Parkinson’s Disease Psychosis

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Number of People Living with Parkinson’s Disease

• An estimated seven to 10 million people worldwide are living with Parkinson's disease.

• As many as one million Americans live with Parkinson's disease.

• Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of people that go undetected.

• A further 3.5-5 million people worldwide have Parkinson’s disease dementia or dementia with Lewy bodies.
Parkinson’s disease: α-Synuclein Pathology Spreads throughout the brain Over Time

LBs stained for ubiquitin

Lewy neurites stained for α-synuclein
What is Parkinson’s disease

Psychosis

- Hallucinations (usually Seeing and hearing things that are not there, sometimes other sensations such as smell or touch) (hallucinations eg friends/family, other people, animals, insects, snakes)
- Delusions: false unshakeable beliefs not based on reality, usually paranoid in nature. The most common delusions are
  - Theft/stealing
  - People in the house, thinking their house is not really theirs
  - Spousal infidelity,
  - Being abandoned
Why is PD Psychosis Important

- Distressing to patients
- Increased caregiver stress
- Progressive and worsens over the course of the illness
- Increased nursing home admission
- Increased mortality
- Predicts development of dementia
- Limited treatment options
How Common is PD psychosis

- Parkinson’s disease without dementia
- At any one time
  - Hallucinations 25%
  - Delusions 5%
- Over the course of the illness
  - Hallucinations and delusions combined >50%
  - Symptoms become more severe (from 3-4 hours a week to 3-4 hours a day) and loss of insight
  - ie 5 million of the 10 million people worldwide with Parkinson’s disease will develop psychosis
# Key Clinical Symptoms in PDD/DLB

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency in PDD/DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuating Cognition</td>
<td>70-85%</td>
</tr>
<tr>
<td>Major depression</td>
<td>20-35%</td>
</tr>
<tr>
<td><strong>Visual Hallucinations</strong></td>
<td>65-80%</td>
</tr>
<tr>
<td>Delusions</td>
<td>40-60%</td>
</tr>
<tr>
<td>REM sleep Behaviour Disorder</td>
<td>60-70%</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>65-100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Clinical Practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treating underlying medical causes/delirium</td>
<td>Anecdotal/best practice guide</td>
<td>Good practice for newly presenting symptoms but limited utility for symptoms present for &gt; 4 weeks</td>
</tr>
<tr>
<td>Reducing Parkinson’s medications</td>
<td>Anecdotal</td>
<td>Can sometimes be effective in clinical practice, but limited evidence base and can lead to worsening of motor symptoms</td>
</tr>
</tbody>
</table>
### Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>RCTs Details</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>4 RCTs (4 weeks) total of 192 patients</td>
<td>3 of RCTs show significant benefit in psychosis without worsening of motor symptoms, with an overall Standardized effect size of 0.8. Possible increase of deaths in 1 study. Black box warning for agranulocytosis with mandatory monitoring.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Limited evidence from open clinical trials</td>
<td>Parkinsonian side effects too severe to consider in clinical practice</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3 RCTs</td>
<td>Worsening of motor symptoms too severe for olanzapine to be a viable treatment and no evidence of benefit</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5 RCTs (4-12 weeks) total of 169 patients</td>
<td>3/4 RCTs in people without dementia and the only RCT in people with dementia indicated no benefit in the treatment of psychosis. The other study was small and showed mixed results.</td>
</tr>
</tbody>
</table>
Frequency of Neuroleptic Sensitivity Reactions: Leading to Severe Parkinsonism, Impaired Consciousness, Muscle Breakdown, Kidney Failure and Often Death

<table>
<thead>
<tr>
<th></th>
<th>DLB</th>
<th>PDD</th>
<th>PD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>36</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>No NSR</td>
<td>2(13%)</td>
<td>16(44%)</td>
<td>15(58%)</td>
<td>10(59%)</td>
</tr>
<tr>
<td>Mild NSR</td>
<td>5(33%)</td>
<td>6(17%)</td>
<td>4(15%)</td>
<td>7(41%)</td>
</tr>
<tr>
<td>Severe NSR</td>
<td>8(53%)*</td>
<td>14(39%)*</td>
<td>7(27%)*</td>
<td>0</td>
</tr>
</tbody>
</table>

chi square = 12.4, df=3, p=0.006

* Including clozapine

Aarsland et al et al 2005 J Clin Psych
Neuroleptic Sensitivity Can Happen After One or TWO Antipsychotic Doses

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>MMSE</th>
<th>Symptoms at onset</th>
<th>Neuroleptic resulting in sensitivity</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(^1)</td>
<td>EPS(^2)</td>
<td>VH(^3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>haloperidol</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>F</td>
<td>8</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>risperidone</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>sulpiride</td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>F</td>
<td>16</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>risperidone</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>M</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>sulpiride</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>M</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>thioridazine</td>
</tr>
</tbody>
</table>

1. Fluctuating confusion (present/absent)
2. Spontaneous Parkinsonism (present or absent)
3. Visual hallucinations (present or absent)

Ballard et al Lancet 1998
Major Adverse Outcomes with antipsychotics over 6-12 weeks (Schneider et al 2005, Ballard et al 2009)

- Parkinsonism*
- Sedation
- Gait disturbance*
- Falls*
- Increased respiratory infections
- Oedema
- Accelerated cognitive decline
- Stroke (>3 fold)
- Other thrombo-embolic events
- Mortality (1.5-1.7 fold)
At risk (No. of deaths) in subsequent 12 months:

<table>
<thead>
<tr>
<th>Group</th>
<th>At Risk</th>
<th>Deaths</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue</td>
<td>81 (19)</td>
<td>62 (14)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>82 (17)</td>
<td>65 (4)</td>
<td>32 (6)</td>
</tr>
</tbody>
</table>

Log-rank P=0.03

DART-AD Ballard et al 2009 Lancet Neurology

Cumulative survival (ITT)
### Cholinergic Function and Psychosis in DLB

<table>
<thead>
<tr>
<th></th>
<th>Visual Hallucinations</th>
<th>Delusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes (12)</strong></td>
<td><strong>No (5)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Choline Acetyl</strong></td>
<td>1.7±0.6</td>
<td>2.5±0.7*</td>
</tr>
<tr>
<td><strong>Transferase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pirenzepine</strong></td>
<td>122.3±31.6</td>
<td>106.3±44.8</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td><strong>Yes (14)</strong></td>
<td><strong>No (7)</strong></td>
</tr>
<tr>
<td><strong>Choline Acetyl</strong></td>
<td>1.9±0.6</td>
<td>1.9±0.8</td>
</tr>
<tr>
<td><strong>Transferase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pirenzepine</strong></td>
<td>131.0±31.4</td>
<td>93.5±27.7**</td>
</tr>
</tbody>
</table>

* p=0.02, ** p=0.01

Ballard et al Annals of Neurology 2000
<table>
<thead>
<tr>
<th>Anti-dementia Treatments</th>
<th>4 RCTs</th>
<th>2 RCT in PDD, 1 RCT in DLB, 1 RCT in PDD/DLB. Modest improvement in overall neuropsychiatric symptoms in 3/4 trials in PDD/DLB, secondary analysis indicates benefit for visual hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase inhibitors</td>
<td>3 RCTs</td>
<td>No significant benefit for neuropsychiatric symptoms</td>
</tr>
</tbody>
</table>
## Trials of Rivastigmine in PDD
Aarsland et al 2010 (Systematic Review)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Duration (weeks)</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading 2001</td>
<td>15</td>
<td>Open/ washout</td>
<td>14/3</td>
<td>Improvements on MMSE* and NPI* with deterioration after washout.</td>
</tr>
<tr>
<td>Bullock 2002</td>
<td>5</td>
<td>Case series</td>
<td>20-52</td>
<td>Improvements in cognition and behavioural symptoms, particularly visual hallucinations</td>
</tr>
<tr>
<td>Giladi 2003</td>
<td>28</td>
<td>Open/ washout</td>
<td>26/8</td>
<td>Improvements in mental subscale of UPDRS*, ADAS-cog*, and attention component of MMSE*; no significant change in motor subscale of UPDRS</td>
</tr>
<tr>
<td>Emre 2004</td>
<td>541</td>
<td>RCT</td>
<td>24</td>
<td>Significant treatment differences on ADAS-cog, ADCS-CGIC, ADCS-ADL, NPI, MMSE, CDR, D-KEFS, and Ten Point Clock-Drawing test (all *)</td>
</tr>
</tbody>
</table>

* statistically significant

Less consistent evidence of benefit on neuropsychiatric symptoms with donepezil, but recent Japanese study (Mori et al 2012) indicated some
Primary efficacy results: NPI Items (1)
Patients with Visual Hallucinations

Change from baseline at week 24 individual NPI items

Delusions
Hallucinations
Agitation/Agression
Depression/Dysphoria
Anxiety
Euphoria/Elation
Apathy/Indifference
Disinhibition
Irritability/Lability
Abberant motor behavior

ITT+RDO analysis
*p < 0.05 versus placebo
## 5HT and Psychosis in PDD/DLB

- **Delusions**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B</th>
<th>Wald</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/S</td>
<td>-</td>
<td>6.69</td>
<td>0.04</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>S/L</td>
<td>1.66</td>
<td>3.24</td>
<td>0.07</td>
<td>5.26</td>
<td>0.86-32.11</td>
</tr>
<tr>
<td>L/L</td>
<td>2.44</td>
<td>6.39</td>
<td>0.01</td>
<td>11.52</td>
<td>1.7-76.69</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.1</td>
<td>14.22</td>
<td>&lt;0.001</td>
<td>0.862</td>
<td>0.8-0.93</td>
</tr>
</tbody>
</table>

Underlying mechanism relates to pimavanserin treatment target.

suggests that same mechanism associated with psychosis in PDD and AD
Pimavanserin Development Path

• Preclinical Models of Antipsychotic Activity
• PDP Phase II and Phase III Data
• Schizophrenia Co-therapy Data
• Sleep Data
• Safety Data
• Future Directions
  • Continuation of PDP Program
  • ADP Rationale and POC Study
  • Phase III Schizophrenia Program
-020 Study: Design

<table>
<thead>
<tr>
<th>Pivotal Efficacy, Tolerability and Safety Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Type of design</td>
</tr>
<tr>
<td>Primary endpoint</td>
</tr>
<tr>
<td>Key secondary endpoint</td>
</tr>
</tbody>
</table>

**Patient Pathway From Screening to Open-Label Treatment**

- **Screening**
  - BPST Run-In
  - NPI
- **6-Week Blinded Treatment Period**
  - Baseline SAPS-PD
  - 2-Week Visit
  - 40 mg PIM or PBO (1:1)
  - 4-Week Visit
- **Long-Term Open-Label**
  - 6-Week Endpoint
  - 40 mg PIM

(1) Patients who completed the 6-week treatment period of the -020 Study could elect to roll over into a Phase III openlabel safety extension trial, the -015 Study.
Study Enrollment, Randomization and Disposition

314 Participants Screened

115 Excluded
53 - SAPS/NPI entry criteria
14 - Declined to participate
48 - Other reason

199 Randomized

94 Assigned to PBO
0 Did not take drug
4 Disc’d before any post-baseline SAPS assessment
1 - AE
1 - Withdrew consent
2 – Other reason

105 Assigned PIM 40mg
1 Did not take drug
9 Disc’d before any post-baseline SAPS assessment
6 - AE
2 - Withdrew consent
1 – Other reason

90 in ITT analysis set

3 Disc’d from study
1 – AE
1 - Withdrew consent
1 - Investigator’s decision

87 Completed

6 in ITT analysis set

4 Disc’d from study
4 – AE
1 - Withdrew consent
1 - Non-compliant

89 Completed
-020 Study: Pimvanserin Demonstrated Highly Significant Antipsychotic Efficacy

SAPS-PD (primary endpoint)
(ITT, N=185; change from baseline)

SAPS-PD Improvement (LSM ± SE)

Study Day

Change from Baseline to Day 43
(LSM ± SE)

Placebo
40 mg PIM

p = 0.037
p = 0.001
-020 Study: Pimavanserin’s Antipsychotic Efficacy Supported by CGI Endpoints

CGI – S Change from Baseline (LSM ± SE)

CGI – I (LSM ± SE)

Study Day

Placebo 40 mg PIM

Study Day

Placebo 40 mg PIM

p = 0.0007

p = 0.001

p = 0.022 *

p = 0.01 **

p = 0.001 **
-020 Study: Pimavanserin Improved Nighttime Sleep and Daytime Wakefulness

**Nighttime Sleep**
(ITT, N=185; change from baseline)

**Daytime Wakefulness**
(ITT, N=185; change from baseline)

[Graphs showing SCOPA Improvement (LSM±SE) over Study Days 1, 15, 29, and 43 for Placebo and 40 mg PIM conditions, with p-values noted for each condition.]

- Placebo
  - Nighttime Sleep: p = 0.001
  - Daytime Wakefulness: p = 0.012
- 40 mg PIM
  - Nighttime Sleep: p = 0.045
  - Daytime Wakefulness: p = 0.001
-020 Study: Pimavanserin Reduced Caregiver Burden

**Caregiver Burden**
(ITT, N=185; change from baseline)

- Placebo
- 40 mg PIM

*p = 0.002*
Summary of Safety

- SAEs
  - Only two SAEs occurred in more than 1 patient: UTI (1 PBO and 3 PIM) and psychotic disorder (0 PBO and 2 PIM)
  - 3 deaths (1 PBO [sudden cardiac death], 2 PIM [sepsis & septic shock]), all were considered unrelated to study drug

- Treatment Emergent AEs ≥5% in either group:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=94)</th>
<th>PIM 40 mg (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (%)</td>
<td>Subjects (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (6.4)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>3 (3.2)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (11.7)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>Fall</td>
<td>8 (8.5)</td>
<td>11 (10.6)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>3 (3.2)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5.3)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Hallucination (incl. visual)</td>
<td>4 (4.3)</td>
<td>7 (6.7)</td>
</tr>
</tbody>
</table>

- Pimavanserin met key secondary endpoint for motoric tolerability; with both arms showing improvements in combined UPDRS II+III score (-1.69 for PBO, -1.40 for PIM)
  - The upper 95% CI for the treatment difference met pre-specified criteria for non-inferiority

- Pimavanserin’s safety profile potentially offers important advantages compared to existing antipsychotics