

Parkinson disease

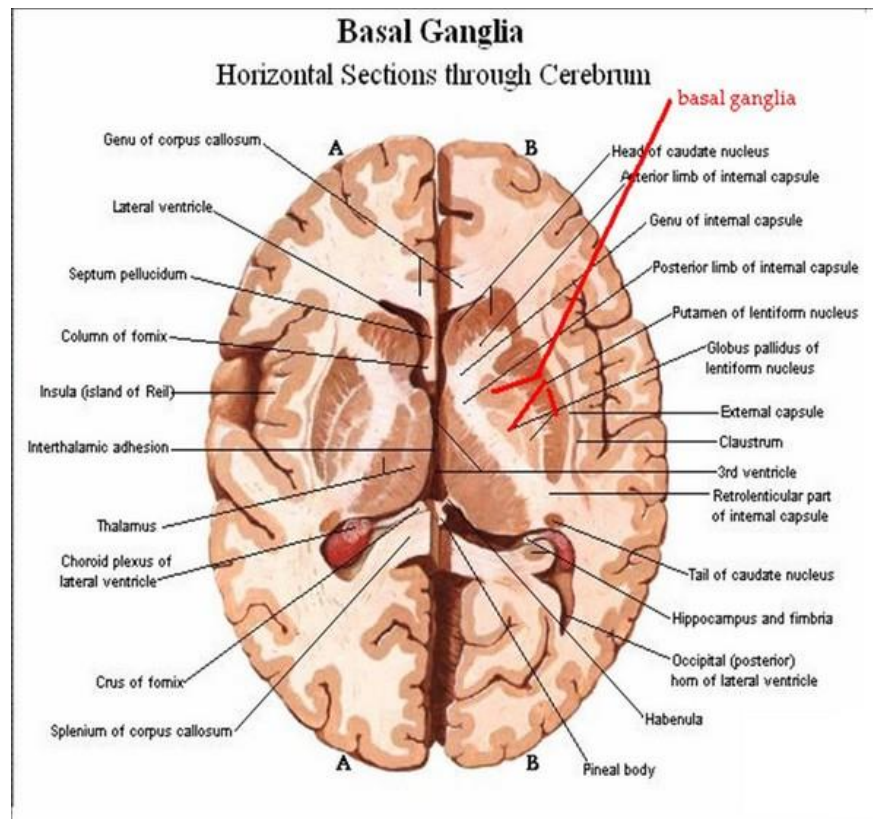
Mohammad Rohani

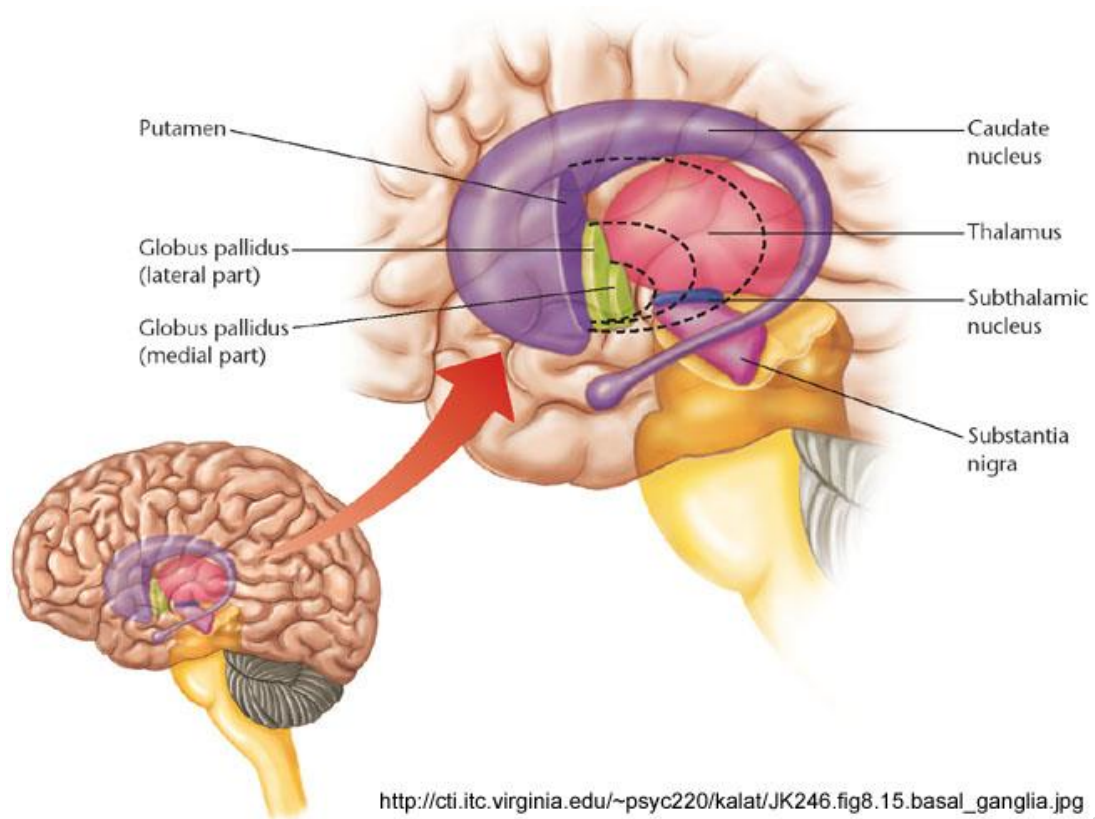
Neurology department

Rasoul Akram Hospital

Iran University of Medical Sciences

Basal ganglia





http://cti.itc.virginia.edu/~psyc220/kalat/JK246.fig8.15.basal_ganglia.jpg

Movement disorders

- ▶ Hypokinetic movement disorders (parkinsonism)
- ▶ Hyperkinetic movement disorders :
 - ✓ Tremor
 - ✓ Chorea
 - ✓ Ballismus
 - ✓ Dystonia
 - ✓ Myoclonus
 - ✓ Tics

Hypokinetic movement disorders



PARKINSON'S DISEASE



AN
ESSAY
ON THE
SHAKING PALSY.

BY
JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
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1817.

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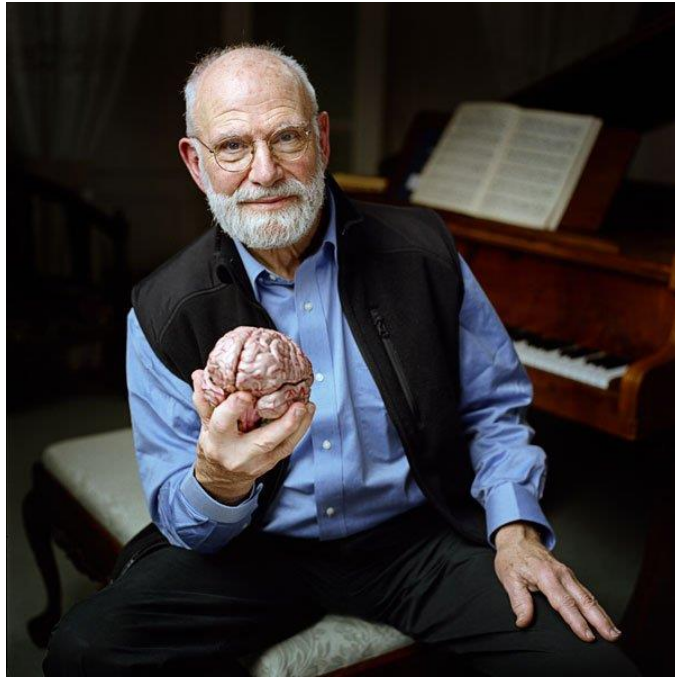
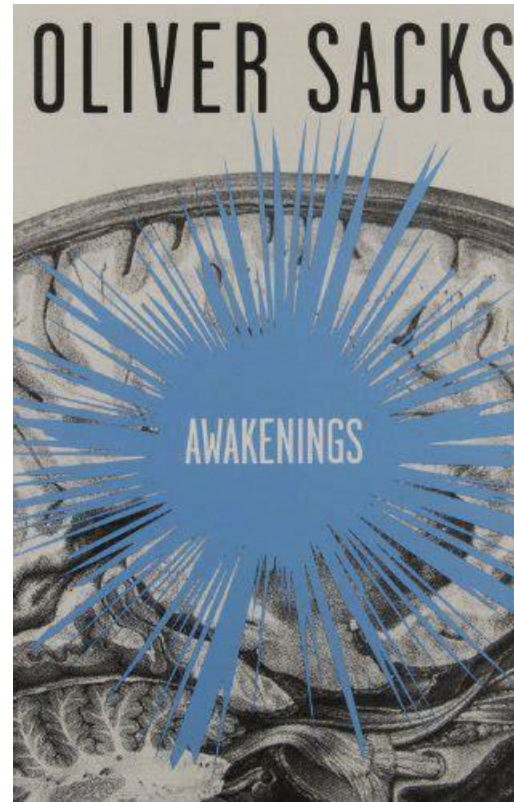
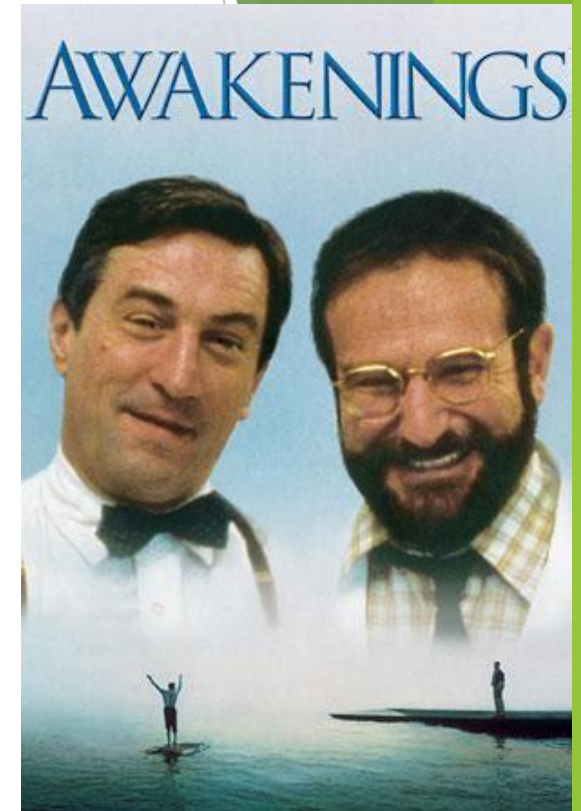
► **Clinical Features**

- ✓ Bradykinesia and hypokinesia plus one of these symptoms:
- ✓ Tremor at rest
- ✓ Rigidity
- ✓ Postural instability

- ▶ 1% of those 55 years.
- ▶ Peak age of onset in the 60s (range is 35 to 85)
- ▶ Course progressive over 10 to 25 years.
- ▶ Tremor (“pill rolling” of hands) at rest (4-6 Hz); worsens with stress.

- 
- ▶ Presentation with tremor confined to one limb or side of body is common.
 - ▶ Other findings:
 - ✓ Rigidity (“cogwheeling”— increased ratchet-like resistance to passive limb movements)
 - ✓ Bradykinesia (slowness of voluntary movements)
 - ✓ Fixed, expressionless face (facial masking) with reduced frequency of blinking

- 
- ▶ Hypophonic voice,
 - ▶ Drooling
 - ▶ Micrographia (small handwriting)
 - ▶ Reduced arm swing while walking
 - ▶ Flexed “stooped” posture with walking
 - ▶ Shuffling gait
 - ▶ Difficulty initiating or stopping walking
 - ▶ En-bloc turning (multiple small steps required to turn)
 - ▶ Retropulsion (tendency to fall backwards)



Spinal column deformities in PD

- ▶ Kyphosis
- ▶ Scoliosis
- ▶ Stooping
- ▶ Camptocormia
- ▶ Pisa syndrome
- ▶ Frozen shoulder
- ▶ Anterocollis
- ▶ Dropped head

Postural disorders (spine)

- ▶ **Kyphosis** is defined as an over-curvature or excessive rounding of the spine
- ▶ **Scoliosis** is a lateral structural curvature, usually coupled with vertebral rotation, that causes an asymmetric deformity of the trunk

Camptocormia

- ▶ Camptocormia or “bent spine syndrome” was first described in the medical literature in the 1800s.
- ▶ In 1915, the French neurologists first proposed the term “camptocormia” from the Greek words “kamptos” (to bend) and “kormos” (trunk).





Pisa syndrome





Dropped head syndrome

- ▶ Dropped head syndrome, also known as forward neck flexion or anterocollis, is considered **a rare feature of PD.**
- ▶ Although incidence estimates in PD are generally around 6%, dropped head syndrome can severely disturb the quality of life in affected patients.



Striatal deformities of the hand and foot in Parkinson's disease

- ▶ The terms “striatal hand” and “striatal foot” were originally used by Charcot to report the distal limb deformities typically associated with Parkinson's disease.



- 
- ▶ Unlike rheumatoid arthritis, local signs of joint involvement, such as pain, tenderness, heat, and swelling, are absent in striatal hand.
 - ▶ Also, rheumatoid arthritis tends to occur bilaterally, whereas focal dystonia before PD tends to be unilateral, with tremor, rigidity, and bradykinesia developing on the ipsilateral side.

Striatal deformity and rheumatoid arthritis

Features	Rheumatoid arthritis	Striatal abnormalities
Pathophysiological features	Proliferative synovitis, autoimmunity, microbial initiator	Non-inflammatory, dystonic features, soft-tissue elastic changes
Joints	Swollen, warm, painful, pannus formation	Painful contractures
Radiographic changes	Joint effusions, juxta-articular osteopenia with erosions, narrowed joint space with loss of cartilage	Normal
Mobility	Morning stiffness, decreased range of motion (active and passive)	Fixed deformity, may respond to levodopa or botulinum toxin
Distribution	Generally symmetrical joint involvement, polyarticular	In most cases develops on one side with ipsilateral emergence of cardinal PD signs
Genetics	Association with HLA DR4 or DR1	Seems to be more common in juvenile-onset PD
Extra-articular features	Cutaneous and visceral rheumatoid nodules, increased serum rheumatoid factor, synovial cysts, vasculitis, episcleritis	Rigidity, bradykinesia, tremor

- ▶ The most typical deformity associated with striatal hand is characterised by flexion of the metacarpophalangeal joints, extension of the proximal interphalangeal joints, flexion of the distal interphalangeal joints, and ulnar deviation.





Striatal foot

- ▶ Charcot and Gowers described this deformity in patients with PD.
- ▶ Talipes equinovarus, and distortion of the toes—extension of the first, and flexion of the other phalanges so as to cause a claw-like deformity.
- ▶ Hallucal hyperextension, flexion of the other toes, ankle inversion “toe curling”

- 
- ▶ Early swing-phase limb advancement and foot clearance are also affected.
 - ▶ Pressure is increased over the lateral aspect of the foot and ankle instability occurs.



Non-motor symptoms in PD

- Non-motor symptoms are common in PD and important determinants of quality of life.
- It is important to be aware of and assess the full breadth of non-motor symptoms as there are a number of available therapies that may provide relief of symptoms.
- Treatment of any symptoms in PD, motor or non-motor, requires consideration of potential adverse effects as they relate to other symptoms experienced by the patient. A personalized treatment approach is critical.

Landscape of Non-motor Symptoms

- **Neuropsychiatric**

- Cognitive Impairment

- Psychosis ✓

Use of dopaminergic medications
limited by visual hallucinations.

- Depression ✓

- 2 • **Anxiety** ✓

- Apathy

- Impulse Control Disorders

- **Autonomic**

- Constipation, early satiety

- Orthostatic Hypotension

- Urinary urgency, frequency, incontinence ✓

- **Disorders of sleep and wakefulness**

- REM sleep behavior disorder

- 1 • **Insomnia** ✓

- Hypersomnia

- **Others**

- Pain

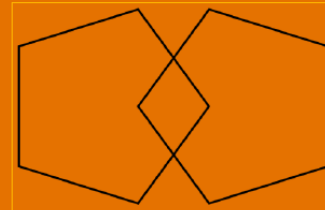
- Fatigue

- Olfactory dysfunction ✓

- Ophthalmologic Dysfunction

Neuropsychiatric Non-motor Symptoms

Cognitive Impairment
Psychosis
Depression
Anxiety
Apathy
Impulse Control Disorders



PD-MCI (mild cognitive impairment) $\frac{1}{3}$

- Diagnosis of Parkinson's disease (UKBB)
- Gradual decline in cognitive ability
- Cognitive deficits on either formal neuropsychological testing or global cognitive assessment.
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present.

Litvan 2011, Litvan 2012

PDD (dementia) $\frac{1}{3}$, >80% lifetime

- Impairment in daily activities
- Probable PDD
 - Typical Cognitive Profile
 - At least one behavioral symptom
 - No alternative diagnoses

Hely 2000, Aarsland 2005, Emre 2007

PDD Treatment: Cholinesterase Inhibitors

	FDA	MDS Task Force	2012 Cochrane, Rolinski 2012	Stinton 2015, Wang 2015
Rivastigmine	Approved PDD	Clinically useful	✓ PDD	Similarly effective LBD
Donepezil		Possibly useful	✓ PDD	Similarly effective LBD
Galantamine		Possibly useful	✓ PDD	

Rivastigmine: 4.6, 9.5, 13.3 mg patch

- Use of patch greatly reduces GI side effects, Oral formulation also available.

Donepezil: 5mg, 10mg

- Once daily, easy titration

Galantamine: Twice daily or extended release daily formulation: 8, 16, 24mg

- Positive allosteric modulator at nicotinic receptors

- **Memantine** deemed investigational. Seppi 2019

Parkinson Disease Psychosis

Common

- Most commonly manifests as visual hallucinations, occurring in 74% of PD patients after 20 years of disease.

Hely, 2008

Varied presentation

- Also minor hallucinations (visual illusions, sense of presence, and passage hallucinations), hallucinations in non-visual sensory modalities, and delusions.

Ravina, 2007

Pathophysiology

Dopaminergic

Cholinergic

- Psychotic symptoms worsened by anticholinergics.
- Improvement with cholinesterase inhibitors.

Serotonergic

- Increase in 5-HT_{2A} receptors in visual processing areas in PD.
- Neuroleptics block 5-HT_{2A} receptors in addition to D₂ receptors.

Fenelon 2008

Parkinson Disease Psychosis Management

- Rule out metabolic causes of delirium.
- Elimination/reduction of possible contributory medications.
- Determine necessity of treatment.
- Reduce dopaminergic medications/ eliminate dopamine agonists.
- Cholinesterase inhibitors if associated with concomitant dementia.
- Atypical Antipsychotics with no (or weak) D2 antagonism and 5HT2A antagonism

	FDA	MDS Task Force	Pro	Con
Pimavanserin	Approved for PD psychosis	Clinically useful	selective 5-HT2A inverse agonist	
Clozapine		Clinically useful		Regular blood monitoring, Anticholinergic effect
Quetiapine		Possibly useful	Easy to acquire and prescribe	Lacks efficacy data, Anticholinergic effect

- Antipsychotic Black Box Warning: Increased mortality in elderly patients with dementia-related psychosis.

Cummings 2014, Seppi 2019, Ray 2009

Depression in PD

Common

- Up to 50% of all PD patients have depression.

Often present with anxiety

- Distinct from other types of depression in that there is more often an anxiety component.

Treatment

- Pramipexole and venlafaxine are clinically useful. Seppi 2019
- Anti-depressants
 - SSRIs: sertraline, fluoxetine > (es)citalopram >> paroxetine
 - SNRIs: venlafaxine, duloxetine
 - Avoid those with anticholinergic effect.
- Psychotherapy

Anxiety in PD

Common • Up to 40% of patients experience anxiety symptoms, panic attacks, social phobia

Treatment • Pharmacotherapy

- No high-quality RCTs. Seppi, 2019
- Dopaminergic therapy adjustment if anxiety is a wearing off symptom.
- SSRIs: sertraline, fluoxetine
- SNRIs
- Buspirone
- Benzodiazepines rarely and with caution

• Psychotherapy

Impulse Control Disorders in PD

- Compulsive gambling, buying, sexual behavior, and eating
- It's very important to screen patients and informants about these symptoms.
- More frequently observed with dopamine agonists.
- Treatment: Reducing dopamine agonists or dopaminergic therapies; CBT possibly useful.

Seppi 2019

Impulse control behaviors and related disorders

- Range of behaviors
 - Pathological gambling, compulsive shopping, hypersexuality, binge eating
 - Punding
 - Dopamine dysregulation syndrome (DDS)
- Frequency ~2-10%
- Characteristics
 - Impulsivity - failure to resist the impulse or temptation to perform a certain behavior
 - Compulsivity - repetitive execution with a lack of self-control
 - Functional impact - negative consequences
- Risk factors
 - Psychiatric, addiction history
 - Dopamine agonists
 - Impaired decision making
 - Younger age at PD onset, motor fluctuations, male gender



- Linked to dopamine
 - Meds – D2, D3; resolves upon d/c
 - Enhanced DA release to conditioned cues and gambling task on ^{11}C -raclopride PET
 - Increased ventral striatal activity to rewards on fMRI
 - Lower striatal DAT levels on ^{123}I -FP-CIT (R caudate/putamen) in PD with ICD compared to PD without ICD
- Structural and functional abnormalities
 - Cortical thinning in fronto-striatal-limbic regions
 - Altered connectivity between striatal and associative/limbic cortical regions

Weintraub and Claassen 2017
Voon et al., 2013; Biundo et al., 2015; Carriere et al., 2015

Robin Williams: Lewy Body Dementia, Suicide and Parkinson's

Jul 14, 2021



Autonomic Non-motor Symptoms

GI: Constipation, early satiety, sialorrhea

Cardiovascular: Orthostatic Hypotension

Urinary: urgency, frequency, incontinence

Sexual dysfunction: erectile dysfunction

Thermoregulatory aberrance

Pupillo-motor and tear abnormalities

Gastrointestinal Autonomic Dysfunction

Early PD: constipation = 43.6%, straining for defecation = 58.7%, early satiety = 20.8%. Malek 2017

- Constipation Treatment
 - Reduce or stop anticholinergic medications.
 - Probiotics and pre-biotic fiber clinically useful; polyethylene glycol (Miralax) and lubiprostone (Amitiza) possibly useful. Seppi 2019
 - Consider stool softener docusate.
- Early Satiety Treatment – multiple, small meals

Early PD, sialorrhea was present in 51.4% of patients.

- Sialorrhea Treatment
 - Botulinum toxin A and B clinically useful.
 - Glycopyrrolate possibly useful; ipratropium spray investigational. Seppi 2019

Orthostatic Hypotension

Early PD, Orthostatic symptoms were reported by 39.6%.

Malek 2017

Postprandial hypotension is present in 30% of individuals with PD.

Yalcin 2016

Confirmation: Record blood pressure and heart rate when lying down and after standing for 3 min.

- A drop of ≥ 20 in SBP without a concomitant rise in heart rate less than half the drop in SBP is consistent with neurogenic orthostatic hypotension.

Freeman 2011, Norcliffe-Kaufmann 2018

Treatment:

- Reduce or discontinue antihypertensives.
- Increased salt and fluid intake.
- Support Stockings, Abdominal Binders
- Fludrocortisone, midodrine, and droxidopa possibly useful.
- Droxidopa has FDA indication for neurogenic OH in autonomic failure related to PD.
- Further options: Pyridostigmine 30mg three times daily, Atomoxetine

Seppi 2019

Urinary and Sexual Dysfunction

Early PD, urinary frequency in 79.1% and urinary urgency in 40.8%. Male erectile dysfunction in 56.1% and female anorgasmia in 57.4%. Malek 2017

Treatment:

- Recommend evaluation with urologist, possibly with urodynamic testing, to evaluate for urinary retention and overflow incontinence.
- Anticholinergic
 - Solifenacin possibly useful. Seppi 2019
 - Trospium: Among anticholinergics it is less likely to cross the blood-brain barrier
- Mirabegron/Vibegron: Mechanism of action is β_3 adrenergic agonist.
- Sildenafil clinically useful for male sexual dysfunction. Seppi 2019

Disorders of Sleep and Wakefulness

REM sleep behavior disorder

Insomnia

Hypersomnia

Restless legs and periodic limb movements

Non-REM sleep related movement disorders

Sleep disordered breathing

Vivid dreaming

REM sleep behavior disorder (RBD)

- Manifests as dream enactment with complex motor behaviors and vocalizations matching dream content
- Diagnosis of RBD based on REM sleep without atonia during polysomnogram.
- RBD is characteristic sleep disorder of alpha-synucleinopathies.
- Treatment
 - No high-quality RCTs.
 - Environmental modification
 - Melatonin (3-12 mg)
 - Clonazepam (0.25mg) (or other benzodiazepines with shorter half-life)

Seppi 2019

Insomnia Management

- Dopaminergic therapies
 - Rotigotine possibly useful. Seppi 2019
 - Nighttime dosing of levodopa formulations or dopamine agonists.
- Other options Schütz 2022
 - Behavioral approaches, e.g., sleep hygiene
 - Melatonin for sleep-onset insomnia.
 - Trazodone or mirtazapine.
 - Exercise can improve sleep quality. Amara 2020

Hypersomnia Assessment and Management

- Co-occurrence of obstructive sleep apnea should be considered. CPAP helpful for those with OSA. Seppi 2019
- Other options Schütz 2022
 - Optimization of dopaminergic treatment
 - Scheduled Napping
 - Caffeine Investigational Seppi 2019
 - Modafinil Possibly Useful Seppi 2019
 - Atomoxetine/Methylphenidate/Dextroamphetamine

Other Non-Motor Symptoms

Pain

- MDS-NMS assesses muscle, joint, back pain; deep or dull pain; dystonia; other pain
- The use of oxycodone/naloxone-PR is possibly useful for treatment of central, musculoskeletal, and nocturnal pain in PD. Seppi 2019

Olfactory dysfunction

- Affects up to 90% of individuals with PD. Chaudhuri 2006
- Most commonly assessed with UPSIT.

Fatigue

- Can be divided into physical fatigue and mental fatigue.
- Rasagiline possibly useful based on high-quality study. Seppi 2019

Dermatologic features

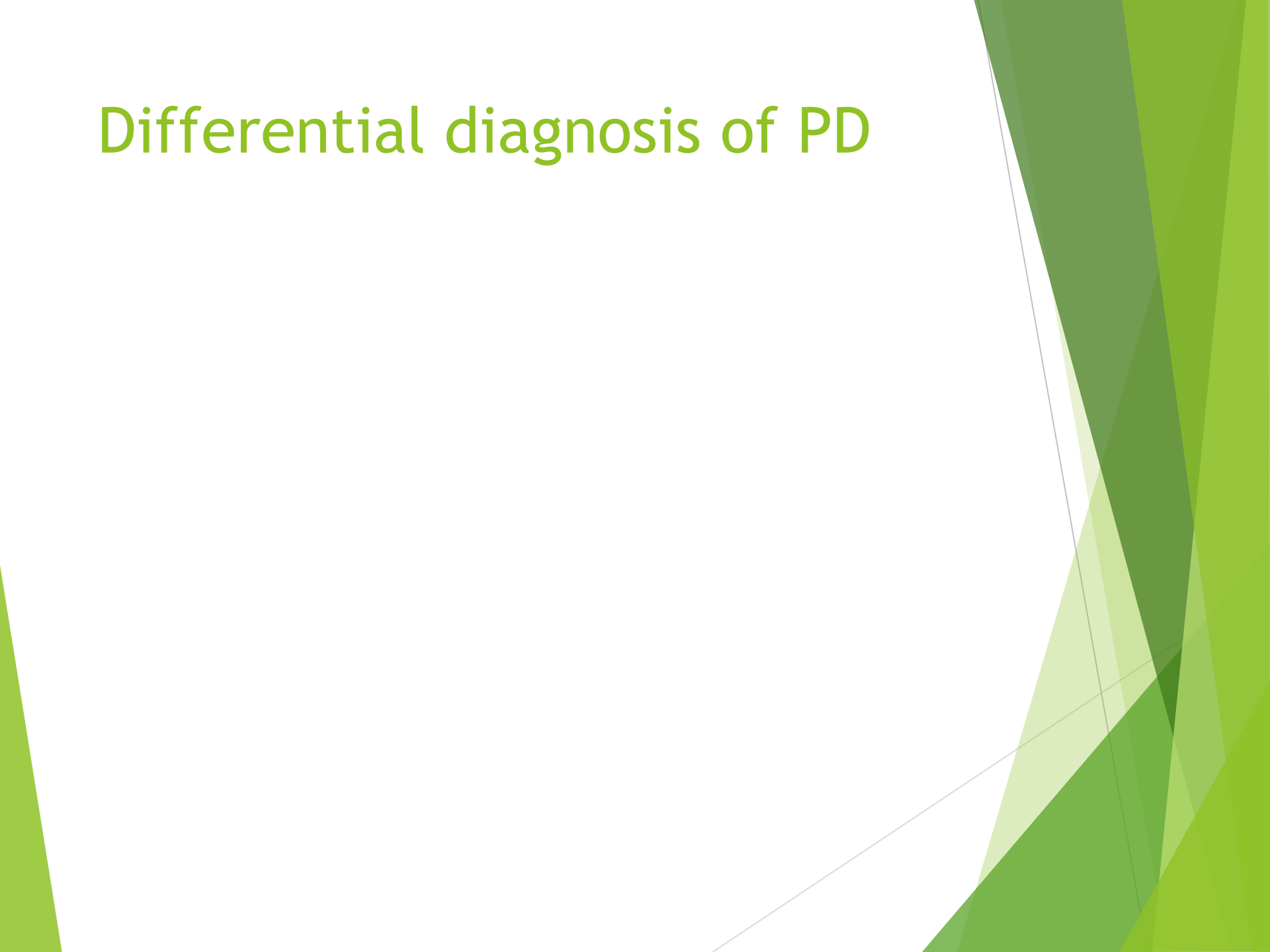
- Seborrhea - oily, flaking or inflamed skin
 - Dry skin
 - Excessive sweating or too little perspiration
 - Livedo (with amantadine)
 - Increased melanoma risk (?)
 - Irritation / skin changes due to subcutaneously delivered drugs or DBS leads
-
- Management depends on etiology
 - Dermatology referrals
 - Corticosteroid topicals, cyclines, botulinum toxin, etc.



<http://www.aafp.org> <http://www.patienthelp.org>

Neimann et al., PRD 2021

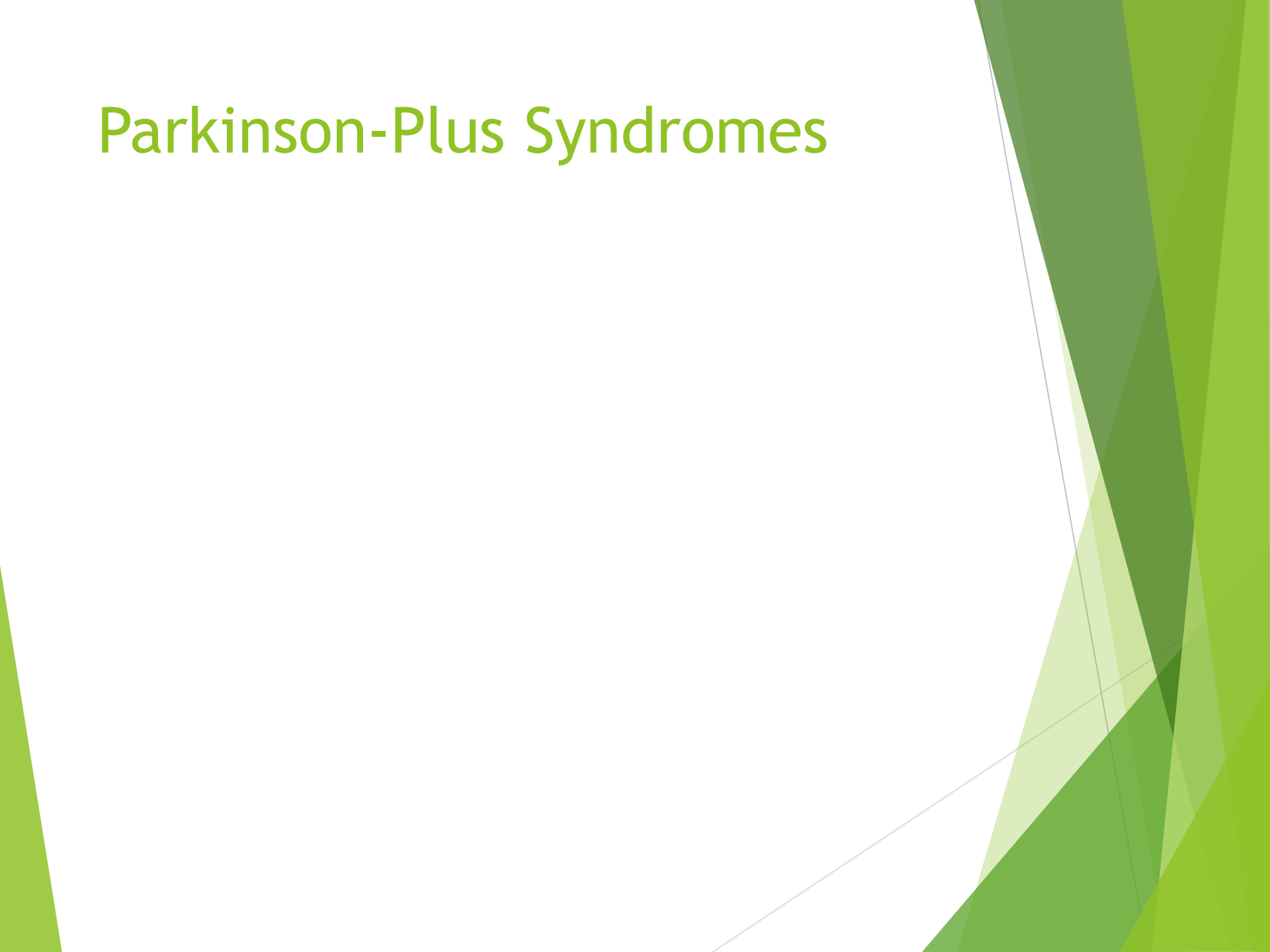
Differential diagnosis of PD

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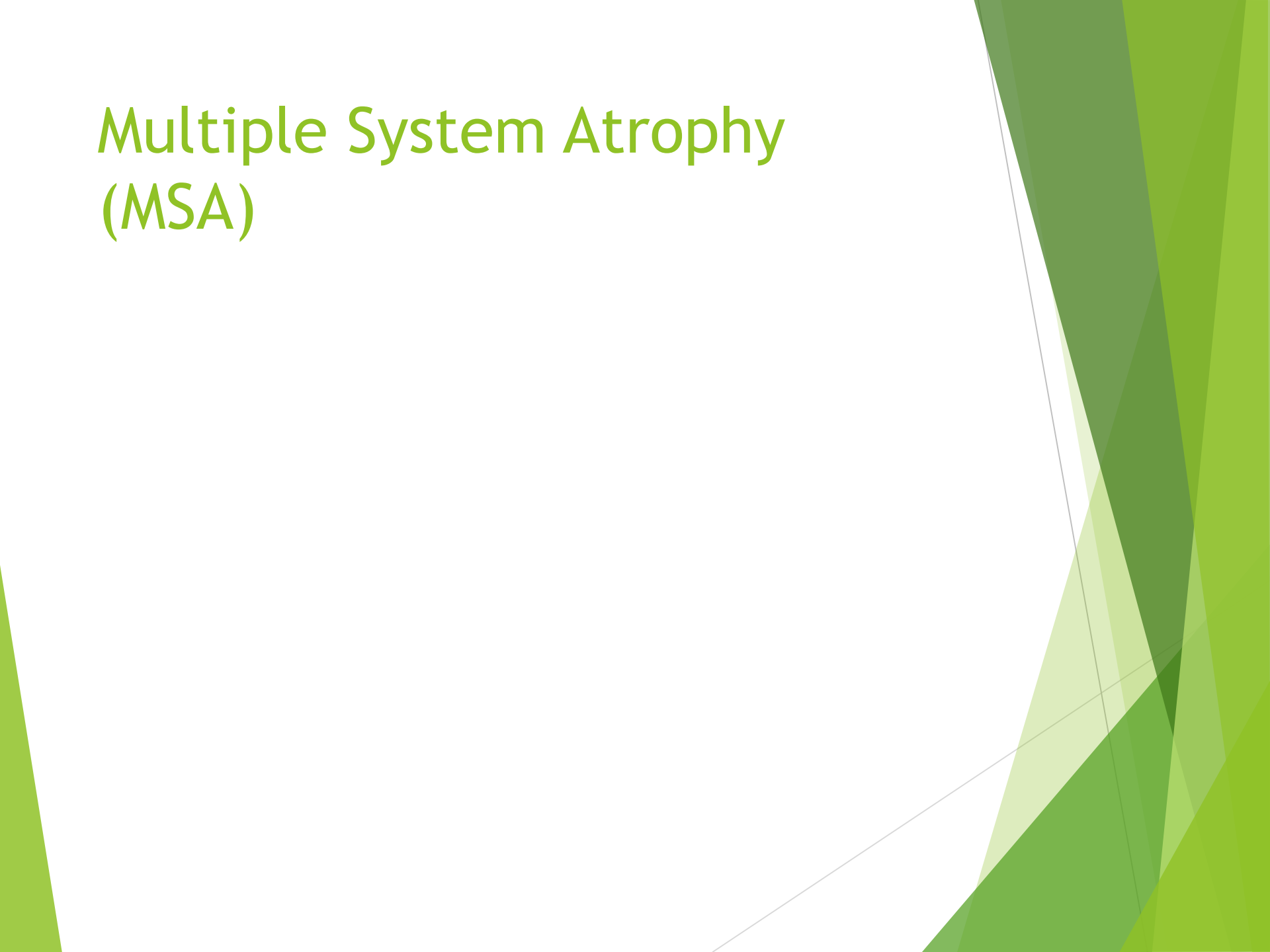
Essential Tremor (ET)

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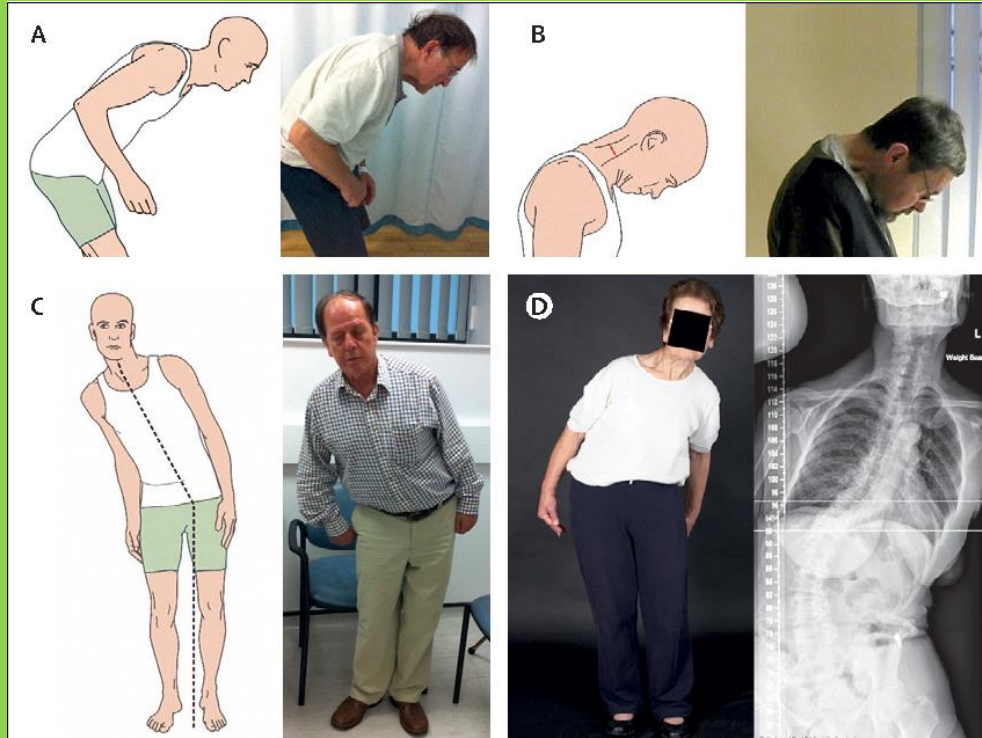
Parkinson-Plus Syndromes

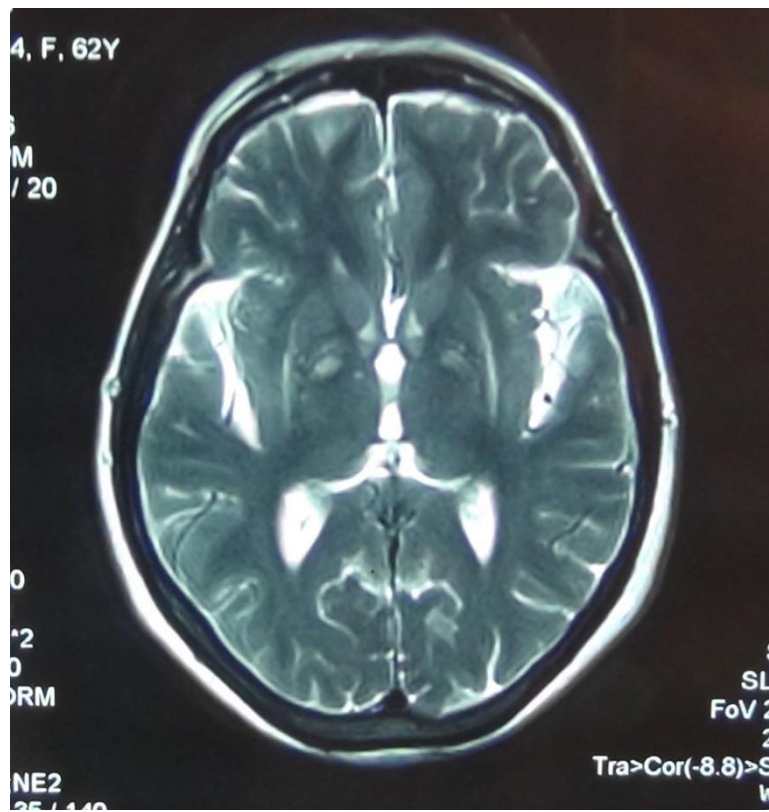
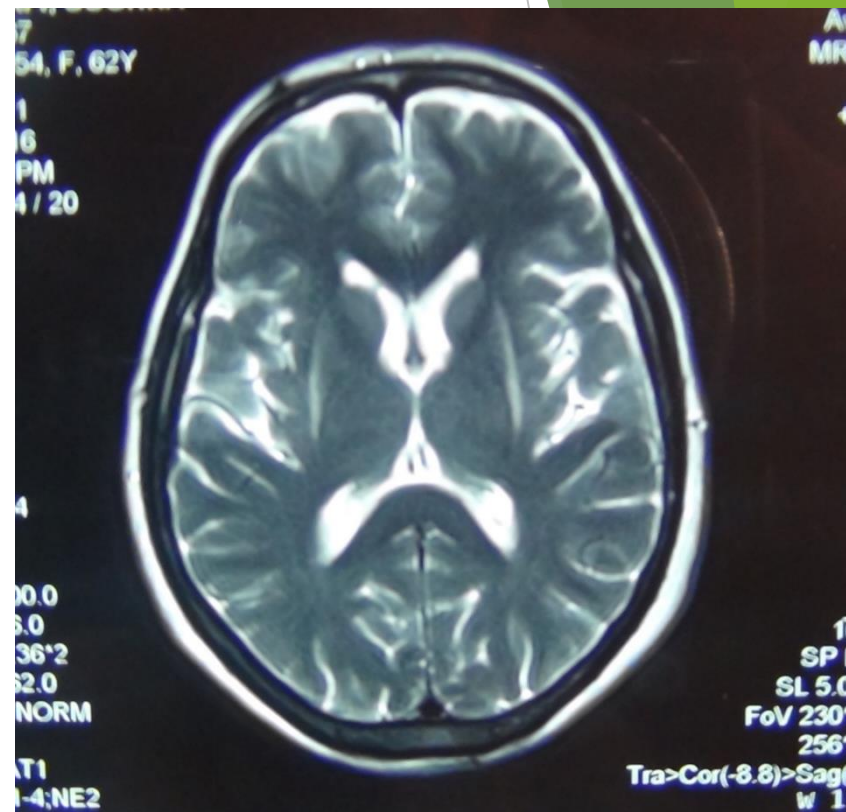
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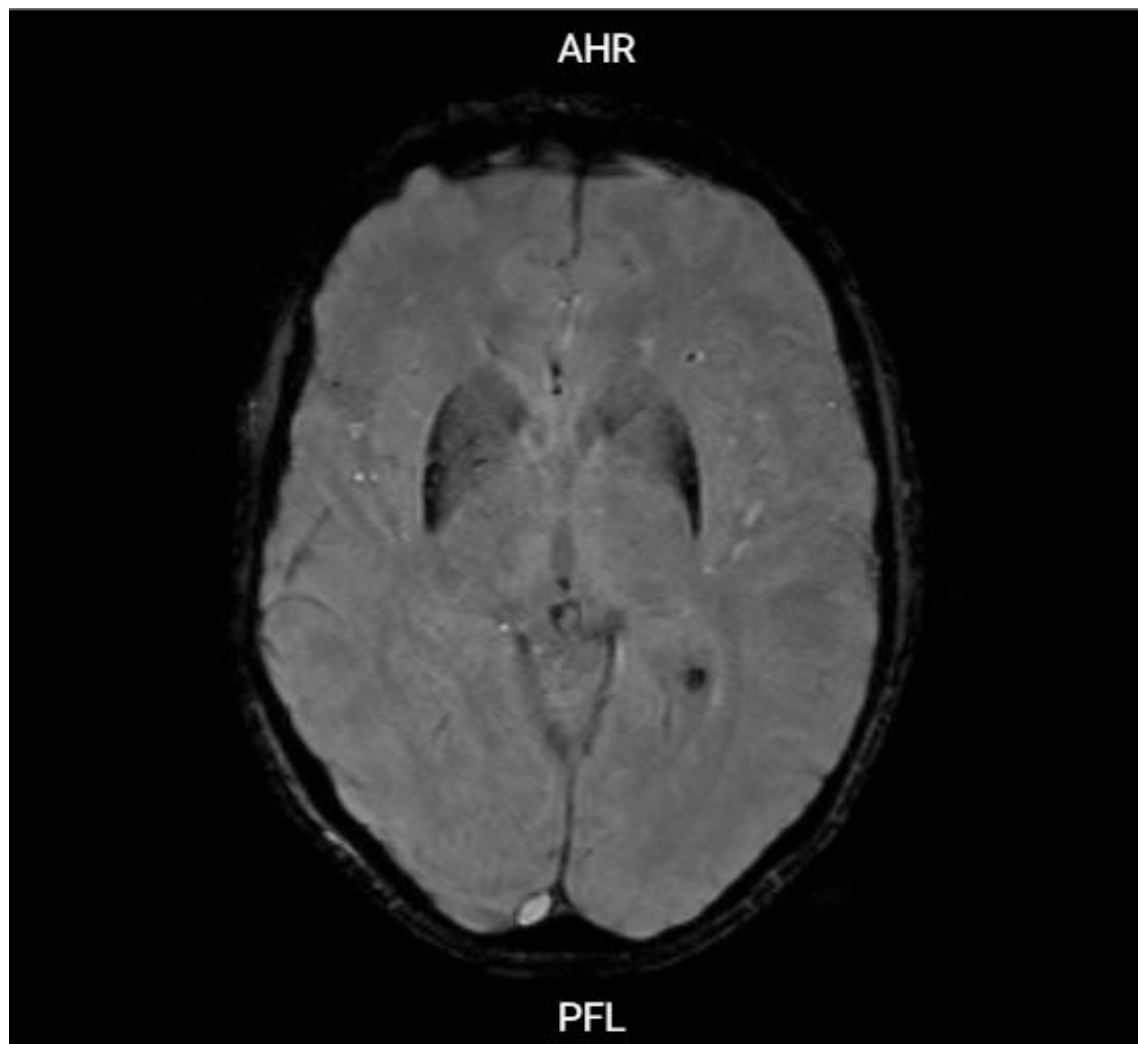
Multiple System Atrophy (MSA)



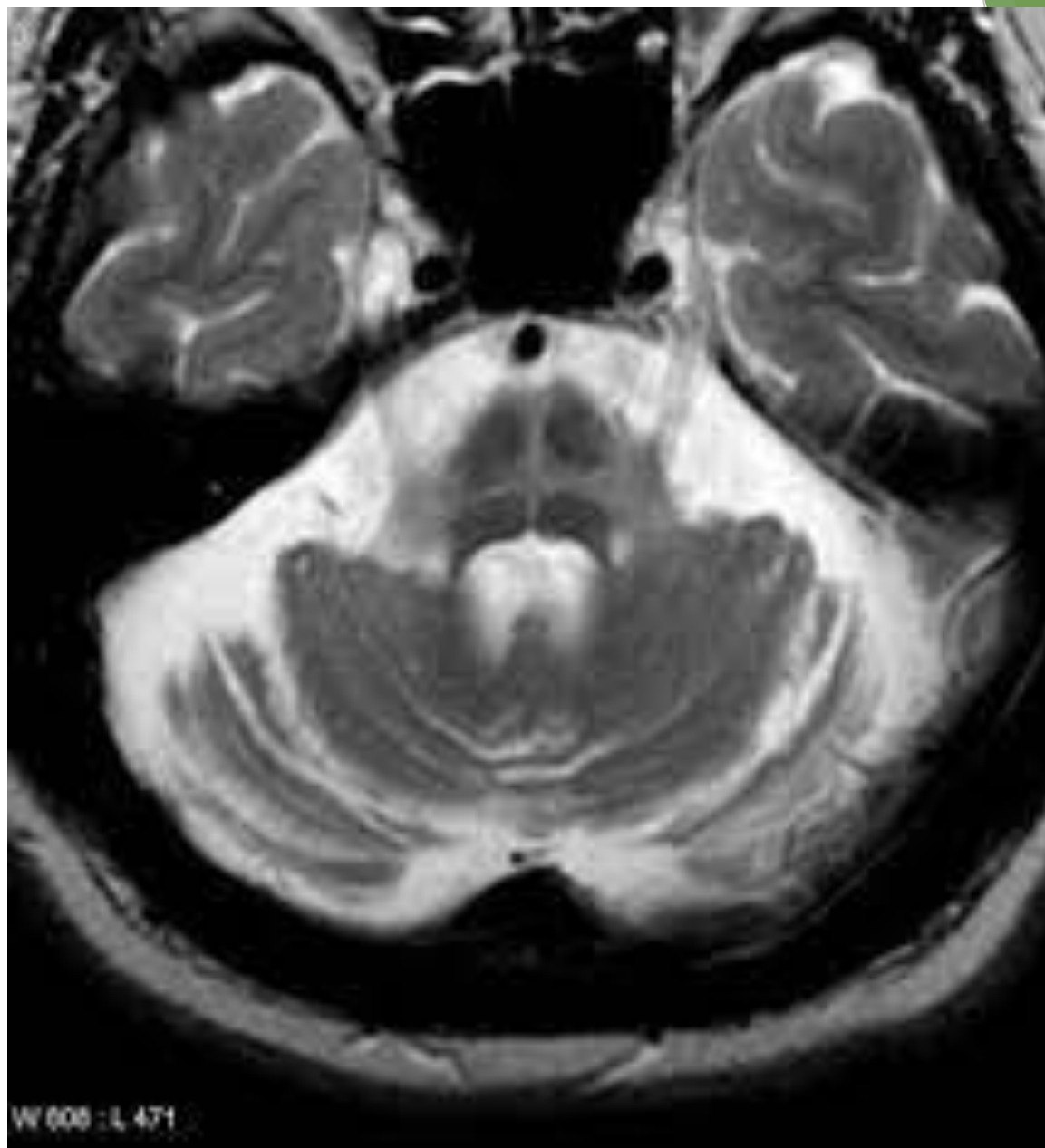
Camptocormia Pisa syndrome











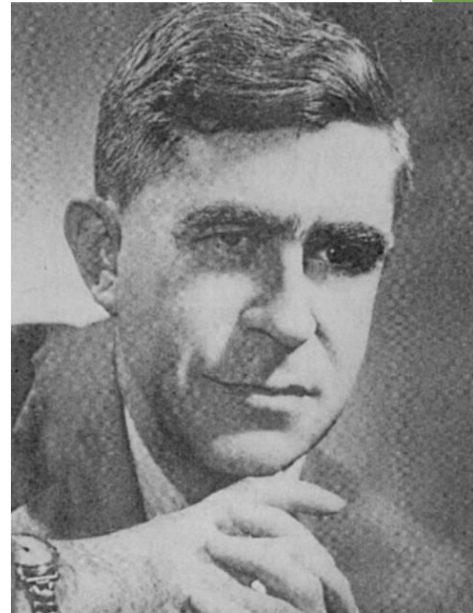
Progressive supranuclear palsy

- ▶ PSP is a degenerative disease characterized by symmetrical parkinsonism, cognitive changes, a characteristic supranuclear (upper motor neuron) palsy of vertical gaze, early falls, dysarthria, and dysphagia.

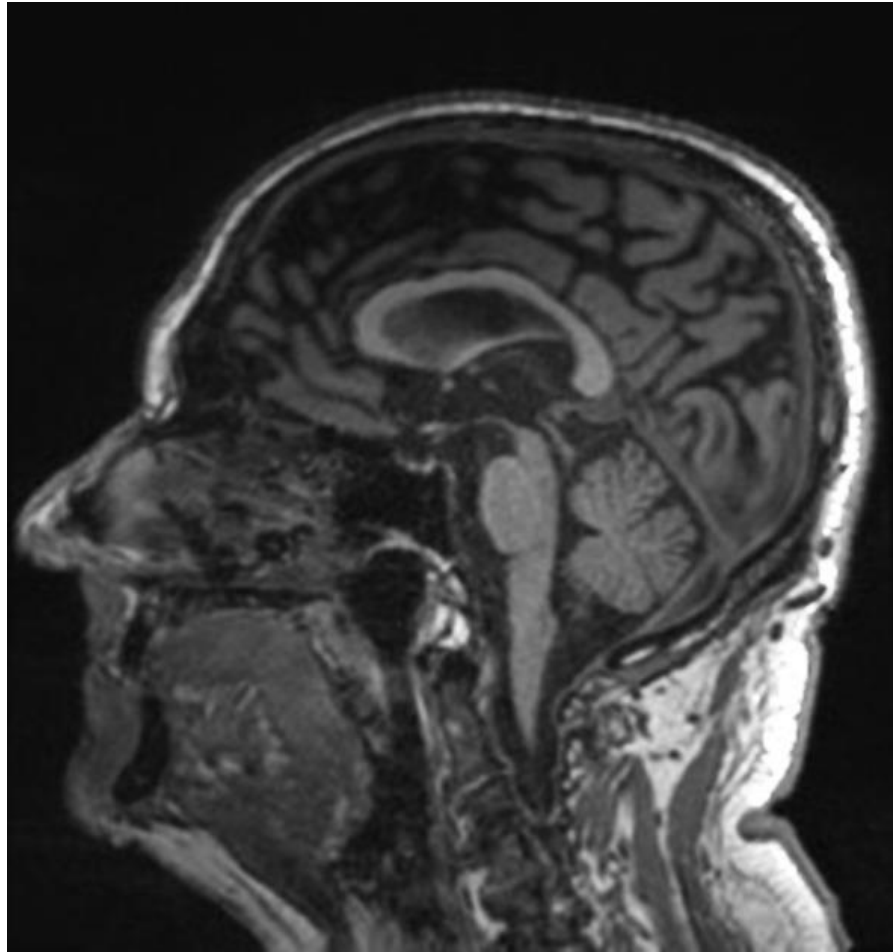
Steele
Olszewski



Richardson

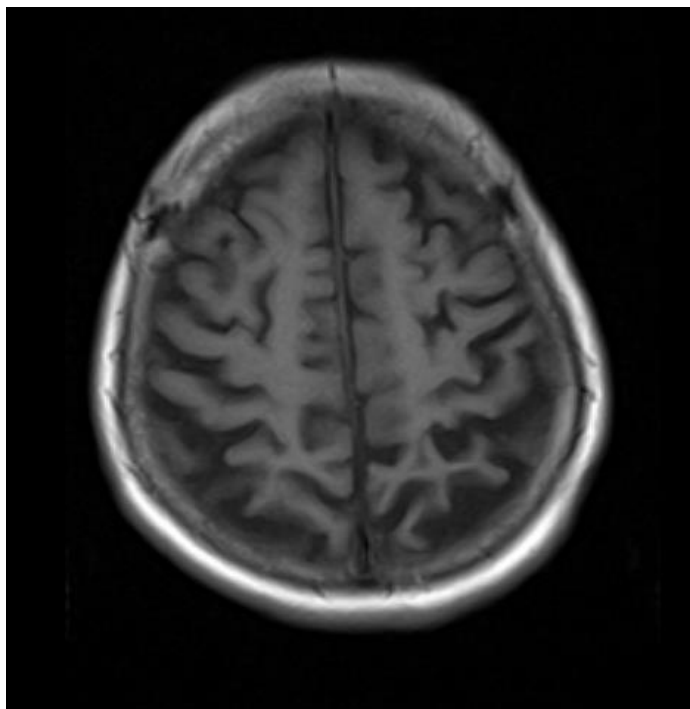
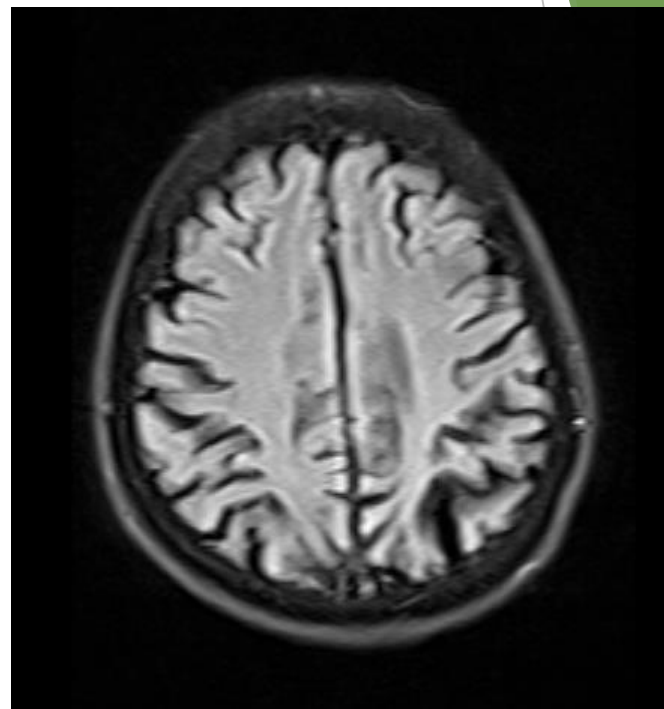






Corticobasal degeneration (CBD)

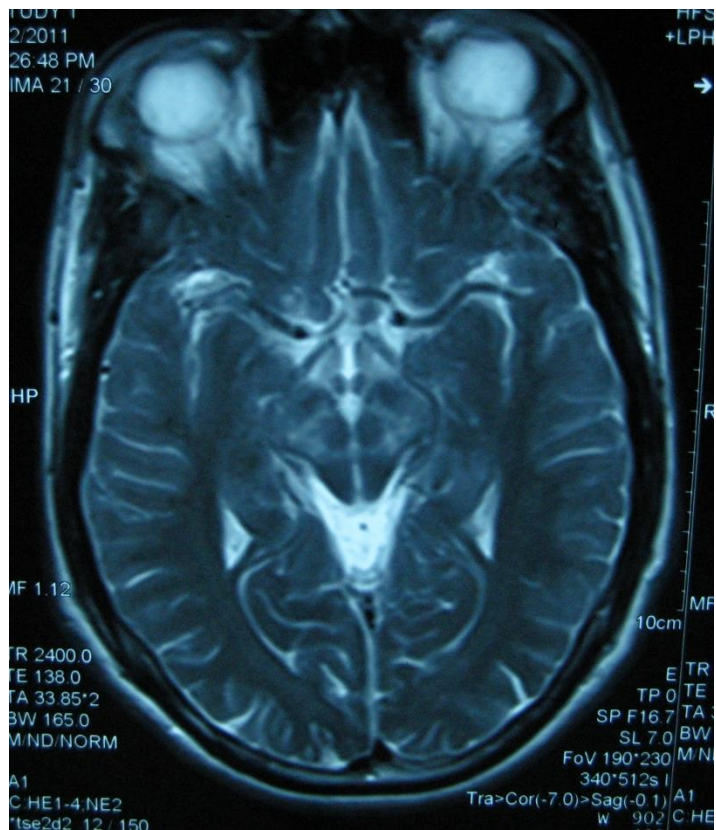
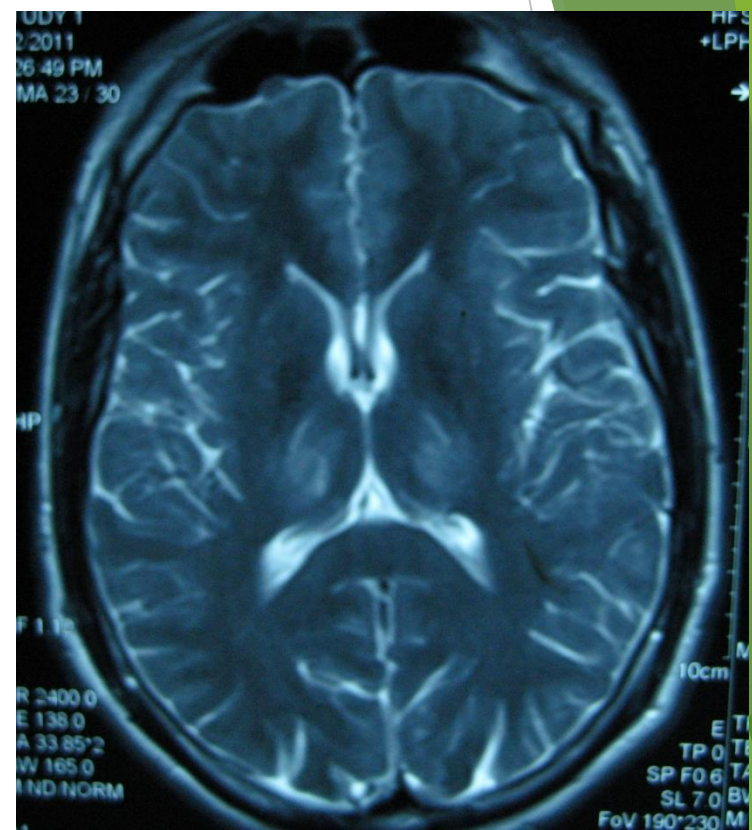




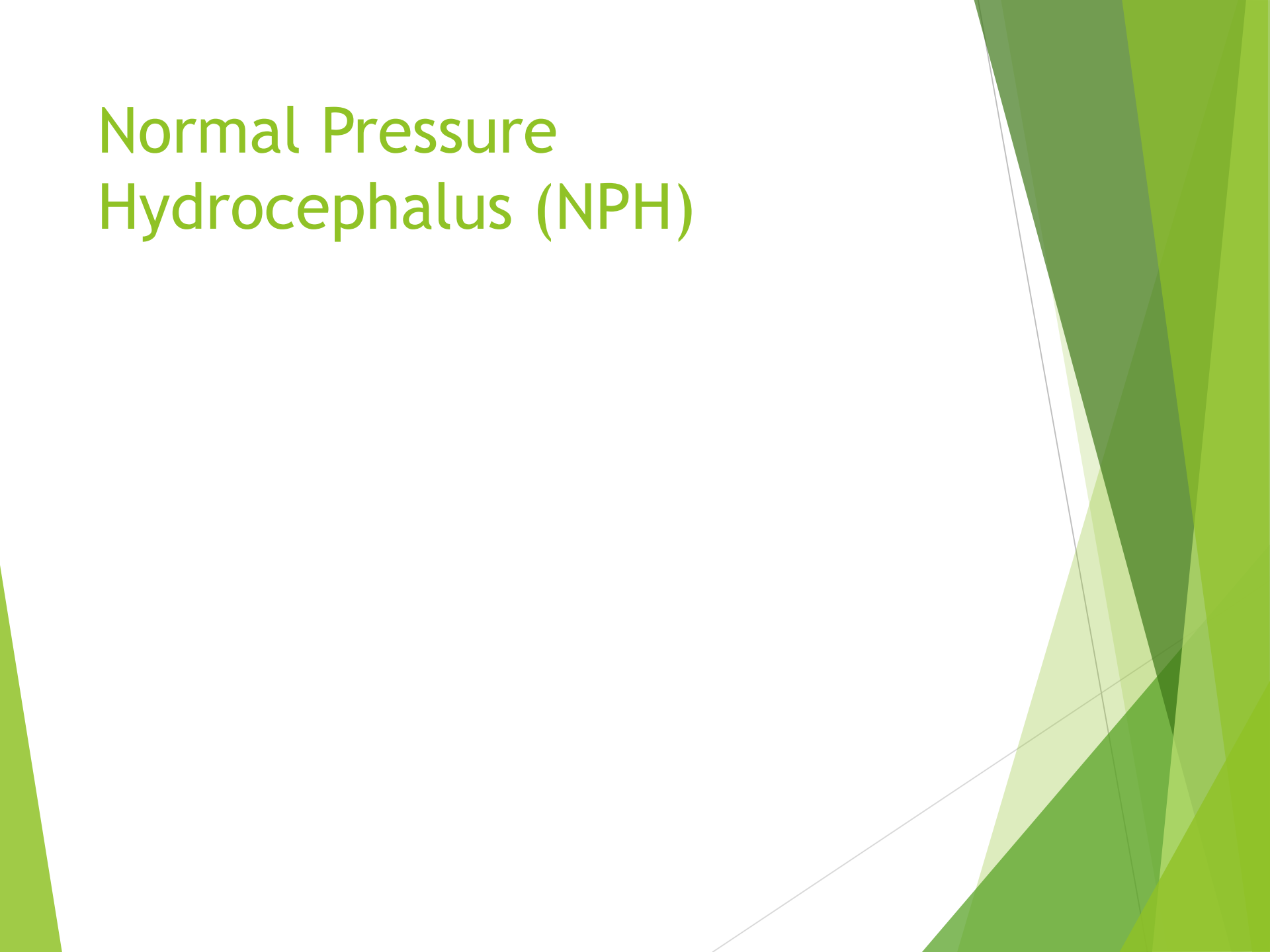


Wilson's Disease

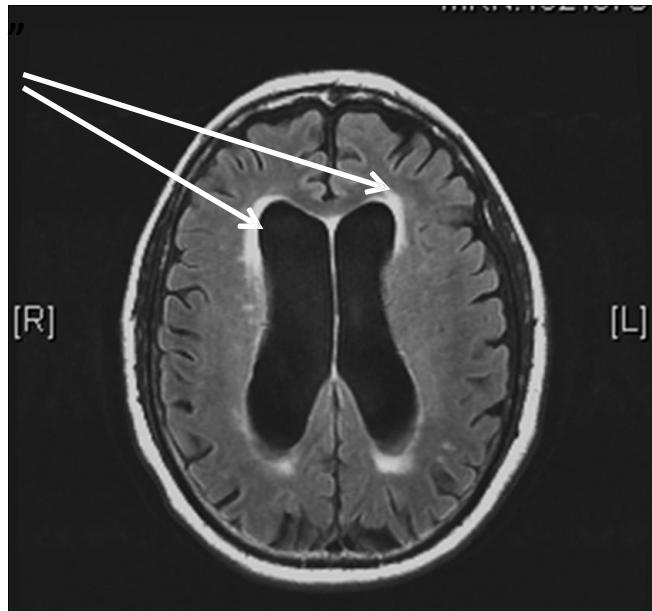
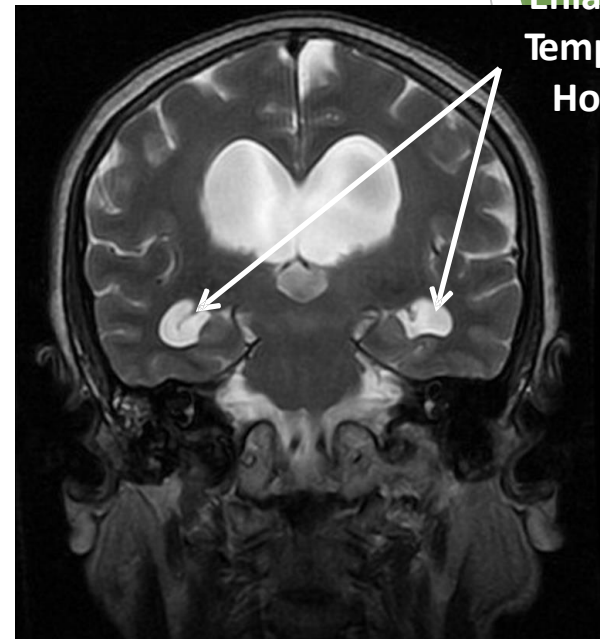




Normal Pressure Hydrocephalus (NPH)

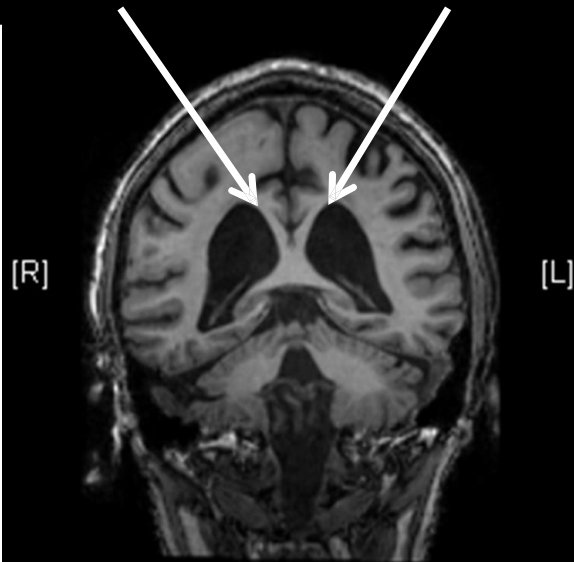


Ventricles are symmetrically enlarged in NPH

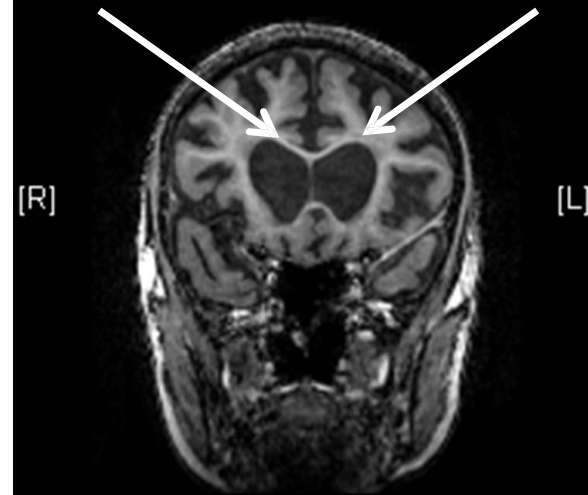


Callosal Angle is steeper in NPH
than in degenerative disorders

NPH



Alzheimer's



Coronal Reformatted T1-weighted images

Vascular Parkinsonism

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5/17/2014, M, 70Y
STUDY 1
5/17/2014
3:27:44 PM
4/11/15

APR

DOHREYARD MRI CEN. 5/17/2014, M, 70Y
Acqno: 4/11/15
MR DT7
HFS
+LP1

RFP

MF 1 15
T1 2500.3
TR 6000.0
TE 38.0
TA 24.38°
BW 188.0
MAGNOMEDIC/CHMFI
AURUMIFS
C151-4
NOVI_20/150
5/17/2014, M, 70Y
4/11/15

Scale

15
E
TP-0
DP F82.1
BL 7.50/75
FOV 180/220
113°250s
Tra-Cont: 15 Gy-Dose: 11
W 384
C 204

5/17/2014, M, 70Y
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1 of 1

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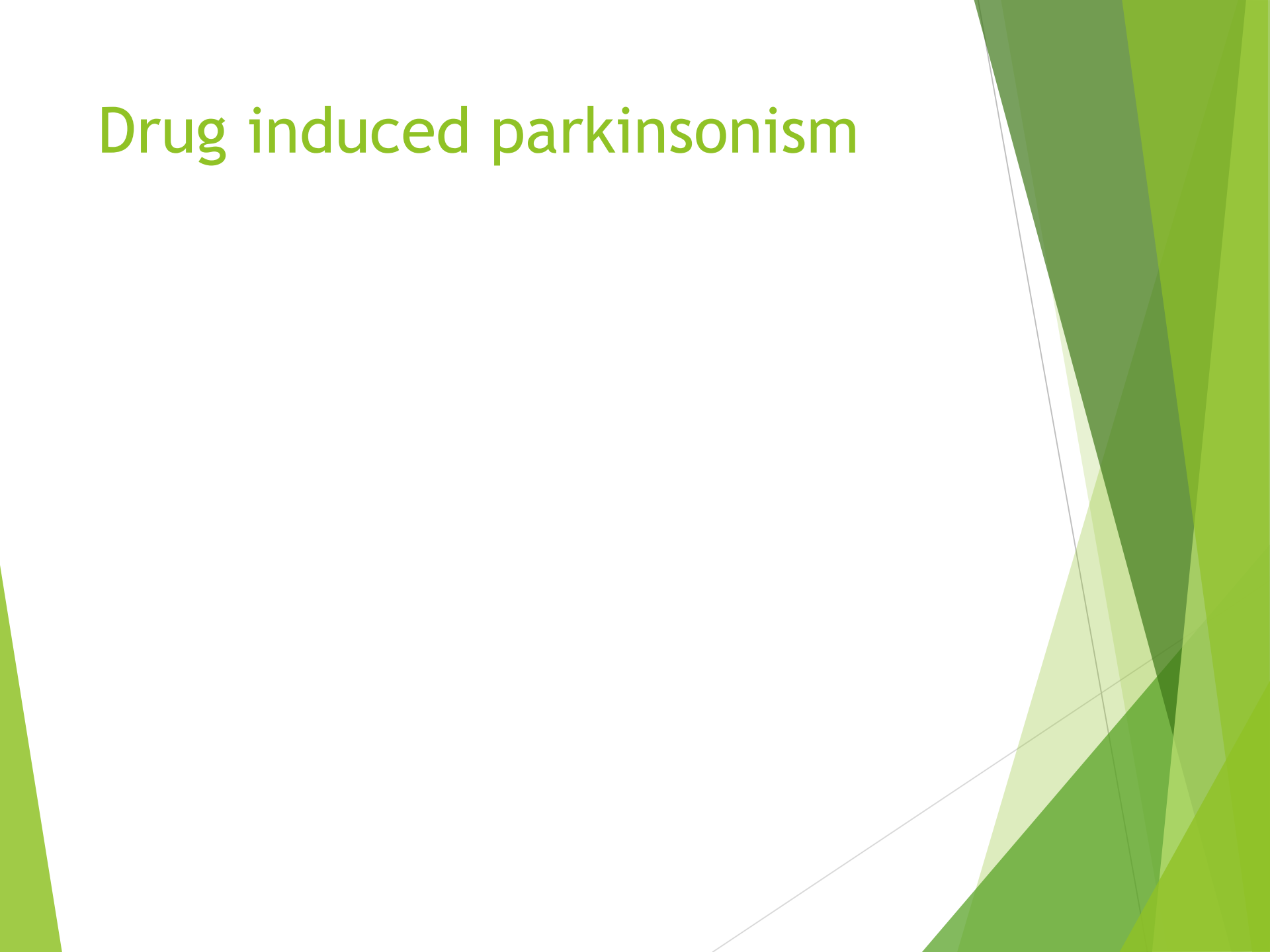
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5/17/2014, M, 70Y
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Drug induced parkinsonism

The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern, layered effect on the right side of the frame.



Management of Parkinson's disease

- ▶ There is little argument about the utility of early nonpharmacological interventions such as education, exercise, nutrition, and general support, which most agree should be applied from the time of diagnosis.
- ▶ However, there is considerable debate about when and how to initiate pharmacological therapy.

- ▶ Logically, **once the diagnosis of PD is made, treatment should be immediately started with an effective neuroprotective agent.**
- ▶ However, to date, *no treatment has been shown to have unequivocal neuroprotective effects or to clearly modify the natural course of the disease.*
- ▶ Antioxidant (vitamin E), antiexcitotoxic (riluzole), and antiapoptotic agents.

Carbidopa/Levodopa Formulations

- ▶ Carbidopa blocks peripheral levodopa decarboxylation into dopamine and thus symptoms of nausea and orthostasis often associated with the initiation of levodopa.



Levodopa is the best treatment for PD

- Most effective
 - Sustained benefit
 - Well tolerated
 - Long track record
- **And its cheaper –**
 - *“Over 4 years, levodopa was associated withlower mean costs £5,083 ($\pm$ 287) vs £8,473 ($\pm$ 225) v dopamine agonist/MAOBI”*

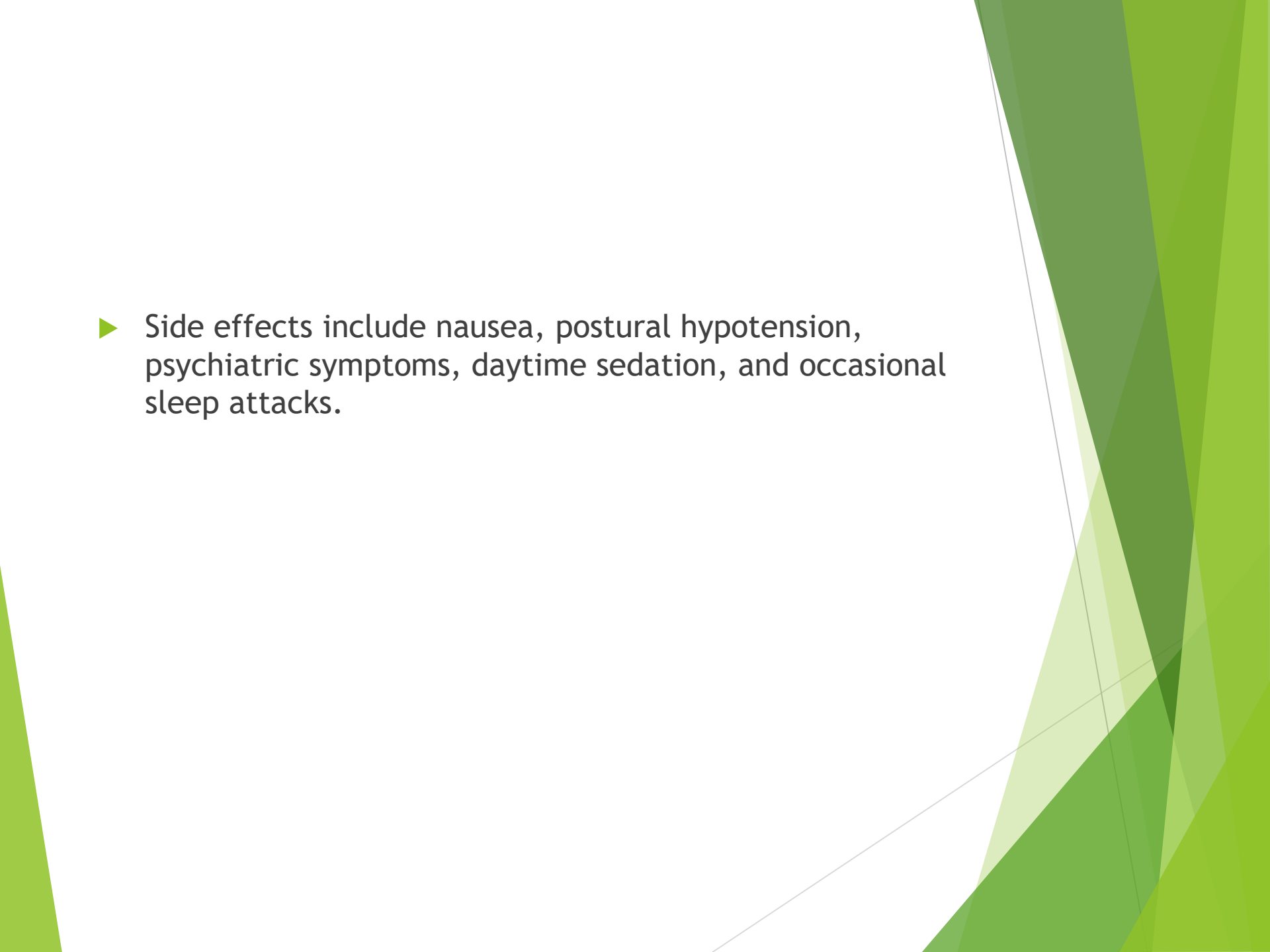
Cost-Effectiveness of dopamine agonists and MAOB-I in Early PD. McIntosh E, et al PD MED Collaborative Group. Mov Disord. 2021 36:2136-2143.



Dopamine Agonists

- ▶ Non-ergot alkaloids:
 - Ropinirole
 - Pramipexole
- ▶ Ergot alkaloids
 - Pergolide
 - Bromocriptine
 - Cabergoline
 - lisuride

- ▶ ***Compared to levodopa, they are longer acting and*** thus provide a more uniform stimulation of dopamine receptors.
- ▶ They are effective as monotherapeutic agents and as adjuncts to carbidopa/levodopa therapy.

- 
- The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.
- ▶ Side effects include nausea, postural hypotension, psychiatric symptoms, daytime sedation, and occasional sleep attacks.

ROBERT DE NIRO ROBIN WILLIAMS

Nominated for Three Academy Awards®
Including Best Picture, Best Actor (Robert De Niro) and Best Screenplay!

AWAKENINGS



Based on a True Story



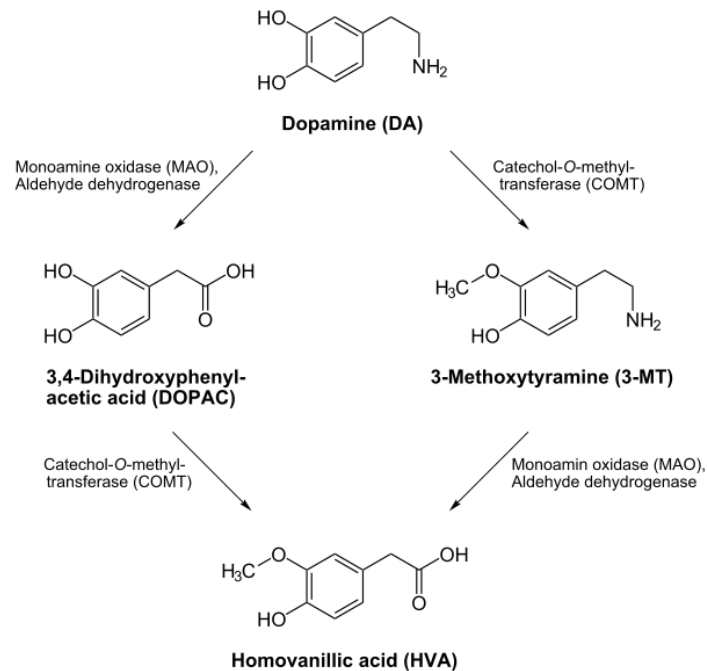
There is no such thing as a simple miracle.



MAO inhibitors B

- ▶ ***Selegiline*** is a selective and irreversible monoamine oxidase (MAO) B inhibitor with a weak symptomatic effect when used as monotherapy or as an adjunct to carbidopa/levodopa.
- ▶ **Rasagiline**
- ▶ The potential role of selegiline as neuroprotective therapy remains controversial.

Levodopa Augmentation



- ▶ The catechol *O*-methyltransferase (COMT) inhibitors *entacapone* and *tolcapone* offer yet another strategy to augment the effects of levodopa by blocking the enzymatic degradation of levodopa and dopamine. Entacapone is preferred
- ▶ These agents alleviate wearing-off symptoms and increase time a patient remains “on” (i.e., well medicated) during the day.

Trihexyphenidyl

Biperiden

Anticholinergics

COMT inhibitors

- ▶ Entacapone
- ▶ Tolcapone

Amantadine



Advanced PD



Advanced PD is characterized by at least one of the following conditions:

- (1) Presence of **problematic motor complications from levodopa**, either fluctuations or dyskinesias
- (2) **disability** that interferes with independence despite levodopa therapy
- (3) loss of postural reflexes leading to **gait imbalance and falls**
- (4) presence of **freezing phenomenon** that markedly interferes with walking
- (5) marked **postural deformities**

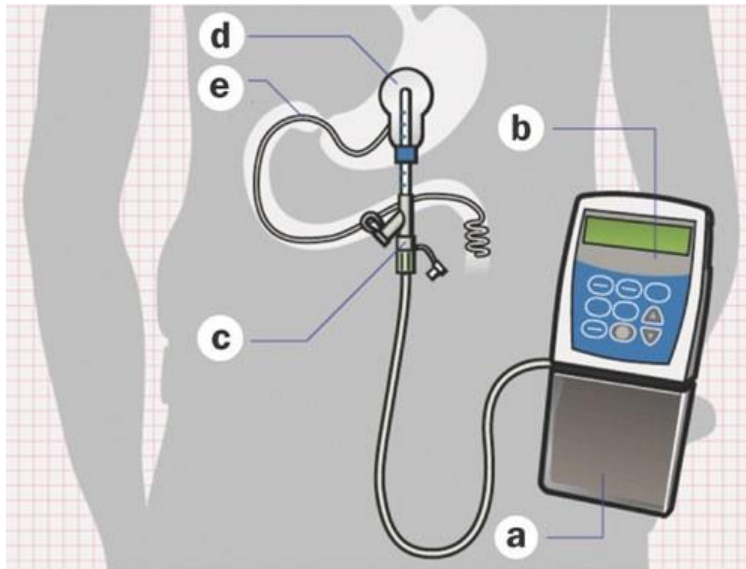
DEFINING FLUCTUATIONS AND DYSKINESIAS

- ▶ After an average of 3 years on levodopa, due to progressive degeneration of the dopaminergic system, patients with PD may start experiencing a variety of motor complications.
- ▶ These are grouped into 2 categories:
 - **Fluctuations (OFF states)**
 - **Dyskinesias**

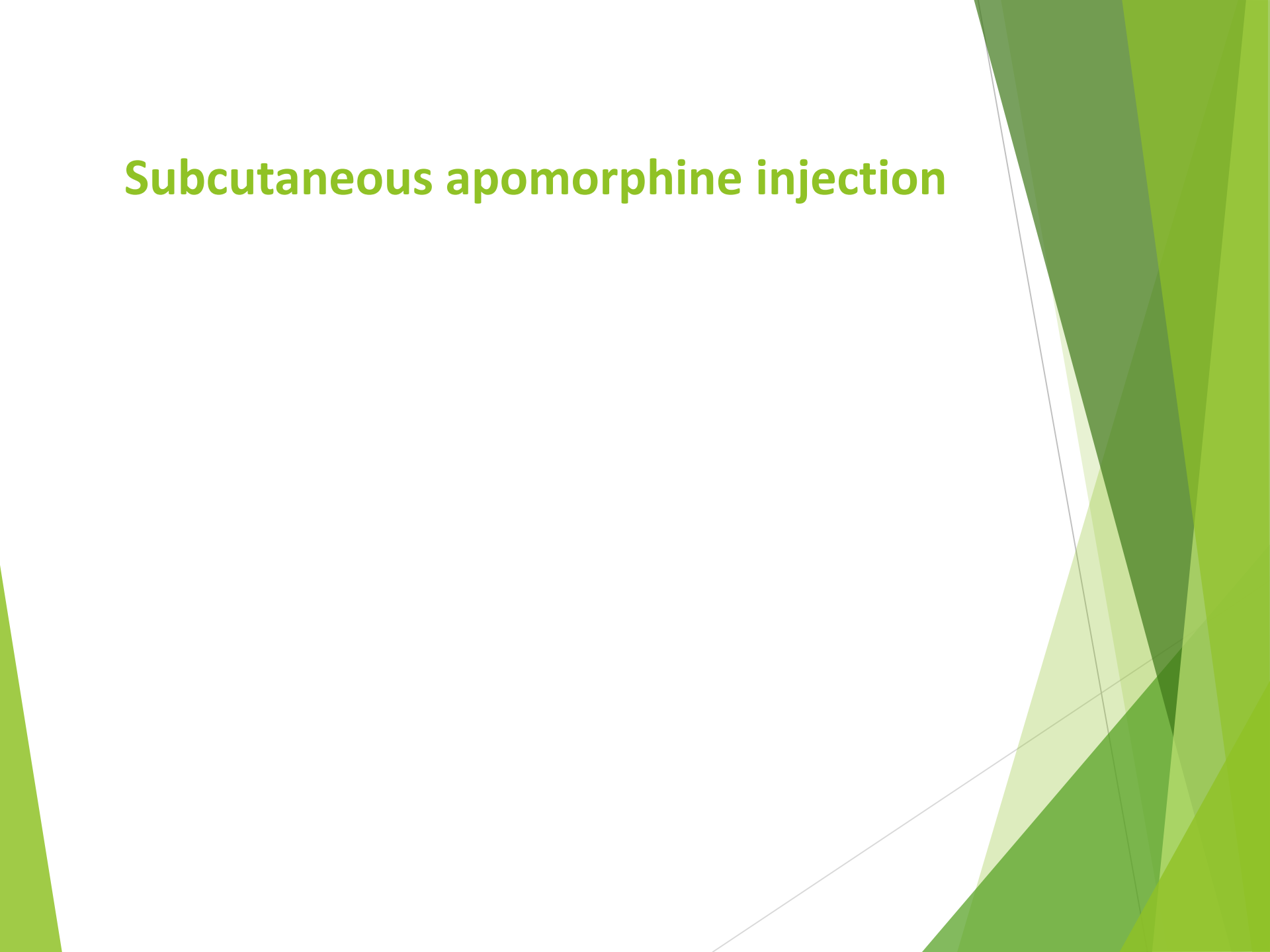
ADVANCED TREATMENTS OF PARKINSON DISEASE

- ▶ Deep brain stimulation (DBS)
- ▶ Levodopacarbidoopa intestinal gel infusion (LCIG)
- ▶ Subcutaneous infusion of apomorphine.

Levodopa-Carbidopa Intrajejunal Gel Infusion



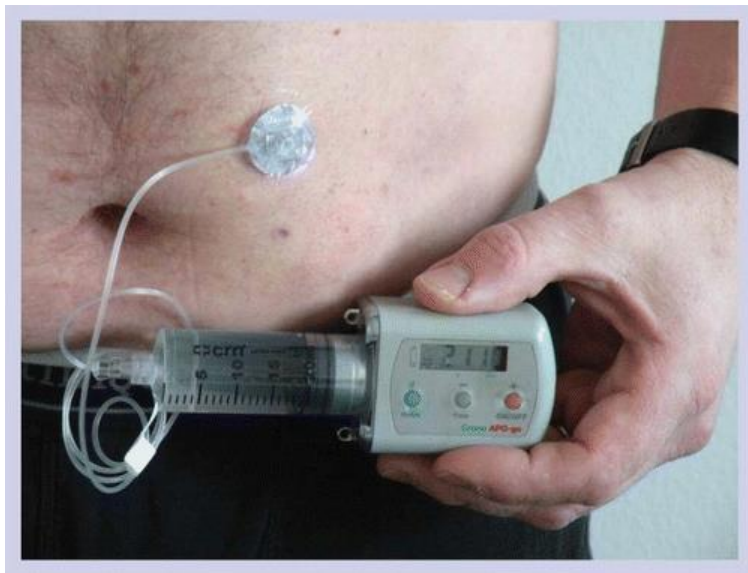
Subcutaneous apomorphine injection

The background of the slide features abstract, overlapping green geometric shapes, primarily triangles and polygons, in various shades of green, creating a modern and dynamic visual effect.

Apomorphin Pen

- ▶ Subcutaneous apomorphine, a rapidly acting dopamine agonist self administered with an autoinjector device.
- ▶ Onset of action is generally seen within 5 to 15 minutes, and effects last from 40 to 90 minutes.







Thank
You!