Parkinsonism, Parkinson's Disease

Last updated: December 22, 2020

Parkinson's disease (PD) - idiopathic, slowly progressive, neurodegenerative disorder.

- 4th most common neurodegenerative disease of elderly.
- first reported by James Parkinson in 1817.

PATHOLOGY

In SUBSTANTIA NIGRA:

1. **Depigmentation & 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.

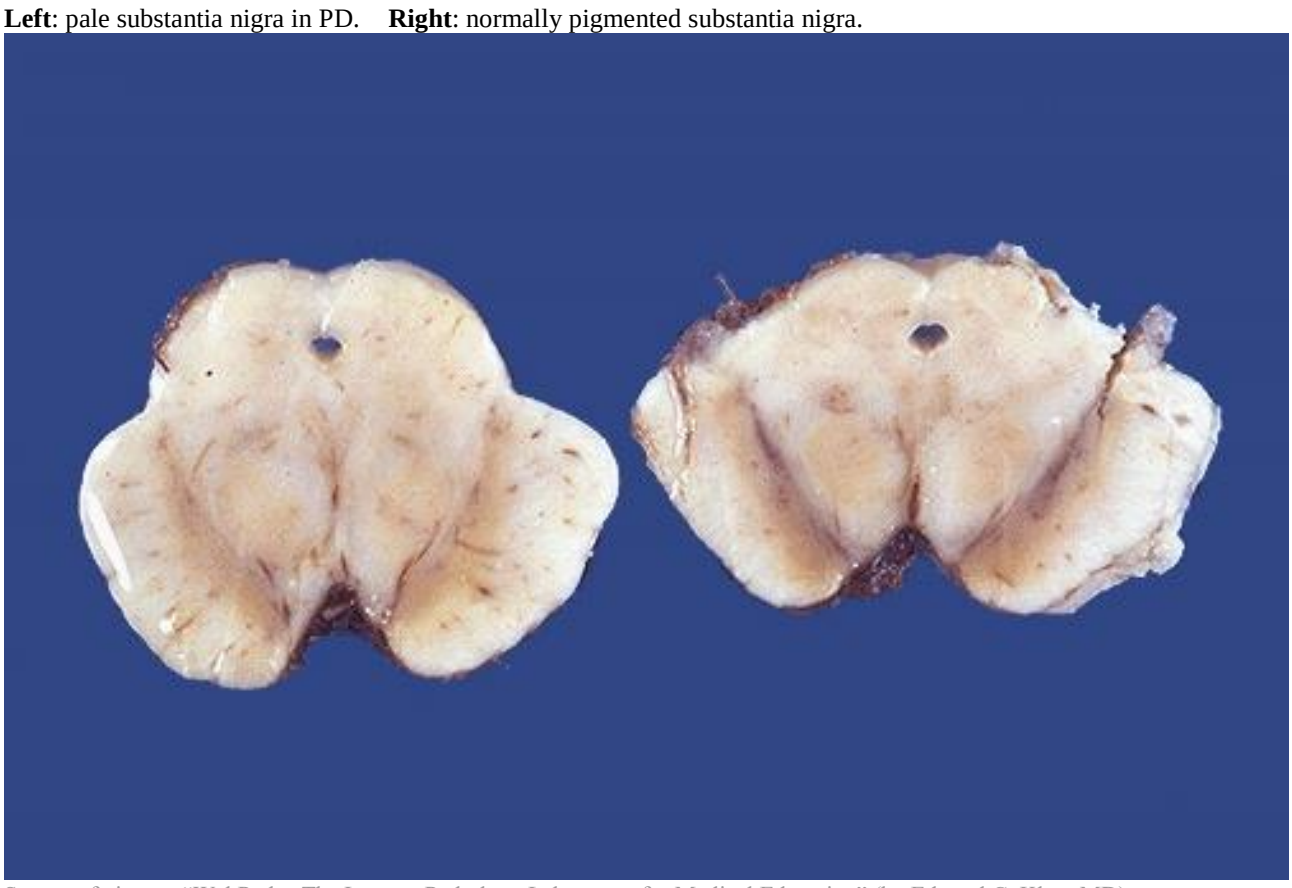
2. **LEWY bodies** - pathologic hallmark of disease!!! - eosinophilic cytoplasmic inclusions in surviving neurons.
   - single or multiple, round to elongated; dense core surrounded by pale halo.
   - composed of ***neurofilament***, ***tubulin***, ***α-synuclein*** and ***ubiquitin***.
   - also seen 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.

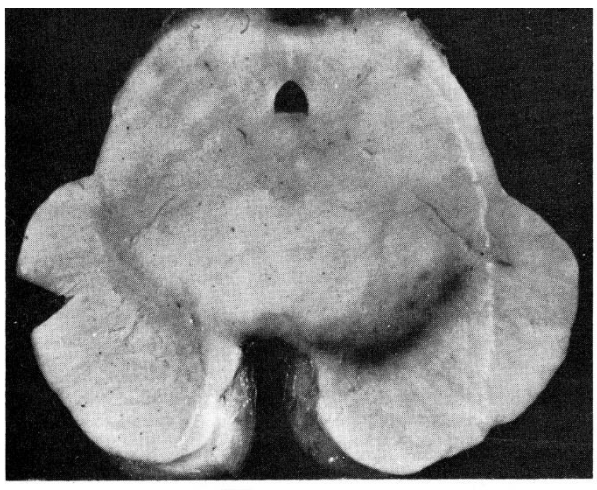
Degenerative process is highly localized at illness beginning - area first affected is **pars compacta in ventrolateral SN**.

MACROSCOPY

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

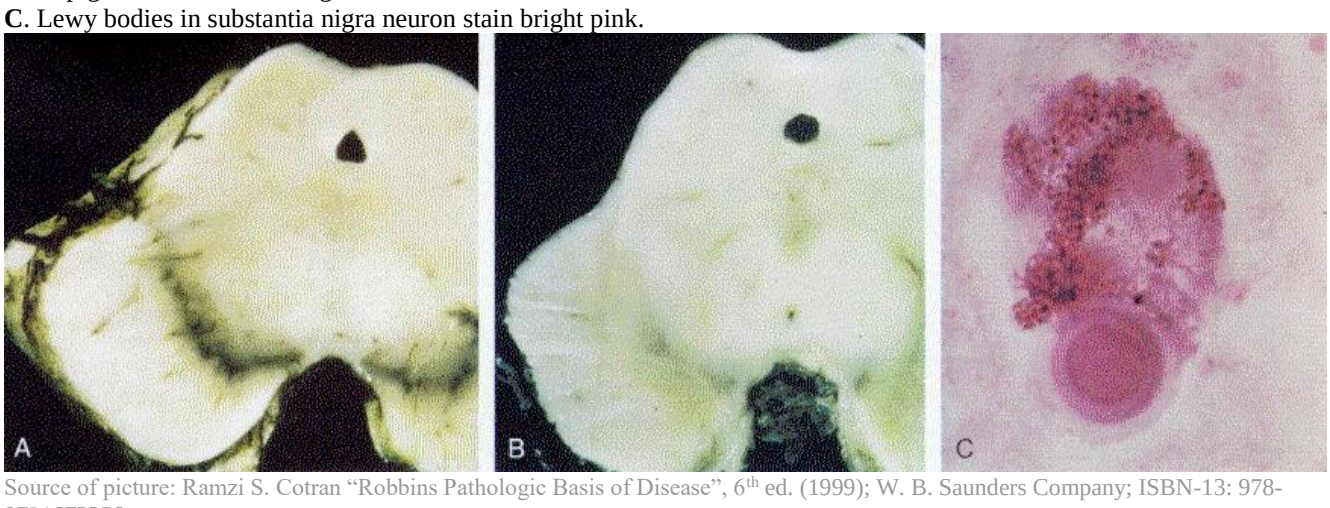


Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



Idiopathic Parkinson's disease (paralysis agitans). Unilateral loss of pigment (*left*) in substantia nigra. This is a rare occurrence; most cases show bilateral depigmentation.

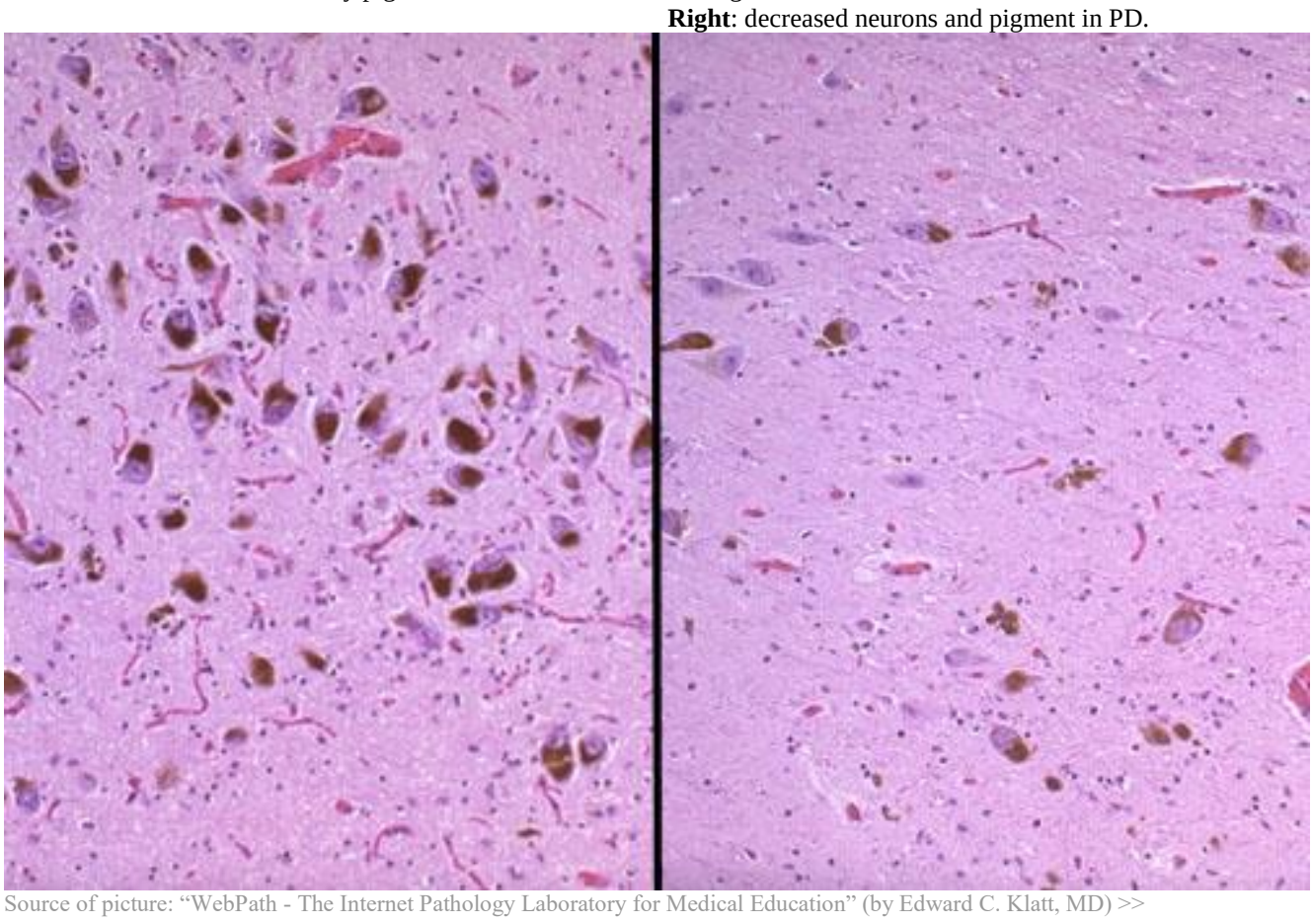
A. Normal substantia nigra.
B. Depigmented substantia nigra in PD.
C. Lewy bodies in substantia nigra neuron stain bright pink.



Source of picture: Ramzi S. Cotran "Robbins Pathologic Basis of Disease", 6th ed. (1999); W. B. Saunders Company; ISBN-13: 978-0721673356 >>

MICROSCOPY

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



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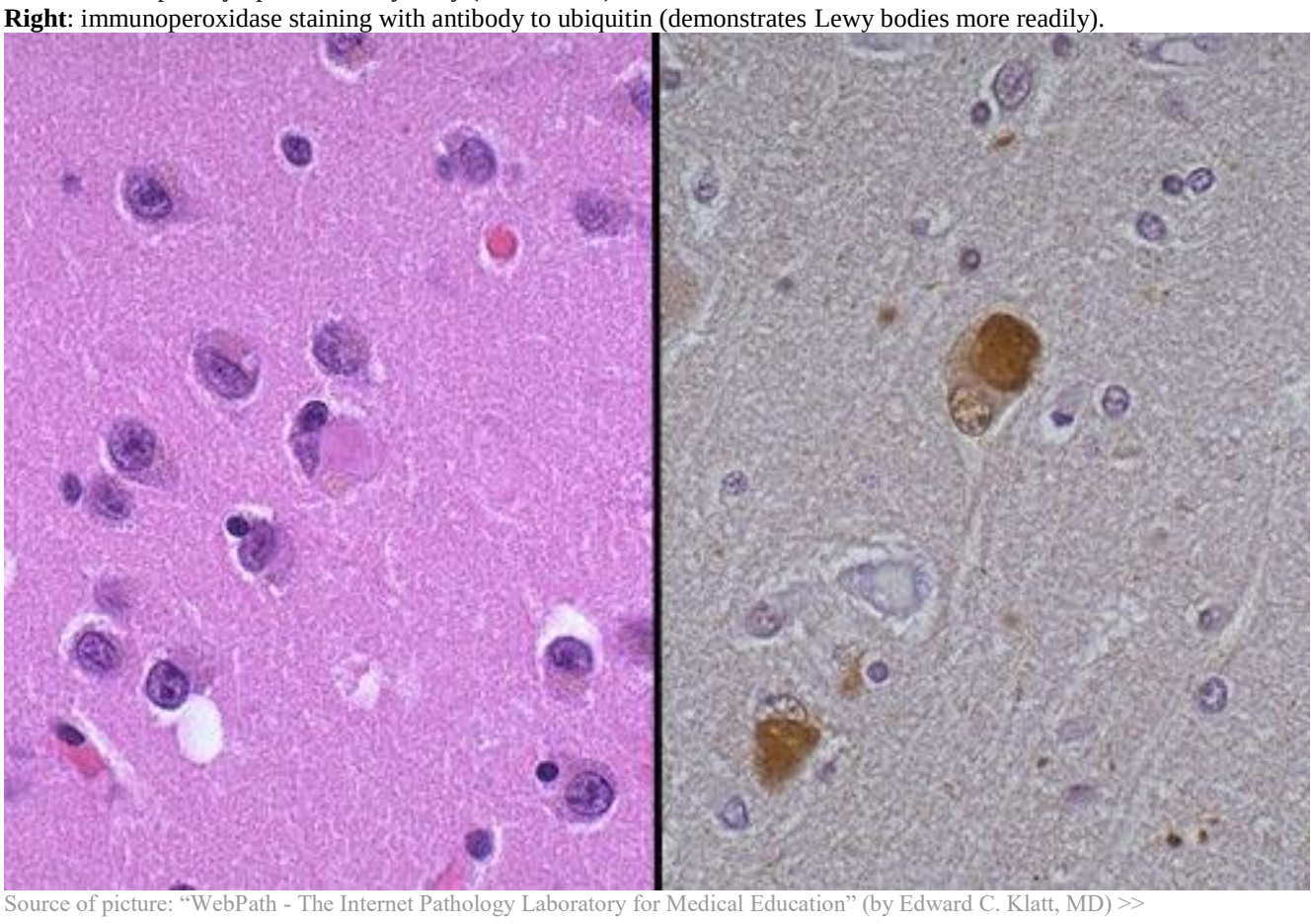
Left: rounded pink cytoplasmic Lewy body (H & E stain).
Right: immunoperoxidase staining with antibody to ubiquitin (demonstrates Lewy bodies more readily).



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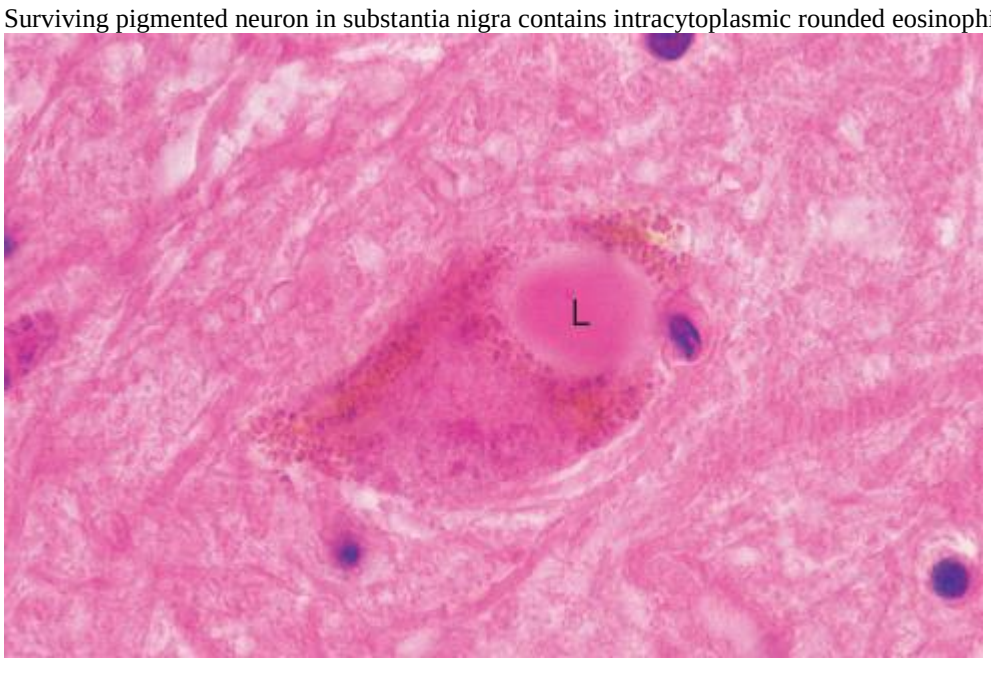
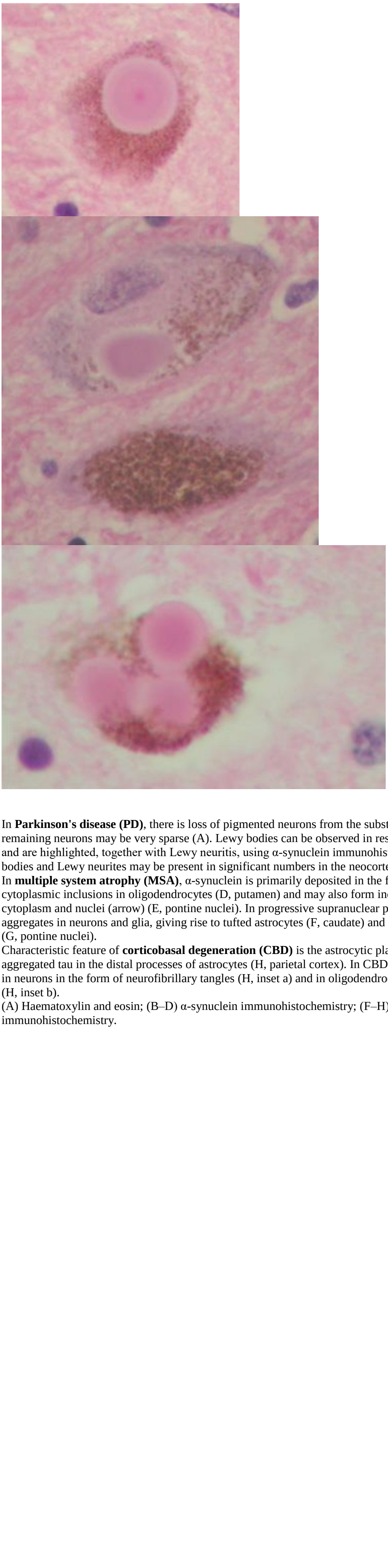
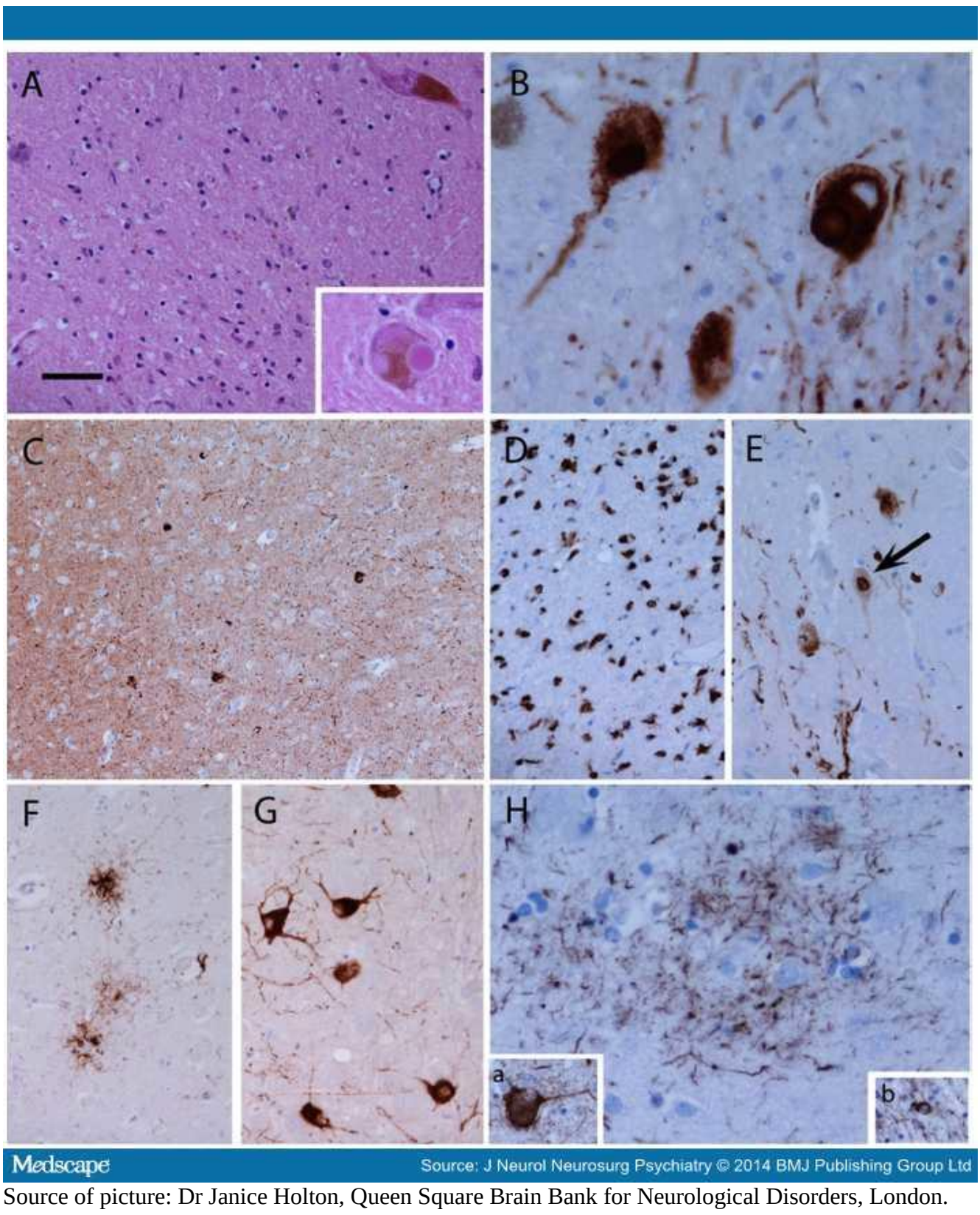
Surviving pigmented neuron in substantia nigra contains intracytoplasmic rounded eosinophilic inclusion (Lewy body, L):





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.



Source of picture: Dr Janice Holton, Queen Square Brain Bank for Neurological Disorders, London.

ETIOLOGY

Most actively studied hypothesis - **SELECTIVE OXIDATIVE STRESS**.

- source may be:
  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. H_2O_2, superoxide anions, -OH radicals) → lipid peroxidation, membrane disruption.
     – dopamine auto-oxidation generates superoxide radicals; dopamine metabolized by monoamine oxidase generates H_2O_2.
     – **superoxide dismutase** catalyzes conversion of superoxide to H_2O_2, which is converted by **glutathione peroxidase** and **catalase** to water; however, H_2O_2 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-1 *et al. Science 01 Sep 2017: Vol. 357, Issue 6354, pp. 891-898*
Salbutamol, a β2-adrenoreceptor, cuts the risk for PD by about a third. On the other hand, propranolol, a β-blocker, is linked to a doubling of the risk for PD.

Liu B, Fang F, Pedersen NL, et al. Vagotomy and Parkinson disease: a Swedish register-based matched-cohort study. Neurology. 2017;88:1996-2002.
Svensson E, Horvath-Puho E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol. 2015;78:522-529.
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!

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. *α-synuclein* (*SNCA*) - autosomal dominant PD
3. *parkin* (*PARK2*) - autosomal recessive early-onset PD
4. *UCH-L1* (*PARK5*)
5. *PINK1* (*PARK6*) - autosomal recessive PD
6. *DJ-1* (*PARK7*) - autosomal recessive PD
7. *ATP13A2* (*PARK9*) - autosomal recessive PD
8. GBA
9. VPS35
10. EIF4G1
11. PARK16

PATHOPHYSIOLOGY

Dopaminergic & cholinergic deficits

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!

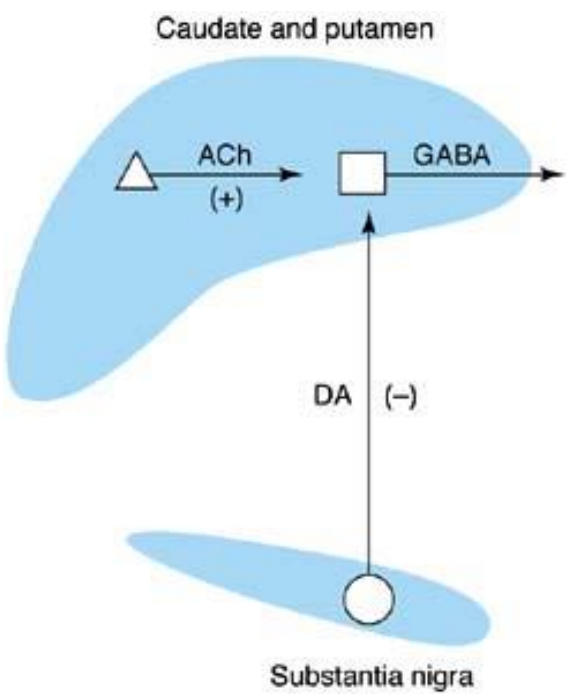
- in a staging study of PD pathology, Braak et al. reported that *basal forebrain pathology occurs simultaneously with nigral pathology*, and the pathological change in the nucleus basalis of Meynert occurs early in PD.
- study by Kim 2011, indicates that the contribution of the substantia innominata atrophy to cognitive performance is greater in alpha-synucleinopathy-related cognitive impairments (PD, Lewy body disease) than in Alzheimer's disease.

DOPAMINERGIC deficit

NORMA

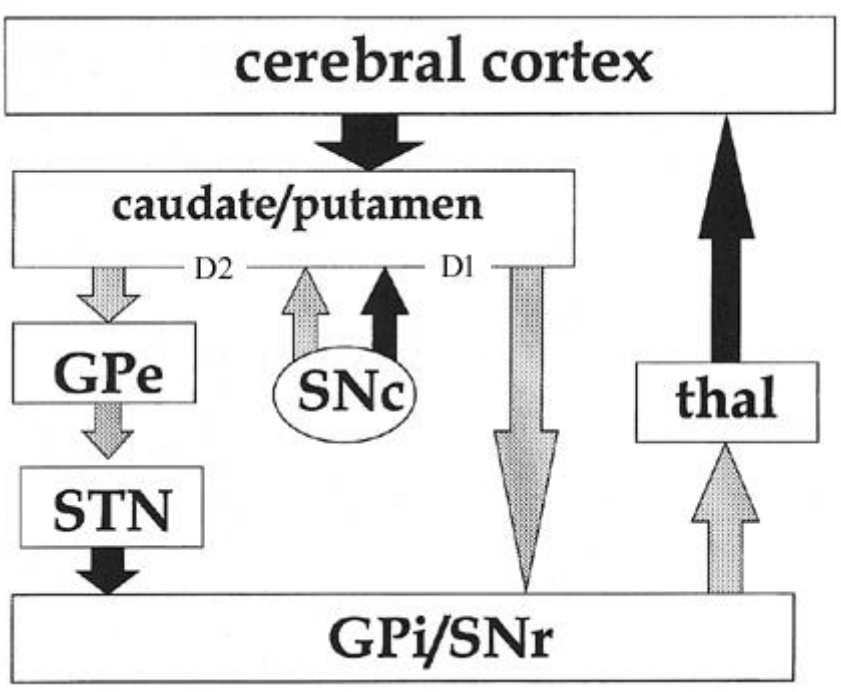
see p. A103 >>

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



black arrows – ***excitation***;
speckled arrows – ***inhibition***.

GP_i = globus pallidus internal segment;
GP_e = globus pallidus external segment;
STN = subthalamic nucleus;
SNr = pars reticularis of substantia nigra;
SNc = pars compacta of substantia nigra;
thal = thalamus.

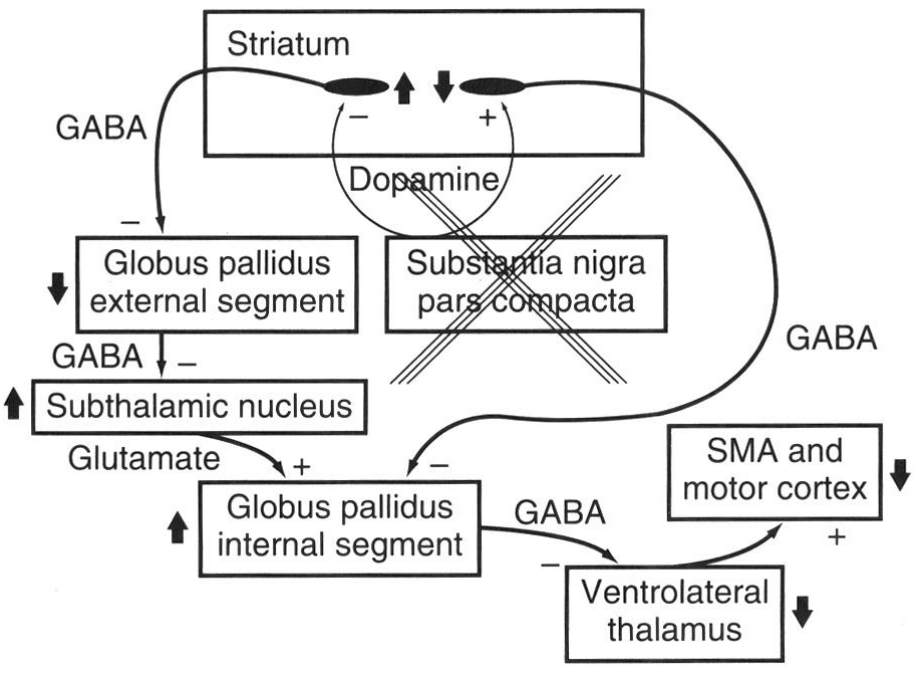


- striatum acts via 2 pathways:
  direct pathway inhibits GP_i / SNr;
  indirect pathway stimulates GP_i / SNr.
- normally, dopaminergic input *activates* **direct pathway** neurons that express **D_1 receptors** and *inhibits* **indirect pathway** neurons that express **D_2 receptors** – net effect is decreased stimulation of GP_i / SNr.

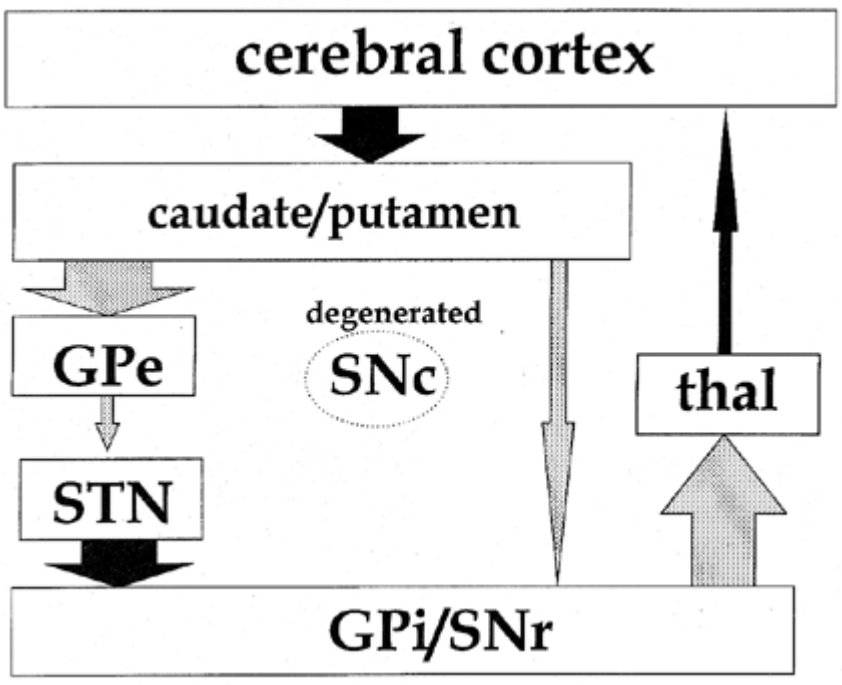
PARKINSONISM

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).

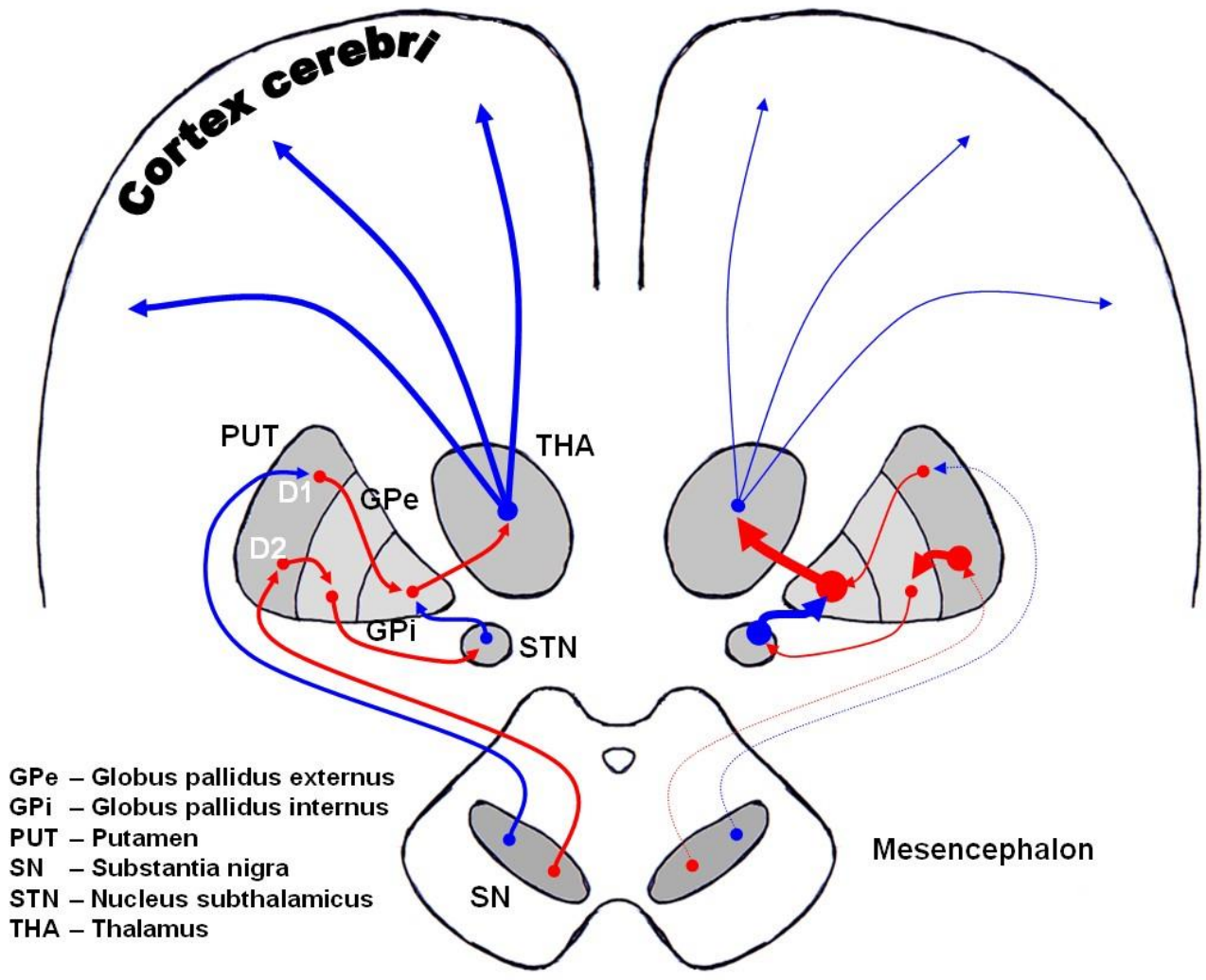
*fibers to putamen are most severely affected.



SMA – supplementary motor area

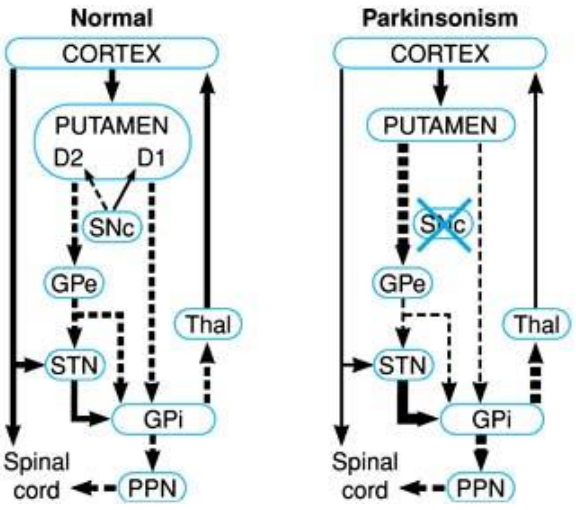


Dopaminergic pathways in normal condition (left) and Parkinsons Disease (right). Red arrows indicate suppression of the target, blue arrows indicate stimulation of target structure:



Due to nigrostriatal deficiency:

- indirect D_2–mediated pathway is activated → stimulation of GPi.
- direct D_1–mediated pathway is deactivated → loss of inhibition on GPi.
- in addition, D_2 receptors are compensatory increased (*upregulated*), whereas D_1 receptors are reduced (*downregulated*).
- net effect – hyperactivity of GPi → thalamic inhibition → less cortical activation → HYPOKINESIA.



PPN - pedunculopontine nuclei

Direct lesioning of subthalamic nucleus / GP_i / thalamus can relieve HYPOKINESIA

N.B. D_2 receptors are more important in mediating parkinsonian symptoms!

In concert, there appears to be altered **phasic responsiveness by GP_i 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.
     α-synuclein (synaptic protein of undetermined function) is component of Lewy bodies!
   - 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 at < 20 years is *juvenile parkinsonism* (pathology different from PD)

- 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 HYPOKINETIC and HYPERKINETIC 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* or coexistent *essential tremor*).

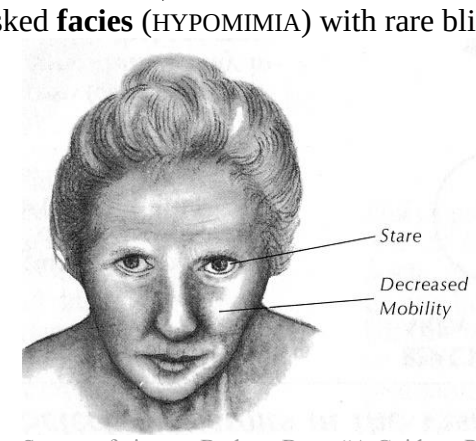
2. **RIGIDITY** - hyperkinetic feature see p. Mov3 >>
   - tendon reflexes are normal.

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 gesturing, patient sits motionless.
   4) ***rapid alternating movements*** are performed slowly with decreasing amplitude (DECREMENTING).
   5) masked **facies** (HYPOMIMIA) with rare blinking (staring expression).



PARKINSON'S DISEASE
Decreased facial mobility blunts expression. 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 peer upward toward the observer. Facial skin becomes oily, and drooling may occur.

Source of picture: Barbara Bates "A Guide to Physical Examination", 3rd ed. (1983); J.B. Lippincott Company; ISBN-13: 978-0397543991 >>

   6) **speech** abnormalities:
      - soft (HYPOPHONIA);
      - monotonous voice with lack of inflection (speech APROSODY).
      - not clear enunciation (DYSARTHRIA), do not separate syllables clearly - running words together (TACHYPHEMIA).
   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.
      - DYSPHAGIA in advanced disease → choking and aspiration.
   8) slow small **handwriting** (MICROGRAPHIA).
   9) "**freezings**" (motor block) – sudden transient (maximum several seconds) inability to perform active movements.
      - most often affects legs when walking; see p. Mov7 >>
      - also can involve eyelid opening (*apraxia of lid 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 1.
     - 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 by 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. **POSTURAL INSTABILITY**: PRO-, LATERO-, RETROPULSION (tendency to fall when center of gravity is displaced) → **festinating gait, falls**.
   - pathophysiology may be related to bradykinesia and not to unique postural response deficit.
   - specific **PARKINSONIAN GAIT** with **FLEXED POSTURE** see p. Mov7 >>
   - "**pull test**" - examiner stands behind patient and, with advance warning, tugs 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 into chair on attempting to sit down (*sitting en bloc*).

Tremor, **rigidity**, **flexed posture** are POSITIVE PHENOMENA (S. RELEASE PHENOMENA);
In general, positive phenomena are *amenable to surgery*!
Bradykinesia, **loss of postural reflexes**, **freezing** are NEGATIVE PHENOMENA.

In general, *negative phenomena are more disabling*!

– patients with axial (akinetic-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 gaits:
Shuffling gait – slow small steps
Festinating gait – walks faster and faster, then falls
Dyskinetic gait – wobbly (H: amantadine)
Freezing – main cause of falls (H: may or may not respond to L-dopa; PPN DBS; modafinil)
Dystonic gait – leg posturing (H: L-dopa*, Botox)

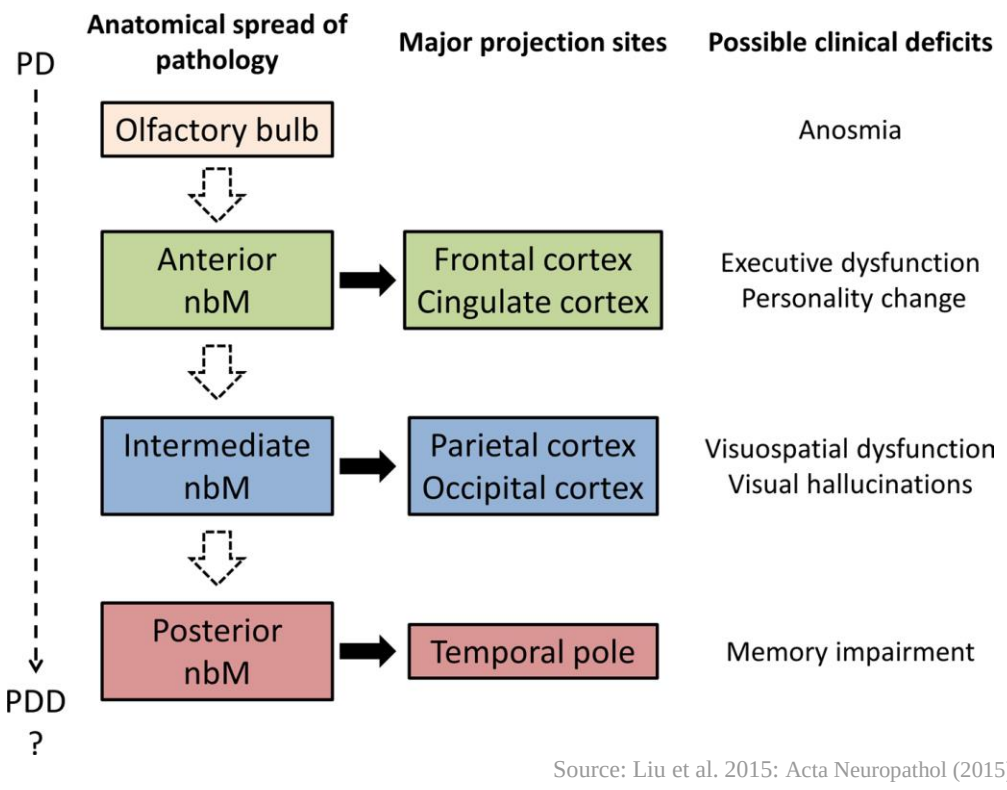
*dystonic gait may also be a side effect of L-dopa

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, indecisive, passive.
   – most common ***delusion*** (in case of drug-induced psychosis in Parkinson's disease) is of ***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, Gilmor 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. A136>>
   – ***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 (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:



Source: Liu et al. 2015: Acta Neuropathol (2015) 129:527–540

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, ↓sense of smell.

6. **Autonomic disturbances** (due to dopamine depletion in hypothalamus) - ***seborrhea*** (particularly in face), ***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

(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

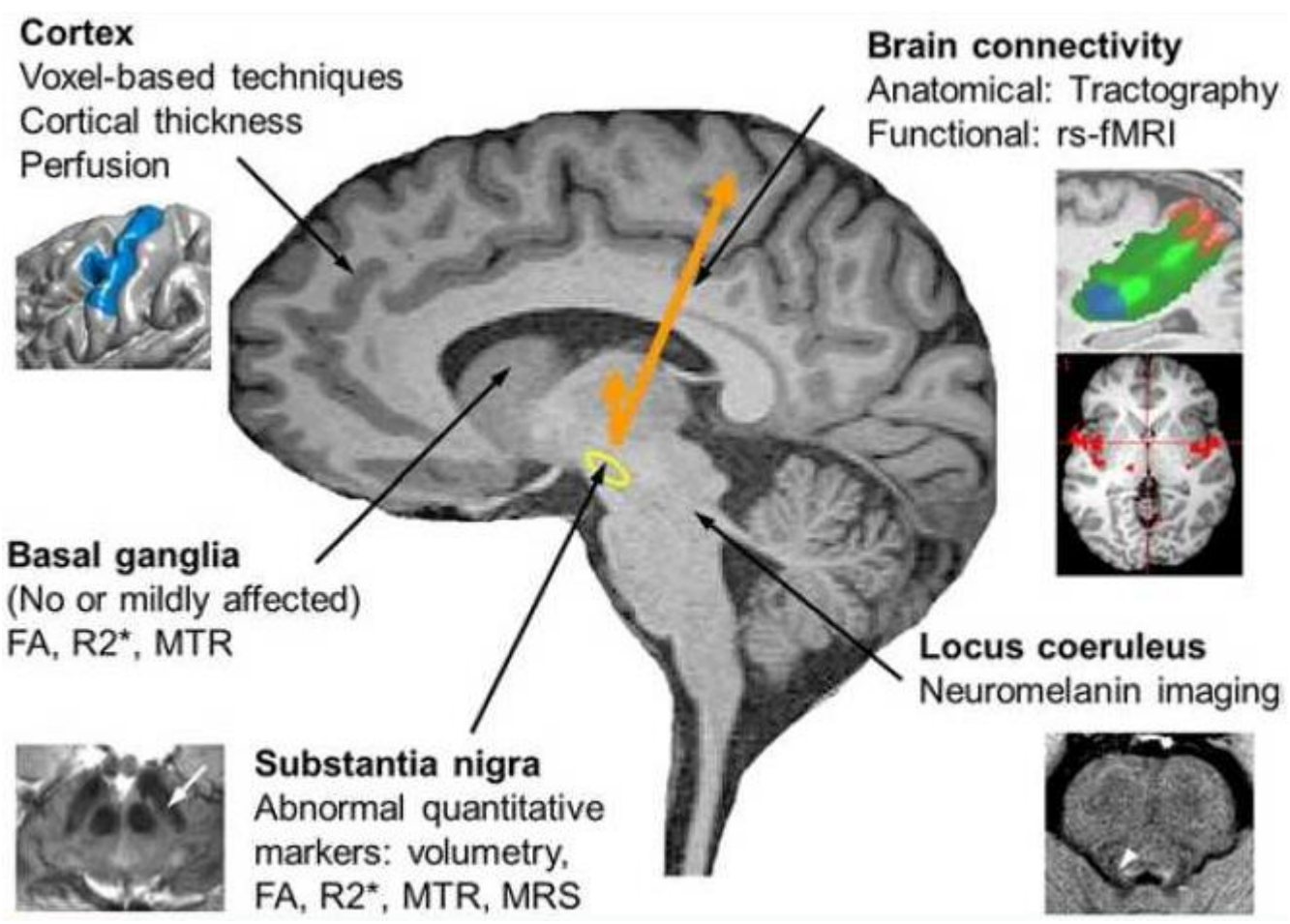
- **CSF homovanillic acid* / xanthine ratio** may become future marker of disease activity.
  *final metabolite of dopamine

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. 4R-tau: 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 (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.

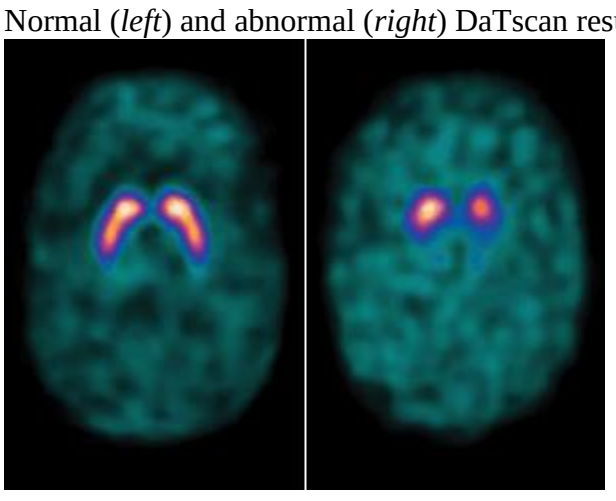


DATSCAN

IOFLUPANE 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,

Normal (*left*) and abnormal (*right*) DaTscan 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 smeller" 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**.
  UPDRS V: **Schwab and England Activities of Daily Living scale**.
  *PD medications withheld for > 12 hours (so 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 SOCIETY A REVISION OF 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

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

The median time to transit H&Y stages:

Stage	Median Time to Transit (Months)
1	-
2	20
2.5	62
3	25
4	24
5	26

*Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, Pica EC, Li SC, Luo N, Tan LC (2010). "Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times.". Mov Disord. **25** (6): 710–716.*

"STEP-SECOND 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. Lytico-Bodig (parkinsonism-dementia-ALS complex of Guam (PDACG))
4. Cortical-basal ganglionic degeneration (CBGD)
5. Progressive pallidal atrophy
6. Dementia syndromes (Alzheimer disease, diffuse Lewy body disease)

– ***additional features*** not typical of Parkinson's disease.
– *poorer 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. Heredodegenerative 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 spinocerebellar degenerations (OPCA and SCA)
8. Familial amyotrophy-dementia-parkinsonism
9. Disinhibition-dementia-parkinsonism-amyotrophy complex
10. Gerstmann-Straüssler-Scheinker disease
11. Familial progressive subcortical gliosis
12. Lubag (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 see p. Mov11 >>

1. **Drugs** (8% of all cases!): dopamine receptor-blocking drugs (neuroleptics, metoclopramide), reserpine, tetrabenazine, α-methyldopa, lithium, flunarizine, cinnarizine, amiodarone.
2. **Infectious**: postencephalitic, AIDS, SSPE, Creutzfeldt-Jakob disease, prion diseases.
3. **Toxins** (can cause acute parkinsonism!): MPTP, CO, Mn, Hg, CS_2, cyanide, methanol, ethanol.
4. **Vascular**: multi-infarct, Binswanger disease.
5. **Trauma**: pugilistic encephalopathy.
6. **Other**: hemiatrophy-hemiparkinsonism, parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic diseases, normal pressure hydrocephalus, noncommunicating hydrocephalus, syringomesencephalia, peripherally induced tremor and Parkinsonism, psychogenic disorders.

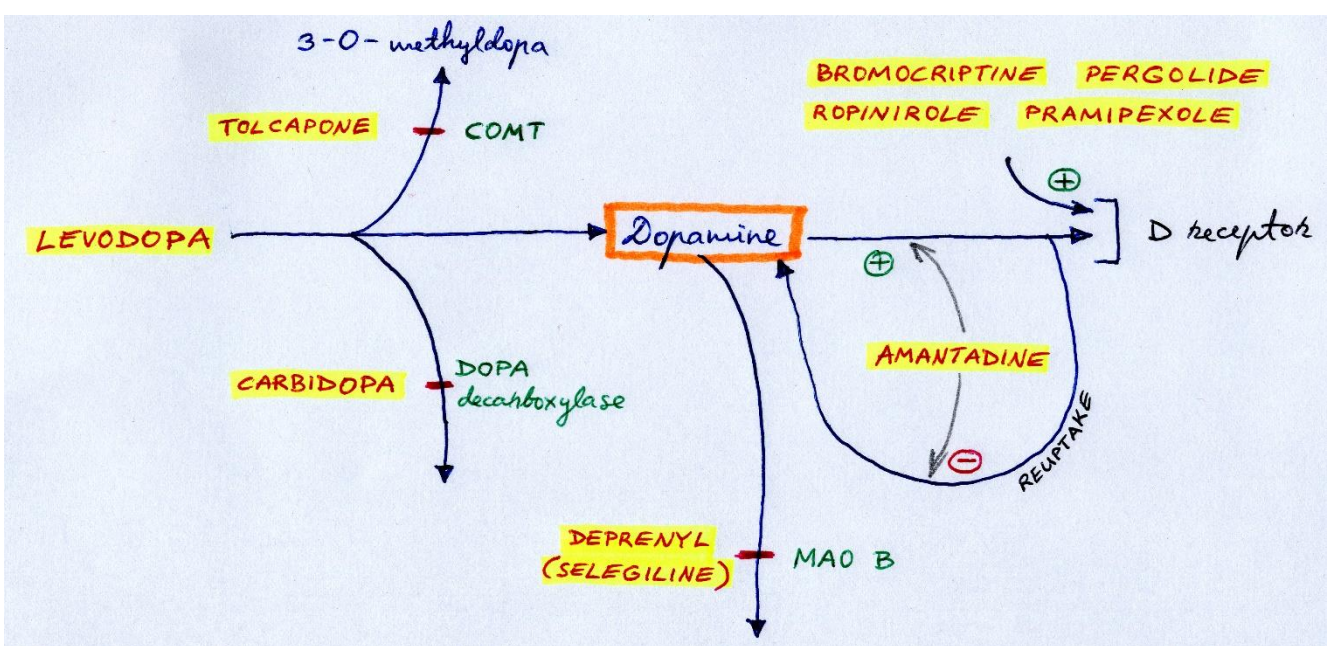
TREATMENT - MEDICAL

Treatment is lifelong!
Remaining as active as possible is important!

- some patients find *Pilate's exercises* to be extremely helpful!

Strategies to increase dopamine activity in CNS → see p. A4b >>

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



Source of picture: Viktoras Palys, MD >>

Levodopa equivalent daily dose (LEDD)

Medication	Dose, mg
levodopa	100
controlled-release levodopa	125
bromocriptine	10
pergolide	1
ropinirole	4
amantadine	100
entacapone	333
pramipexole	1
Stalevo	80

Wenzelburger et al., 2002

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 3-5th 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*

ELLDOPA 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 95% 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!).
≈ 75-100 mg/d of CARBIDOPA is needed for effective peripheral blockade.

SINEMET® – fixed combination CARBIDOPA : LEVODOPA (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 – intestinal gel for continuous infusion;
Olanow CW "Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study" Lancet Neurol. 2014 Feb;13(2):141-9.

- continuous intestinal infusion of a levodopa-carbidopa gel in advanced Parkinson's disease; system is inserted by general surgeons. There was 4-hour reduction in "off-time" accompanied by a similar increase in "on" time without troubling dyskinesias - this is comparable to DBS. However, 97% adverse-event rate (90% device-related complications - jejunostomy tube dislocation or occlusion, pump malfunction; 17% wound-infection) - far greater than device-related complication rates for nearly all major DBS studies to date. It is alternative to DBS in those cases where cranial surgery is a poor option.

BENSERAZIDE – another inhibitor of *DOPA decarboxylase*.

MADOPAR CR® – slow release form of BENSERAZIDE + LEVODOPA.

- start on 10/100 mg ×2/d (or 25/100 mg ×3/d) with or after meals (to decrease nausea) → increase dosage gradually every other day (or every 4 days) until desired therapeutic effect is reached or side effects occur.
- most patients require 25/250 mg ×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 (inhaler makes a unique "whirl" (spin) sound so the user knows the inhaler is working and the medicine is being delivered).

Adverse effects

Peripheral side effects (α and β – adrenergic):

1) **nausea & vomiting** (stimulation of emetic center in area postrema [outside BBB!]);
   H: more **CARBIDOPA**, add **DOMPERIDONE** (dopamine receptor antagonist that does not enter CNS).
2) **tachyarrhythmias**, orthostatic **hypotension**
3) mydriasis
4) brownish saliva and urine (melanin from catecholamine oxidation)
5) positive Coombs' reaction.
6) intraocular pressure↑

CNS side effects:

1) **dyskinesias** (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 tuberoinfundibular system)

DRUG INTERACTIONS:

PYRIDOXINE increases peripheral metabolism (*DOPA decarboxylase* is pyridoxine-dependent); no effect if CARBIDOPA is used!
MAO inhibitors → enhanced catecholamine production → hypertensive crisis.
neuroleptics – antagonistic action.

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

MOTOR RESPONSE patterns - short $T_{1/2}$ (≈ 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].

- 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 solvent is required to dissolve levodopa and to prevent auto-oxidation of drug.
c) combination with ***dopamine agonist*** ($T_{1/2}$ is longer than that of LEVODOPA) or ***selegiline*** or ***COMT inhibitor***.

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 dystonia);
   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, postsynaptic receptor alterations.
- treatment:
  a) combination with ***dopamine agonist***
  b) ***APOMORPHINE*** s/c (FDA approved for "off" periods!)
  c) consider **DBS**.
  d) recent finding - ***AMANTADINE*** (at higher doses than classic) can reduce dyskinesias and motor fluctuations in late-stage disease when given as adjuvant to LEVODOPA!
- **freezings** that occur during "off" ("off-freezing") - feature of parkinsonism itself; "on-freezings" remain enigma.
- **"OFF" DYSKINESIAS** may appear during "off" states (e.g. painful **"off" dystonia**).
- combinations of fluctuations and dyskinesias occur:
  – good "ons" for parts of day; intermittently disabled by dyskinesias or "offs" - narrow therapeutic window for levodopa!
  – ***yo-yoing*** - patient moves rapidly from severe dyskinesias to severe akinetic "offs" with only brief "on" state.
- motor "offs" are often accompanied by changes in mood (depression), thought (bradyphrenia↑), and sensory symptoms.

End-stage - response to *DOPAMINERGICS* is inadequate to allow patient-assisted activities of daily living.

- mechanism – combined loss of ***presynaptic*** dopaminergic neuron + ***postsynaptic*** striatal dopamine receptors.

OUTCOMES (after ≥ 5 years of LEVODOPA therapy):

1. Smooth, good response (only 25%)
2. Troublesome fluctuations (43%)
3. Troublesome 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 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." Brain. 2014 Oct
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.

COMT INHIBITORS

TOLCAPONE

– selective COMT inhibitor (central & peripheral).

- normally, methylation (by COMT) of LEVODOPA to **3-O-methyldopa** is minor catabolic 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.

STRIDE-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 (Ongentys®)

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

DIRECT D RECEPTOR AGONISTS

All activate D_2 receptors!

– only minority benefit adequately from D agonist alone.
– D agonists do not work if LEVODOPA does not work!
– relatively long $T_{1/2}$ - 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* (21%)*
  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:
  - CIMETIDINE [inhibits tubular secretion of organic acids] increases $T_{1/2}$ of PRAMIPEXOLE by 40%.

- fluoroquinolones inhibit metabolism of ROPINIROLE.

3. CABERGOLINE - potent D_2-agonist with $T_{1/2}$ = 65 hours.

4. APOMORPHINE (Apokyn®) – injectable (s/c only!) D agonist.

- ***short-acting*** ($T_{1/2}$ = 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! – antiemetic 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) **DOMPERIDONE** (peripheral D receptor blocker).

N.B. *contraindicated use with 5-HT$_3$ antagonists* (ondansetron, granisetron, dolasetron, etc) – risk of profound hypotension and loss of consciousness!

5. ROTIGOTINE (Neupro®) - non-ergoline $D_3/D_2/D_1$ 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.

Agonist	D_1 receptor	D_2 receptor	D_3 receptor	D_4 receptor	5-HT receptor
BROMOCRIPTINE	–	+			0
PERGOLIDE	+	+			0
PRAMIPEXOLE			+		
ROPINIROLE	–	+	–		
CABERGOLINE		+			
LISURIDE	–	+			+
APOMORPHINE	±	+	+	++	±
ROTIGOTINE	+	+	+		

DOPAMINE RELEASE STIMULATORS & RE-UPTAKE 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 (purplish-reddish venous skin mottling, particularly below knees) - does not require drug discontinuation.
  - agitation, confusion, hallucinations; at high doses may induce acute toxic psychosis.
- ***bradykinesia & rigidity*** respond better (more effective than *ANTICHOLINERGICS*); little effect on tremor.
- mostly used to abolish ***dyskinesias*** so often can be stopped after DBS.

  GOCOVRI® (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; excreted 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.

DEPRENYL, s. **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 slows (up to 50%) parkinsonism progression (by reducing free radicals formation; drug prevents experimental MPTP toxicity)
- Selegiline *skin patch* (EMSAM®) is FDA approved for major depression. see p. Psy15 >>

N.B. antioxidant ***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 analgetics (meperidine, 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 a 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 safinamide 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 cyclobenzaprine.

ANTIMUSCARINICS

BENZTROPINE, **TRIHEXYPHENIDYL** (Artane®), **BIPERIDEN** – all are ≈ similar.

- 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 see p. A35 >>
  - can cause forgetfulness and even psychosis (avoid in those > 70 yrs).

ANTIHISTAMINES WITH ANTICHOLINERGIC ACTION

(e.g. **DIPHENHYDRAMINE**) are weak antiparkinsonian agents.

ADENOSINE A_{2A} RECEPTOR ANTAGONISTS

ISTRADEFYLLINE (Nourianz®) – FDA approved as oral adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "OFF" episodes

OTHER SYMPTOMATIC TREATMENT

Psychosis (esp. frightening visual hallucinations – common with chronically used dopaminergic drugs)

1) stop all drugs except LEVODOPA (lower its dose)
2) CLOZAPINE (selective D_4 antagonist - few extrapyramidal side effects).
3) PIMAVANSERIN (Nuplazid) - atypical antipsychotic FDA approved to treat hallucinations and delusions associated with psychosis experienced in Parkinson's disease

Depression, sleep fragmentation – AMITRIPTYLINE (tricyclic 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: electric stimulation of ***anterior mid cingulate cortex (aMCC)***

Neurosurgery. 2014 Aug;75(2)
Inducing the "will to persevere": electric stimulation as a potential treatment for apathy.
Banks GP1, Mikell CB, McKhann GM 2nd.

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

Dystonic cramps - BACLOFEN.

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

Constipation – high-fiber diet and adequate fluid, CISAPRIDE.

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 hematoma; 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).

Cooper IS. 1953. Ligation of the anterior choroidal artery for involuntary movements of parkinsonism. Psychiat Quart 27: 317–319.

- ***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 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_i** / **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); ≥ moderate dementia is contraindication.
- surgery does not help patients who fail to respond to LEVODOPA.

Targets:

1) **THALAMUS, MAGNICELLULAR PART OF VIM [VENTRALIS INTERMEDIUS] NUCLEUS** → improved severe contralateral ***tremor***.
   - does not improve bradykinesia, rigidity, and dexterity.
     Although tremor is the most visible of symptoms of PD, it is not the most disabling (difficulties in advanced parkinsonism are essentially related to akinesia and rigidity)
   - bilateral operations result in *dysarthria* 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;

– 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) **PEDUNCULOPONTINE TEGMENTAL NUCLEUS (PPN)**.

- 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 striatum level:

CELL TRANSPLANTS

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

2) **fetal ventral mesencephalic (nigral)** *transplantation* into postcommissural putamen; it is proven that transplanted cells can survive up to 16 years:

Kordower JH , Chu Y , Hauser RA , Freeman TB , Olanow CW . Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease . Nat Med 2008 ; 14 : 504 – 506.

Li JY , Englund E , Holton JL , Soulet D , Hagell P , Lees AJ , Lashley T , Quinn NP , Rehncrona S , Bjorklund A , Widner H , Revesz T , Lindvall O , Brundin P . Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. N at Med 2008 ; 1 4 : 501 – 503.

Mendez I , Vinuela A , Astradsson A , Mukhida K , Hallett P , Robertson H , Tierney T , Holness R , Dagher A , Trojanowski JQ , Isacson O : Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years . N at Med 2 008; 1 4: 5 07– 5 09.

Summary of studies above:

- long-term graft survival was demonstrated in all 7 patients at post-mortem, 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-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 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 improvements in measures of PD function (incl. UPDRS motor 'off' medication scores, 'off' time and dyskinesias, 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 post-mortem.
  - no adverse events such as graft-induced dyskinesias.

Freed CR , Greene PE , Breeze RE , Tsai WY , DuMouchel W , Kao R , Dillon S , Winfield H , Culver S , Trojanowski JQ , Eidelberg D , Fahn S . Transplantation of embryonic dopamine neurons for severe Parkinson's disease . N Engl J Med 2001 ; 3 44 : 710 – 719.

- 40 patients randomized to receive either bilateral solid tissue putaminal 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.

Olanow CW , Goetz CG , Kordower JH , Stoessl AJ , Sossi V , Brin MF , Shannon K M, Nauert G M, P erl D P, Godbold J , Freeman TB A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease . Ann Neurol 2003 ; 54 : 403 – 414.

- 34 patients randomized to receive bilateral putaminal fetal VM solid tissue from one or four donors per side or undergo a placebo procedure.
- 6-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 NEURTURIN

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 (4 de-novo PD patients diagnosed within 1 year; examined D2 receptor availability using [18F]fallypride PET, postural control, and motor function after intensive treadmill exercise, thrice 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
Education, 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)
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
add 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 >>