. J Neurol Neurosurg Psychiatry 84: 365-72, 2013

methods – A total of 131 non-demented patients with PD were examined using the Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Starkstein Apathy Scale, Multidimensional Fatigue Inventory (MFI), Beck Depression Inventory-II, and Epworth Sleepiness Scale. Results – The prevalence and severity of fatigue and apathy were significantly higher in depressed PD patients. However, our results show that depression, fatigue, and apathy can be clearly distinguished in PD. Apathy was
Table 4—Results of nocturnal polysomnography among subjects with and without significant insomnia or daytime sleepiness (n = 50)

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
<th>HI-s3</th>
<th>HI-s16</th>
<th>HI-10</th>
<th>ESS-s16</th>
<th>ESS-s10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (h)</td>
<td>7.1 ± 1.6</td>
<td>5.0-9.3</td>
<td>5.2-9.3</td>
<td>5.7-7.9</td>
<td>6.4-6.6</td>
<td>5.0-6.6</td>
<td>5.0-6.6</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>17 ± 17.1</td>
<td>6-67.0</td>
<td>6-67.0</td>
<td>6-67.0</td>
<td>6-67.0</td>
<td>6-67.0</td>
<td>6-67.0</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>76 ± 13.7</td>
<td>53.0-93.4</td>
<td>72.0-94.1</td>
<td>74.2-82.0</td>
<td>73.9-94.3</td>
<td>73.9-94.3</td>
<td>73.9-94.3</td>
</tr>
<tr>
<td>Sleep stages</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 (%)</td>
<td>22 ± 16.7</td>
<td>6-51.8</td>
<td>21-59.4</td>
<td>21-59.4</td>
<td>21-59.4</td>
<td>21-59.4</td>
<td>21-59.4</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>55 ± 15.8</td>
<td>27-89.7</td>
<td>44-74.7</td>
<td>44-74.7</td>
<td>44-74.7</td>
<td>44-74.7</td>
<td>44-74.7</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>5 ± 10.2</td>
<td>0-64.8</td>
<td>7-20.6</td>
<td>7-20.6</td>
<td>7-20.6</td>
<td>7-20.6</td>
<td>7-20.6</td>
</tr>
<tr>
<td>REM (%)</td>
<td>14 ± 7.9</td>
<td>6-24.0</td>
<td>18-27.8</td>
<td>18-27.8</td>
<td>18-27.8</td>
<td>18-27.8</td>
<td>18-27.8</td>
</tr>
<tr>
<td>Narcolepsy latency (s)</td>
<td>27 ± 27.9</td>
<td>6-63.6</td>
<td>26-90.4</td>
<td>26-90.4</td>
<td>26-90.4</td>
<td>26-90.4</td>
<td>26-90.4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>56 ± 9.7</td>
<td>40-70.7</td>
<td>51-67.0</td>
<td>51-67.0</td>
<td>51-67.0</td>
<td>51-67.0</td>
<td>51-67.0</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>50,000 ± 16,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>50,000 ± 16,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>50,000 ± 16,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
<td>24,000-35,000</td>
</tr>
</tbody>
</table>

Dysfunctional sleep beliefs in Parkinson’s disease: Relationships with subjective and objective sleep

Deborah Adams*, Lakme S. Nair*, Chen Ye, Zdenek Tepperling, Steven G. Lewis

Aim 1: To assess the prevalence and determine the severity of sleep disturbances in Parkinson’s disease. 

Aim 2: To compare sleep hygiene, sleep beliefs, and sleep quality between Parkinson’s disease and control groups.

Aim 3: To investigate the relationships between sleep disturbances, sleep hygiene, sleep beliefs, and sleep quality.

No relationships were found between dysfunctional beliefs and attitudes about sleep and any objective or subjective measure of sleep disturbance. These findings suggest that beliefs and attitudes about sleep in Parkinson’s disease are associated with mood disturbance, rather than objective measures of sleep. Thus, it is possible that interventions targeting mood may lead to more accurate perceptions of sleep and improved quality of life in Parkinson’s disease patients.
Pre-motor features of Parkinson's disease: the Honolulu-Asia Aging Study experience

Ross GW et al., Mov Disord 2012

The Honolulu-Asia Aging Study is a population-based prospective study of neurodegenerative and cerebrovascular diseases in 8006 Japanese-American men, born 1900-1919. Beginning in 1965, ........

Impaired olfaction, constipation, slow reaction time, excessive daytime sleepiness, and impaired executive function were all associated with future development of PD and/or with increased likelihood of either incidental Lewy bodies. Compared with persons without any, those with combinations of 2 or more of these pre-motor features had up to a 10-fold increase in risk for development of PD.

Predictors of dementia in Parkinson's disease; findings from a 5-year prospective study using the SCOPA-COG

Kangku Bui, Jacobs J, van Hout, Johan Maruis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Risk</th>
<th>Ratio 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired olfaction</td>
<td>1.48 (1.40-1.56)</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Impaired constipation</td>
<td>1.40 (1.33-1.49)</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Slow reaction time</td>
<td>1.45 (1.35-1.55)</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>1.40 (1.33-1.49)</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Impaired executive function</td>
<td>1.40 (1.33-1.49)</td>
<td>1.01</td>
<td></td>
</tr>
</tbody>
</table>

Compared with persons without any, those with combinations of 2 or more of these pre-motor features had up to a 10-fold increase in risk for development of PD.

Treatment of the Sleep Disorders Associated with Parkinson’s Disease

Lynne Wang Tuchs; Donald L. Bibbo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Improvement ESS Score</th>
<th>Improvement Sleep Efficiency</th>
<th>Improves Sleep Quality</th>
<th>Improves Mood</th>
<th>Improves Overall QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>300 mg/night</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Modafinil</td>
<td>200 mg</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Vilkabenzol</td>
<td>500 mg/night</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Riluzole</td>
<td>500 mg/night</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>80 mg/night</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 mg/day</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150 mg/day</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Lithium</td>
<td>600 mg/day</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Lithium</td>
<td>900 mg/day</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
<tr>
<td>Lithium</td>
<td>1200 mg/day</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

Significant improvements in sleep quality and overall quality of life.
Daytime somnolence and nocturnal sleep disturbances in Huntington disease.

Excessive daytime somnolence, as defined by the ESS score ≥10, was present in fifteen patients (50%). Median ESS score was 9.5 (range 0–15). Daytime somnolence was associated with co-existent depression (p = 0.004). Median ESS score was 12 (range 4–15) among depressed patients, and 4.5 (range 0–12) among non-depressed patients. There was no correlation between EDS and disease duration (p = 0.32), irritability (p = 0.81), OFDROS score (p = 0.37), antidepressants use (p = 0.49), or antipsychotics use (p = 0.52).

Sleep and circadian rhythm alterations correlate with depression and cognitive impairment in Huntington’s disease.

N. Ahmed Aria, Galia N. Angelova, Johan Marinus, Gert Jan Lamers, Raymund A.C. Roos

Sleep and circadian rhythm alterations correlate with depression and cognitive impairment in Huntington’s disease.