PARKINSON'S DISEASE

SPOTLIGHT ON PARKINSON'S DISEASE: WHAT'S NEW IN BRAIN HEALTH

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WELCOME AND INTRODUCTIONS

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PRESENTATION

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FINANCIAL DISCLOSURES

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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

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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)

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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**

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CAVEATS - II

- Having the illness or its treatments may have under-recognized **beneficial effects**
  - Potential mood or cognition benefits for dopamine agonists or monoamine oxidase inhibitors
  - Enhanced creativity for dopamine agonists
  - Greater understanding and appreciation of life and relationships
    - Perceiving positive consequences, such as personal growth, as a result of personally having PD or a spouse with PD is related to greater marital quality for both members of the marital dyad

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DEPRESSION

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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

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RISK FACTORS OR SYMPTOMS ACCOMPANYING DEPRESSION

- Higher frequency in females and those with cognitive impairment
- Impact of deep brain stimulation (DBS) unclear
  - Depression severity improves on average
  - Preliminary evidence GPi better than STN placement
- Model of 5 traditional depression risk factors classified 75% of depressed PD patients
  - Age, sex, prior depression history, family depression history, other medical conditions
  - PD-specific variables added little to the model

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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

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RECENT EVIDENCE FOR DEPRESSION TREATMENT IN PD

- Recent positive studies for medications:
  - Tricyclic antidepressants (i.e., nortriptyline)
  - SSRI (paroxetine)
  - SNRI (venlafaxine)
  - Dopamine agonist (pramipexole)
- Recent positive study for psychotherapy
  - Cognitive-behavioral therapy (CBT)

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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

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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**

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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

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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

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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

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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

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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

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IMPULSE CONTROL DISORDERS

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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)

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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

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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

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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

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COGNITIVE CHANGES

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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

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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

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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

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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

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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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OTHER DISORDERS

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APATHY

- Decrease initiation or engagement in activity, speech and emotion
  - Appears to be associated with cognitive impairment to frontal part of brain
- Often confused with depression
- No anti-apathy treatments, but stimulants and stimulating antidepressant (bupropion) used

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DAYTIME SLEEPINESS AND FATIGUE

- Thought to be distinct disorders
- Fatigue can be physical or mental
- Few treatment studies have been done
  - Stimulants and stimulating antidepressant (bupropion) are used clinically

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REM SLEEP BEHAVIOR DISORDER (RBD)

- Verbal & physical acting out of dreams during rapid eye movement (REM) phase of sleep
- Can be disruptive
  - Associated with daytime fatigue/sleepiness
  - Can be a burden to spouse
- Not to be confused with hallucinations
  - Hallucinations occur while awake, RBD while asleep
- Often treated with clonazepam at bedtime

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PSEUDOBULBAR AFFECT (PBA)

- Repeated, spontaneous, brief episodes of emotionality
  - Typically crying, can be laughing
- Not to be confused with depression
  - Not usually connected with underlying mood
- Treatment is typically antidepressants
- Combination of dextromethorphan and quinidine (Nuedexta®) is FDA-approved

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CONCLUSIONS

- PD is a motor disease in which neuropsychiatric symptoms (NPS) are increasing recognized as common and important
- Co-morbidity of NPS is common
- NPS associated with disease-related brain changes
- PD medications and treatments appear to have mixed effects
- Under-recognition and under-treatment of most disorders
- Still a need for new treatments for most disorders

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QUESTION & ANSWER

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CLOSING REMARKS

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