**Parkinsonism, Parkinson’s Disease**

Last updated: August 8, 2020

**PATHOLOGY**

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 core surrounded by pale halo.
   - Composed of neurofilament, tubulin, α-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 interspersed with vacuolar granules.
   - Also present in basal ganglia, cortex, brain stem, spinal cord.

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

**MACROSCOPY**

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

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**In SUBSTANTIA NIGRA:**

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Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward A. Kran, MD)
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 nuclei). 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.

a) exogenous toxin (e.g. such as MPTP, CO, manganese) - see p. Mov11 >

Gianni Pezzoli, MD and Emanuele Cereda, MD, PhD “Exposure to pesticides or solvents and risk of Parkinson disease” - exposure to bug or weed killers and solvents increased risk of developing Parkinson’s disease by 33-80%.

b) endogenous substance; e.g. metabolism of dopamine generates numerous toxic byproducts (incl. $\text{H}_2\text{O}_2$, superoxide anions, -$\text{OH}$ radicals) → lipid peroxidation, membrane disruption.

- dopamine auto-oxidation generates superoxide radicals; dopamine metabolized by monoamine oxidase generates $\text{H}_2\text{O}_2$.
- superoxide dismutase catalyzes conversion of superoxide to $\text{H}_2\text{O}$, which is converted by glutathione peroxidase and catalase to water; however, $\text{H}_2\text{O}_2$ can also react with ferrous iron to form highly reactive -$\text{OH}$ radicals.

$\beta_2$-Adrenoreceptor is a regulator of the $\alpha$-synuclein gene driving risk of Parkinson’s disease. Shuchi Mittal http://science.sciencemag.org/content/357/6354/891.full - Salmotamol, a $\beta_2$-adrenoreceptor, cuts the risk for PD by about a third. On the other hand, propranolol, a $\beta$-blocker, is linked to a doubling of the risk for PD.


Patients who underwent vagotomy for ulcers of the stomach 20-50 years ago have a lower risk of developing PD than do patients who did not have vagotomy - some pathogen actually may travel via the vagus nerve into the brain and leads to the development of PD.

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!"
**CHOLINERGIC deficit**

- responsible for cognitive decline (present in up to 75% of patients 10 years after disease onset); the cell loss in the 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**

- Dopaminergic & cholinergic deficits

**PATHOPHYSIOLOGY**

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**DOPAMINERGIC deficit**

**NORMAL**

DA neurons inhibit and ACh neurons excite GABAergic output from striatum:

- 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.

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**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.

**SMA** – supplementary motor area
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 compensated increased (upregulated), 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 akinesia.
- 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. RHYTHMIC TREMOR - hyperkinetic feature

- 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 in coexistent essential tremor).

2. RIGIDITY - hyperkinetic feature

- tendon reflexes are normal.

3. BRADYKINESIA, AKINESIA

- 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 gait; patient sits motionless.
4) rapid alternating movements (decerebration).
5) masked facies (HYPOPHONIA) with rare blinking (startling expression).

PARKINSON'S DISEASE

- Decreased facial mobility (dis有兴趣).
- A mask-like face may result, with decreased blinking and a characteristic stare. Since the neck and upper trunk tend to flex forward, the patient seems to push upward toward the observer. Facial skin becomes oily, and drooling may occur.

- speech abnormalities:

- soft (HYPOMICRA),
- monotonous voice with lack of inflection (SPEECH APATHY),
- not clear enunciation (SIVARTHRIA), do not separate syllables clearly - running words together (TACHYPHRA).}

7) failure to swallow spontaneously (SIALORRHEA [DROOLING])

- patients can swallow properly when asked to do so, but only constant reminders allow them to keep swallowing.
- DYSARTHRIA in advanced disease (CHOOKING AND ASPIRATION).

8) slow small handwriting (MICROGRAPHIA)

9) "freezing" (motor block) - a sudden transient (maximum several seconds) inability to perform active movements.

- must often affects legs when walking.
- also can involve eyelid opening (tarsal opening), speaking (palilalia), writing.

- bradykinesia is commonly misinterpreted by patients as "weakness".
- fatigue is common complaint (related to bradykinesia or rigidity).
- despite severe bradykinesia, patients may rise suddenly and move normally for short burst of motor activity (Kinesia paradoxica).
- patient eventually sits much of day and is inactive unless encouraged to exercise.

- camptocormia - abnormal, severe and involuntary forward flexion of the thoracolumbar spine, during standing and walking and subsides in the recumbent position.

- originally described as a psychogenic disorder, particularly in soldiers involved in long-term trench service during World War I.
- prominent and disabling phenomenon during the course of Parkinson's disease (PD).
- in most patients, the severity of camptocormia is unchanged during the "on" and "off" phases.
- in some patients it is associated with back pains, whereas in others it is painless.

- pathogenesis is unknown; it may be due to a peculiar dystonia or to an extreme form of rigidity.

- occasional patients may benefit from intramuscular botulinum toxin injections or from DBS.

4. POSURAL INSTABILITY

- PRO-LATERO-RETROPULSION (tendency to fall when center of gravity is displaced) - "feeling healthy, falls
- pathophysiologic may be related to bradykinesia and not to unique postural response deficit.

- specific PARKINSONIAN GAIT with FLEXED POSTURE

- "pallid test" - examiner stands behind patient and, with advance warning, nags 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 and examiner must attempt to sit down (sitting en bloc).


6) speech abnormalities:

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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
Festination gait – faster and faster, then falls
Dyskinetic gait – wobbly (H. amantadine)

Freezing – main cause of falls (H. may or may not respond to L-dopa; PPi DBS; modafinil)

Dystonic gait – leg posturing (H. L-dopa). Botox

* Dyskinetic 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 depression (in case of drug-induced psychosis in Parkinson’s disease) is of spurious indolence, problem that is often not shared with neurologist owing to embarrassment by both patient and spouse.

2. Cognitive decline, up to dementia
- up to 95% 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, 1985).
- 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; Hanayu et al. 2002). Further see p. A1695.
- frontal release signs are common, even early in disease! (e.g. sustained globellar blink response – Myers sign).
- apathy; patient is slow in responding to questions (bradyphrenia) - 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 leg syndrome

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

6. Autonomic disturbances (due to dopamine depletions in hypothalamus) – restless (Particularly in MPTP, 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-hypokinesia):
(1) tremor at rest
(2) bradykinesia-hypokinesia
(3) rigidity


Parkinsonism, Parkinson’s Disease

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
- DA42 has a role in predicting cognitive decline in PD
- t-α-Syn: most promising marker; differentiates synucleinopathies from other neurodegenerative diseases and controls but is not specific
- t-tau and p-tau: inconsistent data, can help differentiate PD from AD and can be useful in combination with other markers
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**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), relaxometry (increased R2* indicating increased iron load and more recently susceptibility-weighted imaging), magnetization transfer ratio (MTR reduced), 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.

**SPECT**
- Iodine-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 DaTscan; failure to do so may increase the long term risk for thyroid neoplasia.

**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 smell” who detected a distinct odor on the skin of his 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.
- 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 7–12 hours (no typically, patient needs special clinic visit for some medications or for patients with GI motility, medications may need to be withheld for ≥ 48 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 Disorder Scale (Modified UPDRS (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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Modified Hoehn and Yahr Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unilateral involvement only with minimal or no functional disability</td>
</tr>
<tr>
<td>1.5</td>
<td>Unilateral involvement</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral or midline involvement without impairment of balance</td>
</tr>
<tr>
<td>2.5</td>
<td>Bilateral involvement without impairment of balance</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral disease: mild to moderate disability with impaired postural reflexes, physically independent</td>
</tr>
<tr>
<td>4</td>
<td>Severe disabling disease; still able to walk or stand unassisted</td>
</tr>
<tr>
<td>5</td>
<td>Confinement to bed or wheelchair unless aided</td>
</tr>
</tbody>
</table>

Wheelchair bound or bedridden unless aided

**Interim-End-States** of care:
- measures the number of steps and time required to walk: 15 feet and back

**CLASSIFICATION, DIFFERENTIAL DIAGNOSIS**

- **I. Primary Parkinsonism**
  - Parkinson's disease (PD) (~80% parkinsonism cases)
  - 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 (SN)
  2) olivopontocerebellar atrophy (OPCA)
  3) Shy-Drager syndrome (SDS)
  3. Lytic-Bodig (parkinsonism-dementia-ALS complex of Guam (PDACG))
  4. Cortical-basal ganglionic degeneration (CBGD)
  5. Progressive bulidal atrophy
  6. Dementia syndromes (Alzheimer disease, diffuse Lewy body disease)
    - additional features not typical of Parkinson's disease.
    - poover 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 misdiagnosis, after 5
  10 years only true PD patients survive

- **III. Hereditary degenerative Diseases** (in which parkinsonism is manifestation) see p. Mov12 >>
  1. Hereditary juvenile dystonia-parkinsonism
  2. Autosomal dominant Lewy body disease
  3. Huntington's disease (HD)
  4. Wilson's disease (WD)
  5. Hereditary ceruloplasmin deficiency
  6. Hallervorden-Spatz disease (HSD)
  7. Olivopontocerebellar and spinopontine degenerations (OPCA and SCA)
  8. Familial amytrophy-dementia-parkinsonism
  9. Disinhibition-dementia-parkinsonism-amyotrophy complex
  10. Gerstmann-Sträussler-Scheinker disease
  11. Familial progressive subcortical gliosis
  12. Lathig (X-linked dystonia-parkinsonism)
  13. Familial basal ganglia calcification
  14. Mitochondrial cytopathies with striatal necrosis
  15. Ceroid lipofuscinosis

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

IV. Secondary (Acquired, Symptomatic) Parkinsonism

1. Drugs (90% of all cases!): dopamine receptor-blocking drugs (neuroleptics, metoclopramide), reserpine, tremelamine, a-methyldopa, lithium, flunarizine, clonazepam, amiodarone.
3. Toxins (can cause acute parkinsonism?): MPTP, COP, Mn, Hg, CS₂, cyanide, methanol, ethanol.
5. Trauma: pugilistic encephalopathy.
6. Other: heterochromia-hemiparkinsonism, parathyroid abnormalities, hypothroidism, hepatoencephalic degeneration, brain tumor, parainflamatory diseases, normal pressure hydrocephalus, noncommunicating hydrocephalus, syringomesencephalia, peripherally induced tremor and Parkinsonism, psychogenic disorders.

TREATMENT - MEDICAL

Treatment is lifelong!

- Remaining as active as possible is important!
- Some patients find Pilates’ exercises to be extremely helpful!

Strategies to increase dopamine activity in CNS → see p. 14b

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

Levodopa equivalent daily dose (LEDQ)

<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>benserazide</td>
<td>10</td>
</tr>
<tr>
<td>pergolide</td>
<td>10</td>
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<td>ropinirole</td>
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<td>carbidopa intestinal gel</td>
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<tr>
<td>pramipexole</td>
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</tr>
<tr>
<td>daily dose</td>
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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.
  - Duration 3-5 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).

ELLIDOPA 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:
- Dyskinesias 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 95% of LEVODOPA dose is rapidly decarboxylated to dopamine in GI tract and peripheral tissues – peripheral side effects.

DUODOPA - intestinal gel for continuous infusion;


LEVODOPA equivalent daily dose (LEDQ)

Source: Viktoras Palys, MD

LEVODOPA Dose

- 50/200 mg.

LEVODOPA: peripheral (does not cross BBB) (inhibitor of 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!).

-> 75-100 mg/d of CARBIDOPA is needed for effective peripheral blockade.

SIMEDET® - fixed combination CARBIDOPA: LEVODOPA (1:10 and 1:4); i.e. 100/100, 25/100, 25/250 mg.

DUODOPA - intestinal gel for continuous infusion;
Patterns of “smoothing out” plasma concentration curves: i.e. return of parkinsonian symptoms in less than 4 hours after last dose);

- First manifestation of later stages of loss of effect.
- Early stages of syndrome
- Withdrawal CNS side effects
- Adverse effects

CNS side effects:

- dyskinasias (usually choreic, but sometimes dystonic; dose-related, reversible) – most important side effect
- visual & auditory hallucinations, vivid dreams (due to dopamine in mesolimbic, mesocortical systems)
- depression, anxiety – due to blockade of central amines.
- hyperprolactinemia (due to dopamine) in tuberculosis/hilar tubercles

DRUG INTERACTIONS:

- increases peripheral metabolism (trypa decarboxylase is pyridoxine-dependent)
- no effect if CARBIDOPA is used.

- dopamine agonists – enhanced catecholamine production – hypertensive crisis.
- neuroleptics – antagonistic action.

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

MOTOR RESPONSES patterns - short T4拮 (= 1-2 hours) causes plasma [LEVODOPA] fluctuations.

Early stages of LEVODOPA 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 nigrostriatal nerve terminals, prolonged postsynaptic effect.

Later stages of LEVODOPA therapy – MOTOR FLUCTUATIONS and DYSKINESIAS begin - correlate well with plasma [LEVODOPA] concentrations.

- 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) titration - having patient sip very small quantities of Sinemet dissolved in carbonated water or ascorbic acid* solution every 30 min-60 min throughout day.
- *acidic solvent is required to dissolve levodopa.

Patterns of DYSKINESIAS:

a) typically IDI pattern (peak-dose dyskinesias) improvement – “peak dose” dyskinesia → improvement.

- treatment: reduce doses and make them more frequent.

b) 15% patients have DID pattern (diphasic dyskinesias): initial dyskinesia (within few minutes after levodopa ingestion) → improvement (for 2-4 hours) → recurrence of dyskinesia (usually dyskinesias); 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, unpredictable, 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, postsynaptic receptor alterations.

- treatment: a) combination with dopamine agonist
- b) COMT inhibitor (FDA approved for “off” periods)!
- c) consider DBS.

LEVODOPA/COMT inhibitor may appear during “off” states (e.g. painful or freezing) decreases fluctuations and dyskinesias occur:

- alpha and beta decay
- long T1/2 resulting from dopamine receptor antagonist that does not enter CNS.

b) tachyarrhythmias, orthostatic hypotension
- mydriasis
- brownish saliva and mydriasis
- orthostatic hypotension
- intraocular pressure↑

Adverse effects

Peripheral side effects (a and b – adrenergic):

1) nausea & vomiting (stimulation of emetic center in area postrema [outside BBB]);
2) tachyarrhythmias, orthostatic hypotension
3) mydriasis
4) bradynephrosis (melanin from catecholamine oxidation)
5) positive Coombs’ reaction.
6) intracranial pressure!

INBRIJA® – another indication of snr decarboxylase.

MADOPAR CR® – slow release form of INBRIJA® + LEVODOPA.
1. OFTEN (after ≥ 5 years of LEVODopa therapy):
   - Smoothing motor fluctuations (43%)
   - Troublesome dyskinesias (19%)
   - Toxicity at (sub)therapeutic dosages (4%)
   - 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 wrong!

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 rest of their lives.

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

Fox SH "Don't delay, start today": delaying levodopa does not delay motor complications. "

Physicians should not be afraid of using levodopa (in low doses) to treat patients early in the course of Parkinson's disease. Withholding the most effective anti-parkinsonian drug for fear of motor complications seems inappropriate.

CMT INHIBITORS

TOLCAPONE:

- selective COMT inhibitor (central & peripheral).
- normally, methylation (by COMT) of LEVODopa to 3-O-methyldopa is minor cathartic pathway; however, if CARBIDOPA is administered, significant 3-O-methyldopa concentration is formed; 3-O-methyldopa 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.

STRIPE-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

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

DIRECT D RECEPTOR AGONISTS

- 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 hypotenion, 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.

1. BROMOCRIPTINE, PERGOLIDE – ergotamine derivatives.
- 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 adjuncts (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:

   TIMEDRUG (inhibits tubular secretion of organic acids) increases T1/2 of PRAMIPEXOLE by 40%.
• flavonoids inhibit metabolism of rozipride.

3. CARBENEL
- potent D3-agonist with T1/2 = 65 hours.

4. APOANGORINE (Apokyn®) – injectable (s.c. only!) D agonist.
- short-acting (T1/2 = 30-60 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 – antemesis should be started 3 days prior to initial dose of apomorphine and continued at least during first 2 months of therapy.

a) TRIMETHOBENZAMIDE (300 mg tid)

b) DOPROPRINONE (peripheral D receptor blocker).

N.B. contraindicated use with 5-HT2 antagonists (ondansetron, granisetron, dolasetron, etc.) – risk of profound hypotension and loss of consciousness!

- 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 waking), hallucinations, skin reactions at application site.

DOPAMINE RELEASE STIMULATORS & BLOCKING 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 livedo reticularis (papuloulgus 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 anterograde/ALS), little effect on tremor.
  - mostly used to abolish dyskinesia so often can be stopped after DBS.

GOERG® (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; excrusted 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.

DEPRENYL ± SELEGILINE – selective* inhibitor of MAO-B (dopamine catabolism).
- does not inhibit MAO-A (tyramine, norepinephrine, serotonin catabolism) – little potential for hypertensive (“cheese”) crisis.
- 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 (Exemda®) is FDA approved for major depression. see p. Psy15 >>

N.B. anticoagulant 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.
- indication - initial monotherapy (1 mg × 1/d) or as adjunct to levodopa (0.5-1 mg × 1/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 anxiotics (neroperidol, tramadol, methadone, propoxyphene, dextromethorphan, other MAO inhibitors, sympathomimetics.
- necessary restriction of tyramine-rich foods! see p. Psy15 >>

MAO-B, DOPAMINE UPTAKE, AND EXCESSIVE GLUTAMATE RELEASE INHIBITORS

SAFINAMIDE (Xadago®)
- oral, once a day 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, MOTION and SETTLE, confirmed that safinamide significantly improves motor function in early PD patients on single dopamine agonist at a stable dose (MOTION 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 triazolopyridines), or cyclohexacaprine.

ANTHETAZINES

**ANTAZINE**

* block cholinergic overactivity in striatum.

* only adjuvant role in antiparkinsonism therapy (at any stage of the disease).

* tremor responds best (general indication - tremor not relieved by dopamnergic therapy in young patients)

* adverse effects - usual central & peripheral antimuscarinic actions

- constipation
- restless legs syndrome
- dystonia
- drooling
- apathy
- dementia
- depression, sleep

- levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes

**ISTRADEFYLLINE**

(e.g. dipyridamole/caffeine)

- (e.g. DIPHYDROMINE)

- are weak antiparkinsonian agents.

- constipation

- restless legs syndrome

- depression, sleep fragmentation

- apathy

- dementia

- levodopa

- depression, sleep

- apathy

- dementia

- depression, sleep

**OTHER SYMPTOMATIC TREATMENT**

**Psychosis** (e.g. frightening visual hallucinations - common with chronically used dopaminergic drugs)

1) stop all drugs except LEVODOPA (lower its dose)

2) **CLIFAZINE** (selective D2 antagonist - few extrapyramidal side effects).

3) **PRAMANABIN** (Noralpid) - FDA approved to treat hallucinations and delusions associated with psychosis experienced in Parkinson's disease.

**Depression, sleep fragmentation**

- **ANTHETAZINE** (tricyclic antidepressants and SSRRs are safe!)

- MAO inhibitors are not recommended with LEVODOPA.

**Dementia**

- **RIVASTIGMINE**

- **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:

- electric stimulation of anterior mid cingulate cortex (mCGC)

- Neurourology, 2014 Aug 7;52:

- Inducing the "cell in pause": electric stimulation as a potential treatment for apathy.

- Bonds GPJ, McKib CR, McKhann GM 2nd.

- Droling (PD patients forget to swallow; saliva production is normal) – chewing sugar-free gum and sucking candies (reduce drooling by increasing swallowing).

**Styptic cramps - RACLOIREN**

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

**Constitution** - high-fiber diet and adequate fluid, **CISPAPIN**

**TREATMENT - SURGERY**

- in 1953, by accident, I. Cooper cut anterior choroidal artery during surgery on Parkinsonian patient and was forced to ligate it to prevent hemotoma; unexpected and remarkable relief of tremor and rigidity on contralateral side led to more widespread use of this procedure, though mortality was approximately 10% (Cooper 1953).

- surgery was the only effective treatment of PD until 1960s, when **CITRIZOR** 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 dyskinesias) triggered renewed interest in surgical methods, but now with no or little tolerance for complications.

**DESTRUCTIVE SURGERY**

**OPERATIVE (SURGICAL) TECHNIQUES** - see p. Op360

**Lesioning of GP / thalamus / subthalamic nucleus can relieve HYPERKINESIA**

- surgery fails to improve most advanced cases (those who are unable to walk at any time).

- surgery worsens dementia (but does not produce it; moderate dementia is contraindication).

- surgery does not help patients who fail to respond to LEVODOPA.

**Targets**

1) **THALAMUS**, **MAGNOCULAR PART OF VM** [VENTRALIS INTERMEDIOUS] **NUCLEUS** → improved severe contralateral tremor

- does not improve bradykinesia, rigidity, and dexterity.

- although tremor is the most visible symptoms of PD, it is not the most disabling (difficulties in advanced Parkinsonism are essentially related to akinesia and rigidity)

- bilateral operations result in dyskinesia in 15-20% patients.

2) **GPI, POSTEROLATERAL PART** → improved dyskinesia (contralateral > ipsilateral) and fluctuations; indicated if tremor responds to medications; preferred target for patients with cognitive issues.

- *site of afferent excitatory fibers from subthalamic nucleus.

3) **SUBTHALAMIC NUCLEI, BILATERAL** → pallidotomy (or even better! esp. for gait disturbances)

- Procedure of choice for uncontrollable fluctuations!

- Better than GPI if tremor does not respond to medications

- STN is in strategic position to influence the whole net output of basal ganglia!

- May be first therapy proven to be NEUROPROTECTIVE if applied in earliest stages of disease;
hypoactive 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) PREDUNCULOPONTINE TEGMENTAL NUCLEUS (PPTN):
- 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:

CELL TRANSPLANTS
1) autotransplants of adrenal medullary tissue or cardiac body works for a while, but long-term results are disappointing.
2) fetal ventral mesencephalic (graft) transplantation into postcommnicosural putamen; it is proven that 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 reinnervation of the host striatum.
- grafts in 4 of the 7 patients reported were found to have Lewy body 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 pathology, whereas the remaining grafted neurons were healthy looking).
- solid grafts were found to elicit a stronger host immune reaction than cell suspension grafts, as demonstrated by the presence of activated microglia.
- clinically:
  - clinical outcome was highly variable, ranging from little if any demonstrable benefits to marked improvement in measures of PD function (including UPDRS motor ‘off’ medication scores, ‘off’ time and dyskinesias, and substantially reduced antiparkinsonian drug treatment) leading to prolonged periods of ‘on’ and substantial improvement in activities of daily living.
  - variable clinical benefits were found to correlate with the variation in graft size at postmortem.
  - no adverse events such as graft-induced dyskinesias.


40 patients randomized to receive either bilateral putaminal or pallidal transplants of fetal ventral midbrain tissue from two embryos per side or sham surgery.
- no immunosuppression was given.
- study failed to meet its primary endpoint of clinical improvement (however, a treatment effect was observed in younger patients).
- trial was concluded after only a year – too early for the growth and integration of human fetal dopamine neurons and the development of functional effects (e.g. several more patients showed clinical improvement after the conclusion of the trial, 2-3 years after transplantation surgery).
- ‘off’ dyskinesias were observed in 15% of the patients.


34 patients randomized to receive bilateral putaminal fetal VM solid tissue from one or four donors per side or undergo a placebo procedure.
- study of 16-month course of immunosuppression.
- study failed to meet its primary endpoint of clinical improvement in the motor UPDRS (although a treatment effect was observed in milder disease).
- ‘off’ dyskinesias were observed in 56% of the patients.

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

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 of 4-6 novel PD patients diagnosed within 1 year; examined D2 receptor availability using [18F]Fallypride 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.

TREATMENT – ALGORITHM
All patients:
- exercise, physical-therapy treatment, good nutrition.
No clinically significant disability

**SERTIGLINE** or **RASAGILINE** (‘delays need for LEVDODPA 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 LEVDODPA (at lowest effective dose)

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

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

b) older: **dopamine agonist, AMANTADINE**

c) very elderly (≥ 80): LEVDODPA

Above patients with progressive disability

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

consider **surgery**

**De novo patients** – strategies:

a) LEVDODPA 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 LEVDODPA 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] >>