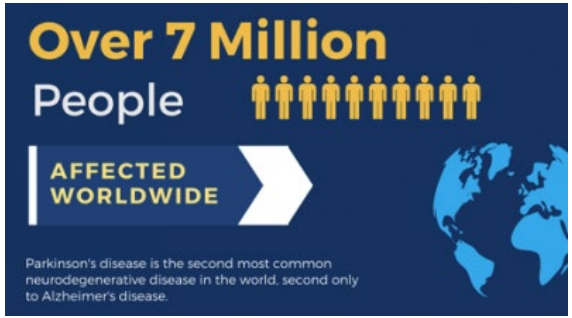
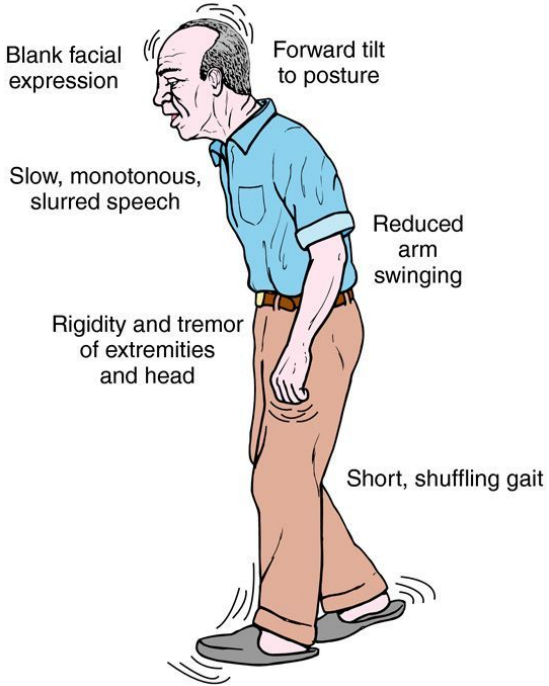
EU Parliament workshop - Parkinson's disease
Brussels 7/11

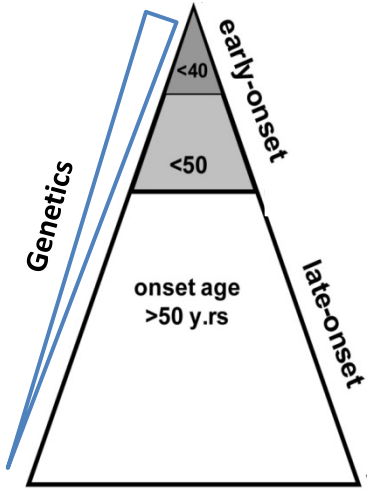
On current treatments of Parkinson’s disease

Per Svenningsson
Karolinska Institutet
Stockholm, Sweden

Parkinson´s disease



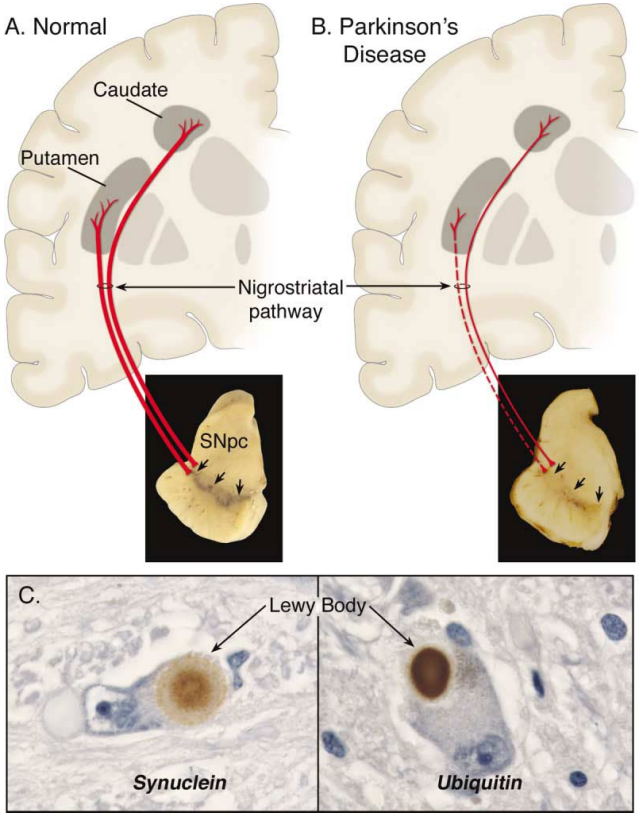




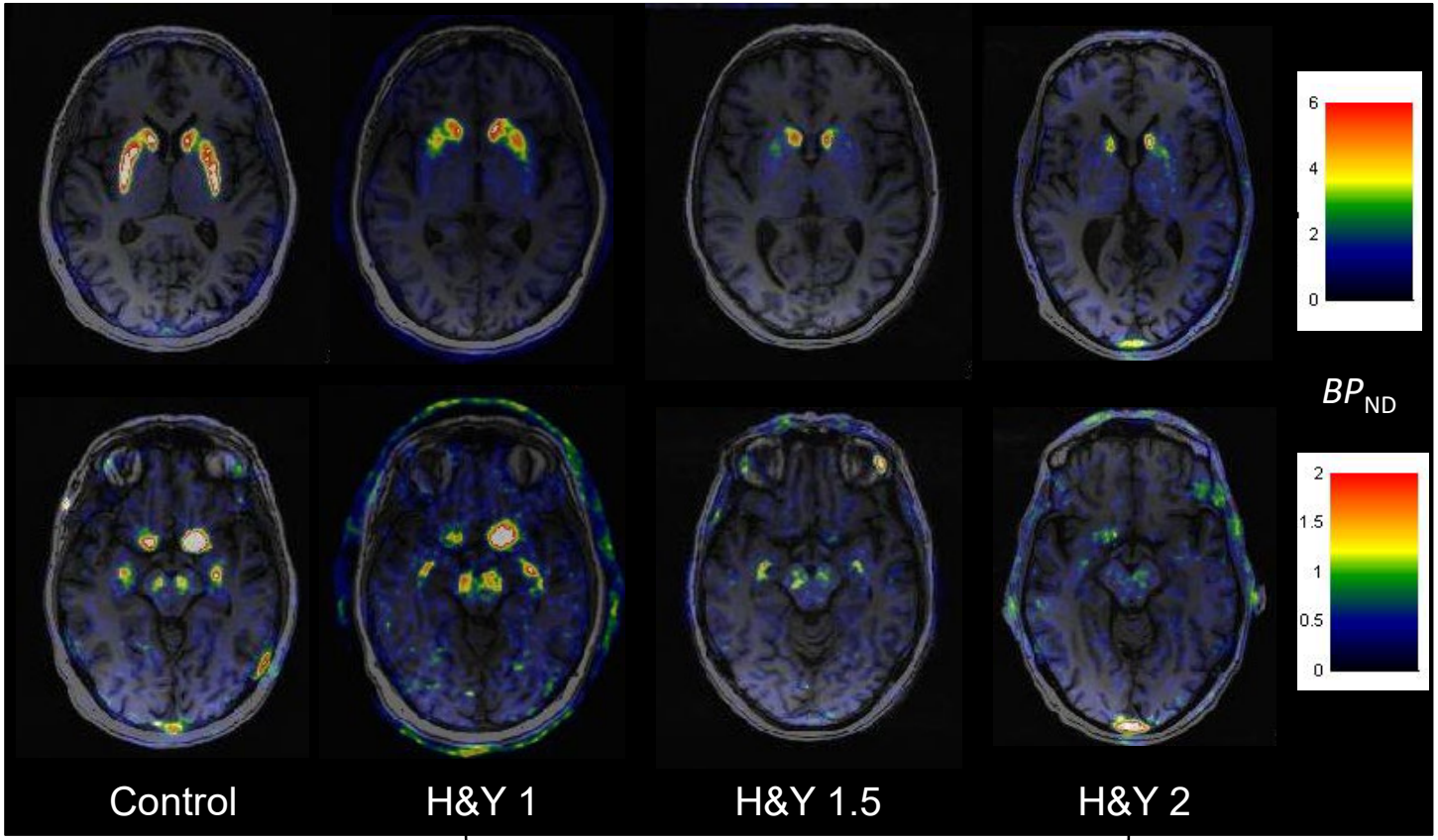
Disease hallmarks in Parkinson´s disease

1. Loss of dopamine neurons

2. Accumulation of Lewy bodies

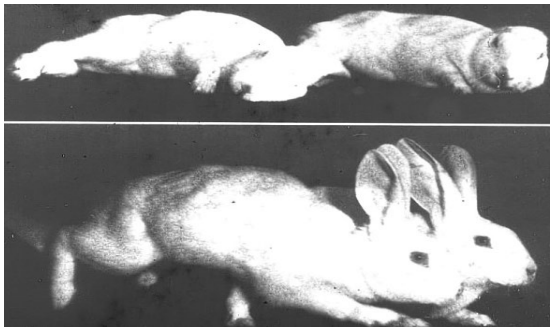


Reduction of dopamine neurons in PD

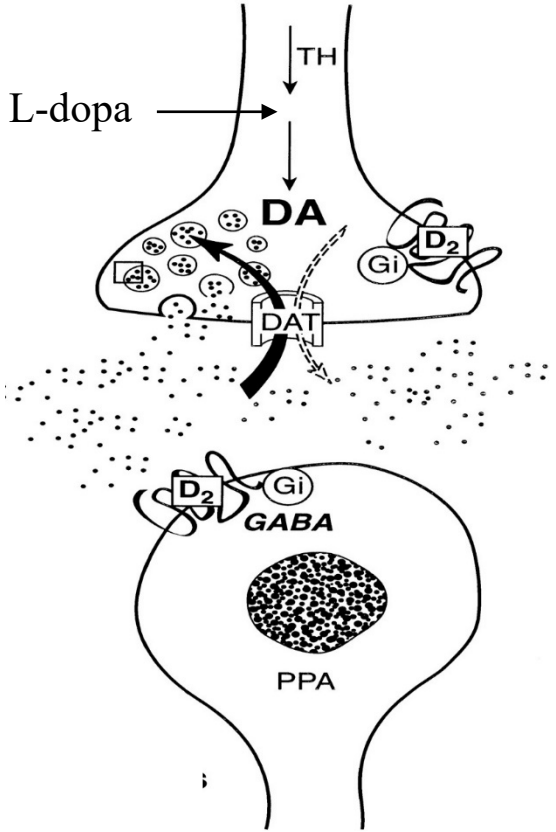


Fazio et al., 2016

Dopamine replacement as therapy in PD

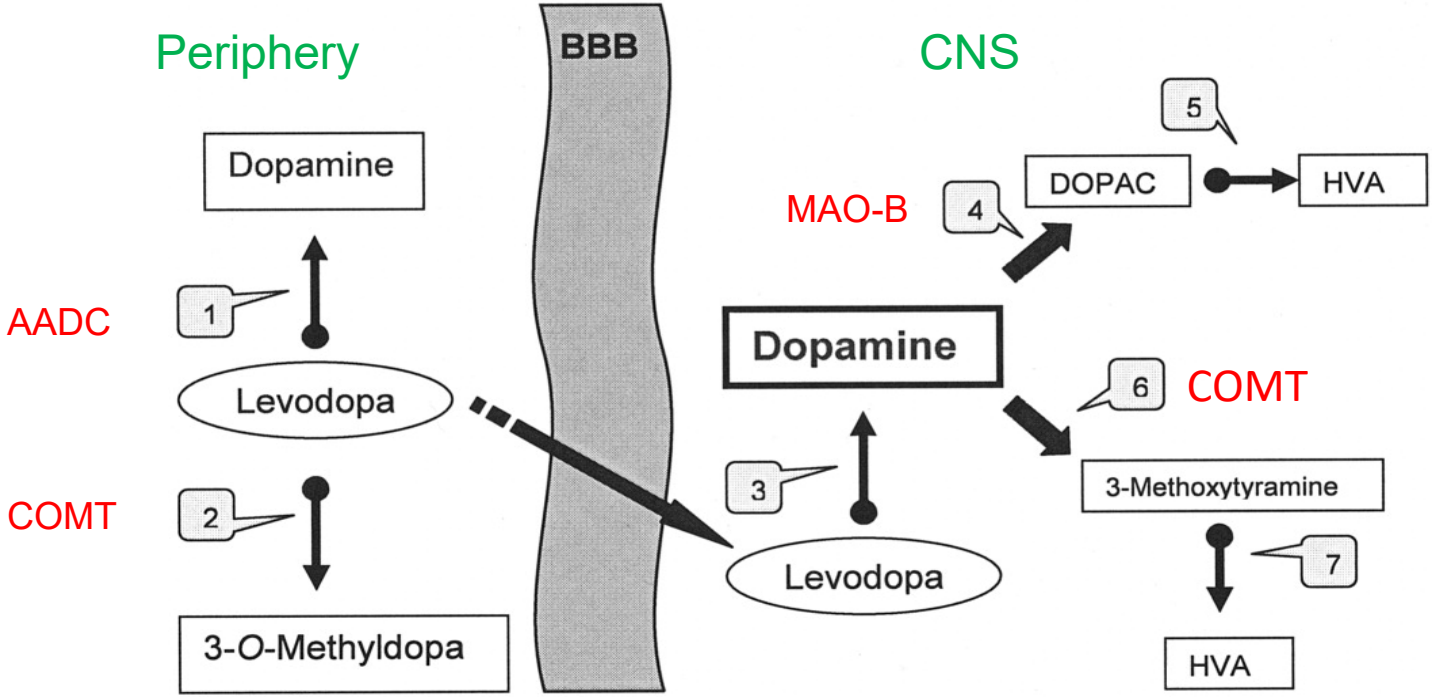


Carlsson et al Nature 1957; 180: 1200



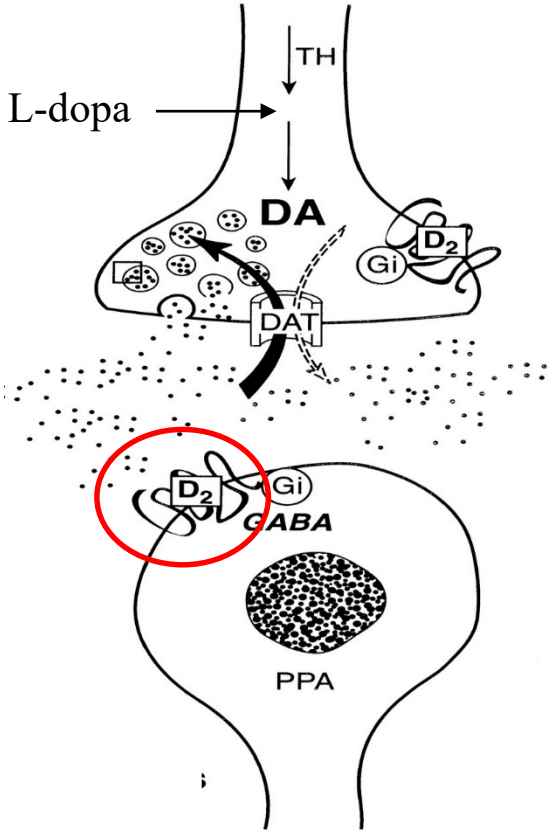

Collage by Per Svenningsson

Metabolism of L-DOPA and dopamine



AADC: L-aromatic amino acid decarboxylase, Peripheral inhibitors:
Carbidopa (Sinemet), Benserazide (Madopark)
COMT: Catechol-O-methyltransferas inhibitors : Entacapone, Tolcapone
MAO-B: Monoamine oxidase B inhibitors : Selegiline, Rasagiline, Safinamide

Dopamine receptor agonists



	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†

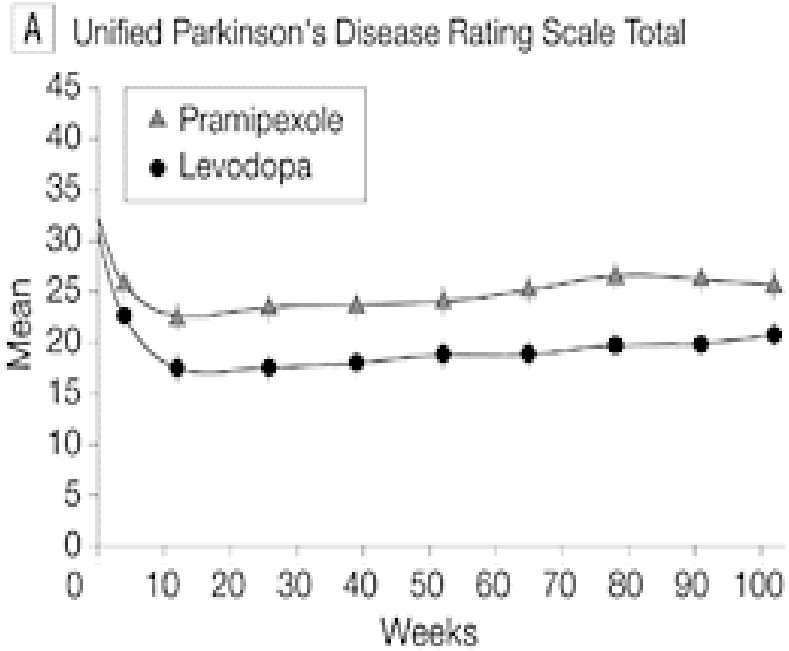
–=no affinity. +=high affinity. +/–=moderate affinity. NE=norepinephrine. *Antagonist. †After transdermal application.

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

Antonini et al Lancet Neurol. 2009;8(10):929-37

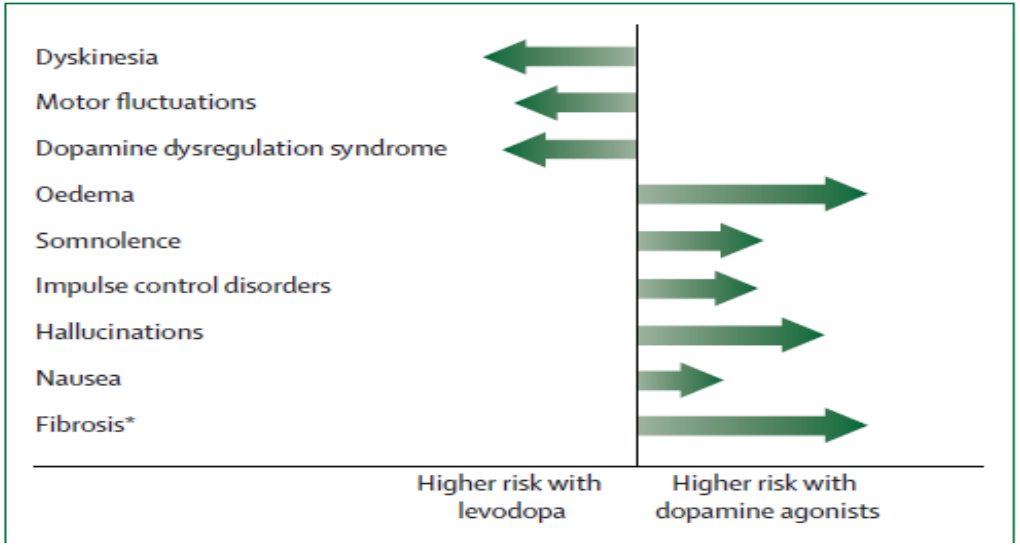
L-DOPA vs Dopamine Agonists

Efficacy



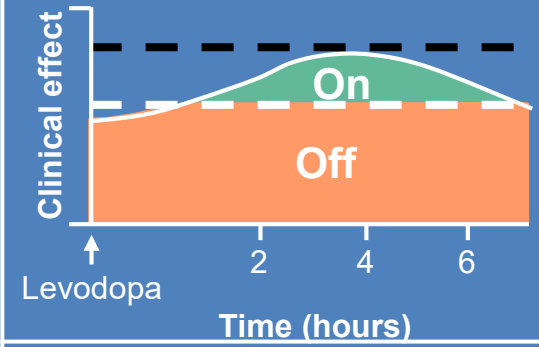
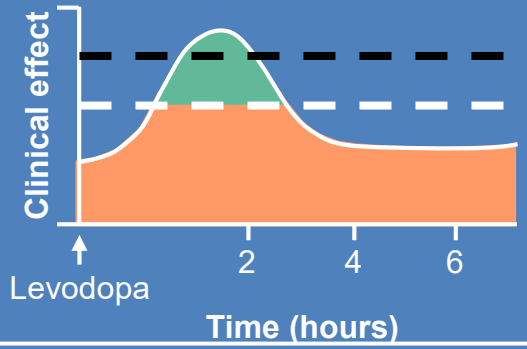
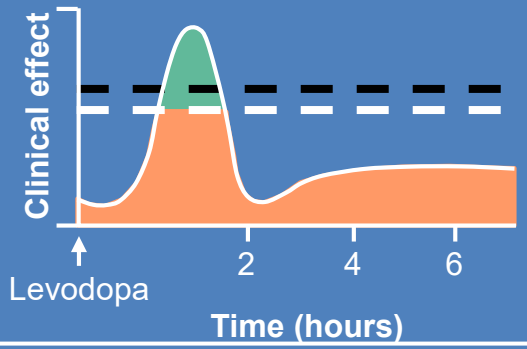
Parkinson Study Group JAMA. 2000;284(15):1931-8.

Side effects



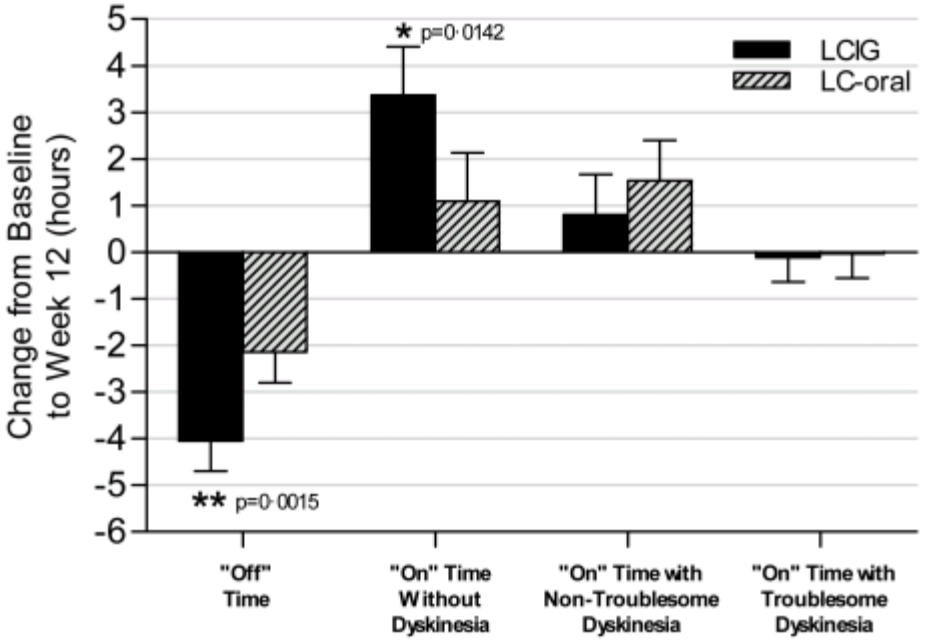
Antonini et al Lancet Neurol. 2009;8(10):929-37

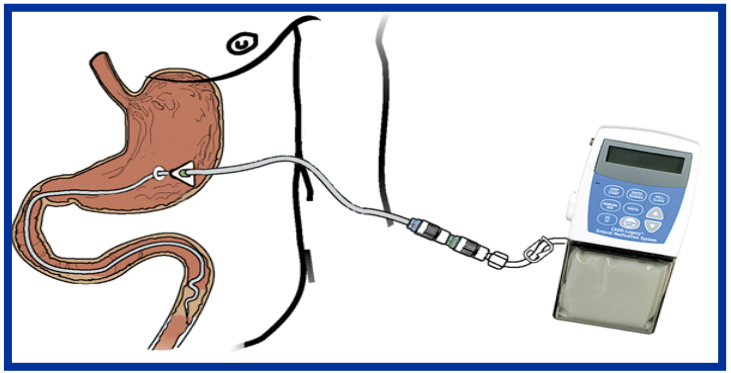
L-DOPA response at different disease stages

Early disease	Mid-stage disease	Advanced disease
		
• Long duration of clinical benefit • Low incidence of dyskinesias	• Diminished duration of clinical benefit • Increased incidence of dyskinesias	• Clinical response mirrors levodopa plasma pharmacokinetic profile • 'On' time is associated with dyskinesias

Obeso et al. Neurology 2000; 55(4 Suppl): S13–20

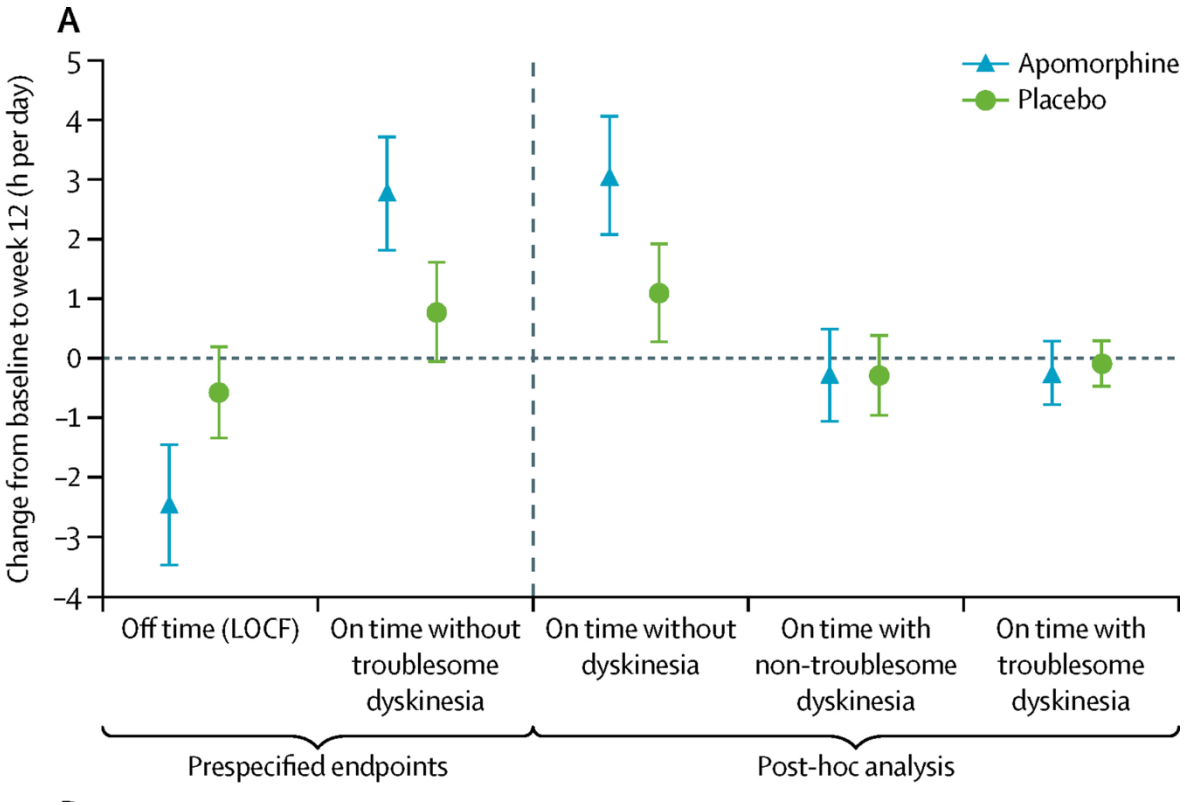
Continuous delivery of levodopa-carbidopa with an intestinal gel

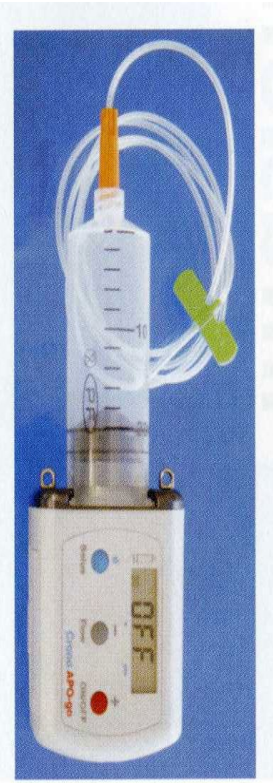




Olanow et al Lancet Neurol. 2014;13(2):141-9

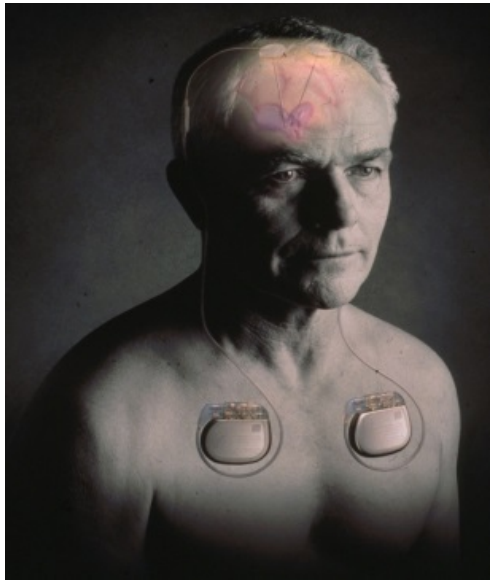
Continuous delivery of apomorphine

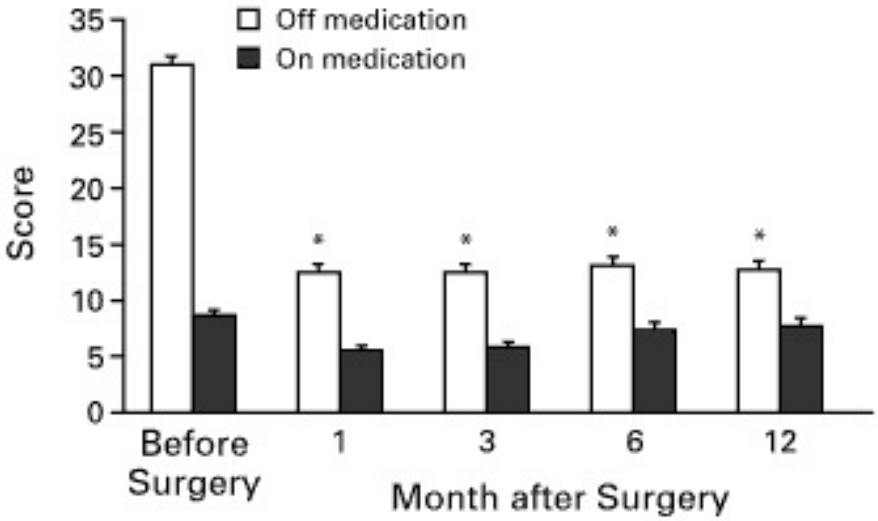




Katzenschlager Lancet Neurol. 2018 Sep;17(9):749-759.

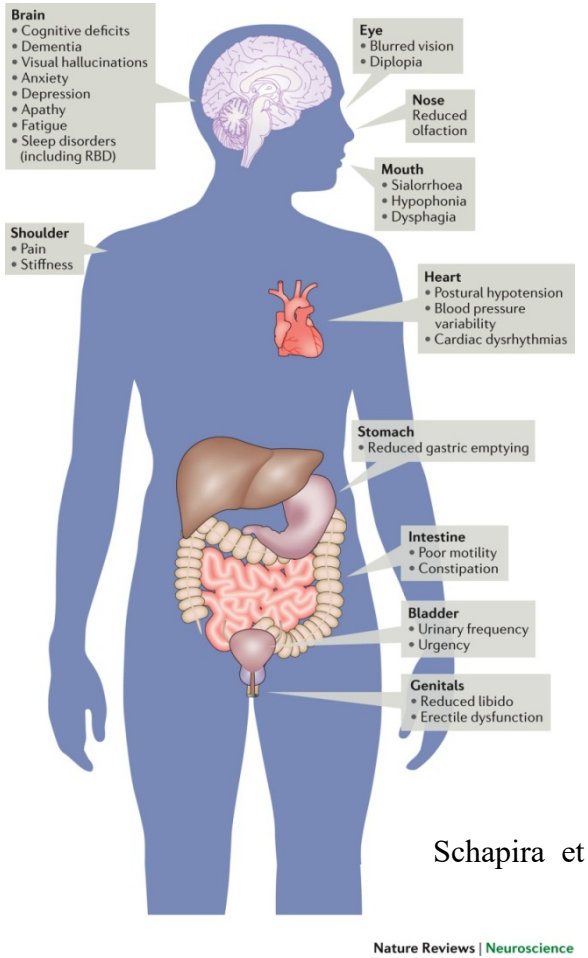
Deep brain stimulation





Limousin et al N Engl J Med 1998 Oct 15;339(16):1105-11.

Non-motor symptoms in PD



Some examples of Therapies

Pimavanserin against PD psychosis

Rivastigmine against PD dementia

Schapira et al Nature Rev Neurosci. 2017;18(7):435-450.

Summary

- Many approved symptomatic therapies against motor symptoms PD

Unmet medical therapy needs in PD

- Therapies against side effects to L-DOPA, primarily wearing off fluctuations and dyskinesias
- Therapies against many non-motor symptoms
- Therapy that slows down disease progression
- Restorative therapies
- Precision medicine therapies

Thank you for your attention