Parkinson’s Disease: The Quintessential Neuropsychiatric Illness

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03/13
Slide Organization

• Introduction
• Pre-clinical non-motor symptoms
• Individual psychiatric / cognitive disorders
  – Epidemiology
  – Neurobiology
  – Assessment
  – Management
• Impact of DBS
• Non-motor fluctuations
• Modeling of non-motor features
Introduction
“The Corrections is a grandly entertaining novel for the new century – a comic, tragic masterpiece about a family breaking down in an age of easy fixes.

After almost fifty years as a wife and mother, Enid Lambert is ready to have some fun. Unfortunately, her husband, Alfred, is losing his sanity to Parkinson’s disease ...”
PD as Neuropsychiatric Model - I

- DSM-IV encapsulated
  1. Depression
  2. Psychosis
  3. Cognitive impairment / dementia (MCI / PDD)
  4. Impulse control disorders (ICDs)
  5. Anxiety
  6. Apathy
  7. Disorders of sleep and wakefulness

- Relatively common disease
PD as Neuropsychiatric Model - II

• Neural substrate relevant to psychiatry
  (1) Brain regions (basal ganglia, prefrontal cortex)
  (2) Neurotransmitter deficits (dopamine, norepinephrine, serotonin, and acetylcholine)
  (3) Neural pathways (cortico-striatal-thalamic circuitry)
• Known neuropathology (α-synuclein)
  – Biomarkers being developed
• Inter- and intra-individual variability allows for comparisons
  – Affective and cognitive changes between “on” and “off” motor states
PD as Neuropsychiatric Model - III

- Extensive psychiatric / cognitive co-morbidity
  - Depression and anxiety
- Psychiatric symptoms can predate motor symptoms
- PD treatments used for psychiatric disorders
  - PD medications and deep brain stimulation (DBS)
- Reversibility of some psychiatric symptoms
  - Certain disorders induced by PD treatments and therefore reversible
Depression
## Relative Risk of Depression in PD

Temporal relationships between first purchase of a study-drug and subsequent purchase of antidepressants compared with the unexposed population (rate ratios)

<table>
<thead>
<tr>
<th></th>
<th>0-0.5 year (95% CI)</th>
<th>0.5-1.0 year (95% CI)</th>
<th>1+ year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiparkinson</td>
<td>4.12 (3.92-4.33)</td>
<td>2.03 (1.88-2.19)</td>
<td>1.59 (1.53-1.66)</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>2.09 (2.02-2.16)</td>
<td>1.29 (1.23-1.35)</td>
<td>1.18 (1.16-1.21)</td>
</tr>
</tbody>
</table>

Sex and age included as co-varyates.

# Depression’s Impact on Function (UPDRS ADL Score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (b)</th>
<th>Standard error (b)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>47.5</td>
<td>9.1</td>
<td>5.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDRS</td>
<td>0.5</td>
<td>0.1</td>
<td>4.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>-1.4</td>
<td>0.3</td>
<td>-4.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Forward stepwise regression method including UPDRS motor score, Hoehn and Yahr stage, and duration of PD in model

Depression Impacts Initiation of PD Medications in *De Novo* PD

### Table 4

<table>
<thead>
<tr>
<th>Predictor</th>
<th>(Adjusted) hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.99 (p = 0.13)</td>
<td>(0.98, 1.00)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.16 (p = 0.34)</td>
<td>(0.85, 1.59)</td>
</tr>
<tr>
<td><strong>GDS-15 ≥ 5 (0 = No, 1 = Yes)</strong></td>
<td>1.83 (p = 0.0012)</td>
<td>(1.27, 2.63)</td>
</tr>
<tr>
<td>Total UPDRS change from baseline (higher score is worse)</td>
<td>1.14 (p &lt; 0.0001)</td>
<td>(1.12, 1.16)</td>
</tr>
<tr>
<td>RBANS change from baseline (higher score is better)</td>
<td>1.05 (p = 0.0006)</td>
<td>(1.02, 1.07)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr change from baseline</td>
<td>11.89 (p &lt; 0.0001)</td>
<td>(8.10, 17.44)</td>
</tr>
</tbody>
</table>

Model adjusts for all covariates in the table. Fifteen-item Geriatric Depression Scale (GDS-15), total Unified Parkinson’s Disease Rating Scale (UPDRS) change, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) change, and Hoehn & Yahr change are time dependent covariates.

Controlled Trial of TCA vs. SSRI

SSRI and SNRI Efficacy

SAD-PD: Study of Antidepressants in Parkinson's Disease

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine vs. Placebo</td>
<td>-6.2</td>
<td>(-9.7, -2.7)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Venlafaxine vs. Placebo</td>
<td>-4.2</td>
<td>(-7.8, -0.6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Dopamine Agonist (Pramipexole) for PD Depression

Effect of DBS

"The level of depression worsened after subthalamic stimulation and improved after pallidal stimulation."


<table>
<thead>
<tr>
<th>Table 3. Changes in Secondary Outcomes at 24 Months,*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Neurocognitive status</td>
</tr>
<tr>
<td>Score on Beck Depression Inventory (range, 0–63)§</td>
</tr>
<tr>
<td>Total score on Mattis Dementia Rating Scale (range, 0–144)§</td>
</tr>
<tr>
<td>Score on Wechsler Adult Intelligence Scales III† †</td>
</tr>
<tr>
<td>Processing speed index (range, 54–250)† †</td>
</tr>
<tr>
<td>Working memory index (range, 50–150)† †</td>
</tr>
<tr>
<td>Verbal fluency I score† †</td>
</tr>
<tr>
<td>Phonemic (sounds of words; range, 7–100)† †</td>
</tr>
<tr>
<td>Semantic (names of animals; range, 0–100)† †</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test T score† †</td>
</tr>
<tr>
<td>Total (learning and memory; range, 19–75)† †</td>
</tr>
<tr>
<td>Delayed recall (range, 19–65)† †</td>
</tr>
<tr>
<td>Finger-tapping T score (average of left and right hands; range, 1–100)† †</td>
</tr>
<tr>
<td>Score on Boston Naming Test (language; range, 0–60)† †</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test T score (perseverative response; range, 19–81)† †</td>
</tr>
<tr>
<td>Stroop interference T score (range, 19–81)§ †</td>
</tr>
<tr>
<td>Brief Visuospatial Memory Test T score§ †</td>
</tr>
<tr>
<td>Delayed recall (range, 19–68)§ †</td>
</tr>
<tr>
<td>Total (range, 19–77)§ †</td>
</tr>
</tbody>
</table>

*All changes were significant (p < 0.05).
Psychotherapy

“Assessed 38 PD patients with depression...Many had concerns about antidepressant therapy, listing side-effects and medication dependency most frequently...many PD patients attribute their depression to psychosocial factors and endorse nonpharmacologic treatment.”

Dobkin et al. AJP 2011; 168:1066-1074.
Psychosis
A 12-Year Population-Based Study of Psychosis in Parkinson Disease

Elin B. Forsaa, MD; Jon Petter Larsen, MD, PhD; Tore Wentzel-Larsen, MSc; Christopher G. Goetz, MD; Glenn T. Stebbins, PhD; Dag Aarsland, MD, PhD; Guido Alves, MD, PhD

Arch Neurol. 2010;67(8):996-1001

<table>
<thead>
<tr>
<th>Year</th>
<th>Psychosis +</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>41/230</td>
<td>18%</td>
</tr>
<tr>
<td>Year 4</td>
<td>51/142</td>
<td>36%</td>
</tr>
<tr>
<td>Year 8</td>
<td>45/88</td>
<td>51%</td>
</tr>
<tr>
<td>Year 12</td>
<td>12/25</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Cumulative</strong></td>
<td><strong>137/230</strong></td>
<td><strong>60%</strong></td>
</tr>
</tbody>
</table>

**Table 2. Baseline Risk Factors for Incident PDP During the 12-Year Follow-up Period**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>Wald $\chi^2$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, y</td>
<td>1.07 (1.02-1.12)</td>
<td>8.75</td>
<td>.003</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>1.04 (0.94-1.16)</td>
<td>0.57</td>
<td>.45</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.64 (0.82-3.27)</td>
<td>1.96</td>
<td>.16</td>
</tr>
<tr>
<td>Education, y</td>
<td>1.05 (0.95-1.17)</td>
<td>0.96</td>
<td>.33</td>
</tr>
<tr>
<td>UPDRS ADL score</td>
<td>0.94 (0.83-1.06)</td>
<td>0.90</td>
<td>.34</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>1.04 (0.99-1.09)</td>
<td>2.15</td>
<td>.14</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>1.29 (0.60-2.78)</td>
<td>0.43</td>
<td>.51</td>
</tr>
<tr>
<td>LED</td>
<td>1.26 (1.06-1.50)</td>
<td>6.65</td>
<td>.01</td>
</tr>
<tr>
<td>MMSE score</td>
<td>1.10 (0.93-1.30)</td>
<td>1.26</td>
<td>.26</td>
</tr>
<tr>
<td>Dementia</td>
<td>2.52 (0.35-17.91)</td>
<td>0.85</td>
<td>.36</td>
</tr>
<tr>
<td>RBD</td>
<td>3.52 (1.27-9.79)</td>
<td>5.83</td>
<td>.02</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>1.19 (1.08-1.32)</td>
<td>10.59</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; CI, confidence interval; LED, levodopa-equivalent dose; MMSE, Mini-Mental State Examination; OR, odds ratio; PDP, psychotic symptoms associated with Parkinson disease; RBD, rapid eye movement sleep behavior disorder; UPDRS, Unified Parkinson Disease Rating Scale.

*Per 100-mg difference in LED.
Non-Visual and Minor Hallucinations are Common

- Visual hall.: 16
- Auditory hall.: 18
- Tactile hall.: 12
- Somatic hall.: 1
- Olfactory hall.: 11
- Gustatory hall.: 3
- Non-visual hall., any type (≥1): 35
- Hall. of any type (≥1): 42
- Sense of presence: 33
- Visual illusions: 27
- Passage hallucinations: 16
- Minor symptoms (≥1): 45
- Delusions: 4
- Psychosis: usual definition: 43
- Psychosis: NINDS NIH: 60

Multifactorial Etiology

- PD medications
  - Recent controversy regarding this
- Cognitive impairment
- Increasing age, duration and severity of PD
- Impairment in visual processing pathways
- Alterations in serotonergic system
- Co-morbid psychiatric disorders
  - Including RBD (REM) and EDS (NREM)

Clinical Management – PD Medications

- **Expert opinion** regarding propensity of PD meds to cause psychosis
  - Anticholinergics
  - MAO-B inhibitors
  - Amantadine
  - Dopamine agonists
  - Levodopa

Discontinue first

Discontinue last

Antipsychotics: Use and Evidence

- AP use common in PD
  - 7-year cumulative use = 35% in new, older PD patients
- Specific antipsychotics
  - Quetiapine medication of choice
    - However, all quetiapine efficacy studies negative
  - Clozapine
    - Efficacious in 2 placebo-controlled studies at low doses (25-36 mg/day)

“Based on randomized trial-derived evidence which is currently available, only clozapine can be fully recommended for the treatment of DIP in PD.”

Concerns Regarding AP Use in Dementia Patients

• Increased morbidity and mortality
  – Increased risk of CVAEs and mortality (1.6-1.7 times) secondary to CVEs and infections

BLACK BOX WARNING

• Warning issued for atypical APs in 2005
  – Extended to typical APs in 2008
• Type 2 diabetes, orthostatic hypotension, dry mouth, sedation, dizziness, constipation
Pimavanserin ((5HT)2A inverse agonist) for PD Psychosis

- Also significant improvement on:
  1. CGI-I
  2. nighttime sleep
  3. daytime wakefulness
  4. caregiver burden

- Good motor tolerability on UPDRS
- Safe and well tolerated
(Mild) Cognitive Impairment and Dementia
PD Dementia (PDD) vs. Dementia with Lewy Bodies (DLB)

- DLB 2nd most common dementia after AD
  - ≈20% of all dementia cases
- Similarities in clinical syndrome
  - Dementia + parkinsonism + psychosis + fluctuating cognition / attention
- PD and DLB very similar neuropathologically
  - More widespread PD pathology earlier in DLB
  - More AD pathology in DLB

Prevalence and Characteristics of Dementia in Parkinson Disease

An 8-Year Prospective Study

Dag Aarsland, MD, PhD; Kjeld Andersen, MD, PhD; Jan P. Larsen, MD, PhD; Anette Loik, MD, PhD; Per Kragh-Sorensen, MD, DMSc

Background: Few longitudinal studies of dementia in Parkinson disease (PD) have been reported, and the proportion of patients with PD who eventually develop dementia is unknown.

Objectives: To examine the 8-year prevalence, characteristics, and risk factors of dementia in patients with PD.

Methods: Patients were recruited from an epidemiological study of PD in the county of Rogaland, Norway, using explicit criteria for PD. Subjects with cognitive impairment at disease onset were excluded. A semistructured caregiver-based interview, cognitive rating scales, and neuropsychological tests were used to diagnose dementia according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition at baseline and 4 and 8 years later. A population-based sample of 3295 subjects in the municipality of Odense, Denmark, was used as a comparison group and examined at baseline and after 2 and 5 years.

Results: We included 224 patients with PD (116 women). At baseline, 51 patients (26%) had dementia. Fifty-five patients died, and 10 refused follow-up without their dementia status known. Forty-three and 28 new cases of dementia were identified at the 4- and 8-year evaluations, respectively. The 4-year prevalence of dementia in PD was nearly 3 times higher than in the non-PD group. The 8-year prevalence in PD was 78.2% (95% confidence interval [CI], 71.1–84.0). Risk factors for dementia were hallucinations before baseline odds ratio [OR]=3.1; 95% CI, 1.6–6.2) and akinesia-dominant or mixed tremor/akinesia PD (OR=3.3; 95% CI, 1.2–8.5).

Conclusions: More than three quarters of this representative PD cohort developed dementia during the 8-year study period. Early hallucinations and akinesia-dominant PD were associated with an increased risk of dementia.

Arch Neurol. 2003;60:387-392
Mild cognitive impairment in Parkinson disease
A multicenter pooled analysis

ABSTRACT

Background: In studies of mild cognitive impairment (MCI) in Parkinson disease (PD), patients without dementia have reported variable prevalences and profiles of MCI, likely due to methodologic differences between the studies.

Objective: The objective of this study was to determine frequency and the profile of MCI in a large, multicenter cohort of well-defined patients with PD using a standardized analytic method and a common definition of MCI.

Methods: A total of 1,346 patients with PD from 8 different cohorts were included. Standardized analysis of verbal memory, visuospatial, and attentional/executive abilities was performed. Subjects were classified as having MCI if their age- and education-corrected z score on one or more cognitive domains was at least 1.5 standard deviations below the mean of either control subjects or normative data.

Results: A total of 25.8% of subjects (95% confidence interval [CI] 23.5-28.2) were classified as having MCI. Memory impairment was most common (13.3%; 11.6-15.3), followed by visuospatial (11.0%; 9.4-13.0) and attention/executive ability impairment (10.1%; 8.6-11.9). Regarding cognitive profiles, 11.3% (9.7-13.1) were classified as nonamnestic single-domain MCI, 8.9% (7.0-9.9) as amnestic single-domain, 4.8% (3.8-6.1) as amnestic multiple-domain, and 1.3% (0.9-2.1) as nonamnestic multiple-domain MCI. Having MCI was associated with older age at assessment and at disease onset, male gender, depression, more severe motor symptoms, and advanced disease stage.

Conclusions: MCI is common in patients with PD without dementia, affecting a range of cognitive domains, including memory, visual-spatial, and attention/executive abilities. Future studies of patients with PD with MCI need to determine risk factors for ongoing cognitive decline and assess interventions at a predementia stage.
Diagnostic Criteria for Parkinson's Disease: Movement Disorder Society Task Force Guidelines

I. Inclusion criteria
- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
- Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III)
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria
- Diagnosis of PD dementia based on MDS Task Force proposed criteria
- Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III. Specific guidelines for PD-MCI level I and level II categories

A. Level I (abbreviated assessment)
- Impairment on a scale of global cognitive abilities validated for use in PD
- Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)

B. Level II (comprehensive assessment)
- Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)
- Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
- Impairment on neuropsychological tests may be demonstrated by:
  - Performance approximately 1 to 2 SDs below appropriate norms
  - Significant decline demonstrated on serial cognitive testing or
  - Significant decline from estimated premorbid levels

IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)
- PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or
- PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)
Diffuse Cholinergic Deficits in PD

Reduced $\alpha_4\beta_2^*$–Nicotinic Acetylcholine Receptor Binding and Its Relationship to Mild Cognitive and Depressive Symptoms in Parkinson Disease

Philipp M. Meyer, MD; Karl Strecker, MD; Kai Kendziorra, MD; Georg Becker, PhD; Swen Hesse, MD; Dominique Woelpel, MD; Anke Hensel, PhD; Marianne Patt, PhD; Dietlind Sorger, PhD; Florian Wegner, MD; Donald Lobsien, MD; Henryk Barthel, MD; Peter Brust, PhD; Hermann J. Gertz, MD, PhD; Osama Sabri, MD; Johannes Schwarz, MD

Figure 4 Receiver operating characteristic (ROC) curves for ability of pathology to classify cases as demented or non-demented created using the probabilities obtained in the binary regression models: (A) Cortical Lewy body (LB) scores alone (area under the curve = 0.83, 95% CI = 0.70–0.97, P = 0.001); (B) tau stages alone (area under the curve = 0.82, 95% CI = 0.70–0.93, P = 0.0001); (C) cortical amyloid-β (A-β) scores alone (area under the curve = 0.83, 95% CI = 0.69–0.97, P = 0.001); and (D) all three pathologies in combination (area under the curve = 0.95, 95% CI = 0.88–1.00, P = 0.000003). AD = Alzheimer’s disease.

Cortical amyloid-β scores (P = 0.017) along with an older age at onset (P = 0.001) were associated with a shorter time-to-dementia period. A combination of Lewy- and Alzheimer-type pathologies is a robust pathological correlate of dementia in Parkinson’s disease, with quantitative and semi-quantitative assessment of Lewy pathology being more informative than Braak α-synuclein stages. Cortical amyloid-β and age at disease onset seem to determine the rate to dementia.
Effect of Deep Brain Stimulation

<table>
<thead>
<tr>
<th>Neurocognitive Tests</th>
<th>BMT</th>
<th>DBS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory score(^d)</td>
<td>11.7 (6.1)</td>
<td>10.2 (5.9)</td>
<td>-1.5</td>
</tr>
<tr>
<td>Mattis Dementia Rating Scale total score(^d)</td>
<td>136.6 (6.8)</td>
<td>137.5 (5.5)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Wechsler Adult Intelligence Scales III\(^d\)**

| Working memory index\(^d\) | 97.3 (13.6) | 98.3 (14.9) | 1.0 | (-0.2 to 2.2) | 0.05 |
| Processing speed index\(^d\) | 89.4 (14.1) | 90.1 (13.9) | 0.7 | (-0.7 to 2.2) | 0.06 |

| Phonemic fluency\(^d\)     | 44.7 (12.1)     | 45.7 (11.8)     | 1.1 | (-0.3 to 2.6) | <.001 |

| Category (animal) fluency\(^d\) | 49.5 (11.6)   | 47.4 (11.9)   | -2.0 | (-4.0 to -0.1) | 0.06 |

| Boston Naming Test\(^d\)     | 55.9 (4.3)      | 56.2 (4.0)      | 0.3 | (0.0 to 0.6)  | .13 |
| Finger tapping\(^d\)         | 37.6 (12.9)     | 38.7 (13.2)     | 1.0 | (-0.7 to 2.7) | .32 |

| Stroop interference\(^d\)    | 51.0 (7.6)      | 51.8 (6.4)      | 0.7 | (-0.7 to 2.1) | .11 |
| WCST perseveration response\(^d\) | 43.7 (12.2) | 45.0 (11.5) | 1.3 | (-0.9 to 3.4) | .29 |

| Hopkins Verbal Learning Test\(^d\) | 39.9 (11.5) | 40.2 (11.2) | 0.3 | (-1.3 to 2.0) | .82 |

| Delayed recall               | 38.1 (13.4)    | 37.6 (13.4)    | -0.5 | (-2.4 to 1.4) | 0.52 |
| Brief Visuospatial Memory Test\(^d\) | 39.7 (11.8) | 40.0 (12.4) | 0.3 | (-1.8 to 2.2) | .45 |

| Delayed recall               | 42.4 (13.3)    | 44.6 (13.7)    | 2.2 | (0.2 to 4.1)  | .03 |

Weaver et al. *JAMA* 2009;301:63-73.
Montreal Cognitive Assessment (MoCA)

- Assesses a broad range of cognitive domains
  - Attention/concentration (5 points)
  - Executive function (4 points)
  - Memory (5 points)
  - Language (6 points)
  - Visuospatial skills (4 points)
  - Orientation (6 points)
- Education adjusted
  - +1 point if ≤ 12 years
- Maximum possible score = 30 points
- Score <26 indicative of at least MCI

Rivastigmine for PDD

Improvement

Decline

Mean (± SEM) Change From Baseline ADAS-Cog Rating**

-5

-4

-3

-2

-1

0

1

2

3

4

5

Rivastigmine
Placebo

n=284
P<0.001

n=256
P<0.001

n=150

n=139

Weeks During Treatment

16

24

Observed case (OC) analysis
Emre et al. NEJM 2004;351:2509-2518.
Memantine in DLB – Neuropsychiatric Benefit?

ADCS-CGI = Alzheimer’s Disease Cooperative Study-Clinical Global Impression
NPI = Neuropsychiatric Inventory
Impulse Control Disorders
Presentation in PD

• ICDs
  – Gambling
    • From high (table games) to low stakes (slots, scratch cards)
  – Sexual behavior
    • Internet, sex clubs, prostitution, same sex
  – Buying
  – Eating
    • Cravings for certain foods, overnight eating

• Other compulsive behaviors
  – Dopamine dysregulation syndrome (DDS)
    • Akin to substance abuse disorder
  – Punding (meaningless manipulation of objects)
  – Hobbyism (higher level activities, task preoccupation)
  – Others (hoarding, walkabout)
Screening for impulse control symptoms in patients with de novo Parkinson disease
Case-control study

There were no statistically significant differences found for frequencies of ICD or related behavior symptoms between PD patients and HCs (p≥0.05), except for obbyism, which was more common in HCs (p=0.04).

DOMINION Study

- Study of frequency and correlates of 4 ICDs in PD
  - Gambling, buying, sexual behavior, and for binge-eating
- 46 PD centers in US and Canada
- 3,090 patients ≤75 years old completed the ICD assessments
- 66% of patients were taking a dopamine agonist (DA)
  - Overall, 87% of patients were taking levodopa

Weintraub et al. *Archives of Neurology* 2010;67:589-595.
DOMINION Study

• An ICD identified in 14% of patients
  – 29% of ICD patients had ≥2 ICDs

• Frequencies of individual ICDs were:
  – Problem/pathological gambling = 5.0%
  – Compulsive sexual behavior = 3.5%
  – Compulsive buying = 5.7%
  – Binge-eating disorder = 4.3%
### ICDs Associated with Dopamine Agonist (DA) Treatment

<table>
<thead>
<tr>
<th>ICD type</th>
<th>DA treatment status</th>
<th>Current ICD N (%)</th>
<th>No current ICD N (%)</th>
<th>P value (CMH-test); odds ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ICD</td>
<td>No dopamine agonist</td>
<td>72 (6.9)</td>
<td>978 (93.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>348 (17.1)</td>
<td>1692 (82.9)</td>
<td>2.72 [2.08;3.54]</td>
</tr>
<tr>
<td>Problem/pathological gambling</td>
<td>No dopamine agonist</td>
<td>24 (2.3)</td>
<td>1026 (97.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>130 (6.4)</td>
<td>1910 (93.6)</td>
<td>2.82 [1.81;4.39]</td>
</tr>
<tr>
<td>Pathological gambling only</td>
<td>No dopamine agonist</td>
<td>17 (1.6)</td>
<td>1033 (98.4)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>72 (3.5)</td>
<td>1968 (96.5)</td>
<td>2.15 [1.26;3.66]</td>
</tr>
<tr>
<td>Compulsive sexual behaviour</td>
<td>No dopamine agonist</td>
<td>18 (1.7)</td>
<td>1032 (98.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>90 (4.4)</td>
<td>1950 (95.6)</td>
<td>2.59 [1.55;4.33]</td>
</tr>
<tr>
<td>Compulsive buying</td>
<td>No dopamine agonist</td>
<td>30 (2.9)</td>
<td>1020 (97.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>147 (7.2)</td>
<td>1893 (92.8)</td>
<td>2.53 [1.69;3.78]</td>
</tr>
<tr>
<td>Binge-eating disorder</td>
<td>No dopamine agonist</td>
<td>18 (1.7)</td>
<td>1032 (98.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>114 (5.6)</td>
<td>1926 (94.4)</td>
<td>3.34 [2.01;5.53]</td>
</tr>
</tbody>
</table>
Multifactorial Analysis of ICD Correlates

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Entire Study Population (N=3090)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio [95% CI]</td>
<td>P value</td>
<td>PAR%&amp;</td>
</tr>
<tr>
<td>Age (≤65 years vs. &gt;65 years)</td>
<td>2.50 [1.98; 3.15]</td>
<td>&lt;0.001</td>
<td>41.2%</td>
</tr>
<tr>
<td>Marital status (not married vs. married)</td>
<td>1.48 [1.16; 1.89]</td>
<td>0.002</td>
<td>7.4%</td>
</tr>
<tr>
<td>Country (living in United States)</td>
<td>1.62 [1.25; 2.10]</td>
<td>&lt;0.001</td>
<td>27.9%</td>
</tr>
<tr>
<td>Current smoking (yes vs. no)</td>
<td>1.70 [1.07; 2.70]</td>
<td>0.02</td>
<td>2.9%</td>
</tr>
<tr>
<td>Family history gambling problems (yes vs. no)</td>
<td>2.08 [1.33; 3.25]</td>
<td>0.001</td>
<td>1.5%</td>
</tr>
<tr>
<td>DA treatment (yes vs. no)</td>
<td>2.72 [2.07; 3.57]</td>
<td>&lt;0.001</td>
<td>49.3%</td>
</tr>
<tr>
<td>Levodopa treatment (yes vs. no)</td>
<td><strong>1.51 [1.09; 2.09]</strong></td>
<td><strong>0.01</strong></td>
<td><strong>9.6%</strong></td>
</tr>
</tbody>
</table>

* Clinical and demographic variables included were those with P value <0.10 on univariate analysis; data presented for significant results only; & PAR% (population attributable risk percentage) for exposure variable = ([prevalence in the entire population – prevalence in unexposed population] / prevalence in entire population) x 100. The PAR% is a univariate calculation, so the sum of the PAR% for multiple variables can exceed 100%.
Current Management Options

• Do nothing
  – Assess significance
  – Some patients unable to adjust PD medications
    • Dopamine agonist withdrawal syndrome (DAWS) described

• Alterations to PD pharmacotherapy
  – Discontinue, lower, or switch DA therapy
  – Not clear if role for levodopa adjustment

• Psychopharmacology
  – Antidepressants (SSRIs), antipsychotics, and mood stabilizers (anticonvulsants) used clinically

• Consider deep brain stimulation (DBS)
## Changes in Dopaminergic Therapy and UPDRS Motor Scores Over Time

<table>
<thead>
<tr>
<th></th>
<th>Time 1 (mean [SD])</th>
<th>Time 2 (mean [SD])</th>
<th>Average % Change</th>
<th>Statistic (Z score [P value])¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine agonist LEDD</td>
<td>358.7 (179.4)</td>
<td>170.2 (233.3)</td>
<td>-52.6%</td>
<td>-3.1 (.002)</td>
</tr>
<tr>
<td>Levodopa LEDD</td>
<td>349.7 (381.3)</td>
<td>482.3 (358.9)</td>
<td>+37.9%</td>
<td>-1.9 (.05)</td>
</tr>
<tr>
<td><strong>Total LEDD</strong></td>
<td>708.3 (482.9)</td>
<td>652.5 (465.3)</td>
<td>-7.9%</td>
<td>-0.5 (.64)</td>
</tr>
<tr>
<td>UPDRS motor score²</td>
<td>22.6(8.7)</td>
<td>24.6(10.2)</td>
<td>+8.8%</td>
<td>-1.3(.19)</td>
</tr>
</tbody>
</table>

¹ Wilcoxon Signed Ranks Test
² N=14 (UPDRS scores unavailable for 1 patient)

**Dopamine Agonist Withdrawal Syndrome (DAWS)**

- 26 underwent DA taper for clinical reasons
  - 19% developed DAWS
  - All DAWS subjects had ICDs
  - Symptoms of DAWS resembled other drug withdrawal syndromes
    - Anxiety attacks, agoraphobia, depression, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings

Deep Brain Stimulation?

- 7 pathological gamblers underwent DBS
- Pre-surgery LEDD = 1,390 mg/day
  - Post-surgery 74% reduction in overall LEDD
- PG resolved postoperatively in all patients over mean = 18 months (range 0-48)
- Now case report literature of ICDs starting post-DBS surgery??

LEDD = levodopa equivalent daily dosage

Amantadine Study for PD Gambling

- Symptom Assessment Scale (SAS) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores

- Both scores reduced by amantadine (p<0.001 compared to baseline)

P = placebo
A = amantadine

DOMINION Study - Amantadine Data

TABLE 3: Multivariable Logistic Regression Model (Stepwise Selection) of ICD Correlates

<table>
<thead>
<tr>
<th>Step</th>
<th>Variablea</th>
<th>Odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (≤65 years vs &gt;65 years)</td>
<td>2.40 (1.91–3.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>DA use (yes vs no)</td>
<td>2.64 (2.01–3.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>Levodopa LEDD (median ≥ 450mg/day)</td>
<td>1.50 (1.21–1.86)</td>
<td>0.0002</td>
</tr>
<tr>
<td>4</td>
<td>Amantadine use (yes vs no)</td>
<td>1.29 (1.02–1.63)</td>
<td>0.0342</td>
</tr>
</tbody>
</table>

aClinical and demographic variables included were those with p < 0.10 on univariate analysis, only data for significant results presented. Other variables included in model were PD duration, Hoehn and Yahr stage, history deep brain stimulation, education, and family history of alcohol abuse.

Stratified by country.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel test.

Completed Clinical Trial

• Michael J. Fox Foundation grant
• Randomized, double-blind, placebo-controlled clinical trial of naltrexone for all ICDs
  – Naltrexone is a competitive opioid receptor antagonist
  – Modulatory role for opioid peptides in the nigrostriatal dopaminergic pathway
• 50 subjects with ≥1 of 4 common ICDs randomized to naltrexone or placebo
• Results to be presented at 2013 MDS meeting
Conclusions

1. PD is neuropsychiatric/cognitive disease
2. Multi-morbidity of psychiatric disorders is norm
3. Need for PD-specific screening instruments, rating scales, and diagnostic criteria
4. Under-recognition and under-treatment persists
5. Limited or lack of efficacy evidence for many existing treatments
6. PD treatments may have mixed effects on psychiatric and cognitive status
Acknowledgements - I

- Grant support from NIMH, NINDS, Department of Veterans Affairs, State of Pennsylvania, Fox Foundation, and Novartis
- Patients, family members, and colleagues at PD centers at Penn and Philadelphia VA
- Current and past research staff
  - Eugenia Mamikonyan, Kimberly Papay, Sarra Nazem, Staci Stewart
Acknowledgements - II
Acknowledgements - III

“Everything is impermanent in life; things (sickness, people, money, honours) come and go. The only thing that always stays is true friendship.”

– Dr. Sergio Starkstein (colleague)