Assessment and Management of Psychiatric & Cognitive Complications in Parkinson’s Disease

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Introduction
Common Psychiatric and Cognitive Disorders

• Depression
• Psychosis
• Cognitive impairment / dementia
• Impulse control disorders (ICDs) and related behaviors
• Anxiety
• Disorders of sleep and wakefulness
• Pseudobulbar affect (i.e., IEED)
Depression
Prevalence

• Widely varying estimates
  – Neurology clinics vs. population-based
• Fluctuating course in some
• **20-40%** is accepted range for all types of depression
  • Major depression ≈ 5-20%
  • Other forms of depression ≈ 10-30%
  – Higher than in elderly in general, and *probably* than in other neurodegenerative or chronic diseases
Impact of Depression on Functional Ability (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

Suicidal and Death Ideation in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death or Suicide Ideation (n=35)</th>
<th>95% Confidence Interval for Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (Exp[B])</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IDS score</strong></td>
<td>2.76</td>
<td>1.88 – 4.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1.12</td>
<td>0.37 – 3.43</td>
<td>.84</td>
</tr>
<tr>
<td>History of ICD</td>
<td>2.27</td>
<td>0.49 – 10.04</td>
<td>.30</td>
</tr>
</tbody>
</table>

IDS = Inventory of Depressive Symptomatology

# Under-Recognition and Treatment

<table>
<thead>
<tr>
<th>N=106</th>
<th>Depressed (n=31)</th>
<th>Not Depressed (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Antidepressant Treatment (n=24)</td>
<td>10 (9%*)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>No Antidepressant Treatment (n=82)</td>
<td>21 (20%)</td>
<td>61 (58%)</td>
</tr>
</tbody>
</table>

*Percentage of entire sample.

Is Depression in PD Different? Heterogeneity is the Rule

- Stage and severity of PD
- Mix of motor symptoms
- Age
- Cognitive impairment
- Psychiatric co-morbidity
- Range of depression severity
- Specific depressive symptoms
- Treatment effects

The difficulty in distinguishing PD depression from depression in general is in trying to define a single construct of PD depression.
Diagnosing Depression in PD

• Symptom overlap on 5/9 DSM-IV items
  • Sleep (hypersomnia and insomnia)
  • Appetite change / weight loss
  • Psychomotor changes
  • Fatigue
  • Changes in concentration and thinking

• Inclusive vs. etiologic criteria when rating?
  – Applies to both diagnostic criteria and rating scales
GDS-15 for Depression Screening in PD

- GDS-15 score of 5 best cut-off under ROC curve
- 88% sensitivity and 85% specificity

# Meta-Analysis of Antidepressant Studies in PD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>k</th>
<th>(d_+)</th>
<th>95% CI</th>
<th>(Q_w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Treatment</td>
<td>11</td>
<td>+0.93</td>
<td>+0.73&lt;(\delta)&lt;+1.13</td>
<td>29.80*</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>+1.18</td>
<td>+0.55&lt;(\delta)&lt;+1.81</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*Note: \(Q_B=0.59, p=0.44\)

*p<0.001

### Key:
- Treatment = active treatment versus placebo administration
- \(k\) = number of studies in analysis
- \(d_+\) = mean weighted effect size
- 95\% CI = 95 percent confidence interval for \(d_+\)
- \(Q_w\) = within-class effect (test for homogeneity)
- \(Q_B\) = between-class effect

Possible Reasons for Limited SSRI Response in PD

• Misdiagnosis
  – Apathy (instead of anhedonia)
  – Symptom overlap
• Serotonergic impairments in PD
• Pan-neurotransmitter impairments
  – Dopamine + norepinephrine + cholinergic impairment
• Executive impairment
• Impairments in neural circuitry
• Psychiatric co-morbidity
  – Psychosis, anxiety, disorders of sleep and wakefulness
Placebo-Controlled Trial of Nortriptyline vs. Paroxetine

Randomized Study of Pramipexole vs. Sertraline for Depression in PD

*Significant changes ($P < .001$) from baseline to endpoint.

Anxiety – The Neglected Affective Disorder in PD

• Up to 40% of PD patients experience an anxiety disorder

• Most patients with anxiety disorder also have depression diagnosis, and vice versa

• Anecdotally, anxiety often more disabling than depression
  – Can be more distressing both psychologically and physically
Presentation

- Anxiety attacks (i.e., panic attacks)
  - Often associated with “off” periods or part of “non-motor fluctuations”
- Generalized anxiety disorder (GAD)
- Social phobia symptoms also common
Correlation Between Mood, Motor Function and Levodopa Levels

“Mood changes and tapping speed were somewhat discordant, which argues that mood changes are not simply a consequence of improved motor function.”

Treatment

• No existing treatment studies
• Newer antidepressants also have anti-anxiety effects in non-PD patients
• Sometimes need to use low doses of benzodiazepines
  – Lorazepam, alprazolam, clonazepam
  – Beware of (1) cognitive side effects, (2) sedation, and (3) changes in balance / gait
Psychosis
Prevalence

• Hallucinations in **15-40%** of PD patients
  – Typically visual, other modalities less common
  – ≈5% of patients also experience delusions

• PD psychosis may serve as model for delirium
  – Induced / reversible (PD medications)
  – Fluctuations in attention and alertness
  – Visual hallucinations
Multifactorial Etiology

- Factors commonly associated with psychosis:
  - PD medications
    - Controversy about role of specific agents
  - Cognitive impairment
  - Increasing age
  - Increasing severity and duration of PD
  - Visual impairment
  - Co-morbid psychiatric disorders
    - Including vivid dreaming
- Likely complex interaction of above factors
# Risk Factors - PD Medications

<table>
<thead>
<tr>
<th>Variable (Mean [SD] or %)</th>
<th>Psychosis</th>
<th>Depression</th>
<th>P value</th>
<th>Psychosis</th>
<th>Depression</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Psychosis N=96 (74%)</td>
<td>Psychosis N=34 (26%)</td>
<td>P value</td>
<td>Non-Depressed N=83 (64%)</td>
<td>Depressed N=47 (36%)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (# years)</td>
<td>71.9 (8.6)</td>
<td>69.9 (9.2)</td>
<td>.25</td>
<td>72.6 (7.6)</td>
<td>69.5 (10.2)</td>
<td>.08</td>
</tr>
<tr>
<td>Education (# years)</td>
<td>14.6 (3.3)</td>
<td>14.2 (3.4)</td>
<td>.52</td>
<td>14.7 (3.5)</td>
<td>14.1 (3.1)</td>
<td>.35</td>
</tr>
<tr>
<td>Duration of PD (# years)</td>
<td>6.5 (4.9)</td>
<td>8.5 (6.2)</td>
<td>.05</td>
<td>7.1 (5.6)</td>
<td>6.9 (5.0)</td>
<td>.81</td>
</tr>
<tr>
<td>Sidedness (% right-sided PD)</td>
<td>42.7</td>
<td>41.2</td>
<td>.99</td>
<td>42.2</td>
<td>42.6</td>
<td>.79</td>
</tr>
<tr>
<td>Levodopa dosage (mg/day)</td>
<td><strong>392 (312)</strong></td>
<td><strong>579 (406)</strong></td>
<td>&lt;.01</td>
<td><strong>376 (312)</strong></td>
<td><strong>555 (381)</strong></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Dopamine agonist use (% yes)</td>
<td>44.1</td>
<td><strong>72.7</strong></td>
<td>&lt;.01</td>
<td>54.4</td>
<td>46.8</td>
<td>.41</td>
</tr>
<tr>
<td>UPDRS score</td>
<td>22.1 (11.2)</td>
<td>24.8 (11.0)</td>
<td>.26</td>
<td>22.4 (12.0)</td>
<td>23.3 (9.6)</td>
<td>.70</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.1 (1.8)</td>
<td>27.6 (2.7)</td>
<td>.24</td>
<td>28.3 (1.6)</td>
<td>27.3 (2.6)</td>
<td>.03</td>
</tr>
<tr>
<td>ESS score</td>
<td>10.0 (5.3)</td>
<td>10.5 (4.5)</td>
<td>.67</td>
<td>9.8 (5.2)</td>
<td>10.7 (4.7)</td>
<td>.35</td>
</tr>
</tbody>
</table>

### Risk Factors – Cognitive Impairment

<table>
<thead>
<tr>
<th></th>
<th>PD without Dementia (N=83)</th>
<th>PD with Dementia (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hallucinations</strong></td>
<td>14%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>Major Depression</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Non-major Depression</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

Treatment - Antipsychotics

• Balancing benefits (antipsychotic effects) and risks (worsening parkinsonism)

• Atypical antipsychotics
  – Concerns about worsening parkinsonism
  – Quetiapine medication of choice (range 25-200 mg/day)
    • However, only two efficacy studies were negative

• Clozapine
  – Efficacious in three randomized studies
  – Low doses (mean of 25-36 mg/day)
Other Treatments

• Concern about atypical antipsychotic use in neurodegenerative diseases
  – Increased morbidity and mortality risks
    • Increased risk of CVAs and increased mortality risk (1.6-1.7 times) secondary to cardiovascular events and infections
    • Hyperglycemia/Type 2 diabetes, hematologic abnormalities, orthostatic hypotension, cataracts, hyperlipidemia, dry mouth, sedation, dizziness, constipation

• Cholinesterase inhibitors
  – In DLB study, rivastigmine improved Neuropsychiatric Inventory (NPI) subscale including psychosis
  – In PDD study, rivastigmine group less likely to report psychosis as an adverse event

Cognitive Impairment and Dementia
Cumulative Prevalence Rate of Dementia in PD

- Study controlled for survival bias and was longitudinal
- 8-year community-based PD study in Norway
  - Large Danish non-PD control group of similar age
- 224 PD patients
  - Mean age = 73 years and PD duration = 10 years
- Dementia rates
  - 22% at baseline
  - 4-year prevalence rate of 52%
    - 19% of controls with dementia at 5 yrs
  - 8-year prevalence rate of 78%

Risk Factors for PD Dementia

- **Increasing age**
- **Male sex**
- **Lower education**
- **Non-tremor predominant features**
  - Rigidity, gait imbalance, postural instability
- **Psychiatric symptoms**
  - Depression and psychosis
- **Increasing severity of PD**
  - Neuropathology, longer duration of PD
- **Older age of PD onset**

Some of the variables confounded by age
“Classical” Cognitive Profile in PD

• Executive dysfunction
  – Concept formation, problem solving, set shifting
  – Tasks that require planning and sequencing

• Attention impairment
  – Reaction times and vigilance
  – Fluctuations

• Visuospatial impairment

• Impaired memory (retrieval vs. encoding deficits)
  – Preserved recognition
  – Benefit from external cues

• Language skills and praxis relatively less affected
Electrophysiologic Characterization of Fluctuating Cognition in DLB

Proposed Diagnostic Criteria for PDD

• Impairment in ≥2 core cognitive domains
  – Impaired attention, executive, visuospatial, and free recall memory abilities, the latter usually improves with cueing
  – Shifts focus away from memory impairment

• Presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports diagnosis
  – Emphasize behavioral symptoms

• End result
  – More sensitive
  – Bring in line with existing criteria for DLB

MCI and Progression to Dementia in PD

- Population-based PD sample without dementia (N=72) followed for 4 years (N=60)
- Baseline status
  - Cognition intact = 47%
  - MCI = 53%
- 4-year follow-up
  - Dementia = 42%
- MCI predicted dementia:
  - OR 4.8 (95% CI=1.6-14.8)

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
- Total score <26 indicative of at least MCI

MoCA Study

• 103 idiopathic PD outpatients administered MoCA and MMSE
  – Counterbalanced administration

• Only patients with a MMSE score in the top 75th percentile (age- and education-corrected) were included in the analyses
  – 77% (N=79) of original sample
  – Mean (SD) MMSE = 28.9 (1.1)

Nazem et al. Annual Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement Disorders 2007 meeting (oral presentation).
### MoCA Performance in PD & Controls

<table>
<thead>
<tr>
<th></th>
<th>PD Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired (MoCA &lt;26)</td>
<td>42 (53.2%)</td>
<td>12 (13.5%)</td>
</tr>
<tr>
<td>Unimpaired (MoCA ≥26)</td>
<td>37 (46.8%)</td>
<td>77 (86.5%)</td>
</tr>
</tbody>
</table>

\[
\chi^2 (df=1) = 30.21, \ P < .001
\]
# PD Performance on MoCA Subscores by Impairment Status

<table>
<thead>
<tr>
<th>MoCA Subscore</th>
<th>Mean (SD)</th>
<th>t (df)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD Impaired</td>
<td>PD Non-Impaired</td>
<td></td>
</tr>
<tr>
<td>Visuospatial/Executive</td>
<td>3.6 (1.0)</td>
<td>4.4 (0.7)</td>
<td>4.35 (73.93)</td>
</tr>
<tr>
<td>Naming</td>
<td>2.7 (0.5)</td>
<td>3.0 (0.2)</td>
<td>3.14 (61.21)</td>
</tr>
<tr>
<td>Attention</td>
<td>5.4 (0.8)</td>
<td>5.9 (0.4)</td>
<td>3.65 (57.75)</td>
</tr>
<tr>
<td>Language</td>
<td>1.5 (1.0)</td>
<td>2.7 (0.5)</td>
<td>6.62 (64.70)</td>
</tr>
<tr>
<td>Abstraction</td>
<td>1.4 (0.7)</td>
<td>1.7 (0.6)</td>
<td>1.64 (77)</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>1.8 (1.5)</td>
<td>3.9 (1.0)</td>
<td>7.35 (71.10)</td>
</tr>
<tr>
<td>Orientation</td>
<td>5.9 (0.3)</td>
<td>6.0 (0.0)</td>
<td>2.08 (41.00)</td>
</tr>
</tbody>
</table>
Cholinergic Function in PD, PDD, and AD

AChE = acetylcholinesterase activity

Rivastigmine Study for PDD

- **Objective**
  - Evaluate the efficacy and safety of cholinesterase inhibitor (rivastigmine) in patients with PDD

- **Study design**
  - 24-wk, double-blind, randomized, placebo-controlled, parallel-group, multicenter study in Europe and Canada
  - 541 patients
  - Randomized 2:1 (rivastigmine: placebo)
  - 3 to 12 mg/day

Cholinesterase Inhibitor Treatment for PDD*

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

- Improvement
- Decline

Rivastigmine
Placebo

-5
-4
-3
-2
-1
0
1
2
3
4
5

Weeks During Treatment

0 16 24

n=284
P<0.001

n=150

n=256
P<0.001

n=139

* Observed case (OC) analysis.
** ADAS-Cog = Alzheimer’s disease Assessment Scale – Cognitive
Study Conclusions

- Efficacy demonstrated for cholinesterase inhibitor for PDD
- Clinically meaningful improvement in only 20% of subjects (15% of placebo)
  - Based on CGI (global improvement) score
- AD measures used to assess outcomes
  - ADAS-Cog primarily assesses memory, language and praxis
- Well tolerated overall
  - Tremor significantly more common in active treatment group, but no significant differences in UPDRS motor score
Impulse Control Disorders
Presentation in PD

• Compulsive
  – Gambling
    • Can involve frequent low stakes (slots, scratch cards)
  – Sexual behavior
    • Internet, sex clubs, same sex
  – Buying
  – Eating
    • Cravings for certain foods, overnight eating

• Related behaviors
  – Punding (fascination with meaningless objects or activities)
  – Task preoccupation (“hobbyism”)
  – “Dopamine dysregulation syndrome” (DDS)
    • Akin to substance abuse disorder
DOMINION Study

• Study of frequency and correlates of 4 ICDs in PD
  – MAGS for gambling, MIDI for buying and sexual behavior, and DSM-IV criteria for binge-eating
• 46 PD centers in US and Canada
• 3090 patients completed the ICD assessments
• 66.0% of patients were taking a dopamine agonist
  – Overall, 86.8% of patients were taking levodopa

ICD Frequencies

- At least one ICD identified in 13.6% of patients
  - 36.0% of ICD patients had >1 ICD
- Frequencies of single ICDs were:
  - problem/pathological gambling (5.0%)
  - compulsive sexual behavior (3.5%)
  - compulsive buying (5.7%)
  - binge-eating disorder (4.3%)
### Current ICD Frequencies in DA- vs. Non-DA-Treated Patients

<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><strong>Any ICD</strong></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><strong>Problem/pathological gambling</strong></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><strong>Pathological gambling only</strong></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><strong>Compulsive sexual behaviour</strong></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><strong>Compulsive buying</strong></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><strong>Binge-eating disorder</strong></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>
### Current ICD Frequencies by DA Type

<table>
<thead>
<tr>
<th>ICD type</th>
<th>Specific DA</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>Ropinirole</td>
<td>101 (15.5)</td>
<td>550 (84.5)</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>228 (17.7)</td>
<td>1058 (82.3)</td>
<td>1.22 [0.94;1.57]</td>
</tr>
<tr>
<td>Problem/pathological gambling</td>
<td>Ropinirole</td>
<td>37 (5.7)</td>
<td>614 (94.3)</td>
<td>.44</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>83 (6.5)</td>
<td>1203 (93.5)</td>
<td>1.17 [0.78;1.76]</td>
</tr>
<tr>
<td>Pathological gambling only</td>
<td>Ropinirole</td>
<td>24 (3.7)</td>
<td>627 (96.3)</td>
<td>.69</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>42 (3.3)</td>
<td>1244 (96.7)</td>
<td>0.90 [0.54;1.51]</td>
</tr>
<tr>
<td>Compulsive sexual behaviour</td>
<td>Ropinirole</td>
<td>28 (4.3)</td>
<td>623 (95.7)</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>58 (4.5)</td>
<td>1228 (95.5)</td>
<td>1.08 [0.68;1.71]</td>
</tr>
<tr>
<td>Compulsive buying</td>
<td>Ropinirole</td>
<td>51 (7.8)</td>
<td>600 (92.2)</td>
<td>.58</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>87 (6.8)</td>
<td>1199 (93.2)</td>
<td>0.90 [0.63;1.30]</td>
</tr>
<tr>
<td>Binge-eating disorder</td>
<td>Ropinirole</td>
<td>28 (4.3)</td>
<td>623 (95.7)</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td>80 (6.2)</td>
<td>1206 (93.8)</td>
<td>1.53 [0.98;2.39]</td>
</tr>
</tbody>
</table>

22% of patients on pergolide (N=50) had an ICD.
# Multivariate Analysis of ICD Correlates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤65 years vs. &gt;65 years)</td>
<td>2.39 [1.90;3.00]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dopamine agonist LEDD (&gt;150mg vs. ≤150mg)</td>
<td>2.15 [1.73;2.68]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Levodopa LEDD (&gt;450mg vs. ≤450mg)</td>
<td>1.45 [1.18;1.80]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marital status (not married vs. married)</td>
<td>1.47 [1.15;1.88]</td>
<td>.002</td>
</tr>
<tr>
<td>Family history gambling problems (yes vs. no)</td>
<td>2.21 [1.42;3.44]</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
ICD Assessment Instruments

- No screening instruments developed or used for ICDs in PD
- Lack of established, formal diagnostic criteria for some of the ICDs seen in PD
- No rating scales have been tested in PD to determine changes in ICD severity over time

Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP)

• Guiding principles
  – Draw on existing questionnaires to extent possible
  – Comprehensive for ICDs and other compulsive disorders
  – Brief (several minutes to complete)
  – Simple and clear
  – Self-administered
  – Consistency between disorders
  – For use in clinical or research settings
  – Meant to be screening questionnaire (maximize sensitivity)
Validation Study*

• 31.2% of patients had a history of $\geq 1$ ICD, other compulsive disorder, or compulsive medication use sometime during PD
  – Half of those subjects (15.3%) had a history of two or more disorders

• Diagnostic interview results:
  – Gambling 7.0%
  – Sexual behavior 8.9%
  – Buying 6.4%
  – Eating 4.5%
  – Hobbyism 14.6%
  – Punding 10.2%
  – Walkabout 3.2%
  – Compulsive medication use $<0.1%$

*N=157 at 4 PD centers (Penn, Philadelphia VA, U. of Kansas, Mayo Phoenix)
## Validation Brief ICD Section

<table>
<thead>
<tr>
<th></th>
<th>Cutoff Points&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gambling (N=11)</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91</td>
</tr>
<tr>
<td>Specificity</td>
<td>95</td>
</tr>
<tr>
<td>PPV</td>
<td>59</td>
</tr>
<tr>
<td>NPV</td>
<td>99</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>.95 (.84-1.05)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 2 questions per ICD, 8 questions in total
### Validation Other Compulsive Disorders

<table>
<thead>
<tr>
<th>Gateway Questions</th>
<th>Hobbyism (N=23)</th>
<th>Punding (N=16)</th>
<th>Walkabout (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Specificity</td>
<td>90</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>PPV</td>
<td>61</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>NPV</td>
<td>99</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>.93 (.87-.98)</td>
<td>.78 (.63-.92)</td>
<td>.79 (.52-1.05)</td>
</tr>
</tbody>
</table>

Only 1 subject diagnosed with compulsive medication use.
Study Conclusions

• QUIP valid as self-administered screening instrument for ICDs and other compulsive disorders that occur in PD
• QUIP is simple and brief (median completion time <5 minutes), so appropriate for use in clinical care and research
• Brief QUIP (13 questions in total) may perform as well as the full QUIP (30 questions in total)
• QUIP validated as screening instrument, so clinical interview needed for patients who screen positive
• Clinical interview should focus on all ICDs and related behaviors
• There remains need to develop: (1) rating scales to assess the severity of ICDs and other compulsive disorders, and (2) consensus diagnostic criteria for some of these disorders
Current Management Options

• Do nothing
  – Assess clinical significance
  – Some patients unable or reluctant to make adjustments to PD pharmacotherapy

• Alterations to PD pharmacotherapy
• Consider DBS
• Psychopharmacology
• Psychosocial treatments
Long-Term Follow-Up of ICDs

• 15 ICD subjects completed f/u telephone interview
  – Mean time period = 29 months after ICD identification
• 12 (80.0%) patients discontinued or significantly decreased (>30% reduction) DA treatment
  – 83.3% (10/12) no longer met diagnostic criteria for an ICD

**BUT**

• 26.7% of subjects overall still met ICD criteria, including 50% of subjects who continued DA treatment

## Changes in Dopaminergic Therapy and UPDRS Motor Score Over Time

|                        | Time 1 (mean [SD]) | Time 2 (mean [SD]) | Average % Change | Statistic (Z score [P value])
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine agonist LEDD</strong></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><strong>Levodopa LEDD</strong></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>
</tbody>
</table>

**UPDRS motor score**

|                        | Time 1 (mean [SD]) | Time 2 (mean [SD]) | Average % Change | Statistic (Z score [P value])
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPDRS motor score</strong></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)
Deep Brain Stimulation?

• Seven patients with pathological gambling underwent DBS
• Pre-surgery levodopa equivalent dose = 1,390 mg/day
  – Post-surgery 74% reduction in overall LEDD
• PG resolved postoperatively in all patients over mean of 18 months
• Conclusions:
  – “Dopaminergic dysregulation commonly attributed to pulsatile overstimulation of the limbic dopaminergic system may be subject to desensitization on chronic subthalamic stimulation, which has a relative motor selectivity and allows for decrease in dopaminergic treatment.”
• However, emerging case literature of ICDs starting post-DBS surgery

Antidepressants (SSRIs), atypical antipsychotics, and mood stabilizers (anticonvulsants) used clinically
- Case reports for atypical antipsychotics in treatment of ICDs in PD

Need for medications that will allow patients to stay on PD medications and not worsen parkinsonism
- Specific D₃-receptor antagonists?
- Partial dopamine agonist + 5-HT₁A agonist?
- Medications targeting opioid and glutamate systems
Conclusions

1. PD is a neuropsychiatric/cognitive disease
2. Multi-morbidity of psychiatric disorders is the norm
3. Need for PD-specific screening instruments, diagnostic criteria, and rating scales
4. Under-recognition and under-treatment of most disorders
5. Lack of evidence for efficacy of almost all existing treatments
6. Existing PD treatments may have mixed effects for psychiatric and cognitive complications
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• Colleagues at Penn and the VA
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