**Parkinsonism, Parkinson’s Disease**

Last updated: December 22, 2020

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**Parkinson’s disease** (PD) - idiopathic, slowly progressive, neurodegenerative disorder.
- 4th most common neuro-degenerative disease of elderly.
- First reported by James Parkinson in 1817.

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**PATHOLOGY**

In **substantia nigra**:

1. **Degeneration & neuronal loss** (→ gliosis)
   - Occurs normally with aging, but is greatly accelerated in parkinsonism.
   - Degenerating cells in SN normally synthesize dopamine.
   - 60-85% nigral neurons are lost prior to development of symptoms.

2. **Lewy bodies** - pathognomonic hallmark of disease!!!
   - Cosinophilic cytoplasmic inclusions in surviving neurons.
   - Single or multiple, round to elongated; dense cores surrounded by pale halo.
   - Composed of **neurofilament**, **tau** and **alpha-synuclein** and **ubiquitin**.
   - Also seen in Alzheimer’s disease, Hallervorden-Spatz disease, ataxia-telangiectasia, rarely in patients without clinical neurological disease.

3. **Pale bodies** - composed of neurofilament interpersed with vacuolar granules.
   - Also present in basal ganglia, cortex, brainstem, spinal cord.

Degenerative process is highly localized at illness beginning - area first affected is pars compacta in ventrolateral SN.

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**MACROSCOPY**

Left: pale substantia nigra in PD. Right: normally pigmented substantia nigra.

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A. Normal substantia nigra.
B. Depigmented substantia nigra in PD.
C. Lewy bodies in substantia nigra neuron stain bright pink.

**MICROSCOPY**

Left: normal number of normally pigmented neurons in substantia nigra.
Right: decreased neurons and pigment in PD.

Left: rounded pink cytoplasmic Lewy body (H & E stain).
Right: immunoperoxidase staining with antibody to ubiquitin (demonstrates Lewy bodies more readily).

Surviving pigmented neuron in substantia nigra contains intracytoplasmic rounded eosinophilic inclusion (Lewy body, L).
In Parkinson’s disease (PD), there is loss of pigmented neurons from the substantia nigra and remaining neurons may be very sparse (A). Lewy bodies can be observed in residual neurons (A, inset) and are highlighted, together with Lewy neuritis, using α-synuclein immunohistochemistry (B). Lewy bodies and Lewy neurites may be present in significant numbers in the neocortex (C, frontal cortex).

In multiple system atrophy (MSA), α-synuclein is primarily deposited in the form of glial cytoplasmic inclusions in oligodendrocytes (D, putamen) and may also form inclusions in neuronal cytoplasm and nuclei (arrow) (E, pontine nucleus). In progressive supranuclear palsy tau forms, aggregates in neurons and glia, giving rise to tufted astrocytes (F, caudate) and neurofibrillary tangles (G, pontine nuclei).

Characteristic feature of corticobasal degeneration (CBD) is the astrocytic plaque, formed from aggregated tau in the distal processes of astrocytes (H, parietal cortex). In CBD, tau also accumulates in neurons in the form of neurofibrillary tangles (H, inset a) and in oligodendrocytes as coiled bodies (H, inset b).

(A) Haematoxylin and eosin; (B-D) α-synuclein immunohistochemistry; (F-H) tau immunohistochemistry.
Etiology

Most actively studied hypothesis - selective oxidative stress.

- Source may be:
  - a) Exogenous toxic (e.g., MPTP, CO, manganese).
    - See p. Mov11 >>
  - b) Endogenous substance; e.g., metabolism of dopamine generates numerous toxic byproducts (incl. H₂O₂, superoxide anions, -OH radicals) → lipid peroxidation, membrane disruption.
    - Dopamine auto-oxidation generates superoxide radicals; dopamine metabolized by monoamine oxidase generates H₂O₂.
    - Superoxide dismutase catalyzes conversion of superoxide to H₂O₂, which is converted by glutathione peroxidase and catalase to water; however, H₂O₂ can also react with ferrous iron to form highly reactive -OH radicals.

β₂-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Shuchi Mittal, http://science.sciencemag.org/content/357/6354/891.full - aff 2017:


Supporting findings (in SN):

1. Markedly reduced glutathione peroxidase (normally is reduced with oxidative stress).
2. Increased elemental iron (facilitates formation of free radicals).
3. Decreased or normal concentration of ferritin (iron-chelating protein) – i.e. no compensatory increase to handle free iron.
4. Specific enzymatic activity defects in complex 1 of mitochondrial respiratory chain.

Actual precipitant (whether genetic, environmental, dietary, or multifactorial) remains to be determined.

No specific cause has been found.

Genetics

Isolated to be responsible for PD based on family based linkage analysis:

1. LRRK2 (PARK8) - autosomal dominant PD
  - Leucine-rich repeat kinase 2 (LRRK2) - large, widely expressed, multi-domain and multifunctional protein (product of this gene is known as dardarin).
  - LRRK2 mutations are the common genetic cause of both familial and sporadic PD.
  - Clinical features resemble those of late-onset sporadic PD.
2. SNCA (PARK2) - autosomal dominant PD
3. Parkin (PARK2) - autosomal recessive early-onset PD
4. UCHL1 (PARK5)
5. PINK1 (PARK6) - autosomal recessive PD
6. DJ-1 (PARK7) - autosomal recessive PD
7. ATP13A2 (PARK9) - autosomal recessive PD
8. GLAlpha
9. VPS35
10. EIF4G1
11. PARK16
PATHOPHYSIOLOGY

CHOLINERGIC deficit
- responsible for cognitive decline (present in up to 75% of patients 10 years after disease onset); the
cell loss in nucleus basalis of Meynert is more pronounced than in Alzheimer’s disease!
• in a staging study of PD pathology, Braak et al. reported that basal forebrain pathology occurs
simultaneously with nigral pathology, and the pathological change in the nucleus basalis of
Meynert occurs early in PD.
• study by Kim 2011, indicates that the contribution of the substantia innominata atrophy to
cognitive performance is greater in alpha-synucleinopathy-related cognitive impairments (PD,
Lewy body disease) than in Alzheimer’s disease.

DOPAMINERGIC deficit
NORMAL: see p. A103 >>
DA neurons inhibit and ACh neurons excite GABAergic output from striatum:

black arrows – excitation; speckled arrows – inhibition.

GPi = globus pallidus internal segment;
GPe = globus pallidus external segment;
STN = subthalamic nucleus;
SNc = pars reticulata of substantia nigra;
SNC = pars compacta of substantia nigra;
thal = thalamus.

• striatum acts via 2 pathways:
direct pathway inhibits GPi / SNr;
indirect pathway stimulates GPi / SNr.
• normally, dopaminergic input activates direct pathway neurons that express D1 receptors and
inhibits indirect pathway neurons that express D2 receptors; net effect is decreased stimulation
of GPi / SNr.

PARKINSONISM
DOPAMINERGIC UNDERACTIVITY (less than 20% of normal) at nigrostriatal projection* → relative
muscarinic cholinergic overactivity (ACh > DA) in striatum → increased GABAergic output from
striatum (to indirect pathway).

*fibers to putamen are most severely affected.
Dopaminergic pathways in normal condition (left) and Parkinson's Disease (right). Red arrows indicate suppression of the target, blue arrows indicate stimulation of target structure:

Due to nigrostriatal deficiency:
- indirect D₂-mediated pathway is activated → stimulation of GPi.
- direct D₁-mediated pathway is deactivated → loss of inhibition on GPi.
- in addition, D₁ receptors are deacivated (downregulated), whereas D₂ receptors are reduced (downregulated).
- net effect → hyperactivity of GPi → thalamic inhibition → less cortical activation → HYPOKINESIA.

Direct lesioning of subthalamic nucleus / GPi / thalamus can relieve HYPOKINESIA.

N.B. D₂ receptors are more important in mediating parkinsonian symptoms!

In concert, there appears to be altered phasic responsiveness by GPi to proprioceptive stimuli - numbers of responding cells increase, and receptive field becomes less specific → loss of directional effects and responses from multiple joints (account for rigidity and for altered timing and coordination of volitional movements in hypokinesia).

- other pigmented nuclei also degenerate: locus ceruleus → norepinephrine ↓
- dorsal raphe → serotonin ↓

EPIDEMIOLOGY

PREVALENCE 107-187 per 100,000 population.
- PD affects 1% of those ≥ 65 yr old.
- at least 1/3 of elderly exhibit some parkinsonian evidence.
- male : female ratio is 3 : 2.

RISK FACTORS:
1) family history of PD.
- one autosomal dominant pedigree (in Italy) - gene locus in 4q21.23 (Ala53Thr substitution in α-synuclein gene).
- one pedigree in Iowa – four copies (instead of normal two) of normal α-synuclein gene.
- another autosomal recessive form (in Japan) - mutation of parkin (protein associated with ubiquitination) on chromosome 6.
- Lewy bodies are rich in ubiquitin!
- in general, familial cases are uncommon.
2) insecticide / herbicide exposure, rural residency, well water exposure
3) nut or seed eating 10 years prior to diagnosis.
4) essential tremor (PD and ET coexist relatively frequently!)

Numerous controversial reports suggest that PD frequency is decreased with cigarette smoking.
**CLINICAL FEATURES**

Mean age of clinical onset is 55 years, but range is very wide (20-80 years) and bell-shaped!

- onset is insidious
- young patients often present with tremor-predominant disease; elderly patients - with gait dysfunction and akinnesia
- early in course, signs are usually asymmetrical (disease may be confined for one body side even for several years!) but eventually become bilateral and progressively worse.

**vs. secondary parkinsonism or Parkinson-plus syndromes - almost always symmetric!**

**MOTOR FEATURES**

- Parkinson's disease has both hyperkinetic and hypokinetic features ("paralysis agitans", "shaking palsy")

1. **Resting tremor**: hyperkinetic feature  [see p. Mov1]  
   - first symptom in 70% cases.
   - occurs in 80% patients with idiopathic PD.
   - rarely is seen in Parkinson-plus syndromes or secondary parkinsonism (except in drug-induced and MPTP-induced parkinsonism).

   N.B. resting tremor helps distinguish idiopathic PD from other causes of parkinsonism!

   - most patients also have postural tremor (re-emergence of rest tremor on coexistent essential tremor).

2. **Rigidity**: hyperkinetic feature [see p. Mov3]  
   - tendon reflexes are normal.

3. **Bradykinesia, akinesia** [see p. Mov1]  
   - term "hypokinetic syndrome" is synonymous with "parkinsonism"

   N.B. hypokinesia is not caused by rigidity!

   1) slowing of activities of daily living.
   2) difficulty in turning in bed / rising from deep chair / getting out of automobiles.
   3) loss of posturing; patient sits motionless.
   4) rapid alternating movements are performed slowly with decreasing amplitude (DECREMENTING).
   5) masked facies (HYPOMIMIA) with rare blinking (startling expression).

4. **Postural instability**  [see p. Mov3]  
   - stepping gait, falls
   - pathophysiology may be related to bradykinesia and not to unique postural response deficit.

   **specific PARNSONIAN GAIT with FLEXED POSTURE**  [see p. Mov7]  
   - "pill test" - examiner stands behind patient and, with advance warning, tegs briskly on shoulders.
   - normal person can recover in one step.
   - patient takes several small steps backward (retropulsion), possibly falling into examiner's arms.

   N.B. make sure examiner has a wall behind (helps to brace if heavy patient falls into you)

   - patient collapses backward on attempting to sit down (sitting en bloc).

5. **Tremor, rigidity, flexed posture are POSITIVE PHENOMENA (S. RELEASE PHENOMENA).**

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In general, negative phenomena are more disabling:
- patients with axial (akineti-rigid, no-tremor) disease are more resistant to both medical treatment and DBS; they are more likely to be on complex medication regimens and are considered to have more severe disease (incl. cognitive decline).

Gait

Parkinsonian patient gait:
- Shuffling gait – slow small steps
- Freezing gait – walks faster and faster, then falls
- Dyskinetic gait – wobbling (H. amartaudine)
- Freezing – main cause of falls (H. may or may not respond to L-dopa; PPN DBS; modafinil)
- Dystonic gait – leg posturing (H. L-dopa*, Rotox)

*dystonic gait may also be a side effect of L-dopa

Non-Motor Features

1. Behavioral changes, depression (at least 1/3 patients; develops 2% per year) – due to degeneration of noradrenergic locus ceruleus.
   - patient slowly becomes more dependent, fearful, indolent, passive.
   - most common feature (in case of drug-induced psychosis in Parkinson's disease) is a spousal infidelity, problem that is often not shared with neurologist owing to embarrassment by both patient and spouse.

2. Cognitive decline, up to dementia
   - up to 96% of nucleus basalis of Meynert neurons are lost in both AD and PD dementia patients compared to age-matched controls (Candy et al. 1983, Etienne et al. 1986, Gaspar and Gray 1984, Whitehouse et al. 1983, 1981).
   - strong correlations have been shown between NBM neuronal loss, resultant cortical cholinergic deficits and the degree of cognitive impairment in both diseases (Etienne et al. 1986, Gilmore et al. 1999, Perry et al. 1985).
   - loss of NBM cell bodies is more extensive in PD, while degeneration of the cholinergic projection axons is predominant in AD, although both produce a common cortical cholinergic deficit (Candy et al., 1983; Perry et al., 1985).
   - degree of NBM atrophy correlates significantly with cognitive decline on objective measures such as the mini-mental state examination (MMSE) (Choi et al. 2012; Hanyu et al. 2002). Further see p. A104.
   - frontal release signs are common, even early in disease! (e.g. sustained glabellar blink response - MYERSON sign).
   - apathy: patient is slow in responding to questions (BRADYPHRASEA) - correct answer can be obtained if patient is given enough time.
   - 75% of patients develop dementia after 8 years, possibly rising to 83% at 20 years.
   - it is hard to predict when dementia will appear but markers for its imminent appearance are falls and hallucinations.
   - tremor predominant patients seem to have later onset of the dementia.
   - 15-20% patients develop profound dementia (concurrent Alzheimer disease or diffuse Lewy body disease*).

* it is not known whether spread of Lewy bodies into cortex is feature of Parkinson disease progression or distinct entity.
- PD dementia is of “subcortical” type predominantly marked by a dysexecutive syndrome (characterized by impaired planning and concept formation) with significant deficits in attention and hallucinations.
- dementia limits tolerance of antiparkinsonian agents (because they increase confusion and produce psychosis; anti-dementia cholinergic treatment worsens parkinsonism!!!).

Hypothetical schema of anatomical progression (dashed arrows) of pathology within the nucleus basalis of Meynert with possible clinicopathological correlations.


3. Sleep disruption (fragmented sleep, frequent awakenings) - REM behavioral disorder.

4. Akathisia, restless legs syndrome

5. Sensory symptoms (< 50%) – pain (often misdiagnosed as arthritis / bursitis), burning, coldness, numbness, 1% of small.

6. Autonomic disturbances (due to dopamine depletion in hypothalamus) - rebother (particularly in PDG), constipation, neurogenic bladder (inadequate bladder emptying), erectile dysfunction, hypotension.

7. 6-fold increased risk of skin melanoma.

Diagnosis

Parkinson’s disease = all four cardinal signs + brisk response to LEVODopa.

N.B. cases of presynaptic secondary parkinsonism (e.g. MPTP, postencephalitic) and many Parkinson-plus syndromes in early stages (e.g. multiple system atrophy) also respond to LEVODopa.

Diagnosis of definite PARKINSONISM - at least two of following features (with at least one being either tremor at rest or bradykinesia-hyperkinesia):
- (1) tremor at rest
- (2) bradykinesia-hyperkinesia
- (3) rigidity

Parkinson’s disease = all four cardinal signs + brisk response to LEVODopa.

PARKINSONISM, PARKINSON’S DISEASE

Move 10 (8)
(4) Flexed posture
(5) Loss of postural reflexes
(6) Freezing phenomenon.

Alternative diagnosis: bradykinesia + at least one (resting tremor, rigidity, postural instability)

There is no diagnostic test to confirm diagnosis! Diagnosis is clinical!

**CSF**
- CSF homovanillic acid* / xanthine ratio may become future marker of disease activity. *Final metabolite of dopamine
1. Aβ42 has a role in predicting cognitive decline in PD
2. t-α-Syn: most promising marker; differentiates synucleinopathies from other neurodegenerative diseases and controls but is not specific
3. t-tau and p-tau: inconsistent data, can help differentiate PD from AD and can be useful in combination with other markers
4. NF-L: useful in differentiating PD from atypical parkinsonian conditions
5. t-Ran: possible marker of disease progression in PSP
6. DJ1: potential role in discriminating MSA from PD

**IMAGING**
- Structural imaging has limited role (except to exclude other diseases) - traditional MRI and CT are normal!
- Functional imaging: PET with F-DOPA (fluorodopa) - activity of nigrostriatal dopaminergic system (correlation between fluorodopa uptake and striatal dopamine content); may allow preclinical diagnosis!

Overview of MRI methods used to study PD:
- Cortex - changes detected using voxel-based techniques, cortical thickness measurements and perfusion imaging.
- Brain connectivity - investigated using resting-state functional MRI (rs-fMRI) for functional connectivity and tractography for structural connectivity.
- Substantia nigra - changes detected using DTI (reduced fractional anisotropy - FA), relaxometry (increased R2* indicating increased iron load and more recently susceptibility-weighted imaging), magnetization transfer ratio and spectroscopy.
- Basal ganglia: studies showed no or mild changes in FA, R2* or MTR.
- Locus coeruleus area: reduced signal intensity was detected using neuromelanin imaging.

**DASPECT**
- EDDINE-123 injection – FDA approved for use with SPECT in suspected parkinsonian syndromes.
- Schedule II controlled substance - high potential for abuse!!!
- Abnormal distribution of dopamine transporters (DaT) in striatum in parkinsonian syndromes but are normal in other conditions, such as essential tremor and Alzheimer's disease.
- To decrease thyroid accumulation of I-123, block the thyroid gland at least 1 hour before administration of DASPECT; failure to do so may increase the long term risk for thyroid neoplasia.

Normal (left) and abnormal (right) DASPECT results.

**EARLY DIAGNOSIS**
- Test based on the smell of skin may allow the early diagnosis of Parkinson's disease. The study was inspired by a "super sniffer" who detected a distinct odor on the skin of her husband, who had Parkinson's disease that was strongest both before he was diagnosed and toward the end of his life. The research is led by Perdita Barran, PhD, professor of mass spectrometry and director of the Michael Barber Centre for Collaborative Mass Spectrometry, University of Manchester, UK.

**RATING SCALES**

Unified Parkinson's Disease Rating Scale (UPDRS)
- scale used to follow longitudinal course of Parkinson's disease.

- made up of following sections:
  - UPDRS I (mentation, behavior, and mood)
  - UPDRS II (ADL): self-evaluation of the activities of daily life (ADLs) - speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, cutting food.
  - UPDRS III (motor): clinician-scored monitored motor evaluation in off-state and on-state.
  - UPDRS IV (complications of therapy): Hoehn and Yahr scale.

- PD medications withheld for > 12 hours (no typically, patient needs special clinic visit; for some medications or for patients with G1 immotility, medications may need to be withheld for > 24 hours).

- score 0 means normal.

- for most patients, “mentation, behavior and mood” scores increase later in disease, but there is a subset for whom those symptoms develop early on.

- too low emphasis on non-motor features of PD.

## Movement Disorders Society and Parkinson's Disease (MDS-UPDRS)
- four-scale structure with re-organization of various subscales:
  1) non-motor experiences of daily living (13 items)
  2) motor experiences of daily living (13 items)
  3) motor examination (18 items)
  4) motor complications (6 items).

- each subscale has 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

### Hoehn & Yahr (H&Y) staging

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<tr>
<th>Stage</th>
<th>Hoehn and Yahr Scale</th>
<th>Modified Hoehn and Yahr Scale</th>
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<tbody>
<tr>
<td>1</td>
<td>Unilateral involvement only with minimal or no functional disability</td>
<td>Unilateral involvement only</td>
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<tr>
<td>1.5</td>
<td>Unilateral axial involvement</td>
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<tr>
<td>2</td>
<td>Bilateral or midline involvement without impairment of balance</td>
<td>Bilateral involvement without impairment of balance</td>
</tr>
<tr>
<td>2.5</td>
<td>Mild bilateral disability with recovery on pull test</td>
<td></td>
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<tr>
<td>3</td>
<td>Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Severe disability; still able to walk or stand unassisted</td>
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</tbody>
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| 5     | Confined to bed or wheelchair unless aided | Wheelchair bound or bedridden unless aided

The median time to transit H&Y stages:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Time to Transit (Months)</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>20</td>
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<td>2.5</td>
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<td>24</td>
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<td>26</td>
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**UPDRS-2ND Test of Gait**
- measures the number of steps and time required to walk: 15 feet and back

## Classification, Differential Diagnosis

### I. Primary Parkinsonism
1. Parkinson's disease (PD) (< 80% parkinsonism cases)
2. Juvenile parkinsonism

### II. Parkinsonism-Plus Syndromes (10-15%) - degenerative disorders in which parkinsonism is one of several neurological features (but usually no tremor). see p.Mov12

- 1. Progressive supranuclear palsy (PSP)
- 2. Multiple system atrophy (MSA) syndromes:
  - 1) striatonigral degeneration (SND)
  - 2) olivopontocerebellar atrophy (OPCA)
  - 3) Shy-Drager syndrome (SDS)
- 3. Lytic-Bodig (parkinsonism-dementia-ALS complex of Guam (PDACC))
- 4. Cortical-basal ganglionic degeneration (CBGD)
- 5. Progressive supranuclear palsy
- 6. Dementia syndromes (Alzheimer disease, diffuse Lewy body disease)
  - additional features not typical of Parkinson's disease.
  - poower response to antiparkinsonian therapy (destroyed postsynaptic D receptors).
  - overall worse prognosis – most patients are dead at 5 years after diagnosis.

N.B. first 5 years after PD diagnosis have greatest risk of misdiagnosing, after 5: 10 years only true PD patients survive

### III. Heredodegenerative Disease (in which parkinsonism is manifestation) see p.Mov12

1. Hereditary juvenile dystonia-parkinsonism (HJD)
2. Autosomal dominant Lewy body disease
3. Huntington's disease (HD)
4. Wilson's disease (WD)
5. Hereditary cerebropalatins deficiency
6. Hallervorden-Spatz disease (HSD)
7. Olivopontocerebellar and spinocerebellar degenerations (OPCA and SCA)
8. Familial amyotrophy-dementia-parkinsonism
9. Disinhibition-dementia-parkinsonism-amyotrophy complex
10. Gersmann-Striainser-Scheinkier disease
11. Familial progressive subcortical gliosis
12. Louh (X-linked dystonia-parkinsonism)
13. Familial basal ganglia calcification
14. Mitochondrial cytopathies with striatal necrosis
15. Ceroid lipofuscinosis
IV. Secondary (Acquired, Symptomatic) Parkinsonism

1. Drugs (90% of all cases!): dopamine receptor-blocking drugs (neuroleptics, metoclopramide), rexinipine, terfenadine, a-methyldopa, fenfluramine, flunarizine, amiodarone.
3. Toxins (can cause acute parkinsonism?): MPTP, CTOP, Hg, CsI2, cyanide, methanol, ethanol.
5. Trauma: pugilistic encephalopathy.
6. Other: hemotypophis-hemiparkinsonism, parathyroid abnormalities, hypothyroidism, heparinocerebral degeneration, brain tumor, parainflamatory diseases, normal pressure hydrocephalus, noncommunicating hydrocephalus, syringomyelencephalopathy, peripherally induced tremor and Parkinsonism, psychogenic disorders.

**Levodopa equivalent daily dose (LEDD)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>100</td>
</tr>
<tr>
<td>Controlled-release levodopa</td>
<td>125</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>70</td>
</tr>
<tr>
<td>Pergolide</td>
<td>250</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>100</td>
</tr>
<tr>
<td>Carbidopa intestinal gel</td>
<td>50/200 mg</td>
</tr>
</tbody>
</table>

**Source of picture:** Viktoria Pally, MD **

**DOPAMINE PRECURSORS**

L-DOPA (LEVODOPA)—natural immediate precursor of dopamine that can cross BBB.

- most effective symptomatic treatment!
- quick response is guaranteed in nearly all patients! (most patients improve within few days, some with first dose).
  - if response is nil or minor, disorder probably is not PD; adequate response, however, does not assure diagnosis of PD!
- bradykinesia & rigidity respond better than tremor (tremor may never respond satisfactorily?)
- action depends on surviving dopaminergic neurons (that must convert LEVODOPA to dopamine);
  - not a problem in early disease
  - during 5-10 year of therapy efficacy decline begins;
  - after 5 years of therapy 75% patients start to experience complications - fluctuations (irregular and unpredictable responses to medications - **on-off** phenomenon), dyskinesias, lack of efficacy, etc. see below.

**ELDOPA study**—after only 40 weeks of treatment, both efficacy and levodopa-induced motor complications increased in a dose-dependent fashion in de novo PD patients who were within 2 years of diagnosis:
- dyskinesia were reported in 16.5% of patients receiving 600 mg/day of levodopa, which was significantly greater than 2-3% reported in those receiving 150 mg/day or 300 mg/day.
- motor fluctuations were reported in 30% of patients in the 600 mg/day group, which was significantly greater than 13-18% reported with lower doses.

**Pharmacokinetics**

- absorbed rapidly from small intestine;
- N.B. must be taken on empty stomach (at least 45 min before meals!) - large neutral amino acids (e.g. Leu, Ile) compete with LEVODOPA for absorption from gut and transport across BBB.
- **commercial dietary preparation** with carbohydrate : protein = 7 : 1 is available.

- large doses are required because 50% of LEVODOPA dose is rapidly decarboxylated to dopamine in GI tract and peripheral tissues - peripheral side effects.

**CARBIDOPA**—peripheral (does not cross BBB) inhibitor of dopa decarboxylase when co-administered with LEVODOPA, more LEVODOPA remains available for CNS! LEVODOPA dose can / must be lowered 4-5 fold! -> less peripheral side effects!.

\[
\text{LEVODOPA}^{\text{an}} \times \text{CARBIDOPA} = \text{LEVODOPA}^{\text{an}} \times \text{CARBIDOPA}^{\text{an}}
\]

**SINEMET®, SINEMET CR®**—fixed combination LEVODOPA : CARBIDOPA (1:10 and 1:4); i.e. 10/100, 25/100, 25/250 mg; available in controlled-release formulation (SINEMET CR®) 50/200 mg.

**DUODOPA®**—intestine gel for continuous infusion;

**Mov10 (111)** 16. Familial parkinsonism with peripheral neuropathy
17. Parkinsonian-pyramidal syndrome
18. Neuroacanthocytosis (NA)
19. Hereditary hemochromatosis

**TREATMENT - MEDICAL**

Treatment is lifelong!

Remain as active as possible is important!

- some patients find Pilate’s exercises to be extremely helpful!
- Strategies to increase dopamine activity in CNS → see p. Abb.>>

N.B. orally administered DOPAMINE cannot cross blood-brain barrier!

**Source of picture:** Viktoria Pally, MD **
• start on 10/100 mg x 2/d or (25/100 mg x 3/d) with or after meals (to decrease nausea) → increase dosage gradually every other day (for every 4 days) until desired therapeutic effect is reached or side effects occur.
• most patients require 25/250 mg x 3-4/d.
• before concluding that LEVODOPA is ineffective, reasonable test dose of 2000 mg/d should be given.

INBRIJA® - levodopa oral inhalation formulation - FDA approved for OFF episodes in PD patients taking a carbidopa/levodopa regimen.
• can be used up to five times daily.
• breath-actuated - does not need to be pressed or manipulated in coordination with inhalation (inhaled makes a unique "whistle" sound so the user knows the inhaler is working and the medicine is being delivered).

Adverse effects

Peripheral side effects (a and β – adrenergic):
1) nausea & vomiting (stimulation of emetic center in area postrema [outside BBB]);
2) tachycardia/bradycardia, orthostatic hypotension
3) mydriasis
4) brownish saliva and urine (melanin from catecholamine oxidation)
5) positive Coombs’ reaction.
6) intraocular pressure!

CNS side effects:
1) dyskinasias (usually choreic, but sometimes dystonic; dose-related, reversible) – most important side effect; see below
2) visual & auditory hallucinations, vivid dreams (due to dopamine in mesolimbic, mesocortical systems)
3) depression, anxiety – due to buildup of central amines.
4) hypoprolactinemia (due to dopamine!) in tuberculosis/fibribular disorder

<table>
<thead>
<tr>
<th>Drug inter-action</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERGOLIDE</td>
<td>increases peripheral metabolism (turns decarboxylase to pyridoxine-dependent); no effect if carbidopa is used.</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>enhanced catecholamine production → hypertensive crisis.</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>antagonistic action.</td>
</tr>
</tbody>
</table>

Withdrawal must be gradual over 4 days (otherwise – fever, rigidity, confusion, neuroleptic malignant syndrome).

MOTOR RESPONSE patterns - short T2/4 (< 1-2 hours) causes plasma [LEVODOPA] fluctuations.

Early stages of LEVODOA therapy, - smooth improvement throughout day (no dose-timing variations); response is evident in morning despite lack of medication throughout night; dose skipping is without loss of effect.
• mechanism - prolonged storage of dopamine from exogenous LEVODOPA in residual nigростriatal nerve terminals, prolonged postynaptic effect.

Later stages of LEVODOA therapy, - MOTOR FLUCTUATIONS and DYSKINESIAS begin - correlate well with plasma [LEVODOPA] levels.
• mechanism – denervation hypersensitivity of dopamine receptors → dyskinetic effects, shortened duration of response.

First manifestation of FLUCTUATIONS → slow "wearing off" (end-of-dose deterioration in mobility – i.e. return of parkinsonian symptoms in less than 4 hours after last dose); treatment is based on “smoothing out” plasma concentration curves:

- a) controlled-release forms
- b) titrating - having patient sip very small quantities of Sinemet dissolved in carbonated water or ascorbic acid* solution every 30-60 min throughout day.
• acidic solvents are required to dissolve levodopa and to prevent auto-oxidation of drug.
- c) combination with dopamine agonist (Tits is longer than that of LEVODOPA) or selegiline or COMT inhibitor.

Patterns of DYSKINESIAS:
a) typically IDI pattern (peak-dose dyskinasias) improvement → "peak dose" dyskinasias → improvement:
• treatment: reduce doses and make them more frequent.

b) 15% patients have DID pattern (diphasic dyskinasias): initial dyskinasias (within few minutes after levodopa ingestion) → improvement (for 2-4 hours) → recurrence of dyskinasias (usually dose-related); treatment: increase doses or switch to PERGOLIDE (low doses of LEVODOPA are left as adjunctive).

Chronic LEVODOPA therapy - MOTOR FLUCTUATIONS become less predictable - "on-off", - random, abrupt, temporary, not related to timing of LEVODOPA intake.
• for example; normal function may change to frozen akinetic state in as little as 15 seconds (sudden "off")
• mechanism - loss of presynaptic DA storage capacity, postynaptic receptor alterations.
• treatment: a) combination with dopamine agonist
b) ASPRODOPAINE v/c (FDA approved for "off" periods?)

D) consider DBS.
• d) recent finding - AMANTADINE (at higher doses than classic) can reduce dyskinasias and motor fluctuations in late-stage disease when given as adjuvant to LEVODOPA/PERGOLIDE!
• freezings that occur during "off" ("off-freezing") - feature of parkinsonism itself; "on-freezings" remain terminal.

"On-off" dyskinasias may appear during "off" states (e.g. painful "off" dystonia).
• combinations of fluctuations and dyskinasias occur:
  - good "on" for parts of day; intermittently disabled by dyskinasias or "offs" - narrow therapeutic window for levodopa!
  - patient moves rapidly from severe dyskinasias to severe akinetic "offs" with only brief "on" state.
  - motor "offs" are often accompanied by changes in mood (depression), thought (bradyphrenia?), and sensory symptoms.
2. Troubleshooting (43%)
3. Troubleshooting dyskinesias (19%)
4. Toxicity at (sub)therapeutic dosages (4%)
5. Total / substantial loss of efficacy (8%)

N.B. 75% patients have serious complications after 5 years of levodopa therapy.

Two alternative opinions about fact that onset of levodopa-induced complications is related to duration of levodopa therapy:

a) levodopa therapy hastens advent of problems – rationale to withhold levodopa as long as possible (“dopa-sparing” strategy) – it is working!

b) it is part of natural course of disease – start levodopa early to obtain maximal improvement in quality of life.

N.B. eventually all patients end up taking levodopa and will then continue on it for their rest of lives.

PD-MED trial - patients started on levodopa versus levodopa-sparing therapies have very similar long-term outcomes.

FDA approved (4/27/2020) as adjunctive to levodopa for PD.

Direct D receptor antagonists:

- All activate D2 receptors!
  - only minority benefit adequately from D agonist alone.
  - D agonists do not work if levodopa does not work.
  - relatively long T1/2, used to smooth out motor fluctuations with levodopa therapy.
  - some specialists start D agonists in early phases (before levodopa), others introduce D agonists after levodopa dose has reached 300-600 mg/d or when levodopa-related fluctuations emerge.
  - side effect (common to all D agonists):
    1) postural hypotension, syncope
    2) daytime sleepiness (215)!
    3) impulse control disorders (17% vs. 7% on other anti-Parkinson’s medications – DOMINION study).
  - *sudden onset of sleep, which can occur while driving, has been reported in 1% of patients taking dopamine agonists.

  - used together with levodopa (little effect if patient does not respond to levodopa).
  - dose is increased gradually over 2-3 months.
  - side effects – levodopa, but mental & cardiovascular* problems are more severe, whereas dyskinesia is less prominent.
  - *can produce peripheral vasospasm (erythromelalgia).

Pergolide is withdrawn from market due to cases of serious heart valve damage.

2. Pramipexole. Mirapex®. ropinirole (Requip®) – non-ergot compounds.
  - effective as first-line (in levodopa-naive patients) and as adjunctive (in advanced parkinsonism patients).
  - side effects – ergotamine-derived D agonists (except – no risk of vasospasm); risk for heart failure with pramipexole.
  - eliminated by kidneys.
  - ropinirole is extensively metabolized (vs. pramipexole).
  - drug interactions
    - TITRATED (inhibits tubular secretion of organic acids) increases T1/2 of pramipexole by 40%.

COMT inhibitors:

tolcapone – selective COMT inhibitor (central & peripheral).

- normally, methylation (by COMT) of levodopa to 3-O-methyl-dopa is minor catalytic pathway; however, if carbidopa is administered, significant 3-O-methyl-dopa concentration is formed; 3-O-methyl-dopa competes with levodopa for active transport into CNS; tolcapone prevents this!

- used only with levodopa + carbidopa.

- reduces “on-off” frequency.

- taken orally without regard to food.

- adverse effects:
  1) increased levodopa-related adverse effects
  2) diarrhea – most common side effect!
  3) fulminating hepatic necrosis (regularly follow liver enzymes?) – WRITTEN PATIENT CONSENT is needed before starting treatment.

entacapone – only peripheral COMT inhibitor, hepatic failure not described.

- carbidopa/levodopa/entacapone is not good treatment option for early PD.

strike-PD study – dyskinesia were significantly more frequent with carbidopa/levodopa/entacapone, and they developed significantly earlier than with carbidopa/levodopa; there were no significant differences in motor fluctuations or motor function in the two groups, but dopaminergic adverse events were more common with carbidopa/levodopa/entacapone.

first-step study – early PD patients were randomized to either carbidopa/levodopa or carbidopa/levodopa/entacapone – there were no significant differences in the incidence of motor fluctuations or dyskinesia; however, UPDRS activities of daily living and motor scores favored carbidopa/levodopa/entacapone group.

Opicapone (Ogentyll®)

- FDA approved (4/27/2020) as adjunctive to levodopa for PD.
3. CARBONELINE - potent D4-agonist with T1/2 = 65 hours.

4. APOMORPHINE (Apokyn®) – injectable (s.c only!) D agonist.
   - short-acting (T1/2 = 30-40 min).
   - FDA approved for "rescuing" from acute unpredictable “off” periods.
   - may lower BP?
   - may cause drowsiness.
   - start dose 2 mg; max dose 6 mg.
   - strong emetic – anticholinergic therapy should be started 3 days prior to initial dose of apomorphine and continued at least during first 2 months of therapy:
     a) TRIMETHOBENZAMINE (300 mg tid)
b) DOPERINebine (peripheral D receptor blocker).
   N.B. contraindicated use with 5-HT agonists (ondansetron, granisetron, dolasetron, etc.) – risk of profound hypotension and loss of consciousness!

5. ROTIGOTINE (Neopset®) - non-ergoline D3/D2 dopamine agonist.
   - transdermal delivery system - applied once daily to intact skin - continuously delivers drug over 24-hour period
   - available in three strengths: 2, 4, and 6 mg/24 hours
   - FDA approved for early-stage idiopathic Parkinson’s disease.
   - adverse effects - falling asleep (sometimes without warning), hallucinations, skin reactions at application site.

   Pharmacokinetics
   - D4 receptor: D4 receptor
   - D receptor: D4 receptor
   - D receptor: D4 receptor
   - 5-HT receptor: D4 receptor
   - Bromocriptine: 0
   - pergolide: 0
   - pramipexole: +
   - ropinirole: 0
   - carbidopa: +
   - lisuride: 0
   - apomorphine: ±
   - rotigotine: ±

Dopamine Release Stimulators & Reuptake Blockers & NMDA Antagonists

AMANTADINE - stimulates dopamine release & blocks re-uptake + N-methyl-D-aspartate (NMDA) glutamate antagonist
   - action depends on surviving dopaminergic neurons
   - also has some anticholinergic properties.
   - efficacy is less than LEVODOPA, but adverse effects are also less frequent:
     - Best tolerated of all PD medications
       - pitting edema and levodopa reticulata (papilled reddish venous skin motting, particularly below knees) - does not require drug discontinuation.
       - agitation, confusion, hallucinations; at high doses may induce acute toxic psychosis.
       - bradikinesia & rigidity respond better (more effective than ANTIACHTENRECEPTORS), little effect on tremor.
     - mostly used to abolish dyskinesias so often can be stopped after DBS.
     - Goetzocrine® (AMANTADINE extended release) - first and only medicine approved by FDA for dyskinesias in PD patients receiving levodopa-based therapy, with or without concomitant dopaminergic medications. It is 274 mg amantadine (equivalent to 340 mg amantadine HCl) taken once-daily at bedtime.
   - well absorbed orally; excruted unchanged in urine.
   - response is seen within few days; requires little or no dose titration.
   - tolerance develops within few months if used alone (rather than as adjunct) so it is not usually good choice for first drug (i.e. initiating therapy).

MAO-B inhibitors

Both selegiline and rasagiline have been studied as potential neuroprotective agents; however, at this time there is insufficient evidence to consider either of them to be definitely neuroprotective.

DEPRENEL + SELEGILINE – selective* inhibitor of MAO-B (dopamine catalysis).
   - starts working after 15-30 days, increases dopamine levels.
   - primarily used as 5-HT reuptake inhibitor and has some dopamine agonist activity.
   - substantially reduces required LEVODOPA dose; in general, indicated only to increase duration of LEVODOPA response.
   - early use (up to 50% parkinsonism progression) (by reducing free radicals formation, drug prevents experimental MPTP toxicity).
   - Selegiline skin patch (EndaPatch®) is FDA approved for major depression. see p. Psy15 >>

N.B. antioedmic TOCOPHEROL had no effect in delaying need for levodopa in controlled trials!

RASAGILINE (Azilect®) – potent, irreversible inhibitor of MAO-B
   - whether selective for MAO-B is not established.
   - indicated - initial monotherapy (1 mg x 1/2 d) or as adjunct to LEVODOPA (0.5-1 mg x 1/2 d).
   - tablets - 0.5 and 1 mg; can be administered with or without food.
   - dosing need not be modified in presence of LEVODOPA.
   - should be discontinued at least 14 days prior to elective surgery (if surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously).
   - contraindicated with some anesthetics (neostigmine, tramadol, methadone, propoxyphene).
   - dextromethorphan, other MAO inhibitors, sympathomimetics.
   - necessary restriction of tyramine-rich foods! see p. Psy15 <<

MAO-B, Dopamine Uptake, and Exclusive Glutamate Release Inhibitors

SAFINAMIDE (Xadago®)
   - oral, once a daily adjunctive therapy for any stage of PD.
   - dual mechanism of action – enhancement of the dopaminergic function (potent reversible inhibition of MAO-B and of dopamine uptake) + inhibition of the excessive release of glutamate.
   - results from Phase III studies, MOVEMENT and SETTLE, confirmed that safinamide significantly improves motor function in early PD patients on single dopamine agonist at a stable dose (MOVEMENT study) and significantly improves motor fluctuations in mid-to late stage PD patients on levodopa and other PD drugs at a stable dose (SETTLE study).
   - Both short (6 months) and long
*term (18–24 months) treatment with sulfinamide has shown statistically significant improvement in Quality of Life.*

**FDA approved (March 21, 2017):** as adjunctive treatment for patients with Parkinson's disease who experience "OFF" episodes while taking levodopa/carbidopa.

- risk of serotonin syndrome - should not be used in patients with severe liver problems or those taking dextromethorphan, an MAO inhibitor, an opioid, St. John's wort, and certain antidepressants (such as serotonin-norepinephrine reuptake inhibitors, tricyclics, tetracyclics, and triazolopyridazines), or cyclohexacrine.

**ANTIDEPRESSANTS**

**BENZTROPINE**
- block cholinergic overactivity in striatum.
- only adjuvant role in antiparkinsonism therapy (at any stage of disease).

- tremor responds best (general indication – tremor not relieved by dopaminergic therapy in young patients)

- adverse effects – usual central & peripheral antimuscarinic actions

**DESTRUCTIVE SURGERY**

**OTHER SYMPTOMATIC TREATMENT**

**Benztrapine** (propranolol) – FDA approved for oral adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson’s disease (PD) experiencing “OFF” episodes

**Depression, sleep fragmentation** – antidepressants

**Psychosis** – antipsychotics

**Apathy** – electric stimulation as a potential treatment for apathy.

**Constipation** – high-fiber diet and adequate fluid, osmotic laxatives.

**Parkinson’s Disease** – Drug Treatment

**Lesioning of GPi / thalamus / subthalamic nucleus** can relieve HYPOKINESIA

- surgery fails to improve most advanced cases (those who are unable to walk at any time).
- surgery worsens dementia (but does not produce it).

**Depression** – antidepressants and SSRIS are safe! (MAO inhibitors are not recommended with levodopa).

**Dementia** – RIVASTIGMINE.

**Apathy** – not usually mitigated by DBS and reduction of medication that occurs after DBS may actually worsen apathy severity (as motivation appears to be dopaminergic-driven process). H/Shman GM 1985 – electric stimulation of anterior mid cingulate cortex (SMCC) – electric stimulation as a potential treatment for apathy.

**Dystonic cramps** – RABEFLAXIN.

**Restless legs syndrome** – opioids (propoxyphene, oxycodone, codeine).

**Constipation** – high-fiber diet and adequate fluid, osmotic laxatives.

**TREATMENT - SURGERY**

- surgery was the only effective treatment of PD until 1960s, when Cotzias introduced treatment with levodopa based on the pioneering work of Arvid Carlson.

- drawbacks of ablative surgery, when contrasted with strikingly beneficial effects of levodopa, were responsible for almost total disappearance of ablative lesions until recognition of long-term side effects of levodopa (mainly motor fluctuations and dyskinesia) triggered renewed interest in surgical methods, but now with no or little tolerance for complications.

**OPERATIVE (SURGICAL) TECHNIQUE**

- surgery only effective treatment of PD until 1960s, when Cotzias introduced treatment with levodopa based on the pioneering work of Arvid Carlson.

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**Lesioning of GPi / thalamus / subthalamic nucleus can relieve HYPOKINESIA**

- surgery fails to improve most advanced cases (those who are unable to walk at any time).
- surgery worsens dementia (but does not produce it).

**Cognitive issues**

- surgery only effective treatment of PD until 1960s, when Cotzias introduced treatment with levodopa based on the pioneering work of Arvid Carlson.

- drawbacks of ablative surgery, when contrasted with strikingly beneficial effects of levodopa, were responsible for almost total disappearance of ablative lesions until recognition of long-term side effects of levodopa (mainly motor fluctuations and dyskinesia) triggered renewed interest in surgical methods, but now with no or little tolerance for complications.
hyperactive subthalamic nuclei promote glutamate excitotoxicity, accelerating dopaminergic cell death in substantia nigra (DBS removes source of toxic glutamate input → preservation of dopaminergic cells → slowed PD progression).

4) PREDUCLOPOTINE TEGMENTAL NUCLEUS (PPT)

- STN vs GPi: at 36 months, motor function is improved similarly in both STN and GPI groups, however, STN group declines significantly faster than GPI group on Mattis Dementia Rating Scale and on other neurocognitive measures.

**CONSTRUCTIVE SURGERY**

- to provide new cell source of dopamine at striatal level:

1) autotransplants of *adrenal medullary tissue* or carefult body works for a while, but long-term results are disappointing.

2) fetal ventral mesencephalic (nigral) transplantation into postcommisural putamen; it is proven that fetal nigral cells can survive up to 16 years.


**Summary of studies above:**

- long-term graft survival was demonstrated in all 7 patients at postmortem, ranging from 9 to 16 years after transplantation.

- grafts contained numerous tyrosine hydroxylase (TH) positive dopamine neurons, in the order of 10,000 to 100,000 per graft.

- grafts were well integrated and provided reinervation of the host striatum.

- grafts in 4 of the 7 patients reported were found to have Lavy body-like pathology, typical of PD, as demonstrated by immunostaining with alpha-synuclein, phosphorylated alpha-synuclein, and ubiquitin (only 1–5% of grafted neurons contained Lewy body-like pathology, whereas the remaining grafted neurons were healthy looking).

- solid grafts were found to elicit a stronger host immune reaction than cell suspensions, as demonstrated by the presence of activated microglia.

- clinically:

  - clinical outcome was highly variable: ranging from little or any demonstrable benefit to moderate benefit in measures of PD function (including UPDRS motor ‘off’ medication scores, ‘off’ time and dyskinesia, and substantially reduced antiparkinsonian medication requirements) with benefits lasting for over a decade.

  - variable clinical benefits were found to correlate with the variation in graft size at postmortem.

- no adverse events such as graft-induced dyskinesias.

**Exercise**

- Review of 39 exercise trials conducted in 1827 PD patients at various stages of disease.

- most studies reported short-term benefits from exercise, particularly for gait balance, and disability based on UPDRS scores.

- there is no definitive evidence that one form of exercise is more beneficial than another.

- Pilot study (4–6 novo PD patients diagnosed within 1 year), examined D2 receptor availability using [123I]I-QNB PET, postural control, and motor function after intensive treadmill exercise, three weekly for 8 weeks (n = 2) compared with no exercise (n = 2): results indicated that dopamine D2 receptor availability was increased and postural control was improved in 2 patients undergoing intensive exercise compared with those that did not exercise.

**GROWTH FACTORS**

Growth factors / neurotrophins infusion into ventricular CSF or brain tissue itself. e.g. gene therapy – injecting virus that carries gene to produce growth factor.

**TREATMENT – LIFESTYLE**

- All patients

  - physical-exercise therapy, good nutrition.
No clinically significant disability

**SELEGILINE** or **RASAGILINE** (?delays need for LEVODOPA by ≤ 9 months?)

All symptomatic drugs can induce side effects – should be delayed until symptoms become more pronounced!

Refer to study centers (for trials of new neuroprotective strategies)

Clinically significant disability

**Job security threatened** or **health endangered** – controlled-release LEVODOPA (at lowest effective dose)

**All symptomatic drugs can induce side effects** – should be delayed until symptoms become more pronounced!

Refer to study centers (for trials of new neuroprotective strategies)

**Clinically significant disability**

**Job security threatened or health endangered** - controlled-release LEVODOPA (at lowest effective dose)

**No clinically significant disability**

**SELEGILINE** or **RASAGILINE** (?delays need for LEVODOPA by ≤ 9 months?)

Refer to study centers (for trials of new neuroprotective strategies)

**Clinically significant disability**

**Job security threatened or health endangered** - controlled-release LEVODOPA (at lowest effective dose)

**Clinically significant disability**

**Job security NOT threatened and health NOT endangered** - try to delay LEVODOPA – so-called “dopa-sparing” strategy:

a) young and tremor-predominant disease: anticholinergic or AMANTADINE

b) older: dopamine agonist, AMANTADINE

c) very elderly (≥ 80): LEVODOPA

Above patients with progressive disability

**LEVODOPA**

if effect prolongation is needed - add **SELEGILINE** (if not currently taking it) or **COMT inhibitor**

**Consider surgery**

**De novo patients – strategies:**

a) LEVODOPA may be initial treatment of choice in patients who are currently employed or because of other aspects of their lifestyle, need maximum control of their symptoms, but rather than increasing dosages above 600 mg/day, another agent such as dopamine agonist / MAO-B inhibitor could be added in attempt to delay onset of motor complications.

b) begin treatment with MAO-B inhibitor / dopamine agonist, particularly in younger patients, and add LEVODOPA as needed to maintain control of symptoms.

**PROGNOSIS**

- disease slowly progresses - if untreated, patient eventually becomes wheelchair-bound and bedridden.

- **MORTALITY:**

  prior to levodopa advent - **three times** normally expected mortality.

  after advent of levodopa - **almost same** as age-matched control population without disease.

- patients are more likely to die from **infection** (e.g. aspiration pneumonia) than from **cancer** (compared to age-matched controls).

**BIBLIOGRAPHY** for ch. “Movement disorders, Ataxias” – follow this **LINK >>**