EMORY UNIVERSITY | Jean and Paul Amos Parkinson's Disease and Movement Disorders Program

Making Strides in Movement

VIRTUAL SYMPOSIUM

Parkinson's Disease for the Clinician
SATURDAY, SEPTEMBER 26, 2020 • 8:30 AM–12:10 PM

Hyperkinetic Movement Disorders for the Clinician
SATURDAY, OCTOBER 3, 2020 • 8:30 AM–12:10 PM
Motor Features of Parkinson’s Disease

Stewart A. Factor, DO
Disclosures

• Honoraria: Lundbeck, Sunovion, Biogen, Acadia, Impel, Acorda, CereSpir.

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• Royalties: Demos, Blackwell Futura, Springer for textbooks, Uptodate

• Other Bracket Global LLC, CNS Ratings LLC
PD defined pathologically by loss of pigmented dopaminergic cells in the substantia nigra and the presence of Lewy bodies.
PD Epidemiology

- ~1 million with PD in US
- Annual Incidence High income countries (Hirtz 2007):
  - 14 per 100,000 total population
  - 160 per 100,000 population over 65 years of age
- Lifetime risk: 2% for men, 1.3% women for individuals age >40 in the US (Elbaz et al 2002)
- Age adjusted prevalence (reflects incidence & mortality) Europe & Americas & Asia > Africa
- Male: Female 1.3-2 most countries

Ascherio Lancet Neurology 2017
The Emerging Evidence of the Parkinson Pandemic

Key factors:
- Aging
- Longevity
- Decreased smoking
- Increased industrialization
- Increases with Socio-demographic Index

E. Ray Dorsey, Todd Sherer, Michael S. Okun and Bastiaan R. Bloem

Fig. 2. Projected global burden of Parkinson disease accounting for changes in aging, longevity, smoking rates, and industrialization, 1990–2040.
Parkinson’s Disease
Age of Onset (N=671)

Average age of onset 55-60
Parkinson’s Disease: Cardinal Motor Features

• Early
  • Postural change
  • Resting Tremor
  • Muscle rigidity with cogwheeling
  • Bradykinesia/Akinesia

• Late
  • Gait disorder (festination) and postural change
  • Postural instability
  • Freezing
Postural Change

• Flexed posture

Sculpture of a PD patient by Paul Richter 1892
From Tyler 1987
Tremor

Involuntary rhythmic oscillating movement that results from the alternating or synchronous contraction of reciprocally innervated antagonist muscles.
TYPES OF TREMOR

➢ Resting (Static) Parkinsonian

➢ Postural (Static, Action) Essential tremor

➢ Kinetic (Action, Intention) Cerebellar/ET
Facial Tremor

Parkinson’s disease

Essential Tremor
Parkinsonian Tremor
PD Tremor
Essential Tremor
Rigidity

• Increase in resistance to passive movement
• “Lead-pipe”
• “Cogwheel”
• Patients may complain of stiffness but not a major source of disability
Akinesia/ Bradykinesia

- Slowness, fatiguing, arrests in on-going movement
- Decreased amplitude of movement (Decrement)
- Absence of movement
- Interferes with all activities
- One of the most disabling features of parkinsonism
- Results in many additional features and complaints
Parkinson’s disease: Bradykinesia
Bradykinesia
Postural Instability & Gait Disturbances

• Postural instability – retropulsion, propulsion, falls (en bloc) - pull test
• Shuffling, lack of arm swing, Flexion posture
• Festination
• Freezing – turns, start hesitation, enclosures, role of visual cues, falls
Parkinson’s Disease: Gait Disorder

Early

Advanced
Parkinson’s disease: Festination
Parkinson’s disease: Gait Freezing
Postural Instability
Parkinson’s Disease
Other Motor Features

• Masked face
• Micrographia
• Low voice volume
• Drooling
• Dysphagia (late)
• Asymmetry
Facial expression
Dr. Facter

Medicare has denied all of the cost of my visit with you on 2/12/87. If I submit these to my private insurer they will need a copy of your bill. Will you obtain one and send it to me please.

William Weiner, M.D.
University of Miami
Miami, Florida

Dear Dr. Weiner:

Dr. Mark Hallock suggested I write to you concerning a national multi-center trial for depression. I would be interested in participating in such a trial and would be willing to do some travelling if necessary.

I am 53 and have had symptoms of mild depressive behavior for about 4 years and a half. I was started on imipramine at the Mayo Clinic but was only able to take it for 3 months before having a reaction. I am now taking chlordiazepoxide for mild hypotension which may be helping the depression. I am otherwise in good health.

Yours very truly yours, 

Lawrence.
PARKINSON’S DISEASE
TYPE OF ONSET (N=100)

- Asymmetric 70%
- Symmetric 29%

- Upper limb in isolation 58%
- Upper limb with lower limb 29%

- Tremor 68%
- Tremor alone 41%
- Tremor with bradykinesia or rigidity 27%
- Bradykinesia / rigidity 30%

EARLY SYMPTOMS OF PD (N=140)

- Unilateral tremor 74%
- Clumsiness or difficulty with dexterity 27%
- Handwriting difficulties (micrographia) 26%
- Slowness 19%
- Shuffling gait 15%
- Dragging one leg 11%
- Stooping of posture 10%
- Muscle stiffness 10%
- Flexed, adducted arm 9%
- Weakness 9%

Mean duration of symptoms prior to evaluation 14.2 months (range 1-60)
Parkinson’s Disease
Motor Fluctuations & Dyskinesia - Frequency

• Ahlskog & Muenter 2001 Mov Disord
  • Literature review modern studies
    » Differences in early vs modern studies were duration of disease and dosing
• 4-6 yr estimates: dyskinesia & fluctuations ~40%
• 10% per year
Motor Fluctuations & Dyskinesia

- Type of dyskinesia: Chorea, dystonia, ballism, stereotypy, myoclonus.

- What fluctuates?
  - motor
  - sensory (pain, akathisia, internal tremor)
  - Autonomic (sweating, hypotension)
  - psychiatric (Panic disorder)
Motor Fluctuations

- **Patterns of fluctuations:**
  - Wearing-off effect
  - Complicated wearing-off
  - Delayed-on
  - No-on (dose failures)
  - On-off phenomenon
  - Yo-yoing

- **Patterns of dyskinesia:**
  - Peak dose dyskinesia
  - Diphasic dyskinesia
  - Square wave dyskinesia
  - Early morning dystonia
  - Off-period dystonia
Dyskinesia
Severe Dyskinesia
Ballism
“Off” & “On” in Parkinson’s disease
Diagnosis of PD

• Clinical; No biomarkers

• Conventional Criteria:
  • 2 of 3 (or 4) of the cardinal features of PD
  • No historical aspects that suggest other causes (neuroleptic use, abrupt onset)
  • No signs on exam suggesting other parkinsonian syndromes (early dementia, early falls, eye movement abnormalities, autonomic failure)
  • Low specificity, high false positive rate
United Kingdom Brain Bank Diagnostic Criteria

- Diagnosis of Parkinsonism
  - Bradykinesia
  - At least 1 of these
    - Rigidity
    - 4-6 Hz rest tremor
    - Postural instability

- Supportive criteria
  - Unilateral onset
  - Rest tremor
  - Progressive disorder
  - Persistent asymmetry
  - Excellent response to LD
  - LD induced dyskinesia
  - LD response > 5 yrs

Exclusion Criteria

- History of stroke
- History of repeated head injury
- History of encephalitis
- Oculogyric crisis
- Neuroleptic therapy
- Sustained remission
- Unilateral features for >3 yrs
- Supranuclear gaze palsy
- Cerebellar signs
- Early autonomic failure
- Early severe dementia
- Babinski sign
- Tumor or hydrocephalous
- No response to Levodopa

Hughes et al JNNP 1992
Clinically established/probable PD

1) Presence of parkinsonism
   ▪ Bradykinesia plus either
     ▪ Rest tremor OR
     ▪ Rigidity

2) Absence of “Absolute Exclusionary Criteria”
   ▪ Lack of observable response to levodopa
   ▪ Recent exposure to DA blocking agent
   ▪ Cerebellar signs
   ▪ Vertical supranuclear ophthalmoplegia (down gaze)
   ▪ Cortical sensory loss, apraxia, aphasia, etc.
   ▪ Normal functional imaging of presynaptic DA transporter
   ▪ Other
3) Supportive criteria
- Clear and dramatic response to DA therapy
- Rest tremor
- Levodopa-induced dyskinesia
- Olfactory loss or cardiac sympathetic denervation

4) No - red flags
- Rapid progression
- Early bulbar dysfunction
- Early falls
- Early autonomic failure
- Absence of non-motor features
  - Autonomic
  - Sleep
  - Neuropsychiatric
  - Hyposmia
- Others
Forest plot: Pooled accuracy of studies

Figure 2. The data from the studies using pathologic examination as gold standard are highlighted in gray. *Excluding the single community-based study, Bower et al., 30 pooled accuracy for the clinic-based studies using pathologic examination as gold standard was 81.4% (95% credible interval [CrI] 76.5%-85.7%), with 86.4% (95% CrI 76.5%-85.7%) for refined clinical diagnosis by experts. UKPDSBRC = United Kingdom PD Society Brain Research Center.
Low clinical diagnostic accuracy of early vs advanced Parkinson disease
Clinicopathologic study

Charles H. Adler, MD, PhD
Thomas G. Beach, MD, PhD
Joseph G. Henrzi, MS
Holly A. Shill, MD
John N. Caviness, MD
Erika Driver-Dunckley, MD
Marwan N. Sabbagh, MD
Lucia I. Sue
Sandra A. Jacobson, MD
Christine M. Belden, PhD
Brittany N. Dugger, PhD

ABSTRACT

Objectives: Determine diagnostic accuracy of a clinical diagnosis of Parkinson disease (PD) using neuropathologic diagnosis as the gold standard.

Methods: Data from the Arizona Study of Aging and Neurodegenerative Disorders were used to determine the predictive value of a clinical PD diagnosis, using 2 clinical diagnostic confidence levels, PossPD (never treated or not clearly responsive) and ProbPD (responsive to medications). Neuropathologic diagnosis was the gold standard.

Results: Based on first visit, 9 of 34 (26%) PossPD cases had neuropathologically confirmed PD while 80 of 97 (82%) ProbPD cases had confirmed PD, PD was confirmed in 8 of 15 (53%) ProbPD cases with <5 years of disease duration and 72 of 82 (88%) with ≥5 years of disease duration. Using final diagnosis at time of death, 91 of 107 (85%) ProbPD cases had confirmed PD. Clinical variables that improved diagnostic accuracy were medication response, motor fluctuations, dyskinesias, and hyposmia.

Conclusions: Using neuropathologic findings of PD as the gold standard, this study establishes the novel findings of only 26% accuracy for a clinical diagnosis of PD in untreated or not clearly responsive subjects, 53% accuracy in early PD responsive to medication (<5 years' duration), and >85% diagnostic accuracy of longer duration, medication-responsive PD. Caution is needed when interpreting clinical studies of PD, especially studies of early disease that do not have autopsy confirmation. The need for a tissue or other diagnostic biomarker is reinforced.

Classification of evidence: This study provides Class II evidence that a clinical diagnosis of PD identifies patients who will have pathologically confirmed PD with a sensitivity of 88% and specificity of 68%. Neurology® 2014;83:1–7
### PPV for ProbPD Divided by Disease Duration at First Visit

<table>
<thead>
<tr>
<th></th>
<th>ProbPD</th>
<th>ProbPD &lt;5 y</th>
<th>ProbPD ≥5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>97</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>Female</td>
<td>32 (33%)</td>
<td>4 (27%)</td>
<td>28 (34%)</td>
</tr>
<tr>
<td>Age at Visit</td>
<td>76.8 (7.5)</td>
<td>78.4 (6.7)</td>
<td>76.6 (7.7)</td>
</tr>
<tr>
<td>Age at Death</td>
<td>80.6 (7.0)</td>
<td>82.4 (6.0)</td>
<td>80.3 (7.1)</td>
</tr>
<tr>
<td>Duration of PD Symptoms at Visit</td>
<td>11.0 (6.6)</td>
<td>2.4 (1.2)</td>
<td>12.6 (6.0)</td>
</tr>
<tr>
<td>Duration of PD Symptoms at Death</td>
<td>14.8 (6.9)</td>
<td>6.4 (3.4)</td>
<td>16.3 (6.3)</td>
</tr>
<tr>
<td>Neuropathologically Confirmed PD</td>
<td>80 (82%)</td>
<td>8 (53%)</td>
<td>72 (88%)</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>73% to 89%</td>
<td>27% to 79%</td>
<td>79% to 94%</td>
</tr>
</tbody>
</table>
Role of DaTscan

• Indication of DaTscan: *clinically uncertain cases* (10% of parkinsonism cases)
  • Essential and other non-PD tremors
  • Dystonic tremor: rest tremor (pill rolling), jaw tremor, hypomimia, decreased arm swing
  • Mixed tremor, multiple diagnoses, multiple neurologists
  • Atypical tremor – postural or action with gait disorder
  • Long term ET followed by development of rest tremor
  • Dopa responsive dystonia
  • Drug-induced parkinsonism and tremor
  • Psychogenic parkinsonism
  • Gait disorders of unclear etiology
  • Young patients (under 40)
  • Isolated slowness
  • Camptocormia
  • Does not differentiate PD from atypical parkinsonism
Christine Esper, MD

Motor Treatment of Parkinson’s Disease

Parkinson’s Disease for the Clinician Virtual Symposium

September 26, 2020
LECTURE OUTLINE

GOALS OF THERAPY
EARLY PARKINSON’S DISEASE TREATMENT
MODERATE/ADVANCED PARKINSON’S DISEASE TREATMENT
EMPHASIS ON NEWER DRUGS
JAMES PARKINSON (1817)

AN ESSAY ON THE SHAKING PALSY.

CHAPTER I. DEFINITION—HISTORY—IllustrATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.
PD - MANAGEMENT

Diagnostic assessment

Motor symptoms
- Tremor
- Bradykinesia
- Rigidity
- Gait impairment

Non-motor
- Autonomic dysfunction
- Sleep disorders
- Skin disorders
- Deconditioning

Affective
- Anxiety
- Depression
- Apathy
- Psychosis

Cognitive
- Neuropsychological deficits
- Intention deficits
- Dementia
- Delirium, agitation
PD - TREATMENT

- Dopamine replacement
  - Carbidopa/Levodopa (Sinemet®)
  - Rytary
- Amantadine IR & ER
- Anti-cholinergics
- Dopamine agonists
  - Pramipexole (Mirapex®)
  - Ropinirole (Requip®)
  - Rotigotine
  - Apomorphine
- COMT inhibitors
  - Entacapone (Comtan®)
  - Tolcapone
  - Opicapone
- Istradefylline
- MAO inhibitors
  - Selegiline
  - Rasagiline
  - Safinamide
GOALS OF THERAPY

• Some patients are just looking for reassurance and a confirmation of the diagnosis
• Control symptoms and maintain QOL
• Minimize drug-induced motor complications
• Ameliorate or eliminate established motor complications
COMMON CAUSES OF TX FAILURE

– Wrong diagnosis
– Homeopathic dose of dopaminergic meds
– Drug-induced parkinsonism
– L-Dopa or other med complications
– Progressive cognitive decline
– Significant depression, stress/anxiety
– Disease progression - surgical candidate?
PD – WHEN TO START TX?

• The decision to initiate symptomatic medical therapy depends on the degree in which the symptoms are interfering with everyday activities.

• Factors to consider:
  – Effect of disease on dominant hand
  – How much the symptoms interfere with work, hobbies, or social activities.

• Patients with very mild symptoms do not necessarily need to start therapy if not interfering with QOL and prefer to avoid med side effects.

• Age considerations: <50 y/o, 50-65 y/o, vs. >65 y/o
SHOULD WE START THERAPY IMMEDIATELY?

• Theory: dopamine replacement therapy “normalizes” unstable basal ganglia and may help reduce metabolic stress on surviving dopaminergic neurons
  – 1993 DATATOP: “Effects of tocopherol and deprenyl on the progression of disability in Parkinson’s Disease”
  – 2002/2004 “A Controlled Trial of Rasagiline in Early Parkinson Disease: the TEMPO Study”
  – 2004 ELLDOPA “Levodopa and the Progression of Parkinson’s Disease”

• These studies used various dopaminergic agents in patients with early PD and demonstrated that those who were treated vs. placebo were better off, even when the treatment stopped.

PD – SITES OF ACTION OF DRUGS

Substantia Nigra
- Levodopa Rytary
- Levodopa IR & ER

BBB
- Dopamine
- Levodopa
- 3-OMD
- Carbidopa
- DDC
- COMT

DDC
- dopamine
- levodopa
- 3-OMD

STN
- Amantadine
- NMDA antagonists

DA
- GABA
- ACh

Striatum
- Selegiline
- Rasagiline
- Safinamide
- Amantadine

Dopamine agonists:
- Pramipexole
- Ropinirol
- Rotigotin
- Apomorphine
- Amantadine
- NMDA antagonists
- Trihexiphenidyl
- Glatamate

GP

STN

BBB
EARLY PD TX

• MAO-B inhibitors: selegiline, rasagiline
  • Selectively inhibits MAO type B, increasing extracellular dopamine in the striatum
  • Given 1-2x/day
  • Generally well tolerated
  • Relatively low potency in terms of dopaminergic effects
  • Selegiline, Rasagiline – they have not been directly compared with each other

• Amantadine:
  • Mechanism of action uncertain: known to increase dopamine release, inhibit dopamine reuptake, stimulate dopamine receptors, and has NMDA receptor antagonist properties that may account for its therapeutic effect by interfering w excess glutamate neurotransmission in the BG
  • Low-potency antiparkinson tx for PD pts w mild symptoms, esp. if tremor is prominent
  • Benefit induced by Amantadine is transient in some pts and often limited to 1-2 years
  • Available in IR and ER (Gocovri) formulations. IR and ER formulations seem to be similarly effective; ER more expensive.
EARLY PD TX - TRIHEXYPHENIDYL

• Tremor-predominant disease
  – In PD, dopamine depletion produces a state of cholinergic sensitivity so anticholinergic drugs can improve parkinsonian sx’s
  – May be helpful for PD pts with isolated tremor without significant bradykinesia or gait impairment
  – Although these pts may consider a DA or L-Dopa for tx, some younger pts may benefit from initial therapy with an anticholinergic alone

• Trihexyphenidyl
  – 0.5 mg – 1 mg bid, w gradual increase to 2 mg tid as tolerated
  – Watch for side effects! Cognitive impairment, constipation, urinary retention
  – Reserve for younger patients due to s/e profile
Monoamine Oxidase Type B Inhibitors In Early Parkinson's Disease: Meta-Analysis Of 17 Randomised Trials Involving 3525 Patients

Author(s): Natalie J. Ives, Rebecca L. Stowe, Joanna Marro, Carl Counsell, Angus Macleod, Carl E. Clarke, Richard Gray and Keith Wheatley

Source: BMJ: British Medical Journal, Vol. 329, No. 7466 (Sep. 11, 2004), pp. 593-596

- Tx with MAO-B inhibitors led to:
  - Small but statistically significant improvements in UPDRS motor scores at 1 years (mean difference 3.8 points)
  - Reduction in the need for L-Dopa at 1 year
  - Reduction in the development of motor fluctuations
Motor sx’s begin to interfere with QOL: DA vs. L-Dopa is indicated
Factors to consider: age, severity of sx’s
Age ≤ 65 years: DA vs. L-Dopa
  – L-Dopa is more effective than DAs for reduction of motor sx’s, but more frequently produces dyskinesias than DAs, especially in younger pts
  – When given alone, DAs rarely cause dyskinesias, and some are available in once-daily formulations
  – DAs produce more frequent non-motor s/e (e.g. somnolence, peripheral edema, nausea, impulse control d/o) than L-Dopa
While some pts may choose to start w DA for convenience, esp if sx’s mild, other may choose L-Dopa for its greater antiparkinson potency and better tolerability.
PD – SITES OF ACTION OF DRUGS

**Substantia Nigra**
- Levodopa
- Rytary
- Levodopa IR & ER

**DDC**
- Carbidopa

**COMT**
- Tolcapone
- Entacapone
- Opicapone

**DA**
- Dopamine
- Levodopa
- 3-OMD

**Striatum**
- Selegiline
- Rasagiline
- Safinamide

**GABA**
- Dopamine agonists:
  - Pramipexole
  - Ropinirole
  - Rotigotine
  - Apomorphine
  - Trihexiphenidyl
  - Benztpine

**NMDA antagonists**
- Amantadine

**Glutamate**
- STN

**BBB**
- dopamine

**GP**
- dopamine

**STN**
- levodopa

**3-OMD**

- 29 trials (5247 pts) with early PD in which a DA w or wo L-Dopa was compared with placebo, L-Dopa, or both.
- DA reduce motor sx’s, although symptomatic control was better w L-Dopa in most trials that compared them directly
- Pts assigned to a DA were less likely to develop dyskinesias, dystonia, and motor fluctuations, but more likely to develop non-motor s/e including edema, somnolence, hallucinations, and nausea.
PD TX: DOPAMINE AGONISTS

• The few studies that have compared the efficacy of various DAs with each other have found no significant difference or only mild differences.
• Choice is based on: formulation, dosing frequency, and cost
• Oral DAs:
  – Pramipexole: IR and ER
    • IR: start @ 0.125 mg tid, increase gradually by 0.125 mg/dose over 5-7 days
    • ER: start @ 0.375 mg qhs and titrate by 0.375 mg increments q 5-7 days for goal of 1.5-4.5 mg
    • Need to adjust dose for renal insufficiency; no ER with CR Cl <30
  – Ropinirole: IR and ER
    • IR: start @ 0.25 mg tid, increase gradually by 0.25 mg/dose qweek x 4 wks for total 3mg/day. After week 4, may increase qweek by 1.5 mg up to max of 24 mg/day.
    • ER: start @ 2 mg qhs and titrate by 2 mg increments q 5-7 days, up to max 24
• Transdermal DA – Rotigotine
  – Once daily patch, start at 2mg/24 hrs and titrated qweek by 2mg/24 hr increments to a dose of 6mg/24 hrs
• Injection DA – Apomorphine (to be discussed in motor fluctuations)
Levodopa Therapy Impact on Parkinson’s Disease

“...nothing less than a therapeutic revolution. Profoundly rigid and bradykinetic patients who were confined to beds and chairs could suddenly get up and walk. Wheelchairs and stretchers vanished from the Parkinson’s disease clinic almost overnight.”

Duvoisi
Ann Neurol 1987
L-DOPA

• Age ≥ 65
  – DA not as well tolerated in older population
  – Use when MAO-B is inadequate to control sx’s
  – 65 years is a somewhat arbitrary cut-off: consider cognitive state/health status as well as severity of motor sx’s

• Also consider for younger PD pts who prefer as initial tx or are intolerant to DA or no longer receiving benefit

• Side effects: dyskinesias, orthostatic hypotension, nausea, hallucinations/confusion
L-DOPA

- Most effective drug for symptomatic tx of PD
- Superior effects on motor fctn, ADLs, and QOL compared with other drugs and classes.
- Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor (carbidopa)
- Although L-Dopa is associated w a higher risk of dyskinesias than DAs, there is increasing evidence that the choice of initial tx (L-Dopa, DA, MAO-B) has little impact on the long-term outcome of PD w/r/t motor fluctuations and dyskinesias.
L-DOPA IR vs. CR

L-DOPA IR:
• Tx should begin with small doses of IR L-dopa, such as Sinemet 25/100 ½ tab 2-3x/day with meals
• Watch for s/e; take with meals initially to minimize nausea. For more advanced dz, more effective if taking 30 min before or 1 hour after a meal to improve GI absorption.
• Complete lack of response up to 1000–1500 mg/qd suggests an incorrect diagnosis or tremor-predominant subset

L-DOPA CR:
• CR tablets are less completely absorbed and require a dose up to 30% higher to achieve the same clinical effect.
• Not recommended as initial tx. Peak clinical effect of each CR tab is usually less than for IR tabs, as CR tabs reach the brain more slowly. This makes it more difficult to assess a response in a pt just initiating tx.
• Sinemet IR half-life: 0.75-1.5 hr; Sinemet CR half-life: 1.5h-2h. Half-life may be prolonged due to continuous absorption.
• The use of CR tabs does not necessarily offer any long-term advantage in terms of motor fluctuations.
DISEASE PROGRESSION

• Motor fluctuations
  – Up to 50% of patients after 5 years of treatment
  – 70% of patients after 15 years of treatment
  – End-of-dose “wearing off” phenomenon
  – Unpredictable “on-off” fluctuations

• Dyskinesias
  – Peak dose or biphasic
  – Not all symptoms are responsive: imbalance, dementia, autonomic dysfctn, tremor in a subset (some tremor pred)

• Neuropsychiatric disturbances: hallucinations, psychosis, confusion

L-DOPA AND PROGRESSION OF PD

- **Early PD**
  - Long duration motor response
  - Low incidence of dyskinesias

- **Moderate PD**
  - Shorter duration motor response
  - Increased incidence of dyskinesias

- **Advanced PD**
  - Short duration motor response
  - “On” time consistently associated with dyskinesias

MOTOR FLUCTUATIONS
TREATMENT GUIDELINES

- Individualize therapy with any number of medications.
- Keep the regimen as simple as possible for better compliance.
- Make the response as predictable as possible.
- Goal: Reduce off time, avoid psychosis & minimize dyskinesia.
- Alterations of medications should be gradual; make one change at a time.
- Take Levodopa on an empty stomach and control protein intake.

Factor SA Neurotherapeutics 2008
FLUCTUATION THERAPY
CURRENTLY AVAILABLE, NEWER OPTIONS

Wearing off

• New formulations of CD/LD
  – *Rytary*
  – *Inbrija*

• Dopamine agonists
  – Pramipexole
  – Ropinirole
  – Rotigotine patch
  – Apomorphine injectable (‘rescue’)  
    – *Apomorphine sl (FDA approval 5/2020)*

• COMT inhibitors
  – Tolcapone
  – Entacapone
  – Carbidopa/levodopa/entacapone (Stalevo®)
  – *Opicapone (FDA approval 4/24/20)*

• Monoamine Oxidase Inhibitors
  – Selegiline
  – Rasagiline
  – *Safinamide (Xadago)*

With Dyskinesia

• Amantadine
  – *Gocovri*
  – *Osmolex ER*

• Other
  – *Istradefylline (Nourianz)*
The ER capsule contains IR and ER beads of CD/LD that are absorbed in the GI tract at different rates. ER capsules reach an initial peak of 1 hr, very similar to IR tabs, and the peak is sustained for 4-5 hrs, following by a gradual “wearing off” over 6+ hrs.
Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson’s disease and motor fluctuations: a phase 3 randomised, double-blind trial

Robert A Hauser, Ann Hsu, Sheron Kell, Alberto J Espay, Kapil Sethi, Mark Stacy, William Ondo, Martin O’Connell, Suned Gupta, for the IPX066 ADVANCE-PD investigators

Lancet Neurology 2013

Rytary vs. Sinemet in PD w motor fluctuations

- 1.17 hour reduction in off time with Rytary vs. CD/LD IR
- 3.6 v 5 doses per day
- Patients still had 4h OFF time per day
- Rytary dose ~2x CD/LD IR
- No increase in ON time with troublesome dyskinesias
- Safety profile comparable to IR
- Expensive: can be >$3/capsule
## SINEMET IR TO RYTARY CONVERSION

Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY

<table>
<thead>
<tr>
<th>Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa</th>
<th>Recommended Starting Dosage of RYTARY</th>
<th>RYTARY Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg to 549 mg</td>
<td>855 mg</td>
<td>3 capsules RYTARY 23.75 mg / 95 mg taken TID^a</td>
</tr>
<tr>
<td>550 mg to 749 mg</td>
<td>1140 mg</td>
<td>4 capsules RYTARY 23.75 mg / 95 mg taken TID</td>
</tr>
<tr>
<td>750 mg to 949 mg</td>
<td>1305 mg</td>
<td>3 capsules RYTARY 36.25 mg / 145 mg taken TID</td>
</tr>
<tr>
<td>950 mg to 1249 mg</td>
<td>1755 mg</td>
<td>3 capsules RYTARY 48.75 mg / 195 mg taken TID</td>
</tr>
<tr>
<td>Equal to or greater than 1250 mg</td>
<td>2340 mg or 2205 mg</td>
<td>4 capsules RYTARY 48.75 mg / 195 mg taken TID or 3 capsules RYTARY 61.25 mg / 245 mg taken TID</td>
</tr>
</tbody>
</table>

^a TID: three times a day

Reference: Parkinson’s Foundation
INBRIJA (INHALED L-DOPA)

• LD inhalation encapsulated powder formulated for pulmonary absorption
• Fine-particle dose: quantity of LD estimated to reach the lungs
• On time in 5 minutes & improvements persisted through assessments at 90 minutes.
• Plasma LD concentrations increase more rapidly and with less variability than observed after oral LD dosing

FDA Approval early 2019
INBRIJA (INHALED L-DOPA)

Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled phase 3 trial

Lancet Neurol 2019;18: 145-54

Peter A LeWitt, Robert A Hauser, Rajesh Pahwa, Stuart H Isaacs, Hubert H Fernandez, Mark Lew, Marie Saint-Hilaire, Emmanuelle Pourcher, Lydia Lopez-Manzanares, Cheryl Waters, Monika Rudzinska, Alexander Sedkov, Richard Batycky, Charles Oh, on behalf of the SPAN-PD Study Investigators

- CVT-301 delivered by oral inhalation, as an as-needed adjunct therapy to a daily CD/LD regimen, for treatment of off periods in PD patients.
- Daily off periods of ≥2 h, improvement of ≥25% on UPDRS motor in a LD challenge.
- Each study dose consisted of two capsules administered with an inhaler.
- Self-administer up to five doses per day.
INBRIJA (INHALED L-DOPA)

- One dose (84 mg) = two 42-mg capsules
  - For oral inhalation only
- No more than 1 dose per OFF period
- May be taken prn up to a max of 5x/day
  - Average number of doses: ~ 2/day
- Effective only in combination w CD/LD
**APOMORPHINE RESCUE THERAPY**

- Apomorphine sc inj – approved in 2004
- Apomorphine sl (Kynmobi) – FDA approval in 5/2020
- Dopamine agonist with other properties
  - D1-D5: pre- and post-synaptic
  - Adrenergic: 1D, 2B, 2C
  - Serotonin: 5HT1A,2A,2B,2C
- Subq injection: 0.2-0.6 ml SC prn
- Fast acting: 7.5-10 min
- Short duration of action: up to 120 min
- Consistent response: rare dose failures
- Similar response to L-dopa
- Pre-tx w anti-emetic x 3 days before initiating
- Long-term consistent effect
- Less psychosis than po DA

[Image: apokyn.com]
APOMORPHINE RESCUE THERAPY

At 20 min, mean UPDRS scores were reduced by 24.2 points in Apokyn-tx’d group vs. 7.4 points with placebo

In clinical trials, Apokyn reversed 95% of off episodes when taken as needed, up to 5x/day


Sublingual Apomorphine (Kynmobi)

Old Drug, New Delivery

Bilayer Strip
First layer: apomorphine drug layer
Second layer: separate buffer layer
Bilayer strip is placed on the underside of the tongue
No mucosal irritation in hamster model or Phase 2 trial

Bilbault T et al. Ther Deliv. 2016;7(9):611-618
Hauser RA et al. Mov Disord. 2016;31(9):1366-1372
Sublingual Apomorphine (APL-130277) for the Acute Conversion of OFF to ON in Parkinson’s Disease

Mean Dose: 18.4 mg
Mean ON duration: 50 mins
15/19 (78.9%) achieved a full ON response (mITT)
13/15 (86.7%) in per protocol population achieved a full ON response
AE: Dizziness, somnolence, nausea

Max improvement = -16.7 points at 30 mins & -17.3 points at 45 mins

Hauser RA et al. Mov Disord. 2016;31(9):1366-1372
MOTOR FLUCTUATIONS: COMT INHIBITORS

- Selectively inhibits peripheral catechol O-methyltransferase (COMT), increasing central bioavailability of L-dopa
- Entacapone, Tolcapone, Opicapone (FDA approved 4/24/20)
- Tolcapone: use sparingly; associated with transaminitis and rare cases of fulminant hepatotoxicity
- Give with each dose of CD/LD (adjunct tx)
- Improves “wearing off”
- Monitor and adjust dosing of CD/LD as needed to avoid peak-dose dyskinesias
MOTOR FLUCTUATIONS: AMANTADINE

- Mild-to-moderate benefit (initial tx discussed earlier)
- Starting dose of Amantadine for dyskinesias:
  - 100 mg qd, increasing to 100 mg bid after 1-2 weeks
  - Doses up to 400 mg/qd, divided in 2-4 doses/day
- Several short-term trials show benefit of Amantadine, with ~25-50% relative reduction of dyskinesia compared w placebo.
- The effect can be sustained for a year or more.

Lugiger E et al. Mov Disord 2000; 15:873
Snow BJ et al. Neuropharmacol 2000; 23:82
Thomas A et al. J Neurol Neurosurg Psychiatry 2004; 75:141
Metman LV et al. Arch Neurol 1999; 56:1383
Pooled Analyses of Phase III Studies of ADS-5102 (Amantadine) Extended-Release Capsules for Dyskinesia in Parkinson’s Disease
Lawrence W. Elmer, Jorge L. Juncos, Carlos Singer Daniel D. Truong, Susan R. Criswell, Sotirios Parashos, Larissa Felt, Redd Johson and Rajiv Patni
CNS Drugs 2018

- ADS-5102 extended-release capsules are an oral formulation of amantadine administered once daily at bedtime in patients with PD to treat dyskinesia associated with the use of levodopa.
- Pooled results from two randomized, double-blind, placebo-controlled, phase III trials confirm that treatment with ADS-5102 is associated with a significant improvement over placebo for dyskinesia in as early as two weeks and maintained over 12 weeks.
- Relative treatment difference between groups = 27.3%; p<0.0001.
- A significant reduction in the total daily duration of OFF time was achieved.
- These results provide further evidence supporting ADS-5102 as an adjunct to Levodopa for both dyskinesia and OFF time in PD patients with dyskinesia.

Courtesy of JL Juncos, MD
TREATMENT OF NEUROPSYCHIATRIC DISORDERS IN PARKINSON’S DISEASE

Adriana P. Hermida, MD
Geriatric Psychiatry Fellowship, Director
Department of Psychiatry and Behavioral Science
Emory University School of Medicine
Parkinson’s Disease: an illness beyond motor symptoms
PSYCHIATRIC SYMPTOMS OF PD

Parkinson’s disease is associated with a number of non-motor symptoms including:

- Depression
- Anxiety
- Impulse Control disorders
- Psychosis
- Sleep disturbance
- Apathy
“MOTION-EMOTION CONUNDRUM”

Improve emotion

Worsen motion
“MOTION-EMOTION CONUNDRUM”
COMPREHENSIVE CARE CLINIC FOR PD AT EMORY UNIVERSITY

- Participants undergo an assessment by providers in the following disciplines over two days:

  **Day 1:**
  - Nursing
  - Sleep Medicine
  - Psychiatry
  - Medicine
  - Physical Therapy
  - Occupational Therapy

  **Day 2:**
  - Speech & Language Therapy
  - Neuropsychology
  - Social Work
  - Movement Disorder neurologist
Some patients had more than one psychiatric condition. Other psychiatric conditions include: adjustment disorder, substance abuse disorder, and panic disorder.
DEPRESSION
40% of patients fulfill the DSM criteria for major depressive disorder.

Minor depression, depression without sadness, non-dysphoric depression are much more common (75%–86%).

SUICIDE IN PD

• Suicidal ideation common in PD

• No clear relationship between the severity of motor symptoms and a diagnosis of depression.

• Kostic et al. followed a cohort of 102 with PD from an OP clinic for 8 years and found that suicide-specific mortality was 5.3 times higher than matched controls¹.

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DESIPRAMINE VS. CITALOPRAM

• Devos et al. 2008 RCT of 48 depressed PD
  • Desipramine 75 mg / Citalopram 20 mg

• Both produced significant improvements in the MADRS score after 30 days.

• Desipramine induced a more intense short-term effect on parkinsons-depression than citalopram but its lower tolerability may outweigh its slight short-term clinical advantage.

• Mild adverse events were twice as frequent in the desipramine group as in the other groups.
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• Mild adverse events were twice as frequent in the desipramine group as in the other groups.
NORTRIPTYLINE VS PAROXETINE

- Menza et al. 2009 RCT 52 patients with PD and depression to paroxetine, nortriptyline, or placebo for 8 weeks.

- nortriptyline (up to 75 mg) paroxetine (up to 37.5 mg)

- Nortriptyline, but not paroxetine, was significantly more effective than placebo

- TCAs have been associated with reductions in motor symptoms and less drooling, most likely due to their anticholinergic properties

- Orthostatic hypotension, delirium, and memory impairment associated more w/ nortriptyline.

M Menza, RD Dobkin and H Marin et al., A controlled trial of antidepressants in patients with Parkinson disease and depression, Neurology 72 (2009), pp. 886–892
PAROXETINE VS. VENLAFAXINE XR VS. PLACEBO

- Richard 2012 the largest randomized 12 weeks (115 subjects)
  - Paroxetine (42) up to 40 mg
  - Venlafaxine XR (34) up to 225 mg
  - Placebo (39)

- HAM-D primary outcome
  - Improvement with paroxetine vs placebo
  - Improvement with venlafaxine XR vs placebo.
  - No significant differences between paroxetine and venlafaxine XR

SAD-PD Study Group
DOPAMINE AGONISTS

PRAMIPEXOLE VS. PLACEBO

- Barone et al. (2010) 296 subjects. 12-week, randomized, double-blind, placebo-controlled (1:1 ratio), parallel-group trial of pramipexole (0.125–1.0 mg, 3 times per day)

- GDS, BDI

- Significant improvement with pramipexole vs placebo.

PRAMIPEXOLE VS. PERGOLIDE

- Rektorova et al. (2003) 41 subjects flexibly dosed at 1.5 to 4.5 mg/day.

- UPDRS decreased in both groups

- Only pramipexole showed significant decrease in scale scores MADRS
OTHER ANTIDEPRESSANTS

MIRTAZAPINE

• Mirtazapine vs placebo in a RTC 20 depressed PD patients mirtazapine was superior to placebo in reducing HAMD scores

• Mirtazapine attenuates parkinsonian tremor and levodopa-induced dyskinesias

• It could worsen REM Sleep Behav DO (RBD), agranulocytosis

BUPROPION

• Dual norepinephrine and dopamine reuptake inhibitor with no serotonin associated side effects such as weight gain, sedation, sexual dysfunction

• Bupropion has less potential interaction with Selegilene (MAOI- B)

• Less RBD

• High doses could worsen psychosis

ECT

- Effective in treating motor and non-motor symptoms of PD
- Rapid response
- RUL
- Hold Parkinson's medications the morning of ECT
- Monitor cognition

[Image of diagrams showing different ECT techniques: BITEMPORAL, RIGHT UNILATERAL, BIFRONTAL]

NONPHARMACOLOGIC THERAPY

• Regular exercise program: Aerobic, Tai Chi
• PD support groups and national organizations
• PSYCHOTHERAPY
  • Cognitive-behavioral therapy: A systematic review of cognitive-behavioral therapy for depression in PD found 2 randomized controlled trials. Cognitive-behavioral therapy lead to significant reductions in depression scores with a maintenance of the effect over the follow-up periods of 1 and 6 months.

• Repetitive transcranial magnetic stimulation (rTMS):
  • No clear evidence of an improvement of mood symptoms when compared with sham TMS
  • others concluded some beneficial effect of rTMS on depression in PD lasting at least 30 days after treatment.
WHAT IS THE BEST ANTIDEPRESSANT FOR PARKINSON'S PATIENTS?
CLINICAL EXPERIENCE

• CBT
• Start an SSRi (Escitaloram, sertraline)
• If partial response add / If no response switch to
  • Mirtazapine if there is no RBD. Improves sleep and appetite. It may improve tremor.
  • Venlafaxine XR watch for BP. It may benefit patients with low BP.
  • Bupropion XL—more activating, may worsen anxiety, higher dose may psychosis. Best option if patients have RBD or on Coumadin
  • Consider Nortriptyline
• Consider Dopamine agonist---watch for psychosis, ICD, DDS
• Consider ECT

RBD: Rem Sleep Behavior Disorder
ANXIETY
ANXIETY

• About 30% of PD patients have DMS-5 diagnosis of an anxiety disorder

• Up to 55% have significant anxiety symptoms
ANXIETY

- Generalized Anxiety Disorder 14%
- Social Phobia 13.8%
- Anxiety NOS 13.3%
- Specific Phobia 13.0% (fear of off periods or freezing)
- Panic Disorder 6.8%
- ~30% had more than one anxiety disorder
**Motor Fluctuations**

**Non-motor fluctuations**

Table 3 The most frequent nonmotor fluctuations and their rate of coincidence with the “off” state

<table>
<thead>
<tr>
<th>NMF</th>
<th>Frequency, %</th>
<th>Frequency during off state, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>66</td>
<td>88</td>
</tr>
<tr>
<td>Drenching sweats</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>Slowness of thinking</td>
<td>58</td>
<td>83</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>75</td>
</tr>
<tr>
<td>Akathisia</td>
<td>54</td>
<td>63</td>
</tr>
<tr>
<td>Irritability</td>
<td>52</td>
<td>88</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>49</td>
<td>25</td>
</tr>
</tbody>
</table>

NMF = nonmotor fluctuation.
ANXIETY

• Higher levels of care dependency
• Increased caregiver distress
• Associated with more frequent freezing and on-off fluctuations
• Worsen quality of life
ANXIETY TREATMENT

- Adjusting dose of dopamine agonist
- SSRIs, SNRI, Buspar
- CBT
- Mindfulness (MBCT)
- Body awareness training in the treatment of wearing-off related anxiety in PD (BEWARE) - VU University Medical Center Amsterdam, The Netherlands, Ghielen I et al.
- Caution with benzodiazepines

Ghielen et al. BEWARE: Body awareness training in the treatment of wearing-off related anxiety in patients with Parkinson's disease: study protocol for a randomized controlled trial. 2015
IMPULSE CONTROL DISORDERS
Compulsive behaviors in PD
Dopamine Pathways

Frontal cortex

Nucleus accumbens

VTA

Hippocampus

Raphe nucleus

Serotonin Pathways

Striatum

Substantia nigra

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions
- Mood
- Memory processing
- Sleep
- Cognition
IMPULSE CONTROL DISORDERS

- Do not confuse ICD with a manic episode

- Reduce dopamine agonist

- Antidepressants may help with ICD but some may facilitate dopaminergic neurotransmission. May worsen ICD (avoid Venlafaxine > 300 mg, Sertraline > 200 mg)

- The atypical antipsychotics clozapine, risperidone, and quetiapine have been reported to help control ICD

- Recently, the opioid antagonist, naltrexone, was studied in an RCT in 45 patients with PD and ICD:
  - (CGIC) response rate was not significant
  - greater improvement in QUIP-Rating Scale ICD score over time compared to placebo

• DBS in combination with a reduction of PD meds has been effective in controlling *dopamine dysregulation syndrome*.

• ICD can have devastating financial and social consequences for patients and families.

• This highlights the importance of inquiring about multiple ICDs when assessing patients with PD.
PSYCHOSIS
Psychotic events in patients with PD can range from:

- Occasional non-disturbing hallucinations
- Mild illusions
- Vivid dreams
- Sense of presence
- Paranoid delusions
- Othello syndrome
PSYCHOSIS

- r/o Delirium
  - Infections
  - Pneumonia
  - Urinary tract infections
  - Electrolyte imbalances

- Decrease dopamine agonist
OLANZAPINE VS. PLACEBO

• Nichols et al, (2013) N= 23 PD patients with drug-induced psychosis. 4-week RCT. Olanzapine 2.5mg or 5mg/day

  Brief Psychiatric Rating Scale ratings, CGI, UPDRS motor subscale. No significant difference between olanzapine and placebo groups in outcome measures, but more mild side effects with motor worsening in olanzapine group.

• Breier et al, (2002) RCTs (N=160). Olanzapine dose 2.5 to 15 mg/d. Motor function worsen with Olanzapine. No benefit over placebo in psychosis ratings.

CLOZAPINE VS. PLACEBO

- 46 patients with PD 4-week, RCT clozapine (mean dose after 4 weeks 35.8 mg/d) and placebo\(^1\)

- 25 (55.6%) had complete recovery from delusions and hallucinations.

- No significant changes in UPDRS or MMSE scores occurred in either group.

---

CLOZAPINE VS. QUIETAPINE

- Mermis et al N= 27 with PD and psychosis. clozapine or quetiapine for 22 weeks

- Quetiapine dosage: 25–150 mg/y, (mean 91 mg/d)  
  Clozapine dosage: 6.25–50 mg/d  
  (mean 13 mg/d)

- Both agents were equally efficacious, no significant difference in controlling frequency of hallucinations, significant advantage of clozapine over quetiapine in reducing delusions

CLOZAPINE

- Clozapine - small (<1%) but serious risk of developing agranulocytosis.
- D4 antagonist
- Fewer motor side effects
- First line
PIMAVANSERIN

- Cummings et al, 2014
- Pimavanserin, 40 mg/day trial (recommended dose 34 mg/day)
- Inverse agonist and antagonist at 5-HT2A, 5-HT2C receptors
- 6-week RCT
- N=199 (aged ≥40 years) with PD psychosis
- Parkinson’s disease-adapted scale for Assessment of Positive Symptoms (SAPS-PD)
- −5.79 decrease in SAPS-PD scores for pimavanserin vs −2.73 for placebo
  
  (difference −3.06, 95% CI −4.91 to −1.20; p=0.001; Cohen’s d 0.50).
- 10 patients on pimavanserin discontinued because of an adverse event vs 2 on placebo (UTI, falls), it could cause QT prolongation


124
CONCLUSIONS

• Neuropsychiatric symptoms are associated with greater disability, rapid progression of motor symptoms and increased mortality

• Treat depressive symptoms even if they do not meet DSM criteria

• Assess whether anxiety coincides with motor fluctuations
CONCLUSIONS

• ALWAYS ask about ICD

• Treat psychosis if symptoms are ego-dystonic

• ECT is an effective treatment in PD depression

• Clozapine ---First line treatment for PD psychosis
Adriana Hermida, MD
Associate Professor

Director
Geriatric Psychiatry Fellowship
Department of Psychiatry
and Behavioral Science
Emory University
Dementia in Parkinson’s Disease

Lenora Higginbotham, MD
Movement Disorders Neurology
September 26, 2020
I have no disclosures.
The Lewy Body Dementias include Parkinson’s disease dementia (PDD) and Dementia with Lewy bodies (DLB), distinguished by the timing of cognitive decline relative to motor symptoms.
It is hypothesized that PDD results from the propagation of α-synuclein rich Lewy body inclusions in a largely caudo-rostral direction through brainstem centers to the midbrain, forebrain, and cerebral cortex.

How Common is Dementia in PD?

The Sydney Multicenter Study of Parkinson’s Disease: The Inevitability of Dementia at 20 years

Mariese A. Hely, MBBS, Wayne G.J. Reid, PhD, Michael A. Adena, PhD, ASTAT, Glenda M. Halliday, PhD, and John G.L. Morris, MD

1Department of Neurology, Westmead Hospital, Westmead, New South Wales, Australia
2Covance Pty Ltd, Braden, Australian Capital Territory, Australia
3Prince of Wales Medical Research Institute, Randwick, New South Wales, Australia

80%
How Common is Dementia in PD?

The prevalence figures combined in this study ranged from 4 to 93%.

Cumulative prevalence studies suggest dementia is frequent in PD.

“The 8-year prevalence in PD was 78.2%. More than three quarters of this representative PD cohort developed dementia during the 8-year study period.”

Cumulative prevalence studies suggest dementia is frequent in PD.

“Dementia is present in 83% of 20-year survivors.”

Hely et al. Movement Disorders 2008;23(6): 837-44.
Parkinson's Disease: The Quintessential Neuropsychiatric Disorder

Daniel Weintraub, MD,1,2* and David J. Burn, MD3,4

1Department of Psychiatry, University of Pennsylvania, Philadelphia, PA
2Parkinson’s Disease and Mental Illness Research Center, University of Pennsylvania, Philadelphia, PA
3Institute for Ageing and Health, Newcastle University, Newcastle Upon Tyne, England
4Newcastle University Clinical Ageing Research Centre, Newcastle University, Newcastle upon Tyne, England

FIG. 1. Number of articles published devoted to Parkinson’s disease, 1986–2010. Cognition = Parkinson+ and (dementia or cognitive impairment); Depression = Parkinson+ and depression; Psychosis = Parkinson+ and (psychosis or hallucination); Anxiety = Parkinson+ and anxiety; ICD’s = Parkinson+ and (impulse control disorder or dopamine dysregulation syndrome); Sleep and wakefulness = Parkinson+ and (insomnia or sleepiness or fatigue or REM); Apathy = Parkinson+ and apathy.

Risk Factors for Dementia in PD

- Older age
- Male gender
- Longer duration of illness
- Greater motor impairment
- Early hallucinations


Younger-onset patients may be spared the “inevitability” of dementia, even after decades of living with the disease.

Hely et al. Movement Disorders 2008;23(6): 837-44.

**TABLE 1. Comparison of CDR, MMSE, and brief cognitive testing for patients examined at 20 years**

<table>
<thead>
<tr>
<th>CDR</th>
<th>No.</th>
<th>Age at 20 years</th>
<th>MMSE</th>
<th>Mean letter fluency N &gt; 9</th>
<th>Animal category fluency, N &gt; 17</th>
<th>Mean clockface normal = 4</th>
<th>Const. apraxia (%)</th>
<th>Perseveration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>5</td>
<td>64</td>
<td>29</td>
<td>8</td>
<td>19</td>
<td>4</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>75</td>
<td>25</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>76</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>79</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Dementia has been increasingly more recognized to be a common feature in PD, especially in old age. Specific clinical criteria for PDD however, have been lacking.

Probable PDD

- **Cognitive Features**
  - Impairment in at least 2 of the following domains: attention, executive functions, visuospatial, and memory*.
  - Largely preserved language except word-finding difficulties.

- **Behavioral Features**
  - Apathy
  - Depression / Anxiety
  - Hallucinations
  - Delusions
  - Excessive Daytime Sleepiness

*Amnestic syndrome is often the result of impaired retrieval of stored information.
The amnestic syndrome of PDD is often the result of impaired retrieval of stored information and improves with cueing.
Clinical Diagnosis of PDD

Diagnostic Procedures for Parkinson’s Disease Dementia: Recommendations from the Movement Disorder Society Task Force

Bruno Dubois, MD,1* David Burn, MD,2 Christopher Goetz, MD,3 Dag Aarsland, MD, PhD,4,5 Richard G. Brown, PhD,6,7 Gerald A. Broe, HB, BS,8,9 Dennis Dickson, MD,10 Charles Duyckaerts, MD, PhD,11 Jefferey Cummings, MD,12 Serge Gauthier, MD,13 Amos Korczyn, MD, MSc,14 Andrew Lees, FRCP,15 Richard Levy, MD, PhD,16 Irene Litvan, MD,17 Yoshikuni Mizuno, MD,18 Ian G. McKeith, MD,19 C. Warren Olanow, MD,20,21 Werner Poewe, MD,22 Cristina Sampaio, MD, PhD,23 Eduardo Tolosa, MD,24 and Murat Emre, MD25

“The main focus of this article is to operationalize the diagnosis of PDD.”

MDS PDD Screening Exam

- **Attention**
  - Serial 7s
  - Months reversed

- **Executive Function**
  - Lexical fluency

- **Visuo-constructive Ability**
  - Copy two overlapping pentagons

- **Memory**
  - Free recall of three words

---

**TABLE 2. Diagnostic rating sheet for probable PD-D, recommended by the Movement Disorder Task Force**

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Parkinson’s disease</td>
<td>□</td>
</tr>
<tr>
<td>2. Parkinson’s disease developed before dementia</td>
<td>□</td>
</tr>
<tr>
<td>3. MMSE &lt;26</td>
<td>□</td>
</tr>
<tr>
<td>4. Dementia has Impact on ADLs</td>
<td>□</td>
</tr>
<tr>
<td>5. Impaired cognition (For Yes, at least of 2 of 4 tests below are abnormal)</td>
<td></td>
</tr>
<tr>
<td>Mark which Tests are abnormal</td>
<td></td>
</tr>
<tr>
<td>□ Months reversed or Sevens backwards</td>
<td></td>
</tr>
<tr>
<td>□ Lexical fluency or clock drawing</td>
<td></td>
</tr>
<tr>
<td>□ MMSE pentagons</td>
<td></td>
</tr>
<tr>
<td>□ 3-word recall</td>
<td></td>
</tr>
<tr>
<td>6. Absence of Major Depression</td>
<td>□</td>
</tr>
<tr>
<td>7. Absence of delirium</td>
<td>□</td>
</tr>
<tr>
<td>8. Absence of other abnormalities that obscure diagnosis</td>
<td>□</td>
</tr>
<tr>
<td>Probable PD-D (items 1–8 must all be YES)</td>
<td>□</td>
</tr>
</tbody>
</table>

“When subjects met all 8 screening checklist criteria, the designation of PDD was 100% accurate as determined by the traditional gold standard of more time-consuming full neuropsychological evaluations. For cases that did not meet these criteria, however, full neuropsychological testing was still needed.”

Remember, pathological overlap of PDD with Alzheimer’s Disease is fairly common!
Pharmacological Treatment of PDD

• Acetylcholinesterase Inhibitors
  • Donepezil, rivastigmine*, galantamine

• NMDA Antagonists
  • Memantine

• Atypical Antipsychotics
  • Quetiapine, clozapine, pimavanserin

• Dopaminergic Therapy Adjustments

*Rivastigmine is the only drug FDA approved for the treatment of Parkinson’s disease dementia.
SYN120 Fails to Show Efficacy Against Parkinson Dementia in Phase 2a SYNAPSE Trial

Disappointing performance for the dual serotonin receptor antagonist

Recent clinical results of emerging 5-HT6 / 5-HT2A antagonist were disappointing.

https://consultqd.clevelandclinic.org/syn120-fails-to-show-efficacy-against-parkinson-dementia-in-phase-2a-synapse-trial/

Fernandez H. Neurology Apr 2019, 92 (15 Supplement) S4.005.
Early frontal executive dysfunction in Parkinson’s disease is not necessarily associated with the development of dementia.

Mild Cognitive Impairment in PD
Dysexecutive Syndrome

- Trouble with multi-tasking, organizing, or planning
- Difficulty switching tasks
- Deficits in attention and working memory
- “Tip-of-the-tongue” phenomenon
This trial of rivastigmine in MCI patients revealed no statistically significant improvement in multiple cognitive measures.

Question and Answer Session after the Stretch Break
Autonomic Features of Parkinson Disease

Camille Vaughan, MD, MS
Associate Professor & Division Director, Geriatrics & Gerontology
Emory Department of Medicine
Atlanta Site Director, Birmingham/Atlanta VA GRECC
September 26, 2020
Disclosures

• Grant funding from U.S. Department of Veterans Affairs
• Spouse full-time employee Kimberly-Clark Corp.
Learning Objectives

• Describe the burden of autonomic symptoms
• Define common autonomic symptoms of PD
  • Orthostatic hypotension
  • Bladder dysfunction
  • Constipation
  • Erectile dysfunction
• Determine initial evaluation and management strategies
Burden of Autonomic Symptoms in Parkinson Disease (PD)

- Non-motor symptoms (particularly bladder & bowel) often impact quality of life more than motor symptoms as PD progresses
- Frequently unrecognized by practitioner
- Typically not responsive to dopaminergic therapy

Gallagher et al. Mov Disord 2010
Shulman et al. Parkinson Relat Disord 2002
Orthostatic Hypotension

• Associated with falls, dizziness, fatigue
• May occur in up to 30% of persons with PD

• Evaluation:
  • Lying/sitting and standing blood pressures in clinic
  • 24-hour ambulatory blood pressure
  • Tilt table may be necessary

• Management:
  • Consider conservative management
  • Medications are investigational
## Orthostasis – Conservative Treatments

<table>
<thead>
<tr>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid sudden head up/ stool strain</td>
<td>Early morning or after nighttime voids</td>
</tr>
<tr>
<td>Avoid large meals and alcohol</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Adequate fluid and salt intake</td>
<td>Maintain plasma volume</td>
</tr>
<tr>
<td>Avoid excessive heat</td>
<td>Intravascular volume / vasodilatation</td>
</tr>
<tr>
<td>Elevate bed head 20-30°</td>
<td>Reduce renal artery pressure and increased renin</td>
</tr>
<tr>
<td>Elastic stockings</td>
<td>Prevent venous pooling</td>
</tr>
<tr>
<td>Avoid vasoactive drugs</td>
<td>Psychotropics may contribute</td>
</tr>
</tbody>
</table>

Hindle & Chaudhuri, Birmingham Syllabus
Orthostatic Hypotension

• Insufficient evidence for medications

• Fludrocortisone
• Midodrine
• Droxidopa study – negative for primary outcome
  • Not powered for systolic BP evaluation, may be helpful in short term
• Domperidone
• Indomethacin
• Yohimbine

Hauser et al. Mov Disord 2014
Hauser et al. J Parkinsons Dis 2014
Seppi et al. Mov Disord 2019
Pfeiffer R. Neurotherapeutics 2020
Pathogenesis of Urinary Symptoms in PD

Sensory input and the ability to integrate sensory input from the bladder may be overall decreased in PD.

PMC = Pontine micturition center
Activation leads to sphincter relaxation and detrusor contraction

Dopamine Dysregulation

Alpha-Synuclein Pathology
Central and Peripheral

McDonald C, Winge K, Burn DJ. Parkin Relat Disord 2016
Epidemiology of Urinary Symptoms

Prevalence of the most frequently reported urinary symptoms in PD

Fig. 3. The prevalence of the most frequently reported symptoms in patients with PD. Urge incontinence is not addressed in IPSS.

Winge et al. Neurouro Urodyn 2006
Evaluation: Post-Void Residual

• < 50 mL is adequate emptying and ≥ 200 mL may warrant a referral
• If PVR is > 100 mL – consider multiple system atrophy
Treatment – Lifestyle Modifications

• Assess fluid and caffeine intake
• Control constipation
• Sleep hygiene
  • www.medlineplus.gov
• Exercise
• Continence products
• Scheduled/Prompted voiding
Pelvic Floor Muscle-Based Behavioral Therapy for Urinary Symptoms in PD

**URGE SUPPRESSION STRATEGY**

*When the Urge Strikes*

Stop and stay still. Sit down if you can.

Squeeze your pelvic floor muscles quickly 3 to 5 times and repeat as needed.

Relax the rest of your body. Take a deep breath.

Concentrate on suppressing the urge.

Wait until the urge calms down.

Walk to the bathroom at a normal pace.

If the urge returns on the way to the bathroom, stop and squeeze away the urge again.

**Remember: FREEZE AND SQUEEZE**

Burgio, Pearce & Lucco, 1989
Vaughan et al. 2019
McDonald et al. 2020
Medications

- Selective alpha-blockers in men
  - Side effect: orthostasis
- 5-α reductase inhibitors in men
  - Side effect: decreased libido
- Bladder relaxants
  - Anticholinergic antimuscarinic
    - Side effects: constipation, dry mouth, possibly cognitive
  - Beta-3-agonist (noradrenergic)
    - Side effect: hypertension

Zeseiwicz T et al. Neurology 2010
Gubiotti et al. Ther Adv Neurol Disord 2019
Antimuscarinic Drugs and Cognition

Tolterodine
- Low lipophilicity
- Charged
- Relatively “bulky”

Fesoterodine
- High lipophilicity
- Neutral
- Relatively “small”

Oxybutynin
- Lipophilic, small
- “M3 selective”

Solifenacin
- Relatively “bulky”
- Highly polar

Darifenacin

Trospium

Courtesy JG Ouslander
Neuromodulation

• **Implantable Sacral Nerve Stimulation**
  • Small study evaluating 33 patients with neurogenic bladder
  • 4/6 (67%) PD underwent permanent implantation

• **Percutaneous Tibial Nerve Stimulation**
  • Small uncontrolled study in 7 men with PD
    • Hoehn and Yahr less than 2.5
    • Failed behavioral, drug therapy
  • Five of the seven were considered ‘responders’
  • Improvement in UI, frequency, lower PVR

Finazzi et al. Italian Society of Urodynamics 2006
OnobotulinumtoxinA in PD

• Risk of retention – especially if PVR elevated initially

• Study of 16 (10 women, 6 men) – 500 units
  • Symptoms, QOL, and caregiver burden improved
  • 8 required antimuscarinic at 12 months
  • 4 asked for repeat injections

• Study of 8 (7 women, 1 man) - 100 units
  • Decreased daytime/nighttime frequency

Giannantonio et al.  J Urol 2009
Kulaksizoglu et al. Parkin Rel Disord 2010
Giannantonio et al.  J Urol 2011
Constipation

• Fewer than 3 bowel movements per week
  • Occurs in 40-50% of persons with PD

• May precede motor symptoms in PD

• Peripheral autonomic dysfunction may predominate
  • Lewy body pathology in bowel

• Evaluation
  • Appropriate screening for colon cancer
  • Consider culprit medications/iatrogenic causes

Sakakibara et al. J Neural Transm 2008
Pfeiffer R. Neurotherapeutics 2020
Constipation Management

- **Fluid and fiber intake essential**
  - 6-8 eight oz. glasses per day of fluid
  - 20-25g fiber per day
    - tree nuts, fruits with edible peel, greens, beans, whole grains
- If medication is needed:
  - Polyethylene glycol likely safe/effective
  - Lubiprostone (activates chloride channels)
    - Evidence for improvement in 4 week RCT with 54 PD participants

Ondo W et al. Neurology 2012
Seppi K et al. Mov Disord 2019
Constipation Recipe

- 1 cup crushed 100% bran flakes
- 1 and ½ cups canned pears
- Blend together
  - Store in refrigerator for up to a week
- Take 1 tbsp in the AM with a warm beverage of choice (decaffeinated)
- Can increase by 1 tbsp per week
  - Maximum of 5 tbsp daily
Sexual Dysfunction

• Occurs in up to 80% of men and women with PD

• Evaluation:
  • Not necessary to check testosterone levels

• Management:
  • Consider timing to coincide with best ‘on’ related to PD symptoms
  • Couples therapy may be helpful
  • Phosphodiesterase inhibitors in men
    • Sildenafil – may have less impact on orthostasis
    • Efficacious and likely safe
  • Caution with testosterone

Seppi K et al. Mov Disord 2019
Post Questions in Q & A?
Differential Diagnosis of Parkinsonism

Daniel Huddleston, MD
Declaration of Financial Interests or Relationships

I have the following financial interest or relationship to disclose relating to the subject matter of this presentation:

• No relevant disclosures
DDx of Parkinsonism

Neurodegenerative vs. Secondary
• Conditions
• Diagnostic Approach

MSA, PSP, DLB and Other Atypical Parkinsonism
• Overview
• Clinical Features
• Diagnostic Approach

Parkinson’s Disease vs. Atypical Parkinsonism
• PD Diagnostic Approach

Diagnostic Imaging Tools:
• SPECT: DaTscan and MIBG
• Neuromelanin-sensitive MRI
Parkinsonism

Primary/Neurodegenerative
- Parkinson’s Disease
  - Sporadic
  - Familial

Atypical Parkinsonian Disorders
- Multiple System Atrophy
- Dementia with Lewy Bodies
- Progressive Supranuclear Palsy
- Corticobasal Degeneration

Secondary
- Vascular Medications
- Functional
- Toxins
- Others

Parkinsonism DDx: Non-neurodegenerative

• Pseudo-Parkinsonism
  o Essential Tremor
  o Arthritis
  o Spinal Stenosis

• Vascular Parkinsonism

• Drug-induced Parkinsonism:
  o Neuroleptics, Dopamine depleters (VMAT2 inhibitors), Antiemetics, Valproic acid, Lithium, Amiodarone

• Psychogenic Parkinsonism

• Post-encephalitic parkinsonism

• Others:
  o Toxins: Manganese, CO, Carbon disulfide, Cyanide, Methanol, MPTP
  o Miscellaneous: Post-traumatic, Uremia, NPH
# Parkinsonism DDx: Neurodegenerative vs. Other

## ET vs. PD TREMOR

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>ET</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor location</td>
<td>Hands, head, voice</td>
<td>Hands, legs, mouth</td>
</tr>
<tr>
<td>Associated signs</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Duration</td>
<td>Many years (decades)</td>
<td>Short (few years)</td>
</tr>
<tr>
<td>Family History</td>
<td>60-75%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Alcohol response</td>
<td>Typical/Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Tremor type</td>
<td>Postural/Action/Intention&gt;Rest</td>
<td>Resting &gt; Postural</td>
</tr>
<tr>
<td>Response to levodopa</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Response to propranolol</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Handwriting samples</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Parkinsonism

Primary/Neurodegenerative
- Parkinson’s Disease
  - Sporadic
  - Familial
- Atypical Parkinsonian Disorders
  - Multiple System Atrophy
  - Dementia with Lewy Bodies
  - Progressive Supranuclear Palsy
  - Corticobasal Degeneration

Secondary
- Vascular Medications
- Functional Toxins
- Others

Others
Common Features Among Synucleinopathies:

- REM sleep behavior disorder (all)
- Hallucinations/Psychosis (PD & DLB > MSA)
- Olfactory Loss (PD & DLB > MSA)
- Pure autonomic failure (PAF) is a synucleinopathy of the autonomic nervous system predominantly affecting the autonomic ganglia and nerves. Lewy bodies are found predominantly in the peripheral portions of the autonomic nervous system.

https://www.researchgate.net/publication/235368619_Cerebrospinal_Fluid_Biomarker_Candidates_for_Parkinsonian_Disorders
Neurodegenerative Parkinsonism: Atypical Parkinsonism

- Multiple System Atrophy (MSA) – synucleinopathy
- Dementia with Lewy Bodies (DLB) – synucleinopathy
- Progressive Supranuclear Palsy (PSP) – tauopathy
- Corticobasal Degeneration (CBD) – tauopathy
- Parkinsonism part of a broader ND syndrome: Huntington’s, Wilson’s, SCAs (2,3,6,8,17)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PD</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>Usually Slow</td>
<td>Usually Rapid</td>
</tr>
<tr>
<td>Falls, Severe dysphagia</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Cognitive Impairment</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Response to Levodopa</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>UMN Signs/Babinski Sign</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Survival</td>
<td>Mildly reduced</td>
<td>Markedly Reduced</td>
</tr>
</tbody>
</table>

Multiple System Atrophy

- **Characterized by Prominent Autonomic failure**
  - Orthostatic hypotension (syncope)
  - Incontinence/ Bowel & bladder dysfunction
  - Erectile dysfunction/ Gonadal hyposensitivity
  - Abnormal sweating/ Anhidrosis, Microcirculatory changes

  → Early falls, Early Dysphagia, Stridor, Anterocollis

- **Subtypes:**
  - **MSA-P:** Autonomic failure with predominant motor signs of parkinsonism
  - **MSA-C:** Autonomic failure with predominant cerebellar ataxia
    - MSA-A (Shy-Drager) → isolated autonomic failure < 5 years, progresses to MSA-P>MSA-C (+ RBD common, MIBG normal)
    - PAF → persistent autonomic failure without parkinsonism > 5 years (RBD uncommon, MIBG abnormal)

- **Probable vs. Possible MSA-P and MSA-C:** Delineated by Consensus Diagnostic Criteria (Gilman et al, 2008)

- **Epidemiology:**
  - Onset in 6th decade typically. Younger age of onset than PD
  - Affects an estimated 0.6 per 100,000 people per year, which increases to 3 per 100,000 people per year in those older than 50 years of age
  - Median survival from onset to death is 6-10 years

## MSA: Diagnostic Criteria

### Table 1

<table>
<thead>
<tr>
<th>Criteria for the diagnosis of probable MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A sporadic, progressive, adult (&gt;30 y)-onset disease characterized by</td>
</tr>
<tr>
<td>• Autonomic failure involving <strong>urinary incontinence</strong> (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an <strong>orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic</strong> or 15 mm Hg diastolic and</td>
</tr>
<tr>
<td>• <strong>Poorly levodopa-responsive parkinsonism</strong> (bradykinesia with rigidity, tremor, or postural instability) or</td>
</tr>
<tr>
<td>• <strong>A cerebellar syndrome</strong> (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)</td>
</tr>
</tbody>
</table>

Table 2  Criteria for possible MSA

A sporadic, progressive, adult (>30 y)-onset disease characterized by

- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
- At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
- At least one of the additional features shown in table 3

Table 3  Additional features of possible MSA

<table>
<thead>
<tr>
<th>Possible MSA-P or MSA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babinski sign with hyperreflexia</td>
</tr>
<tr>
<td>Stridor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible MSA-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly progressive parkinsonism</td>
</tr>
<tr>
<td>Poor response to levodopa</td>
</tr>
<tr>
<td>Postural instability within 3 y of motor onset</td>
</tr>
<tr>
<td>Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction</td>
</tr>
<tr>
<td>Dysphagia within 5 y of motor onset</td>
</tr>
<tr>
<td>Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum</td>
</tr>
<tr>
<td>Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible MSA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism (bradykinesia and rigidity)</td>
</tr>
<tr>
<td>Atrophy on MRI of putamen, middle cerebellar peduncle, or pons</td>
</tr>
<tr>
<td>Hypometabolism on FDG-PET in putamen</td>
</tr>
<tr>
<td>Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET</td>
</tr>
</tbody>
</table>
Glial cytoplasmic inclusions (GCIs) in cerebellar white matter

All are immunoreactive for α-synuclein.

Neuronal cytoplasmic inclusions (NCIs) (double arrows) and an early formation of a neuronal nuclear inclusion (NNI) (triple arrow) in neurons of pontine nuclei

• **DaTScan**
  - Reduced dopamine transporter (DaT) uptake in striatum → Not specific

• **MRI**
  - MSA-P: Putaminal atrophy with the putaminal rim sign (hyperintense T2 border of the lateral putamen)
    - Non-specific at 3T. (Lee et al, 2005)
  - MSA-C: Hot Cross Bun sign (cruciform T2 hyperintensities of the pons)
    - These can be supportive but are not highly sensitive.

• Cardiac functional imaging with 123I-MIBG and 6-[18F] fluorodopamine PET typically show normal cardiac innervation → Typically abnormal in PD and Pure Autonomic Failure. Conflicting studies though.

• Urodynamic studies may reveal an atonic bladder with low urethral pressure and detrusor-sphincter dyssynergia
Lewy Body Dementias

LBD

PDD

Parkinson’s Disease Dementia

DLB

Dementia With Lewy Bodies
Round α-synuclein aggregates called **Lewy bodies** (LBs), in the neuronal body, and fibrils made of α-synuclein, called **Lewy neurites** in neuronal processes and in astrocytes and oligodendroglia.
Dementia with Lewy Bodies

• **Epidemiology:**
  - Second most common neurodegenerative dementia
  - Approximately 4-16% of cases of dementia seen in the clinic.
  - Underdiagnosed and true prevalence is likely much higher.
  - Frequently misdiagnosed as Alzheimer’s disease.

Core Clinical Features:
- Fluctuating Cognition
- Visual Hallucinations
- REM Sleep Behavior Disorder (RBD)
- One or more spontaneous cardinal feature of parkinsonism
  - Slowness of movement
  - Reduced amplitude of movement
  - Resting tremor
  - Rigidity

Indicative Biomarkers:
- SPECT/ PET: Reduced dopamine transporter (DaT) uptake in basal ganglia
- Abnormal 123I-MIBG myocardial scintigraphy
- Polysomnographic evidence of RBD without atonia (RSWA)

Probable DLB:
- Two or more core clinical features, with or without the presence of indicative biomarkers, or
- Only one core clinical feature, but with one or more indicative biomarkers

Possible DLB:
- Only one core clinical feature, with no indicative biomarker evidence, or
- Only one or more indicative biomarkers, but no core clinical features

**Clinical Features:**
- **Cognitive Impairment:** + Progressive, + Fluctuations, + Precedes motor parkinsonism, or occurs within 1 year of its onset (vs. PDD)
- Recurrent visual hallucinations – usually people or animals (same in PDD)
- REM sleep behavior disorder – dream enactment, vocalizations, “fights in sleep”
- Parkinsonism
- Delusions, paranoia, behavioral disturbances
- Autonomic dysfunction (MSA>DLB>PD in severity)
- Postural instability with falls
- Neuroleptic sensitivity → Never give antipsychotics (except quetiapine, clozapine or pimavanserin) or other DA blockers (e.g. metoclopramide, compazine)
- Other neuropsychiatric manifestations: apathy, anxiety, depression

**Diagnostic Markers:**
- Reduced dopamine transporter (DaT) uptake in striatum [DaTscan (+)]
- Abnormal $^{123}$I-MIBG SPECT
  - Shows cardiac autonomic denervation.
- FDG-PET shows “Cingulate Island Sign” (Posterior hypometabolism with preserved posterior cingulate cortex metabolism)
- PSG showing REM sleep without atony (RSWA) – polysomnographic evidence of RBD
- Relative preservation of medial temporal lobe structures on CT/ MRI scan
Prodromal Synucleinopathies

- **REM sleep behavior disorder (RBD):**
  - Loss of muscle atonia during REM sleep with accompanying vivid dream enactment.
  - Idiopathic RBD (occurring without overt synucleinopathy) has 74-93% conversion rate to symptomatic synucleinopathy (PD, DLB or MSA) over long term follow up. (Iranzo et al, 2013; Postuma et al, 2019).
  - NAPS Consortium – Longitudinal cohort study of RBD / prodromal synucleinopathy with 10+ centers, >230 RBD patients enrolled. Goal of NAPS Consortium is biomarker development leading to prodromal neuroprotection trials.

- **Idiopathic Anosmia: (loss of smell)**
  - PARS study- combination of hyposmia and putaminal DAT uptake deficit was highly predictive of conversion to PD within 4 years of clinical follow-up.
  - New DDx for anosmia: COVID-19 infection (history). This will impact the epidemiology of anosmia.

- **LRRK2 gene mutation carriers:** (penetrance and time to phenoconversion not well established)
  - Commonest cause of autosomal dominant PD, accounting for about 1% of all PD cases

- **GBA gene mutation carriers:** (penetrance and time to phenoconversion not well established)
  - Homozygous mutations cause type 1 Gaucher’s disease (GD), the commonest lysosomal storage disorder and patients with GD are at increased risk of PD.
  - About 5%–10% of PD patients have mutations in the GBA1 gene

Progressive Supranuclear Palsy

• **Epidemiology:**
  - Prevalence is around 6 per 100,000
  - Older age of onset than PD
  - Rapid progression, mean survival 6-7 years

• Also called Steele-Richardson-Oszewski Syndrome

PSP: Clinical Features

• Parkinsonism: Akinetic–rigid syndrome
• Early gait dysfunction (falls within 1 year), progressive freezing of gait.
• Eye movement abnormalities
  o Supranuclear vertical gaze palsy
  o Slowed vertical saccades
  o Vertical OKN loss
  o Square wave jerks
  o Blepharospasm
  o Eyelid opening apraxia
• Dystonic postures – Axial & limb
• Pseudobulbar affect & speech
• Executive dysfunction & slow processing
• Apathy
Oculomotor Dysfunction: Severe impaired pursuits in all directions, vertical moreso than horizontal.
Subtypes From pathological Cohorts

• PSP with Richardson syndrome (PSP-RS), the classic form of PSP
• PSP with predominant parkinsonism (PSP-P)
• PSP with predominant oculomotor dysfunction (PSP-OM)
• PSP with predominant postural instability (PSP-PI)
• PSP with progressive gait freezing (PSP-PGF)
• PSP with predominant frontal presentation (PSP-F)
• PSP with predominant speech/language disorder (PSP-SL)
• PSP with predominant corticobasal syndrome (PSP-CBS)
• PSP with predominant cerebellar ataxia (PSP-C)
• PSP with predominant primary lateral sclerosis (PSP-PLS)
<table>
<thead>
<tr>
<th>Ocular Motor Dysfunction</th>
<th>Postural Instability</th>
<th>Akinesia</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1: Vertical supranuclear gaze palsy</td>
<td>P1: Repeated unprovoked falls within 3 years</td>
<td>A1: Progressive gait freezing within 3 years</td>
<td>C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech</td>
</tr>
<tr>
<td>O2: Slow velocity of vertical saccades</td>
<td>P2: Tendency to fall on the pull-test within 3 years</td>
<td>A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant</td>
<td>C2: Frontal cognitive/behavioral presentation</td>
</tr>
<tr>
<td>O3: Frequent macro square wave jerks or “eyelid opening apraxia”</td>
<td>P3: More than two steps backward on the pull-test within 3 years</td>
<td>A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive</td>
<td>C3: Corticobasal syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Certainty</th>
<th>Combinations</th>
<th>Predominance Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite PSP</td>
<td>Neuropathological diagnosis</td>
<td>Any clinical presentation</td>
</tr>
<tr>
<td>Probable PSP</td>
<td>(O1 or O2) + (P1 or P2)</td>
<td>PSP with Richardson’s syndrome</td>
</tr>
<tr>
<td></td>
<td>(O1 or O2) + A1</td>
<td>PSP with progressive gait freezing</td>
</tr>
<tr>
<td></td>
<td>(O1 or O2) + (A2 or A3)</td>
<td>PSP with predominant parkinsonism</td>
</tr>
<tr>
<td></td>
<td>(O1 or O2) + C2</td>
<td>PSP with predominant frontal presentation</td>
</tr>
<tr>
<td>Possible PSP</td>
<td>O1</td>
<td>PSP with predominant ocular motor dysfunction</td>
</tr>
<tr>
<td></td>
<td>O2 + P3</td>
<td>PSP with Richardson’s syndrome</td>
</tr>
<tr>
<td></td>
<td>A1</td>
<td>PSP with progressive gait freezing</td>
</tr>
<tr>
<td></td>
<td>(O1 or O2) + C1</td>
<td>PSP with predominant speech/ language disorder</td>
</tr>
<tr>
<td></td>
<td>(O1 or O2) + C3</td>
<td>PSP with predominant CBS</td>
</tr>
</tbody>
</table>
PSP and CBD

- Neurofibrillary tangles, tufted astrocytes and neuropil threads
- Tau-positive neurons

Typical Tufted Astrocytes with phosphorylated tau

Mickey Mouse Sign/Morning Glory Sign
Concavity of the lateral margin of the tegmentum of the midbrain
Hummingbird Sign

a.k.a. Penguin Sign
Cortico-Basal Ganglionic Degeneration

**Epidemiology:**
- Prevalence is around 5 per 100,000
- Age of onset = 50-70 years
- Rapid progression, low life expectancy

**Key Clinical Features:**
- Parkinsonism: Akinetic-Rigid syndrome
- Marked asymmetry of signs
- Classically presents with single rigid and/or dystonic limb, jerky/tremulous (myoclonus)
- Apraxia – progressive asymmetric ideomotor limb apraxia
- Impaired cortical sensation
- Useless limb/ “alien limb”
- Early gait instability (falls)
- Dementia
- Poor response to levodopa

Cortico-Basal Ganglionic Degeneration

Limb apraxia
Clinical syndromes associated with CBD Pathology

- Corticobasal syndrome (CBS), 37 percent
- Progressive supranuclear palsy syndrome, 23 percent
- Frontotemporal dementia, 14 percent
- Alzheimer-like dementia, 8 percent
- Aphasia, typically categorized as primary progressive aphasia or progressive nonfluent aphasia, 5 percent
- Mixed diagnoses involving the above phenotypes, 6 percent
- Parkinson disease, 4 percent
- Dementia with Lewy bodies, 1 percent
- Other, 1 percent
Parkinsonism

Primary/Neurodegenerative

- Parkinson’s Disease
  - Sporadic
  - Familial

- Atypical Parkinsonian Disorders
  - Multiple System Atrophy
  - Progressive Supranuclear Palsy
  - Corticobasal Degeneration
  - Dementia with Lewy Bodies

Secondary

- Vascular Medications
- Functional Toxins
- Others

Others
United Kingdom Brain Bank Diagnostic Criteria for Parkinson’s Disease

- **Cardinal Features:**
  - Bradykinesia
  - At least 1 of these
    - Rigidity
    - 4-6 Hz rest tremor
    - Postural instability

- **Supportive criteria**
  - Unilateral onset
  - Rest tremor
  - Progressive disorder
  - Persistent asymmetry
  - Excellent response to LD
  - LD induced dyskinesia
  - LD response > 5 yrs

- **Exclusion Criteria**
  - History of stroke
  - History of repeated head injury
  - History of encephalitis
  - Oculogyric crisis
  - Neuroleptic therapy
  - Sustained remission
  - Unilateral features for >3 yrs
  - Supranuclear gaze palsy
  - Cerebellar signs
  - Early autonomic failure
  - Early severe dementia
  - Babinski sign
  - Tumor or hydrocephalous
  - No response to Levodopa

Hughes et al JNNP 1992
Absolute exclusion criteria: The presence of any of these features rules out PD:

1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades) → MSA-C, SCA

2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades → PSP

3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 y of disease → FTD

4. Parkinsonian features restricted to the lower limbs for more than 3 y → vascular parkinsonism, NPH

5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

7. Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive Aphasia → Corticobasal Syndrome/CBD

8. Normal functional neuroimaging of the presynaptic dopaminergic system

9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient’s symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD → DLB and 1-year rule not addressed.

Follow patients with fragments of syndromes, overlap or otherwise not fitting criteria cleanly!!

→ I do not consider this an absolute exclusion criterion in my own practice.
Ancillary Features
- Levodopa Responsiveness

- Parkinsonism may improve with L-dopa in 80-87% of DLB patients
- SCA-2 patients may have dopa responsive parkinsonism
- Some drug-induced cases respond (Valproic acid)
Ancillary Features
- Levodopa dyskinesias

- Seen in a majority of patients with autopsy diagnosed PD.
- Not specific to PD and may be seen in MSA. The dyskinesia in MSA patients are usually facial.
- Dyskinesia have been reported rarely to occur in PSP and even in autopsy proven CBD.
- Also reported in dopa responsive parkinsonism in SCA-2.
- Some drug-induced Parkinsonian cases develop dyskinesia.
DDx of Parkinsonism

Neurodegenerative vs. Other
- Conditions
- Diagnostic Approach

MSA, PSP, DLB and Other Atypical Parkinsonism
- Epidemiology
- Clinical Features
- Diagnostic Approach

Parkinson’s Disease vs. Atypical Parkinsonism
- Clinical Features
- Diagnostic Approach

Diagnostic Imaging Tools:
- SPECT: DaTscan and MIBG
- Neuromelanin-sensitive MRI
Iodine-123-Ioflupane (FP-CIT) SPECT

- Commercially available in Europe since 2000
- FDA approved in the US since 2011 to differentiate PD from ET
- “Indicated for loss of dopamine neuron terminals in the striatum in patients with clinically uncertain parkinsonian syndromes”
- Also used to differentiate DLB from AD
- And PD from DIP and FMD
- Early possible parkinsonism, fragments of syndrome, prodromal features
- Doesn’t differentiate PD, MSA and PSP.
If dopamine transmission is normal, DaTSCAN will be distributed in a ‘comma’ shaped striatum.

Loss of dopamine neurons in DLB reduces DaTSCAN uptake, resulting in a ‘full stop’ shape.
The melanized catecholamine neurons of substantia nigra pars compacta (SNc) and locus coeruleus (LC) degenerate profoundly in PD.

- Neuromelanin-sensitive MRI (NM-MRI) generates hyperintense contrast in SNc and LC.
- We studied 38 PD and 26 controls to assess classification accuracy based on NM-MRI + clinical features.
- 6 clinical items/summaries from validated questionnaires were selected along with 4 MRI features to be included in the classification model. MRI features were generated with a semi-automated method with operator independent segmentation of SNc and LC.
- A logistic regression + elastic net model with 5-fold cross validation was used for multivariate classification of PD and control subjects.
The ROC curve for the classification model is shown in the figure.

The average AUC was **0.9571**.

The central thin line is the mean ROC, and the grey patch is the 95% confidence interval from 5-fold cross-validation.

Most informative features were NM-MRI SNc volume and the MDS-UPDRS Part II self-report questionnaire (motor aspects of EDL).

**Conclusion:** The classifier's performance is in a clinically useful range, and it warrants further development as a clinical and research tool.
Authors manually segmented SN volume in NM-MRI dataset (11 PSP, 51 PD, 26 control). They found perfect group classification in PSP vs. PD. SNc volume is lower in PSP than in PD.

Needs replication with more PSP participants and a semi-automated segmentation approach free of potential operator-dependent bias.
Acknowledgements:

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- This work supported in part by funding from a Shared Instrumentation Grant (S10) grant 1S10OD016413-01 to the Emory University Center for Systems Imaging Core.
Collaborators

- NAPS Consortium
- Don Bliwise
- Jason Langley
- Xiaoping Hu
- Stewart Factor
- Babak Mahmoudi
- Bruce Crosson
- Charles A. Ellis

Lab Members & MRI Technicians

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- Sonny Roh
- Samira Yeboah
- Richa Tripathi
- Morgan Lane
Deep Brain Stimulation for Parkinson’s disease

Svjetlana Miocinovic, MD, PhD
Assistant Professor, Neurology
Emory University School of Medicine

Emory Movement Disorders Virtual Symposium
Sept 26, 2020
Disclosures

• None
DBS – pacemaker for the brain

• Implanted pulse generator sends brief electrical pulses into brain areas responsible for motor function

Drawing by Bona Kim, Emory
Basal ganglia
DBS video – Parkinson’s disease

Video courtesy of Jill Ostrem (UCSF)
History of DBS

• 1940-50s: lesioning (ablative) surgery for PD&tremor
• 1960: Levodopa discovery largely ended the era of ablative surgery (except for tremor)
• 1987: DBS for tremor by Benabid and Pollak (Grenoble, France)
• Studies in the normal and MPTP primates
• 1993: First STN DBS (Pollak et al., 1993)
• DBS replaces lesioning surgery because it is reversible/adjustable

Dr. Mahlon DeLong
DBS is established therapy

- Standard of care in movement disorders
- Covered by insurance

<table>
<thead>
<tr>
<th>Year of FDA approval</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Thalamus</td>
<td>Essential and Parkinson’s disease tremor</td>
</tr>
<tr>
<td>2002</td>
<td>STN, GPi</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>2003</td>
<td>STN, GPi</td>
<td>Primary dystonia (HDE)</td>
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<tr>
<td>2009</td>
<td>Anterior limb of the internal capsule</td>
<td>Obsessive compulsive disorder (HDE)</td>
</tr>
<tr>
<td>2018</td>
<td>Anterior thalamus</td>
<td>Epilepsy</td>
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</tbody>
</table>
DBS equipment

Brain electrodes

Stimulator

Patient programmer

Clinician programmer
### FDA approved DBS devices

<table>
<thead>
<tr>
<th></th>
<th>Medtronic</th>
<th>Abbott (St Jude)</th>
<th>Boston Scientific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPG type</strong></td>
<td>Non-rechargeable; Rechargeable (15 yrs)</td>
<td>Non-rechargeable</td>
<td>Non-rechargeable; Rechargeable (15 yrs)</td>
</tr>
<tr>
<td><strong>Electrical field steering capabilities</strong></td>
<td>4 Ring lead 0.5 or 1.5mm spacing Single current source</td>
<td>4 Segmented lead 0.5 or 1.5mm spacing Single current source</td>
<td>8 Ring lead 4 Segmented Lead 0.5mm spacing Multiple current sources</td>
</tr>
<tr>
<td><strong>MRI conditional</strong></td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes (rechargeable IPG only)</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>1997</td>
<td>2016</td>
<td>2018</td>
</tr>
</tbody>
</table>

* Whole body MRI is contraindicated for older Medtronic systems
DBS surgery
“Asleep DBS”
DBS programming
DBS complications

• Cerebral hemorrhage:
  • 0.5-2%
  • Usually within first 24 hrs

• Infection:
  • 3-10%
  • Usually within first month

• Stimulation-induced side effects (motor, sensory, visual, autonomic, cognitive or affective)
  • Variable occurrence
  • Reversible, adjustable
DBS clinical efficacy well established
STN DBS is effective treatment for advanced PD

- 49 PD patients, 5 year follow up
- open label, unblinded assessments
- 54% motor function, 49% ADL improvement (OFF levodopa)
- ON levodopa motor function did not improve, except dyskinesia
- Akinesia, speech, postural stability, and freezing of gait worsened between years 1-5 (ON meds)
STN DBS improves early complications

• 251 PD patients, randomized, 2 yr follow up
  • STN DBS + medications
  • medications alone

• Early complications
  • mean age 52
  • disease duration 7.5 yrs

• Blinded assessments

• 26% vs -1% improvement in QOL

• 53% vs 4% improvement in motor score (off levodopa)
DBS Mechanisms

- DBS reduces abnormal synchronization in the motor network

Silberstein et al. Brain 2003

De Hemptinne et al. 2015, Nature Neurosci
When to consider DBS for PD?

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (levodopa-responsive) PD</td>
<td>Dementia</td>
</tr>
<tr>
<td>Motor fluctuations (wearing off)</td>
<td>Severe mood disturbance</td>
</tr>
<tr>
<td>Levodopa-induced dyskinesia</td>
<td>Medical contraindications</td>
</tr>
<tr>
<td>Medication-resistant tremor</td>
<td>Unrealistic expectations</td>
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</table>

<table>
<thead>
<tr>
<th>Dyskinesias</th>
<th>&quot;On&quot; time without dyskinesias</th>
<th>&quot;Off&quot; time</th>
<th>Time (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without DBS Therapy</td>
<td>With DBS Therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Emory DBS Team

neurology.emory.edu/movement

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- Cady Block, PhD

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- Sherry Dey, MS
- David Loring, PhD
- Cady Block, PhD

Not pictured:
- Neurology: Laura Scorr, MD; Pratibha Aia, MD; Shirley Triche, NP
- Neuropsychology: Ekaterina Staikova, PhD
DBS Process at Emory

• Initial evaluation with a DBS neurologist
• DBS screening
  • Video exam (off and on levodopa)
  • Neurocognitive testing
  • Psychiatry evaluation
  • Motion analysis (objective motor exam)
  • MRI brain
• Multidisciplinary conference
• Neurosurgery consultation
• Surgery
• Initial programming
• Follow up programming
• Comprehensive assessments at 6m, 12m, 24m
Emory DBS


- Emory Brain Health Center: (404) 778-3444

- Email: Svjetlana.Miocinovic@emory.edu
Video Presentation

Daniel Huddleston, MD
Stewart Factor, DO
Parkinson’s vs Drug-induced Parkinsonism

• 71-year-old man, hx of bipolar disorder since his 50’s and anxiety disorder.
• 2001 developed right hand tremor.
• It progressed slowly after 9 years was diagnosed with PD.
• He later noted shuffling gait and has had two falls. Micrographia developed. He recently developed start hesitation.
• For his bipolar he is treated with neuroleptics: Aripiprazole and olanzapine both for 9 years.
Worsening ET vs New onset Parkinson’s disease

• 70-year-old woman
• 20 yrs history of Essential Tremor
• New onset rest tremor
• Also has gait difficulty & rigidity, bradykinesia, micrographia, & Orthostatic tremor on exam
Progressive Supranuclear Palsy
Primary Progressive Freezing of Gait
77-year-old woman presented with progressive gait hesitating, difficulty arising from a chair, and bradykinesia.
Multiple System Atrophy
36 year old woman with gait disorder and autonomic dysfunction
Disproportionate Anterocollis

Myopathy vs dystonia
55 year old Man seen in 2018

• Age of onset 42.
• Periodic falling backwards.
• Developed tremor in 2007.
• Started on carbidopa/levodopa in 2007 - Responsive. He is on 2 tabs now 9am, 1pm, 6pm, and 10pm.
• He developed wearing off 1 year ago and dyskinesia in 2014.
• He has used a cane to walk for 3 years and a walker in the last year.
• He says he has periodic freezing of gait.
• His voice is slurred and low volume, he has dysphagia choking daily,
• Needs help cutting food and dressing. He has to sit in the shower but bathes himself otherwise.
• He denies loss of sense of smell and RBD.
Diagnosis: SCA2
Corticobasal Syndrome
Other cases
72 year old man with a 2 yr history of gait disorder
19 year old presents with handwriting change, problems with fine motor movements, drooling and irritability