Treatment of Non-Motor Symptoms of Parkinson’s disease

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Braak Hypothesis: Evolving Concept of Disease Progression and Timing

- Hyposmia
- Constipation
- Sleep disorder
- Bladder disorder
- Depression
- Unilateral tremor
- Rigidity
- Akinesia
- Bilateral disease
- Poor balance
- Falls
- Dependency
- Cognitive decline
- Chair/bed bound
- Dementia

Conceptual Diagram of the Phases of Parkinson’s Disease

<table>
<thead>
<tr>
<th>Pre-Motor</th>
<th>Non-Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td>Neuropsychiatry</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>- Cognitive Impairment, dementia</td>
</tr>
<tr>
<td><strong>Loss of smell</strong></td>
<td>- Depression, anxiety</td>
</tr>
<tr>
<td><strong>REM Sleep disorder</strong></td>
<td>- Psychosis</td>
</tr>
<tr>
<td><strong>Sleep Disorders</strong></td>
<td>- REM Sleep disorder</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>- Excessive Day time sleepiness</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>- Insomnia</td>
</tr>
<tr>
<td></td>
<td>- RLS/PLMS</td>
</tr>
<tr>
<td></td>
<td>- Fatigue</td>
</tr>
</tbody>
</table>
Fluctuations in non-motor symptoms of PD may be as important as fluctuations in motor symptoms

In a study of 50 PD patients, the incidence of non-motor symptom fluctuations was as follows:

- Anxiety (66%)
- Drenching sweats (64%)
- Slowness of thinking (bradyphrenia) (58%)
- Fatigue (56%)
- Irritability (52%)

28% of patients indicated that non-motor fluctuations were more disabling than motor fluctuations

Consider adjustments to PD medications if symptoms occur in “off” state

## Early PD: Common Adverse Events

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dizziness</th>
<th>Hallucinations</th>
<th>Nausea</th>
<th>Orthostatic Hypotension</th>
<th>Pedal Edema</th>
<th>Somnolence</th>
<th>Confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa/levodopa(^1)</td>
<td>6-15%</td>
<td>6-8%</td>
<td>13-49%</td>
<td>12%</td>
<td>6%</td>
<td>19-21%</td>
<td>NR</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>1%</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Selegiline</td>
<td>14%</td>
<td>6%</td>
<td>20%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6%</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>25%</td>
<td>9%</td>
<td>28%</td>
<td>&gt; 1%</td>
<td>5%</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>Pramipexole ER</td>
<td>12%</td>
<td>5%</td>
<td>22%</td>
<td>3%</td>
<td>5%</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>40%</td>
<td>5%</td>
<td>60%</td>
<td>6%</td>
<td>7%</td>
<td>40%</td>
<td>5%</td>
</tr>
<tr>
<td>Ropinirole PR</td>
<td>6%</td>
<td>5%</td>
<td>19%</td>
<td>5%</td>
<td>5%</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>14-22%</td>
<td>NR</td>
<td>34-48%</td>
<td>1-2%</td>
<td>2-4%</td>
<td>12-20%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Data from package inserts; ER – extended release; PR – prolonged release

1 PI does not list frequency of AEs; taken from ELLDOPA, CALM-PD and 056
2 PI lists AEs in moderate to advanced disease compared to carbidopa/levodopa
# Advanced PD: Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Dizziness</th>
<th>Hallucinations</th>
<th>Nausea</th>
<th>Orthostatic Hypotension</th>
<th>Somnolence</th>
<th>Dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa/levodopa¹</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td>1%</td>
<td>NR</td>
<td>13%</td>
</tr>
<tr>
<td>Carbidopa/levodopa ER²</td>
<td>3%</td>
<td>4%</td>
<td>6%</td>
<td>1%</td>
<td>NR</td>
<td>16%</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>2%</td>
<td>5%</td>
<td>12%</td>
<td>9%</td>
<td>6%</td>
<td>18%</td>
</tr>
<tr>
<td>Selegiline</td>
<td>14%</td>
<td>6%</td>
<td>20%</td>
<td>2%</td>
<td>2%</td>
<td>NR</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>26%</td>
<td>17%</td>
<td>28%</td>
<td>53%</td>
<td>9%</td>
<td>47%</td>
</tr>
<tr>
<td>Pramipexole ER</td>
<td>2%</td>
<td>9%</td>
<td>11%</td>
<td>NR</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>26%</td>
<td>10%</td>
<td>30%</td>
<td>&gt;1%</td>
<td>20%</td>
<td>34%</td>
</tr>
<tr>
<td>Ropinirole PR</td>
<td>8%</td>
<td>8%</td>
<td>11%</td>
<td>5%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>23%</td>
<td>7%</td>
<td>28%</td>
<td>NR</td>
<td>32%</td>
<td>14%</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>20%</td>
<td>10%</td>
<td>30%</td>
<td>20%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Entacapone</td>
<td>8%</td>
<td>4%</td>
<td>14%</td>
<td>4%</td>
<td>2%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Data from package inserts; ER – extended release; PR – prolonged release
¹ PI does not list frequency of AEs; taken from ELLDOPA, CALM-PD and 056
² PI lists AEs in moderate to advanced disease compared to carbidopa/levodopa
Parkinson Disease Dementia
Cholinergic Deficits in PD and PD Dementia

PD Dementia: Treatment

- Cognitive and behavioral symptoms in PD patients are greatest contributors to caregiver distress\(^1\)
- Risk of mortality increased when PD patients develop dementia\(^2\)
- Start by work up for treatable conditions
  - MRI
  - Blood work: metabolic panel, thyroid studies, B12, folate, etc
  - Review of medication schedule
  - Rule out presence of infection
  - Evaluate social stressors, e.g., moving, etc
- Reduce antiparkinsonian medications if possible

# PD Dementia: Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Rivastigmine                | Emre¹ (2004) n = 541            | Mean dose: 8.6 mg/day  
Treatment effect: ADAS-Cog score*: +11.7%  
Discontinuation: 27% (Rivastigmine) vs 17% placebo  
Worsening of PD: 27% (Rivastigmine) vs 16% (placebo) |
| Donepezil (not approved for PD dementia) | Aarsland² (2002) n = 14 (cross over) | Treatment effect: MMSE**: 2.4  
Discontinuation: 14% (donepezil)  
No change in UPDRS scores |
| Galantamine (not approved for PD dementia) | Litvinenko⁵ (2008) n = 21 (open label) | Treatment: MMSE + 3.7, ADAS – Cog 3.3  
No significant change in UPDRS scores |


* Alzheimer Disease Assessment Scale–Cognition ** Minimental Status Examination *** Unified Parkinson Disease Rating Scale  
**** Dementia Rating Scale
### PD Dementia: Memantine

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leroi(^1) (2009) n = 25</td>
<td>Treatment effect: No change in DRS(^c), MMSE(^d), NPI(^e) Worsening of PD: None</td>
</tr>
<tr>
<td>Aarsland(^2) (2009) n = 72 (included LBD(^a))</td>
<td>Treatment effect: Better CGI-C(^f) score 1.4; better response in PDD(^g) versus LBD Discontinuation: 22% Worsening of PD: None</td>
</tr>
<tr>
<td>Emre(^3) (2010) n = 121 (PDD) n = 78 (LBD)</td>
<td>Treatment effect: ADCS-CGIC(^h) – 0.1 NPI – 1.4 MMSE: +2.0 Discontinuation: 11 patients in the memantine group and 12 placebo group No change in UPDRS scores</td>
</tr>
</tbody>
</table>

* Memantine not approved for PD dementia

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\(^1\) Mov Disord 2009;24:1217-1221 \(^2\) Lancet Neurology 2009;8:613-618 \(^3\) Lancet Neurology 2010;9:969-977

\(^a\) Lewy Body Dementia \(^c\) Dementia Rating Scale \(^d\) Minimental Status Examination \(^e\) Neuropsychiatric Inventory

\(^f\) Clinical Global Impression-Clinician \(^g\) Parkinson Disease Dementia \(^h\) Alzheimer disease Cooperative Study Clinical Global Impression of change
PD Dementia Treatment - Summary

- Correct underlying problems
- Reduce antiparkinsonian medications
- Consider cholinesterase inhibitors like rivastigmine, donepezil, galantamine
  - Common side effects include: nausea, vomiting, diarrhea, anorexia, tremor, dizziness, hypotension
- Consider memantine
  - Common side effects include: dizziness, confusion, headache, constipation
PD: Depression

- Approximately 40% of the patients experience depression
- Independent of age, disease duration, disease severity, or cognitive impairment
- Associated with increased disability, increased caregiver burden, declining quality of life
- Uncertain if depression is endogenous, exogenous or both
- In some patients depression may be correlated with motor fluctuations

Olanow et al Neurology 2009;72:S1-S136
PD Depression: Treatment

- Treat Parkinson’s symptoms including motor fluctuations
- Non pharmacologic: psychotherapy, etc
- Selective Serotonin Reuptake Inhibitors (SSRIs):
  - Most widely used
  - Safe, effective, once-daily dosing
  - Long-term issues: weight gain, sexual dysfunction
- Bupropion, mirtazapine, nefazodone, venlafaxine
  - Less sexual dysfunction
- Tricyclic antidepressants (TCAs) & trazodone
  - Utility limited by side effects: anticholinergic, orthostatic hypotension, weight gain
  - Sedative at low-doses
- Others: Dopamine agonists, ECT, etc
# PD Depression: SSRI

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Wermuth¹ (1998) n = 37</td>
<td>Dose: &lt; 65 years 20 mg; &gt; 65 years 10 mg Treatment effect: No difference in HDRS&lt;sup&gt;a&lt;/sup&gt; scores Discontinuation: 21%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Leentjens² (2003) n = 12</td>
<td>Dose: Maximum dose 100 mg/day Treatment effect: No difference in MADRS&lt;sup&gt;b&lt;/sup&gt; scores, significant treatment effect in both groups</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Fregni³ (2004) n = 42</td>
<td>Dose: 20 mg/day Control group: Transcranial magnetic stimulation Treatment: HDRS improved by 41% and BDI&lt;sup&gt;c&lt;/sup&gt; by 33% No change in UPDRS&lt;sup&gt;d&lt;/sup&gt; scores</td>
</tr>
<tr>
<td></td>
<td>Avila⁴ (2003) n = 16</td>
<td>Mean Dose: 25 mg/day Control group: Nefazodone mean dose 200 mg/day Treatment: Significant improvement in BDI in both groups UPDRS scores improved in nefazodone group</td>
</tr>
</tbody>
</table>


<sup>a</sup> Hamilton Depression Rating Scale  <sup>b</sup> Montgomery Asberg Depression Scale  <sup>c</sup> Beck Depression Inventory  <sup>d</sup> Unified Parkinson Disease Rating Scale
# PD Depression: Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Nortriptyline | Menza\(^1\) (2009) n = 52 | Mean Dose: 49 mg/day; paroxetine CR 28 mg/day  
Control group: Paroxetine CR, placebo  
Treatment effect: Nortriptyline superior to placebo regarding change in HDRS* score; 53% responded vs 11% in paroxetine group vs 24% placebo  
Discontinuation: 35% |
| Desipramine | Devos\(^2\) (2008) n = 48  | Dose: 75 mg/day; citalopram 20 mg/day  
Control group: citalopram, placebo  
Treatment: Both citalopram and desipramine showed significant improvement in MADRS** scores  
Discontinuation: 6%  
More side effects in desipramine group |
| Amitriptyline | Antonini\(^3\) (2006) n = 31 | Dose: 25 mg/day; sertraline 50 mg/day  
Control group: sertraline, placebo  
Treatment: HDRS improved in both groups  
Discontinuation: 25%  
No change in UPDRS*** scores |

\(^1\) Neurology 2009;72:886-892  \(^2\) Mov Disord 2008;23:850-857  \(^3\) Mov Disord 2006;21:1119-1122  
* = Hamilton Depression Rating Scale  ** = Montgomery Asberg Depression Rating Scale  *** Unified Parkinson Disease Rating Scale
# PD Depression: Dopamine Agonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Pramipexole    | Barone¹ (2010)  
n = 296                   | Mean Dose: 2.2 mg/day  
Treatment effect: BDI<a> 1.9  
UPDRS<b> scores improved by 2.2 group difference  
Path analysis showed that direct effect of pramipexole on depression accounted for 80% of treatment effect |
|                | Barone² (2006)  
n = 76                                     | Mean Dose: 3.2 mg/day, sertraline 48 mg/day  
Control group: sertraline  
Treatment: HDRS<c> scores declined in both groups  
Discontinuation: 12%  
UPDRS scores improved in pramipexole group  
AEs were more common in sertraline group |
| Pramipexole    | Barone³ (2003)  
n = 41  
Open label                   | Mean Dose: 2.7 mg/day, pergolide 3 mg/day  
Control group: pergolide  
Treatment: MADRS<d> improved significantly in the pramipexole group but not in pergolide group  
Discontinuation: 5 patients  
UPDRS scores improved in both groups |

¹ Lancet Neurol 2010;9:573-580  
² J Neurol 2006;253:601-607  
³ Eur J Neurol 2003;10:399-406  
⁴ Beck Depression Inventory Hamilton Depression Rating Scale  
⁵ Unified Parkinson Disease Rating Scale  
⁶ Hamilton Depression Scale  
⁷ Montgomery Asberg Depression Rating Scale
Parkinson’s Disease and Anxiety

- Approximately 40% of PD patients have anxiety
- Either alone or associated with depression
- Generalized anxiety disorder or panic disorder
- Panic and anxiety may be manifestation of “off” episodes

Olanow et al Neurology 2009;72:S1-S136
PD Anxiety: Treatment

- Treat motor fluctuations with antiparkinsonian medications
- Non pharmacological: e.g., psychotherapy
- Low dose SSRI or tricyclic
- Short acting benzodiazepines like lorazepam or alprazolam
- Buspirone: slow onset of action
- Low dose antipsychotic: quetiapine

Olanow et al Neurology 2009;72:S1-S136
In a study of 289 PD patients, 18% had hallucinations; 7% had hallucinations plus confusion; 4% had hallucinations plus delusions. Risk factors for psychosis include antiparkinsonian medications, cognitive impairment, severity of PD, visual impairment, comorbid depression and anxiety, and are strong predictors of nursing home placement.
PD Psychosis: Treatment

- Eliminate reversible causes like dehydration, infection, electrolyte imbalance or structural lesions of the brain
- Evaluate medication profile, reduce polypharmacy
- Reduce antiparkinsonian medication if possible: anticholinergics, amantadine, dopamine agonists, COMT and MAO-B inhibitors and finally reduce levodopa
- Add atypical antipsychotic like clozapine/quetiapine
- If depression present add antidepressants
- If dementia add cholinesterase inhibitors

Olanow et al Neurology 2009;72:S1-S136
<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG(^1) (1999) n = 60</td>
<td>Mean dose: 25 mg/day&lt;br&gt;Treatment effect: Significant improvement in psychosis severity&lt;br&gt;Worsening of PD: None</td>
</tr>
<tr>
<td>Pollak(^2) (2004) n = 60</td>
<td>Mean dose: 36 mg/day&lt;br&gt;Treatment effect: Significant improvement in psychosis&lt;br&gt;Worsening of PD: None</td>
</tr>
<tr>
<td>Morgante(^3) (2004) n = 20</td>
<td>Mean dose: 26 mg/day, quetiapine 91 mg/day&lt;br&gt;Control: quetiapine&lt;br&gt;Treatment: Psychosis improved in both groups&lt;br&gt;Discontinuation: 3 clozapine; 2 quetiapine&lt;br&gt;UPDRS(^a) scores unchanged but motor worsening reported in 3 quetiapine patients</td>
</tr>
<tr>
<td>Merims(^4) (2006) n = 27</td>
<td>Mean dose: 13 mg/day, quetiapine 91 mg/day&lt;br&gt;Control: quetiapine&lt;br&gt;Treatment: Both drugs were equally effective, more significant reduction in delusions with clozapine&lt;br&gt;Discontinuation: 10 clozapine; 6 quetiapine&lt;br&gt;No worsening in UPDRS</td>
</tr>
</tbody>
</table>

## PD Psychosis: Quetiapine

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Ondo¹ (2005)  | Mean dose: 170 mg/day  
Treatment effect: No change  
Discontinuation: 4 in quetiapine, 2 in placebo  
Worsening of PD: Subjective in 4 patients |
| n = 31        |                                                                                                                                       |
| Rabey² (2007) | Mean dose: 119 mg/day  
Treatment effect: No improvement in psychosis  
Discontinuation: 45%, mainly due to lack of efficacy  
Worsening of PD: None |
| n = 58        |                                                                                                                                       |
| Shotbolt³ (2009) | Mean dose: 73 mg/day  
Treatment: No significant change in psychosis  
Discontinuation: 11 patients  
UPDRS* scores unchanged but motor worsening reported in 3 quetiapine patients |
| n = 24        |                                                                                                                                       |
| Fernandez⁴ (2009) | Mean dose: 58 mg/day  
Treatment: Significant improvement in hallucination, decrease in REM stage but not in psychosis scale  
Discontinuation: 5  
Non significant improvement in UPDRS in quetiapine group |
| n = 16        |                                                                                                                                       |

¹ Mov Disord 2005;20:958-963  
² Mov Disord 2007;22:313-318  
³ Neuropsych Dis Treat 2009;5:327-332  
⁴ Int J Neurosci 2009;119:2196-2205  
* Unified Parkinson Disease Rating Scale
**PD Psychosis: Olanzapine**
Not recommended

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Breier\(^1\) (2002) n = 160 | Mean dose: 4.2 mg/day  
Treatment effect: Significant improvement in both groups, no treatment differences  
Worsening of PD: Significant worsening in olanzapine group |
| Ondo\(^2\) (2002) n = 30  | Mean dose: 4.6 mg/day  
Treatment effect: No difference with placebo  
Discontinuation: 3 patients  
Worsening of PD: significant worsening in olanzapine group |

\(^1\) Biol Psychiat 2002;52:438-445  \(^2\) Mov Disord 2002;17:1031-1035
Sleep Disorders: REM Sleep Behavior Disorder

- Vigorous motor and vocal behavior during REM sleep
- May represent a pre-motor feature of PD
- Occasionally obstructive sleep apnea may mimic RBD
- Clonazepam is the most commonly used medication for treatment
- Isolated reports of improvement with pramipexole, sodium oxybate, SSRI, melatonin
- Tricyclics may worsen RBD

Olanow et al Neurology 2009;72:S1-S136
Shmidt et al Sleep Med 2006;7:418-423
Takahashi et al Sleep Med 2008;9:317-319
Iranzo et al Sleep 2005;28:203-206
PD: Excessive Daytime Sleepiness

- Occurs in 15-75% of PD patients
- PD-related disturbance in sleep–wake regulation
- Rarely unintended sleep episodes (sleep attacks) may occur
- Disturbed nocturnal sleep due to PD-related motor symptoms
- Parasomnias with vivid dreams, nightmares, hallucinations
- Sleep disorders such as RLS, RBD, sleep apnea
- Coexisting medical and psychiatric conditions such as urinary frequency and depression
- Medications that can cause sedation
  - Dopaminergic drugs (dopamine agonists, L-dopa)
  - Sedative medications; benzodiazepines, antidepressants, neuroleptics, and anxiolytics
- Endocrine dysfunction such as hypothyroidism

Olanow et al Neurology 2009;72:S1-S136
Excessive Daytime Sleepiness: Treatment

- Screen for EDS with sleepiness scale (e.g., Epworth)
- Assess possibility of sleep disorder (e.g., sleep apnea, RLS) and treat
- Treat night time parkinsonian motor symptoms
- Reduce, eliminate, or reschedule dopaminergic medications and concomitant sedating medications (e.g., benzodiazepines, antidepressants)
- Evaluate for possible contributing medical conditions (e.g., hypothyroidism)
- Evaluate for depression and treat accordingly
- Consider CNS stimulating medications

Olanow et al Neurology 2009;72:S1-S136
# PD: Excessive Daytime Sleepiness

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>n</th>
<th>Modafinil (max 200 mg/day)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogl (2002)</td>
<td>Double blind randomized placebo controlled cross over</td>
<td>15</td>
<td>ESS improved by 3.4</td>
<td>ESS improved by 0.8</td>
</tr>
<tr>
<td>Adler (2003)</td>
<td>Double blind randomized placebo controlled cross over</td>
<td>21</td>
<td>ESS improved by 3.4</td>
<td>ESS worsened by 1.0</td>
</tr>
<tr>
<td>Ondo (2005)</td>
<td>Double blind placebo controlled parallel design</td>
<td>40</td>
<td>ESS improved by 2.7</td>
<td>ESS improved by 1.5</td>
</tr>
</tbody>
</table>

PD: Insomnia

- Occurs in 60-90% of PD patients
- Sleep fragmentation (frequent nocturnal awakening)
- Multiple factors: persistence or recurrences of PD symptoms, effect of medications on sleep, depression, Restless Leg Syndrome, nocturia
- Identify and minimize the above factors
- Sleep hygiene
  - Reduce excessive time in bed
  - Increase physical activity
  - Reduce caffeine intake
  - Observe sleep awake cycle
  - Avoid naps
  - Limit fluid intake after 5 pm
  - Adjust medication times for selegiline, amantadine
- Medications: mirtazapine, trazodone, nortriptyline, eszopiclone, temazepam, ramelteon, zolpidem, melatonin

Olanow et al Neurology 2009;72:S1-S136
## PD: Insomnia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Controlled-release carbidopa/levodpa | Stocchi\(^1\) (1998) n = 40 | Treatment effect: No change in sleep latency, sleep rating; improved trend for increased sleep time  
Significant improvement in nocturnal akinesia |
| Eszopiclone                      | Menza\(^2\) (2010) n = 30 | Dose: Maximum dose 100 mg/day  
Treatment effect: No difference in total sleep time to placebo; reduced number of awakening, quality of sleep  
Discontinuation: 11 patients |
| Melatonin                        | Dowling\(^3\) (2005) n = 43 | Dose: 5 mg/day vs 50 mg/day vs placebo  
Treatment: Melatonin 50 mg/day increased sleep time; 5 mg/day improved overall sleep quality  
Discontinuation: 3 patients |
|                                  | Medeiros\(^4\) (2007) n = 20 | Mean Dose: 3 mg/day  
Treatment: Significant improvement in sleep quality  
Discontinuation: 2 patients |

\(^1\) J Neurol 1998;245:S15-S18  
\(^2\) Mov Disord 2010;25:1708-1714  
\(^3\) Sleep Med 2005;6:459-466  
\(^4\) J Neurol 2007;254:459-464
Orthostatic Hypotension

- Defined as drop in systolic BP of > 20 mmHg or a decrease of diastolic BP of > 10 mmHg on standing within 3 minutes.

- Affects 30-60% of PD patients.

- Can be due to central or peripheral autonomic dysfunction.

Olanow et al Neurology 2009;72:S1-S136
Orthostatic Hypotension: Treatment

- Taper or discontinue unnecessary hypotensive medications
- Elevate head end of bed 10-30 degrees
- Increase dietary salt and fluid intake
- Correct anemia if present
- Consider waist high stockings or abdominal binders
- Caffeine
- Frequent small meals
- Avoid low sodium carbohydrate rich meals
- Avoid vigorous exercise, hot water/weather, standing quickly
Treatment of Orthostatic Hypotension: Fludrocortisone

- Is a salt retaining steroid and is used to increase intravascular volume
- Usually initiated at 0.1 mg/day to 0.3 mg/day

- Double blind, placebo controlled, randomized, cross over study of fludrocortisone and domperidone
- Both medications improved CGI

Schoffer et al Mov Disord 2007;22:1543-1549
Orthostatic Hypotension: Treatment

- Midodrine is a selective $\alpha_1$ agonist used in doses up to 10 mg three times a day
- Other sympathomimetic agents like ephedrine
- Desmopressin administrated intranasally promotes reabsorption of water and increases intravascular volume
- Erythropoietin increases red blood cell volume and blood viscosity
- Pyridostigmine, an acetyl cholinesterase inhibitor with a possible mechanism of action of enhanced sympathetic ganglionic transmission
- Other medications include dihydroergotamine, indomethacin

Gastroparesis/Nausea

- Nausea/Gastroparesis
  - May be related to dopaminergic medications
- Treatments
  - Additional carbidopa
  - Domperidone (not available in USA)
  - Trimethobenzamide
  - Hydroxyzine
  - Avoid dopamine antagonists such as metoclopramide (Reglan) and prochlorperazine (Compazine) as they can worsen PD symptoms

Pfeiffer RF, Bodis-Wollner I. Parkinson’s Disease and Nonmotor Dysfunction, Humana, 2005; Appenzeller O, Goss JE. Arch Neurol 1971;24:50-57.
PD: Fatigue

- Occurs in up to 60% of PD patients
- Multiple factors: severity of PD, sleep disturbances, neuropsychiatric symptoms like depression, medications, comorbidities
- Identify and minimize the above factors
- Exercise, weight loss
- Medications: CNS stimulants like modafinil, methylphenidate

Olanow et al Neurology 2009;72:S1-S136
<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Methylphenidate | Mendonca¹ (2007) n = 36 | Dose: 30 mg/day  
Treatment effect: Significant improvement in FSS* and MFI** scores, no direct comparison made to placebo  
Discontinuation: 18% |
| Modafinil       | Lou² (2009) n = 19      | Dose: Maximum dose 200 mg/day  
Treatment effect: No difference in MFI scores  
Discontinuation: 3 patients on active treatment |
| Melatonin       | Tyne³ (2010) n = 13     | Dose: 400 mg/day  
Treatment: No change in FSI*** and FSS                                                                                                     |

* = Fatigue Severity Scale  
** = Multidimensional Fatigue Inventory  
*** = Fatigue Severity Index  
¹ Mov Disord 2007;22:2070-2076  
² Clin Neuropharm 2009;32:305-310  
³ J Neurol 2010;257:452-456
The impact of bilateral subthalamic stimulation on non-motor symptoms of Parkinson’s disease

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\textbf{ABSTRACT}

\textbf{Objective:} To evaluate the impact of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) on the prevalence of non-motor symptoms reported by Parkinson’s disease (PD) patients one year following surgery and to examine whether there was an association between number of non-motor symptoms reported and quality of life (QoL).

\textbf{Methods:} Twenty-four patients who received bilateral STN DBS and had follow-up evaluations one year after surgery were included in this study. Patients’ motor function was evaluated with the Unified Parkinson’s Disease Rating Scale, non-motor symptoms were assessed with the Non-Motor Symptom questionnaire (NMSQuest) and quality of life was assessed with the PDQ-39.

\textbf{Results:} There was a mean of 12 non-motor symptoms reported prior to surgery which was significantly reduced to a mean of 7 symptoms one year after surgery. Autonomic symptoms were the most frequently reported and demonstrated the greatest reductions following surgery. Twenty-seven of the 30 items represented in the NMSQuest were reported less frequently one year after surgery compared to before surgery. The reduction in non-motor symptoms was significantly correlated with total QoL scores and the subscales of mobility, activities of daily living, cognition and bodily discomfort.

\textbf{Conclusions:} Non-motor symptoms are common in patients with advanced PD. The number of non-motor symptoms was significantly decreased one year following bilateral STN DBS which was associated with a significant improvement in QoL. Further studies focused on specific non-motor symptoms are warranted in order to fully understand the impact and mechanisms of STN DBS on these symptoms.
## STN Stimulation & Non Motor Symptoms

<table>
<thead>
<tr>
<th>Non-Motor Symptoms</th>
<th>Baseline</th>
<th>One Year Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drooling</td>
<td>54.2%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Loss or change in Taste or smell</td>
<td>50%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Difficulty Swallowing</td>
<td>37.5%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Nausea or Vomiting</td>
<td>16.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>62.5%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Bowel incontinence</td>
<td>16.7%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Incomplete bowel emptying</td>
<td>45.8%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Urinary Urgency</td>
<td>62.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Nocturia</td>
<td>79.2%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Unexplained pains</td>
<td>41.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Unexplained weight change</td>
<td>29.2%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Problems remembering</td>
<td>45.8%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Loss of interest</td>
<td>41.7%</td>
<td>25%</td>
</tr>
<tr>
<td>Hallucination</td>
<td>8.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Difficulty with concentrating</td>
<td>50%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Feeling sad</td>
<td>45.8%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>20.8%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Sex interest increased or decreased</td>
<td>62.5%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Sex difficulty upon trying</td>
<td>62.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Dizzy or weak on standing</td>
<td>54.2%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Failing</td>
<td>33.3%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Sleepiness during activities</td>
<td>29.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>41.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Vivid dreams</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Acting out dreams</td>
<td>37.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Restless Legs</td>
<td>54.2%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>37.5%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
Summary

- Cholinesterase inhibitors like rivastigmine are commonly used for treatment of dementia
- SSRI are the drug of choice for depression and anxiety
- Quetiapine is the most commonly used drug for psychosis
- Clonazepam is helpful for RBD
- Fludrocortisone and midodrine are widely used for orthostatic hypotension