Parkinson Disease (PD) Treatment Update

Outlines

- The Basics:
  - PD Introduction and motor symptoms.
  - DDx not to miss.
  - Different classes of Anti PD.
    - Dopamine.
    - Dopamine Agonist.
    - MAO inhibitors.
    - COMT inhibitors.
    - Anticholinergics
    - Amantadine
  - Non motor symptoms and Rx.
  - Role of Surgery.

Objectives

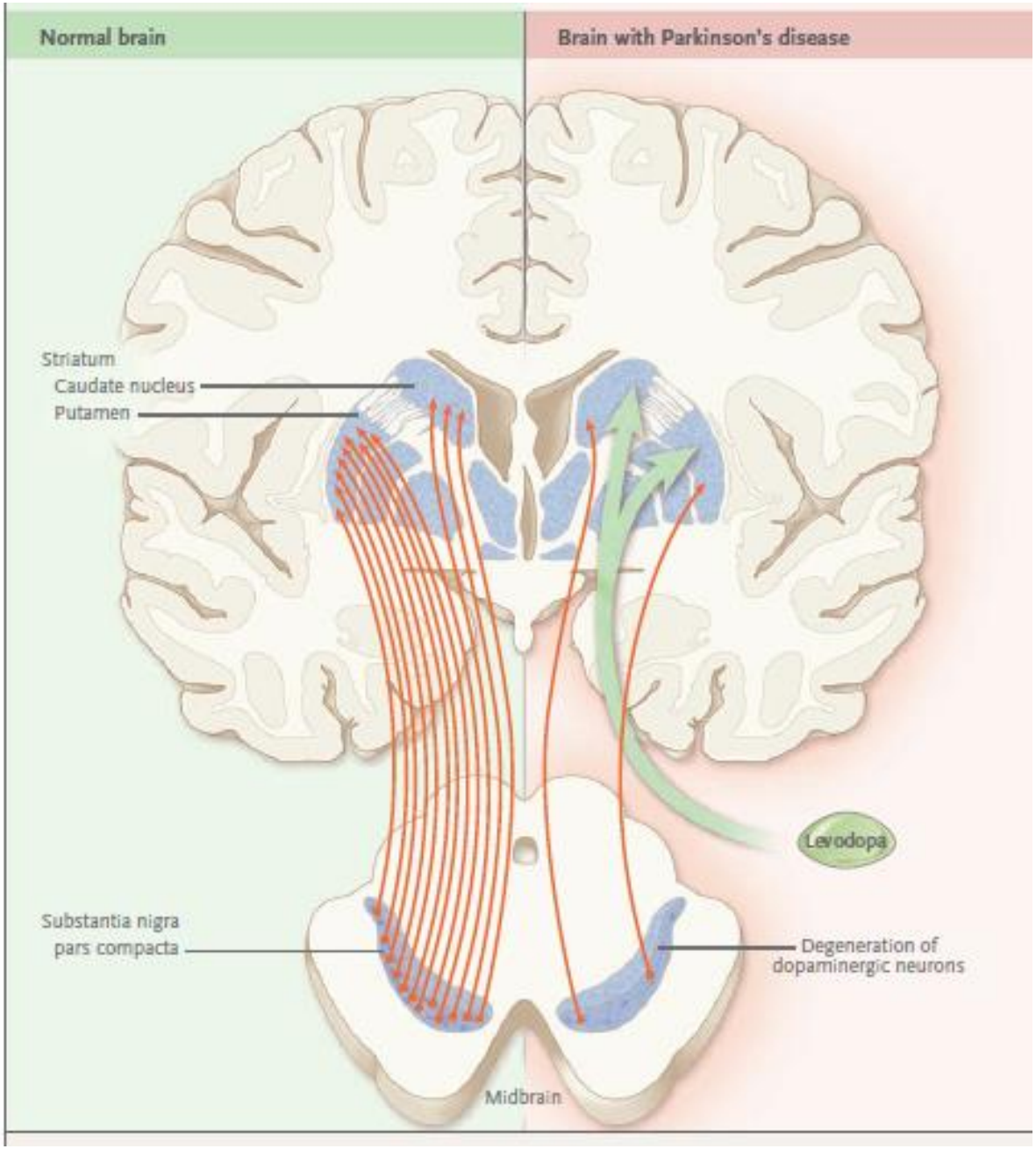
- Describe the characteristics of different classes of drugs used in Parkinson disease treatment.
- Treatment of non-motor symptoms
- Role of Surgery in PD Rx.

PD Introduction and Cardinal features

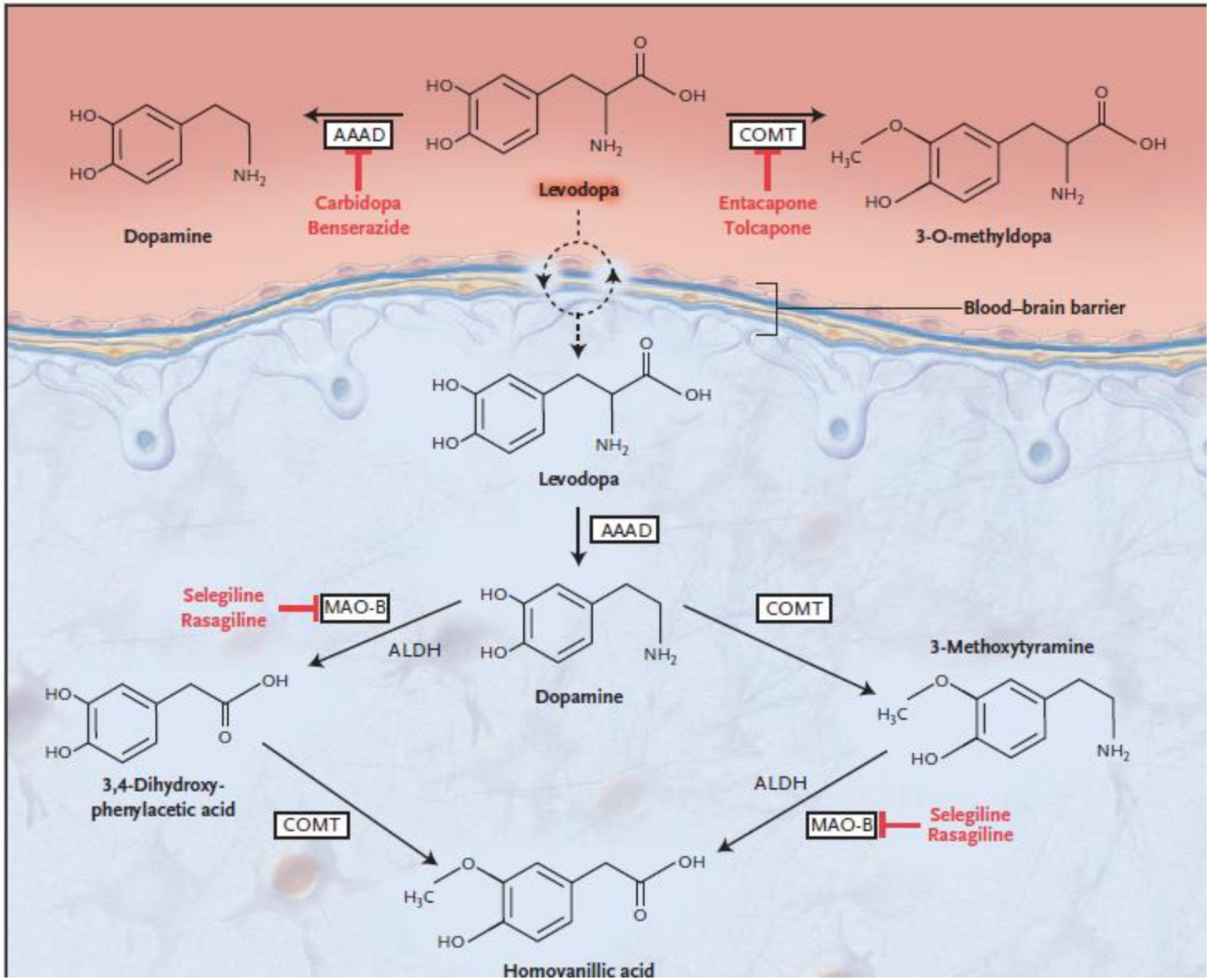
- Described 1st by James Parkinson 1817
- Average incidence 200 in 100000 .
- Multifactorial, dopaminergic neuronal loss SNc.
- Cardinal Motor features:
  - Resting tremor: absent in 20% of patient.
  - Bradykinesia
  - Rigidity
  - Impairment of postural reflex.
- Diagnosis is clinical.

TYPE OF PARKINSONISM	CLINICAL FEATURES	EXPECTED COURSE	RESPONSE TO LEVODOPA
Drug induced[27]	Gait disturbance less prominent More commonly involves upper limbs Might be more symmetrical than PD	Usually improves after discontinuation of medication, but might uncover underlying PD	Discontinue or change medication causing symptoms rather than treat with levodopa
Vascular[21]	Might have more abrupt onset and stepwise decline Symmetrical bradykinesia and shuffling gait	Depends on risk of further small-vessel disease	Minimal
Progressive supranuclear palsy[24,28]	Prominent early postural instability and falls Truncal rigidity Limitation of vertical gaze, especially downward "Startled" facial expression	More rapid progression than PD; median survival 5-6 years	About 20% to 30% respond initially
Multiple system atrophy[22,23,25]	Autonomic failure Cerebellar ataxia Corticospinal dysfunction Parkinsonism	More rapid progression than PD; median survival 6-7 years	About 40% have good initial response
Dementia with Lewy bodies[26]	At least 2 of: Motor parkinsonism Dementia with fluctuations in attention and awareness Hallucinations	Similar to course of Alzheimer disease	Variable but should be considered after treatment with cholinesterase inhibitor

- Think of other Diagnosis if :
  - Early falls
  - Poor response to levodopa
  - Symmetry at onset
  - Rapid progression
  - Lack of tremor
  - Prominent dysautonomia.
- Predictors of benign course: Young onset, Resting tremor.
- Poor outcome: elder, male, hypokinesia…


Normal brain
Brain with Parkinson's disease
Striatum
Caudate nucleus
Putamen
Levodopa
Substantia nigra
pars compacta
Degeneration of
dopaminergic neurons
Midbrain

Dopamine pathway



Levodopa

- Naturally occurring amino acid (3,4-dihydroxy-l-phenylalanine), intermediate in dopamine synthesis.
- Absorbed actively by neutral amine transporter.
- Crosses blood brain barrier. Carbidopa dose not.
- Metabolism: Decarboxylation and O-methylation
- Half life: 1.5 hour with carbidopa.
- Time to peak: 0.5 hours; Controlled release: 2 hours.
- Excretion: Urine (metabolites).

Levodopa

- Uses:
  - PD any stage.
  - Help all motor symptoms, but not retropulsive imbalance. Some times dose not help tremor.
- Dose:
  - Initial: 150 mg of levodopa and 37.5 mg of carbidopa/benserazide divided in 3 doses.
  - Max 2000 mg /200mg levo/carbodopa.
  - Sustained release form available 100 to 250 mg tablets.
- Side effects:
  - Nausea / hypotension. Reduced by carbidopa.
  - Chronic: motor fluctuation, dyskinesia. As early as 2 years. By 5 years 50% have it. Correlate with high dose and younger age.
  - Abrupt stop may cause a syndrome similar to malignant neuroleptic S.

levodopa

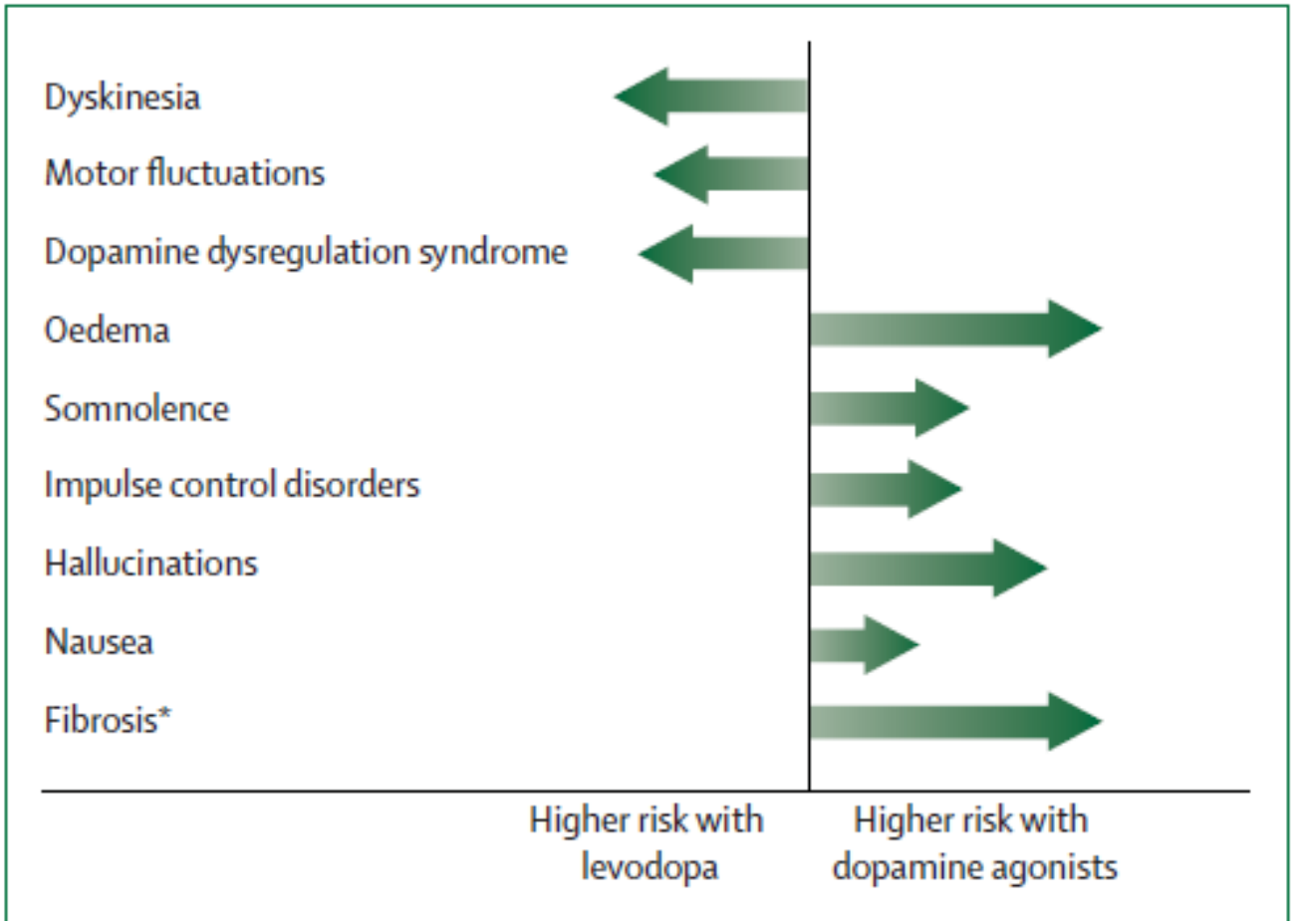
- Motor fluctuation:
  - Off phenomena:
    - Occurs before next dose (return of bradykinesia/tremor).
    - some patients may experience dysphoria, anxiety, or sensory phenomena. Other non-motor symptoms.
    - Painful leg cramps early AM (off dystonia).
  - Dyskinesia:
    - Choreoathetoid movement any part (legs/cervical).
    - Stress induced initially. At peak-dose of LD.

Dopamine Agonist

	D2/D3 receptor affinity	D1 receptor affinity	NE receptor affinity	5-HT_{2B} receptor affinity	Half-life (h)
Ergot agonists					
Bromocriptine	D2	–	+	+/–	3–6
Cabergoline	D3>D2	–	+	+	65
Dihydroergocriptine	D2	+/–	+	+	12–16
Lisuride	D2	–	+	+*	2–3
Pergolide	D3>D2	+	+	+	15–20
Non-ergot agonists					
Apomorphine	D3>D2	+	–	–	0·5
Piribedil	D3>D2	–	+/–	–	20
Pramipexole	D3>D2	–	+/–	–	10
Ropinirole	D3>D2	–	–	–	6
Rotigotine	D3>D2	+	–	–	5–7†

–=no affinity. +=high affinity. +/–=moderate affinity. NE=norepinephrine. *Antagonist. †After transdermal application.

Dopamine Agonist SEs



Dopamine Agonist

- Pramipexole:
  - Uses: early PD, Late PD with motor fluctuation…RLS
  - More specific to D3 receptor. Less hypotension.
  - Improve motor activity within 2-3 wks.
  - Kinetics: 15% protien bound, active excretion kidney(90%) unchanged drug.
  - Dose: (start low go slow) 0.25 mg TID, max 1.5TID
  - Reduction of L-Dopa requirment by 25%.

Dopamine Agonist

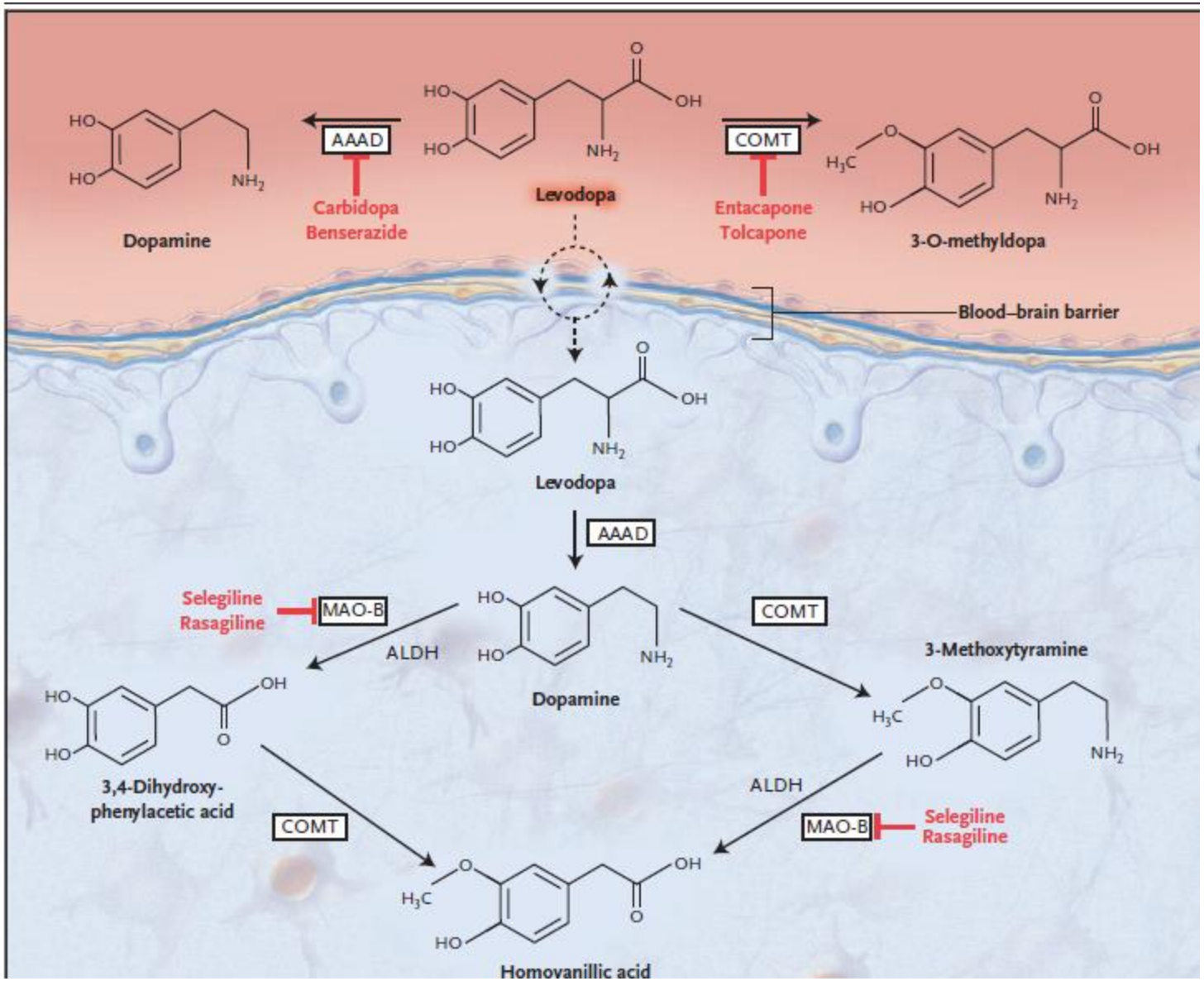
- Ropinirol:
  - Uses:
  - Act on both D2,3 centrally. D2 peripherally (SE conteracted by Domperidone).
  - Metabolised by cytochrome P-450 , inactive metabolites…urine 90%.
  - Doses: initial 0.25 mg TID weekly increment. Max dose 24mg/day.
  - Discontinuation: gradual over one week.

Dopamine Agonist

- Bromocriptine:
  - Uses: early and advanced PD, hyperprolactin.
  - Reduce L-Dopa requirement by 40%.
  - 90% protein bound, biliary excretion.
  - Dose 1.25mg BID increase by 2.5mg 1-2 wks. Max100mg.

Dopamine Agonist

- Apomorphine:
  - SC DA. Onset 7-15 min. duration 2 hours.
  - Useful as rescue for off times.
  - Emesis within 3-10 min. hypotension.
  - Extensive hepatic metabolism.
  - Initials doses 1mg SC TID. Max 20mg/day.


Dopamine
AAAD
Carbidopa
Benserazide
Levodopa
COMT
Entacapone
Tolcapone
3-O-methyldopa
Blood–brain barrier
Levodopa
AAAD
Selegiline
Rasagiline
MAO-B
ALDH
Dopamine
COMT
3-Methoxytyramine
3,4-Dihydroxy-
phenylacetic acid
COMT
ALDH
MAO-B
Selegiline
Rasagiline
Homovanillic acid

catechol-*O*-methyltransferase (COMT) inhibitors

- Tolcapone:(Inhibit central COMT, Fatal hepatoixcty).
- Entacapone: (peripheral COMT inhibition).
  - Increase on time by 1-1.7 hour.
  - reduction in l-dopa dose.
  - Safe with other DA.
  - Dose : 200 mg with each L-dopa (combined tablet Stalevo).
  - SE: increase Dyskinesia (decrease 20-30% L-dopa)
  - N/V, abd pain, urine discoloration, diarrhea.

AAN recommendations

- Either L-Dopa (better for motor disability) or dopamine agonist(less motor complication) may be used for initial Rx of PD. (Level A).
- Either sustained release or immediate release L-dopa may be considered in initial treatment of PD. (Level B)

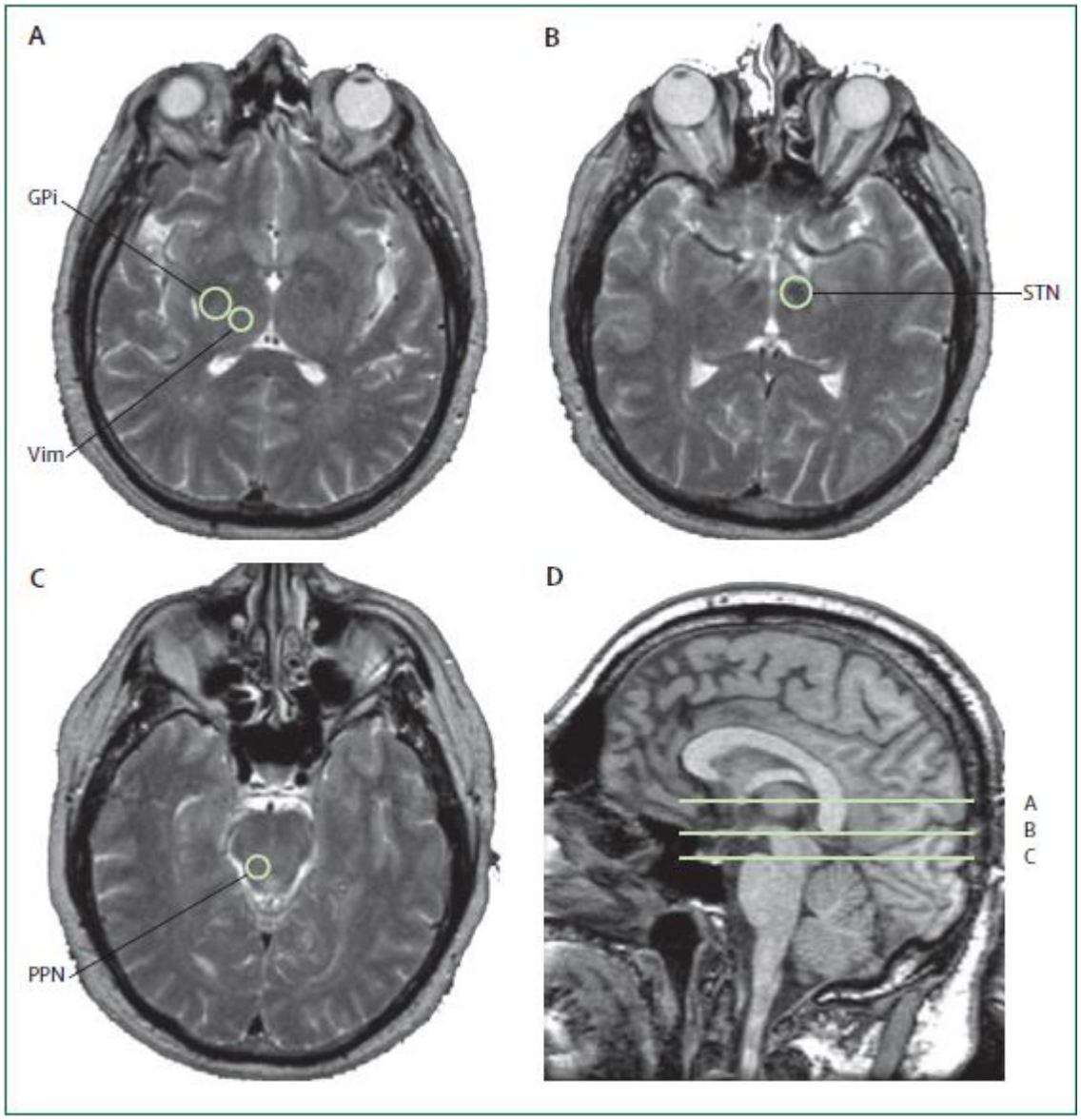
AAN recommednations

- Use Entacapone and Rasagiline to reduce off time (Level A).
- Pramipexol, ropinirole, pergolide, tolcapone should be considered to reduce off time. (Level B).
- Apomorphine, cabergoline, selegiline may be cosidered to reduce off time. (Level C).
- Bromocribtine, sustained release l-dopa may be disregarded to reduce off time (level C).

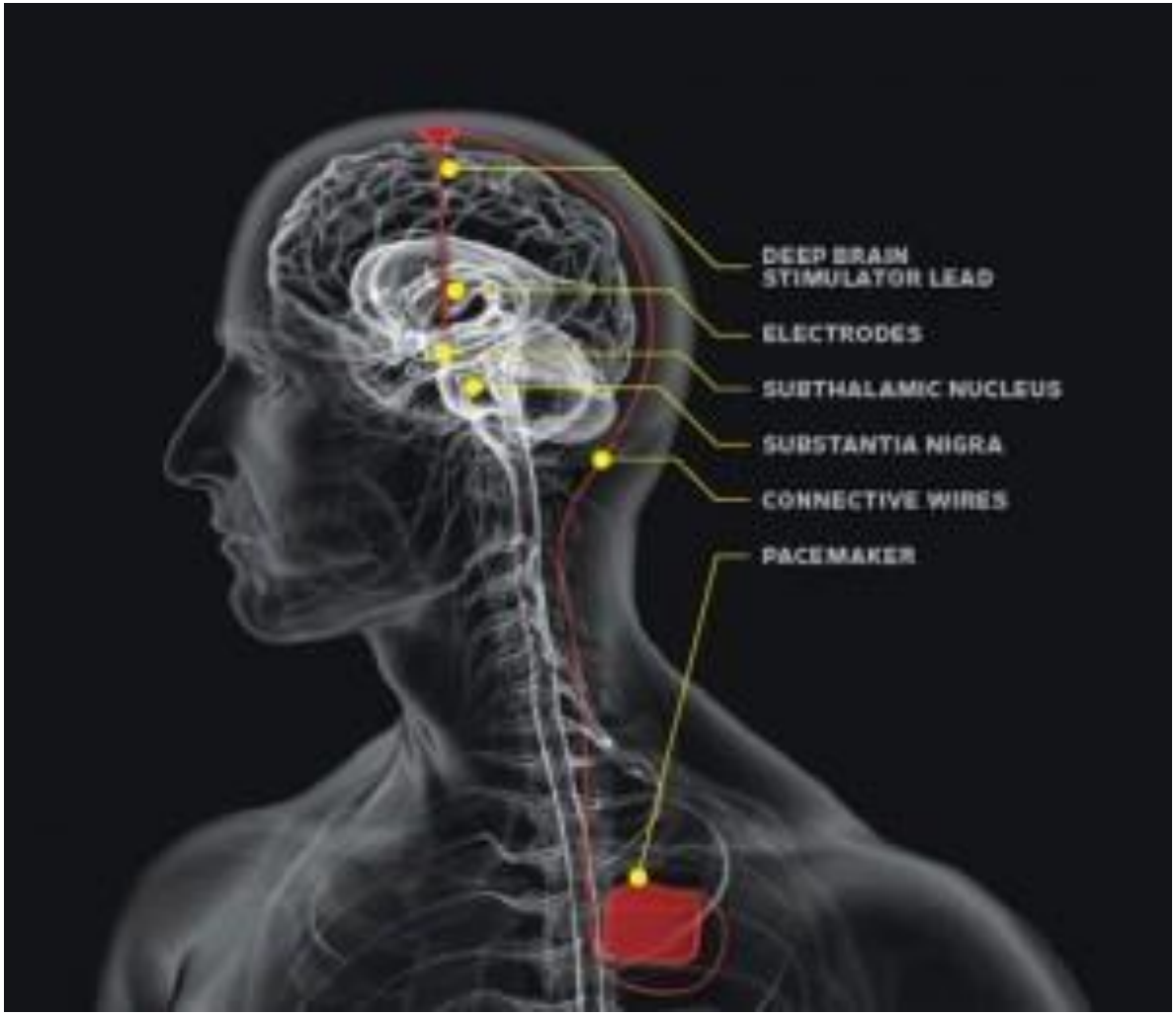
Surgical Rx

- Steriotatic lesion to pallidothalamic pathways used before L-dopa discovery.
  - Limited due to risk of permanent neuro damage.

- Deep Brain electrical stimulation:
  - Restricted to those who failed medical Rx.
  - Subthalamic N
  - Globus Pallidus


A
GPi
Vim
B
STN
C
PPN
D
A
B
C

DBS


DEEP BRAIN STIMULATOR LEAD
ELECTRODES
SUBTHALAMIC NUCLEUS
SUBSTANTIA NIGRA
CONNECTIVE WIRES
PACEMAKER

AAN updated evidence

- DBS of STN possibly effective in improving motor function/reduce motor fluctuation/dyskinesia. Class III (level C).
- Preoperative response to L-Dopa, younger age and less duration of PD predict greater improvement after DBS of STN. (level B)
- DBS of Gpi: insufficient evidence to support of refute effectiveness. class III

references

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  Treatment of PD with motor fluctuation and dyskinesia.