The Psychiatry of Parkinson’s Disease

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Goals of Presentation

• Provide overview of the neuropsychiatric symptoms and cognition in Parkinson’s disease (PD):
  – Presentation
  – Potential risk factors
  – Assessment
  – Management

• Recognize that non-motor symptoms currently may have the greatest impact on quality of life, function, and caregiver burden in PD
Potential Neuropsychiatric Symptoms in PD

- Depression and Anxiety
- Psychosis
- Impulse control disorders (ICDs)
- Cognitive changes
- Others
  - Disorders of sleep and wakefulness / fatigue (e.g., REM sleep behavior disorder [RBD])
  - Apathy (i.e., decreased motivation)
Caveats

• Many PD patients have no psychiatric or cognitive complications
• Psychiatric and cognitive complications are not the fault of and do not represent weakness in a patient
• PD patients in general cope extremely well given they have a chronic, progressive, and sometimes disabling disease
• The family members and caregivers of PD patients are in general remarkably supportive and understanding
Depression
The Robin Williams Effect

- Etiology of depression in PD
  - Psychological
    - Being diagnosed with chronic, progressive neurodegenerative disease is life-altering event
    - Additional challenges every step of the way
  - Biological
    - Brain regions and chemicals affected by PD also those responsible for mood regulation
    - Increased rates of depression prior to onset of motor symptoms, now called “prodromal PD”
- In reality the two are intricately linked and can’t be separated
Impact of Depression in PD

• ↑ disability and ↓ quality of life
  – Is as significant as severity of motor symptoms
• ↑ decline in motor and cognitive abilities
• ↓ time to onset of initiation of PD medications in early PD
• Associated with suicide and death ideation
  – However, suicide attempts / completion appear rare in PD
Complexity in Diagnosing Depression in PD

• Symptom overlap on 5 of 9 DSM-5 items
  – Sleep (hypersomnia and insomnia)
  – Appetite change / weight loss
  – Psychomotor changes (e.g., mental-physical slowing)
  – Fatigue
  – Changes in concentration and thinking

• Attribute symptoms to depression or PD?
  – Consensus recommendation is to count toward depression

• Emphasizing mood (as opposed to interest/pleasure) and cognitive symptoms of depression may be more specific
Recent Evidence for Depression Treatment in PD

• Recent positive studies for medications:
  – Tricyclic antidepressants (i.e., notriptyline)
  – SSRI (paroxetine)
  – SNRI (venlafaxine)
  – Dopamine agonist (pramipexole)

• Recent positive study for psychotherapy
  – Cognitive-behavioral therapy (CBT)
Good Antidepressant Tolerability

• SSRIs
  – Case literature in psychiatry of SSRIs causing parkinsonism (primarily tremor)
  – Recent venlafaxine and paroxetine study found both well tolerated from motor standpoint

• Combination with selective MAO-B inhibitors is controversial
  – Selegiline or rasagiline causing serotonin syndrome
  – Anecdotal experience is that this is extremely rare
    • <1% based on data from recent clinical trial
Anxiety Overview

- Most patients with anxiety disorder also have depression, and vice versa
- Anxiety often more disabling than depression
  - More psychologically and physically distressing
- Presentation
  - Generalized anxiety disorder (GAD)
    - One trigger can be mild cognitive changes
  - Social anxiety symptoms also common
    - Often related to embarrassment over PD symptoms
  - Anxiety attacks (i.e., panic attacks)
    - May be associated with fluctuations or “off” periods, now called non-motor fluctuations
Treatment

- No published treatment studies
- Newer antidepressants have anti-anxiety effects
- Sometimes need to use benzodiazepines
  - Lorazepam, alprazolam, clonazepam
  - Beware of (1) cognitive side effects, (2) sedation, and (3) changes in balance / gait
  - Start at low dosage
  - Can be as needed (“prn”) or scheduled
- Clinical experience that cognitive enhancing medications may improve anxiety in those with mild cognitive deficits
Psychosis
Presentation of Psychosis

- **Hallucinations**
  - Visual, but also auditory, olfactory and tactile
    - Illusions are misidentifications of actual stimulus
    - Also passage and presence phenomena

- **Delusions**
  - Subset of patients also experience delusions
    - Typically those with more severe cognitive impairment
    - Usually “paranoia” (persecutory ideation)
      - Spousal infidelity, intruders in house

- If severe can lead to institutionalization due to agitation, impaired sleep, caregiver burden
Complex Etiology

- Factors commonly associated with psychosis:
  - PD medications
  - Increasing severity of PD
  - Cognitive impairment
  - Increasing age
  - Visual impairment
  - Co-morbid psychiatric disorders
    - Including REM sleep behavior disorder (RBD)

- Likely complex interaction also involving 3 key brain chemicals
  - Dopamine, serotonin, acetylcholine
Clinical Management: PD Medications

- Expert opinion regarding propensity of PD medications to cause psychosis
  - Anticholinergics
  - Amantadine
  - Dopamine agonists
  - MAO-B inhibitors
  - Levodopa

Discontinue first
Discontinue last
Antipsychotic (AP) Treatment

• Balancing benefits (AP effects) and risks (worsening parkinsonism)
• Atypical APs
  – Quetiapine has been AP of choice (range 25-200 mg/day)
    • However all clinical trials negative or inconclusive
  – Clozapine
    • Shown to work at low doses (mean of 25-36 mg/day)
• Pimavanserin recently FDA-approved
  – Affects serotonin system but not dopamine, so less concern about worsening motor symptoms
  – Recent popular press (CNN) story raised concerns about elevated death risk
    • No clear scientific evidence of increased death risk in PD yet, although there is evidence for other existing APs used in PD
Impulse Control Disorders
Impulse Control Disorder
Presentation

• Compulsive gambling, sex, buying and eating behaviors
  – Frequent low stakes (slots, scratch cards), casinos
  – Demands on spouse, internet, prostitution, changes in sexual orientation
  – Purchasing same items repeatedly, hoarding
  – Cravings for certain foods (sweets), overnight eating

• Related behaviors
  – “Dopamine dysregulation syndrome” (DDS)
    • More like addiction (misuse and escalating dose of PD medications)
    • Occurs with levodopa or subcutaneous apomorphine typically
  – Hobbyism (more complex task preoccupation)
Frequency of Behaviors

- 15-20% of patients on dopamine agonist (DA)
- Adding in related behaviors then likely 20-25% patients over time
  - Compared with 7% of patients on levodopa only
- If 1 ICD present, >25% chance of ≥2 ICDs
- Symptoms may not present until years after initiating DA treatment
  - 1 study showed median time of onset 4-5 years
Associated Factors

• PD medications
  – DA treatment of any dose
  – Higher dose levodopa
  – Amantadine treatment
  – Rasagiline treatment?

• Younger age

• Sex
  – Male sex for sexual behaviors
  – Female sex for buying and eating

• Personal and family history of similar behaviors
Management

• Modify PD medications
  – Usually levodopa increased to offset DA decrease
  – Recognition of dopamine agonist withdrawal syndrome (DAWS)
    • Physical and mental symptoms of substance withdrawal
  – Preliminary evidence that long-acting oral or alternate delivery (patch) DAs may be associated with less ICDs

• Deep brain stimulation (DBS) when accompanied by PD medication decrease

• Psychiatric medications (antidepressants, antipsychotics)

• Opioid antagonist
  – Naltrexone study showed benefit on ICD rating scale

• Psychotherapy or counseling often crucial
Cognitive Changes
Definitions

- **Mild cognitive impairment (MCI)**
  1. Report of cognitive decline
  2. Impairment on neuropsychological testing
  3. Lack of *significant* functional impairment

- **Dementia**
  - Greater impairment on neuropsychological testing
    - Can be number of cognitive domains affected or severity of impairment
  - Clinically significant functional impairment

- **Related diseases**
  - Parkinson’s disease dementia and dementia with Lewy bodies (DLB) are different clinical syndromes
  - Don’t diagnose Alzheimer’s disease in patient with established Parkinson’s disease
Risk Factors for Cognitive Changes

- Increasing age
- Increasing severity of PD
- Male sex
- Less formal education
- “Atypical” PD features
  - Akinetic-rigid syndrome or postural instability gait difficulty (PIGD) subtype
- Deep brain stimulation (DBS)
  - Recent review identified mild decline on average in:
    - Executive functions (most notably word finding) and memory
  - Might be mix of surgical + stimulation effects
Cognitive Profile in PD: Multiple Domains Potentially Affected

- **Executive impairment**
  - Tasks that require planning, sequencing, adapting, problem solving, involve concepts
- **Attention impairment**
  - Reaction times and vigilance
  - Fluctuations
- **Visuospatial impairment**
  - Relationship of objects in space
- **Impaired memory (retrieval vs. encoding deficits)**
  - Retrieval more impaired than recognition (unlike AD)
  - Benefit from external cues or reminders
- **Language skills relatively less affected early on**
  - Word-finding problems are reported commonly
Montreal Cognitive Assessment (MoCA)

- Assesses range of cognitive domains
  - Attention/concentration (5 points)
  - Executive function (4 points)
  - Memory (5 points)
  - Language (6 points)
  - Visuospatial skills (4 points)
  - Orientation (6 points)
- Maximum possible score = 30 points
- Total score <24-26 suggests some cognitive impairment
Treatment: Cholinesterase Inhibitors & Memantine

- Cholinesterase inhibitors
  - Rivastigmine FDA-approved for PD dementia
  - Clinically meaningful improvement in only 20% of subjects (15% of placebo)
  - Well tolerated overall
    - Most significant side effects are nausea / vomiting, tremor
- Two recent memantine studies in mixture of patients with PDD and DLB
  - One partially positive and one negative study for PDD
  - Improvement in global impression and in attention and memory using computerized battery
What Else Can Be Done to Preserve Cognition?

- Cardiovascular exercise and good BMI
- Cognitive “exercise”
- Manage vascular risk factors
- Limit anticholinergic, benzodiazepine and opiate medication use
- Treat psychiatric symptoms
- Good night sleep (treat obstructive sleep apnea, RBD)
- Treat orthostatic hypotension
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