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The Psychiatric Symptoms of Parkinson’s Disease and its Treatments

July 20, 2017

Featured Speaker

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  - Assistant Professor of Neurology, Stony Brook University Hospital

Conflict of Interest & Disclosure Statements

Dr. Schwartz is a consultant for Allergan.

The other planners and presenters do not have any financial arrangements or affiliations with any commercial entities whose products, research or services may be discussed in this activity.

No commercial funding has been accepted for this activity

Thank You to Our Sponsors

- University at Albany School of Public Health
- New York State Department of Health
Learning Objectives

- Recognize the biologic underpinnings of psychiatric symptoms of Parkinson's disease;
- Identify at least three strategies to reduce the psychiatric adverse effects resulting from treatment for the disease; and
- Describe the impact on quality of life and caregiver burden resulting from the psychiatric symptoms of the disease.

Parkinson’s Disease Dementia (PDD)

- Spectrum from mild cognitive impairment, PDD, to Lewy body dementia
  - Non-demented patients 62% diagnosed with dementia at 5 years
  - 26% with dementia cumulative 70% at 8 years

Risk factors
- Older age
- Later disease onset
- More advanced disease and severity of motor symptoms

“Dysexecutive Syndrome”

Frontal subcortical dementia
- Executive function
- Attention
- Cognitive flexibility
- Planning sequential tasks
- Visuospatial processing

Cortical dementias (a-a-a)
- Amnesia
- Aphasia
- Agnosia

Frontal Lobe Executive Function
Testing & Circuitry
1. Digit span
2. Luria hand sequence test
3. Go-no-go task
4. Wisconsin card sorting
5. Verbal fluency tasks
6. Memory retrieval tasks

Lewy Body Dementia
Probable DLB – from DLB Consortium 4th Report
- Central features = 3 core features
- One core feature + one biomarker (dat-spect, PET, 123-I-MIBG, PSG)

Clinical criteria:
A. Central features (obligatory)
   - Progressive cognitive decline interfering with daily life
   - Prominent and persisting cognitive impairment
   - Deficits on testing for executive dysfunction, attention and visuospatial abilities

B. Core features
   - Recurrent visual hallucinations
   - Fluctuating cognition
   - REM-sleep behavior disorder
   - Parkinsonism

Rivastigmine for Dementia
NEJM Article- Rivastigmine for Dementia Associated with Parkinson’s Disease
- 410 individuals with PD
- Mild-moderate dementia
- Randomized placebo-controlled Rivastigmine 3 mg or 12 mg vs placebo
- 24 weeks follow-up
1. Alzheimer’s Disease Assessment Scale (ADAS-cog): memory, language, visuospatial and praxis function
2. Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)
PDP Semiology

Hallucinations of presence, visual illusions, hallucinations with retained insight, delusions (can be multi-modal including auditory and olfactory) and agitated delirium

- Short-lived (secs)
- Paroxysmal without clear triggers (initially can be hypnopompic)
- Vivid dreams may portend psychosis

Risk factors:
- Age
- Cognitive impairment
- Dopaminergic, amantadine and anticholinergic medications (esp. DA agonists)
- Hospital delirium

Visual Hallucinations

- Usually involve human images
- May be threatening, indifferent and invited or welcomed
- May take the form of non-human images
- May occur only when transferring from sleep state to waking, only at night or throughout the day and night
- Eventually can become malignant and associated with persecutory thoughts, suspiciousness, agitation, aggression, abnormal sexual behavior and confusion
- Patient may develop false beliefs of family members stealing and adulterous spouse, leading to accusatory behavior

Epidemiology of PDP

No reliable published incidence

Point prevalence:
- 33% → 55% in 6 years
- 23% → 56% in 4 years
- 21% → 77% in 20 years

Lifetime prevalence:
- 50% of 445 patients with PD who died

Period prevalence:
- 74% over 20 years
- 12% over 14 years

Tx of Drug-Induced Psychosis in PD

Low Dose (up to 50 mg/day) Clozapine

Randomized, double-blinded, placebo-controlled study of 60 patients, 4 weeks follow-up

- Visual hallucinations or delusions; and
- Impairment of communication and social problems

Primary Outcomes:
- Clinical Global Impression Scale (CGIS)
- Brief Psychiatric Rating Scale (BPRS)
- Scale for the Assessment of Positive Symptoms (SAPS)
- Mini Mental Status Exam (MMSE)

Low-Dose Clozapine for Tx of Drug-induced Psychosis in PD

<table>
<thead>
<tr>
<th>PRIMARY OUTCOME MEASURE</th>
<th>PLACEBO GROUP (N=27)</th>
<th>CLOZAPINE GROUP (N=27)</th>
<th>P VALUE</th>
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<tbody>
<tr>
<td></td>
<td>change in score</td>
<td>change in score</td>
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<tr>
<td>SAPS score</td>
<td>-3.8±1.9</td>
<td>-11.8±2.0</td>
<td>0.01</td>
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<tr>
<td>MMSE score</td>
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<td>0.0±0.5</td>
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Pimavanserin PD Psychosis

Phase 3 Trial Pimavanserin (5-HT2A selective serotonin inverse agonist) 40 mg/day
- 185 participants, 6 weeks

Primary endpoints:
- Blinded raters Scale for Assessment of Positive Symptoms (SAPS-PD)
- Clinical Global Impression (CGI)
SAPS-PD Improvement

![Graph showing SAPS-PD Improvement](image)

Cummings J. et al., *Lancet* 2014

### SAPS-PD Improvement

**Graph:**
- **Placebo:** 40 mg Pimavanserin
- **SAPS-PD Improvement Study:**
  - **Day:**
    - **Study Day:**
      - **Study Day 1:**
      - **Placebo:**
      - **40 mg Pimavanserin:**
      - **p=0.056**
      - **p=0.0014**

### Quetiapine for Agitation/Psychosis

- **Multi-center, double-blind, randomized, placebo-controlled parallel groups**
- **40 patients with DLB (23) vs PDD (9) vs AD with parkinsonism (8)**
- **Brief psychiatric rating scale (BPRS) primary endpoint**

Quetiapine is well-tolerated, does not worsen motor symptoms, but is not efficacious

### Negative Studies of Quetiapine in PDP

<table>
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<tr>
<th>First Author</th>
<th>N</th>
<th>max dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>Fernandez H.H. (2003)</td>
<td>78</td>
<td>600</td>
</tr>
<tr>
<td>Ballard C. (2005)</td>
<td>31</td>
<td>100</td>
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<tr>
<td>Rabey, J.M. (2007) *</td>
<td>58</td>
<td>175</td>
</tr>
<tr>
<td>Kurlan R. (2007) *</td>
<td>40</td>
<td>300</td>
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</table>

*controlled study

### PDP Treatment Paradigm

**Address risk factors:**
- When possible avoid DA (dopamine) agonists
- Reduce dopaminergic medications
- Monotherapy
- Treat inter-current infections and illnesses

**Pharmacotherapy:**
1. Clozapine
2. Pimavanserin
3. When possible avoid antipsychotics due to worsening of motor symptoms

### Dopaminergic Medications-induced Syndromes

**Hedonistic Homeostatic Dysregulation Syndrome:** compulsion and craving for dopaminergic drugs (prevalence 3.4%)

**Diagnostic Criteria:**
1. PD with levodopa response
2. Need for increasing dose beyond required
3. Pattern of pathological use (medications abuse, hording)
   - **Concurrent mood disorder:** depression, anxiety, euphoria, hypomania, **OR**
   - **Behavioral disorder:** pathological gambling, obsessive shopping, hyper-sexuality, aggression, social isolation, **OR** Alteration of perception of the ON state, walkabout, stereotypies

### Impulse Control Disorder

**Rerpetitive, maladaptive and disinhibited behavior in the face of awareness about harm to self and others**

**Typical Maladaptive Behavior:**
- Pathological gambling
- Hyper-sexuality
- Pyromania
- Compulsive eating
- Compulsive buying
- Kleptomania
- Trichotillomania
- Intermittent explosive behavior

**Prevalence of 14% in PD in comparison to 1% in general population**

**High correlation with use of dopamine agonists (esp. D3-R agonists)**
Punding
- Stereotyped behavior characterized by fascination with complex, repetitive, excessive and non-goal oriented behaviors
- Ego-syntonic with lack of awareness but can result in social isolation and caregiver effects
- Association with dopaminergic medications esp. DA-R agonists
- Can be a symptom of dementia, bipolar disorder and brainstem stroke

History of DBS Surgery
- Stereotactic surgery
- Minimally invasive surgical procedure
- Allows for targeting of brain structures using an x-y-z coordinates system
- Ernest Spiegel & Henry T. Wycis - 1947
  Leksell stereotactic frame
- Biopsy
- Stimulation*
- Implantation
- Epilepsy resection/lesioning
- Radiosurgery

Irwin’s Cooper’s Serendipitous Discovery
- Accidental ligation of the anterior choroidal artery resulted in treatment of tremor in a patient with Parkinson’s disease
- Pallidotomy and thalamotomy became first effective treatments for Parkinson’s disease until supplanted by levodopa in the 1960s
- Later recognized complications of levodopa paved the way for deep brain stimulation surgery in the 1990s

Mahlon DeLong’s
Cracking of the Basal Ganglia Code
- 1980s studied the basal ganglia discovering that the subthalamic neurons were overactive
- Ablation of the nucleus resulted in symptomatic improvement in a PD animal model

Post-DBS Psychiatric Complications
- Cognitive impairment
- Mania/hypomania
- Depression
- Psychosis
- Suicide – 0.9% attempted and 0.45% completed in first year – Highest during the first year – Post-op depression and impulse control disorder are risk factors

Case Report 1: Post-DBS Mania
- Female, 65 with previous unilateral thalamotomy
- Frontal executive dysfunction but no psychiatric symptoms
- DBS → improvement in motor functions
- DBS → hypomania
- Stimulation arrest → severe parkinsonism and deterioration of mood
- Clozapine 150 mg/day improved psychosis
- Adjunctive carbamazepine → affective symptoms disappeared
- Both medications tapered off after 3 months
- Subsequent toleration of increasing stimulation parameters
Case Report 2: Post-DBS Psychosis
- Male, 10-year history of PD & suboptimal response to dopaminergic meds
- Frontal-subcortical executive dysfunction
- Bilateral STN-DBS & implantable generators under anesthesia
- Day-3 post op presentation at ED with paranoid delusions
- Asymptomatic left thalamic hemorrhage; Quetiapine 150 mg/day prescribed & discharged while symptomatic
- DBS → marked improvement of motor symptoms
- Psychosis emerged at 18 days post DBS: frontal lobe-patter cognitive decline
- Clozapine 150 mg/day and venlafaxine 300 mg/day, then divalproex
- Some improvement but not to pre-op cognitive/emotional functioning

Neurophysiologic & Anatomic Considerations of Post-DBS Psychosis
- Neuropsychiatric symptoms from medial, ventral and anterior electrode placement
- Depression from left substantia nigra
- Left dorsal electrode placement associated with impaired verbal fluency
- Psychosis stimulation of pars reticulata of the substantia nigra

Dysthymic Disorders
- Depressive symptoms in 36-50% (in 30% premorbid)
- Minor depression and dysthymic disorder
  - Predominantly anxiety and (OFF) panic attacks
  - Anhedonia and chronic fatigue
Anatomic relevance:
- Mesolimbic dopamine projections
- Dorsal raphe serotonin

Treatment of Affective Symptoms
Positive studies:
- Nortriptyline 25-150 mg/day controlled study
- Paroxetine 20 mg/day
Inconclusive studies:
- Sertraline
- Transcranial magnetic stimulation
- Electroconvulsive therapy
Serotonin syndrome/tyramine phenomenon with MAOI:
- Extremely rare drug-drug interact. with SSRIs and SNRIs (venlafaxine)
- No safety warnings with food or anesthetics

In Conclusion
Affective disorders
- Recognize higher incidence in PD
- Optimize treatment of motor symptoms
- Use best clinical practice for treatment of depression
Medication-induced psychiatric adverse effects
- Stratify risk
- Avoid dopamine agonists when possible
- Role for DBS as means of reducing medications use

In Conclusion
Psychosis
- Reduce anti-parkinsonian medications when possible
- Seek reversible causes of delirium
- Pimavanserin >> clozapine
DBS psychiatric complications
- Vigilance of symptoms at around time of micro-lesion period
- Use proven antipsychotics but also role for mood stabilizers/AEDs
Dementia
- Recognize as important milestone in disease and counsel accordingly
- Role for rivastigmine
American Parkinson Disease Association

APDA National Network
- Chapters and Information & Referral Centers
- National Research Program and Centers for Advanced Research
- Support Groups and Wellness Programs
- Webinar Series
- Educational Literature
- Educational Symposia

www.apdaparkinson.org 800-223-2732

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