Psychosis in Parkinson’s Disease

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and The Department of Neurology
Baylor College of Medicine

Disclosures

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Dept Veterans Affairs;

Honoraria Roche Pharmaceuticals (2013)
Royalties Taylor & Francis/Informa

Approved/Unapproved Uses
The following presentation may contain information concerning a use that has not been approved by the US Food and Drug Administration.
Psychosis in Parkinson’s Disease

Objectives

I. Understand the epidemiology of psychotic symptoms in PD
II. Understand the evidenced-based treatment of psychotic symptoms in PD

I. Epidemiology of Psychosis in PD
II. Diagnosis of Psychosis in PD
   a. Associated psychiatric conditions
   b. Assessment tools
III. Practical management of Psychosis
Prevalence of Psychosis in PD

- Depends on definition of psychosis, PD, and cognitive impairment
- ~ 8%–40% reported rates\(^1\)
  - ~ 5%–17% without significant dementia
  - ~ 42%–81% with significant dementia
- Persistent and progressive\(^2\)

Greene P, et al. 1993; de Maindreville AD et al. 2005; Hely et al., 2005

### Psychiatric Symptoms in PD

<table>
<thead>
<tr>
<th>Neuropsychiatric Inventory Scores, n=139</th>
<th>Percent with symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>0%  20%  40%  60%  80%  100%</td>
</tr>
<tr>
<td>Euphoria</td>
<td>□ 20%  38%  61%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>□ 17%  17%</td>
</tr>
<tr>
<td>Irritability</td>
<td>□ 16%</td>
</tr>
<tr>
<td>Aberrant Motor Behavior</td>
<td>□ 11%</td>
</tr>
<tr>
<td>Delusions</td>
<td>□ 10%</td>
</tr>
<tr>
<td>Delusions</td>
<td>□ 7%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>□ 1%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>□ Any one symptom</td>
</tr>
</tbody>
</table>

Aarsland et al., 1999, Rogaland, Norway Epidemiological Sample
Prevalence of Hallucinations and Delusions
Hopkins PD Research Center Longitudinal Study

<table>
<thead>
<tr>
<th>Type</th>
<th>Psychotic group, n=25, 22%</th>
<th>Total sample, n=116</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hallucinations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td>92%</td>
<td>20%</td>
</tr>
<tr>
<td>Auditory</td>
<td>84%</td>
<td>18%</td>
</tr>
<tr>
<td>Olfactory</td>
<td>60%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Tactile</td>
<td>12%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Visceral</td>
<td>4%</td>
<td>0.03%</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid, nonspecific</td>
<td>64%</td>
<td>14%</td>
</tr>
<tr>
<td>Paranoid, systematized</td>
<td>28%</td>
<td>6%</td>
</tr>
<tr>
<td>Spousal infidelity</td>
<td>36%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Other (sexual, 1st rank, somatic)</td>
<td>24%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Other (sexual, 1st rank, somatic)</td>
<td>20%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Marsh L et al. Neurology 2004; 63: 293-300
Psychiatric Co-morbidities are Common with PD-Psychosis

Hopkins PD Research Center Longitudinal Study, n = 116

<table>
<thead>
<tr>
<th>Co-morbid Disorder</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive</td>
<td>10</td>
<td>71%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>21%</td>
</tr>
<tr>
<td>Apathy</td>
<td>2</td>
<td>14%</td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td>14%</td>
</tr>
</tbody>
</table>

Marsh L. Neurology. 2004;63:293-300

2-year Follow-up – Treated Patients

Baseline N=59 patients enrolled in PSYCLOPS, duration psychosis =12.4(15.5) years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Persistent Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>Paranoia</td>
<td>60%</td>
<td>27%</td>
</tr>
<tr>
<td>Hallucinations &amp; Paranoia</td>
<td>55%</td>
<td>23%</td>
</tr>
<tr>
<td>Dementia (MMSE&lt;25)</td>
<td>56%</td>
<td>68%</td>
</tr>
<tr>
<td>Nursing Home</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td>Death, n=15</td>
<td>-</td>
<td>25%</td>
</tr>
</tbody>
</table>

Neuropsychiatric Features – Most disabling aspect of PD over disease course

**Sydney Multi-center Study – 15-year Follow-up**
- n=149, 52 surviving (71 ± 8; 55-86 years)
- Most disabling long term symptoms
  - Cognitive decline - 84%
  - Dementia - 48%, MCI - 36%
  - Hallucinations – 50%
  - Depression – 39%

Hely et al, 2005

**High Prevalence of Psychosis in PD – Broad Impact on Clinical Practice, Patient, Family, & Society**

- Major challenge for clinicians
- Greater carer burden
- Greater healthcare costs
- Greater disability, nursing home placement, and mortality
  - Aggravated motor deficits, dysfunction, progression
  - Aggravated cognitive deficits and dysfunction
  - More concurrent medical and psychiatric conditions
- Lower quality of life

Schrag 2000; McDonald 2003; Starkstein 1992; Kuopio 2000; Marsh 2004, 2007; Pontone 2011
### Diagnosis of Psychosis

Psychiatric Disturbances in PD do not fall into typical DSM categories

<table>
<thead>
<tr>
<th>DSM NOS Dx (Not Otherwise Specified)</th>
<th>N</th>
<th>% All Subjects</th>
<th>% of all in NOS Dx class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Disorders</td>
<td>30</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>55</td>
<td>22%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Psychosis</strong></td>
<td>61</td>
<td>24.4%</td>
<td>96.8%</td>
</tr>
<tr>
<td>Impulse Control</td>
<td>11</td>
<td>4.4%</td>
<td>69%</td>
</tr>
<tr>
<td>Personality Change</td>
<td>32</td>
<td>13%</td>
<td>100%</td>
</tr>
</tbody>
</table>

(Mood-PD Study, n=250)
NINDS/NIMH Proposed Diagnostic Criteria for PD-Associated Psychosis (Ravina et al. 2007)

A. Characteristic symptoms
Presence of at least one of the following sx (specify which sx fulfill the criteria):
• Illusions
• False sense of presence
• Hallucinations
• Delusions

B. Primary diagnosis
• UK Brain Bank Criteria for PD

C. Chronology of the onset of symptoms of psychosis
• The symptoms in Criterion A occur after the onset of PD

D. Duration
• The symptom(s) in Criterion A are recurrent or continuous for 1 mo

E. Exclusion of other causes
Criterion A Sx not better accounted for by another cause of Parkinsonism (e.g., DLB), other psychiatric disorders (do) (e.g., schizophrenia, schizoaffective do, delusional do, or mood do w/ psychotic features), or genl med condition, incl delirium

F. Associated features: (specify if associated)
• With/without insight; With/without dementia
• With/without treatment for PD (specify drug, surgical, other)

Typical Categorization of PD-Hallucinations

• “Minor” Hallucinations
  • Presence – Vivid sensation
  • Passage – Brief visions in peripheral field
  • + Illusions – sensory distortions

• “Benign” Hallucinations/Hallucinosis (w/ insight)

• Hallucinations w/o insight
  • Formed/Complex versus Unformed
  • Visual, Auditory, Olfactory, Gustatory, somatic/Tactile/Cenesthetic
Yet, Psychosis in PD: Never ‘Minor’ or ‘Benign’

- Community-based PD (n=250)
  - 47.7% Isolated Minor Hallucinations
  - 52.3% Hallucinations or Delusions

- Minor Hallucinations (vs. No Psychosis)
  - Greater physical disability
  - More severe depressive symptoms
  - Reduced quality of life

Note: 90.8% met NINDS/NIMH PD-P Criteria

Hallucinations: Prevalence Increases over Time

3-month prevalence, N=127

<table>
<thead>
<tr>
<th>Type</th>
<th>Baseline</th>
<th>1-year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence (n = 35)</td>
<td>29.1%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Passage (n = 18)</td>
<td>16.2%</td>
<td></td>
</tr>
<tr>
<td>Illusions (n = 9)</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Illusions</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>Complex visual</td>
<td>22.8%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Auditory</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>All types</td>
<td>41.7%</td>
<td>49.6%</td>
</tr>
<tr>
<td>Incidence</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Pred. of hallucinations</td>
<td>Sleep Disorders, Ocular Disorders, Axial Signs</td>
<td></td>
</tr>
</tbody>
</table>


de Maindeville AD, et al. Mov Disord 2005; 20: 212-217s
Hallucinations: 6-year Follow-up
Baseline N=60: no Sx=20, sleep fgmtn=20, vivid dreams=20

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Baseline</th>
<th>6-mo</th>
<th>18-mo</th>
<th>48-mo</th>
<th>72-mo</th>
</tr>
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<tbody>
<tr>
<td>Hallucinators-Prevalence</td>
<td>0%</td>
<td>13%</td>
<td>31%</td>
<td>52%</td>
<td>44%</td>
</tr>
<tr>
<td>Hallucinations-Incidence</td>
<td>-</td>
<td>13%</td>
<td>24%</td>
<td>32%</td>
<td>9%</td>
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Persistence of Hallucinations
O.R. = 4.4

First Hallucinations
Pure Visual = 18/37
Nonvisual = 9/37
Mixed = 10/37


Delusions

• ~ 3% – 30% reported prevalence rates
• Phenomena
  – Delusions of spousal infidelity
  – Feature of affective psychosis
  – Often accompany hallucinations
  – Other persecutory delusions
  – First-rank symptoms
    ➢ Delusions of influence
    ➢ Passivity experiences

### Prevalence of Hallucinations and Delusions

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Marsh L et al. *Neurology* 2004; 63: 293-300

### Psychotic Phenomena

**N=160 patients enrolled in the US and European Olanzapine trials for PD-Psychosis**

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</tr>
<tr>
<td>Auditory</td>
</tr>
<tr>
<td>Tactile</td>
</tr>
<tr>
<td>Olfactory</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
</tr>
<tr>
<td>Stealing</td>
</tr>
<tr>
<td>Not my house</td>
</tr>
<tr>
<td>Infidelity</td>
</tr>
<tr>
<td>Abandonment</td>
</tr>
<tr>
<td>Spouse an imposter</td>
</tr>
</tbody>
</table>

Associated Psychiatric Features

- Depression
- Anxiety
- Apathy/abulia
- Affective lability (nonmotor fluctuations)
- Disinhibition, mania, gambling, hypersexuality
- Agitation
- Aggression
- Confusion/disorganization/dementia
- Delirium
- Caregiver strain


Psychosis Assessment Tools
Rating Scales May Improve Recognition and Treatment of Psychotic Disturbances in PD

- Large and growing range of measurement tools
  - 1970’s – proliferation of instruments
  - 2000’s - Focus on quality and accuracy of instruments, consolidation of information

- Application in PD
  - Increase attention to Psychiatric disturbances in PD
  - Increase recognition & treatment in clinical practice
  - Provide objective measure to facilitate care across disciplines and track outcomes (like BP measures)

Use of Scales to Assess Psychosis

- Current scales all have limitations
  - NINDS Common Elements Database
    http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards

- PD-specific Psychosis Scale - under Development
  - Screening, Clinical Trials, Assist clinical interview
  - Must be comprehensive and yet administered in <10 minutes by non-physician! (Fernandez et al. 2008)
Scales used to assess PD-Psychosis

<table>
<thead>
<tr>
<th>Scale</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson Psychosis Rating Scale</td>
<td>Suggested</td>
</tr>
<tr>
<td>Parkinson Psychosis Questionnaire</td>
<td>Suggested</td>
</tr>
<tr>
<td>Rush Hallucination Inventory</td>
<td>Listed</td>
</tr>
<tr>
<td>Baylor Hallucination Questionnaire</td>
<td>Listed</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>Recommended</td>
</tr>
<tr>
<td>Behavioral Pathology in Alz Disease Rating Scale</td>
<td>Suggested</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale</td>
<td>Recommended</td>
</tr>
<tr>
<td>Positive and Negative Symptom Scale</td>
<td>Recommended</td>
</tr>
<tr>
<td>Schedule for Assessment of Positive symptoms</td>
<td>Recommended</td>
</tr>
<tr>
<td>Nurses’ Observation Scale for Inpt Eval</td>
<td>Listed</td>
</tr>
<tr>
<td>Clinical Global Impression Scale</td>
<td>Suggested</td>
</tr>
<tr>
<td>Unified PD Rating Scale-Part I</td>
<td>Listed</td>
</tr>
</tbody>
</table>

**Recommended**: Applied in PD, data from studies beyond its developer, + Clinimetric studies (valid, reliable, sensitive); **Suggested**: used in PD + one other criterion; **Listed**: Used in PD (Fernandez et al 2008)

Treatment of PD-Psychosis
The Motion–Emotion Conundrum

Maintain motion
- Lower Potency Antipsychotics

Control emotion
- High Potency Antipsychotics

Targeted and individualized approach


Treatment of PD-Psychosis

Primary Prevention

Characterization of primary behavior/psychotic sx and its comorbidities

Medical Review
- Treat medical illnesses
- Eliminate psychoactive and redundant medications
- Review PD medications/ balance effects on motor and psychiatric sx

Step 4:
- Tx comorbid psychiatric illnesses

Step 5:
- Nonpharmacological strategies

Step 6:
- Eliminate antiparkinsonian medications

Step 7:
- Address disrupted sleep

Step 8:
- Trial Cognitive Enhancers

Step 9:
- Trial of antipsychotic medication

Non-pharmacologic Treatments
(Medication Education Skills Support)

- **Education**
  - Psychiatric aspects of PD and Safety Issues
  - Coping strategies
  - Caregiver issues

- **Psychotherapy**
  - Counseling/problem-solving
  - Supportive, directive, insight-oriented, grief counseling,
    Cognitive-behavioral therapy
  - Caregiver support

- **Rehabilitative therapies**
  - Occupational, Physical, Speech Therapies
  - Exercise/Exercise classes/Personal trainers
  - Relaxation training

- **Social Supports**
  - Day Programs, Safety, Socialization, Support groups, Home care; Nursing home placement

Elimination of PD Meds

**Discontinue First**
- Anticholinergics
- Selegiline/Rasagiline
- Amantadine
- Dopamine agonists
- Controlled release meds
- COMT inhibitors
- Levodopa dosage

**Discontinue Last**
Antipsychotic Medications

• May enable increase in PD meds
• Typical D₂ blockers—↑ parkinsonism
• Atypical agents—block D₃, D₄, D₅, 5-HT
• Several open-label and controlled trials
  – Risperidone, olanzapine: poor tolerance
  – Quetiapine: fairly well-tolerated
  – Clozapine: gold standard
  – Ziprasidone: anecdotal only—profile limits use
  – Aripiprazole: anecdotal only—variable tolerance

Early Tx of Minor Psychosis Beneficial

n-=64 new onset minor hall, hall w/ insight
• Average 31-month f/u
• Effects of Antipsychotic med, PD Med reduction, or observation conversion on UPDRS to Hallucinations without insight or delusions

• Antipsychotic medication
  • Reduced risk of deterioration
    • Hazard ratio=0.156, CI= (0.067-0.363), p<0.0001
    • Time to conversion=39 months, vs 12 months with no tx

Goetz et al. 2008.
Yet, Actual Clinical Practice is Concerning

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-Psychosis, n=2597</td>
<td></td>
</tr>
<tr>
<td>2008: 50% prescribed Antipsychotic</td>
<td></td>
</tr>
<tr>
<td>Quetiapine-66%</td>
<td></td>
</tr>
<tr>
<td>High Potency Antipsychotics – 30%</td>
<td></td>
</tr>
<tr>
<td>Clozapine &lt;2%</td>
<td></td>
</tr>
<tr>
<td>Compared to 2002</td>
<td></td>
</tr>
<tr>
<td>Similar rate of AP use</td>
<td></td>
</tr>
<tr>
<td>Decreased use of risperidone and olanzapine</td>
<td></td>
</tr>
<tr>
<td>Increased use of quetiapine</td>
<td></td>
</tr>
<tr>
<td>Introduction of aripiprazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weintraub et al 2012</td>
</tr>
</tbody>
</table>

Inappropriate Antipsychotic Use Also in PD Patients in Long Term Care

| N=479 Retrospective Cohort Study                      |                                 |
| Administrative Database – Ontario Health Insurance Plan and Drug Benefit Database |                                 |
| Quetiapine, n=192                                     | 40%                             |
| Risperidone, n=185                                    | 39%                             |
| Olanzapine, n=81                                      | 17%                             |
| Typical Antips, n=21                                  | 4%                              |
| First l-dopa dose change: reduction, n=469, 98%       |                                 |
|                                                      | Hermann et al 2013              |
Current Evidence Base Recommends Clozapine for PD-P

<table>
<thead>
<tr>
<th>Drug</th>
<th># Reports</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>32 Reports</td>
<td>Efficacious</td>
<td>Acceptable risk w/ specialized monitoring</td>
<td>Clinically Useful</td>
</tr>
<tr>
<td></td>
<td>5 RCTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>9 Reports</td>
<td>Unlikely</td>
<td>Unacceptable risk</td>
<td>Not useful</td>
</tr>
<tr>
<td></td>
<td>3 RCTs</td>
<td>Efficacious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14 Reports</td>
<td>Insufficient</td>
<td>Acceptable risk w/o specialized monitoring</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>4 RCTs</td>
<td>Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>2 RCTs</td>
<td>Efficacious</td>
<td>Appears Acceptable</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

Dose range: 6.25 mg qod ≥ 200 mg/day
Starting dose 6.25 mg/qhs
Escalate as needed/tolerated
Adverse effects
- Sedation
- Orthostasis
- Confusion
- Worse parkinsonism
- Agranulocytosis
- Seizures

Quetiapine

- Dose range: 6.25 mg qhs ≥ 125 mg/day
- Escalate as needed/tolerated
- Adverse effects
  - Sedation
  - Orthostasis
  - Confusion
  - Worse parkinsonism
  - Worsened diabetes


Pipeline Medications

- Selective 5HT2A inverse agonist
- N=199, 40 mg Pimavanserin vs Placebo
  - 6 week trial, incl 2 week placebo lead-in
  - Favorable safety profile, no acute or tardive motor SEs
Pipeline Medications

- **Pimavanserin (ACP-103)**
  - Selective 5-HT2A inverse agonist
  - n=60, 28-day RCT in PD-P
  - Trend in decrease in SAPS Total domain score
  - Decreased SAPS global hallucinations and delusions scores
  - Improved Carer burden, Nighttime sleep, Daytime Wakefulness
  - No adverse motor, sleep, blood pressure effects

Meltzer et al., 2010

Other Strategies:
Address Risk Factors Proactively

- Over 2-year course (n=331), ↑ risk of psychosis
  - Worse Cognition
  - PD Severity/Duration
  - Anticholinergic use (but ↓ with donepezil use)

Sawada 2013
Other Strategies:

- Cognitive Enhancing Agents
  - Cholinesterase inhibitors
    - + PD-D and DLB
    - Variable tolerance, May benefit from lower doses
  - Memantine—DLB, PD-D

- Ondansetron
  - Especially useful post-operatively

- Electroconvulsive therapy (ECT)
  - Especially with psychotic depression

Conclusions

- A range of psychotic phenomena occurs in PD, with increased rates as the disease progresses
- Detection of hallucinations and delusions requires specific and thorough inquiry
- Treatment involves multiple interventions
  - Clozapine is only available evidence-based tx
  - Attention to risk factors may limit incidence and impact