PARKINSONISM
Marsha Smith, MD
Senior Medical Director
SOMC Neurology Associates
DEFINITION

- A constellation of symptoms including:
  - bradykinesia
  - cogwheel rigidity
  - resting tremor
  - postural instability
  - gait difficulties
  - Plus various non motor symptoms
WHY IDIOPATHIC PDISM VS OTHERS

- **PROGNOSIS**—the other forms of parkinsonism have worse prognosis
- **TREATMENT**—other forms aren’t as responsive to treatment. Medications that are studied and have FDA approval are only for Idiopathic PD
**Pathology and Anatomy - Idiopathic PD**

- Motor symptoms due to: loss of dopaminergic neurons in pars Compacta of the Substantia Nigra
- The dopaminergic neurons then project to the Striatum - (Caudate and Putamen) and modulate motor activity with connection to the motor cortex, which is part of the Frontal lobe.
PATHOLOGY AND ANATOMY

- TYPICAL LOOK OF NORMAL SUBSTANTIA NIGRA AND DISEASED NIGRA IN PATIENT WITH IDIOPATHIC PD
IDIOPATHIC PD MRI BRAIN

- MRI BRAIN—showing normal appearing Substantia Nigra
PATHOLOGY AND ANATOMY-IDIOPATHIC PD

- BASIC PATHOLOGY SHOWING MOTOR AND SENSORY CORTEX.
- THE INTERACTION BETWEEN THE CORTEX AND STRIATUM OCCURS VIA 2 PATHWAYS:
  - 1. DIRECT PATHWAY
  - 2. INDIRECT PATHWAY
INDIRECT PATHWAY—inhibits movement

- striatum receives inhibitory dopaminergic input from SNc (D2 receptors) and inhibits Gpe via GABA.
- GPe inhibits subthalamic nucleus, which excites Gpi
- striatal output suppresses GPe activity → increased output from subthalamic nucleus → increased activity within Gpi → inhibition of thalamus → decreased cortical activity = diminished movement
DIRECT PATHWAY – INCREASE MOVEMENT

1. Striatal output suppresses GPi activity and Substantia Nigra pars reticulate using mainly GABA

2. Decreased GPi increases thalamic activity

3. Increased Thalamic activity increases cortical activity to facilitate movement

4. Via D1 receptors
DOPAMINE EFFECT IN DIRECT VS INDIRECT PATHWAY—IDIOPATHIC PD

- **SUBSTANTIA NIGRA** pars compacta—overall effect is to facilitate intended movement and inhibits unintended movement
- EXCITES DIRECT pathway and INHIBITS INDIRECT pathway through action of dopamine
- DIRECT PATHWAY—utilizes D1 receptors and are EXCITED by DOPAMINE
- INDIRECT PATHWAY—utilizes D2 receptors—INHIBITED by DOPAMINE
CLASSIFICATION
PARKINSONISM

- IDIOPATHIC PARKINSONISM-PD-genetic, sporadic cases
- ATYPICAL PARKINSONISM-Multiple Systems Atrophy, Progressive Supranuclear Palsy, Corticobasal syndrome
- HEREDODEGENERATIVE-PLA2G6-associated neurodegeneration, aceruloplasminemia, X-linked dystonia-Parkinsonism, spinocerebellar ataxias)
- SECONDARY-drug induced, vascular, structural, infectious, immunologic, toxic, traumatic, metabolic
CLASSIFICATION OF NEURODEGENERATIVE DISORDERS

- PROTEINOPATHY--based on pathology showing various proteinaceous material in the tissue of most neurodegenerative disorders.

- These proteinaceous material can either be intracellular inclusions or extracellular deposits.

- Examples: alpha synuclein, beta amyloid, tau, ubiquitin
# Proteinopathies

<table>
<thead>
<tr>
<th>Proteinopathy</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid</td>
<td>Alzheimer (AD)</td>
</tr>
<tr>
<td>Ubiquitin-proteosome</td>
<td>Parkinson Disease (PD), Parkin mutation</td>
</tr>
<tr>
<td>Synucleinopathies</td>
<td>PD, Lewy body dementia (LBD), multiple system atrophy (MSA),</td>
</tr>
<tr>
<td>Tauopathies</td>
<td>Progressive Supranuclear palsy (PSP), Corticobasal ganglionic degeneration (CBGD), AD, Frontotemporal dementia (FTD) (with parkinsonism)</td>
</tr>
<tr>
<td>Prion</td>
<td>Creutzfeldt-Jakob disease, Gerstmann-Straussler Scheinker syndrome</td>
</tr>
<tr>
<td>Polyglutamine expansion</td>
<td>Huntington disease, Spinocerebellar ataxia</td>
</tr>
</tbody>
</table>
DIFFERENTIAL DIAGNOSIS
PARKINSON DISEASE

- Atypical Parkinsonian syndromes
- Dementia with Lewy bodies
- Drug-induced Parkinsonism
- Dystonic tremor
- Essential tremor
- Frontotemporal dementia
- Functional or psychogenic parkinsonism
- Normal Pressure Hydrocephalus
- Vascular Parkinsonism
ATYPICAL FEATURES OF PARKINSONISM

- Rapid Progression
- Early Dementia
- Early Frequent Falls
- Ocular Dystonia
- Ataxia
- Prominent Dystonia
- Lack of Tremor
- Alien Limb
PROGRESSIVE SUPRANUCLEAR PALSY

- ALSO CALLED STEELE-RICHARDSON-OLSZEWSKI syndrome based on the names of the doctors that characterized this disease
- 5-6% of patients presenting with PDISM
- Average age onset mid 60’s
- Lifetime prevalence 5/100,000
- HALLMARKS-EARLY- USUALLY WITHIN 1-2 YRS: UNEXPLAINED FALLS, POSTURAL INSTABILITY, VERTICAL SUPRANUCLEAR PALSY, PROGRESSIVE DEMENTIA
- SEVERAL TYPES-SEE TABLE
PROGRESSIVE SUPRANUCLEAR PALSY

- TYPICAL EYE FINDINGS:
  - A-LOOK UP-NOT ABLE
  - B-LOOK SIDE
  - C-LOOK SIDE
  - D-LOOK DOWN-NOT ABLE
  - E AND F—EXAMINER MOVES THE HEAD AND EYES MOVE WHICH TELLS US EYE MUSCLES ARE WORKING—PROBLEM IS NUCLEUS
PROGRESSIVE SUPRANUCLEAR PALSY FEATURES

- GAIT-stiff, broad based, knees extended and arms abducted—"DRUNKEN SAILOR". TURNS--PIVOT
- Falls frequently—mainly going up steps
- HALLMARK—Limitation in downgaze—more sensitive. Up gaze is also affected but also seen as part of aging and other neurodegenerative disorders. MONA LISA STARE
- Square wave jerks—saccadic intrusions seen during fixation
- Blurred vision, diplopia
- Aphasia—speech is monotonous/hypernasal
- Dysphagia
- Cognitive Decline-Frontal/subcortical—slow processing, decrease fluency, bradyphrenia, executive dysfunction.
## Types of PSP

<table>
<thead>
<tr>
<th>PSP Syndromes</th>
<th>Clinical</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>See other slide</td>
<td>GP, Midbrain, dentate nucleus, striatum</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Tremor, bradykinesia, responds Levodopa, late cognitive decline</td>
<td>Substantia nigra, STN</td>
</tr>
<tr>
<td>Pure Akinesia-Gait Freezing</td>
<td>Early gait diff, fog, speech diff, micrographia. Longer disease duration</td>
<td>Motor Cortex, Cerebellum, Pons</td>
</tr>
<tr>
<td>Corticobasal Syndrome</td>
<td>Dystonia, Dyspraxia, cortical sensory loss, speech apraxia</td>
<td>Frontal and Parietal Cortex</td>
</tr>
<tr>
<td>Behavioral Variant/FTD</td>
<td>Cognitive, personality. Late parkinsonism</td>
<td>Frontotemporal Cortex</td>
</tr>
<tr>
<td>Primary Lateral Sclerosis</td>
<td>Bulbar, limb weakness, UMN signs, spasticity</td>
<td>Frontal, Corticospinal Tract</td>
</tr>
</tbody>
</table>
DIAGNOSING PSP

- NO SPECIFIC LAB, IMAGING OR MARKERS
- ANCILLARY TESTING CAN BE SUPPORTIVE--IN RARE CASES MRI CAN BE HELPFUL IF--HUMMINGBIRD SIGN IS SEEN
DIAGNOSING PSP

- MRI BRAIN FINDINGS:
CORTICOBASAL GANGLIONIC DEGENERATION

- Classic presentation: ASYMMETRIC RIGIDITY, DYSTONIA, IDEOMOTOR APRAXIA, ASYMMETRIC HAND CLUMSINESS, EARLY BRADYKINESIA, FRONTAL SYNDROME, TREMOR, RIGIDITY

- ONSET-60’s

- Prognosis: mean survival 7yrs

- POOR LEVODOPA RESPONSE
CBGD-CLASSICAL FEATURES

- Alien limb phenomena
- Coarse rest/action tremor
- Apraxia-limb, speech, gait. Apraxia-inability to perform or movement despite normal function
- Myoclonus
- Cortical sensory loss—agraphesthesia
- Limb dystonia, and later contracture
- Frontal, cortical dementia-slow processing, bradyphernic, decrease fluency
- Gaze palsy
- Postural instability
- Dysphagia
## Types of Corticobasal Degeneration

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features</th>
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<tbody>
<tr>
<td>Classic</td>
<td>See other slide</td>
</tr>
<tr>
<td>Frontal Behavioral</td>
<td>Executive dysfunction, behavior/personality changes</td>
</tr>
<tr>
<td>Posterior Cortical Atrophy</td>
<td>Visuospatial, apraxia, myoclonus, AD pathology</td>
</tr>
<tr>
<td>Progressive Nonfluent/Agrammatic Aphasia</td>
<td>Effortful, aggramatic speech, impaired grammer/sentence comprehension or groping, distorted speech</td>
</tr>
<tr>
<td>PSP Syndrome</td>
<td>Axial or symmetric limb rigid/akinetic, falls, postural instability, gaze palsy, urinary incontinence</td>
</tr>
</tbody>
</table>
DIAGNOSING CBGD

- IMAGING can be helpful
- MRI/CT brain-can show ASYMMETRIC FRONTOPARIETAL ATROPHY.
- Fludeoxyglucose positron emission tomography (FDG-PET) -- can reveal asymmetric cortical metabolism.
- Levodopa–positron emission tomography (DOPA-PET) --uptake is reduced in the striatum and highly asymmetric in the cortex.
- β-CIT (iodine-123-2β-carbomethoxy-3β-[4-iodophenyl]tropane) SPECT-reduced asymmetric striatal binding, but is nonspecific to CBD
CORTICOBASAL DEGENERATION

- Asymmetric atrophy LEFT FRONTAL AND PARIETAL CORTEX
## Multiple Systems Atrophy

### Clinical Presentation

<table>
<thead>
<tr>
<th>Features</th>
<th><strong>Clinical Presentation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonian (Shy Drager/Striatonigral Degeneration)</td>
<td>Onset &gt;40, duration &lt;10yrs, poor response to Levodopa, autonomic failure (OH, bladder dysfunction)</td>
</tr>
<tr>
<td>Cerebellar – (Olivopontocerebellar Atrophy)</td>
<td>Ataxia, mild PDISM, cognitive decline,</td>
</tr>
</tbody>
</table>
MSA Parkinsonian-Higher Incidence

- Tremor-higher frequency, lower amplitude, myoclonic
- More symmetric features at onset unlike idiopathic PD
- Postural instability occurs later
- Speech difficulties
- Respiratory or laryngeal stridor
- Poor response to Levodopa
- Early development of facial dyskinesia
- Rapid progression
- Sleep disturbance-RBD, Sleep apnea
- Dystonia-axial and dysautonomia
MSA CEREBELLAR

- Cerebellar limb and gait ataxia
- Early falls
- Dysarthria (scanning, ataxic)
- Dysphagia
- Gaze impairment
- Upper and lower motor signs
- Progressive dementia
- Depression, anxiety
DIAGNOSING MSA

- MRI-can be helpful-- bilateral T2 hypointensity in the posterolateral putamen, representing iron deposition, and slit hyperintensity in the lateral margin of the putamen.
- Olivopontocerebellar atrophy is consistent with MSA-C. Pontine atrophy and gliosis may be apparent on T2-weighted images in a hot cross bun–like pattern.
- PET scans--decreased striatal and frontal metabolism.
- DAT (\(^{125}\)I-ioflupane) SPECT also typically shows asymmetric reduced striatal binding
AUTONOMIC TESTING FOR MSA

- AUTONOMIC TESTING: TILT TABLE testing, 24-hour ambulatory blood pressure and HR monitoring, and baroreceptor sensitivity -- ability to regulate blood pressure by controlling heart rate, contractility, and peripheral resistance.

- OFFICE—check supine blood pressure with heart rate, then standing repeat after 3 minutes. A drop in systolic blood pressure > 20 mm Hg or drop in diastolic blood pressure > 10 mm Hg with minimal rise in heart rate is diagnostic.

- Other tests: sweat testing (eg, quantitative sudomotor axon reflex test [QSART]) and gastric emptying study (for gastroparesis), and urodynamics for urinary dysfunction
MRI IMAGING AND MSA-P

- HOT CROSS BUN sign
DEMENTIA WITH LEWY BODY

- Brain MRI: diffuse cerebral atrophy with relative preservation of the occipital and mesial temporal lobes. In Alzheimer disease the contrast is seen.
- SPECT--occipital hypoperfusion have reported some specificity/sensitivity in discriminating DLB from Alzheimer disease.
- FDG-PET has also been used to examine occipital (and parietal) lobe changes in DLB. There is emerging evidence for the cingulate island sign, or preservation of FDG-PET metabolism in the posterior cingulate relative to the cuneus and precuneus, that correlates with DLB versus Alzheimer pathology.
- Dopaminergic imaging (ie, DAT-SPECT)- may be useful if there is question regarding the diagnosis of DLB, but is not specific.
DEMENTIA WITH LEWY BODY-DIAGNOSIS

- Pittsburg compound B (PiB) scanning also can be helpful to assess amyloid burden, given the association with DLB more than in PD dementia.
- In Alzheimer disease---CSF total and phosphorylated tau levels are increased and amyloid-β level is reduced.
- CSF tau (and possibly also α-synuclein) is significantly lower in DLB than in Alzheimer disease
- DLB—REMEMBER IS SYNUCLEINOPATHY SIMILAR TO PD WHILE AD IS A TAUOPATHY
IDIOPATHIC PD-UK PD SOCIETY BRAIN BANK CLINICAL CRITERIA

- **STEP 1**—presence of BRADYKINESIA (hypophonia, micrographia, hypomimia) PLUS at least 1 of the following: RIGIDITY, REST TREMOR 4-6hz (70%), Postural instability (mild initially)

- **STEP 2**—ABSENCE OF: repeated stroke, encephalitis, repeated head injury, oculogyric crisis, any period of sustained remission, neuroleptic treatment at onset of symptoms, early severe autonomic involvement, early severe dementia, 1-methyl-4-phenyl 1, 2, 3, 6-tetrahydropyridine (MPTP) exposure.

- OR FINDING ANY OF THE FOLLOWING: strictly unilateral after 3yrs, cerebellar signs, supranuclear gaze palsy, negative response to Levodopa, Babinski sign, cerebral tumor or communicating hydrocephalus on imaging
STEP 3 - PRESENCE OF >3 SUPPORTING CRITERIA: Unilateral onset, resting tremor present, progressive, clear response to Levodopa, Levodopa responsiveness for >5yrs, clinical course >10yrs, persistent asymmetry with side of onset being worse, Levodopa induced dyskinesia,
NONMOTOR SIGNS OF PARKINSON DISEASE

- AFFECTIVE DISORDERS
- AUTONOMIC DYSFUNCTION
- COGNITIVE DYSFUNCTION
- FATIGUE
- SLEEP DISTURBANCE
- SEXUAL DYSFUNCTION
- SOMATOSENSORY DYSFUNCTION
- URINARY DYSFUNCTION
- SPECIAL SENSORY
- VISUAL DISTURBANCE
COMMON NONMOTOR SIGNS

PD

- SLEEP DISTURBANCE - Insomnia (36%), REM SLEEP BEHAVIOR - RBD (28%), Excessive daytime somnolence (28%), Vivid dreams (24%)
- AFFECTIVE DISORDERS - Depression (43%), anxiety (30%), anhedonia (32%)
- COGNITIVE DYSFUNCTION - Orthostatic hypotension (21%)
- COGNITIVE DYSFUNCTION - Memory impairment (32%), bradyphrenia, inattention (28%)
- GI DYSFUNCTION - Constipation (39%)
- SEXUAL DYSFUNCTION - Decrease libido, erectile dysfunction
- SPECIAL SENSORY — Impaired olfaction (46%)
- URINARY DYSFUNCTION — Polyuria (28%), urgency (34%)
GENETICS AND PARKINSON DISEASE

- Sporadic cases account for <10% of idiopathic cases
- Consider genetic causes if onset <40yrs old, strong family history suggestive of recessive or dominant pattern of inheritance,
- Several genes have been implicated including PARKIN,
HOEHN AND YAHRI STAGING
PD

- Stage 1.0—Unilateral involvement only
- Stage 1.5—Unilateral and axial involvement
- Stage 2.0—Bilateral involvement without impairment of balance
- Stage 2.5—Mild Bilateral disease with recovery on pull test
- Stage 3.0—Mild to moderate bilateral disease; some postural instability; physically independent
- Stage 4.0—Severe disability; still with ability to walk or stand unassisted
- Stage 5.0—Wheelchair dependent or bedridden unless aided
BRAAK HYPOTHESIS OF PARKINSON DISEASE

- In 2003, Heiko Braak et al—wrote article in Neurobiology of Aging—article that described 6 stages of Parkinson disease based on presence of Lewy bodies. Heiko Braak et al. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiology of Aging. 2003; 24:197-211

- The pre-symptomatic phase of PD patient usually falls within Stage 1, 2 & 3; while symptomatic phase falls into the stage 3, 4, 5 & 6.
**Braak Stages of PD**

- Stages 1-3—presymptomatic
- Stages 3-6—symptomatic PD
BRAAK HYPOTHESIS

- STAGE 1—Stage 1 (Medulla oblongata)
  Lesions—dorsal glossopharyngeal/vagal motor nucleus and frequently in the anterior olfactory nucleus. MAY EXPLAIN—PRE-SYMPTOMATIC loss of sense of smell. MAY HAVE involvement—intermediate reticular zone. Along with this stage is the Lewy pathology in the enteric nervous system—MAY EXPLAIN CONSTIPATION in pre-symptomatic phase.
BRAAK STAGING OF PD

- STAGE 2 - MEDULLA OBLONGATA, PONTINE TEGMENTUM
  Stage 1 plus lesions in caudal raphe nuclei (SEROTONIN), gigantocellular reticular nucleus, and coeruleus–subcoeruleus (NORADRENALINE) complex.

- STAGE 3 -- MIDBRAIN
  Pathology of stage 2 plus midbrain lesions, particularly in the pars compacta of the substantia nigra—START TO BECOME SYMPTOMATIC PD.
BRAAK HYPOTHESIS PD

- Stage 5 - NEOCORTEX
  Stage 5 and above involved the neocortex. Its lesion include those of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex.

- STAGE 6 NEOCORTEX
  Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field.
BRAAK HYPOTHESIS—"The prion hypothesis in Parkinson's disease: Braak to the future"—Acta Neuropathologica Communications 2013:1:2
IMAGING AND PARKINSONISM--PET

- Fludeoxyglucose positron emission tomography (FDG–PET): Approved in the US--measure differences in glucose metabolism. FDG-PET is currently limited to the differentiation of Alzheimer disease and frontotemporal dementia.

- FDG-PET may be especially useful in the differentiation of atypical parkinsonism—NOT CURRENTLY BUT in the future as the research in this area evolves.
18F-FDG PET images of PD and multiple-system atrophy patient. David J. Brooks J Nucl Med 2010;51:596-609
**DAT SPECT SCAN**

- SPECT -- Ioflupane I-123 single-photon emission computed tomography (SPECT) -- approved in 2011 to aid in diagnosis of PDISM. The compound binds to the presynaptic dopamine transporter (DAT) and acts as a marker for dopamine levels in the striatum. **MAINLY USEFUL IN DIAGNOSIS PARKINSONISM FROM ESSENTIAL TREMOR.**

- **NOT COMMONLY USED CLINICALLY—RESULTS CAN BE MISLEADING. MEDS THAT REDUCE DAT BINDING HAVE TO BE HELD—SSRI, SNRI, AMPHETAMINE, COCAINE**

- **ALSO DAT BINDING DOES NOT CORRELATE WITH DISEASE SEVERITY**
**DAT SCAN**

- **Normal**— distinct “comma-like” or crescent shapes.
- **ABNORMAL**— either two circular “period-like” or oval shapes or a combination of “period” and “comma” shapes, indicating a reduced uptake of DaTscan in certain dopaminergic areas of the brain.

*Example of normal DaTscan image:*

In transaxial images, normal images are characterized by two symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. Striatal activity is distinct relative to surrounding brain tissue.

*Examples of abnormal DaTscan images:*

- Abnormal images fall into at least one of the following three categories (all are considered abnormal)
  - Activity is absent in the putamen of both hemispheres and greatly reduced in one or both caudate nuclei. Activity of the striatum with respect to the background is reduced.
  - Activity is absent in the putamen of both hemispheres and confined to the caudate nucleus. Activity is relatively symmetric and forms two roughly circular or oval foci. Activity of one or both is generally reduced.
  - Activity is asymmetric, e.g., activity in the region of the putamen of one hemisphere is absent or greatly reduced with respect to the other. Activity is still visible in the caudate nuclei of both hemispheres, resulting in a comma or crescent shape in one and a circular or oval focus in the other. There may be reduced activity between at least one striatum and surrounding tissues.
DAT SPECT SCAN

- EMITS RADIATION

--administer Potassium Iodide Oral Solution or Lugol's Solution (equivalent to 100 mg iodide) or potassium perchlorate (400 mg) to block uptake of iodine 123 by the patient's thyroid. Administer at least one hour before the dose of DaTscan

TREATMENT OPTIONS-NONMOTOR

- Sleep dysfunction—RBD—treat with Clonazepam,
- Urinary dysfunction—secondary to detrusor hyperreflexia. Mainstay of treatment is anticholinergics—cognitive side effects. Newer agent—Mirabegron—no beta adrenergic agonist—no cognitive side effects.
- Orthostatic hypotension—appropriate goals systolic standing 90 and supine 180 mm Hg. Abdominal binder, Fludrocortisone, Droxidopa, Midodrine
TREATMENT OF NONMOTOR PD

- Depression—SSRI-selective serotonin reuptake inhibitors first line—Fluoxetine, Citalopram, Sertraline
- Anxiety—can be just anxiety, exist with depression or be a manifestation of “off” period. Treatment options—SSRI, SNRI, Benzodiazepines
TREATMENT OF NONMOTOR SYMPTOMS—COGNITIVE DYSFUNCTION

- PD-MINIMAL COGNITIVE IMPAIRMENT or PD DEMENTIA—RESULTS IN dysfunction in attention, working memory, executive function, memory, and visuospatial function. Mainly affecting frontal lobe. MAINLY SUBCORTICAL DEMENTIA. WHILE AD—CORTICAL DEMENTIA

- Executive function—cognitive abilities that enable and drive adaptive, goal-oriented behavior. These include the ability to generate thought and think flexibly, to update and manipulate information mentally, to inhibit what is irrelevant to current goals, to self-monitor, and to plan and adjust behavior as appropriate. Clinically, it allows us to plan, focus attention, remember instructions and juggle multiple task to get things done.
Cognitive Impairment in PD

- International Parkinson and MDS criteria for PD dementia--memory does NOT have to be impaired in PD dementia and that dementia can be present if other cognitive domains (eg, executive function, visuospatial function) are affected, including behavioral problems (eg, psychosis, sleep disturbances, mood disturbances).

- EVALUATION: acute or new-onset —R/O infections, Metabolic derangements, dehydration, new neurologic problems, new medical problems and medication effects
BEST TREATMENT OPTION—PD COG IMPAIRMENT

PSYCHOSIS—RISK AND TREATMENT OPTIONS

- SEVERAL ETIOLOGIES—dopaminergic medications OR disease-related factors—abnormalities in visual, sleep, mood, and cognitive processes.
- RISK FACTORS: older age, greater axial rigidity, advanced disease, and potentially genetic susceptibilities
- ACUTE RX—short low dose benzodiazepines, r/o treatable causes
COMPLICATION OF TREATMENT—
DYSKINESIA IN IDIOPATHIC PD

- DYSKINESIA—distortion in performing voluntary movements—usually secondary to prolonged dopaminergic use—ONLY IDIOPATHIC PD.

- Video--
COMPLICATIONS OF TREATMENT

- DYSTONIA-usually OFF phenomena
- Video-
COMPICATIONS OF TREATMENT OF PD—IMPULSE CONTROL DISORDER

- **PUNDING**—stereotyped, purposeless, repetitive behavior.
- **DOPAMINE DYSREGULATION**—addictive-like regimen of self-medicating with high doses of dopaminergic medications, especially short-acting medications and levodopa.
- Risk factors: dopaminergic medications OR disease-related OR other: male sex, early onset of PD, unmarried status, past or current cigarette smoking, personal or family history of alcoholism or gambling, and high impulsive or novelty-seeking traits. Weintraub D, David AS, Evans AH, et al. Clinical spectrum of impulse control disorders in Parkinson’s disease. Mov Disord 2015;30(2):121–127
<table>
<thead>
<tr>
<th>NAME</th>
<th>PHARMA</th>
<th>DOSAGE</th>
<th>SIDE EFFECTS</th>
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<tbody>
<tr>
<td>AMANTADINE</td>
<td>Nmda antagonist</td>
<td>100-300md/d</td>
<td>N, livedo reti,</td>
</tr>
<tr>
<td>CARBIDOPA/LEVO</td>
<td>Aroma aa decar in/dopa prec</td>
<td>25/100 –times per day varies</td>
<td>GI, cognitive, OH,</td>
</tr>
<tr>
<td>DOPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/L ER</td>
<td>Convert dopa</td>
<td>23.75mg/95mg-variable</td>
<td>GI, COG, OH, dizziness</td>
</tr>
<tr>
<td>PRAMIPEXOLE IR/</td>
<td>Dopa agon</td>
<td>0.125mg-1.5mg tid//0.375-4.5mg</td>
<td>Nausea, cog, sleep attack, ICD</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
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<tr>
<td>RASAGILINE</td>
<td>MAO-B Inhib</td>
<td>0.5-1mg/day</td>
<td>Dizzy, flu,</td>
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<tr>
<td>ROTIGOTINE</td>
<td>Dopa agon</td>
<td>2mg/d-6mg/d</td>
<td>Nausea, cog</td>
</tr>
<tr>
<td>TRIHEXY</td>
<td>anticholiner</td>
<td>2mg d-tid</td>
<td>Xerostomia, cog</td>
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<tr>
<td>ROPINIROLE IR/ER</td>
<td>Dopa agonist</td>
<td>0.25mg-8mg tid/2-24mg/d</td>
<td>GI, ICD, cog, drowsy, le edema</td>
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<tr>
<td>SELEGILINE</td>
<td>MAO-B INHIB</td>
<td>5mg bid</td>
<td>Cog, low bp</td>
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</tbody>
</table>
PD patients--higher risk of melanoma is well recognized, as is the increased risk of PD in patients with melanoma

gene variant that produces red hair and fair skin in humans and in mice, which is known to increase the risk of the dangerous skin cancer melanoma, may also contribute to the known association between melanoma and Parkinson's disease. Xiqun Chen et al. The melanoma-linked "redhead" MC1R influences dopaminergic neuron survival. Annals of Neurology; (2017)

red-hair variant of MC1R gene, inactivates the gene and reduces the dopamine-producing neurons making them susceptible to damage, increasing risk for PD, over time.

Melanoma risk is known to be increased in those who carry the red hair variant of the melanocortin 1 receptor (MC1R) gene, due to increased production of the lighter pigment called pheomelanin
TREATMENT OF IDIOPATHIC PARKINSON DISEASE

- HOLY GRAIL -- treatment is slowing neurodegeneration and reducing the increased morbidity and mortality associated with the disease.

- Several clinical trials with drugs and supplements such as coenzyme Q$_{10}$, creatine, pioglitazone, rasagiline, and others--NO known definitive disease-slowing therapy exists. Kalia LV, Kalia SK, Lang AE. Disease-modifying strategies for Parkinson’s disease. Mov Disord 2015;30(11):1442–1450
NONPHARMACOLOGICAL THERAPIES

- Yoga, dance, tai chi, boxing, music therapy, and multiple other nonpharmacologic interventions have all shown benefit and might be useful in a given patient. Bloem BR, de Vries NM, Ebersbach G. Nonpharmacological treatments for patients with Parkinson’s disease. Mov Disord 2015;30(11):1504–1520

- Cognitive exercises--crossword puzzles, word finding, Sudoku, card games, keeping up on current events—may be beneficial

- Physical exercise and rehabilitation strategies should also be prescribed on an ongoing basis
DBS of the STN, or more recently, DBS of the globus pallidus internus (GPi) are the most common targets for the patient with PD with advanced motor fluctuations. Comparison studies of STN versus GPi as targets currently suggest both are clinically effective, but GPi DBS may have fewer neuropsychiatric side effects; however, this is not clear.\textsuperscript{39}

- DBS: superior to best medical therapy for the management of fluctuations and dyskinesia in advanced PD


- With STN DBS, patients can reduce medication by about 50%, with less reduction in medication following GPi DBS
INFUSIONAL LEVODOPA

- USEFUL -- advanced PD - poor DBS candidates because of age constraints or cognitive or behavioral concerns.
- Carbidopa/levodopa (5 mg/mL/20 mg/mL) in a stable methylcellulose gel is pumped through a gastrostomy tube with a jejunal extension. The patient carries the pump. The infusion is commenced during waking hours but can be extended overnight if required for nocturnal symptoms. Additional bolus doses can also be used.
INFUSIONAL DELIVERY

- Carbidopa-levodopa--(5 mg/mL/20 mg/mL) in a stable methylcellulose gel is pumped through a gastrostomy tube with a jejunal extension.
DEEP BRAIN STIMULATION

- Only for idiopathic Parkinson’s disease
- Not effective for the other types of parkinsonism
Deep brain stimulation (DBS)

Successful DBS surgery is critically dependent on precise placement of DBS electrodes into target structures.
CONCLUSION—KNOW YOUR SIGNS

- It isn’t always possible after the first or second office visit to differentiate idiopathic Parkinsonism from the other forms of Parkinsonism.
- Always do trial of carbidopa-levodopa.
- If early hallucinations and fluctuating cognitive impairment consider starting cholinesterase inhibitor—rivastigmine should be first line.