Cognitive and Psychiatric Aspects of Parkinson’s disease
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Disclosures

- No relevant financial relationships with commercial interests
- Advisor for Acadia Pharmaceuticals
- The following talk includes unlabeled/unapproved use of medications
Behavioral aspects of Parkinson’s disease

Objectives:
1. To become familiar with behavioral disturbances in Parkinson’s disease (PD) including: anxiety, apathy, depression, impulse control disorders, and mild cognitive impairment
2. Discuss how the physical/biological aspects of PD and its treatments may be associated with behavioral symptoms
3. Review examples of specific behavioral disturbances in PD
I. Overview of Parkinson’s as a ‘disease’ model for behavioral symptoms

II. Anxiety, depression, and apathy in PD

III. Unusual behaviors in PD
Motor symptoms are just the tip…

Bradykinesia, rigidity, tremor

Anxiety, apathy, agitation, constipation, depression, drooling, erectile dysfunction, impulse control disorders, hallucinations, delusions, gastroparesis, orthostatic hypotension, pain syndromes, fatigue, cognitive impairment, sleep disturbances
What causes behavioral changes in PD?

1. Reaction to the diagnosis - altered interpersonal roles, disability, and other psychosocial features

2. Related to the disease process

3. Interaction between the disease and dopaminergic medications
Intersection of mental and physical health in PD

1. Disease diagnosed at time zero
2. Reaction to observable symptoms/diagnosis
3. Medications introduced

Ishihara and Brayne 2006
Anxiety in Parkinson’s disease
Prevalence of anxiety and anxiety disorders in PD

• Up to 55% have clinically significant anxiety symptoms
• 31% have an anxiety disorder (e.g. DSM)

*Anxiety disorder not otherwise specified 13.3%

First Anxiety Disorder Onset Relative to PD Onset

Bimodal distribution of anxiety disorder onset compared to PD onset

Pontone et al 2009
Dopaminergic on-off motor fluctuations

- Improvement in motor symptoms after L-dopa administration = “on”
- Return of parkinsonian movement symptoms at the end of the dosing effect = “off”
Dopaminergic medication on-off fluctuations in PD

Stacey M. and Hauser R. 2007
Mood and motor fluctuation with levodopa infusion

FIG. 3. Relationship of mood change and motor change.
Anxiety fluctuation with levodopa infusion

Maricle RA et al 1995
Evidence based treatments for anxiety in PD

- Cognitive Behavioral Therapy (CBT) for anxiety in PD
- MDS Task Force on Evidenced Based Medicine and the American Academy of Neurology conclude that “the evidence to support or refute specific treatments for anxiety is insufficient”

Zesiewicz et al 2010, Seppi et al 2011
Depression in Parkinson’s disease
• **Parkinson’s Outcomes Project**, a longitudinal look at which treatments produce the best health outcomes in PD n=12,000+

• The impact of depression on quality of life is almost twice that of the motor impairments
Prevalence of Depression in Parkinson’s disease

- up to 50% (major and minor depression or dysthymia)
- Rates of recurrence or treatment resistance unclear
- Anxiety disorders often co-occur

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004; Even 2012; Shakeri 2015; Ghaddar 2016; Reidel 2016
Objective: This study examined the association between physical disability and DSM-IV-TR depression status across six years.

Methods: 137 adults with idiopathic PD. A generalized linear mixed model with Northwestern Disability Scale score as dependent variable to determine the effect of baseline depression status on disability.

Results: 43 depressed at baseline vs 94 without depression. Symptomatic depression predicted greater disability compared to both never depressed ($p=0.0133$) and remitted depression ($p=0.0009$) after controlling for sex, education, dopamine agonist use, and motor fluctuations.
Longitudinal impact of depression on disability in PD (Pontone et al 2016)

Northwestern Disability Score by Visit

ND=never depressed, RD=remitted depression, SD=symptomatically depressed
## Antidepressant treatment for PD (Seppi K et al 2019)

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<thead>
<tr>
<th>Intervention strategy</th>
<th>Drug/Intervention</th>
<th>Efficacy</th>
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<th>Practice implications</th>
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<td><strong>Dopamine Agonists</strong></td>
<td>Pramipexole</td>
<td>Efficacious</td>
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<td>Pergolide</td>
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<td>Rotigotine</td>
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<td><strong>Monoamine oxidase B (MAO-B) inhibitors</strong></td>
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<td>Venlafaxine</td>
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<td><strong>Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors</strong></td>
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<td>Nefazodone</td>
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<td><strong>Alternative therapies</strong></td>
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APATHY IN PARKINSON’S DISEASE
Apathy in Parkinson’s disease

• May affect more than 1/3 of persons with PD
• Associated with more severe motor symptoms and cognitive impairment; more likely to be men and older age

Pagonabarraga et al 2015
Apathy vs depression in PD

Apathetic symptoms
- Reduced initiative
- Decreased participation in external activities unless engaged by another person
- Loss of interest in social events or everyday activities
- Decreased interest in starting new activities
- Decreased interest in the world around him or her
- Emotional indifference
- Diminished emotional reactivity
- Less affection than usual
- Lack of concern for others’ feelings or interests

Overlapping symptoms
- Psychomotor retardation
- Anhedonia
- Anergia
- Less physical activity than usual
- Decreased enthusiasm about usual interests

Emotional symptoms of depression
- Sadness
- Feelings of guilt
- Negative thoughts and feelings
- Helplessness
- Hopelessness
- Pessimism
- Self-criticism
- Anxiety
- Suicidal ideation

Pagonabarraga et al 2015
Management of apathy in PD

• Non-pharmacological interventions
  - scheduled activities (social and physical)
  - establish clear and achievable goals
  - rewards conditional on completion of goals
  - recruit social support for activities

• Dopamine agonists and acetylcholinesterase inhibitors (Seppi et al. 2019)
Impulse control disorders in Parkinson’s disease
Impulse control disorders (ICDs) in PD

• “An assortment of behaviors performed repetitively, excessively, and with a lack of self-control to an extent that interferes with life functioning”

• Associated with dopamine agonist medications and other dopamine replacement therapies
Impulse control disorders in PD

- Pathological gambling
- Compulsive buying/shopping
- Hypersexual behaviors
- Binge eating
Dopamine dysregulation syndrome

- Drug addiction-like state marked by self-medication with inappropriately high doses of dopaminergic medications
- May be more common in early onset PD and males—prevalence 3%-4%
- Co-occurs with ICDs, psychosis, panic attacks
Punding

• Repetitive, purposeless behaviors, characterized by an intense preoccupation with specific items or activities – collecting, arranging, or taking apart objects

• Hobbyism – higher level repetitive behaviors, e.g. excessive internet use, reading, art work, work on projects

Sean S O’Sullivan, Andrew H Evans and Andrew J Lees
Practical Neurology 2007;7;397-399
EXECUTIVE DYSFUNCTION: MENTAL AND PHYSICAL DISEASE INTERACTION IN PD
Executive Dysfunction

- Deficits in initiation, sequencing, planning, and set shifting; impaired mental speed (bradyphrenia)
- One of the earliest detectible cognitive changes

Emre et al 2003
Influence of Task Demands

“Let’s have tea!” Study (Rochester et al, Arch Phys Med Rehab, 2004)

- Looked at how attentional demands during an everyday functional activity contributes to functional performance and gait disturbances

Study

- 20 mild to moderate PD, 10 Controls
- 4 Tasks
  - Simple walking: Walk to kitchen
  - Dual-motor: Walk and carry tray
  - Dual-cognitive: Walk and recall a memory
  - Multiple motor-cognitive task: Walk, carry tray, and recall a memory

Results

- Increased task complexity → ↓ gait speed
Questions?