Impulse Control Disorders in Parkinson’s Disease

Daniel Weintraub, MD

Associate Professor of Psychiatry
University of Pennsylvania;

Parkinson’s Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia VA
Epidemiology
Terminology

• Impulse control disorders (ICDs) are group of psychiatric disorders in DSM-IV
  – Essential feature “a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others”

• ICDs increasingly accepted as term for major disorders reported to occur in PD (also “behavioural addictions”)
  1. Gambling
  2. Buying
  3. Sexual behaviors
  4. Eating
Related Disorders in PD

- Dopamine dysregulation syndrome (DDS) (a.k.a. hedonistic homeostatic dysregulation) thought to differ from ICDs in important ways:
  - DDS more akin to substance abuse disorders
    - Involves medication misuse
  - Mood and behavioral disturbances often present
  - ICD behaviors not necessarily present
  - DDS more commonly occurs with “short-acting” agents (levodopa and sq apomorphine) than with dopamine agonists (DAs)
- Also punding / hobbyism
DOMINION Study:  
Phase I - Observational

- 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 ≤75 years old completed the ICD assessments
- 66% of patients were taking a dopamine agonist (DA)
  - Overall, 86.8% of patients were taking levodopa

ICD Frequencies

- At least one ICD identified in 13.6% of patients
  - 28.7% of ICD patients had $\geq 2$ 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%
## 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>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><strong>348 (17.1)</strong></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>
## 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><strong>Any ICD</strong></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><strong>Problem/pathological</strong></td>
<td>Ropinirole</td>
<td>37 (5.7)</td>
<td>614 (94.3)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>gambling</strong></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><strong>Pathological gambling only</strong></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><strong>Compulsive sexual behaviour</strong></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><strong>Compulsive buying</strong></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><strong>Binge-eating disorder</strong></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.
## Multifactorial Analysis of ICD Correlates

### Entire Study Population (N=3090)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio [95% CI]</th>
<th>P value</th>
<th>PAR%&amp;</th>
</tr>
</thead>
<tbody>
<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>1.51 [1.09; 2.09]</td>
<td>0.01</td>
<td>9.6%</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%.
Dose Effects

- Examining patients on a DA (N=2040)
  - On multivariable analysis there was no DA dosage effect
  - There was a levodopa dosage effect (P=0.008)
- Examining patients on levodopa only (N=991)
  - On multivariable analysis, higher levodopa dosages were associated with a current ICD (P=0.002)
Other Interesting Correlates

• ICDs more common in US (15.0%) than Canada (9.8%)
  – Specifically compulsive gambling and buying
  – Even after controlling for differences in medication exposure

• No sex differences in ICDs overall, but
  – Sexual behaviors far more common in men
  – Buying and binge-eating behaviors more common in women

• Family history of gambling problems more common in three of the four ICDs (all except sexual behaviors)
DOMINION Study: Phase II - Case-Control

• Case-control study of 564 patients
  – 282 ICD patients
  – 282 matched controls (sex, age, DA treatment)

• ICD+ versus matched ICD- patients were:
  – More functionally impaired (p<0.0001)
    • Despite similar UPDRS scores
  – More depressed and anxious, and had more obsessive compulsive symptoms (all p values <0.0001)
  – More impulsive decision-making (p<0.0001) and had higher novelty seeking scores (p<0.05)

Neural Substrate
Possible Link Between PD, Dopamine Replacement Therapies, and ICDs

Necessary …

- Treatment with dopaminergic therapies
  - Dopamine agonists are more selective for D₃ subtype receptors
    - Other dopamine replacement therapies have more non-specific effects

But insufficient?

- Pre-morbid risk factors
  - Psychosocial, substance use exposure, temperament, genetic
- Executive impairment (neural circuitry)
- Decreased dopaminergic tone secondary to loss of substantia nigra (and to lesser degree the VTA) neurons
  - Other neurotransmitters?
Impaired Decision Making in PD – Gambling Task and Executive Abilities

“Frequency of disadvantageous choices correlated with impairment on Card Sorting Test - hypothesized that decision-making deficits related to impairments in two fronto-striatal loops, the limbic-orbitofrontal-striatal loop for feedback processing and the dorsolateral prefrontal-striatal loop involved in executive functions.”

“Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism”

“Dopaminergic medication, by tonically elevating dopamine levels and stimulating D2 receptors, prevents learning from negative decision outcomes. This mechanism may explain pathological gambling behavior in patients treated with D2 agonists.”

Reward-Punishment Learning and Dopamine Agonists in PD

“DA administration in young patients with PD resulted in enhanced reward processing, and decreased punishment processing….may shed light on the cognitive and personality bases of ICDs.”

“It is hypothesised that this dissociation reflects the finding that the dopamine levels are depleted to a greater extent in the dorsal striatum compared with the ventral striatum.”

Neural Substrate – PD ICDs
Relevant Genetic Associations

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Crude OR(^{a,b}) (CI)</th>
<th>(P)</th>
<th>Adjusted OR(^{b,c}) (CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset &lt; 45 yr</td>
<td>2.56 (1.08-6.11)</td>
<td>0.0337</td>
<td>2.09 (0.82-5.28)</td>
<td>0.1204</td>
</tr>
<tr>
<td>PD duration &gt; 10 yr</td>
<td>1.88 (1.06-3.31)</td>
<td>0.0303</td>
<td>1.44 (0.77-2.67)</td>
<td>0.2522</td>
</tr>
<tr>
<td>Agonist use</td>
<td>1.90 (0.96-3.75)</td>
<td>0.0646</td>
<td>1.49 (0.67-3.34)</td>
<td>0.3286</td>
</tr>
<tr>
<td>Total LEDD &gt; 850 mg/day</td>
<td>2.35 (1.34-4.15)</td>
<td>0.0030</td>
<td>1.88 (1.00-3.55)</td>
<td>0.0515</td>
</tr>
<tr>
<td>Agonist LEDD &gt; 100 mg/day</td>
<td>1.91 (1.06-3.46)</td>
<td>0.0322</td>
<td>1.14 (0.54-2.41)</td>
<td>0.7303</td>
</tr>
<tr>
<td><strong>Genotype(^d)</strong></td>
<td>2.60 (1.30-5.20)</td>
<td>0.0069</td>
<td>2.57 (1.27-5.21)</td>
<td>0.0087</td>
</tr>
</tbody>
</table>

\(^{a}\) Crude OR is adjusted for age and sex.
\(^{b}\) Analyses are conducted using multivariate logistic regression.
\(^{c}\) The adjusted ORs are adjusted for other 5 risk factors as well as age and sex.
\(^{d}\) Either DRD3 p.S9G AA genotype or GRIN2B c.366C>G genotype.

Abbreviations as Table 1. OR, odds ratio; CI, confidence interval.

**DRD3** = D3 receptor
**GRIN** = glutamate *N*-methyl- D-aspartate (NMDA) receptor

Lee et al. 2009;24:1803-1810.
The novelty seeking differences were due to lower control scores in PD patients without compulsive behaviors compared with patients with PG who scored similarly to the general population.
**Executive Impairment in PD**

Pathological Gambling

"The results indicate an association between pathological gambling and frontal lobe dysfunctions in nondemented patients with PD."

---

**TABLE 3. Cognitive compares between patients with PD with and without pathological gambling**

<table>
<thead>
<tr>
<th></th>
<th>PD + PG (n = 15)</th>
<th>PD - PG (n = 15)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>27.3 ± 1.9</td>
<td>28.27 ± 1.2</td>
<td>2.768</td>
<td>0.107</td>
</tr>
<tr>
<td>Neuropsychiatric parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D score</td>
<td>11.47 ± 5.57</td>
<td>9.73 ± 8.25</td>
<td>0.454</td>
<td>0.506</td>
</tr>
<tr>
<td>Depression: yes/no (HAM-D score = 15/16)</td>
<td>4/11</td>
<td>2/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurexpsychological parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAB</td>
<td>12.4 ± 2.2</td>
<td>15.7 ± 1.5</td>
<td>21.827</td>
<td>0.001*</td>
</tr>
<tr>
<td>1) Frontal Functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAB</td>
<td>12.4 ± 2.2</td>
<td>15.7 ± 1.5</td>
<td>21.827</td>
<td>0.001*</td>
</tr>
<tr>
<td>2) Cognitive flexibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST-global score</td>
<td>105.3 ± 15.3</td>
<td>80.4 ± 38.9</td>
<td>5.334</td>
<td>0.029b</td>
</tr>
<tr>
<td>Phonological fluency</td>
<td>22.3 ± 11.1</td>
<td>34.8 ± 10.1</td>
<td>10.297</td>
<td>0.003*</td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>14.6 ± 3.3</td>
<td>18.7 ± 4.2</td>
<td>8.747</td>
<td>0.006b</td>
</tr>
<tr>
<td>3) Spatial and verbal working memories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Com's test</td>
<td>4.5 ± 0.9</td>
<td>5.3 ± 1</td>
<td>6.293</td>
<td>0.018b</td>
</tr>
<tr>
<td>Verbal span</td>
<td>3.6 ± 0.8</td>
<td>3.9 ± 0.7</td>
<td>1.411</td>
<td>0.245</td>
</tr>
<tr>
<td>4) Logical abstract thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCPM</td>
<td>241.2 ± 5.9</td>
<td>29 ± 3</td>
<td>8.288</td>
<td>0.006b</td>
</tr>
<tr>
<td>5) Set-shifting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT: B-A</td>
<td>141.1 ± 56.5</td>
<td>79.5 ± 37.7</td>
<td>12.355</td>
<td>0.002a</td>
</tr>
<tr>
<td>b) Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Recall</td>
<td>41.1 ± 10.6</td>
<td>47.9 ± 10.4</td>
<td>3.196</td>
<td>0.085</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>8.3 ± 2.7</td>
<td>10.2 ± 3.1</td>
<td>3.002</td>
<td>0.094</td>
</tr>
<tr>
<td>ROCF-delayed recall</td>
<td>7.9 ± 3.7</td>
<td>13 ± 6.9</td>
<td>6.295</td>
<td>0.018b</td>
</tr>
</tbody>
</table>

MMSE, Mini mental state examination; HAM-D, Hamilton depression rating scale; RCPM, Raven's彩色 progressive matrices; ROCF, Rey-Osterreith complex figure test; TMT, trail making test.

*P < 0.004 (bonferroni's correction).

**FAB = Frontal Assessment Battery**

Santangelo et al. *Movement Disorders* 2009;24:899-905
Altered Reward Learning with ICDs

In PD ICD patients, DA exposure increases reward learning and learning rates.

Voon et al. *Neuron* 2010;65:135-142
Increased Choice Impulsivity with ICDs

K is the steepness of the temporal discounting curve and is used as the measure of choice impulsivity. A higher K represents higher choice impulsivity. **PD=ICD-; PDI=ICD+**

Voon et al. *Psychopharmacology* 2010;207:645-659
Percent reduction in $[^{11}\text{C}]$ raclopride-binding potentials during gambling (as compared to control task) in PD patients with and without PG. *Paired $t$-test, $P = 0.01$.

“Patients with PG demonstrated greater decreases in binding potential in the ventral striatum during gambling,... likely reflecting greater dopaminergic release.”

Increased Striatal Activation & Reward Prediction Error / Outcomes with ICDs

In ICD patients, DA exposure increases striatal reward prediction error (RPE) and predicted outcomes.

Risk Taking in ICD Patients

Balloon Analog Risk Task (BART)

Rao et al. *Movement Disorders* 2010; .
(a) Resting perfusion imaging data showing significant CBF differences in the ventral striatum between ICD and non-ICD PD patients (threshold set as cluster corrected for $P < 0.05$)

(b) Quantitative analysis showing regional resting CBF in the right ventral striatum decreased for the ICD group compared with the non-ICD group (error bar represents standard error, ***$P < 0.001$)
Activation During Risk Taking

(c) The ventral striatum region of interest (ROI) and parametric estimates in ventral striatum showed significantly lower BOLD activation levels for ICD group compared with the non-ICD group (error bar represents standard error; *P < 0.05)

(d) **BOLD activation differences in the right ventral striatum overlapped with resting CBF differences** (red = BOLD, blue = CBF, yellow = both).
Clinical Management
Screening for ICDs & Related Disorders

- QUIP valid as self-administered screening instrument for ICDs & related disorders in PD
- Simple and short (<5 minutes)
- Brief version (13 questions) may perform as well as the full
- Follow-up clinical interview needed for screen + patients
- Clinical interview should focus on all ICDs and related behaviors

Weintraub et al. Movement Disorders 2009;24:1461-1467.
QUIP-Rating Scale

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

Reported by: ________ Patient ________ Informant ________ Patient and Informant
Patient / Subject: ____________________________________________
Date: ________________________________________________

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?
   Gambling? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Sex? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Buying? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Eating? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Performing tasks or hobbies? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Repeating simple activities? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Taking your PD medications? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?
   Gambling? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Sex? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Buying? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Eating? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Performing tasks or hobbies? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Repeating simple activities? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Taking your PD medications? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?
   Gambling? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Sex? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Buying? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Eating? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Performing tasks or hobbies? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Repeating simple activities? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Taking your PD medications? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?
   Gambling? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Sex? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Buying? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Eating? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Performing tasks or hobbies? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Repeating simple activities? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)
   Taking your PD medications? ________ Never (0) ________ Rarely (1) ________ Sometimes (2) ________ Often (3) ________ Very often (4)

Instruction Sheet

TIME FRAME
Either past 4 weeks or any 4-week period in a designated time frame

FREQUENCY OF SYMPTOMS
Never (0) = not at all
Rarely (1) = less than 2 hour a day on average
Sometimes (2) = 1-2 hours a day on average
Often (3) = 2-4 hours a day on average
Very often (4) = greater than 4 hours a day on average

DESCRIPTION OF BEHAVIORS
A. Gambling (casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines)
B. Sex (making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)
C. Buying (too much of the same thing or things that you don’t need or use)
D. Eating (eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry)
E. Hobbyism (specific tasks, hobbies or other organized activities, such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)
F. Punding (repeating certain simple motor activities, such as cleaning, tidying, handling, examining, sorting, ordering, collecting, hoarding, or arranging objects, etc.)
G. Medication Use (consistently taking too much of your Parkinson’s medications, or increasing on your own, without medical advice, your overall intake of Parkinson’s medications)
Current Management Options

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

• Alterations to PD pharmacotherapy
  – Changes to DA therapy
  – Not clear what role levodopa adjustments might play

• Consider deep brain stimulation (DBS)
• Psychopharmacology
## 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)

Deep Brain Stimulation?

- 7 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 (range 0-48)
- However, emerging case report literature of ICDs starting post-DBS surgery

Psychopharmacology

- Antidepressants (SSRIs), atypical antipsychotics (APs), and anticonvulsants used clinically
  - Case reports for atypical APs in treatment of ICDs in PD
- Need for medications that will allow patients to stay on PD medications and not worsen parkinsonism
  - Specific D$_3$-receptor antagonists?
  - Opioid and glutamate antagonists?
Symptom Assessment Scale (SAS) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score changes during the crossover. Both scores are reduced by amantadine (p < 0.001 compared to baseline).

A = amantadine
P = placebo

DOMINION - Amantadine Data

<table>
<thead>
<tr>
<th>ICD type</th>
<th>Amantadine 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 amantadine use (N=2357)</td>
<td>292 (12.4)</td>
<td>2065 (87.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Amantadine use (N=728)</td>
<td>128 (17.6)</td>
<td>600 (82.4)</td>
<td>1.49 [1.19;1.87]</td>
</tr>
<tr>
<td>Problem/pathological gambling</td>
<td>No amantadine use</td>
<td>100 (4.2)</td>
<td>2257 (95.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Amantadine use</td>
<td>54 (7.4)</td>
<td>674 (92.6)</td>
<td>1.78 [1.27;2.50]</td>
</tr>
<tr>
<td>Compulsive sexual behaviour</td>
<td>No amantadine use</td>
<td>71 (3.0)</td>
<td>2286 (97.0)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Amantadine use</td>
<td>37 (5.1)</td>
<td>691 (94.9)</td>
<td>1.70 [1.13;2.56]</td>
</tr>
<tr>
<td>Compulsive buying</td>
<td>No amantadine use</td>
<td>119 (5.0)</td>
<td>2238 (95.0)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Amantadine use</td>
<td>58 (8.0)</td>
<td>670 (92.0)</td>
<td>1.60 [1.15;2.22]</td>
</tr>
<tr>
<td>Binge-eating disorder</td>
<td>No amantadine use</td>
<td>100 (4.2)</td>
<td>2257 (95.8)</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Amantadine use</td>
<td>32 (4.4)</td>
<td>696 (95.6)</td>
<td>1.03 [0.68;1.54]</td>
</tr>
</tbody>
</table>

Ongoing Clinical Trial

• Michael J. Fox Foundation grant

• Randomized clinical trial of naltrexone for ICDs
  – Naltrexone is a competitive opioid receptor antagonist
    • Primarily kappa and mu receptors
  – Modulatory role for mu and delta opioid peptides in the nigrostriatal dopaminergic pathway

• 48 subjects with ≥1 of 4 common ICDs randomized to naltrexone or placebo
  – 17 subjects enrolled so far
Conclusions PD - I

- ICDs in PD are
  - Relatively common
  - A range of ICDs occur
  - ICDs often co-morbid
  - Associated with DA use as a class
  - Associated with levodopa and amantadine use to lesser extent
  - Dose effects for levodopa
  - Psychiatric co-morbidity common
Conclusions PD - II

• May have several other “pre-morbid” risk factors
• Altered reward-punishment learning with DA exposure
• Increased impulsivity in reward choices
• Alterations in ventral striatal activity
• Alterations in dopaminergic system
  • Striatal dopamine activity
  • Genetic associations
Acknowledgments

- Michael J. Fox Foundation for Parkinson’s Research
- Support from MIRECC and PADRECC at Philadelphia VA Medical Center
- Research staff – Kimberly Papay, Gina Mamikonyan, and Staci Hoops
- Colleagues at PD Centers at Penn and Philadelphia Veterans Affairs Medical Center
- PD patients and family members / caregivers