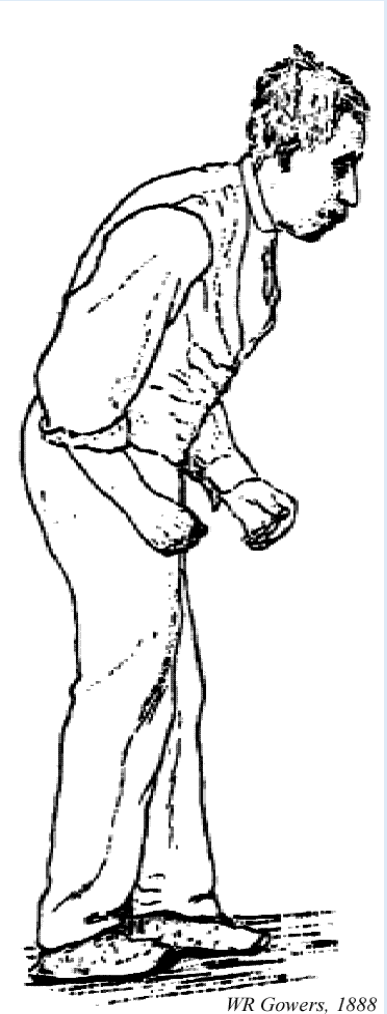
Parkinson’s Disease (PD) Therapies



WR Gowers, 1888

From dopamine precursors to new generations of drugs

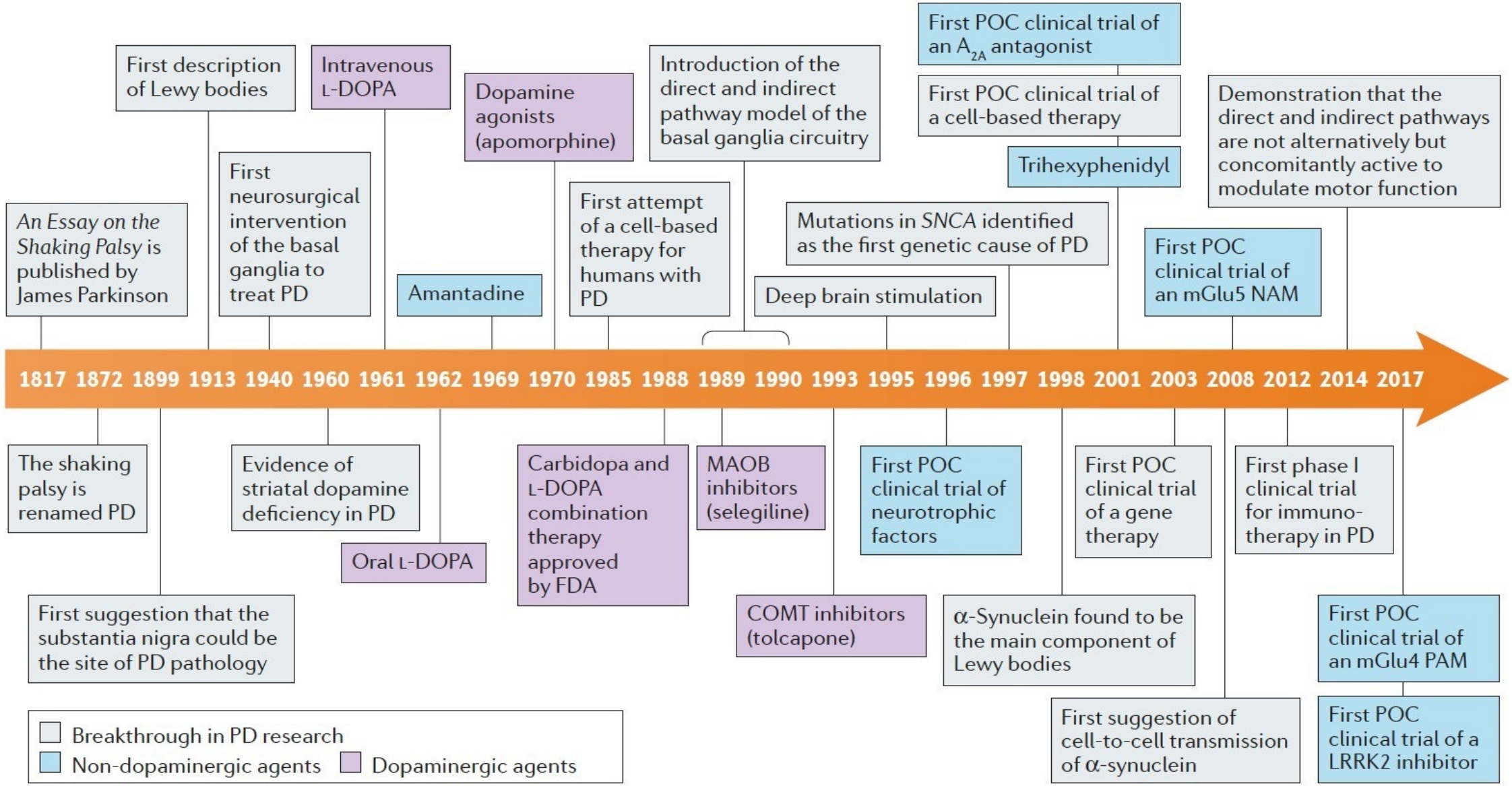


Figure 1 | **History of Parkinson disease research and therapeutic advances.** A_{2A}, adenosine receptor type 2A; COMT, catechol-*O*-methyltransferase; L-DOPA, levodopa; LRRK2, leucine-rich repeat serine/threonine-protein kinase 2; MAOB, monoamine oxidase type B; mGlu, metabotropic glutamate receptor; NAM, negative allosteric modulator; PAM, positive allosteric modulator; PD, Parkinson disease; POC, proof of concept. Adapted from REF.[239], Springer Nature Limited.

THERAPIES FOR THE TREATMENT OF PARKINSON'S DISEASE

Pharmacological treatments

· Levodopa (L-Dopa) - precursor of dopamine (DA)
· Direct DA agonists with long half-lives
· COMT or MAO inhibitors (enzymes that metabolize DA)
· Anticholinergic agents
· Glutamate antagonists

Surgical treatments

· Deep brain stimulation (DBS)
· Pallidotomy
· Stem cell transplantation

Table 1 | **Current drugs for Parkinson's disease**

Drug	Advantages	Disadvantages
Levodopa (L-dopa) + dopa decarboxylase inhibitor	• Probably the most potent dopaminergic drug for symptom relief • Generally well tolerated	• Motor complications (cumulative risk 10% per annum)
Catechol-*O*-methyl transferase inhibitors, for example, entacapone, tolcapone	• Increase levodopa half-life • Reduce 'off' time	• Tolcapone can cause liver damage. • Diarrhoea
Ergot dopamine agonists (for example, bromocriptine, pergolide, cabergoline Non-ergot dopamine agonists for example, pramipexole, ropinirole, rotigitine	• Good efficacy • Delay onset of motor complications • Generally well tolerated • Once-a-day preparations available with some • Transdermal patch for rotigitine • Theoretical neuroprotective action • Some antidepressant action with pramipexole	• Increased risk of somnolence, confusion, hallucinations, peripheral oedema and behavioural changes • Cardiac valve fibrosis with ergot drugs
Monoamine oxidase B inhibitor; selegiline; rasagiline	• Improve motor features in early and late disease • Easy to use, once-a-day • Well tolerated • Theoretical neuroprotective effect	• Relatively mild efficacy • Selegiline metabolized to amphetamines — potential cognitive effects
Amantadine	• Mild anti-Parkinsonian effect • Improves dyskinesias	• Cognitive disturbances • Peripheral oedema • Livedo reticularis
Anticholinergics	• Mild anti-Parkinsonian effect	• Limited by side effects such as confusion

Pharmacological Treatments for Parkinson's Disease

Table 2. Summary of pharmacological therapy in Parkinson's disease (PD).

Drug or class	Indication	Impact on motor symptoms	Characteristic side effects
Levodopa	• First-line therapy	• Excellent	• Motor fluctuations • Dyskinesias
Dopamine agonist	• First-line therapy (younger patients) • Add-on therapy	• Moderate	• Sedation • Impulse control disorder
MAO-B inhibitor	• First-line therapy (mild disease, concomitant depression) • Add-on therapy	• Limited	• Generally well tolerated
COMT inhibitor	• Add-on therapy	• Improves wearing off	• Diarrhoea
Anticholinergic	• Limited use in tremor-dominant PD	• Limited	• Confusion • Dry eyes and mouth • Constipation • Urinary retention
Amantadine	• Reduces dyskinesias in advanced PD	• Limited	• Diarrhoea • Confusion

COMT = catechol-O-methyl transferase; MAO-B = monoamine oxidase type B.

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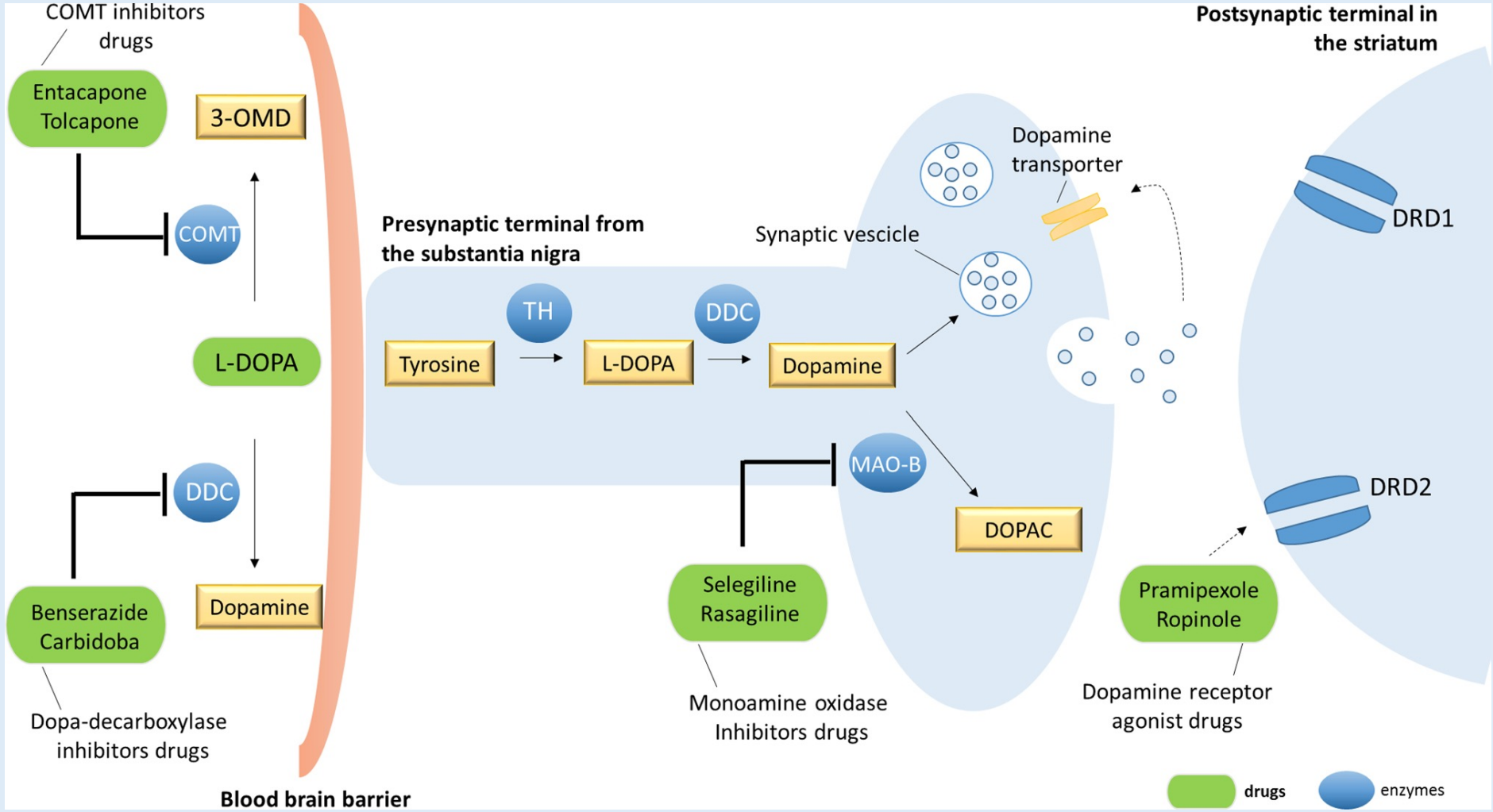
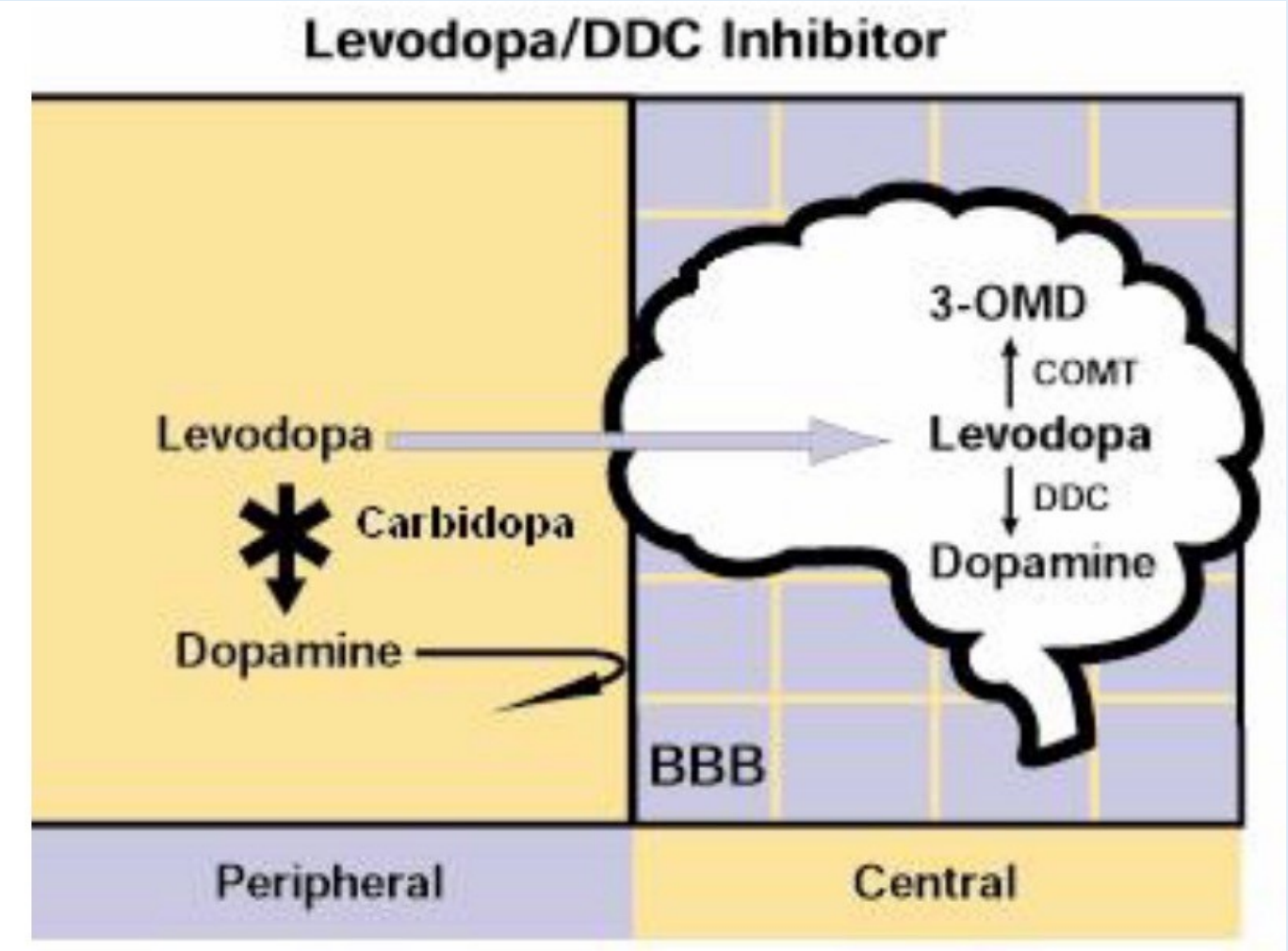


doi: 10.1007/s12017-017-8473-7. PMID: 29305687.

Carbidopa blocks conversion of Levodopa to dopamine in periphery so Levodopa can reach the brain & be converted to dopamine

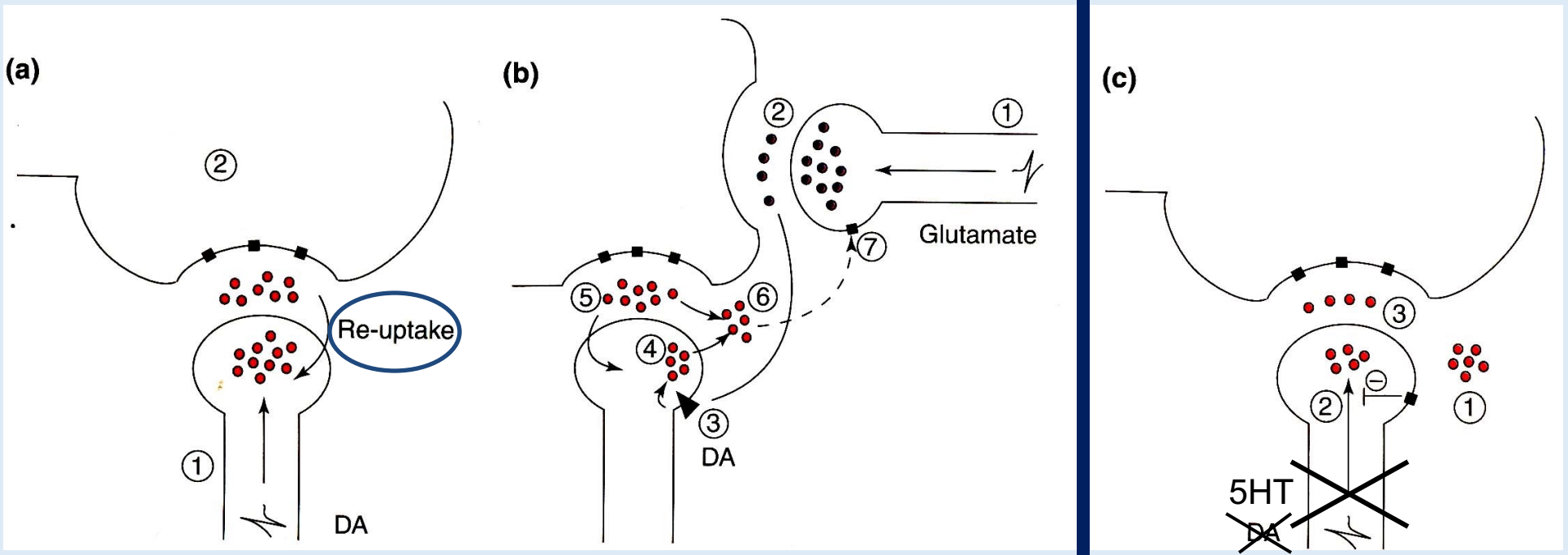


https://sites.psu.edu/nicolehume/files/2013/12/definition-and-description-1dvg9b5.pdf

Levodopa (L-DOPA)

Normal

PD



Marketed preparations:

- L-dopa + benserazide:
  Madopar 125 mg dispersible tablets (Roche)
  Madopar 125 mg tablets (Roche)
  Madopar 250 mg divisible tablets (Roche)
  Madopar HBS 125 mg tablets (Roche) – controlled-release preparation

  Posology: The average efficacious dose is 600–800 mg/day, but should be established on an individual basis. The daily dose of Madopar HBS must be about 50% higher than that of the non-delayed formulations.

- L-dopa + carbidopa:
  Sinemet 25/100 mg tablets (Bristol-Myers Squibb)
  Sinemet 25/250 mg tablets (Bristol-Myers Squibb)
  Sinemet CR 25/100 mg tablets (Bristol-Myers Squibb) – controlled-release preparation
  Sinemet CR 50/200 mg tablets (Bristol-Myers Squibb) – controlled-release preparation

  Posology: The average efficacious dose is 200–600 mg/day, and the maximum dose 2000 mg/day. The average efficacious dose of Sinemet CR is 400–1000 mg/day.

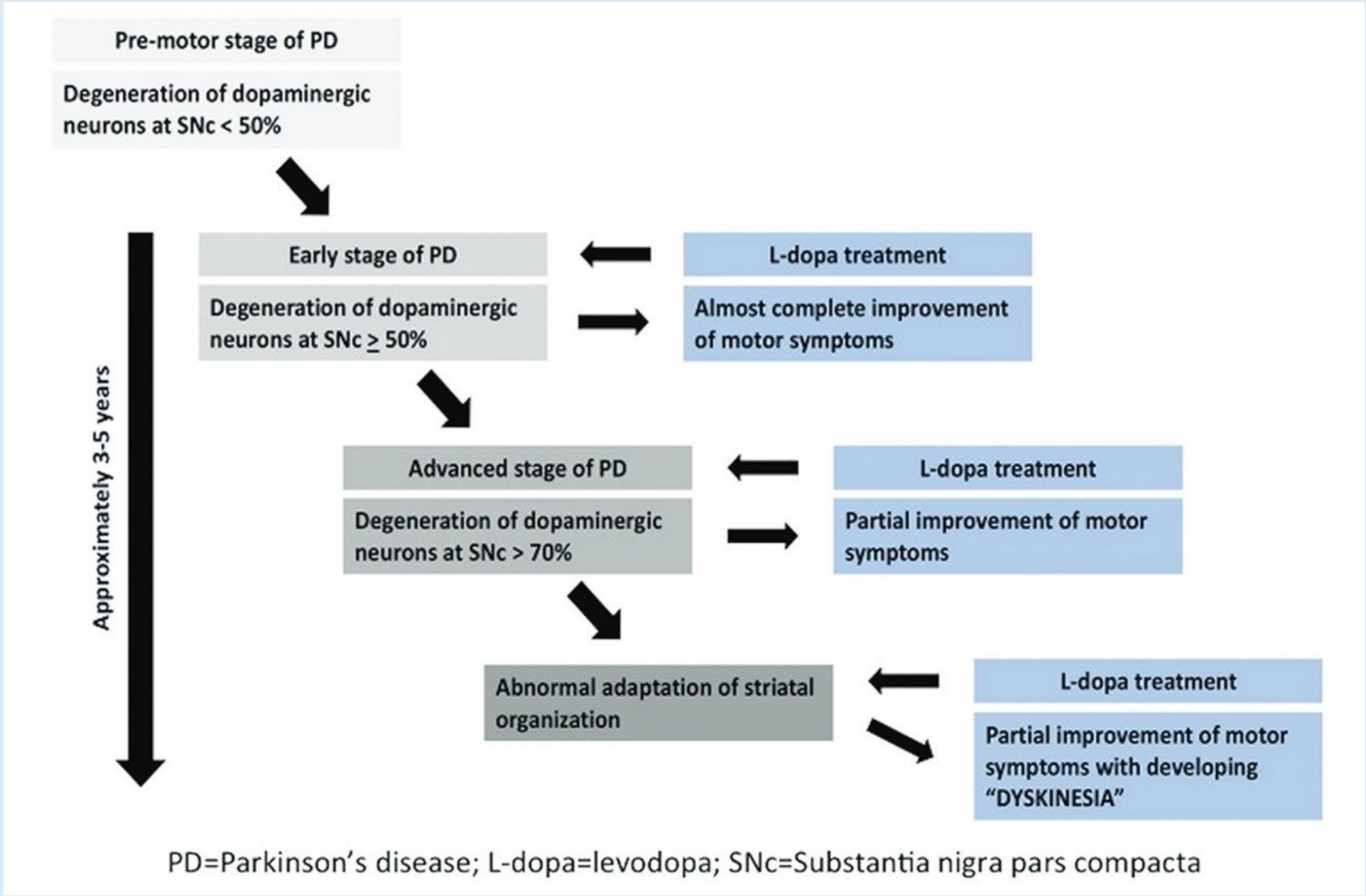
- L-dopa methyl hydrochloride:
  Levomet bottles of powder + solvent: 1 ml of reconstituted solution = 251.2 mg of L-dopa (Chiesi Farmaceutici)

  Posology: As adjunctive "as needed" therapy, the recommended unit dose is 1 ml of solution (251.2 mg/day of L-dopa); more than two administrations/day are not recommended.

Levodopa Therapy - Side Effects

Lethargy
Euphoria, excessive day time sleepiness
Vomit
Orthostatic hypotension
Depression, delusion, delirium, Dryness, Dyskinesia
On off
Psychosis
Athetosis

L-Dopa-Induced Dyskinesia – Development



PD=Parkinson's disease; L-dopa=levodopa; SNc=Substantia nigra pars compacta

Complications of Levodopa Therapy for PD

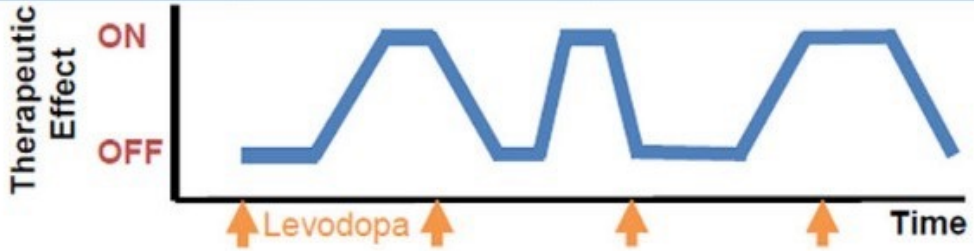
- Motor fluctuations
  Wearing-off deterioration of end-of-dose response
  'On-off', 'on' response deterioration, no 'on' response

- Involuntary movements
  peak dose or biphasic dyskinesia
  peak dose dystonia

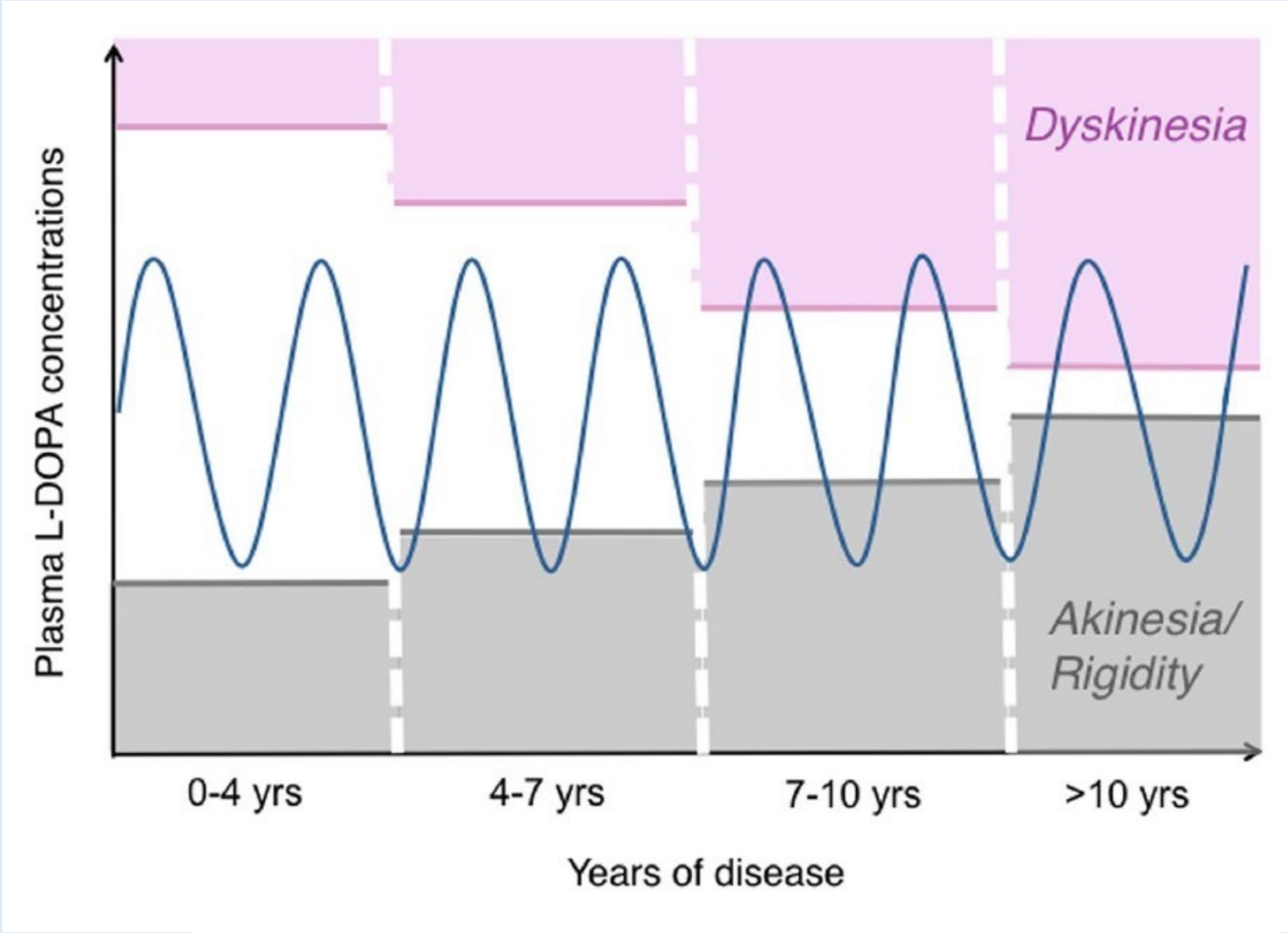
- Neuropsychiatric complications
  psychosis, hallucinations, confusion, depression

- Non-motor complications
  autonomic dysfunctions

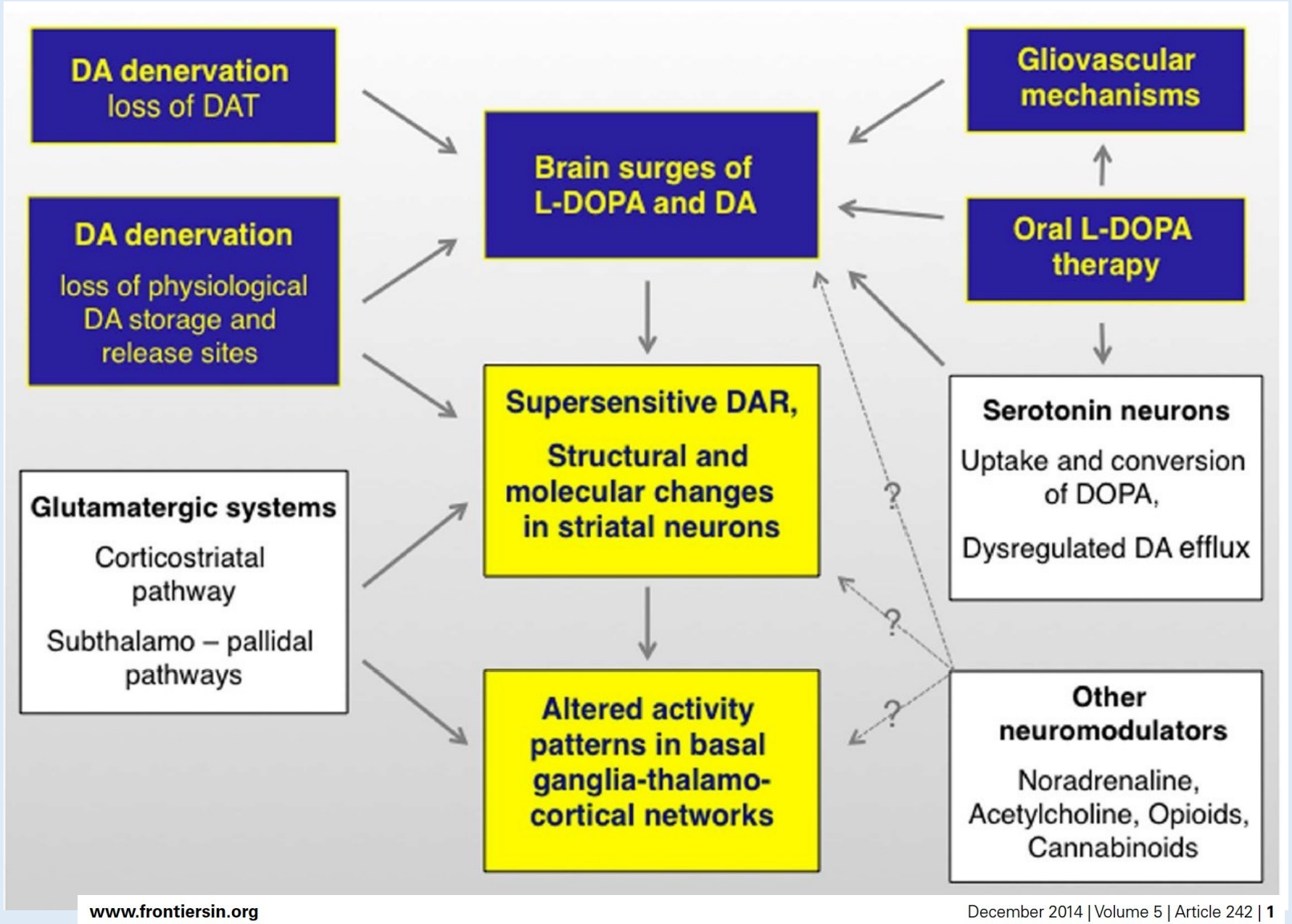
Classification of levodopa-related motor fluctuations in PD

Clinical pattern	Mechanism	
Wearing-off	Levodopa – half-life Pre-synaptic storage	
Delayed-on	Gastric emptying Intestinal absorption	
Dose-failures (No-ON)	Gastric emptying Intestinal absorption Blood–brain barrier transport	
Random ON-OFF	Striatal Pharmacodynamic Changes	

L-Dopa-Induced motor fluctuations-dyskinesia – Development



L-Dopa-Induced Dyskinesia – Mechanisms



L-Dopa-Induced Dyskinesia – Management

Table 1: Different types of levodopa-induced dyskinesia and medical management

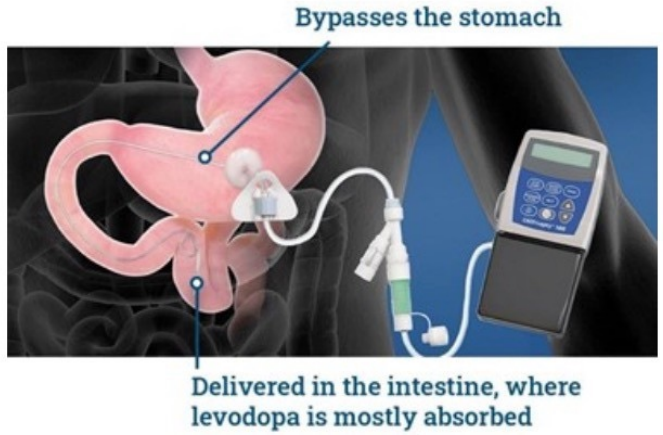
Types	Clinical description	Management strategies
Peak-dose dyskinesia	Most common type of dyskinesia (80%), which occurs at the time of peak plasma levels of levodopa, characterized by stereotypic head movements, choreiform truncal movement, and ballistic limb movement, rarely myoclonus, can be ocular, respiratory, or abdominal muscle	Decrease individual levodopa dosages, discontinue or reduce COMT and MAO-B inhibitors, switch to immediate release preparations and consider adding amantadine
Off-period dystonia	Second most common type (30%) and typically occurs in early morning, before the first dose of levodopa, usually involves leg	Adding long-acting formulations at bedtime for off-period symptoms during night or early morning. For off time during the day, consider adding COMT inhibitors, MAO-B inhibitors, or dopamine agonist
Diphasic dyskinesia "DID" pattern	Least common (20%) and starts 10-15 min after levodopa ingestion with ipsilateral leg movement and then contralateral involvement, followed by improvement of parkinsonian symptoms for several hours and then recurrence of dyskinesia, when levodopa levels decline	Most difficult to treat, LCIG infusion or subcutaneous infusion of apomorphine or surgical intervention, e.g., DBS

MAO-B = Monoamine oxidase B, COMT = Catechol-O-methyl transferase, LCIG = Levodopa/carbidopa intestinal gel, DBS = Deep brain stimulation, DID = Dyskinesia-improvement-dyskinesia

Duodopa – Drug delivery into the small intestine

Carbidopa/levodopa enteral suspension (brand name Duopa™)

Instead of taking carbidopa/levodopa in a pill form, people with PD can receive carbidopa-levodopa in a gel form infused directly into the small intestine where levodopa is known to be absorbed. This system can be useful for those with advancing PD who have motor fluctuations that are no longer controlled by oral medications alone. The system can be particularly helpful for those who have gastroparesis, or delayed gastric emptying, which is a common non-motor symptom of PD and can keep oral medications stuck in the stomach and therefore unable to be absorbed readily by the small intestine.



https://www.apdaparkinson.org/article/carbidopa-levodopa-formulations-and-parkinsons-disease/

Avoids pulsatile stimulation of dopamine receptors

For patients with advanced PD (stage 4-5) not effectively controlled with oral therapy

Levodopa Therapy – Nutrient interactions

Protein

Some people with PD experience what is referred to as the "protein effect" in which dietary protein can interfere with absorption of levodopa. Protein and levodopa use the same transporter to cross the small intestine wall. Therefore it's possible that dietary protein can interfere with absorption of levodopa including beef, chicken, pork, fish and eggs.

Iron

Iron supplements can bind with levodopa and thereby reduce the amount of medication that is absorbed in your system. If you require iron supplementation because of another medical condition, discuss this with your doctor so you can determine how to most effectively get the iron you need while not impacting your PD medications.

Pyridoxine – vitamin B6

Pyridoxine (vitamin B6) may inhibit the activity of levodopa, but only when levodopa is given alone. The vast majority of patients are on a combination of carbidopa *and* levodopa. With carbidopa in the system, the negative effect of pyridoxine on levodopa does not occur and there is no concern in taking vitamin B6 supplementation. People who are taking levodopa-only should avoid vitamin B6.

Tyramine

Patients who are taking medications for PD that are classified as monoamine oxidase (MAO)-B inhibitors (rasagiline, selegiline, and safinamide) are often concerned about having to adhere to a particular diet which is low in the amino acid tyramine. This is because patients who are taking *non-selective* MAO inhibitors (that inhibit both MAO-A and MAO-B) *for reasons other than PD,* such as depression, do have to be concerned about adhering to that diet (which can be difficult, as many foods contain tyramine). When MAO-A is inhibited, the body can no longer break down tyramine effectively. Elevated levels of tyramine can then cause spikes in blood pressure and other negative effects. To be clear, *there are no medications indicated for PD that inhibit MAO-A.* However, at high doses, MAO-B inhibitors can begin to inhibit MAO-A as well. When MAO-B inhibitors are taken at the recommended doses for PD, tyramine is broken down effectively and dangerous levels are not reached.

https://www.apdaparkinson.org/article/nutrition-and-parkinsons-disease-part-one/

Levodopa Therapy – Pharmacological Interactions

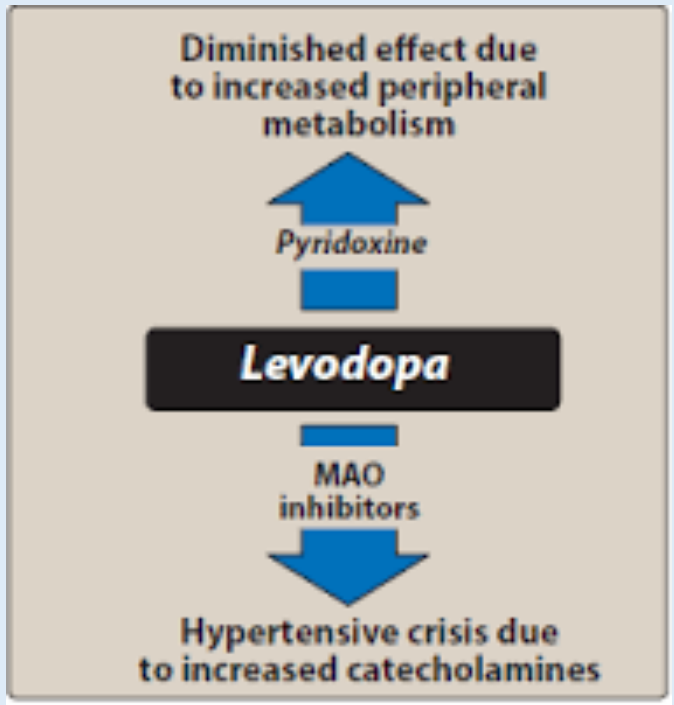


Figure 8.7
Some drug interactions observed with *levodopa*. MAO = monoamine oxidase.

Negative interactions

- **Non-selective MAO inhibitors** (phenelzine, isocarboxazid and tranylcypromine);
- **Tricyclics** (imipramine and amitriptyline);
- **Typical antipsychotics** (haloperidol).

DA agonists

Dopamine Receptor Subtypes & Direct Acting Agonists

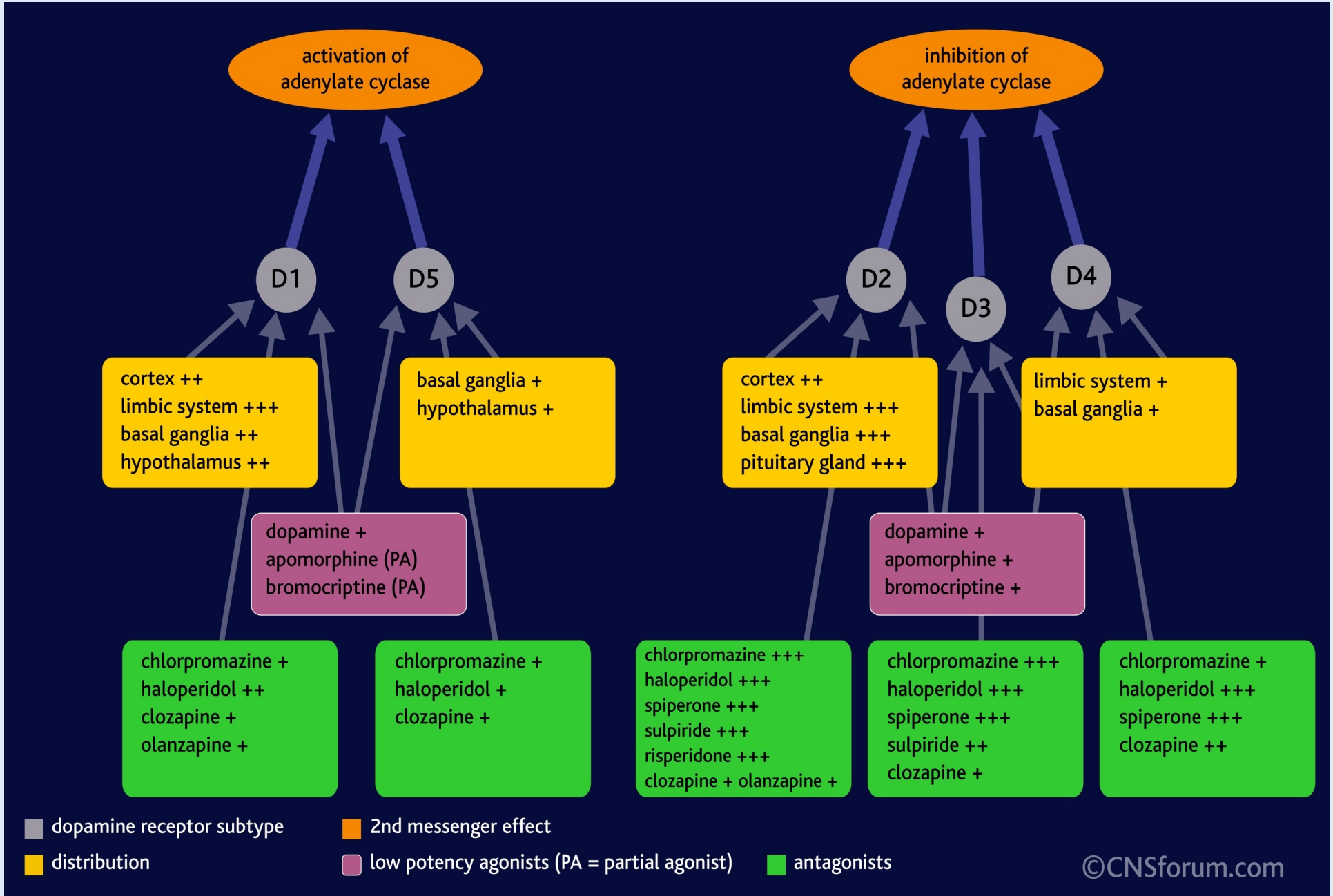
Dopamine receptors

D1-like - Gαs coupled		D2-like - Gαi/o coupled		
D1	**D5**	**D2**	**D3**	**D4**
Substantia nigra Nucleus accumbens Olfactory bulb Lower levels: Cerebellum Hippocampus Thalamus Kidney	Substantia nigra Hypothalamus Kidney Heart Sympathetic ganglia	Substantia nigra Nucleus accumbens Ventral tegemental area Lower levels: Heart Blood vessels Adrenal glands Sympathetic ganglia	Olfactory bulb Nucleus accumbens	Heart Blood vessels Substantia nigra Hippocampus Amygdala Gastrointestinal tract

Fig. 1. Dopamine receptors are G protein-coupled receptors, which are divided into the D_1- and D_2-like families. Some tissues of interest where these receptors are expressed are included here.

https://doi.org/10.1124/jpet.119.256818
J Pharmacol Exp Ther 370:111–126, July 2019

Dopamine Receptor Subtypes & Direct Acting Agonists



Pharmacologic & Pharmacokinetic Properties of Dopamine-Agonists

	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Type of compound	**Ergot derivate**	**Ergot derivate**	Non-ergoline	Non-ergoline
Receptor specificity	D_2, D_1 [a] α_1, α_2, 5-HT	D_2, D_1 α_1, α_2, 5-HT, β	D_2, D_3, D_4 α_2	D_2, D_3, D_4
Bioavailability	8%	20%	> 90%	55% (1st-pass metabolism)
Tmax (min)	70 – 100	60 – 120	60 – 180	90
Protein binding	90 – 96%	90%	15%	40%
Elimination route	Metabolic (hepatic)	Metabolic (hepatic)	**Renal**	Metabolic (hepatic)
Half-life (hr)	3 – 8	27	8 – 12	6

[a] Antagonist

Adapted form Applied Therapeutics: The Clinical Use of Drugs, 8th ed., 2005

	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.

Table 1: **Pharmacological properties of the dopamine agonists**

Effective equivalent doses of the major dopamine receptor agonists

Table 4 Equivalent doses of dopamine agonists

DA-agonists	Equivalent doses (mg)
Apomorphine	2
Bromocriptine	10
Cabergoline	1.5–2
Pergolide	1
Pramipexolo	1
Ropinirolo	5

Bromocriptine (D_2/D_3, D_1)

Efficacy: Efficacious in advanced disease as add-on therapy; probably efficacious in the monotherapy of early disease

Marketed preparations:

Bromocriptina Dorom 5 mg tablets (Dorom)
Bromocriptina Dorom 10 mg tablets (Dorom)
Parlodel 2.5 mg tablets (Novartis Farma)
Parlodel 5 mg tablets (Novartis Farma)
Parlodel 10 mg tablets (Novartis Farma)

Posology: Average efficacious dose: 15–30 mg/day (or more)

Diidroergocriptine (D_2, D_1)

Efficacy: Probably efficacious as monotherapy and an add-on.

Marketed preparations:

Daverium 20 mg tablets (Monsanto)

Posology: 10–120 mg/day (average efficacious dose: 60 mg/day).

Cabergoline (D_2/D_3, alpha)

Efficacy: Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

Marketed preparations:

Cabaser 1 mg tablets (Pharmacia & Upjohn)
Cabaser 2 mg tablets (Pharmacia & Upjohn)

Posology: 2–6 mg/day (average efficacious dose: 4 mg/day).

Lisuride ($D_2/D_3/D_4$, alpha)

Efficacy: Probably efficacious as monotherapy; efficacious as an add-on.

Marketed preparations:

Dopergin 0.2 mg tablets (Farmades)
Dopergin 0.5 mg tablets (Farmades)
Dopergin 1 mg tablets (Farmades)

Posology: 0.6–5 mg/day (average efficacious dose: 1–2 mg/day)

Pergolide (D_2/D_3, D_1/D_4, alpha)

Efficacy: Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

Marketed preparations:

Nopar 0.05 mg tablets (Eli Lilly)
Nopar 0.25 mg tablets (Eli Lilly)
Nopar 1 mg tablets (Eli Lilly)
Nopar Starter (Eli Lilly)

Posology: 1.5–4.5 mg/day (average efficacious dose: 3 mg/day.

Pramipexole (D_3, D_2/D_4)

Efficacy: Efficacious as monotherapy in early disease, and as add-on therapy in advanced disease.

Marketed preparations:

Mirapexin 0.18 mg tablets (equal to 0.25 mg of pramipexolo) (Pharmacia & Upjohn)

Mirapexin 0.7 mg tablets (equal to 1 mg of pramipexolo) (Pharmacia & Upjohn)

Posology: 1.05–3.3 mg/day (equal to 0.375–4.5 mg of pramipexolo per day). Lower doses are recommended in patients with reduced renal function.

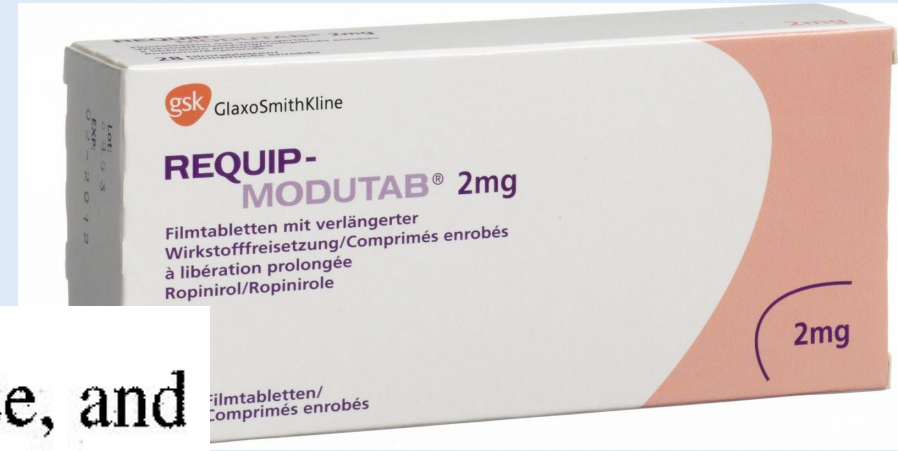
Dopamine agonists

- ***Pramipexole***

The main pharmacokinetics parametres

- Peak Plasma Time: 2 hr (IR); 6 hr (ER),
- Bioavailability: >90%.
- Protein Bound: 15%/
- Vd: 500 L.
- Metabolism <10%.
- Half-Life: 8 hr (12 hr in elderly)/
- Excretion: urine 90%.

Ropinirole ($D_3 > D_2 > D_4$)



Efficacy: Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

Marketed preparations:

Requip 0.25 mg tablets (Glaxo SmithKline)
Requip 0.5 mg tablets (Glaxo SmithKline)
Requip 1 mg tablets (Glaxo SmithKline)
Requip 2 mg tablets (Glaxo SmithKline)
Requip 5 mg tablets (Glaxo SmithKline)

Posology: 3–9 mg/day; maximum dose: 24 mg/day.

Dopamine Direct Acting Agonists – Adverse Effects

Adverse effect	Bromocriptine	Lisuride	Pergolide	Piribedil	Cabergoline	Pramipexole	Ropinirole
Dopaminergic effects							
Central							
Drowsiness, yawning, sedation, confusion, psychosis, hallucinations, dyskinesias, headache	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peripheral							
Hypoprolactinaemia, nausea, vomiting, orthostatic hypotension,[a] cardiac arrhythmias	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other effects							
Constipation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pleural effusion, erythromelalgia, pulmonary fibrosis, retroperitoneal fibrosis	Yes	Yes	Yes	No	Yes	No	No

a Mixed, central and peripheral.

https://link.springer.com/article/10.2165/00023210-200014060-00003/figures/Tab2

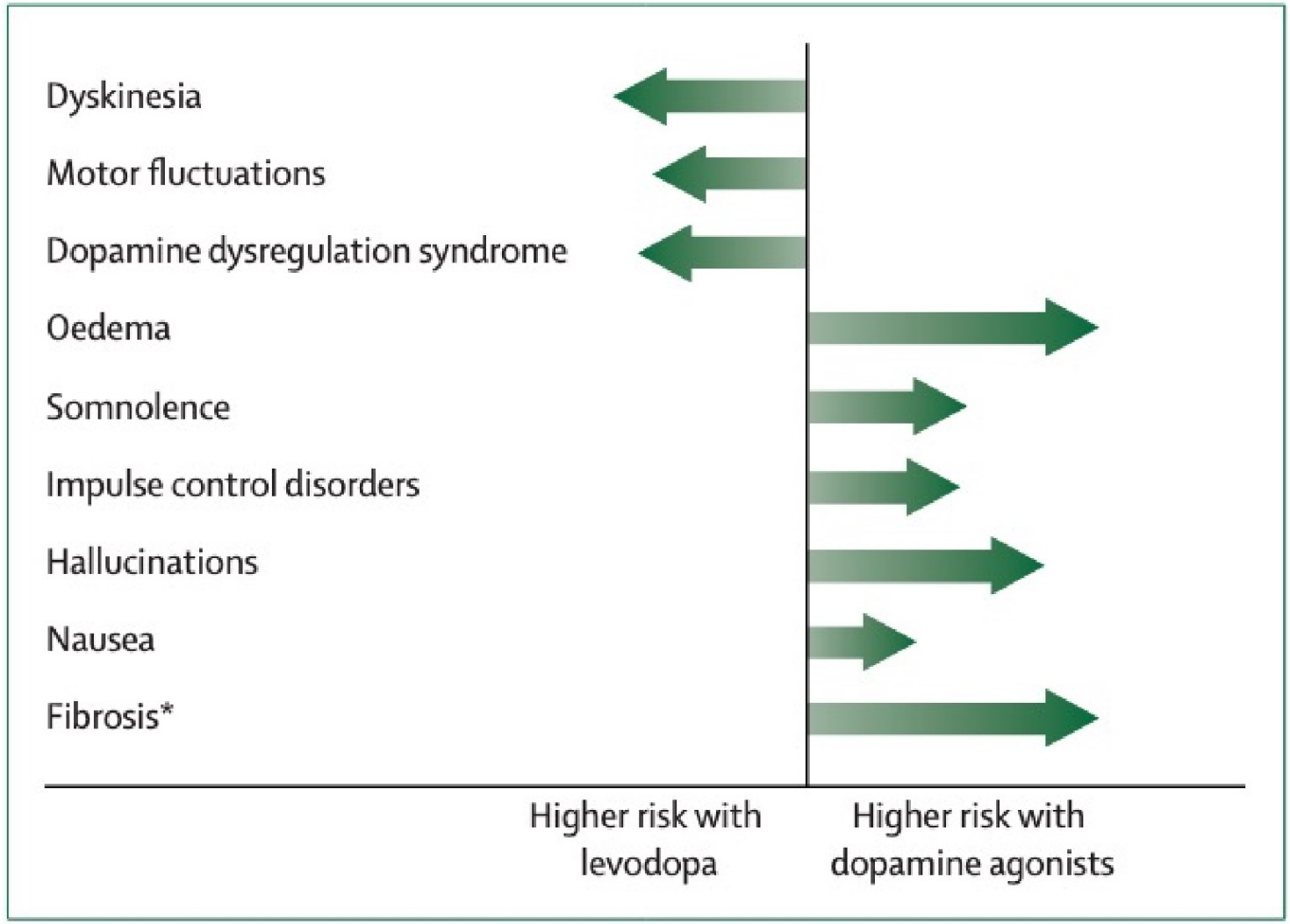


Figure: **Risk of motor complications and other adverse events with dopamine agonists versus levodopa**

The length of the arrows indicates the relative extent of risk. *Ergot agonists *vs* levodopa (see text).

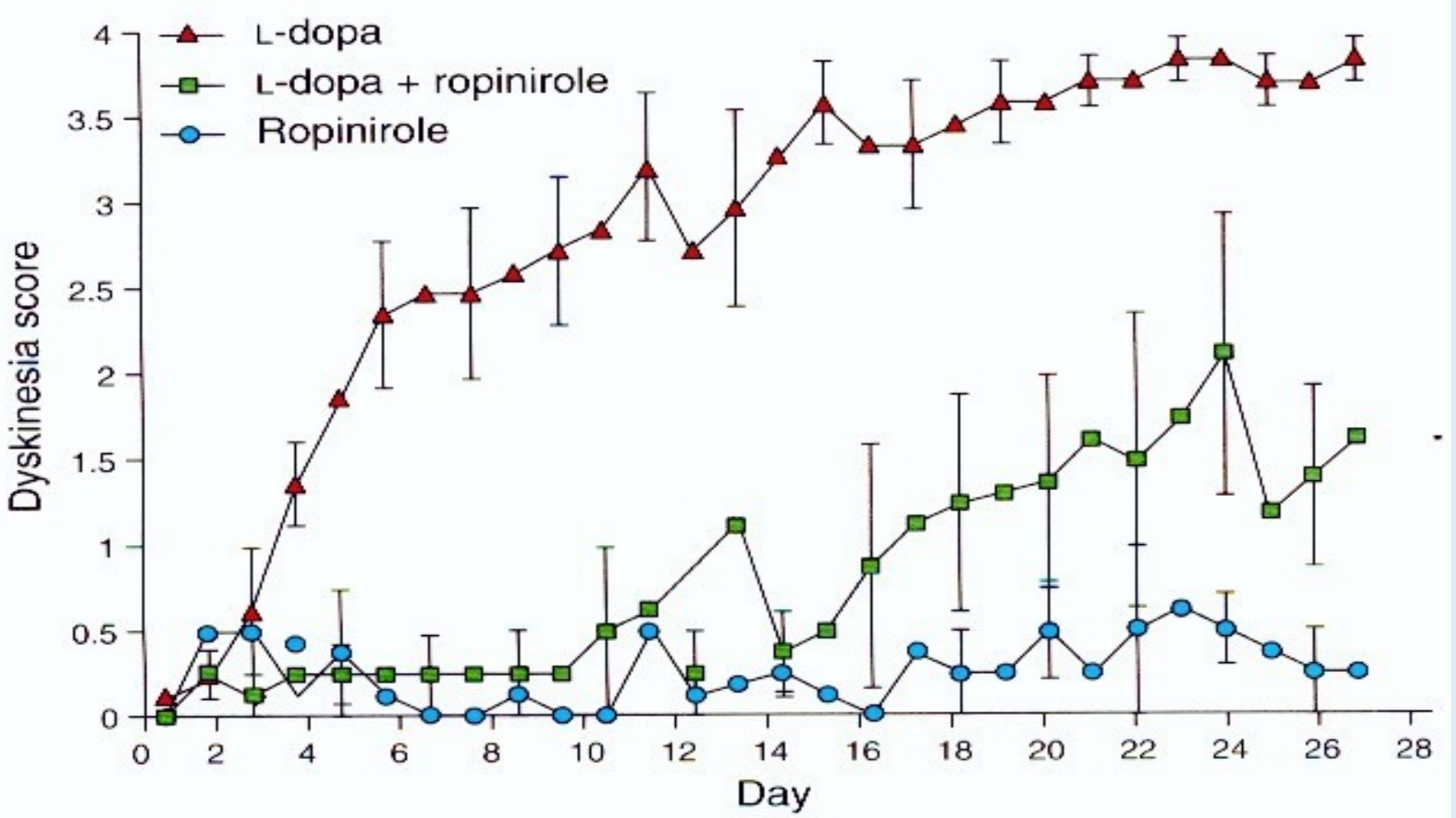


Fig. 1. Dyskinesias in MPTP monkeys. *Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-marmosets treated with L-dopa versus the dopamine-receptor agonist ropinirole, and combined L-dopa plus ropinirole. Note that animals treated with L-dopa have a significantly greater frequency and shorter time to onset of dyskinesia than the agonist-treated animals. The combined treatment group has a lower frequency of dyskinesia than the L-dopa monotherapy group, but a greater frequency than the ropinirole monotherapy group. Behavioral effects were comparable in all groups.* Reproduced courtesy of E. Maratos and P. Jenner.

Apomorphine (D_1/D_2, D_3/D_4, alpha)

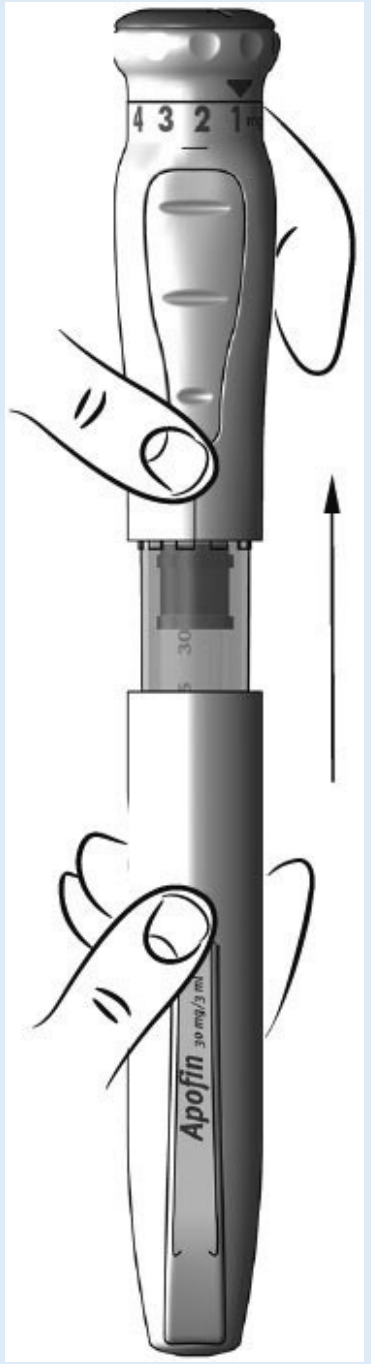
Efficacy: Probably efficacious in advanced disease.

Marketed preparations:

Apofin Stylo 3 ml 1% s.c. (Penject) (Chiesi Farmaceutici)

Apofin 5 ml 1% s.c. (Chiesi Farmaceutici)

Posology: Continuous s.c. infusion: 1–7 mg/hour for 12 hours (but in any case to be individualised). Penject: additional "as needed" dose of 2–6 mg.



Apomorphine Hydrochloride Injection (APOKYN®)

Available Doses: 30 mg/3 ml vial

Typical Treatment Regimen: .2 mL during "off" periods

Side Effects*: Low blood pressure, nausea, leg swelling and discoloration, confusion, sleep attacks, compulsive behaviors like gambling. May receive antinausea medication daily for 3 days before starting medication

Indications: Adjunct therapy as needed for OFF periods. It is the only injectable, fast-acting dopaminergic drug, starts working in 10 minutes and lasts for 90 minutes

Apomorphine hydrochloride (KYNMOBI™)

Available Doses: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg sublingual film

Typical Treatment Regimen: One 10mg film placed under the tongue as needed, up to five doses per day, separated by at least 2 hours. These films are similar in appearance to breath freshening strips. However, these are placed under the tongue rather than on top.

Side Effects*: nausea, oral/pharyngeal soft tissue swelling, oral/pharyngeal soft tissue pain and numbness, dizziness, and sleepiness. May receive anti-nausea medication daily for 3 days before starting medication

Indications: for the acute, intermittent treatment of "off" episodes in Parkinson's disease. It is the only sublingual therapy approved for the on-demand treatment of Parkinson's disease OFF episodes.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Dopamine-Agonists

Dopamine agonists

- ***Apomorphine.*** Initial: 2 mg (0.2 mL) SC

The main pharmacokinetics parametres

- Peak Plasma Time:10-60 min.
- Half-life, elimination: 30-60 min.
- Vd: 218 L.
- Metabolism: hepatic metabolism.
- Excretion: Urine (93%); feces (16%).

Dopamine agonists

- ***Rotigotine***

The main pharmacokinetics parametres

- Bioavailability: 37%.
- Peak plasma time: 15-18 hr.
- Protein Bound: 92% (in vitro); 89.5% (in vivo).
- Vd: 84 L/kg.
- Metabolism: hepatic.
- Half-life, biphasic: 3 hr (initial); 5-7 hr (terminal).
- Excretion: 71% urine; 23% feces.

Rotigotine
Transdermal Preparation

Problems with local crystallization of Rotigotine and local reactions, limit its use

Rotigotine Transdermal System (Neupro®)

Available Doses: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patch

Typical Treatment Regimen: 4–8 mg once/day

Side Effects*: Low blood pressure, nausea, leg swelling and discoloration, confusion, sleep attacks, compulsive behaviors like gambling, skin rashes

Indications: Monotherapy or combination therapy for slowness, stiffness and tremor; skin patch delivery is an advantage for some

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Dopamine-Agonists

Non motor complications associated to DA replacement therapy in PD

DA dysregulation syndrome

Hypersexuality

Euphoria and hypomania

Punding

Pathological shopping

Pathological Gambling

Impulse control disorders and dopamine dysregulation syndrome associated with dopamine agonist therapy in Parkinson's disease
Sandro Fenu, Jadwiga Wardas and Micaela Morelli
Behav Pharmacol. 2009 Sep;20(5-6):363-79

Table 4 **Nonmotor symptoms in PD**

Sensory symptoms	Hyposmia
	Pain
Autonomic dysfunction	Orthostatic hypotension
	Neurogenetic bladder disturbance
	Erectile dysfunction
	Constipation
Neuropsychiatric symptoms	Anhedonia
	Apathy
	Anxiety
	Depression
	Bradyphrenia
	Frontal executive dysfunction
	Dementia
	Psychosis
Sleep disorders	Sleep fragmentation
	Reduced sleep efficiency
	Reduced slow-wave sleep
	Reduced REM sleep
	RBD
	Excessive daytime sleepiness
	Nocturnal akinesia/tremor
	RLS/PLMS

REM, rapid eye movement; RBD, REM sleep behavior disorder; RLS, restless leg syndrome; PLMS, periodic limb movement disorder.

Sites of Action of Various Parkinson's Disease Therapies

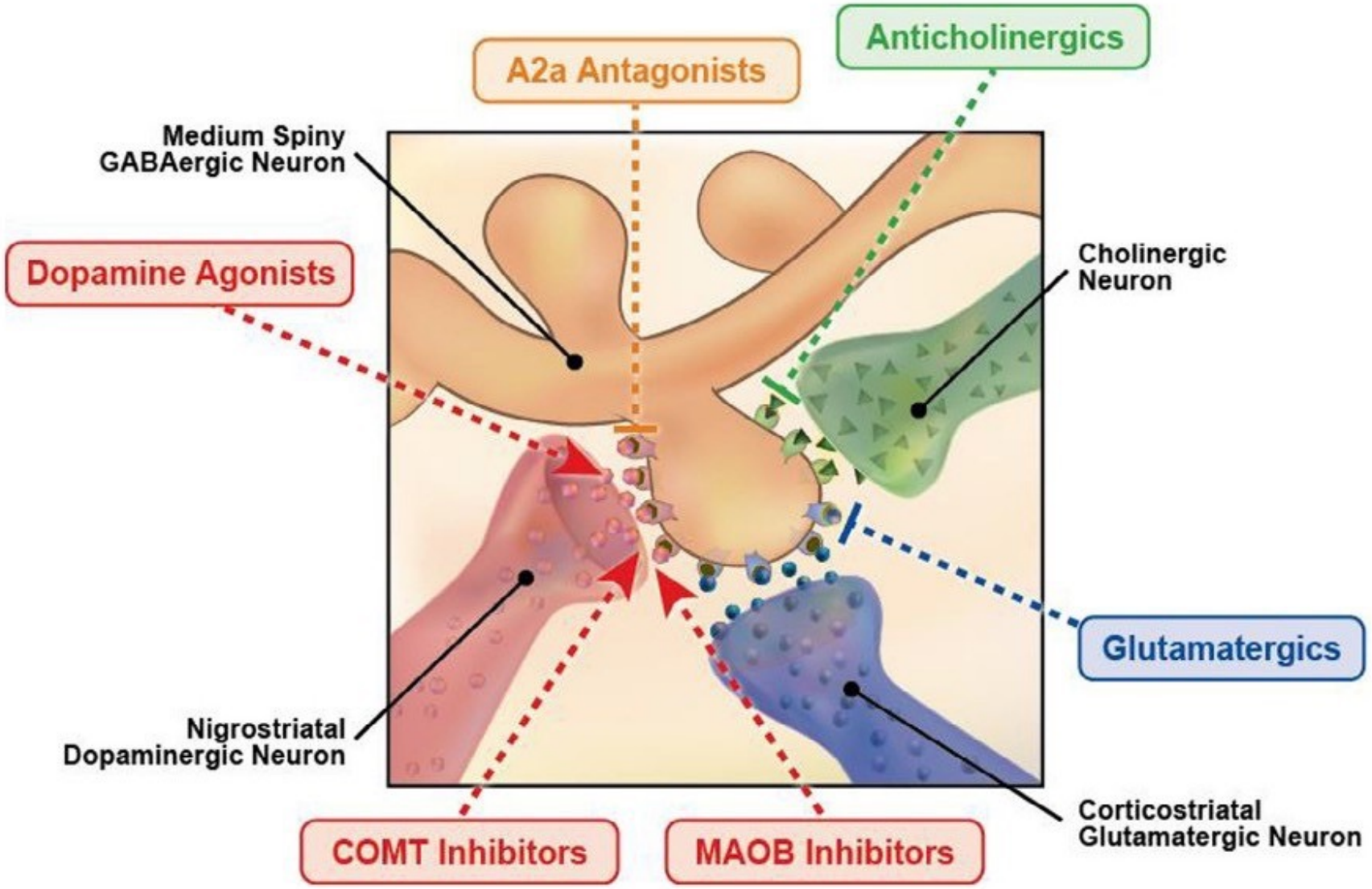


Fig. 1. Schematic of various methods for PD treatment.

Bioorganic & Medicinal Chemistry Letters 27 (2017) 4247–4255

Anticholinergics

Anticholinergics

(tremor, muscular rigidity)

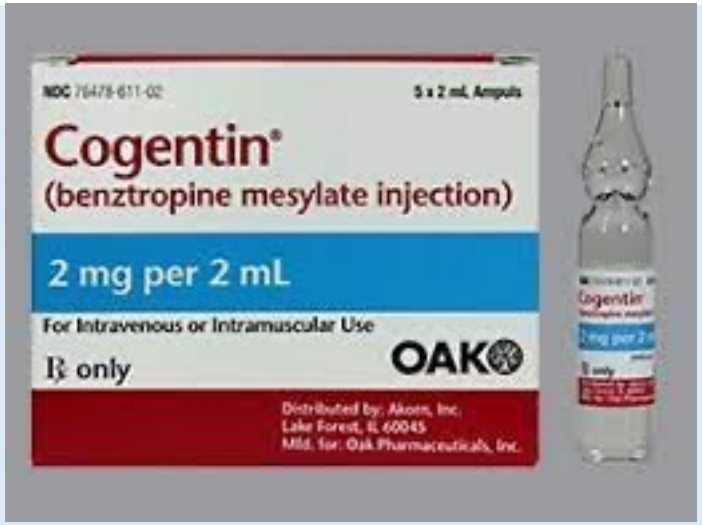
Benztropine (Cogentin®)

Available Doses: 0.5 mg, 1 mg, 2 mg

Typical Treatment Regimen: 0.5–2 mg 2-3 times/day

Side Effects: Confusion, memory issues, hallucinations, dry mouth, blurry vision, urinary retention

Indications: Monotherapy or combination therapy, predominantly for tremor and dystonia in younger people; should be avoided in elderly. Can also be helpful in reducing the amount of saliva to treat excessive drooling due to the side effect of dry mouth.



https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Anticholinergic-Drugs

Trihexyphenidyl HCL (formerly Artane®)

Available Doses: 2 mg, 5 mg tablets. 2 mg/5 ml elixir

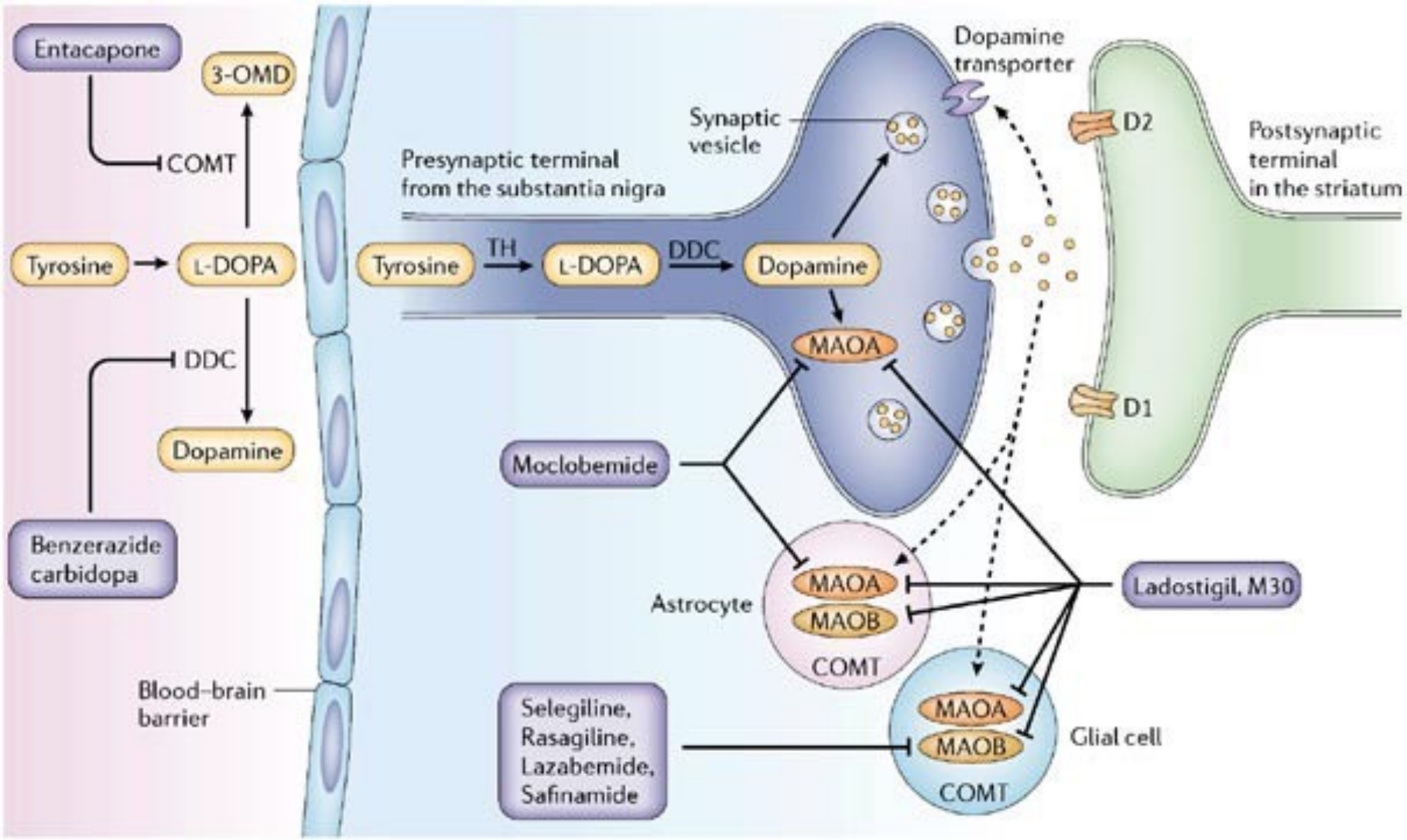
Typical treatment regimen: 1–2 mg 2-3 times/day

Side Effects: Confusion, memory issues, hallucinations, dry mouth, blurry vision, urinary retention

Indications: Monotherapy or combination therapy, predominantly for tremor and dystonia in younger people; should be avoided in elderly. Can also be helpful in reducing the amount of saliva to treat excessive drooling due to the side effect of dry mouth.

MAO and COMT Inhibitors

MAO and COMT Inhibitors



MAO Inhibitors

- **Selegiline**
- **Rasagiline**
- **Safinamide**

- MAO-B enzymes naturally break down and block several chemicals in the brain, including dopamine
- MAO-B inhibitors prevent the break down of dopamine, making dopamine more available
- Provide modest benefit for the motor features of PD
- Usually used early in the disease as monotherapy or as an adjunct (add-on) to other medications
- When used together with other medications, MAO-B inhibitors may reduce "off" time and extend "on" time

Common Side Effects of MAO-B Inhibitors

- Mild nausea
- Dry mouth
- Lightheadedness
- Constipation
- Confusion (can occur in elderly people with PD)
- Hallucinations (can occur in elderly people with PD)

Taking some MAO-B inhibitors with the heavy consumption (greater than 150 mg/day) of foods high in tyramine carries a risk of raising blood pressure to dangerous levels. These foods are typically aged or fermented, and can include things like cheeses, dried or cured meats, fava beans, beer, sauerkraut, and soybeans. This is more of a risk with non-selective MAO-B inhibitors not used to treat Parkinson's disease.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/MAO-B-Inhibitors

Selegiline

Efficacy: Probably efficacious

Marketed preparations:

Jumex 10 mg tablets (Chiesi Farmaceutici)

Jumex 5 mg tablets (Chiesi Farmaceutici)

Posology: 10 mg/day

COMT Inhibitors

- **Entacapone**
- **Opicapone**
- **Tolcapone ***

- Only effective when used in combination with levodopa
- When taking levodopa, an enzyme in the body call catechol-O-methyl transferase (COMT) deactivates levodopa in the body before it is absorbed into the bloodstream; COMT inhibitors prevent this from happening

Common Side Effects of COMT Inhibitors

- May exaggerate some levodopa-related side effects especially dyskinesia
- Confusion
- Hallucinations
- Discoloration of urine (reddish brown or rust-colored)
- Diarrhea

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/COMT-Inhibitors

Entacapone

Efficacy: Efficacious on wearing-off phenomena

Marketed preparations:

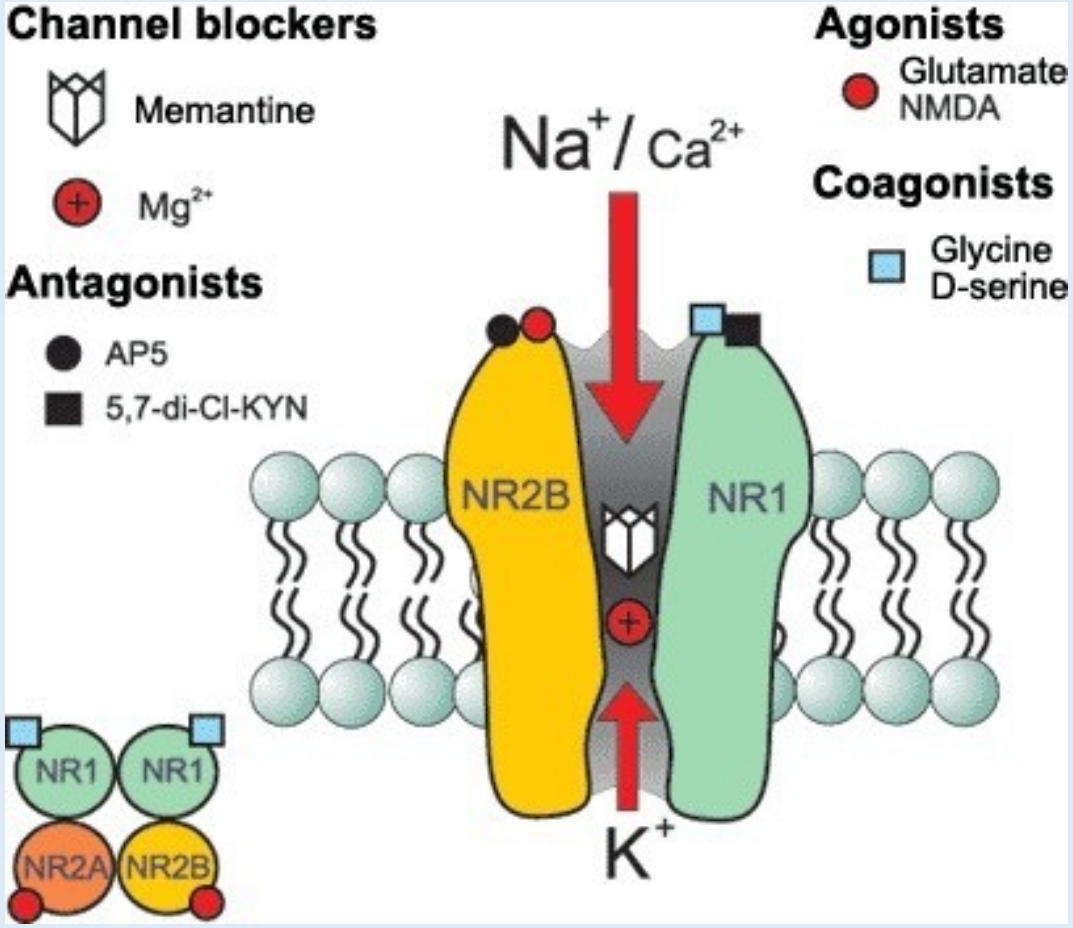
Comtan 200 mg tablets (Novartis Farma)

Posology: 200 mg with every L-dopa administration

Glutamate Antagonists

Glutamate Antagonists

- **Amantadine**
  (NMDA-R, DA release-reuptake)
- **Memantine**
  (NMDA)
- **Budipine**
  (NMDA-R, DA release, MAO-B, M-R)



Amantadine

Efficacy: Probably efficacious in early and advanced disease; efficacious on L-dopa induced dyskinesias.

Marketed preparations:

Mantadan 100 mg tablets (Boehringer Ingelheim)

Posology: 200 mg/day.

Common Side Effects

- Dizziness
- Low Blood Pressure
- Nausea
- Insomnia
- Confusion
- Paranoia
- Hallucinations
- Leg discoloration

Uncommon Side Effects

- Urinary retention
- Livedo reticularis: a lacey, purplish discoloration of the skin on the legs with some leg swelling. **Occurs in less than 1 percent of people with PD who take this medication.**

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Amantadine-Symmetrel

New Therapies under development for PD

-> To modify disease

Table 1 | **Non-dopaminergic therapies currently in development for PD modification**

Compound and/or agent, company	Mechanism of action	Phase of development	Clinical trial number	Refs
AXO-LENTI-PD (OXB-102; ProSavin analogue with increased level of transgene expression), Oxford BioMedica and Axovant Sciences	Triple gene therapy (Lenti-*TH*–*AADC*–*GTPCH*) to restore striatal dopamine production	Phase I/IIa in preparation	ProSavin: • NCT01856439 • NCT00627588	76,77, 79,80
VY-AADC, Voyager Therapeutics	Gene therapy (AAV2–h*AADC*) to restore striatal dopamine production	Pivotal phase II/III ongoing	• NCT01973543 • NCT03065192 • NCT03562494	81–85
PRX002 (RO7046015), ProThena and Roche	Passive immunotherapy targeting α-synuclein	Phase II ongoing	NCT03100149	88–91
PD01A and PD03A, Affiris	Active immunotherapy targeting α-synuclein	Phase I completed	• NCT01885494 • NCT01568099 • NCT02216188 • NCT02618941 • NCT02267434	88,92–94
BIIB054, Biogen and Neurimmune	Passive immunotherapy targeting aggregated α-synuclein	Phase II ongoing	NCT03318523	95,96
NPT200-11, UCB and Neuropore Therapies	α-Synuclein aggregation modulator	Phase I completed	NCT02606682	98
Ambroxol, Lawson Health Research Institute and Van Andel Research Institute	Increase glucocerebrosidase activity	Phase II in preparation	• NCT02941822 • NCT02941822	120,122
LTI-291, Allergan and Lysosomal Therapeutics	Glucocerebrosidase activator	Phase II ongoing	NTR6960 (EudraCT 2017-004086-27)	123
Venglustat (GZ/SAR402671), Sanofi and Genzyme	Glucosylceramide synthase inhibitor in patients with PD carrying a *GBA* mutation	Phase IIa ongoing	NCT02906020	124
Deferiprone, ApoPharma	Iron chelator	Phase II ongoing	• NCT02655315 • NCT02728843	130
Exenatide, National Institute of Neurological Disorders and Stroke	GLP1 agonist	Phase I ongoing	NCT03456687	39,133
Liraglutide, The Cure Parkinson's Trust and Novo Nordisk	GLP1 agonist	Phase II ongoing	NCT02953665	240
DNL151 (backup of DNL201), Denali Therapeutics	LRRK2 inhibitor	Phase I ongoing	NA	141
KM-819 (KR33493), Kainos Medicine	FAF1 inhibitor to protect dopaminergic neurons from apoptosis	Phase I ongoing	NCT03022799	144

AAV2, adeno-associated virus type 2; FAF1, Fas-associated factor 1; GLP1, glucagon-like peptide 1; Lenti, lentiviral vector; LRRK2, leucine-rich repeat serine/threonine-protein kinase 2; NA, not available; PD, Parkinson disease.

New Therapies under development for PD

-> To treat symptoms

Table 2 | **Non-dopaminergic therapies currently in development for the symptomatic treatment of PD**

Compound and/or agent, company	Mechanism of action	Phase of development	Clinical trial number	Refs
Motor fluctuations				
Istradefylline (KW-6002), Kyowa Hakko Kirin Pharma	Adenosine receptor type 2A antagonist	• Approved in Japan • Not approved by the FDA in February 2018	• NCT01968031 • NCT02610231	155–159
Dyskinesia				
Amantadine ER (ADS-5102 (Gocovri)), Adamas Pharmaceuticals	NMDA receptor antagonist	• Approved in United States • Phase III ongoing	NCT02136914	183,184
Dipraglurant (ADX48621), Addex Therapeutics	mGlu5 NAM	Phase III in preparation	NCT01336088	189–191
Buspirone, Assistance Publique, Hôpitaux de Paris, Oregon Health and Science University and University of Rochester	5-HT_{1A} and α_1-adrenergic receptor agonist	Phase III ongoing	• NCT02617017 • NCT02803749 • NCT02589340	196,241
Eltoprazine, Amarantus BioScience Holdings	$5\text{-HT}_{1A/1B}$ receptor agonist	Phase IIb in preparation	NCT02439125	197,198
Motor fluctuations and dyskinesia				
Foliglurax (PXT002331), Prexton Therapeutics and Lundbeck	mGlu4 PAM	Phase IIa ongoing	NCT03162874	192–194, 242,243
Other symptoms				
Varenicline (gait and balance, excessive daytime sleepiness), Rush University Medical Center and VU University Medical Center	Partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor	• Phase II ongoing for gait and balance • Phase IV ongoing for sleep	• NCT01341080 • NCT02473562	244,245
Pimavanserin (formerly ACP-103) (psychosis), Acadia Pharmaceuticals	5-HT_{2A} receptor inverse agonist	Approved in United States	• NCT00550238 • NCT01174004 • NCT00477672	215, 246–249
SYN120 (PD dementia), Acorda Therapeutics	$5\text{-HT}_{6/2A}$ receptor antagonist	Phase II ongoing	NCT02258152	250

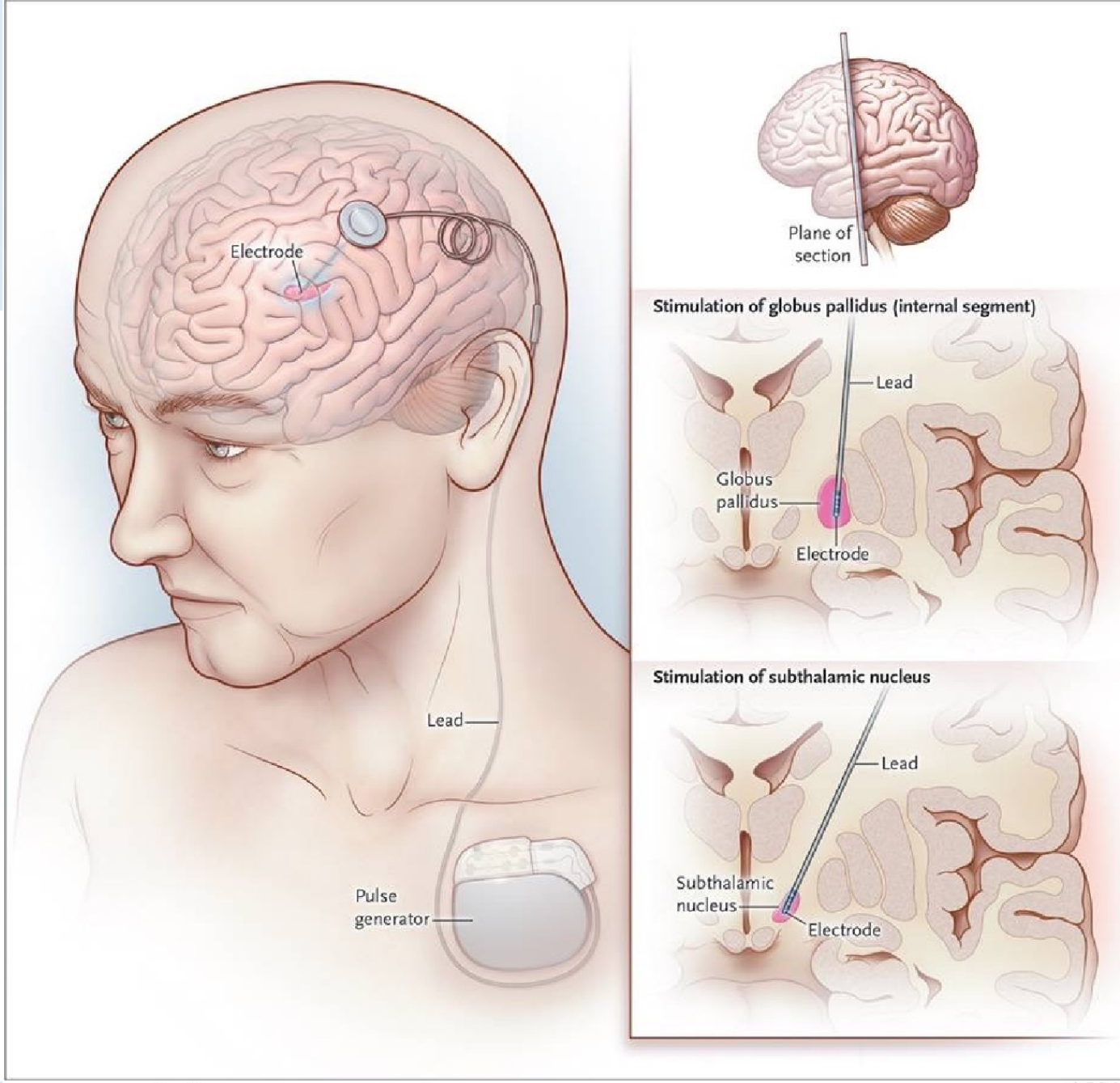
5-HT, serotonin; D_1, dopamine receptor D_1; FDA, US Food and Drug Administration; mGlu, metabotropic glutamate receptor; NAM, negative allosteric modulator; NMDA, *N*-methyl-D-aspartate; PAM, positive allosteric modulator; PD, Parkinson disease.

Surgical treatments

Deep Brain Stimulation (DBS) & Parkinson's Disease

How Deep Brain Stimulation Works

Exactly how DBS works is not completely understood, but many experts believe it **regulates abnormal electrical signaling patterns in the brain**. To control normal movement and other functions, brain cells communicate with each other using electrical signals. In Parkinson's disease, these signals become irregular and uncoordinated, which leads to motor symptoms. DBS may interrupt the irregular signaling patterns so cells can communicate more smoothly and symptoms lessen.

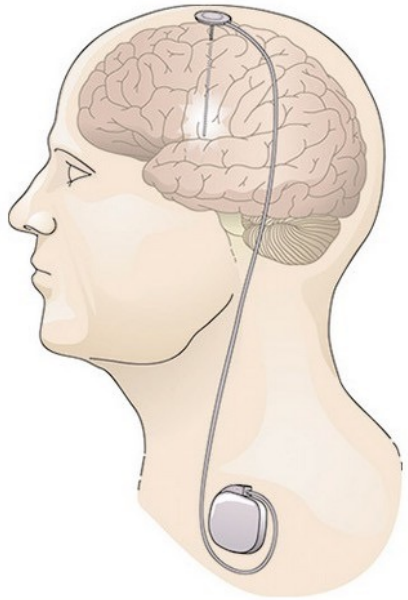


https://www.michaeljfox.org/deep-brain-stimulation

Deep Brain Stimulation (DBS) & Parkinson's Disease

In DBS surgery, electrodes are inserted into a targeted area of the brain, using MRI (magnetic resonance imaging) and recordings of brain cell activity during the procedure. A second procedure is performed to implant an IPG, impulse generator battery (like a pacemaker). The IPG is placed under the collarbone or in the abdomen. The IPG provides an electrical impulse to a part of the brain involved in motor function. Those who undergo DBS surgery are given a controller to turn the device on or off.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Deep-Brain-Stimulation



https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/DBS

DBS typically works best to **lessen motor symptoms of stiffness, slowness and tremor**. It doesn't work as well for imbalance, freezing of gait (sudden inability to move when walking) or non-motor symptoms. As DBS may worsen thinking or memory problems, it's not recommended for people with dementia.

https://www.michaeljfox.org/deep-brain-stimulation