The Neuropsychiatric Complications of Parkinson’s Disease:

Considerations for Effective Assessment and Treatment

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Objectives

1. To describe the prevalence, impact, and key features of the neuropsychiatric complications of Parkinson’s disease (PD), including psychosis, cognitive changes, depression and anxiety.

2. To provide a brief overview of assessment and treatment considerations for these common and debilitating non-motor aspects of the disease process.
Parkinson’s Disease

“The Quintessential Neuropsychiatric Disorder”

“The Perfect Storm...”

What are the neuropsychiatric features of PD?

Weintraub and Burn, 2011; Weintraub and Mamikonyan, 2019.
Neuropsychiatric Symptoms

- Psychosis
- Cognitive Changes
- Depression
- Anxiety
- Sleep
- Fatigue
Neuropsychiatric Symptoms

***VERY COMMON ***

• 80% with at least 1 psychiatric complication

• Significantly higher prevalence rates compared to age-matched controls

See Weintraub and Mamikonyan, 2019 for a review
Neuropsychiatric Symptoms

***FUNCTIONALLY RELEVANT***

• Faster rate of decline
• Greater difficulties with self-care
• Earlier initiation of dopaminergic replacement
• Poor quality of life
• Increased healthcare costs
• Significant caregiver burden
• Higher risk of institutionalization

See Weintraub and Mamikonyan, 2019 for a review; Pontone GM, Bakker CC, Chen S, et al., 2016.
Neuropsychiatric Symptoms

***BUT, DESPITE THESE NEGATIVE EFFECTS***

- Under-diagnosed
- Sub-optimally treated

Effective assessment and treatment approaches are critical in order to optimize global PD management.

Effective Assessment: An Overview

• PD is a heterogeneous disorder
• Each patient needs to tell his/her own story
• Neuropsychiatric complaints are primary for many

➢ Require equal and ongoing attention during assessment and treatment

➢ Skilled clinical interview
➢ Standardized rating scales and measures (e.g., MoCA, GDS, PHQ-9, PAS, baseline neuropsychological testing battery)

Dobkin et al., 2019; Dobkin & Interian, 2019; Dalrymple-Alford J et al., 2010; Williams et al., 2012
Co-morbidities Drive Complexity

- Mood Disorder: 59.2% (n=148)
- Anxiety Disorder: 41.6% (n=104)
- Psychotic Disorder: 25.2% (n=63)

L Marsh, 2010; % of total sample (n=250) with diagnosis
Effective Assessment: An Overview

- Normalize the experience
- Avoid the use of jargon
- *Adjectives* are your friend
- Ask multiple and appropriate follow-up questions
  - Assess for under-reporting and minimization of symptoms
- Evaluate emotional/cognitive component of “on-off”

Effective Assessment: An Overview

- Collateral information
- Symptoms may emerge at any time
- Don’t require change or assume causality
  - Affective symptoms may predate motor symptoms by 4-6 years
  - Depression, anxiety etc. may be the “new baseline”
- Use an inclusive approach
- **Even more intensive assessment required for PWP who are non-adherent to key treatment recommendations**

See Marsh L et al., 2006
Psychosis
PD Psychosis (PDP): Disrupting the Balancing Act

Up to 60% of patients with PD will experience psychosis during the course of their disease

# Examples of PD Psychosis

<table>
<thead>
<tr>
<th>Psychosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Illusions</td>
<td>• Misperceiving or misinterpreting an object really present</td>
</tr>
<tr>
<td></td>
<td>• Mistaking a lamp-post for a person or a chair for a dog</td>
</tr>
<tr>
<td>Presence Hallucinations</td>
<td>• Feeling that someone or a shadow is close by</td>
</tr>
<tr>
<td>Passage Hallucinations</td>
<td>• Experiencing fleeting images in the visual periphery</td>
</tr>
<tr>
<td>Simple Hallucinations</td>
<td>• Seeing flashes of light, colors, lines, patterns</td>
</tr>
<tr>
<td>Complex Hallucinations</td>
<td>• Seeing formed images of people (little children at play; distorted figures; deceased relatives), animals (small furry animals running around), objects</td>
</tr>
<tr>
<td></td>
<td>• Hearing music and voices</td>
</tr>
<tr>
<td>Multi-modal Hallucinations</td>
<td>• Having hallucinations in more than modality: visual, auditory, tactile, and/or olfactory; Most common visual plus auditory modalities</td>
</tr>
<tr>
<td>Delusions</td>
<td>• Having false beliefs; for example, that someone is unfaithful or may harm them (infidelity, paranoia)</td>
</tr>
</tbody>
</table>

Table excerpt from Goldman and Holden, 2014
**Risk Factors and Correlates for PDP**

- Dopaminergic medications for PD
- Cognitive impairment/family history of dementia
- Anticholinergics, other central nervous system (CNS)-acting agents (benzodiazepines and opiates)
- Polypharmacy with psychoactive drugs
- Older age, severity and duration of PD
- Alterations in vision/visual pathways
- Rapid eye movement sleep behavior disorder (RBD)

Management Strategies: Overview

• Treatment of underlying co-morbid medical illness, if needed
• Discontinuation of medications (for secondary conditions) that may exacerbate psychosis (eg, pain, bladder, CNS-acting medications)

***Reduction of PD medications***

***Antipsychotic therapy***

• Treatment with cholinesterase inhibitors

• Nonpharmacologic techniques
  ❖ Stimulus control
  ❖ Caregiver support
  ❖ Education/coping skills training

Balancing PDP and Motor Function

May need to reduce PD medications

Generally done when risks of untreated psychosis clearly outweigh risks of reducing PD medications

Need to monitor for worsened motor function, falls, and safety risk

Typical strategy for adjusting PD medications

Necessary for psychiatrists and neurologists to work together

Suggested order of PD medication reduction:\n1. Anticholinergics
2. Selegiline or rasagiline
3. Amantadine
4. Dopamine agonists
5. COMT inhibitors
6. Levodopa

Abbreviation: COMT, catechol-O-methyl transferase.

## Antipsychotic Treatments for PDP*

<table>
<thead>
<tr>
<th>Treatment for Psychosis</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine&lt;sup&gt;a&lt;/sup&gt; (6.25 to 50mg)</td>
<td>Efficacious</td>
<td>Acceptable risk with specialized monitoring for agranulocytosis</td>
<td>Clinically useful†</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Unlikely efficacious</td>
<td>Unacceptable risk</td>
<td>Not useful†</td>
</tr>
<tr>
<td>Quetiapine&lt;sup&gt;a&lt;/sup&gt; (12.5 to 150mg)</td>
<td>Insufficient evidence</td>
<td>Acceptable risk without specialized monitoring</td>
<td>Possibly Useful† (very commonly used)</td>
</tr>
<tr>
<td>Pimavanserin&lt;sup&gt;b&lt;/sup&gt; (40mg)</td>
<td>Efficacious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Acceptable risk but: 1) no safety data beyond 6 weeks; 2) increase in QT interval without association to cardiac events&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Clinically useful</td>
</tr>
</tbody>
</table>

- Black box warning (increased morbidity and mortality for typical and atypical antipsychotics in elderly patients who have dementia-related psychosis)*
- Other common side effects include sedation and orthostatic hypotension.
- a) Clozapine and quetiapine: antagonist activity at 5-HT<sub>2A</sub>; b) Pimavanserin 5-HT<sub>2A</sub> receptor inverse agonist
- † Not FDA approved for the treatment of PDP

Cognition
Cognition in PD

• Up to 30% have already noticed cognitive changes at time of diagnosis

• Heterogeneity of changes
  ❖ Aspects of cognition affected
  ❖ Order of domains affected

• Different rates of progression
  ❖ Dementia not inevitable but may impact up to 80% of PWP with PD duration over 20 years

See Goldman, Vernaleo et al., 2018 for a review
Cognitive Decline in PD

- Typical areas affected include:
  - Memory
  - Executive functions
  - Visuospatial
  - Attention/Working Memory
  - Language
Contributing Risk Factors for Cognitive Impairment

- Age
- Disease Duration
- Baseline Cognitive Impairment
- Other Medical Illness
- Postural Instability/Gait Disorder
- REM Sleep Behavior Disorder
- Motor Severity
- Neuropsychiatric Issues
- Daytime Sleepiness
- Social Isolation
- Depression
- Exercise
- Diet
- Self Care

See Goldman, Vernaleo et al., 2018 for a review.
Cognitive Continuum

Normal Aging

Mild Cognitive Impairment

Dementia
PD MCI: Task Force Guidelines

• PD diagnosis
• Gradual cognitive decline
• Decline evident on formal neuropsychological testing/screening measures
• Impacts ADLs (more effortful, challenging) but does not compromise functional independence

Litvan, L. et al., 2012.
**PD MCI: Task Force Guidelines**

- Comprehensive assessment in 5 domains
  - Attention/Working Memory
  - Executive Skills
  - Language
  - Visual Spatial
  - Memory

- PD MCI Subtype Classification
  - Single domain: Impairment on 2 tests in 1 domain
  - Multiple domain: Impairment on at least 1 test in 2 or more domains

Litvan, L. et al., 2012.
PD Dementia

• Rates range from 30-80% based on study methodology
• 6x more likely in PD vs. other groups
• Diagnostic criteria:
  ❖ PD
  ❖ Significant impairment in at least 2 cognitive domains
  ❖ Decline from previous level of functioning
  ❖ Associated cognitive and behavioral features

Emre, M. et al., 2007.
# Pharmacological Treatment

<table>
<thead>
<tr>
<th>Treatment for Cognition</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivastigmine (1.5-6mg oral; 4.6-9.5mg patch)</td>
<td>Efficacious</td>
<td>Acceptable risk with no additional monitoring.</td>
<td>Clinically Useful</td>
</tr>
<tr>
<td>Donepezil (5-10mg)</td>
<td>Limited evidence</td>
<td>Acceptable risk</td>
<td>Possibly Useful</td>
</tr>
<tr>
<td>Galantamine (4-24mg)</td>
<td>Limited evidence</td>
<td>Acceptable risk</td>
<td>Possibly Useful</td>
</tr>
<tr>
<td>Memantine (5-20mg)</td>
<td>Limited evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

Non-pharmacological Interventions for Cognitive Health

- Exercise
- Nutrition
- Cognitive Training
- Mood Enhancement

See Goldman, Vernaleo et al., 2018 for a review
Depression & Anxiety
## Symptoms of Depression

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sadness or crying</td>
<td>Helplessness or hopelessness</td>
</tr>
<tr>
<td>Lack of interest/motivation/pleasure</td>
<td>Thoughts of being better off dead</td>
</tr>
<tr>
<td>Appetite/weight changes</td>
<td>Problems with concentration and memory</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>Agitation or Psychomotor Slowing</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Life lacks meaning or purpose</td>
</tr>
<tr>
<td>Feelings of guilt or worthlessness</td>
<td></td>
</tr>
</tbody>
</table>
Anxiety and Parkinson’s

CRITICAL CONCEPTS
- “Avoidance”
- “Off-Anxiety”
- “Anticipatory Anxiety”

COMMON DIAGNOSES
- Panic Disorder
- Social/Specific Phobia
- Generalized Anxiety- “worried well”
- Anxiety NOS

SYMPTOM PROFILES
- Episodic Anxiety with No Depression
- Persistent Anxiety with Depression
- Persistent and Episodic Anxiety with Depression

Starkstein et al., 2014; Dobkin & Interian, 2019.
Conclusions

• Neuropsychiatric complications impact all aspects of PD management

• Collaboration across disciplines is essential to optimize patient care

• It’s everybody’s job to assess and intervene as appropriate
Conclusions

Psychosis
Cognition
Depression
Anxiety

Patient and Caregiver
Neurologist
Psychiatrists
Other Mental Health Professionals

Taylor J, et al., 2016; Dobkin et al., 2019; Dobkin et al., 2011
References

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