Impulse Control Disorders in PD

Per Odin

Professor, Department of Neurology, Lund University, Sweden
Chairman, Department of Neurology, Central Hospital, Bremerhaven, Germany
ICD in Parkinson´s disease

- Dementia
- Depression
- Psychosis
- Anxiety
- Apathy
- Fatigue
- Punding
- Impulse Control Disorder
ICD in Parkinson’s disease

Dopamine is key to reward and addiction

- Amphetamine
- Cocaine
- Ethanol
- Nicotine
- Food
- Sex

Dopamine release
Nucleus Accumbens

\[ \text{HO} \quad \text{OH} \quad \text{NH}_2 \]
ICD in Parkinson’s disease

Compulsive behaviours

Impulse-Dyscontrol

pathological gambling, hypersexuality, compulsive shopping, excessive eating

DA-dysregulation

uncontrolled dopaminergic drug dosing

Punding

purposeless stereotypic behaviours
ICD in Parkinson’s disease

Compulsive behaviours

Definition (DSM-IV-TR):

- Failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others

- Typically pleasureable and performed excessively, repetitively or compulsively.
ICD in Parkinson’s disease
Compulsive behaviours

• Parkinson’s Disease Personality
  • Rigid, Inflexible
  • Punctual, Industrious
  • Cautious, lack of novelty seeking behaviors
  • Low lifetime risks of:
    • smoking, coffee drinking, and ETOH consumption

• Impulse Control Behaviors
  • Gambling
  • Shopping
  • Hypersexuality
  • Paraphilia
  • Binge eating
  • Mania
  • Punding
  • Journaling/Blogging
ICD in Parkinson’s disease
The fine line between problem and pleasant recreation

Predictors of impulsivity and reward seeking behavior with dopamine agonists

William G. Ondo3,*, Dejian Lai1,2,3

1Brigham College of Medicine, 6530 Kumin, Sce 1801, Houston, TX 77096, USA
2University of Texas Health Science Center at Houston, Houston, TX, USA
3Faculty of Statistics, Jiangsu University of Finance and Economics, Nanxang, China

Received 21 February 2007; revised in revised form 6 April 2007; accepted 3 May 2007

Abstract

Three hundred consecutive patients taking DA either for Parkinson’s disease (PD, 207), restless legs syndrome (RLS, 89), or both (4) were interviewed about changes in gambling, spending, sexual activity, or other impulsive activities subsequent to DA. Regression models identified risk factors for impulsivity. Overall, 19.7% reported any increased impulsivity: 30 gambling, 26 spending, 11 sexual activity, and 1 wanting traveling. Only 11.39 felt the change was deleterious. Increased impulsivity correlated with a younger age (p = 0.01), larger doses of DA (p < 0.001), and PD, as opposed to RLS (p < 0.001); but this lost significance after correcting for dose (p = 0.09). Increased impulsivity is common but usually not deleterious.

© 2007 Elsevier Ltd. All rights reserved.
<table>
<thead>
<tr>
<th>Study</th>
<th>Pts with active ICDs</th>
<th>Type of ICD</th>
<th>DA medication (Type of DA agonist)</th>
<th>Sample size (PD on DRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molina, 2000</td>
<td>12</td>
<td>PG</td>
<td>12LD+DA (N.A.)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Driver-Dunckley, 2003</td>
<td>9</td>
<td>PG</td>
<td>9LD+DA (8PPX/1PRG)</td>
<td>1884</td>
</tr>
<tr>
<td>Dodd, 2005</td>
<td>11</td>
<td>PG</td>
<td>11LD+DA (9PPX/2ROP)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Weintraub, 2006</td>
<td>11</td>
<td>PG 6; HS 7; CS 1</td>
<td>11LD+DA (6PPX/4ROP/1PRG)</td>
<td>272</td>
</tr>
<tr>
<td>Voon, 2006</td>
<td>19</td>
<td>PG 10; HS 7; CS 2 (Lifetime prevalence in PD on DA agonists: 7.2% PG, 7.2% HS, 1.4% CS)</td>
<td>PG: 1DAmono; 9LD+DA (4ROP/3PPX/2PRG) HS: 1LDmono; 6LD+DA (5PPX/1ROP) CS: 2LD+DA (1PPX/1ROP)</td>
<td>297</td>
</tr>
<tr>
<td>Grosset, 2006</td>
<td>17</td>
<td>PG</td>
<td>8DAmono; 9LD+DA (9PPX/7ROP/1PRG)</td>
<td>388</td>
</tr>
<tr>
<td>Pontone, 2006</td>
<td>9</td>
<td>PG, HS, CS</td>
<td>1DA mono; 8LD+DA (7PPX/2ROP)</td>
<td>100</td>
</tr>
<tr>
<td>Imamura, 2006</td>
<td>6</td>
<td>PG</td>
<td>2DAmono; 4LD+DA (4PPX/1ROP/1CAB)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Drapier, 2006</td>
<td>6</td>
<td>PG</td>
<td>6LD+DA (2PRG/2BRC/1ROP/1Sel)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Voon, 2007</td>
<td>21</td>
<td>PG</td>
<td>1DAmono; 20LD+DA (8ROP/7PRG/5PPX)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Smeding, 2007</td>
<td>1</td>
<td>PG</td>
<td>STN-DBS/PRG</td>
<td>Case report</td>
</tr>
<tr>
<td>Temel, 2006 (review)</td>
<td>3</td>
<td>HS</td>
<td>STN-DBS</td>
<td>1398</td>
</tr>
</tbody>
</table>
ICD in Parkinson’s disease

Varying Prevalence

- Driver-Dunkley et al. Neurology 2003
  - 1884 patients, 1 yr, 9 pts with PG
- Weintraub et al. Arch Neurol 2006
  - Gambling, Buying, Shopping (MIDI), convenience sample of 272
  - 6.6% ICD “at some point” and 4% active ICD
  - No diff between DA, but doses higher in ICD
- Grosset et al. Mov Disord 2006
  - 4.4%
  - 193 PD v 193 C
  - GSES prospectively enquired
  - 14% + v 0% (C)
  - Younger age, male, DA Rx duration
  - PG period prevalence after Rx: 3.4%; DA: 7.2%
  - Unrelated to specific agonists
  - Novelty seeking behaviour, alcohol abuse, YOPD
ICD in Parkinson’s disease

Varying Prevalence

• Isias et al. Mov Disord 2008
  – 28% rate of at least one abn behaviour (MIDI / SOGS) but 20% in Controls!!!!

• Ondo and Lai
  – 20% in DA use
  – Most did not consider change in behaviour deletorius

• Weintraub et al. Mov Disord 2009 QUIP validation study
  – PG 7%, CS 8.9%, CB 6.4%, EAT 4.5%, Punding 10.2%, Hobbyism 14.6%, Walkabout 3.2%, CRx use (<1%)
  – 31/2% H/O of one or more ICD (almost 50% with previous history)

• Weintraub et al. Arch Neurol 2010
  – 3090 pts, cross sectional, point prev of 4 ICD’s
ICD in Parkinson’s disease

Characteristics of PD gambler

**TABLE 1. Characteristics of 17 patients with pathological gambling**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Duration of PD (yr)</th>
<th>DA</th>
<th>Daily dose DA (mg)</th>
<th>Daily dose LD (mg)</th>
<th>£ per week prior to DA</th>
<th>£ per week on DA</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>m</td>
<td>2.5</td>
<td>Ropinirole</td>
<td>15</td>
<td>300</td>
<td>10</td>
<td>200</td>
<td>Horses/dogs</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>m</td>
<td>5.5</td>
<td>Pramipexole</td>
<td>4.5</td>
<td>400</td>
<td>0</td>
<td>25</td>
<td>Horses/bingo</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>m</td>
<td>3.2</td>
<td>Pramipexole</td>
<td>3</td>
<td>—</td>
<td>5</td>
<td>50</td>
<td>Horses</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>f</td>
<td>2.2</td>
<td>Pramipexole</td>
<td>3</td>
<td>—</td>
<td>50</td>
<td>100</td>
<td>Not stated</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>f</td>
<td>10.9</td>
<td>Pramipexole</td>
<td>5.1</td>
<td>500</td>
<td>0</td>
<td>50</td>
<td>Bingo/interactive TV</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>m</td>
<td>2.6</td>
<td>Ropinirole</td>
<td>6</td>
<td>—</td>
<td>10</td>
<td>1,500</td>
<td>Internet/interactive TV</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>m</td>
<td>3.02</td>
<td>Pramipexole</td>
<td>4</td>
<td>400</td>
<td>20</td>
<td>1,200</td>
<td>Internet/roulette</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>f</td>
<td>6.9</td>
<td>Ropinirole</td>
<td>12</td>
<td>—</td>
<td>5</td>
<td>50</td>
<td>Horses/dogs</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>f</td>
<td>8.8</td>
<td>Ropinirole</td>
<td>24</td>
<td>450</td>
<td>6</td>
<td>1,000</td>
<td>Internet</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>f</td>
<td>1.6</td>
<td>Pramipexole</td>
<td>5.4</td>
<td>—</td>
<td>2</td>
<td>10</td>
<td>Slot machines</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>m</td>
<td>7.8</td>
<td>Ropinirole</td>
<td>15</td>
<td>—</td>
<td>30</td>
<td>1,300</td>
<td>Horses and football</td>
</tr>
<tr>
<td>12</td>
<td>57</td>
<td>f</td>
<td>9.3</td>
<td>Pramipexole</td>
<td>4.5</td>
<td>650</td>
<td>0</td>
<td>100</td>
<td>Slot machines</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>m</td>
<td>4.01</td>
<td>Ropinirole</td>
<td>9</td>
<td>470</td>
<td>1</td>
<td>100</td>
<td>Horses</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>m</td>
<td>2.6</td>
<td>Pramipexole</td>
<td>2.25</td>
<td>—</td>
<td>0</td>
<td>100</td>
<td>Horses</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>m</td>
<td>2.8</td>
<td>Ropinirole</td>
<td>12</td>
<td>—</td>
<td>Unknown, lost 5-figure sum</td>
<td>Unknown, lost £4,000 in total</td>
<td>Internet/scratch cards</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>f</td>
<td>4.6</td>
<td>Pergolide</td>
<td>1.25</td>
<td>400</td>
<td>Unknown, lost £4,000 in total</td>
<td>Unknown, lost £4,000 in total</td>
<td>Internet/scratch cards</td>
</tr>
<tr>
<td>17</td>
<td>53</td>
<td>m</td>
<td>11.95</td>
<td>Pramipexole</td>
<td>4.5</td>
<td>300</td>
<td>30</td>
<td>60</td>
<td>Slot machines</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; DA, dopamine agonist; LD, levodopa.

Risk factors were dopamine agonist mono-therapy or in association with levodopa as well as short-disease duration and age at onset < 60 yrs

Grosset 2006
ICD in Parkinson´s disease

Demographics of largest ICD survey in PD

The group with ICD had lower age, was less often married, more often lived in the US, more often smoker and more often had family history of gambling.
ICD in Parkinson’s disease

Frequency of ICD based on exposure to dopamine agonist

Higher risk with dopamine agonist, but no clear relationship with agonist dose.

Weintraub et al. Arch Neurol 2010
ICD in Parkinson’s disease

Factors associated with ICD

Factors associated with development of ICD are age <65 years, treatment with Dopamine agonist and living in a country where gambling is accessible.

Weintraub et al. Arch Neurol 2010

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ≤65 vs &gt;65 y</td>
<td>2.50 (1.98-3.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not married vs married</td>
<td>1.48 (1.16-1.89)</td>
<td>.002</td>
</tr>
<tr>
<td>Living in the United States</td>
<td>1.62 (1.25-2.10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.70 (1.07-2.70)</td>
<td>.02</td>
</tr>
<tr>
<td>Family history gambling problems</td>
<td>2.08 (1.33-3.25)</td>
<td>.001</td>
</tr>
<tr>
<td>Dopamine agonist treatment</td>
<td>2.72 (2.07-3.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Levodopa treatment</td>
<td>1.51 (1.09-2.09)</td>
<td>.01</td>
</tr>
</tbody>
</table>
ICD in Parkinson´s disease

Compulsive behaviours

Prevalence: 13.6% (3.9% had 2 or more)
Weintraub et al. 2010
(3090 PD patients)

Gambling: 5%
Hypersexuality: 3.5%
Compulsive buying: 5.7%
Binge eating: 4.3%

Dopamine agonist: 17.1% (not DAg: 6.9%)
Pramipexole: 17.7%
Ropinirole: 15.5%

Earlier smaller studies: 6-7% (DAg: 14-17%)

General population: 0.25-3%
ICD in Parkinson´s disease

Compulsive behaviours

Symptoms:
- Compulsive gambling
- Compulsive buying
- Compulsive sexual behaviour
- Compulsive eating
- Compulsive reckless driving/walkabout

Gender differences (similar to general population):
Men: More…
- Compulsive gambling
- Compulsive sexual behaviour
Females: More…
- Compulsive buying
- Compulsive eating
ICD in Parkinson´s disease

Prospective studies

Prospective cohort study in DAg treated patients:
- 39% of patients without ICD at baseline developed ICD over a 4 year period

- Median duration of ICD onset from initiation of DAg: 23 months

- Predictor of ICD: motor complications, caffein use, lifetime cigarette smoking, higher peak DAg doses

Bastiaens et al., 2013
ICD in Parkinson’s disease

Correlation

Risk factor: - Dopamine agonists (L-dopa, amantadine)
- Levodopa use, younger age, early onset, male gender, being unmarried, cigarette smoking, alcoholism or gambling in family, depression
- Persons with high impulsivity and novelty seeking

Psychiatric correlation: affective and anxiety symptoms, obsessionality, novelty seeking, impulsivity, sleep disturbance
ICD in Parkinson’s disease

Correlation

Weintraub and Claassen, 2017
- Meta-analysis of 34 studies

- Significant relationship between ICD and dysfunction of abstraction ability/concept formation, set-shifting, visuospatial/constructional abilities and decision-making

- Findings suggested that people affected by PD with specific frontal dysfunctions are more vulnerable to develop ICD when they take antiparkinsonian drugs
ICD in Parkinson’s disease

Detection

Under-recognized and under-reported, due to:
- embarrassment
- limited awareness of behaviour
- not suspecting association with medication
- difficulty describing feelings (?)

Ask partner/caregiver/friend!

Detection:  
- Minnesota Impulsive Disorder Interview, MIDI
- Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP); ratings-scale: QUIP-RS (self- or rater- administered)
- Parkinson’s Impulse-Control Scale, PICS
ICD in Parkinson’s disease

Compulsive behaviours

Pathophysiology:

- not fully understood

- Imaging studies suggest network dysregulation mainly within the striatal and limbic brain regions. Dopaminergic dysfunction is the main underlying pathology of ICD, but other transmitter systems might be involved.
Figure 1 Conceptualization of impulse control behaviors, punding and compulsive medication use in Parkinson’s disease according to relationship with medications
Dopamine Dysregulation Syndrome

Characterized: Addictive behaviour and excessive use of short-acting dopaminergic medication, driven by desire to maintain „high“ and avoid „low“

Risk factor:   - Early onset PD
               - Male gender

Presentation:  - Physical and social impairment
               - Actions to prevent detection of over-use
               - Mood, anxiety and motor fluctuations

Co-morbidity:  - ICD (61%), Psychosis (32%)

Management:   - Unclear (56% resolve)
              - Valproat suggested (?)

Warren et al., 2017
Punding

Characterized: Repetetive purpose-less behaviors, intense preoccupation with specific items or activities (e.g., collecting, arranging, taking apart objects)

Risk-factors:
- Levodopa
- Dopamine agonists
- ICD
- Patients with RLS with augmentation under dopaminergic therapy have 6-fold increased risk of ICD
- Implies that augmentation and ICD are related
- Patients with RLS with augmentation should be screened for ICD
ICD in Parkinson´s disease

Same risk with ergot and non-ergot

- Weintraub: 0.28 (0.07, 1.20)
- Driver-Dunckley: 2.80 (0.35, 22.49)
- Grosset: 1.43 (0.18, 11.49)
- Antonini: 5.77 (1.32, 25.14)
- Voon: 0.88 (0.17, 4.52)
- Pontone: 1.63 (0.08, 32.79)

Overall (95% CI): 1.78 (0.89, 3.54)
ICD in Parkinson’s disease

Same risk pramipexole and ropinirole

Weintraub: 1.13 (0.26, 4.95)
Driver-Dunckley: 13.74 (0.79, 238.74)
Grosset: 1.91 (0.68, 5.36)
Antonini: 1.60 (0.45, 5.67)
Voon: 0.56 (0.12, 2.67)
Pontone: 0.45 (0.07, 3.01)
Overall (95% CI): 1.55 (0.88, 2.73)

Gallagher 2007
A European multicentre survey of impulse control behaviours in Parkinson’s disease patients treated with short- and long-acting dopamine agonists

A. Rizos\textsuperscript{a,⁎}, A. Sauerbier\textsuperscript{a,b,⁎}, A. Antonini\textsuperscript{c}, D. Weintraub\textsuperscript{d}, P. Martinez-Martín\textsuperscript{e}, B. Kessel\textsuperscript{f}, T. Henriksen\textsuperscript{g}, C. Falup-Pecurariu\textsuperscript{h}, M. Silverdale\textsuperscript{i}, G. Durner\textsuperscript{a}, K. Røkenes Karlsen\textsuperscript{a}, M. Grilo\textsuperscript{a}, P. Odin\textsuperscript{i,k} and K. Ray Chaudhuri\textsuperscript{a,b,j} on behalf of EUROPAR and the IPMDS Non-Motor-PD-Study Group
A European multicentre survey of impulse control behaviours in Parkinson’s disease patients treated with short- and long-acting dopamine agonists

A. Rizos\textsuperscript{a,b,*}, A. Sauerbier\textsuperscript{a,b,*}, A. Antonini\textsuperscript{c}, D. Weintraub\textsuperscript{d}, P. Martinez-Martin\textsuperscript{e}, B. Kessell\textsuperscript{f}, T. Henriksen\textsuperscript{g}, C. Falup-Pecurarui\textsuperscript{h}, M. Silverdale\textsuperscript{i}, G. Durner\textsuperscript{a}, K. Røkenes Karlsen\textsuperscript{a}, M. Grilo\textsuperscript{a}, P. Odin\textsuperscript{j,k} and K. Ray Chaudhuri\textsuperscript{a,b,l} on behalf of EUROPAR and the IPMDS Non-Motor-PD-Study Group

Type of ICD on different DAs

- Binge eating
- Gambling
- Hobbyism
- Hypersexuality
- Multiple ICDs

<table>
<thead>
<tr>
<th>Type</th>
<th>PPX</th>
<th>PPX-IR</th>
<th>PPX-PR</th>
<th>ROP</th>
<th>ROP-IR</th>
<th>ROP-XL</th>
<th>RTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binge eating</td>
<td>4.4%</td>
<td>3.9%</td>
<td>1.9%</td>
<td>2.2%</td>
<td>1.4%</td>
<td>2.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Gambling</td>
<td>6.7%</td>
<td>6.7%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hobbyism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.8%</td>
<td>4.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.3%</td>
<td>6.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Multiple ICDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.5%</td>
<td>6.1%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Lund University

Rizos et al., 2016
A European multicentre survey of impulse control behaviours in Parkinson’s disease patients treated with short- and long-acting dopamine agonists

A. Rizos\textsuperscript{a,\textast}, A. Sauerbier\textsuperscript{a,\textasteriskcentered}, A. Antonini\textsuperscript{c}, D. Weintraub\textsuperscript{d}, P. Martinez-Martin\textsuperscript{e}, B. Kessel\textsuperscript{f}, T. Henriksen\textsuperscript{g}, C. Falup-Pecuraru\textsuperscript{h}, M. Silverdale\textsuperscript{i}, G. Durner\textsuperscript{a}, K. Røkenes Karlsen\textsuperscript{a}, M. Grilo\textsuperscript{a}, P. Odin\textsuperscript{\texttrademark,k} and K. Ray Chaudhuri\textsuperscript{a,\textsuperscript{b,\textasteriskcentered}} on behalf of EUROPAR and the IPMDS Non-Motor-PD-Study Group

<table>
<thead>
<tr>
<th>ICDs (% / total on therapy)</th>
<th>Pooled PPX n=179</th>
<th>PPX IR n=104</th>
<th>PPX PR n=76</th>
<th>Pooled ROP n=208</th>
<th>ROP IR n=42</th>
<th>ROP XL n=166</th>
<th>RTG n=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>25 (14.0%)</td>
<td>20 (19.4%)</td>
<td>5 (6.6%)</td>
<td>30 (14.4%)</td>
<td>6 (14.3%)</td>
<td>24 (14.5%)</td>
<td>9 (4.9%)</td>
</tr>
<tr>
<td>Mean dose all (with ICD’s)</td>
<td>2.7 mg (2.8 mg)</td>
<td>2.6 mg (2.8 mg)</td>
<td>2.8 mg (2.7 mg)</td>
<td>12.1 mg (14.0 mg)</td>
<td>10.9 mg (19.1 mg)</td>
<td>12.4 mg (12.6 mg)</td>
<td>8.4 mg (11.3 mg)</td>
</tr>
<tr>
<td>ICD leading to discontinuation</td>
<td>13 (7.3%)</td>
<td>11 (10.7%)</td>
<td>2 (2.7%)</td>
<td>12 (5.8%)</td>
<td>4 (9.5%)</td>
<td>8 (4.9%)</td>
<td>4 (2.2%)</td>
</tr>
</tbody>
</table>

Rizos et al., 2016
**Objective**

To evaluate the incidence of impulsive and compulsive behaviors (ICBs) reported as adverse events (AEs) in long-term studies of rotigotine transdermal system in Parkinson’s disease (PD).

---

**Table**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, (range), years</td>
<td>63.0 ± 9.7 (31-87)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>510 (64.9)</td>
</tr>
<tr>
<td>Time since diagnosis, mean ± SD (range), years</td>
<td>4.9 ± 4.5 (0-25)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>100 (12.7)</td>
</tr>
<tr>
<td>2</td>
<td>418 (53.2)</td>
</tr>
<tr>
<td>3</td>
<td>184 (23.4)</td>
</tr>
<tr>
<td>4</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>UPDRS II score, mean ± SD</td>
<td>10.7 ± 5.5</td>
</tr>
<tr>
<td>UPDRS III score, mean ± SD</td>
<td>24.3 ± 11.6</td>
</tr>
<tr>
<td>UPDRS II + III score, mean ± SD</td>
<td>35.0 ± 15.6</td>
</tr>
</tbody>
</table>

---

Angelo Antonini, MD, PhD¹, K Ray Chaudhuri, MD, FRCP DSc², Babak Boroojerdi MD, PhD³, Mahnaz Asgharnejad, PharmD⁴, Lars Bauer, MD³, Frank Griefer, Dipl.Stat.³, Daniel Weintraub, MD⁵

---

*Eur. J Neurol 2016*
Frequency of the different categories of ICD-related behaviours reported as AEs.

A total of 106 ICD/ICB type AEs were reported in 71 (9%) patients. The mean ± SD treatment duration at onset of ICD/ICB type AEs was 358 ± 394 days (approximately 12 months).
Frequency of ICD-related behaviour AEs by rotigotine dose: dose at AE onset

<table>
<thead>
<tr>
<th>Rotigotine dose at AE onset, mg/24 h; n (%) [AEs]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 N = 403</td>
</tr>
<tr>
<td>4 N = 737</td>
</tr>
<tr>
<td>6 N = 743</td>
</tr>
<tr>
<td>8 N = 730</td>
</tr>
<tr>
<td>10 N = 622</td>
</tr>
<tr>
<td>12 N = 543</td>
</tr>
<tr>
<td>14 N = 409</td>
</tr>
<tr>
<td>16 N = 310</td>
</tr>
</tbody>
</table>

Any ICD behaviour reported as AEs

<table>
<thead>
<tr>
<th>Compulsive sexual behaviour</th>
<th>1 (0.2)</th>
<th>0</th>
<th>2 (0.3)</th>
<th>3 (0.4)</th>
<th>3 (0.5)</th>
<th>5 (0.9)</th>
<th>6 (1.5)</th>
<th>2 (0.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buying disorder</td>
<td>2 (0.5)</td>
<td>0</td>
<td>3 (0.4)</td>
<td>2 (0.3)</td>
<td>3 (0.5)</td>
<td>1 (0.2)</td>
<td>6 (1.5)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Compulsive gambling</td>
<td>2 (0.5)</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
<td>6 (0.8)</td>
<td>2 (0.3)</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Compulsive eating</td>
<td>0</td>
<td>3 (0.4)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
<td>3 (0.7)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Punding behaviour</td>
<td>1 (0.2)</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
<td>2 (0.5)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
<td>3 (0.5)</td>
<td>2 (0.4)</td>
<td>3 (0.7)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

Outcome by action taken with rotigotine

Of 106 ICD AEs (reported in 71 patients) 3 were severe (2.8%); 54 were mild (51%) and 49 moderate (47%) in intensity.
Dopamine agonists have differing dopamine receptor binding affinities

| Table I. Monoamine and serotonin 5-HT receptor binding affinity of dopamine (D) receptor agonists[^16-20] |
|-------------------------------------------------|---|---|---|---|---|---|
| | D₁ | D₂ | D₃ | 5-HT | α₁ | α₂ |
| Aporphines | | | | | | |
| Apomorphine | ++ | +++ | ++ | 0/+ | 0/+ | ++ |
| Ergot derivatives | | | | | | |
| Bromocriptine | - | +++ | ++ | ++ | ++ | ++ |
| Cabergoline | + | +++ | ++ | + | + | + |
| Lisuride | - | +++ | +++ | ++ | + | + |
| Pergolide | + | +++ | +++ | 0/+ | + | ++ |
| Nonergoline derivatives | | | | | | |
| Piribedil | + | +++ | + | 0 | NA | NA |
| Pramipexole | 0/+ | +++ | +++ | 0/+ | 0/+ | + |
| Ropinirole | 0 | +++ | +++ | 0 | 0 | 0 |

[^16-20]: α = α-adrenoceptors; NA = information not available; - indicates antagonist activity; 0 indicates no affinity; + indicates low affinity; ++ indicates moderate affinity; +++ indicates high affinity.

Deleu D, et al., 2004
Different dopamine receptor affinities confer different clinical effects

- Stimulation of dopamine D1 and D2 receptors is important for motor control and the anti-Parkinsonian action of DAs
- Selectivity of DAs for the D3 receptor has been shown to be related to the development of ICBs

Proportion of PD patients with ICBs in treated with an add-on agonist:

- Pramipexole 32%
- Ropinirole 25%
- Rotigotine 22%
- Pergolide 16%
- Apomorphine 10%
- Bromocriptine 7%

Seeman P, 2015
ICBs are associated with preferential affinity for the dopamine D3 receptor

Analysis of serious adverse drug event reports of ICBs received by the US Food and Drug Administration (FDA) in relation to dopamine receptor agonist drug treatment

- Dopamine agonists had a strong signal associated with ICBs
- The association was strongest for the dopamine agonists **pramipexole** (n=410; PRR=455.9, p<0.001) and **ropinirole** (n=188; PRR=152.5, p<0.001), with preferential affinity for the dopamine D3 receptor.

![Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events](image)

Moore TA, et al., 2014
Apomorphine infusion is associated with a low incidence of ICBs

Open-label, prospective, observational, 6-month, multicentre study

- 43 patients treated with APO, 44 with IJLI
- Both treatments provided robust improvements in motor symptoms, motor complications, quality-of-life, and some non-motor symptoms
- Low incidence of ICDs

TABLE 4. Reported side effects of IJLI and Apo therapy at 6-months follow-up period

<table>
<thead>
<tr>
<th>Apo Group</th>
<th>IJLI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous/local site discomfort</td>
<td>Minor:</td>
</tr>
<tr>
<td>Persisting nausea × 3</td>
<td>Stoma site irritation × 8</td>
</tr>
<tr>
<td>Severe somnolence × 3</td>
<td>Abdominal bloating × 7</td>
</tr>
<tr>
<td>ICD = 4</td>
<td>Serious:</td>
</tr>
<tr>
<td>Hypersexuality × 2</td>
<td>Tube dislocation × 9</td>
</tr>
<tr>
<td>Compulsive shopping × 1</td>
<td>Peritonitis × 1 (not requiring</td>
</tr>
<tr>
<td>Compulsive internet use × 1</td>
<td>discontinuation of IJLI)</td>
</tr>
</tbody>
</table>

Serious = clinically estimated serious side effects.

Martinez-Martin P, et al., 2015
Continuous drug delivery is associated with a relatively low risk for development of ICBs

Data from a 3-year clinical observational screening of PD patients receiving apomorphine (APO) infusion and intrajejunal levodopa infusion (IJLI)

- **APO:** 41 patients; 24 male/17 female; mean dose $106 \pm 24$ mg; mean duration of infusion 16 h/d
- **IJLI:** 19 patients; 13 male/6 female; mean dose $1,990 \pm 807$ mg; mean duration of infusion 16 h/d
- All screened and observed prospectively for development of non-motor symptoms and ICBs at 3 monthly follow-ups for up to 3 years

<table>
<thead>
<tr>
<th></th>
<th>Apo Group, n (%)</th>
<th>IJLI Group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting ICDs</td>
<td>4 (10)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Preexisting ICDs- resolved</td>
<td>1 (2.4)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Preexisting ICDs- attenuated</td>
<td>3 (7.3)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>New troublesome ICDs</td>
<td>4 (9.7)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment stopped due to ICDs</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Strategies utilising continuous drug delivery appear to have a relatively low risk of development of ICBs*

Todorova A, et al., 2015
DBS and ICD

- Relationship controversial

- Early reports of improvement of ICD under DBS, but probably explained by reduction of DAg therapy

- Other studies suggest that DBS might itself cause or exacerbate ICD.

- Studies suggest increased impulsiveness when DBS is turned on.

Weintraub and Claassen, 2017
Management

Prompt identification and treatment imperative!

1. Reduce or discontinue DA (not always possible due to motor worsening or DAWs)

2. Suggested, but very limited evidence: SSRI, bupropion, antipsychotics, mood stabilizers, zonisamide, amantadine

3. Naltrexone: One partly positive study

4. Cognitive behavioural therapy: One positive study

5. LCIG (STN-DBS still controversial)

Weintraub and Claassen., 2017
ICD in Parkinson’s disease

How common is DAWS in patients tapering DA?

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence in the entire cohort</th>
<th>Prevalence in ICD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabinak &amp; Nierenberg 2010</td>
<td>5/28 (19%)</td>
<td>5/15 (33%)</td>
</tr>
<tr>
<td>Connington et al 2012</td>
<td>7/46 (15%)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Pondai et al. 2012</td>
<td>13/84 (15%)</td>
<td>13/42 (31%)</td>
</tr>
<tr>
<td>Total</td>
<td>16%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Anxiety (100%)
Dysphoria
Panic attacks
Autonomic symptoms
Pain

Pondal et al
Before the initiation of treatment, patients and caregivers should be warned about the potential for DAs (and other dopaminergic therapies) to cause ICDs and given suitable written information for future reference.

**Anticipatory care measure for all PD patients**

- Warn patients and carers
- Review for neuropsychiatric and non-motor morbidity
- Exercise vigilance in high-risk groups
- Explore ICBs at each visit
- Monitor for dose escalation

DA, dopamine agonist; ICB, impulse control behaviour; ICD, impulse control disorder

Macphee GJA, 2013
**Treatment options for the management of ICDs in PD**

**Education, prevention, and surveillance**

**Patient education, carer education, and surveillance to facilitate early diagnosis and treatment**

**Adjustment of PD medication**

**Reduction of oral DA:**
- Observe for resolution of ICDs
- Observe for loss of motor control
- Observe for DA withdrawal syndrome (DAWS)

**If loss of motor control with reduced DA dose, consider:**
- Increasing L-dopa
- Adding catechol-O-methyltransferase (COMT) inhibitor

**If concomitant loss of motor control occurs, consider:**
- Adding monoamine oxidase-inhibitor (MAO-I) (efficacy against DAWS is lacking)

**Adjustment of PD medication**

**Consider switching from oral DA to:**
- Transdermal rotigotine
- Continuous subcutaneous apomorphine
- Continuous intrajejunal L-dopa to control motor symptoms

---

DA, dopamine agonist; ICD, impulse control disorder; L-dopa, levodopa; PD, Parkinson’s disease

Samuel M, et al. 2015
Psychiatric management

Consider addition of antidepressants, anxiolytics, atypical neuroleptics, antiepileptics, or naltrexone

Psychological treatment

Cognitive behaviour therapy

Deep brain stimulation

Consider ‘L-dopa-sparing’ types of deep brain stimulation, such as at subthalamic nucleus (or ventral intermediate nucleus), if patient is mainly troubled by tremor

Consider the severity of DAWS vs the severity of ICDs

Re-introduce DA at the lowest possible dose to avoid DAWS

DA, dopamine agonist; DAWS, dopamine agonist withdrawal syndrome; ICD, impulse control disorder; L-dopa, levodopa; PD, Parkinson’s disease

Samuel M, et al., 2015
ICD in Parkinson’s disease

Summary

- ICD originate from dysfunction in normal inhibitory response to an external reward stimuli in individuals with predisposing personality

- ICD are triggered by exposure to dopaminergic medication, primarily dopamine agonists, but the relationship to dose is uncertain

- Management:
  - Patient and caregiver education
  - Vigilant monitoring for ICDs
  - Careful use of DAg