Parkinson Disease Update

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Conflict of Interest Statement

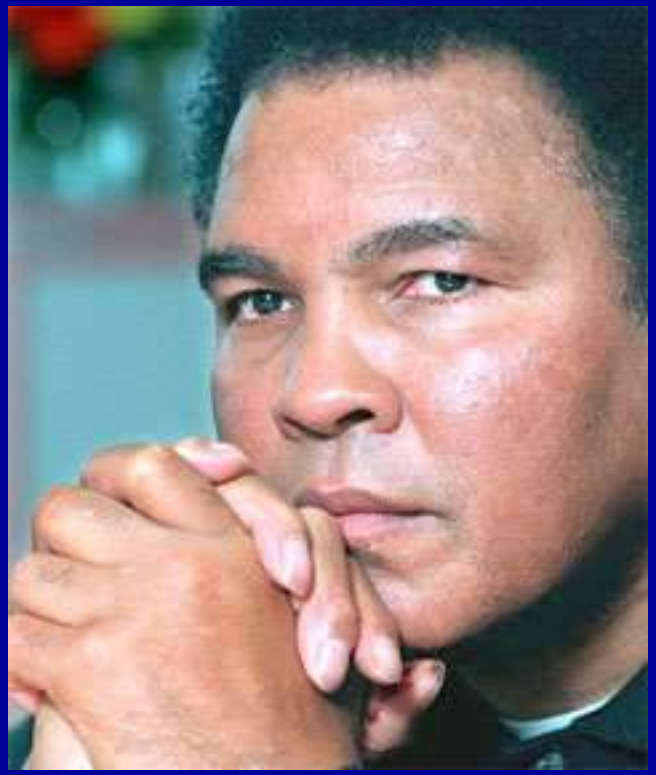
No drug (or medical device) company pays me any money

Parkinson Disease Update

- **Epidemiology**
- **Pathology**
- **Medical treatment**

- **Surgical treatment**

Parkinson Disease Does Not Spare Anyone











History of Parkinson Disease

- 1817: James Parkinson describes “Shaking Palsy”
- 1951: Apomorphine injection improved symptoms in a PD patient
- 1947: Surgical destruction of internal globus pallidus (GPi) and Vim thalamic nucleus (Ernst A. Spiegel)
- 1960: Parkinson disease is a state of dopamine deficiency (Herbert Ehringer* & Oleh Hornykiewicz)
- 1961: First trial of IV levodopa in a PD patient (Birkmayer)
- 1964: Progressive supranuclear palsy: clinical and pathologic description (Steele, Richardson, Olszewski)
- 1968: Corticodentatonigral degeneration with neuronal achromasia (Rubeiz, Kolodny, Richardson)
- 1991: DBS of ventral intermediate thalamic (Vim) nucleus (Alim Benabid)
- 1995: DBS for subthalamic nucleus (STN) in PD (Patricia Limousin)

Prevalence of PD in the World

- **Second most common neurodegenerative disorder after Alzheimer disease**
- **World PD prevalence doubling every 25 years:**
  - **1990: 2.5 million**
  - **2016: 6.1 million**
  - **2021: 11.8 million**
  - **2050: 25.2 million (estimated) - 89% of growth due to aging population**
- **Prevalence in the USA:**
  - **1 million PD patients in the USA (~1/300): expected to triple by 2040**
  - **Prevalence by age: 0.4% at ages 60–69 vs 1.4% at ages 80–89**

Epidemiology of Parkinson Disease

- **Etiology: Genetic vs Environmental**
  - **Man/Woman ratio ~ 2:1**
  - **Age: 47 to 77 /100,000 in >45 yrs, 108 to 212 /100,000 >65yrs**
  - **Race: Whites ~ Hispanics > Blacks/Asians (Willis 2010)**
  - **Urban > Rural (Willis 2010)**
  - **Chemicals:**
    - **Pesticides: paraquat, rotenone, organochlorines and organophosphates**
    - **chlorinated solvents: trichloroethylene, perchloroethylene**
    - **MPTP (1983), Manganese**
    - **Ultra-processed foods**
  - **Head trauma**
  - **High dairy consumption (organochlorine heptachlor builds up in milk)**
  - **Genes: few "causative" genes vs >90 common variant "risk-factor" genes**
- **Neuro-protective factors: Caloric restriction, exercise, antioxidants (?), smoking (???), caffeine (?), alcohol (?), …**

ULTRA-PROCESSED FOOD LIST

Ultra-processed foods are industrial formulations made mostly from substances extracted from foods or synthesized in a lab.

1. SUGARY SNACKS



- Candy bars
- Sugary breakfast cereals
- Fruit-flavored snacks (gummies, fruit chews)
- Pastries (cookies, cakes, donuts)
- Sugary drinks (sodas, energy drinks, sweetened juices)

2. PROCESSED MEATS



- Hot dogs
- Sausages
- Bacon
- Deli meats (ham, turkey, salami)
- Chicken nuggets

3. CONVENIENCE FOODS



- Frozen pizzas
- Microwaveable meals
- Instant noodles
- Frozen dinners
- Boxed macaroni and cheese

4. PACKAGED SNACKS



- Potato chips
- Cheese puffs
- Crackers (especially flavored varieties)
- Pretzels
- Packaged cookies

5. FAST FOOD



- Hamburgers
- French fries
- Fried chicken
- Chicken nuggets
- Onion rings

6. BAKED GOODS



- Store-bought bread (especially white bread)
- Bagels
- Croissants
- Muffins
- Packaged baked desserts

7. PACKAGED SWEETS



- Candies (gummy bears, hard candies)
- Chocolate bars
- Packaged ice cream treats (ice cream bars, novelty cones)
- Cookies and cakes

8. INSTANT FOODS



- Instant soups
- Instant noodles
- Instant mashed potatoes
- Instant rice

9. CONDIMENTS & SAUCES



- Bottled salad dressings
- BBQ sauce
- Ketchup
- Mayonnaise
- Sauces and dips

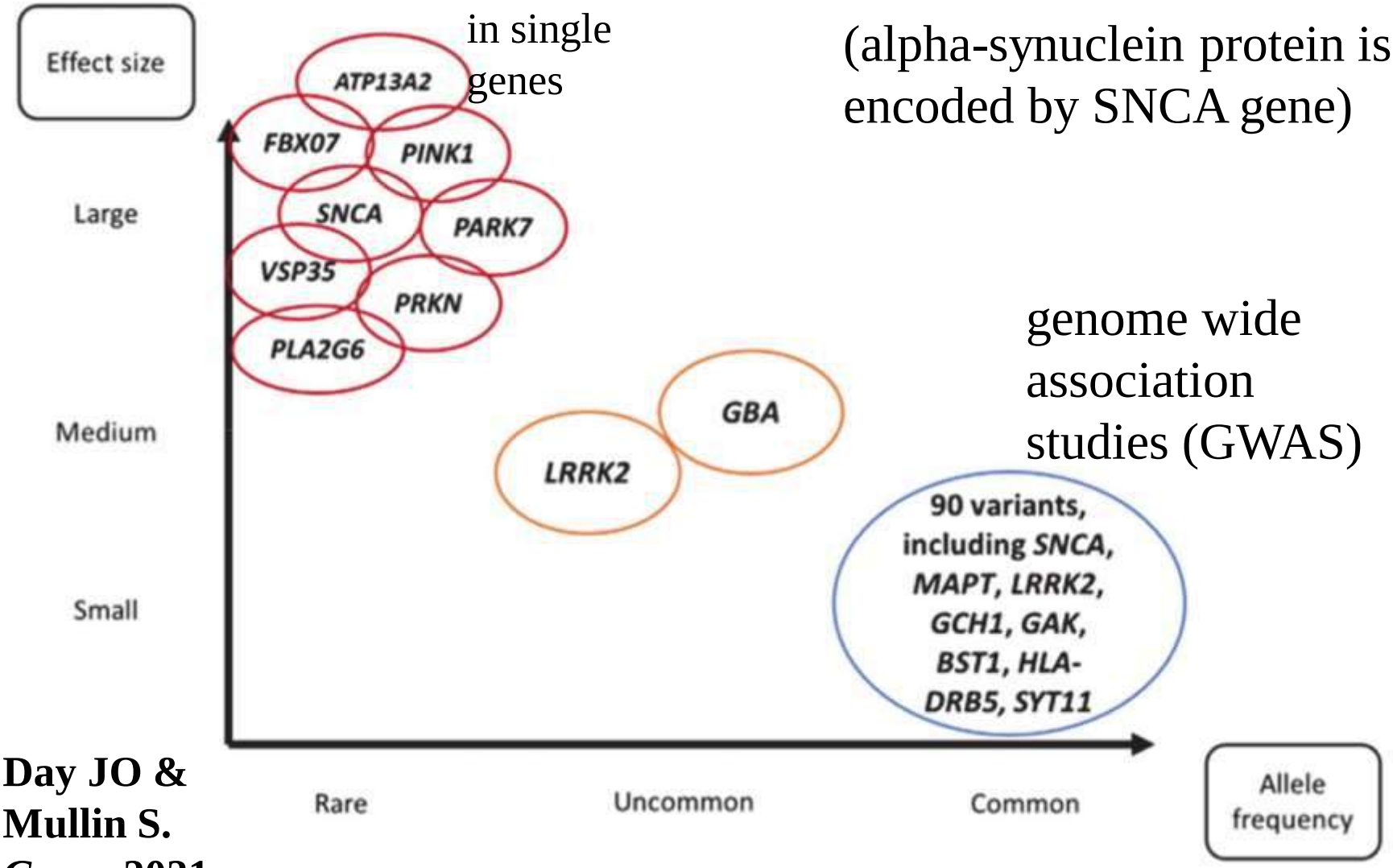
WHY LIMIT ULTRA-PROCESSED FOODS?

- Supports better overall health
- Helps maintain a healthy gut
- May help manage weight
- Reduces risk of chronic diseases
- Supports better mood & energy

Choose whole foods, cook at home when possible, and read labels to make informed choices.

WelloraDesigns
-Etsy

Genetic Variants in PD: Allele Frequency vs Risk of PD



rare variants in single genes

(alpha-synuclein protein is encoded by SNCA gene)

genome wide association studies (GWAS)

Day JO & Mullin S. ***Genes*** **2021**

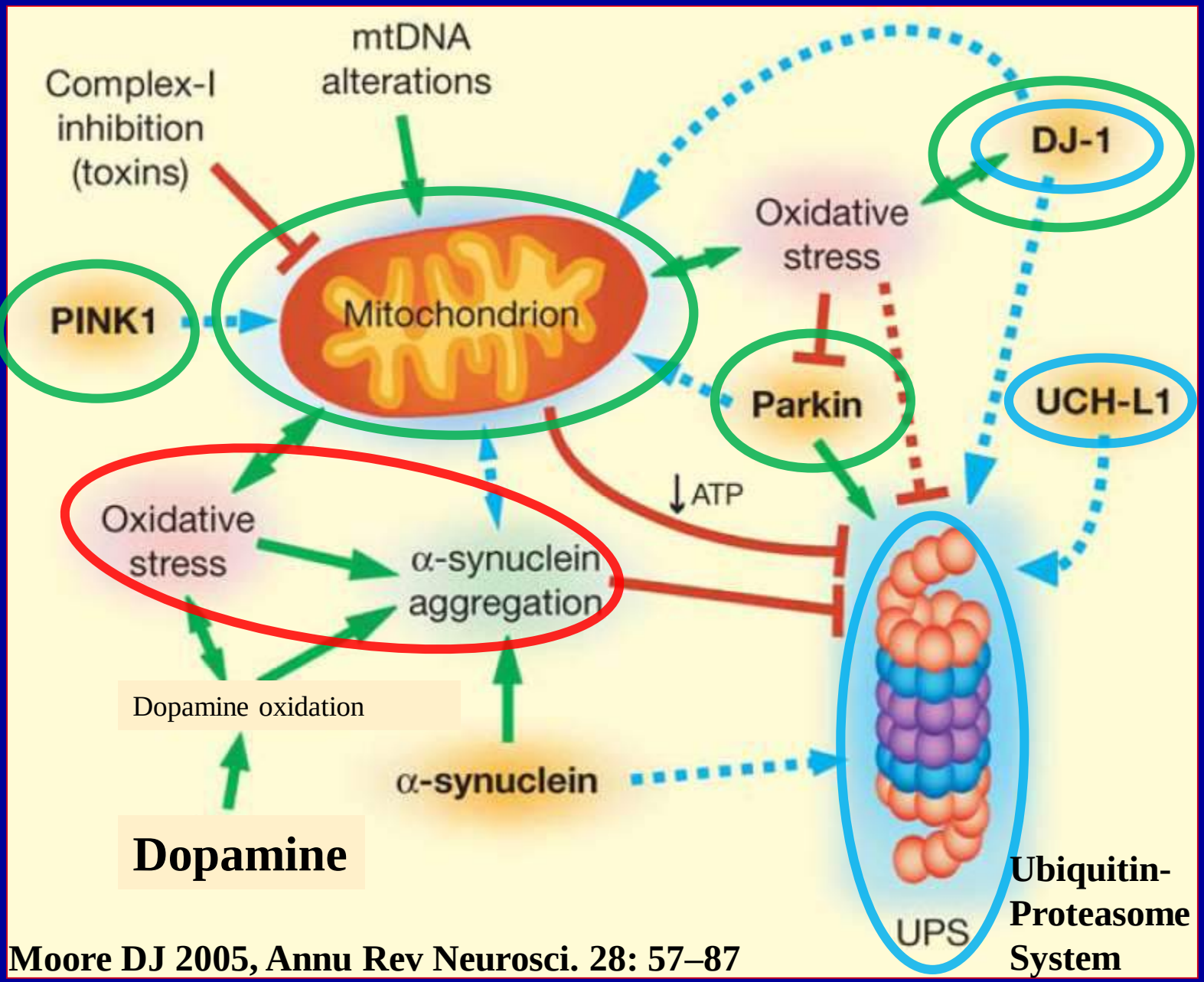
Monogenic Variants Associated With Familial PD (2021)

	Gene (HGNC Approved Name)	Alternative Gene Names	Inheritance	Pathogenicity	PD Phenotype	Function
High penetrance	*SNCA*	*PARK1, PARK4, NCAP*	AD	Pathogenic	Early-onset	Uncertain (encodes α-synuclein)
	VPS35	*PARK17, MEM3*	AD	Pathogenic	Typical	Retromer and endosomal trafficking
	PINK1	*PARK6*	AR	Pathogenic	Early-onset	Mitochondrial
	PARK7	*DJ-1*	AR	Pathogenic	Early-onset	
	PRKN	*PARK2, PARKIN*	AR	Pathogenic	Early-onset	
	PLA2G6	*PARK14, IPLA2*	AR	Pathogenic	Early-onset, atypical	Cell membrane
	ATP13A2	*PARK9*	AR	Pathogenic	Early-onset, atypical	Lysosomal
	FBXO7	*PARK15, FBX7*	AR	Pathogenic	Early-onset, atypical	Mitochondrial
	POLG	*POLG1, POLGA*	AD	Pathogenic	Early-onset, atypical	Mitochondrial DNA maintenance
	DNAJC6	*PARK19, DJC6*	AR	Likely pathogenic	Early-onset	Synaptic vesicle formation and trafficking
	DNAJC13	*PARK21, RME8*	AD	Conflicting reports	Typical	
	TMEM230	*C20ORF30*	AD	Conflicting reports	Typical	
	SYNJ1	*PARK20*	AR	Pathogenic	Early-onset, atypical	
	VPS13C	*PARK23*	AR	Pathogenic	Early-onset	Mitochondrial
	CHCHD2	-	AD	Pathogenic	Typical	Uncertain
	DCTN1	-	AD	Pathogenic	Atypical	Microtubule
Variable penetrance	*LRRK2*	*PARK8, DARDARIN*	AD	Pathogenic	Typical	Lysosomal, mitochondrial, microtubule
	GBA	*GBA1*	AD	Pathogenic	Typical	Lysosomal
Associated with PD but unlikely to be pathogenic	*HTRA2*	-	AD	Uncertain/likely benign	-	Mitochondrial
	UCHL1	*PARK5*	AD	Uncertain/likely benign	-	Ubiquitin-proteasome
	GIGYF2	*PARK11*	AD	Uncertain/likely benign	-	Uncertain
	EIF4G1	-	AD	Benign	-	mRNA translation
	LRP10	*LRP9*	AD [1]	Uncertain	-	Uncertain

[1] AD = autosomal dominant, AR = autosomal recessive, HNGC = HUGO Gene Nomenclature Committee.

Day JO & Mullin S.
***Genes* 2021**

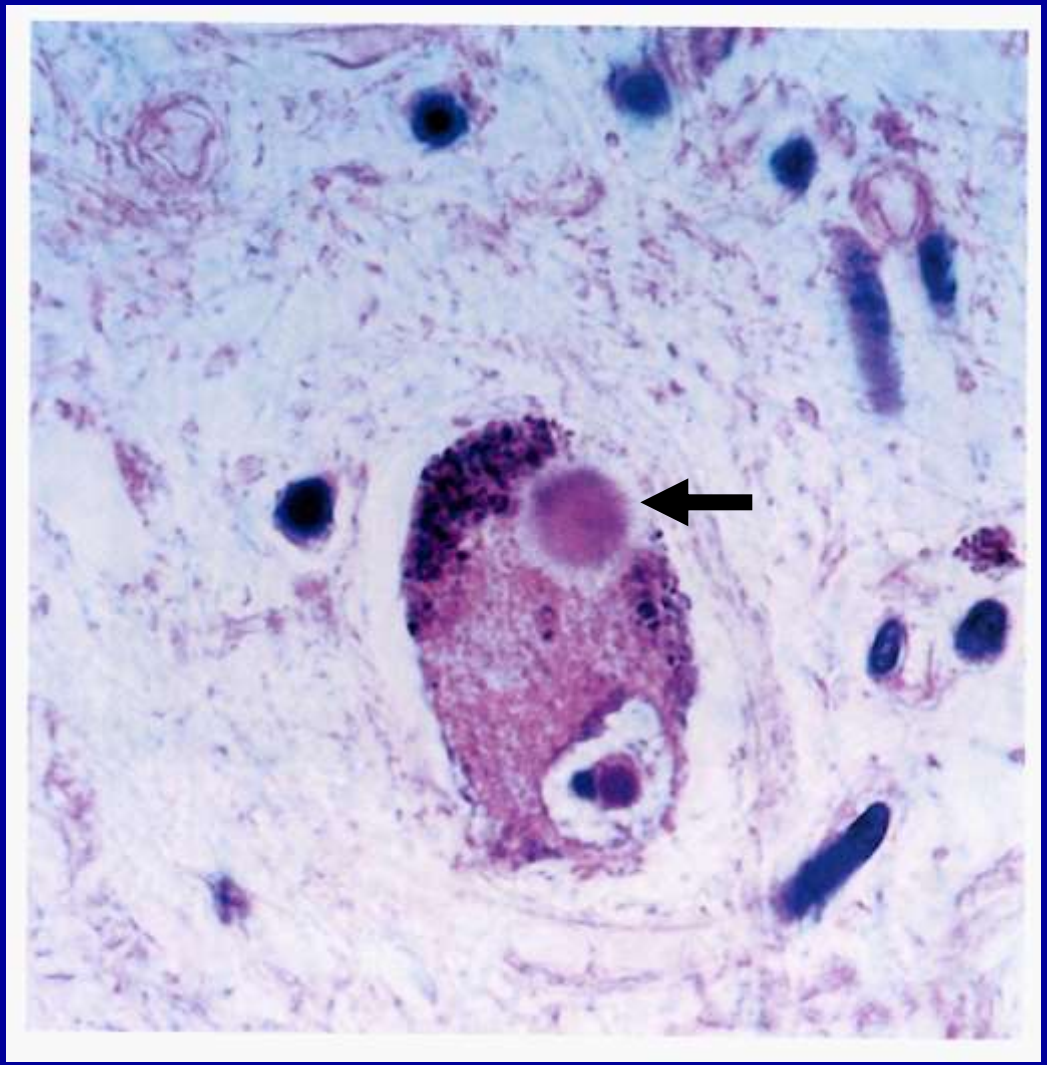
Pathophysiology of PD: Synucleinopathy



Moore DJ 2005, Annu Rev Neurosci. 28: 57–87

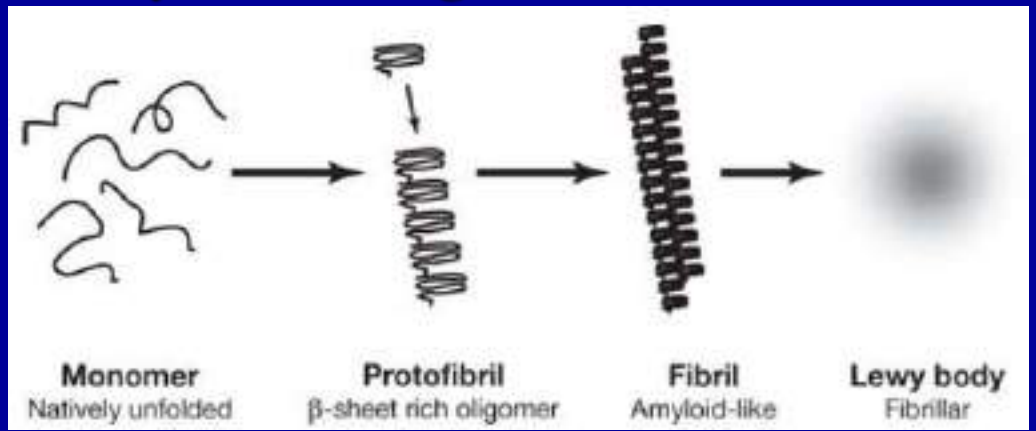
Hallmark of Parkinson Disease & Lewy Body Disease: Lewy Bodies

- **Eosinophillic inclusions in nigral dopaminergic neurons**
- **Contains ubiquitin & α-synuclein**



Alpha-Synuclein

- **Normal α-synuclein (SNCA gene):**
  - **Location: presynaptic membranes and vesicular structures**
  - **Function: synaptic vesicle recycling (?) + affects lysosomal function, mitochondrial function and inflammation**
- **Aggregated α-synuclein:**
  - **aggregation process is accelerated by SNCA pathogenic variants and/or by an increase in intracellular α-synuclein concentration**
  - **disrupts proteasome function and exacerbates oxidative stress**
  - **major component of Lewy bodies (with ubiquitin) & Lewy neurites**
  - **α-synuclein oligomer can transfect neurons, mediating toxicity**



Moore DJ 2005, Annu Rev Neurosci. 28: 57–87

Braak Staging of PD: Spread of Lewy Body

1) Anterior olfactory nerve
Dorsal motor nuclei of:
- **glossopharyngeal nerve**
- **vagal nerve**

2) Ascends in the brain stem:
- **caudal raphe nuclei**
- **gigantocellular reticular nucleus**
- **coeruleus–subcoeruleus complex**

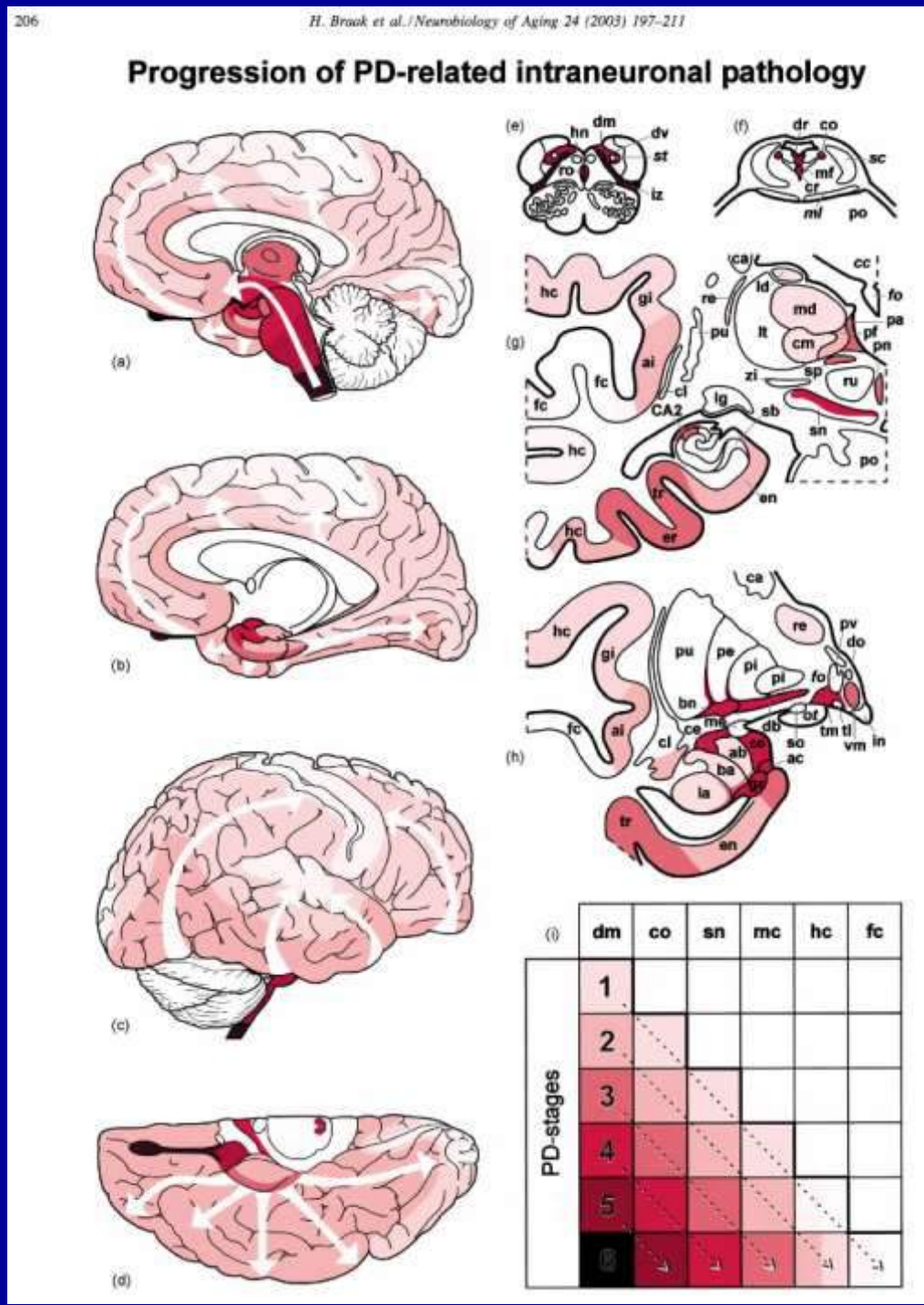
3) Substantia nigra pars compacta

4) Anteromedial temporal mesocortex

5) Neocortex high order sensory association & prefrontal areas

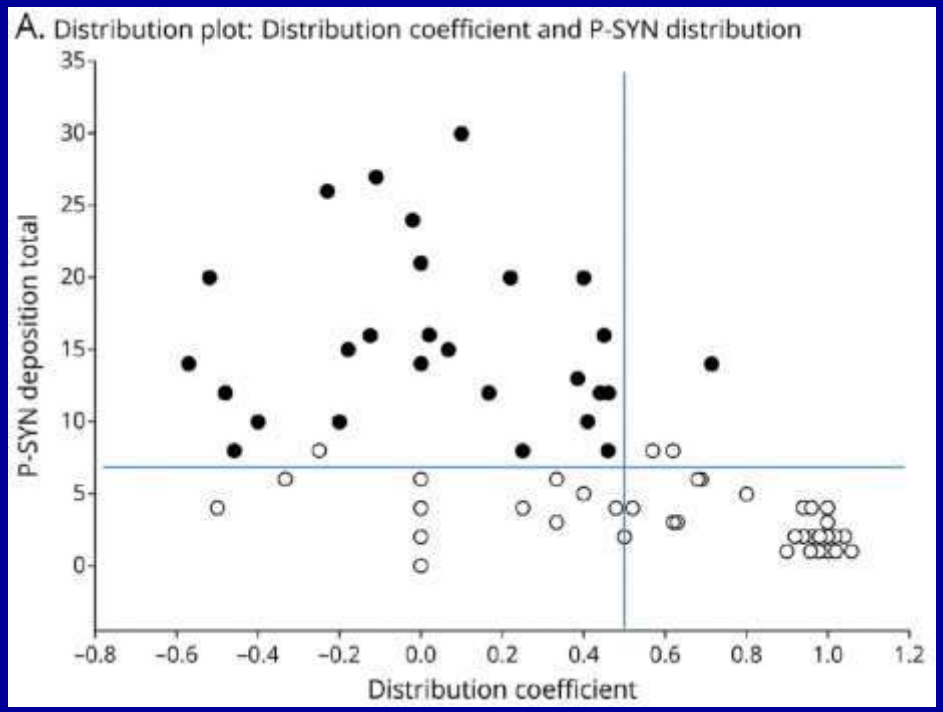
6) First order sensory association/premotor areas & primary sensory/motor fields

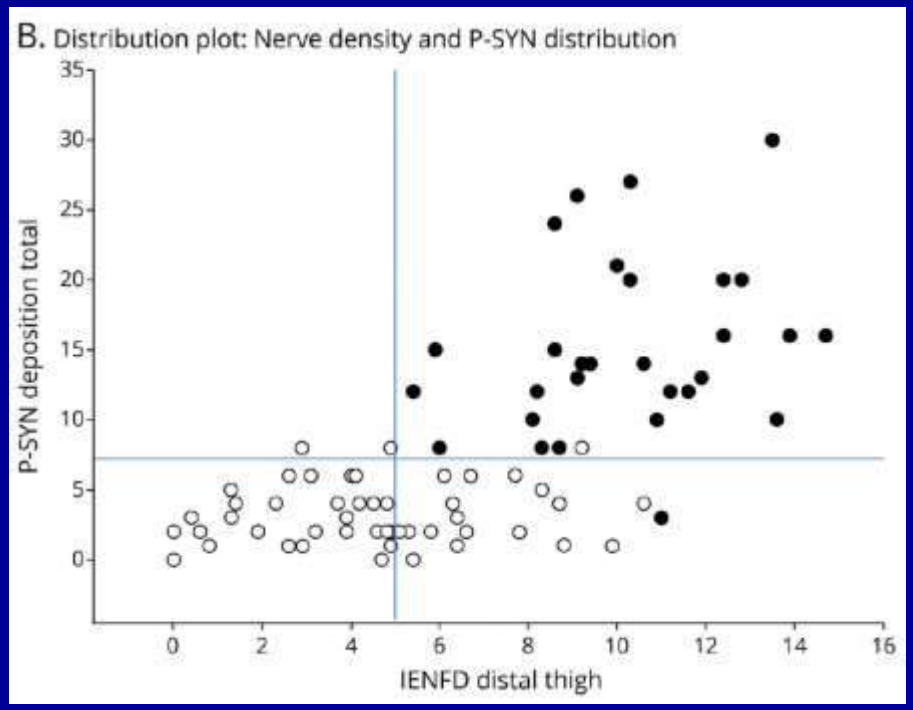
Braak H 2003, *Neurobiol of Aging*



Skin Biopsy for Phosphorylated α-Synuclein (P-SYN)

- **Skin biopsy from distal thigh, posterior cervical and proximal thigh**
- **MSA had greater deposition ($p < 0.0001$) and more widespread peripheral distribution of P-SYN ($p < 0.0001$) than PD.**
- **No P-SYN in controls**





Gibbons C et al, 2023, *Neurology*, 100: e1529-e1539

Pathophysiology of PD

- **Protein handling: ubiquitin & α-synuclein**
- **Mitochondrial dysfunction:**
  - **complex I activity is decreased in substantia nigra**
  - **complex I inhibition induces Lewy body-like inclusions *in vivo***
  - **MPTP and rotenone inhibit complex I**
  - **Mitochondrial dysfunction increases oxidative and nitrosative stress**
  - **Mitochondrial dysfunction promotes α-synuclein aggregation**
  - **PINK1, parkin and DJ-1 contribute to normal mitochondrial function**
- **Oxidative stress: free radicals & iron**
- **Nitrosative stress: Nitric oxide, peroxynitrite & protein nitration**
- **Excito-toxicity: glutamate & calcium**
- **(Glial cells: decreased GDNF & BDNF)**
- **(Apoptosis)**

Current Studies on Neuroprotection

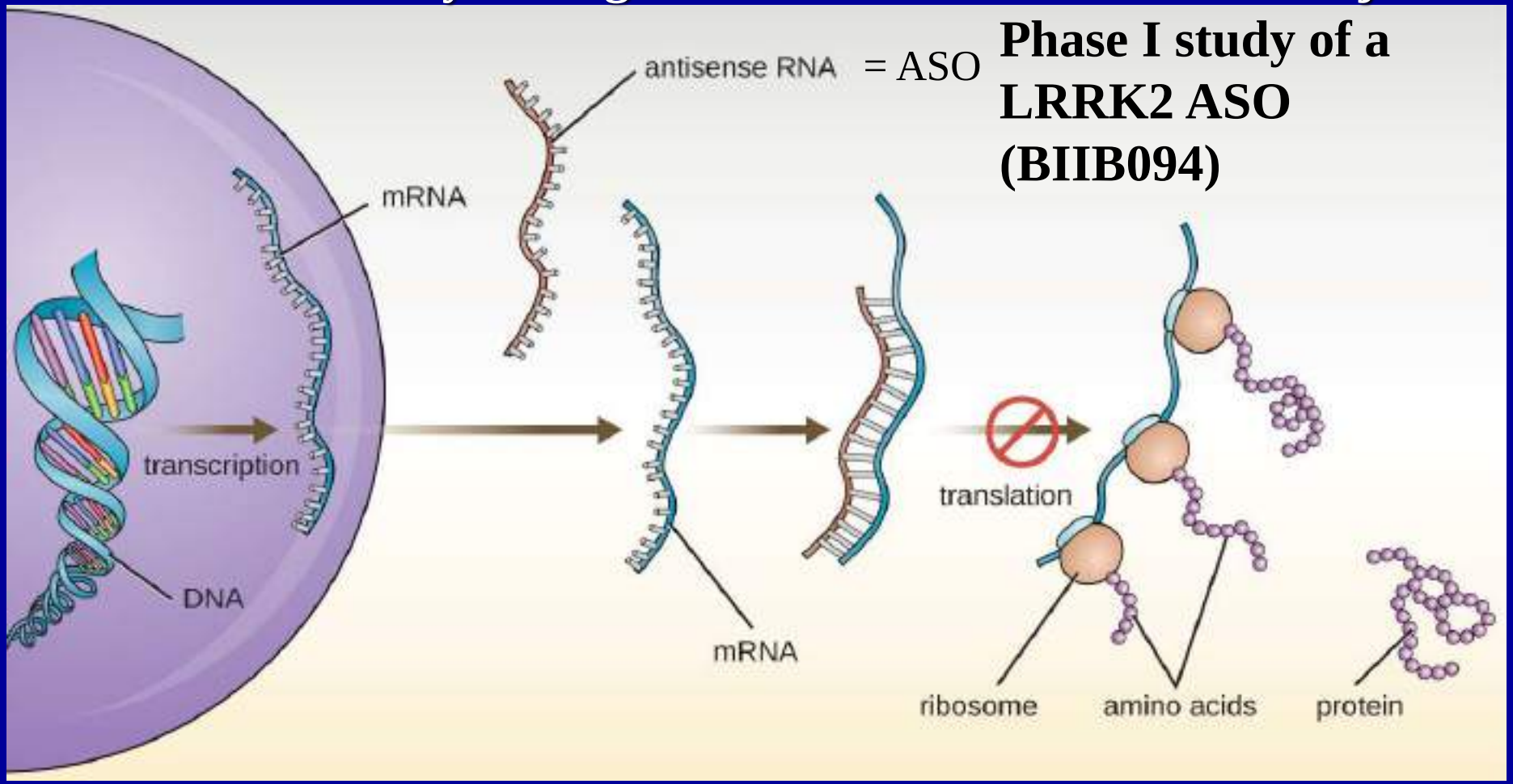
- **Immunotherapy to remove toxic forms of synuclein using:**
  - **antibodies: prasinezumab, cinpanemab (phase II)-Failed**
  - **synuclein peptide mimic which stimulates an immune response: PD01A (passed phase I clinical trial)**
  - **Nilotinib (accelerates synuclein degradation) -Failed**
- **Mitochondrial agents (all phase II):**
  - **ursodeoxycholic acid (phase II)**
  - **terazosin (passed phase I)**
  - **nicotinamide (passed phase I)**
  - **EPI-589 (novel agent)**
- **Antisense Oligonucleotides**

Prasinezumab

- Binds to C-terminus of aggregated α-synuclein and may block cell-to-cell spread of the protein
- It binds aggregated α-synuclein far more tightly than monomeric α-synuclein
- Phase IIb dose was 1500 mg IV every 4 weeks
  - Lowered free serum α-synuclein by up to 97%; CSF α-synuclein did not change
  - Adverse events: constipation, diarrhea, peripheral edema, headache, post-lumbar puncture Sd, allergic reactions (2 pts)
- Phase II studies (n= 316 + 586):
  - No change in MDS-UPDRS Parts I+II+III at 52 weeks
  - But less decline on MDS-UPDRS Part III (motor) scores
  - Larger benefit in patients with faster-progressing disease or those taking MAO-B inhibitors… Now Phase III study

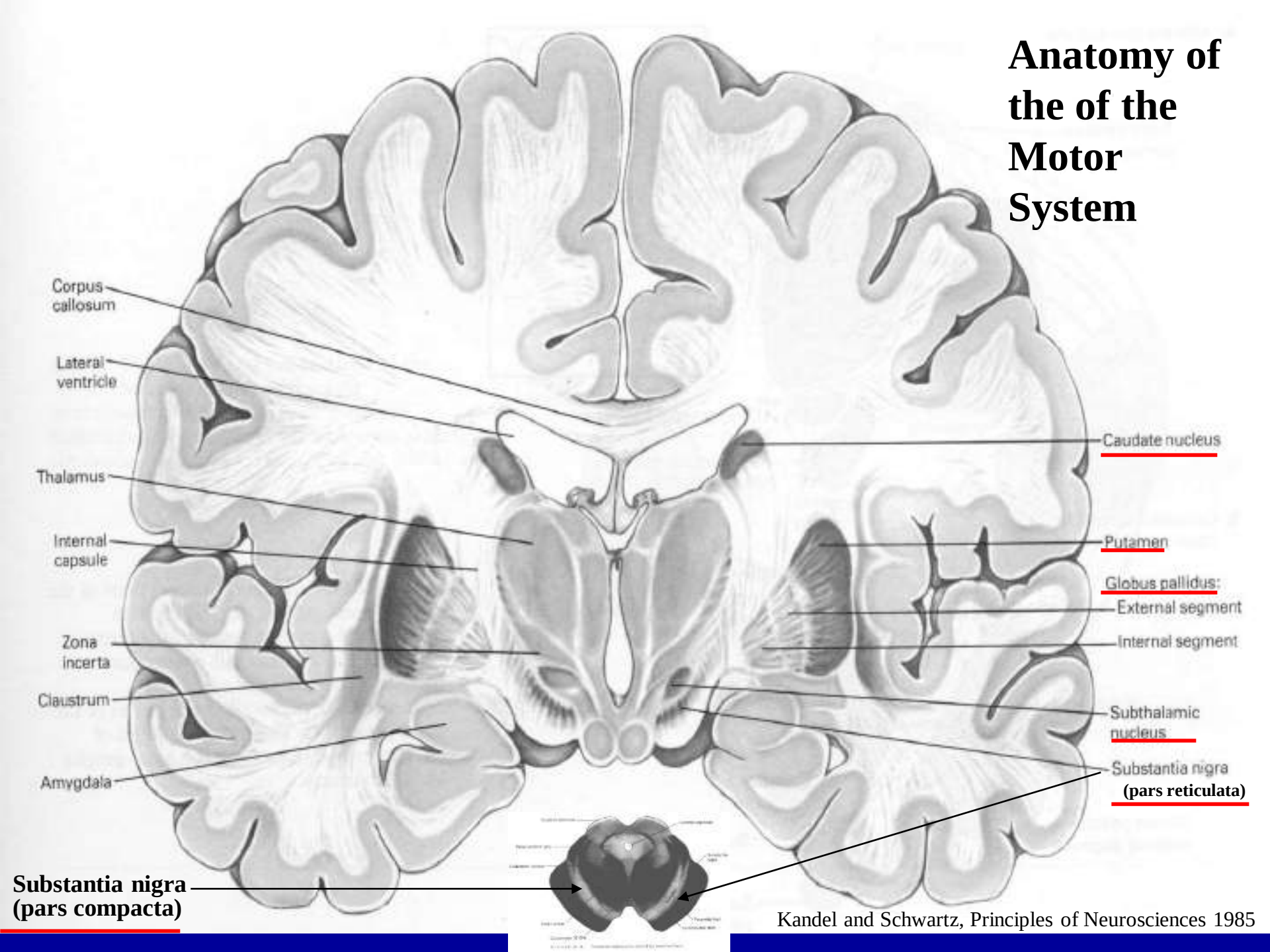
Antisense Oligonucleotides (ASOs)

- **Single-stranded DNA, 8 to 50 base pairs length**
- **Highly charged and large molecule**
- **Distribute widely throughout the CNS after intrathecal injection**



Phase I study of a LRRK2 ASO (BIIB094)

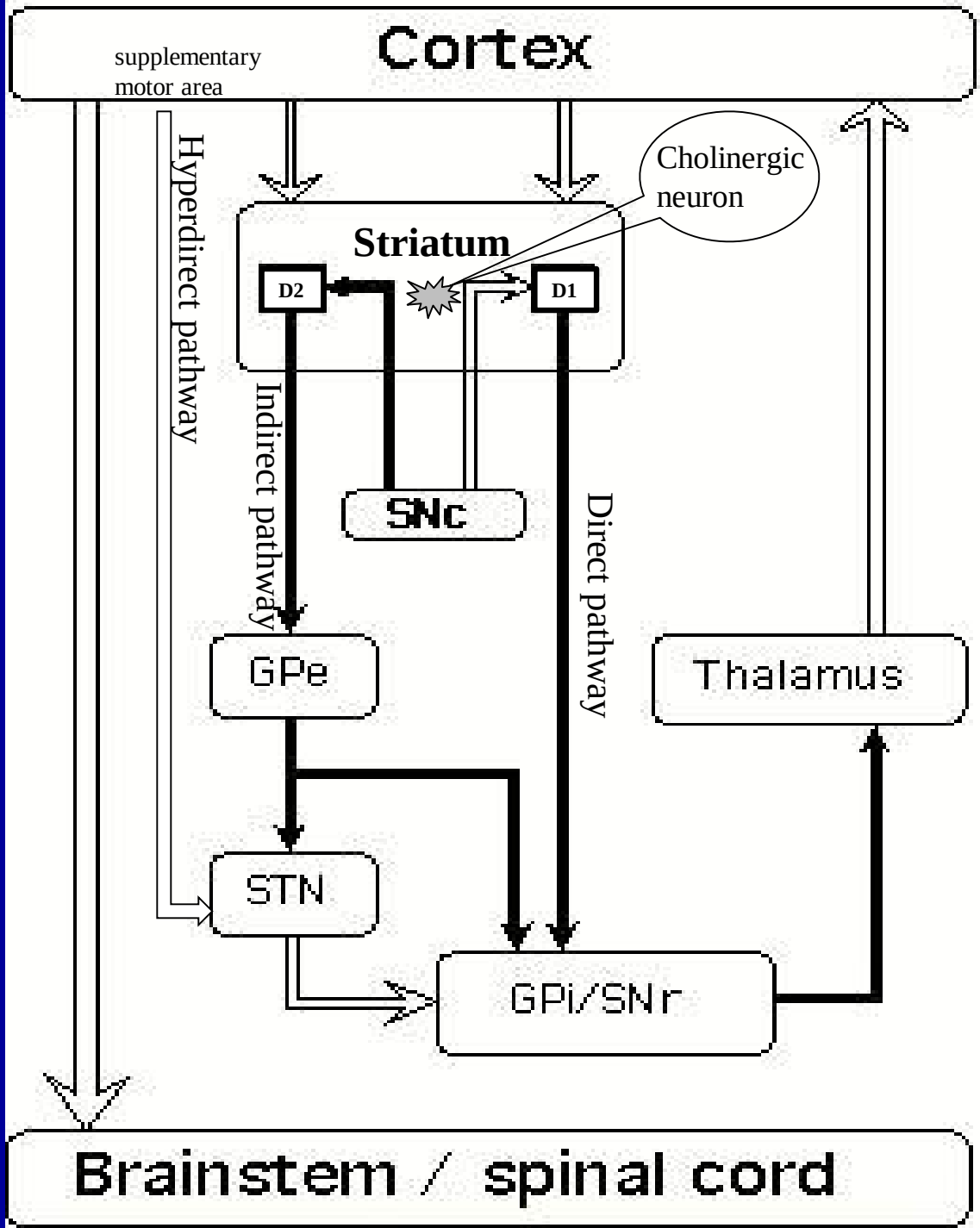
Anatomy of the of the Motor System



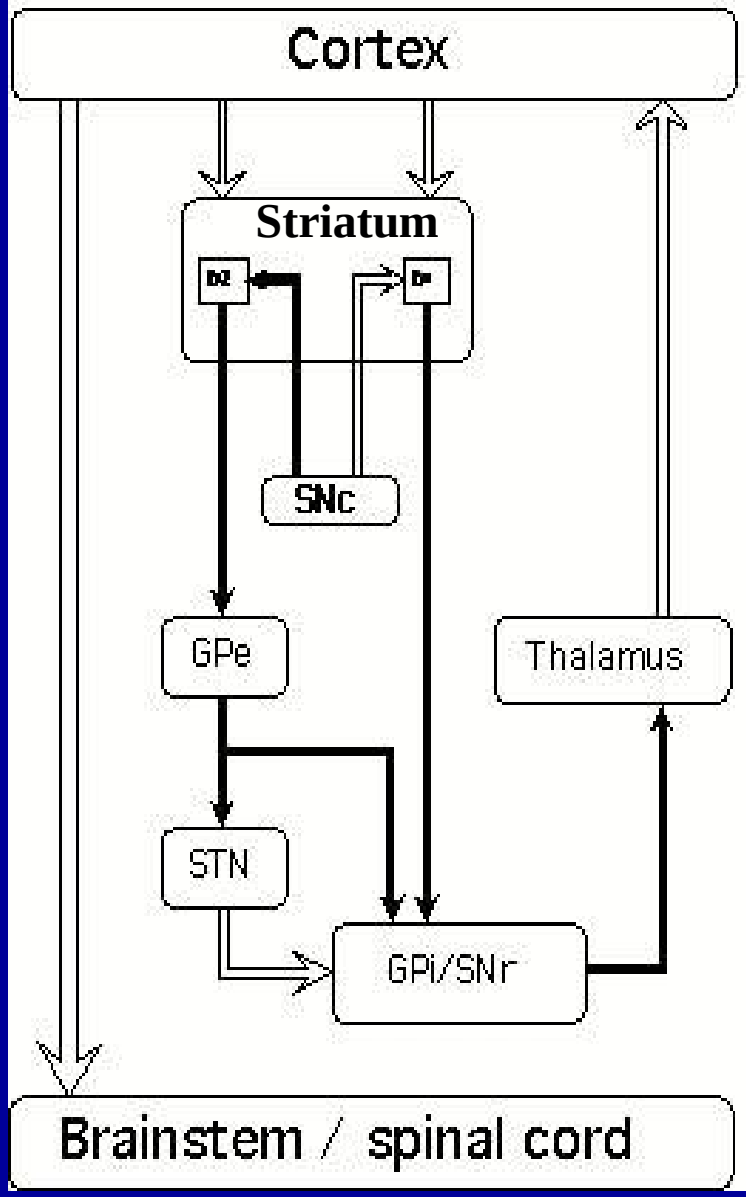
Kandel and Schwartz, Principles of Neurosciences 1985

Normal Basal Ganglia Circuitry

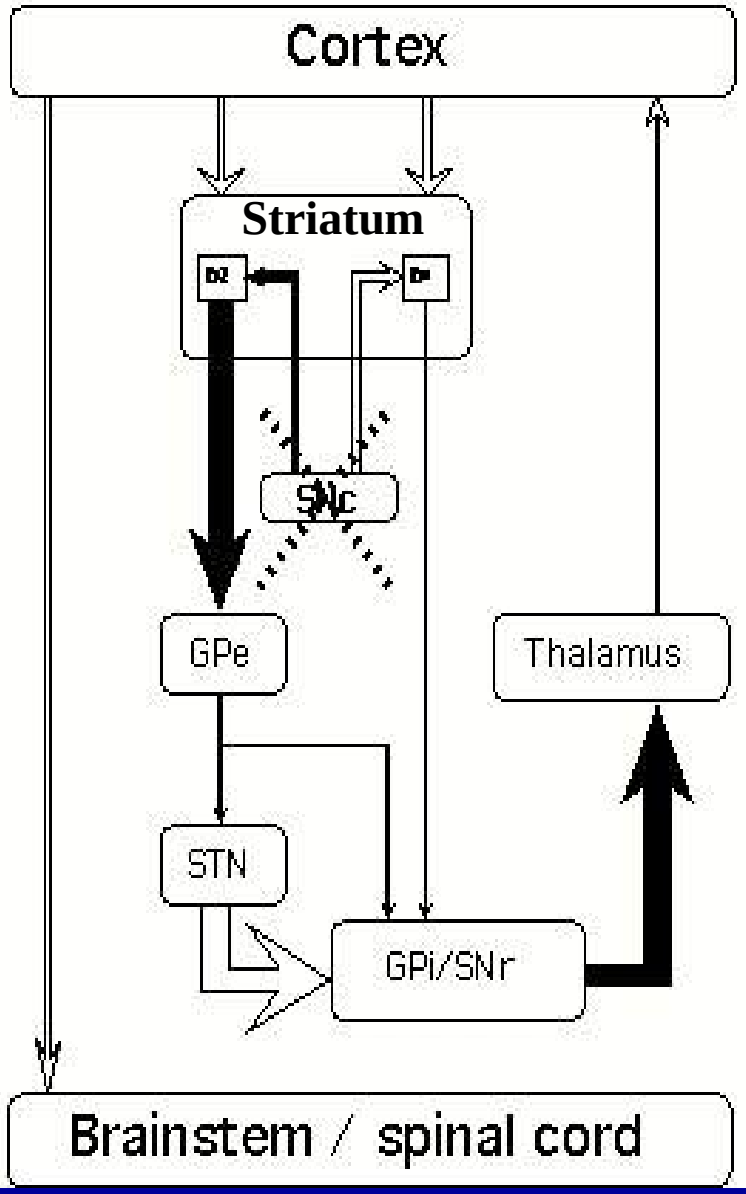
- Role of basal ganglia:
  - Facilitate wanted movements
  - Suppress unwanted movements
  - Initiate and maintain movements
- Two major motor pathways in the basal ganglia:
  - Direct pathway: promotes movement
  - Indirect pathway: inhibits movement
- Also, hyperdirect pathway: cortex-to-STN
- Inhibiting cholinergic neurons promote movement



A. Normal Basal Ganglia Circuitry



B. In Parkinson disease



Idiopathic Parkinson Disease

- **Definition:**
  - Parkinsonism
  - Lewy bodies in degenerating dopaminergic neurons
- **Diagnosis of parkinsonism: 2/3 Cardinal Symptoms**
  - Bradykinesia
  - Tremor at rest (60% of PD patients)
  - Rigidity (lead-pipe)

  (PET, DaTscan or skin biopsy NOT required for Dx)
- **Rule out Parkinson Plus Syndromes (atypical parkinsonism):**
  - 10% of parkinsonian patients
  - Rapidly disabling, poorly treatable

Differential Diagnosis of Parkinsonism

PD vs Parkinson Plus Syndromes

Synucleinopathy

- **Multiple system atrophy**: MSA-P vs MSA-C (cerebellar)
  - Striatonigral degeneration (P + poor response to levodopa)
  - Shy-Drager Sd (P + autonomic Sx)
  - Olivo-ponto-cerebellar atrophy-OPCA (P + cerebellar Sx)

Tauopathy

- **Progressive supranuclear palsy**
  (P + early imbalance + eyes movement abnormalities)
- **Corticobasal ganglionic degeneration**-CBGD
  (P + unilateral dystonia + cortical sensation loss)

Synucleinopathy

- **Parkinsonism + early dementia:**
  - Alzheimer disease + parkinsonian features
  - Diffuse Lewy body disease
  - Vascular dementia + Parkinsonism (white matter disease)
- **Lower body Parkinsonism:**
  - Vascular Parkinsonism (white matter disease)
  - Normal pressure hydrocephalus
- **Drug-induced parkinsonism (D2-receptors blockers)**

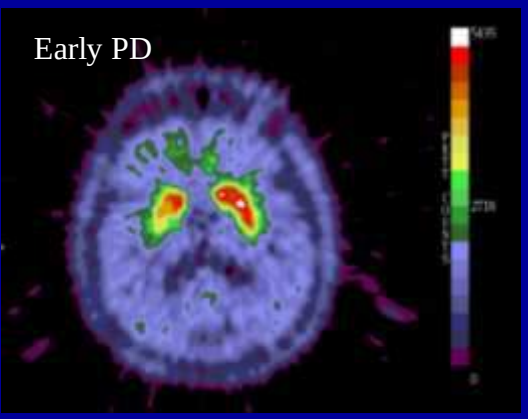
The Red Flags of Atypical Parkinsonism

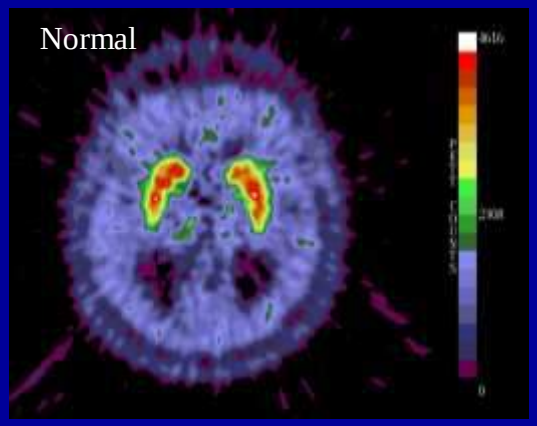
- **Rapid disease progression**
- **Early gait instability and falls**
- **Absence of rest tremor (also in 40% of Parkinson disease)**
- **Symmetry of onset – MSA, PSP, vascular parkinsonism**
- **Poor or absent response to levodopa**
- **eye movements abnormality - PSP**
- **pyramidal tract (Babinski sign, ankle clonus, hyperreflexia) – MSA, CBD**
- **cerebellar signs (ataxia) – MSA-c**
- **prominent autonomic dysfunction (constipation, incontinence, impotence, orthostatic hypotension) – MSA, DLBD**
- **severe dysarthria, dysphonia, laryngeal stridor - MSA**
- **myoclonus - CBD**
- **alien limb - CBD**
- **apraxia - CBD**
- **early dementia - DLBD, PSP, CBD**

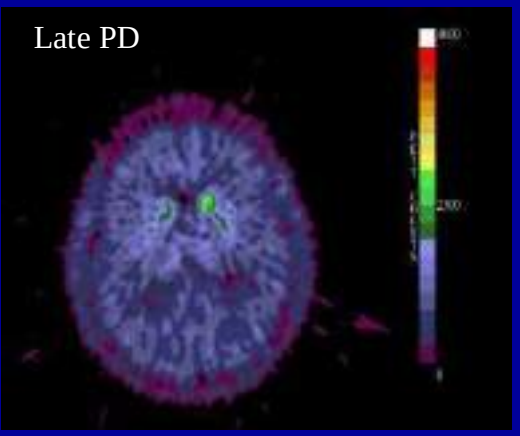
Alpha-Synuclein Skin Biopsy

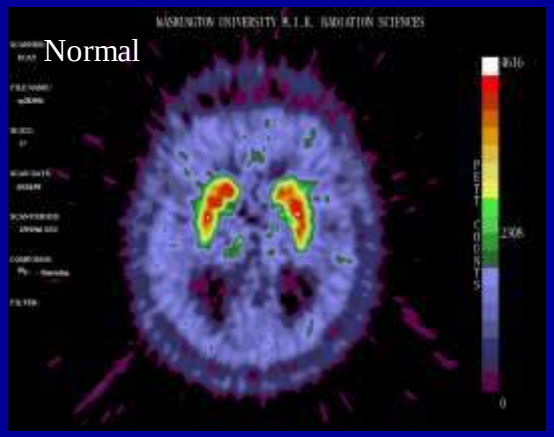
Diagnosis	Detection (sensitivity)	False-negative rate
Parkinson disease	92.7%	~7.3%
Multiple system atrophy	98.2%	~1.8%
Dementia with Lewy bodies	96.0%	~4.0%
Pure autonomic failure	100%	~0%

18-Fluorodopa Positron Emission Tomography in (PET)

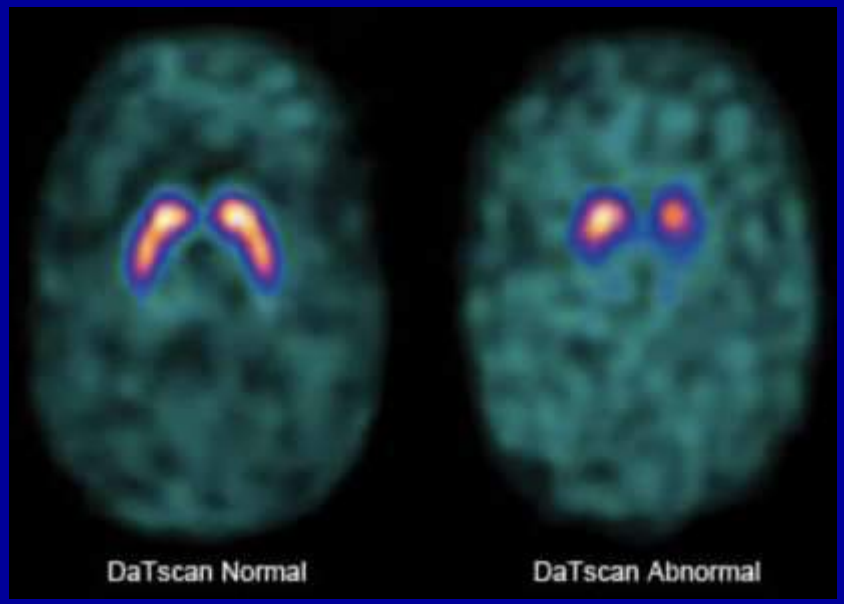








DaTscan (123I-ioflupane SPECT)



DaTscan (^{123}I-ioflupane SPECT)

- **DaTscan highly sensitive for presynaptic dopaminergic degeneration (PD, MSA, PSP, DLB) ~78–100%**
  - **Abnormal in PD, MSA, PSP, DLB**
  - **Normal in CBD**
- **Normal DaTscan practically rules out PD and would imply other dx (essential tremor, drug-induced, psychogenic or usually vascular parkinsonism)**
- **FDA-approved for "distinguishing PD from essential tremor"**
- **Not useful to track progression of illness (does not correlate with motor sx; looks worse if patient on levodopa, looks better if on dopamine agonists)**

Natural History of Parkinson Disease

- **Before levodopa: Death within 10 years**
- **After levodopa:**
  - **"Honeymoon" period (~ 5-7 years)**
  - **Drug-induced motor (ON/OFF) fluctuations & dyskinesias:**
    - **Drug therapy effective initially**
    - **Surgical intervention by 10-15 years**
      - **Deep brain stimulation (DBS) therapy**
  - **Prominent gait impairment and autonomic symptoms by 20-25 years (Merola 2011)**
- **Dementia and psychosis at anytime during the illness:**
  - **When late: Parkinson disease with dementia**
    - **Psychosis is drug-induced**
  - **When early: diffuse Lewy body disease/dementia**
    - **Associated with Lewy bodies in the substantia nigra AND throughout the cortex**
    - **~30% have psychosis even off dopaminergic drugs**

Non-Motor Symptoms of PD

Sensory Sx

- Olfactory: hyposmia/loss of smell
- Gustatory: taste sensation change
- Visual: diplopia, blurred vision, reading difficulty
- Pain syndromes

Sleep disorders

- Insomnia
- Restless legs syndrome (RLS)
- REM-sleep behavior disorder (RBD)
- Excessive daytime sleepiness

Autonomic Sx

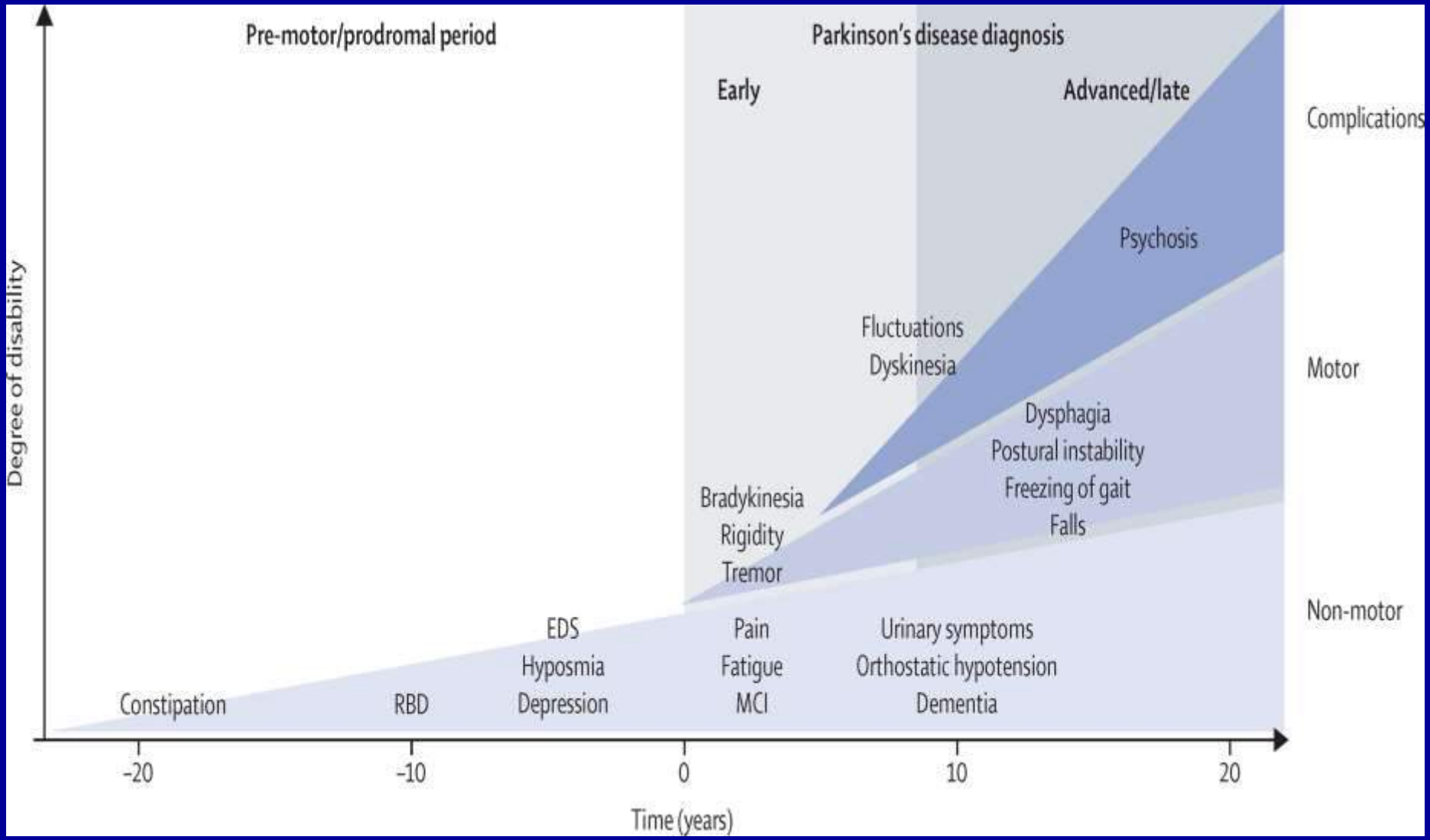
- Cardiac: Orthostatic hypotension
- Urinary: urgency, frequency, nocturia
- Genital: erectile dysfunction
- GI: constipation, hypersalivation
- Skin: Seborrhoea, hyper/hypohidrosis

Neuro-psychiatric Sx:

- depression, anxiety, apathy...
- Psychosis, dementia...

Fatigue

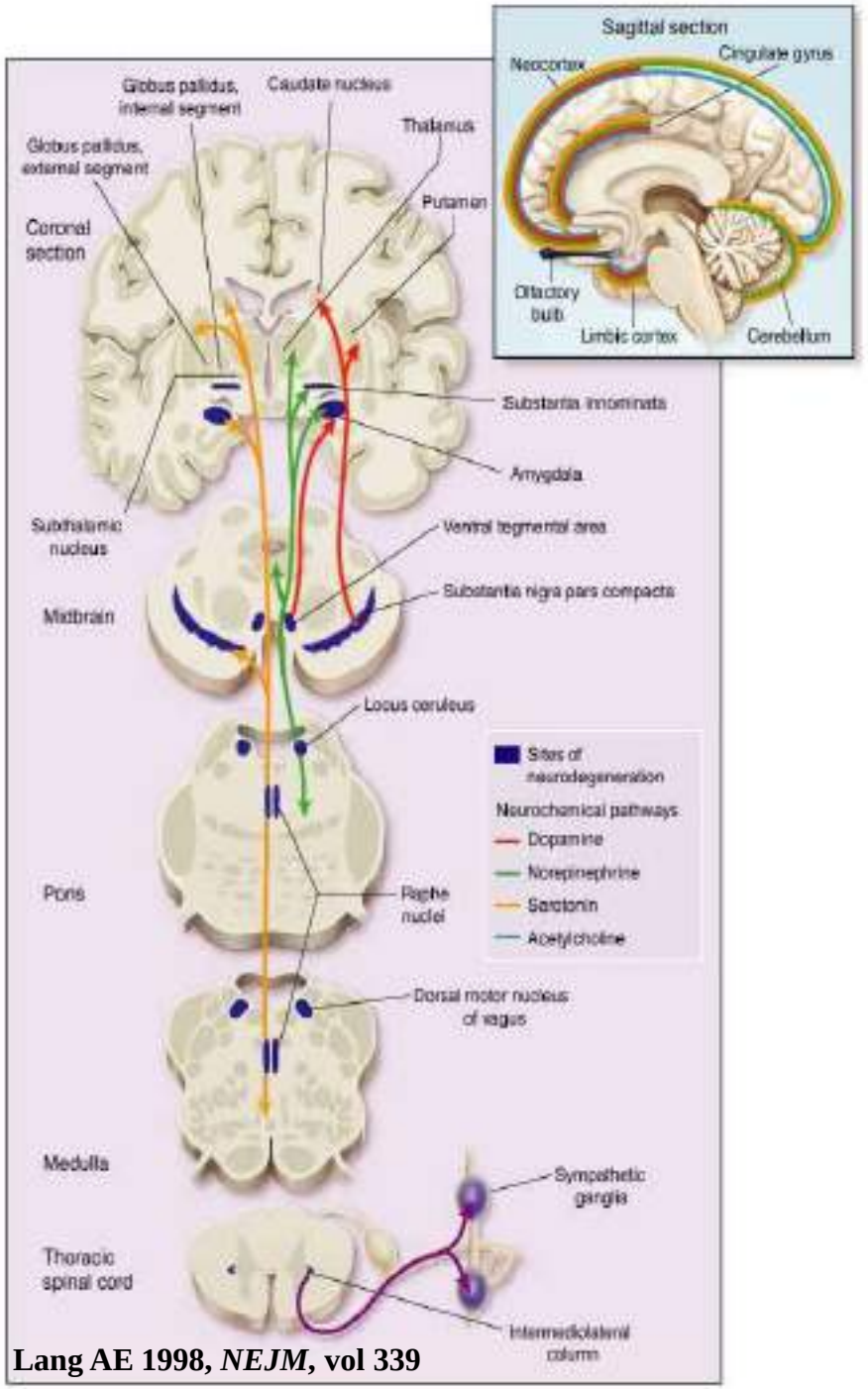
Parkinson Disease
Clinical Progression



Kalia & Lang 2015, *Lancet*, 386: 896–912

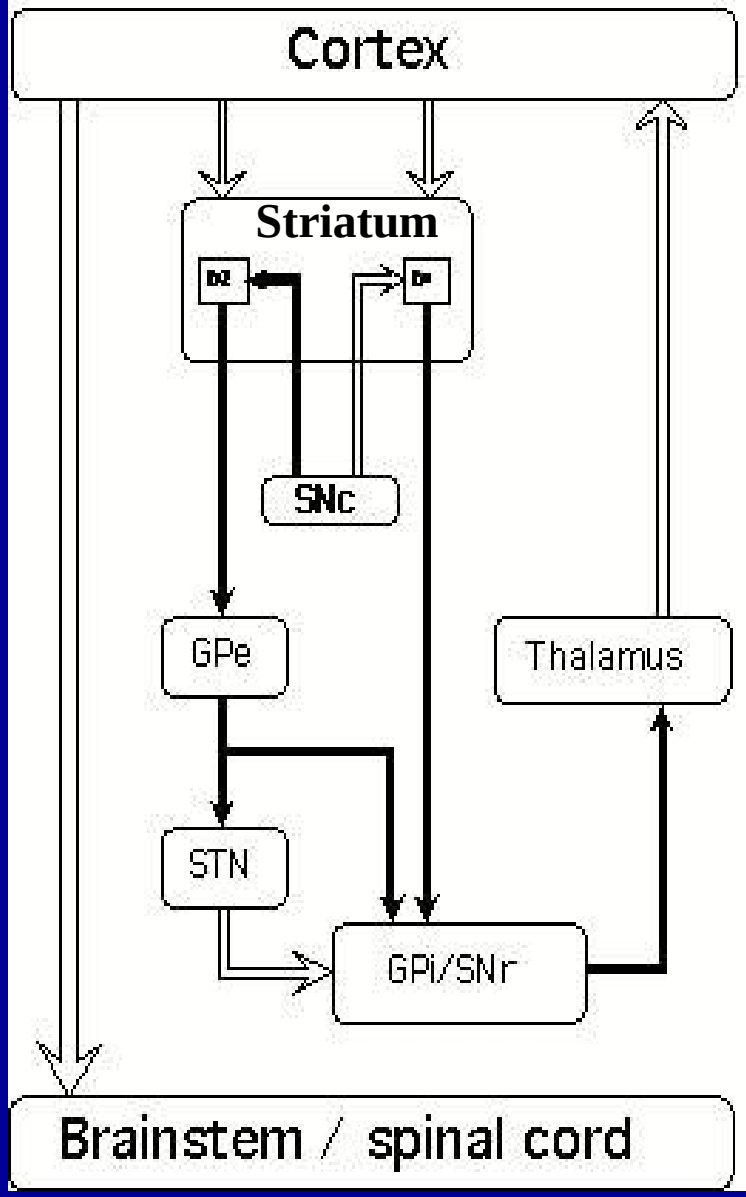
Sites of Neurodegeneration in Parkinson Disease

- Substantia nigra pars compacta
- Substantia innominata
- Amygdala
- Ventral tegmental area
- Locus ceruleus
- Raphe nuclei
- Dorsal motor nucleus of vagus nerve
- Intermediolateral column/Sympathetic ganglia

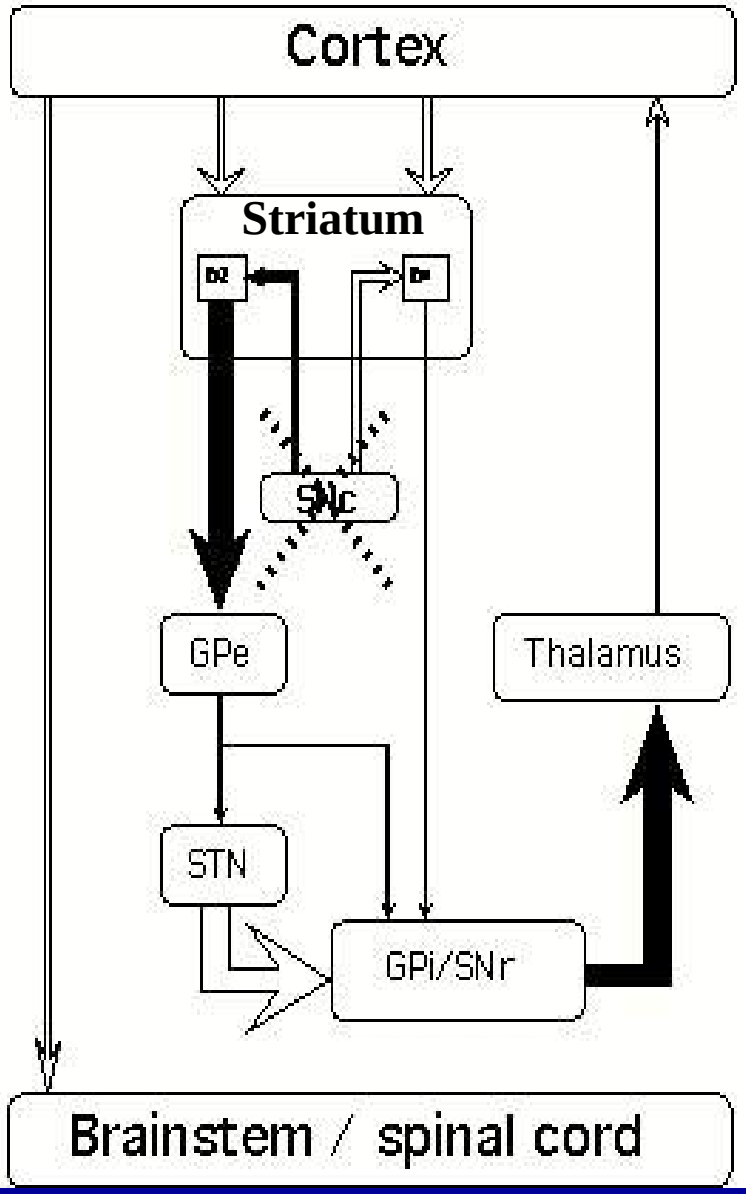


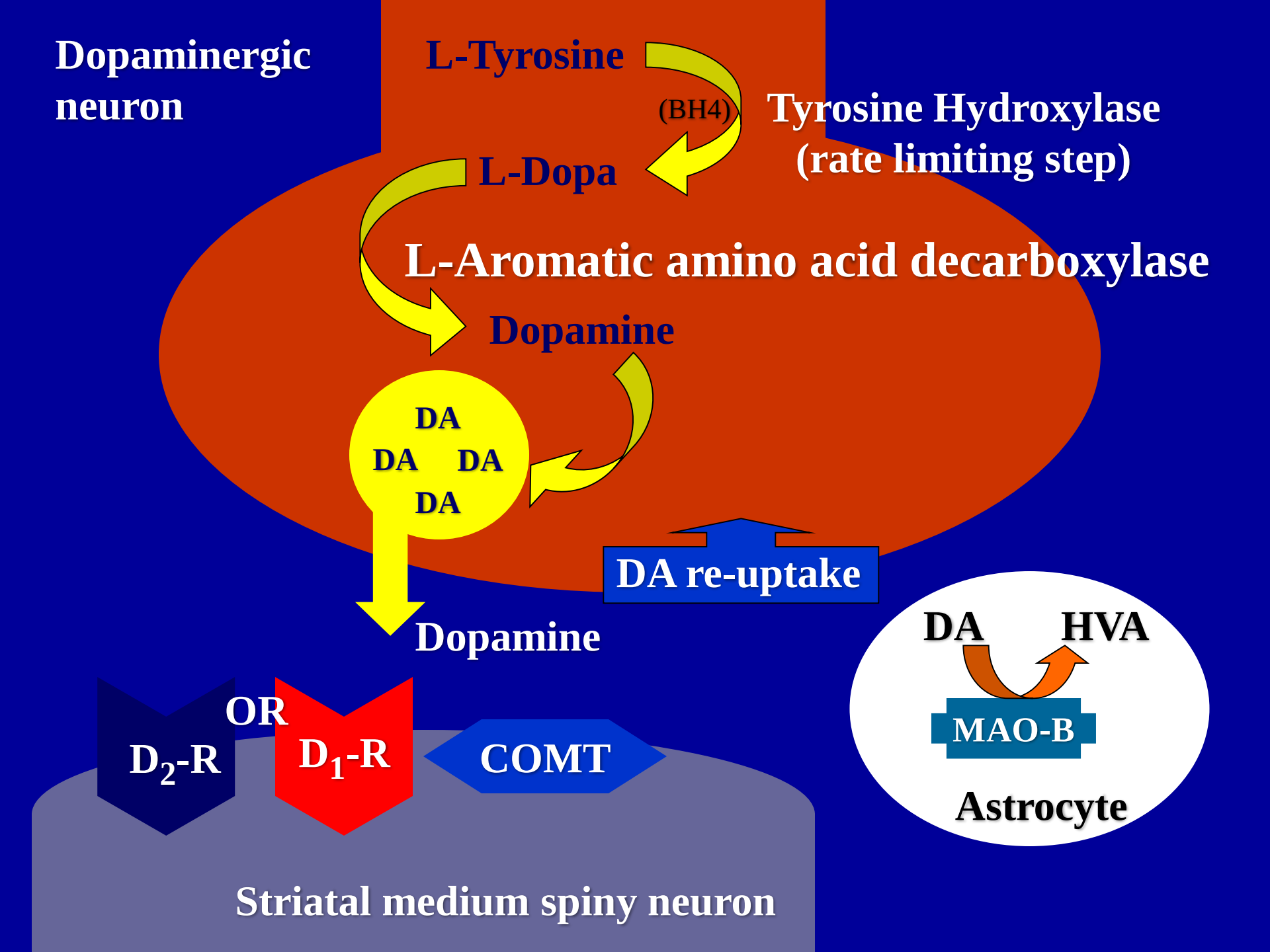
Lang AE 1998, *NEJM*, vol 339

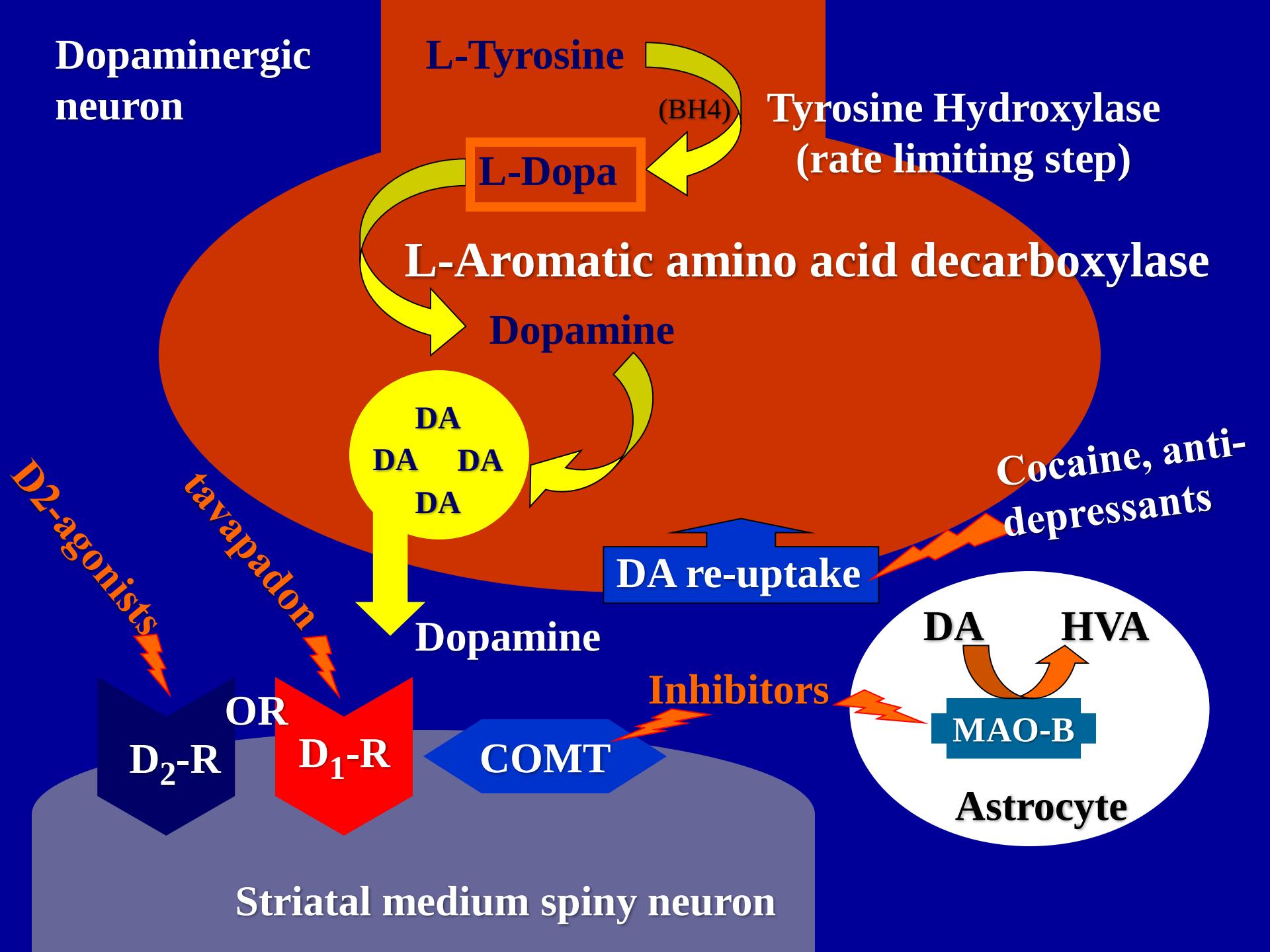
A. Normal Basal Ganglia Circuitry



B. In Parkinson disease




Dopaminergic neuron
L-Tyrosine
(BH4)
Tyrosine Hydroxylase (rate limiting step)
L-Dopa
L-Aromatic amino acid decarboxylase
Dopamine
DA
DA DA
DA
DA re-uptake
Dopamine
OR
D2-R
D1-R
COMT
DA
HVA
MAO-B
Astrocyte
Striatal medium spiny neuron


Dopaminergic neuron
L-Tyrosine
(BH4)
Tyrosine Hydroxylase (rate limiting step)
L-Dopa
L-Aromatic amino acid decarboxylase
Dopamine
DA
DA DA
DA
Cocaine, anti-depressants
D2-agonists
tavapadon
DA re-uptake
Dopamine
DA
HVA
Inhibitors
MAO-B
OR
D2-R
D1-R
COMT
Astrocyte
Striatal medium spiny neuron

Rx of Motor Symptoms of PD

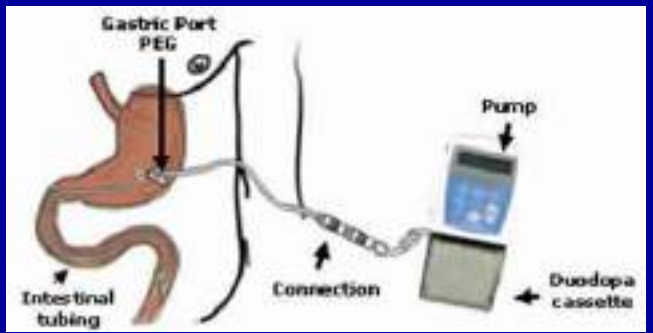
- **Dopamine Replacement:**
  - Levodopa with aromatic amino acid decarboxylase inhibitors (carbidopa or benserazide)
  - Catecholamine-O-methyl transferase (COMT) inhibitors: entacapone, opicapone
  - Dopamine agonists:
    - D2-receptors: bromocriptine, cabergoline, pramipexole, ropinirole, rotigotine patch, apomorphine (s/q injection or pump)
    - D1-receptors: tavapadon
- **Dopamine Releaser/NMDA-blocker:** amantadine
- **Mono-amine oxidase inhibitors (MAOI)-type B :**
  - selegiline, rasagiline, safinamide
- **Selective adenosine A_{2a} receptor agonist:** istradefylline
- **Anticholinergic drugs:** trihexyphenidyl, benztropine, biperiden
- **Surgical Rx:** deep brain stimulation, high-intensity focused u/s

Treatment of Parkinson Disease: General Principles

- **Start low & go slow**
- **Titrate symptoms**
- **Exercise for all before year 2030**

Levodopa

- **Most powerful anti-parkinsonian drug**
- **Formulation:**
  - **Carbidopa/levodopa**
  - **Carbidopa/levodopa/entacapone**
  - **Inhaled levodopa (Inbrija)**
  - **Carbidopa/levodopa beads (Rytary and Crexont)**
  - **Duodenal carbidopa/levodopa gel via Duodopa pump**
  - **Subcutaneous carbidopa/levodopa infusion via Vyalev pump**
- **Adverse effects:**
  - **Nausea: Rx with high-dose of carbidopa (Lodosyn 25-75 mg) or domperidone (Motilium) 10-30 mg tid, ½ hour before each dose of levodopa**
  - **Constipation, hypotension, peak-dose sedation/dizziness**
  - **Motor Fluctuations/Dyskinesia**



Rytary

- **Approved in January 2015 by the US FDA:**
  - **Rytary doses: 23.75/95, 36.25/145, 48.75/195, 61.25/245**
  - **beads of carbidopa and levodopa that dissolve at various rates**
  - **Max dose: 612/2450 mg**
  - **May open capsule and mix with food**
  - **70% bioavailable compared to carbidopa/levodopa**



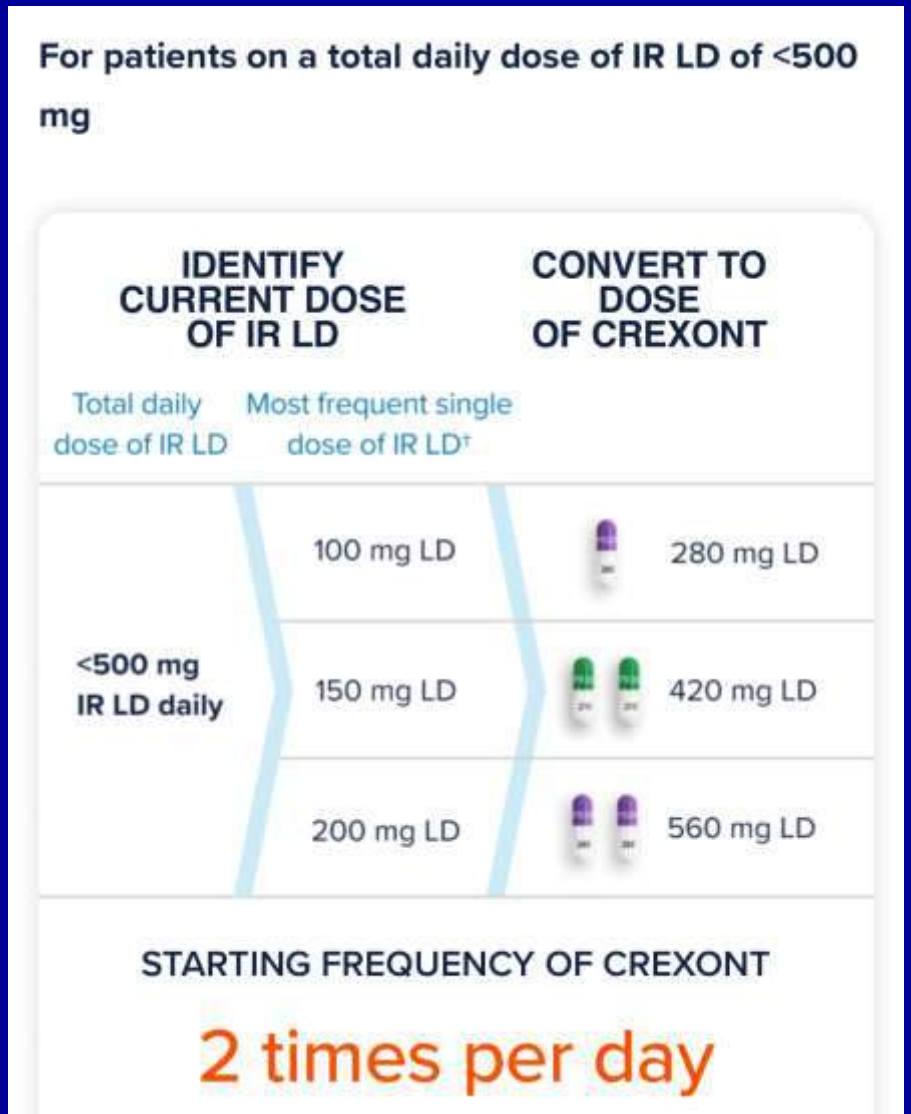
Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY

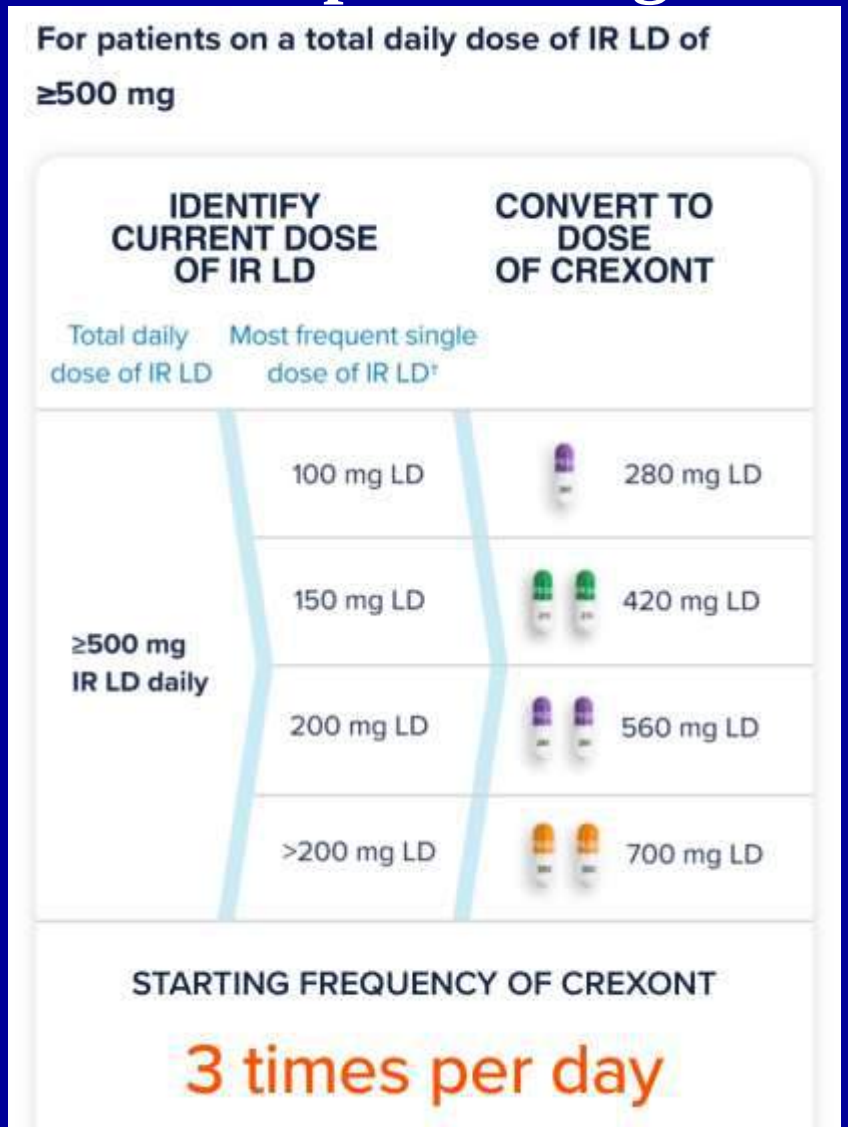
Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa	Recommended Starting Dosage of RYTARY		
	Total Daily Dose of Levodopa in RYTARY	RYTARY Dosing Regimen	
400 mg to 549 mg	855 mg	3 capsules RYTARY 23.75 mg / 95 mg taken TID[a]	$630
550 mg to 749 mg	1140 mg	4 capsules RYTARY 23.75 mg / 95 mg taken TID	$830
750 mg to 949 mg	1305 mg	3 capsules RYTARY 36.25 mg / 145 mg taken TID	$660
950 mg to 1249 mg	1755 mg	3 capsules RYTARY 48.75 mg / 195 mg taken TID	$660
Equal to or greater than 1250 mg	2340 mg or	4 capsules RYTARY 48.75 mg / 195 mg taken TID or	$830 or
	2205 mg	3 capsules RYTARY 61.25 mg / 245 mg taken TID	$790

Levodopa dose x2 = Rytary dose

Crexont

- **Crexont doses:** 35/140 mg, 52.5/210 mg, 70/280 mg, 87.5/350 mg
- **Mucoadhesive polymer to stick to the proximal gut**



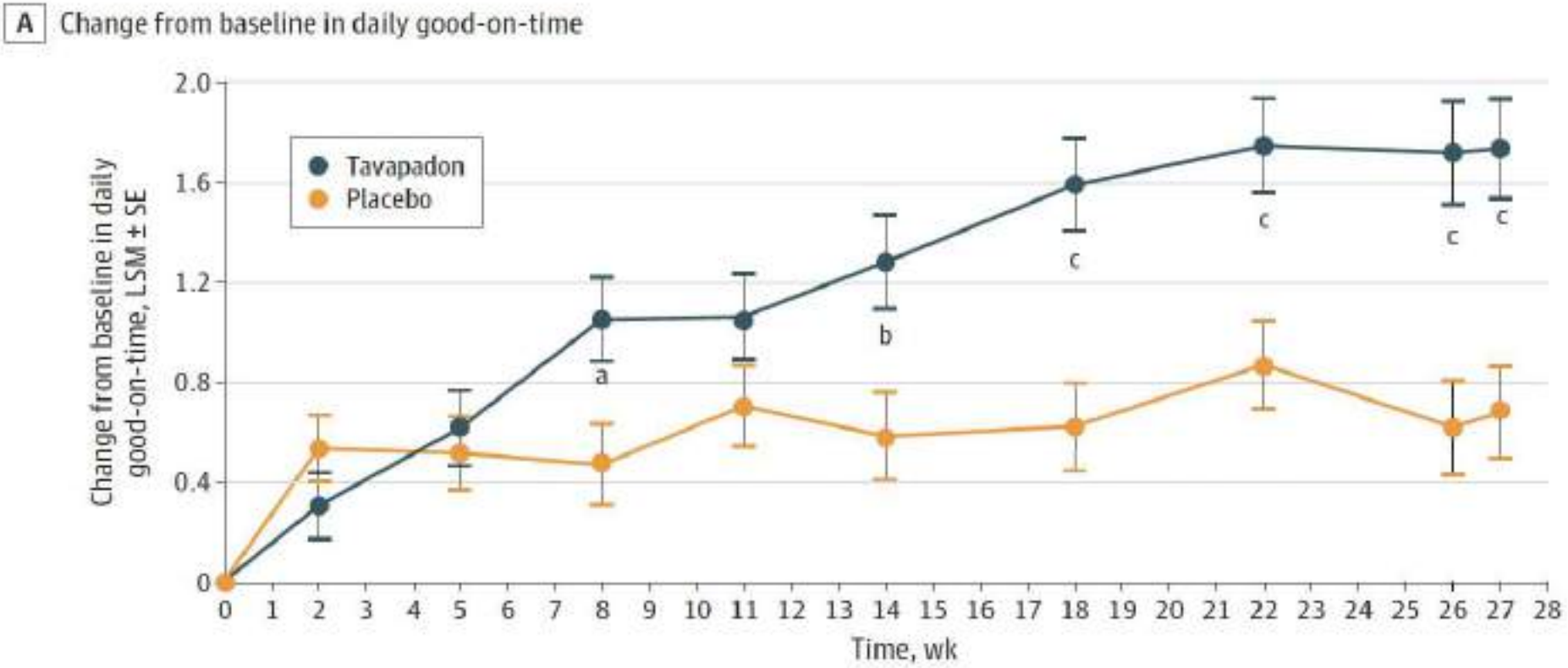


Levodopa vs D2-Receptor Dopamine Agonists

	Levodopa	Dopamine Agonists
Motor benefit	+ + +	+
Motor fluctuations at 10 years	+ + +	+
Dyskinesia at 10 years	+ + +	+
Mental adverse effects - **Hallucinations, delusions** - **Impulse control (hypersexuality, gambling, compulsive shopping)** - **Daytime sedation**	< 70yrs: + > 70 yrs: +	< 70yrs: + + > 70yrs: + + +
Orthostasis at 10 years	+ +	+ + +

Tavapadon Increases Total Daily Good-ON-Time by 1.1 Hours (1.70 hr vs Placebo 0.60 hr)

Figure 2. Line Graphs Showing the Least-Squares Mean Change From Baseline in Daily On-Time (Hours) Without Troublesome Dyskinesia (Good-on-Time) and Off-Time in the mITT Population



Participants										
Tavapadon	242	239	223	206	192	182	174	163	153	151
Placebo	245	239	234	229	218	218	206	202	201	198

Tavapadon: Other End Points at Week 26 Compared With Placebo

- 1.2 point improvement in MDS-UPDRS part II scores (1.4 vs 0.1 points)
- 2.4 points reduction in MDS-UPDRS part III scores at week 26 (7.0 s 4.6 points)
- 3.7 points reduction in MDS-UPDRS part II+III combined scores at week 26 (8.4 vs 4.7 points)

- No notable differences in MDS-UPDRS part I, PDQ-39, or EQ-5D-5L Index and Visual Analogue Scale scores

Tavapadon Summary of Adverse Events

Table 2. Summary of Adverse Events (Safety Population)

Safety outcomes	No. (%) Placebo QD (n = 254)	No. (%) Tavapadon 5-15 mg QD (n = 251)
AEs[a]	140 (55.1)	180 (71.7)
Mild	65 (25.6)	80 (31.9)
Moderate	64 (25.2)	82 (32.7)
Severe	11 (4.3)	18 (7.2)
AE related to study drug[b]	54 (21.3)	105 (41.8)
AEs by phase at onset, No./No. (%)		
Titration	83/254 (32.7)	100/251 (39.8)
Adjustment	54/237 (22.8)	100/214 (46.7)
Maintenance	65/220 (29.5)	71/188 (37.8)
Serious AEs	14 (5.5)	17 (6.8)
AE leading to discontinuation	23 (9.1)	43 (17.1)
Death	0	1 (0.4)[c]

Most common AEs (occurring with ≥5% incidence in tavapadon group), No. (%)	No. (%) Placebo QD (n = 254)	No. (%) Tavapadon 5-15 mg QD (n = 251)
Nausea	11 (4.3)	36 (14.3)
Dyskinesia	4 (1.6)	25 (10.0)
Dizziness	8 (3.1)	19 (7.6)
Headache	7 (2.8)	17 (6.8)
Fall	13 (5.1)	16 (6.4)
Orthostatic hypotension[d]	3 (1.2)	15 (6.0)
Hallucination, visual	3 (1.2)	14 (5.6)
COVID-19	9 (3.5)	13 (5.2)
Somnolence	11 (4.3)	13 (5.2)

Presumably, no impulse control disorder… to date!

Other Novel Delivery Systems of Dopaminergic Drugs

- **VR040:**
  - **Inhalable apomorphine**
- **ND0611:**
  - **Transdermal levodopa ethyl ester**

Solengepras: GPR6 Inverse Agonist

- GPR6 is specifically expressed in the medium spiny neurons of the indirect pathway in the striatum
- Solengepras dampens the overactive indirect pathway, therefore promoting movements

Phase III study:

- Improved good-ON-time: 1.58 hour (vs 0.98 hour in placebo)
- Improved sleepiness: -0.98 point on Epworth sleepiness scale
- Improved quality of life: -2.87 point on PDQ-39
- Improved motor function: -1.91 point MDS-UPDRS part II

Treatment of Behavior in Advanced PD

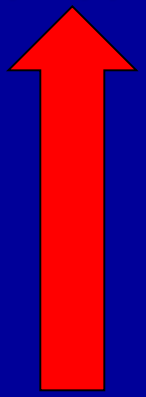
- **Behavioral symptoms:**
  - **Hallucinations with/without insight, paranoid delusions, confusion:**
    - **First, use levodopa as monotherapy if possible (discontinue MAO inhibitor, amantadine and dopamine agonists)**
    - **Drugs for psychosis:**
      - **(Quetiapine: proven NOT effective in PD)**
      - **Clozapine with weekly white blood cell count (1-2% risk of agranulocytosis)**
      - **Pimavanserin 34 mg daily (inverse agonist and antagonist of 5-HT2A and 5-HT2C serotonin receptors) ~ $1,000-2,000/month**
      - **Cholinesterase inhibitors: galantamine, donepezil, rivastigmine**
  - **Dementia: cholinesterase inhibitors**
- **Altered alertness/sleep:**
  - **Drowsiness after taking levodopa dose: give small doses more frequently**
  - **REM-sleep behavior disorder: low dose benzodiazepines (clonazepam 0.25 mg to 1 mg qhs)**
  - **Insomnia: melatonin (5-15 mg 4 hours before sleep), optimize nighttime dopaminergic replacement**

Motor Potency vs Mental Adverse Effects

Motor benefit:

1. Levodopa
2. Dopamine agonists
3. MAO inhibitors, Anticholinergic drugs
4. Amantadine

More effects



Less effects

Mental adverse effects:

(in patients >70 years)

1. Anticholinergic drugs
2. Dopamine agonists
3. Amantadine (myoclonus), MAO inhibitors
4. Levodopa

- **For psychotic patients, the first medications to stop:**
  - Anticholinergic drugs, dopamine agonists, amantadine, then MAO inhibitors
  - then add cholinesterase inhibitors, then pimavanserin, then clozapine
  - then (decrease) levodopa

So:

Do NOT EVER give D2-receptor blocking agents to parkinsonian patients… (including haldol, risperidone, olanzapine, ziprasidone, …)

EVER!

May withhold dopaminergic drugs for aggressiveness

Long Live Dopamine !

