Terapia farmacologica della fase avanzata

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Parkinson disease

NATURE REVIEWS | DISEASE PRIMERS
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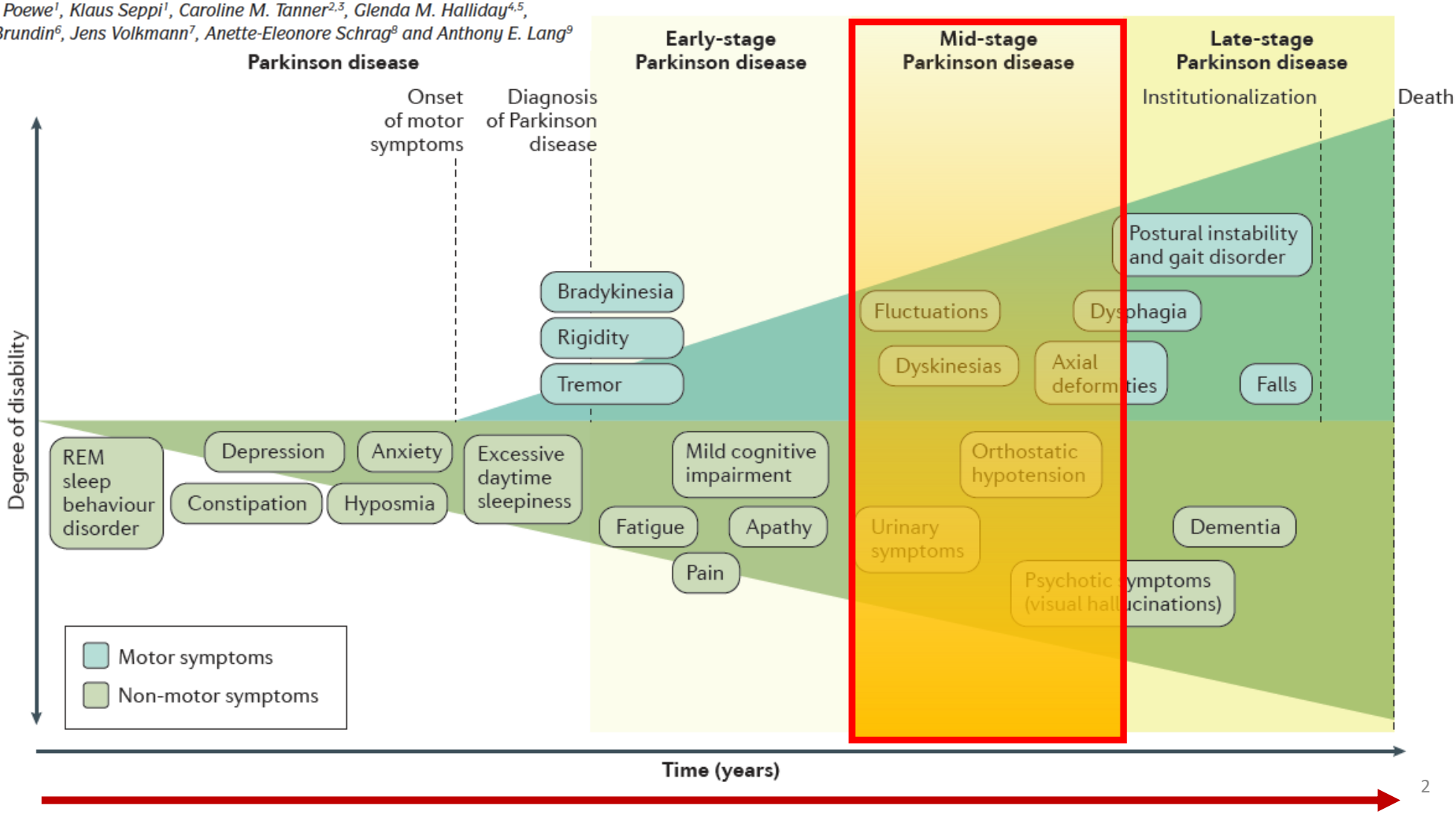
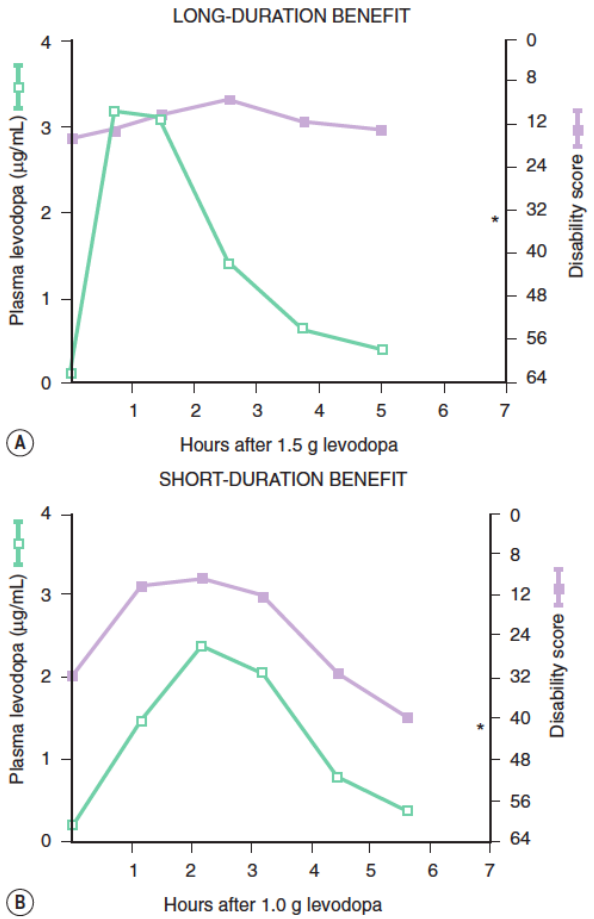


Sottotipi di Parkinson

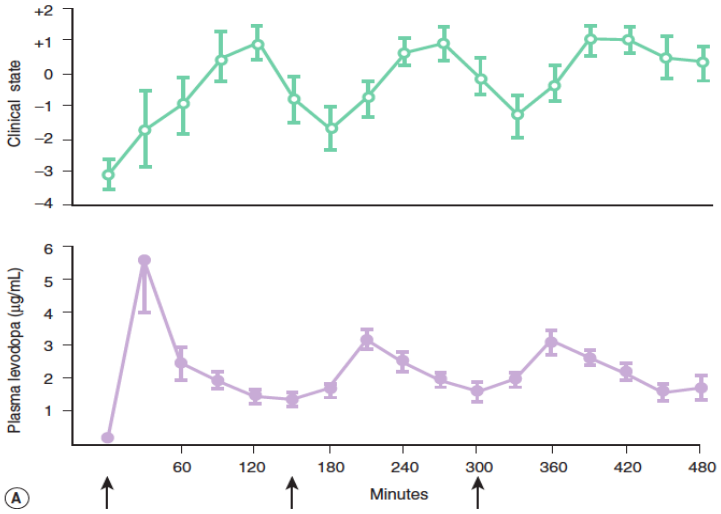
Parkinson Disease Subtype and Estimated Frequency	Disease Presentation	Response of Motor Symptoms to Dopaminergic Medication	Disease Progression
Mild motor predominant 49%-53%	• Young at onset • Mild motor symptoms	Good	Slow
Intermediate 35%-39%	• Intermediate age at onset • Moderate motor symptoms • Moderate nonmotor symptoms	Moderate to good	Moderate
Diffuse malignant 9%-16%	• Variable age at onset • Rapid eye movement sleep behavior disorder • Mild cognitive impairment • Orthostatic hypotension • Severe motor symptoms • Early gait problems	Resistant	Rapid

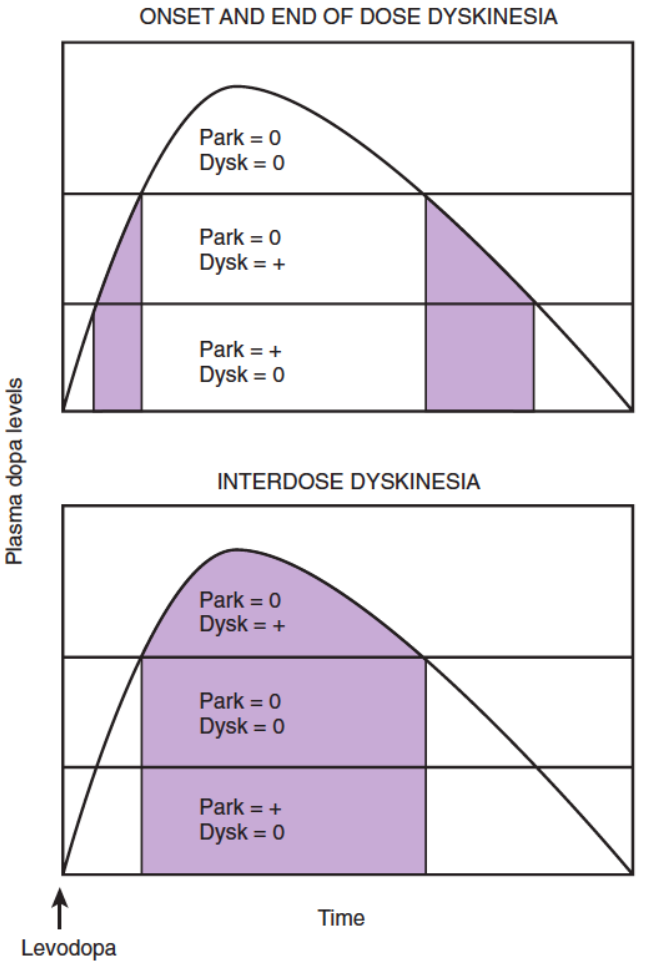
Armstrong MJ et al., JAMA, 2020

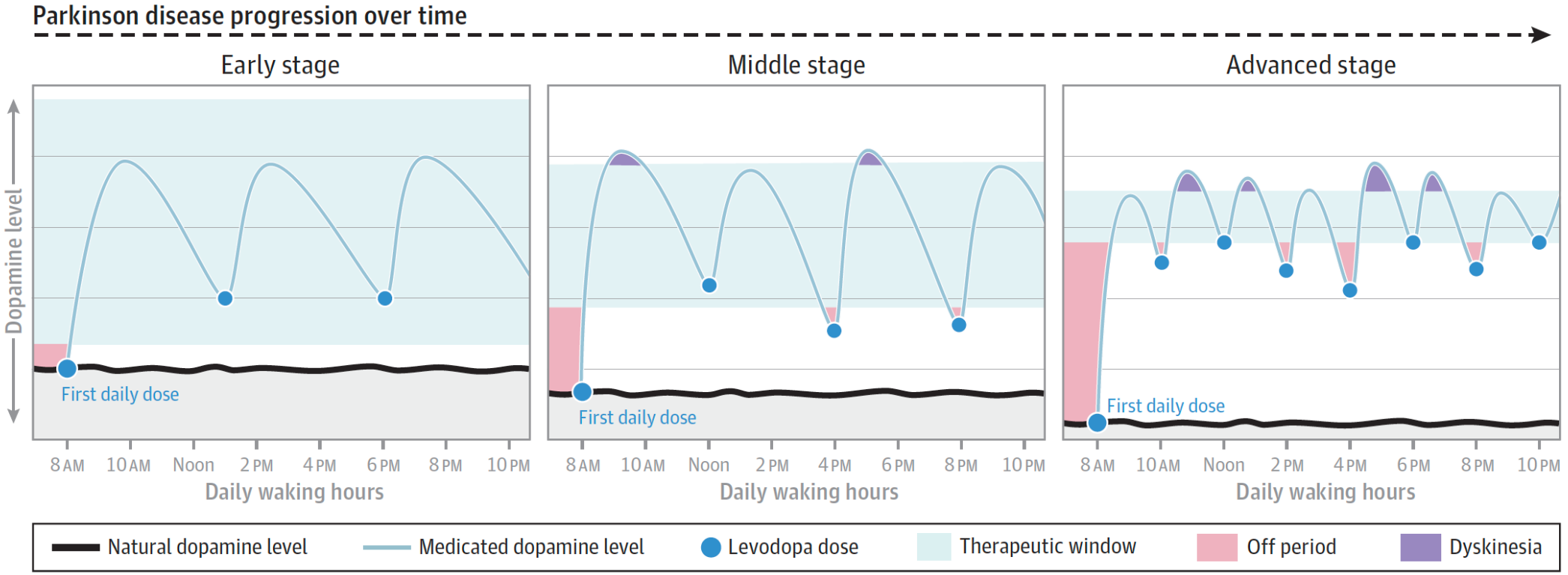


‘la levodopa rimane il trattamento più efficace per la malattia di Parkinson. Nonostante ciò il, suo utilizzo è associato ad alcuni problemi.’

A.E. Lang, NEJM, 1988







M.J. Armstrong et al., JAMA, 2020

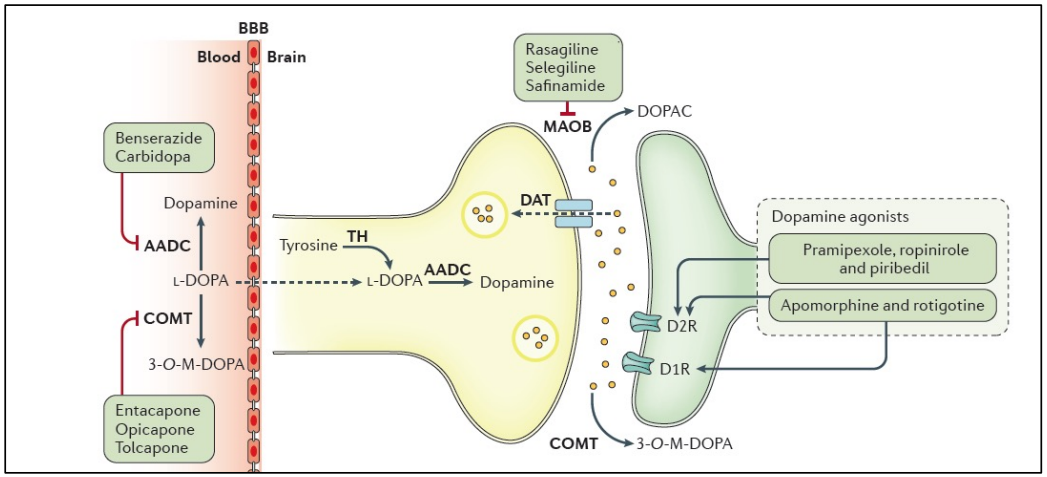
Fase Off

Fase On

OFF-state complications	ON-state complications	Transitional state complications
Drug responsive		
Predictable wearing-off	Peak-dose dyskinesia	Beginning of dose worsening and end of dose rebound
Sudden/unpredictable off	On freezing	Diphasic dyskinesia
Off freezing	Delayed on	
Off dystonia	Tachykinesia	
Dose failure/partial response		
Drug-resistant		
Balance		
On-period freezing		
Speech problems		
Refractory tremor		
Dysarthria and dysphagia		
Postural deformity		

Modified from Oxford Textbook of Movement Disorders, 2013

I farmaci a disposizione

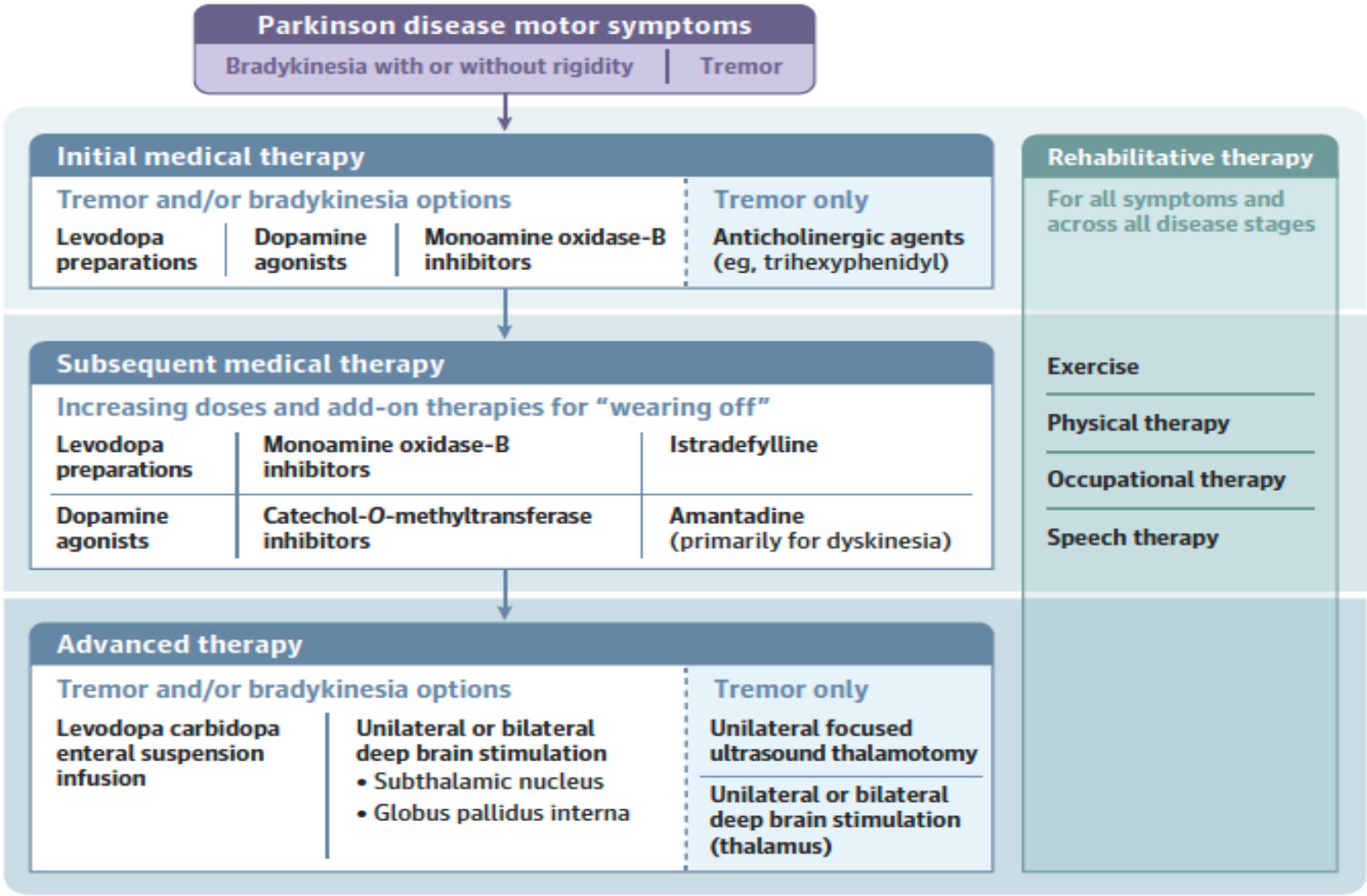


Poewe et al.2017

Category	Specific Agents and Typical Starting Dose	Therapeutic Uses: Early Symptomatic	Therapeutic Uses: Levodopa Adjunct	Therapeutic Uses: Wearing Off	Therapeutic Uses: Dyskinesia	Most Common Adverse Effects Other Than Dyskinesia
Levodopa preparations	Immediate-release **carbidopa-levodopa** (25/100 mg, 3 times/d)	●	○	●	●	Nausea
	Controlled-release **carbidopa-levodopa** (25/100 mg, 3 times/d)	●	○	●	●	Nausea
	Extended-release **carbidopa-levodopa** (23.75/95 mg, 3 times/d for 3 d; then 36.25/145 mg, 3 times/d for 3 d)	●	○	●	●	Nausea
	Enteral suspension **carbidopa-levodopa** (clinical titration)		○	●	●	Nausea
	Inhaled **levodopa** (as needed)		○	●[b]		Nausea, upper respiratory tract infection
Nonergot dopamine agonists[c]	Immediate-release **pramipexole** (0.125 mg, 3 times/d, increasing weekly) or extended-release **pramipexole** (0.375 mg, 1 time/d,increasing weekly)	●	●	●	●	Orthostatic hypotension, dizziness, nausea, sleepiness
	Immediate-release **ropinirole** (0.25 mg, 3 times/d, increasing weekly) or extended-release **ropinirole** (2 mg, 1 time/d, increasing weekly)	●	●	●	●	Orthostatic hypotension, dizziness, nausea, sleepiness
	Transdermal **rotigotine** (2 mg/24 h)	●	●	●	●	Site reactions, dizziness, orthostatic hypotension
	Injected **apomorphine** (as needed)			●		Site reactions, dizziness, orthostatic hypotension
Monoamine oxidase-B inhibitors	**Selegiline** (5 mg, 2 times/d)	●	●	●	●	Nausea, dizziness, insomnia
	Rasagiline (1 mg every morning)	●	●	●	●	Orthostatic hypotension, nausea
	Safinamide (50 mg/d)	●	●	●	●	Nausea
	Zonisamide (25 to 200 mg/d)[d]			●		Sleepiness, loss of appetite
Catechol-O-methyltransferase inhibitors	**Entacapone** (200 mg with each levodopa dose)			●	●	Nausea, diarrhea
	Opicapone (50 mg every night)[e]			●	●	Falls, insomnia, orthostatic hypotension
	Tolcapone (100 mg, 3 times/d)[f]			●	●	Gastrointestinal symptoms, orthostatic hypotension, sleep disorders
Other	**Anticholinergics** (eg, trihexyphenidyl, benztropine; dose varies)[g]	●	●			Dizziness, anxiety
	Amantadine (dose varies by formulation)[h]	●	●		●	Orthostatic hypotension, hallucinations, edema, gastrointestinal symptoms
	Istradefylline (20 mg/d)			●		Nausea, hallucinations
	Clozapine (12.5-25 mg every night)[f]				●	Sleepiness, dizziness, tachycardia, constipation, orthostatic hypotension, sialorrhea

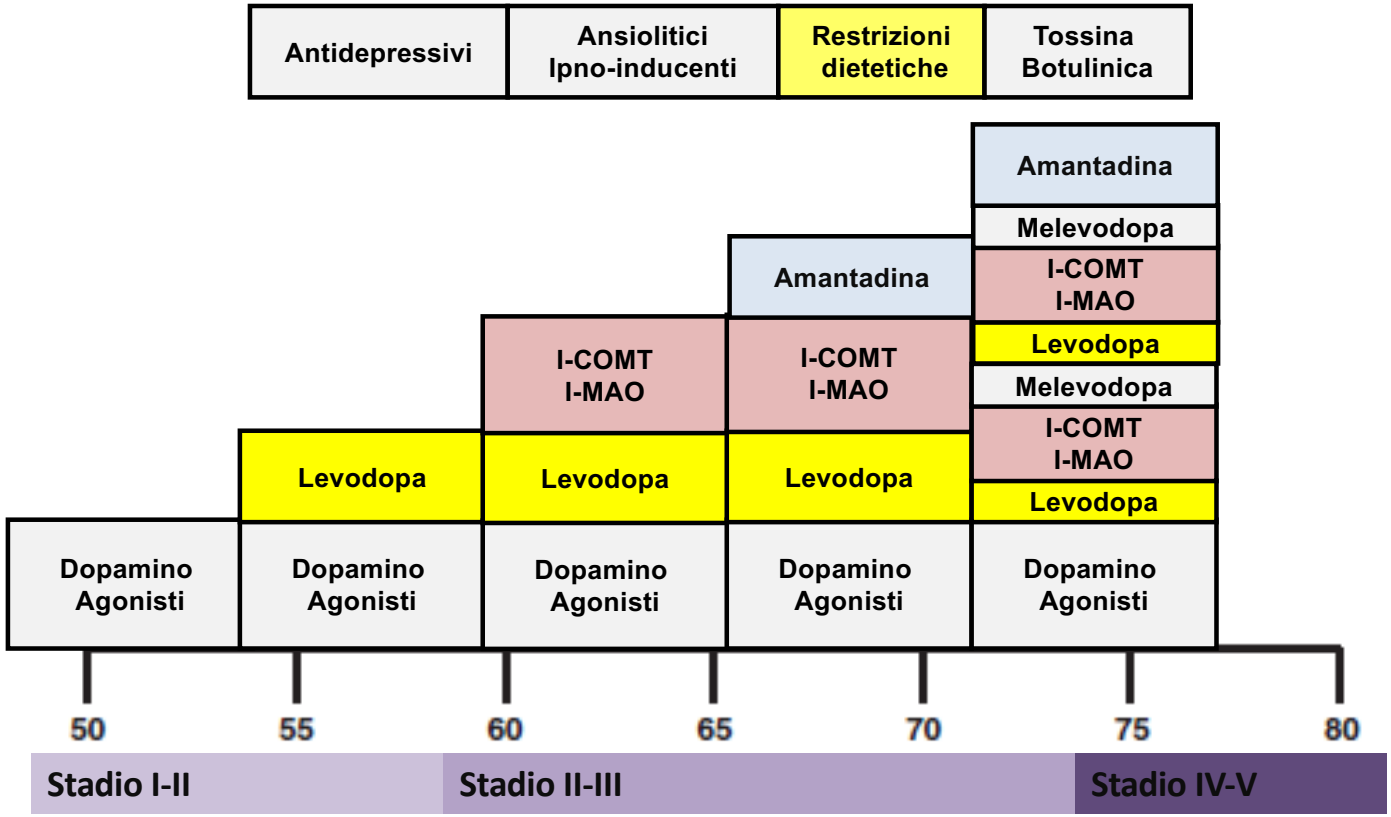
● "Clinically useful" or "possibly useful"[i] ● Used in clinical practice outside of evidence base ● Dose reduction or adjustment may reduce dyskinesia ○ Not relevant

M.J. Armstrong et al., JAMA, 2020



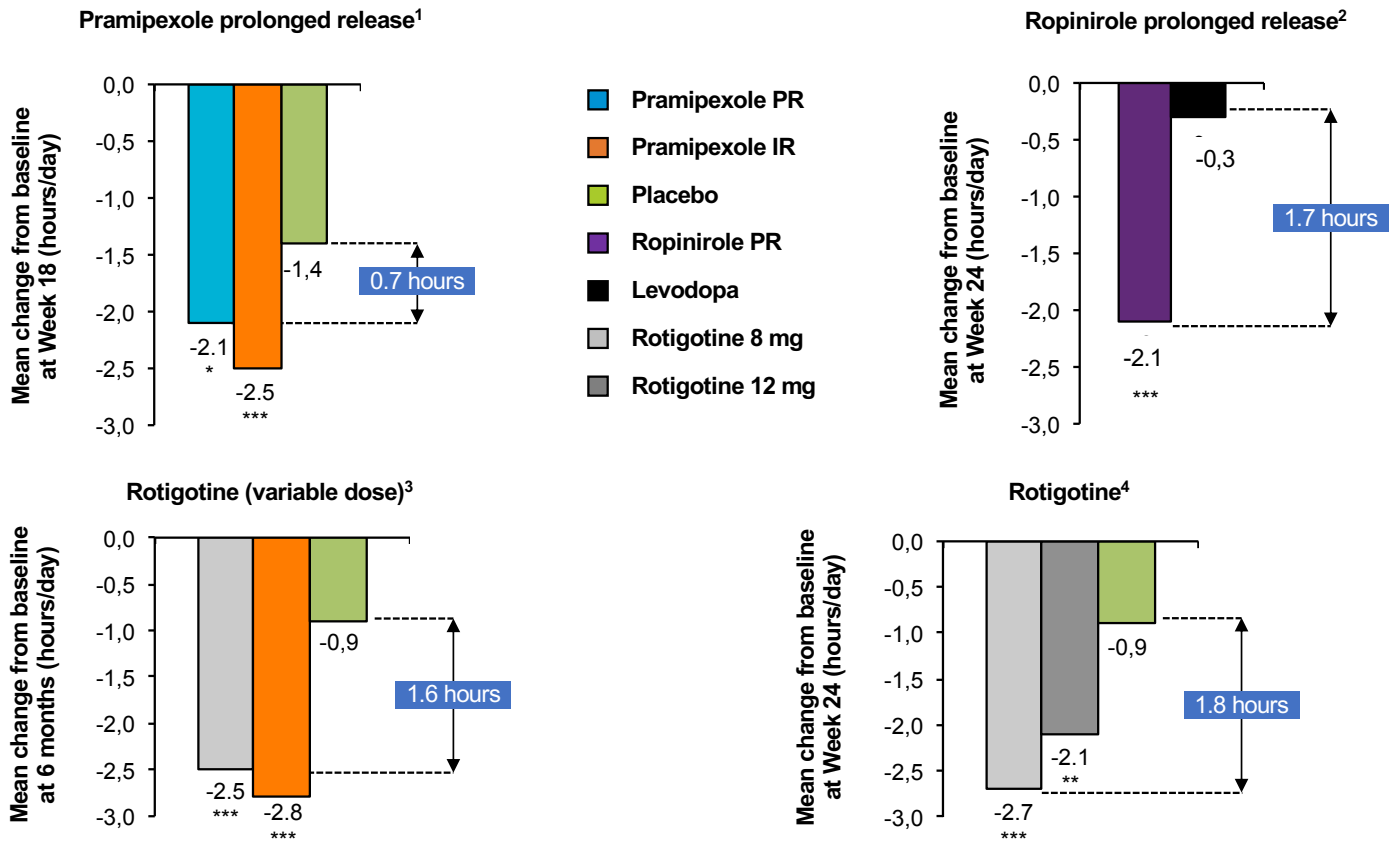
Dietrichs E et al., Acta Neurol Scand, 2017

Complessità della terapia farmacologica con la progressione della malattia



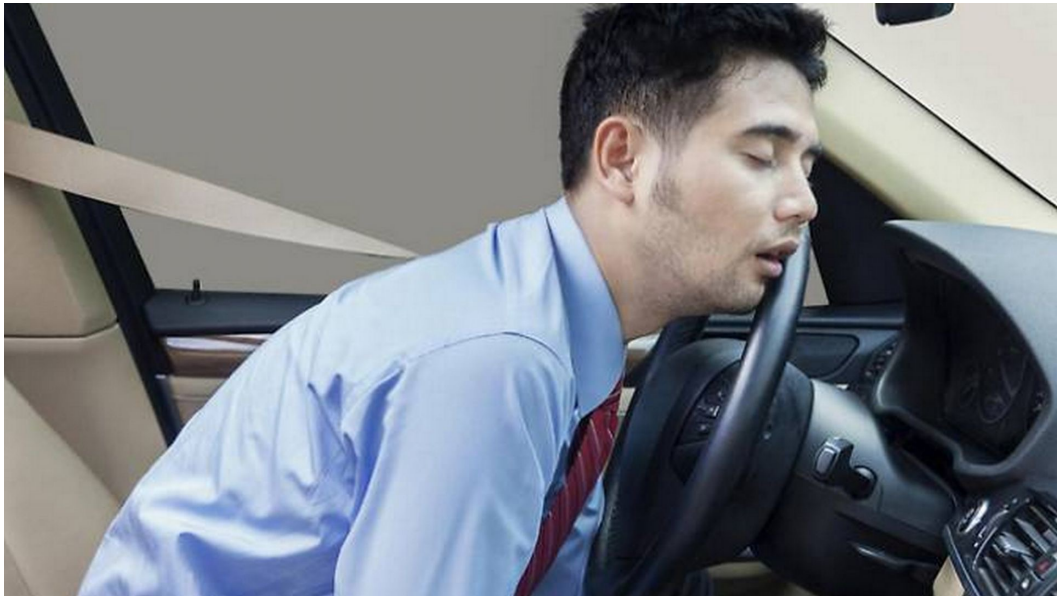
Courtesy of. Prof. Morgante

Dopaminoagonisti RP– riduzione tempo in OFF



PR=prolonged release; IR=immediate release
*p<0.05, **p<0.01 ,***p<0.001 vs. placebo

1. EPAR 2009; EMEA/H/C/000133/X/0051;
2. Pahwa et al. Neurology 2007; 68 (14): 1108–1115;
3. Poewe WH et al. Lancet Neurol. 2007; 6 (6): 513–520;
4. LeWitt P et al. Neurology 2007; 68 (16): 1262–1267



Inibitori COMT

Entacapone

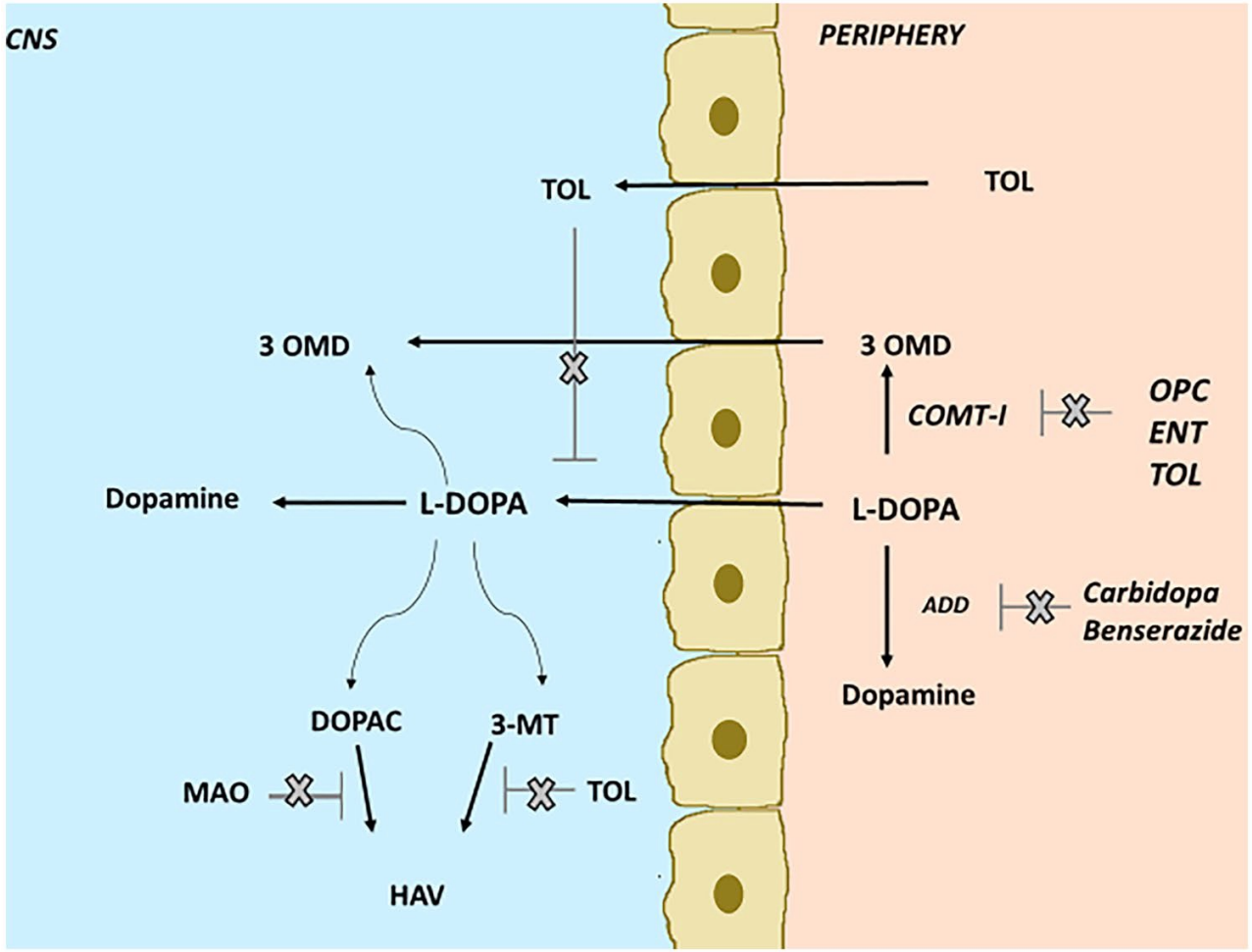
- Somministrazione ad ogni dose di levodopa
- No sorveglianza
- Diarrea

Tolcapone

- Tre dosi al giorno
- Elevata efficacia
- Sorveglianza per epatotossicità

Opicapone

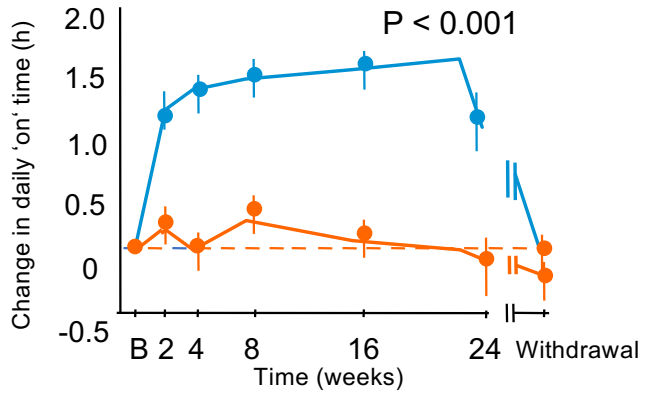
- Monosomministrazione serale
- Elevata efficacia
- No sorveglianza



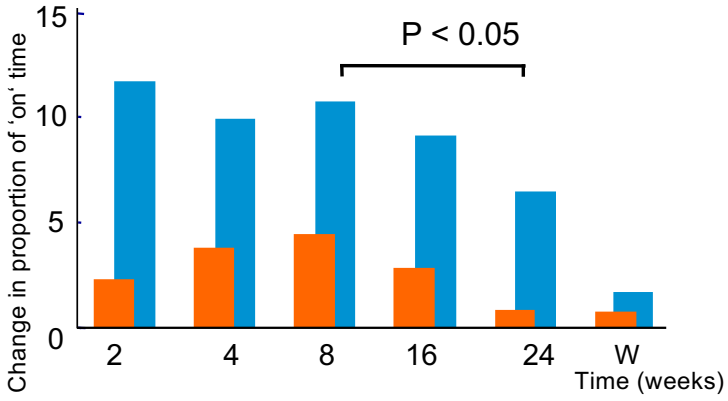
M. Fabbri et al., CNS Drugs, 2022

Inibitori COMT – riduzione tempo in OFF

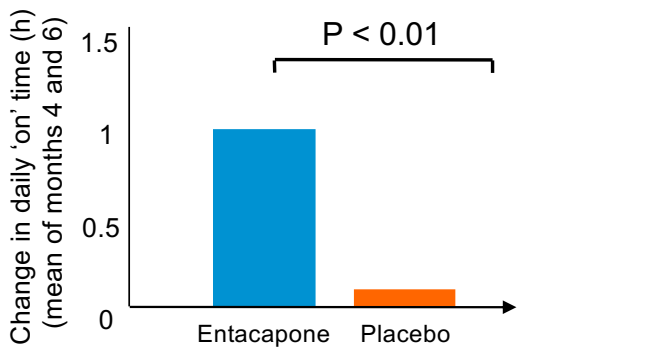
NOMECOMT: Rinne et al. 1998



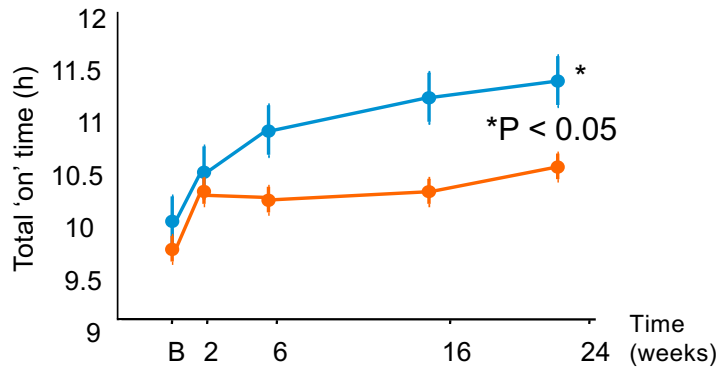
SEESAW: Parkinson Study Group, 1997



UK-IRISH: Brooks et al. 2003



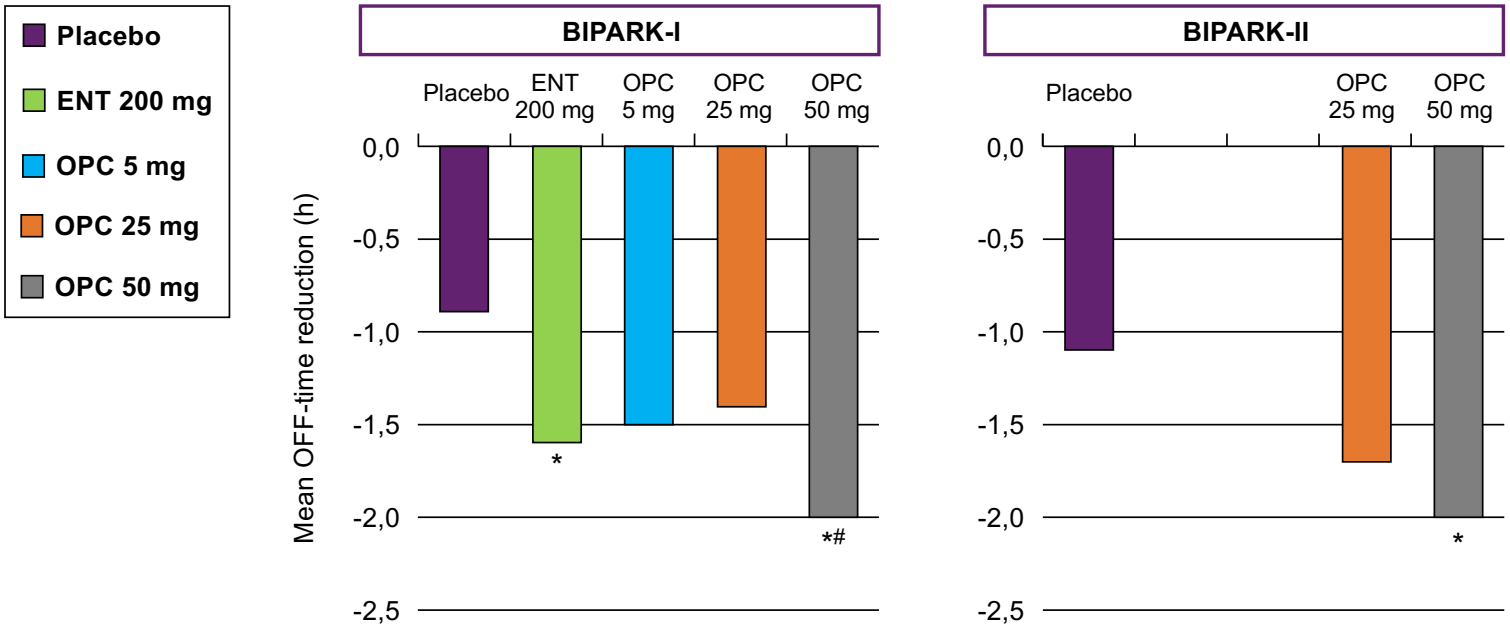
CELOMEN: Poewe et al. 2002



Levodopa/DDCI plus entacapone

Levodopa/DDCI plus placebo

Opicapone (BIPARK I and BIPARK II): variazioni del tempo in OFF



* p<0.05 vs. Placebo

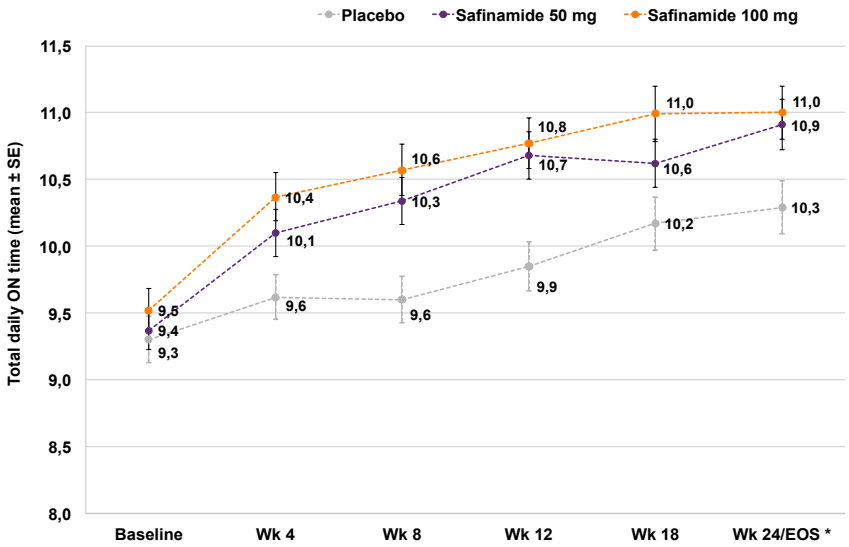
# p<0.05 for non inferiority vs. ENT

BIPARK-I	LS mean (hours)
Placebo	-0.9
200 mg ENT	-1,6
5 mg OPC	-1.5
25 mg OPC	-1.4
50 mg OPC	-2.0

BIPARK-II	LS mean (hours)
Placebo	-1.1
25 mg OPC	-1.7
50 mg OPC	-2.0

1. *Ferreira J et al. Lancet Neurol 2016;15:154-165;*
2. *Lees A et al. JAMA Neurol 2017;74(2): 197-206*
3. *Ferreira J et al. EAN, Berlin 2015*

Inibitori MAO – riduzione tempo in OFF

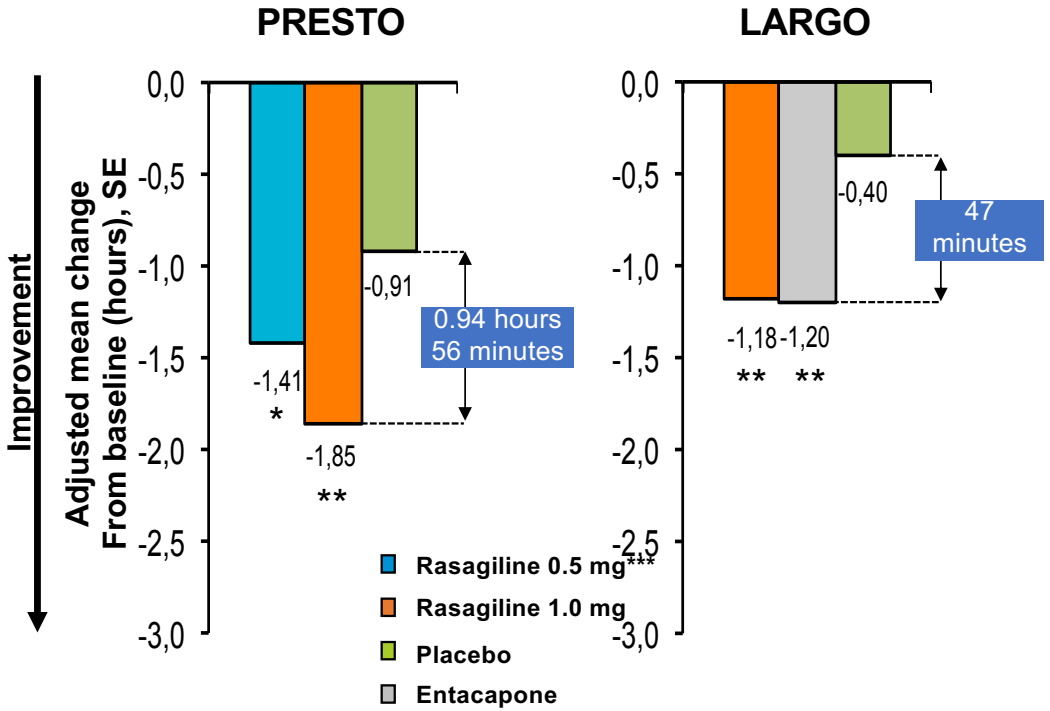


	Safinamide 50 mg	Safinamide 100 mg
LS Mean	1.23	1.28
LS Difference vs. placebo	**0.51**	**0.55**
95% CI of LS Difference	(0.07, 0.94)	(0.12, 0.99)
p-value vs. placebo	0.0223	0.0130

*ON Time = ON time without dyskinesia + ON time with minor dyskinesia

Safinamide (Study 016)

Borgohain R. et al., Mov Disord 2014, Vol. 29, N. 2



*p<0.05 vs placebo, **p<0.001 vs placebo,***Unlicensed dose

Rasagiline (PRESTO and LARGO)

1. *Parkinson Study Group. Arch Neurol 2005;62:241;*
2. *Rascol et al. Lancet 2005;365:947*

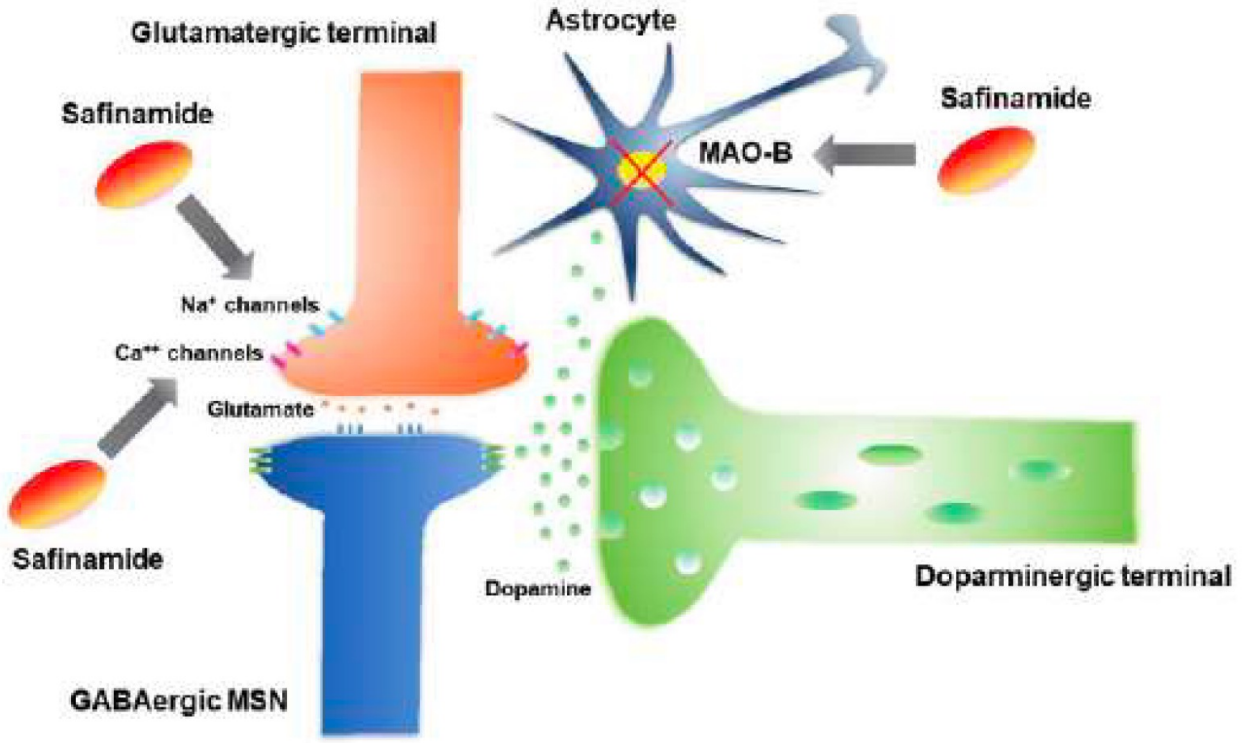
Safinamide

Azione dopaminergica

- Inibizione reversibile MAO-B
- Altamente specifico
- Potente: inibizione totale delle MAO-B alle dosi cliniche, senza intaccare le MAO-A

Azione non dopaminergica

- Inibizione del rilascio di glutammato tramite blocco dei canali del sodio
- La modulazione dei canali del calcio supporta un potenziale ruolo neuroprotettivo, riducendo l'eccitabilità neuronale.

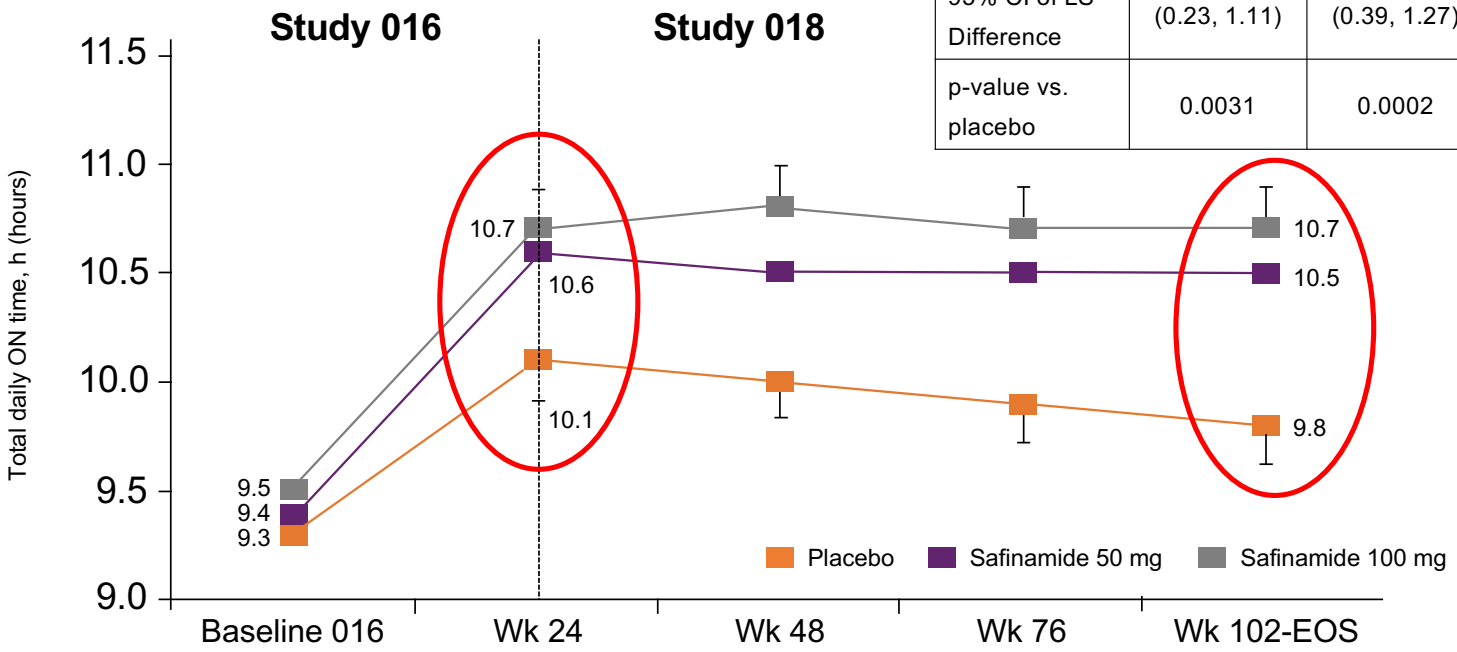


K. Kurihara et al., Exp Op Drug Saf, 2022

Safinamide: tempo in ON senza discinesie*

Maintained clinical effect over 2 years

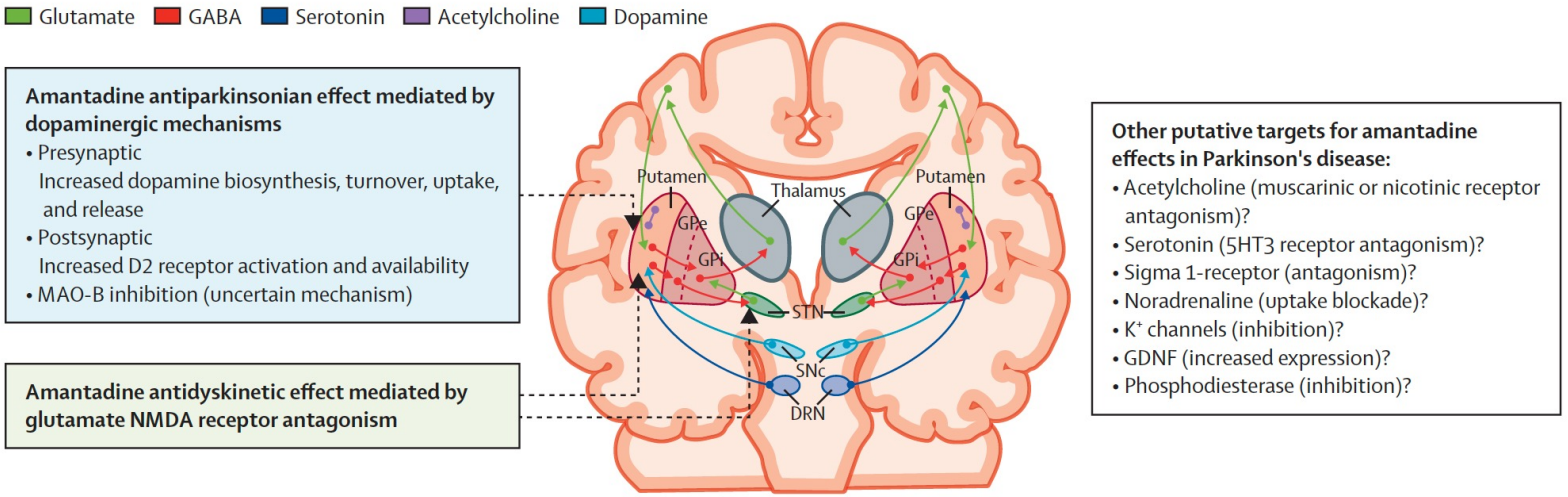
	Safinamide 50 mg/day	Safinamide 100 mg/day
LS Mean	1.01	1.18
LS Difference vs. placebo	0.67	0.83
95% CI of LS Difference	(0.23, 1.11)	(0.39, 1.27)
p-value vs. placebo	0.0031	0.0002



* ON time = ON time without dyskinesia + ON time with minor dyskinesia

Reichmann H. et al; European Neurological Review, 2015;10(2):182–8

O. Rascol et al., Lancet Neurol, 2021



DRN=dorsal raphe nucleus. GPe=external globus pallidus. GPi=internal globus pallidus. MAOB=monoamine oxidase B. SNc=substantia nigra pars compacta. STN=subthalamic nucleus.

Amantadina

- Efficacia confermata nella riduzione delle discinesie in vari studi clinici, anche se probabilmente di breve durata negli anni.
- Nello studio di Thomas et al, 2004, la somministrazione di 300 mg/die di amantadina determinava la riduzione del 45% delle discinesie, ma il beneficio durava meno di 8 mesi.

Unico farmaco antidiscinetico (oltre la clozapina)

Anticolinergici

Numerosi effetti collaterali

- Periferici:
  - annebbiamento visus da difetto di accomodazione
  - ritenzione urinaria
  - nausea
  - stipsi
  - secchezza delle mucose (conseguenti carie, gengiviti, perdita di denti)
  - riduzione delle sudorazione (possibile disturbo della termoregolazione con colpo di calore)

- Centrali:
  - deficit delle funzioni cognitive (anche irreversibile)
  - confusione, sedazione, allucinazioni
  - discinesie oro-buccali

Biperidene: 2 mg – RP 4 mg
Triesifenidile: 2 mg

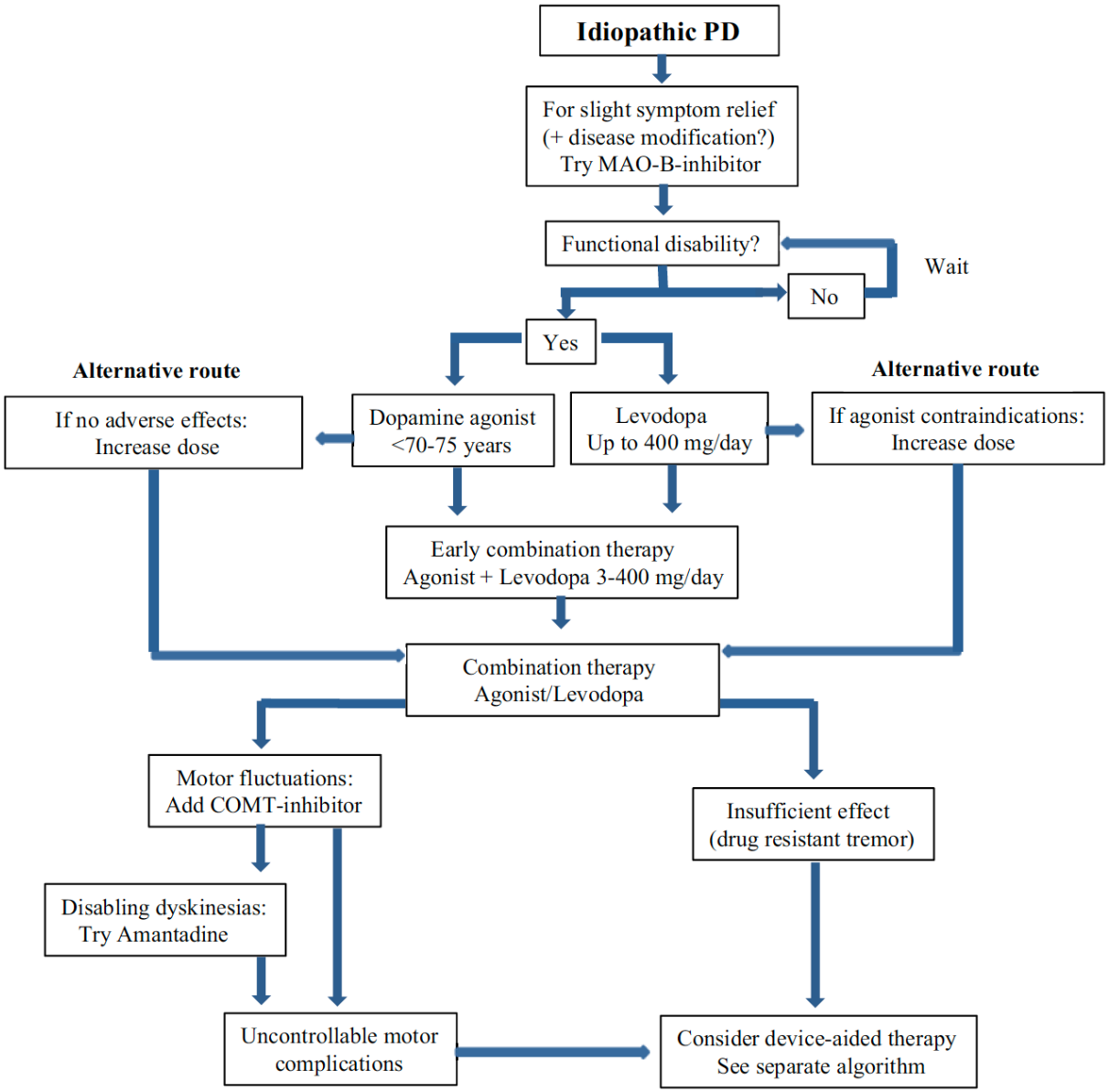
Controindicati in: glaucoma ad angolo chiuso, tachicardia, ipertrofia prostatica, occlusione gastrointestinale o megacolon

Gli effetti sul versante cognitivo sono prevalenti nei soggetti più anziani o con preesistente deficit

Controindicati nei pazienti con demenza

Possibile rebound sintomi parkinsoniani alla sospensione

Tremore farmaco-resistente



E. Dietrichs et al., Acta Neurol Scand, 2017

OFF-state complications	ON-state complications	Transitional state complications
Drug responsive		
Predictable wearing-off	Peak-dose dyskinesia	Beginning of dose worsening and end of dose rebound
Sudden/unpredictable off	On freezing	Diphasic dyskinesia
Off freezing	Delayed on	
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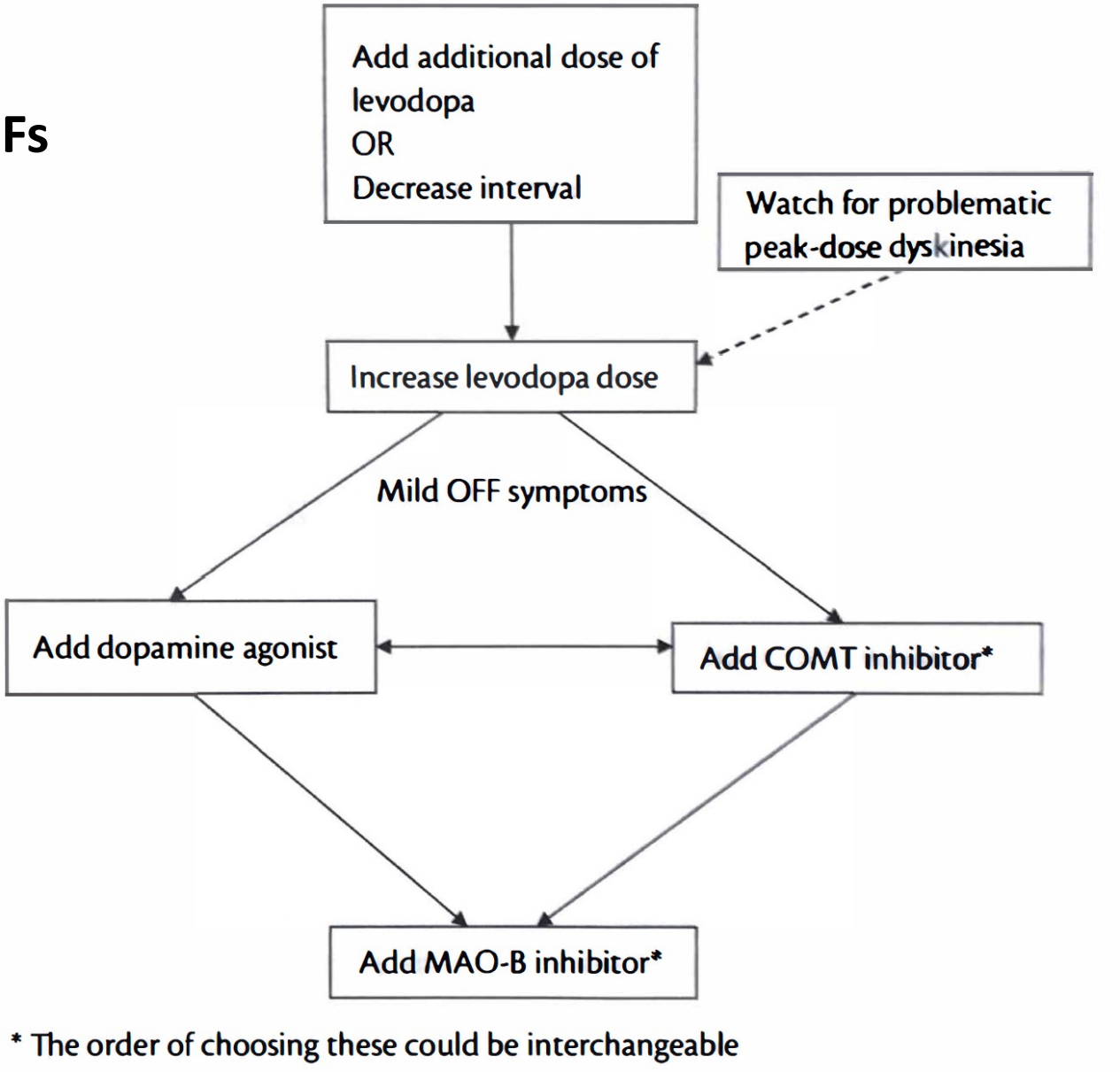
Dose failure/partial response		
Drug-resistant		
Balance		
On-period freezing		
Speech problems		
Refractory tremor		
Dysarthria and dysphagia		
Postural deformity		

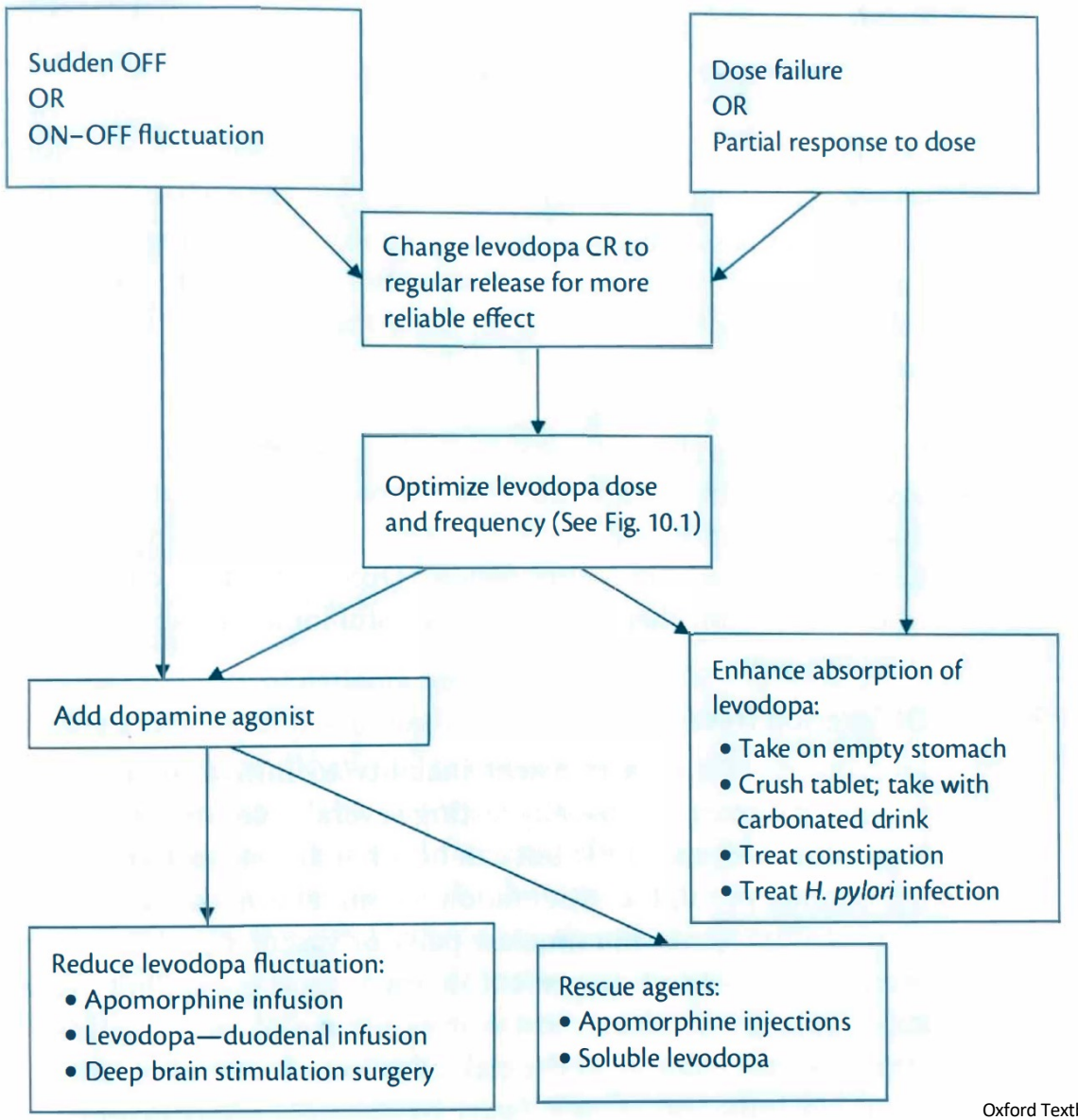
Modified from Oxford Textbook of Movement Disorders, 2013

Predictable OFFs



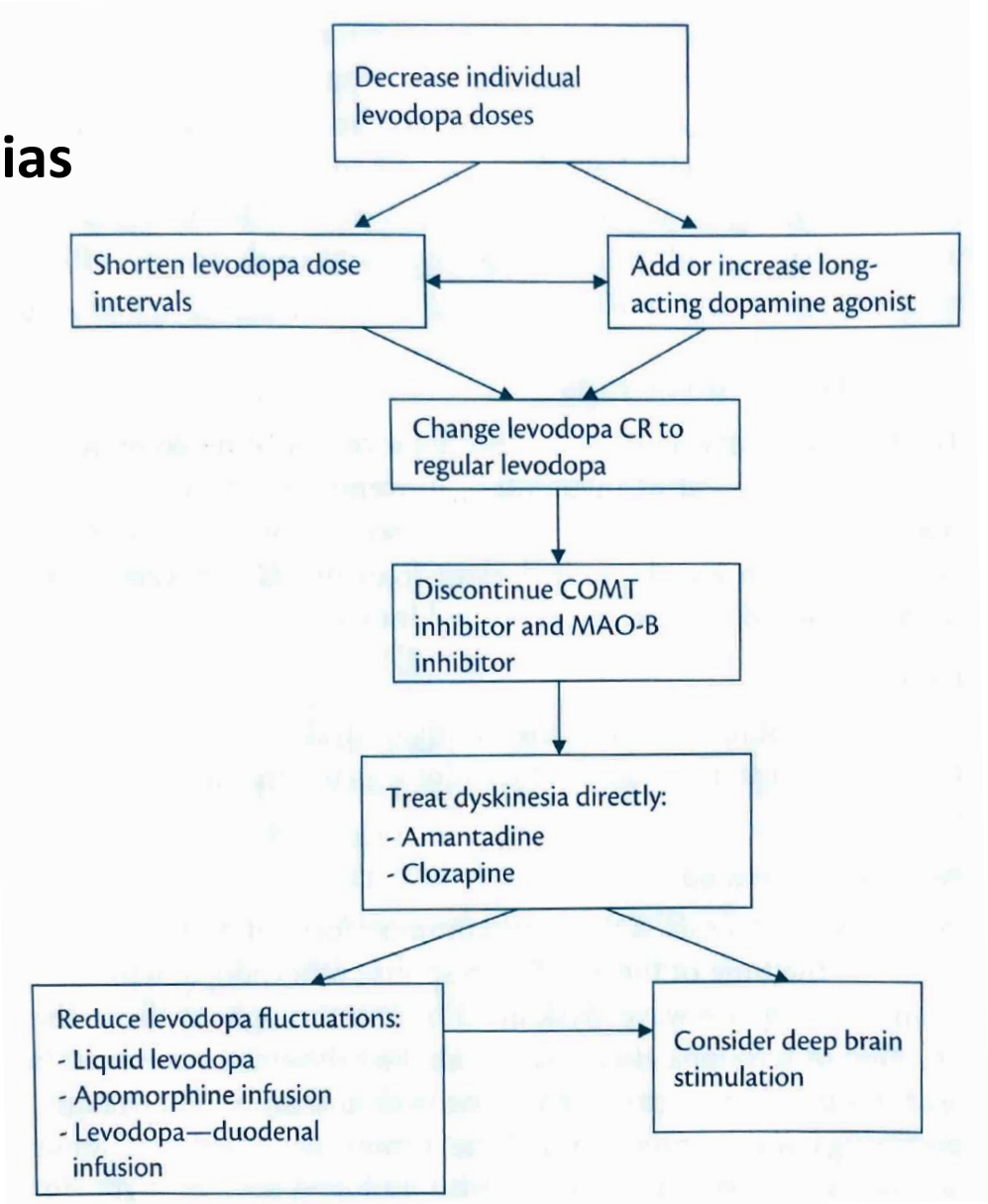
Oxford Textbook of Movement Disorders, 2013

Unpredictable OFFs



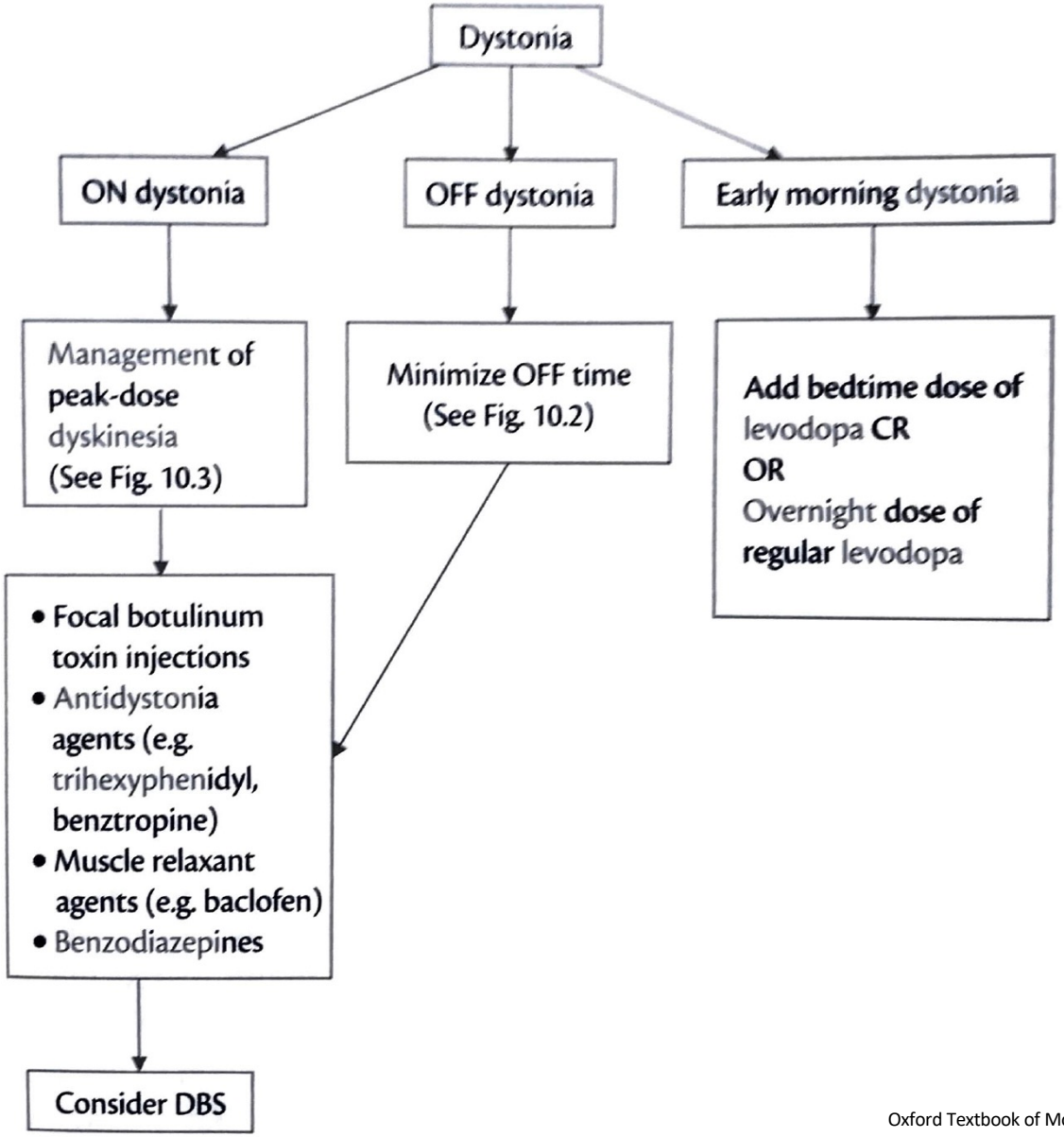
Oxford Textbook of Movement Disorders, 2013

Peak-dose dyskinesias



Oxford Textbook of Movement Disorders, 2013

Dystonia

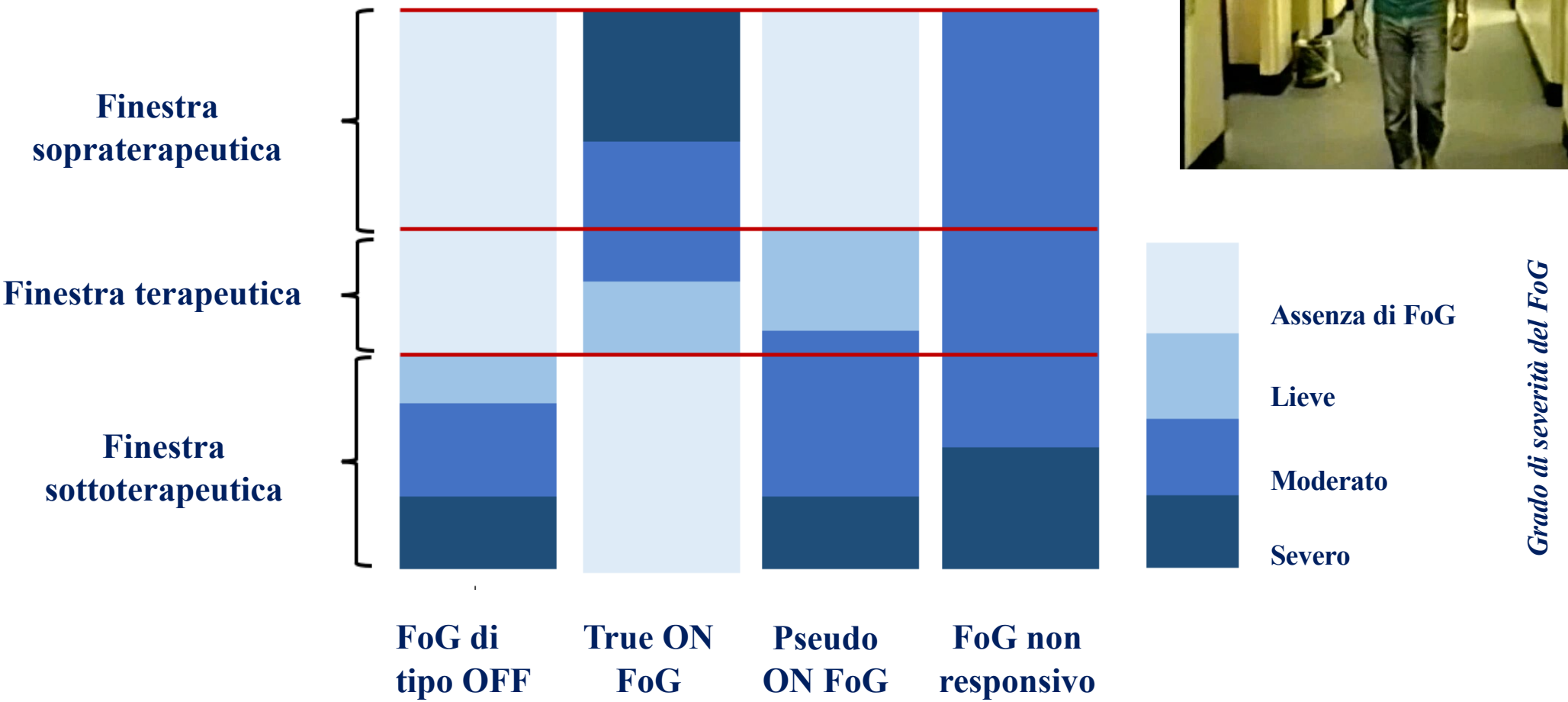


Oxford Textbook of Movement Disorders, 2013

Sudden OFFs: apomorfina pen injector

- Somministrazione di boli sc al bisogno negli off imprevedibili
- Breve latenza: 10-15 minuti
- Durata dell'effetto fino a 120 minuti
- Dosaggio: iniziale 1 mg; aumentare fino a dosaggio efficace (in media 2-6 mg)
- Possibile Tachifilassi
- Ripetibile fino a max 10 volte die

Tipologie di freezing



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Current Medical Research and Opinion

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Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach

Angelo Antonini, A. Jon Stoessl, Leah S. Kleinman, Anne M. Skalicky, Thomas S. Marshall, Kavita R. Sail, Koray Onuk & Per Lars Anders Odin

Motor symptoms	• Troublesome dyskinesia and off-periods • At least 2 hours of off-time • Off-period postural instability • Dystonia with pain • Freezing of gait during off
Non-motor symptoms	• Nighttime sleep disturbances
Functional impacts	• Limited ADL

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Taylor & Francis

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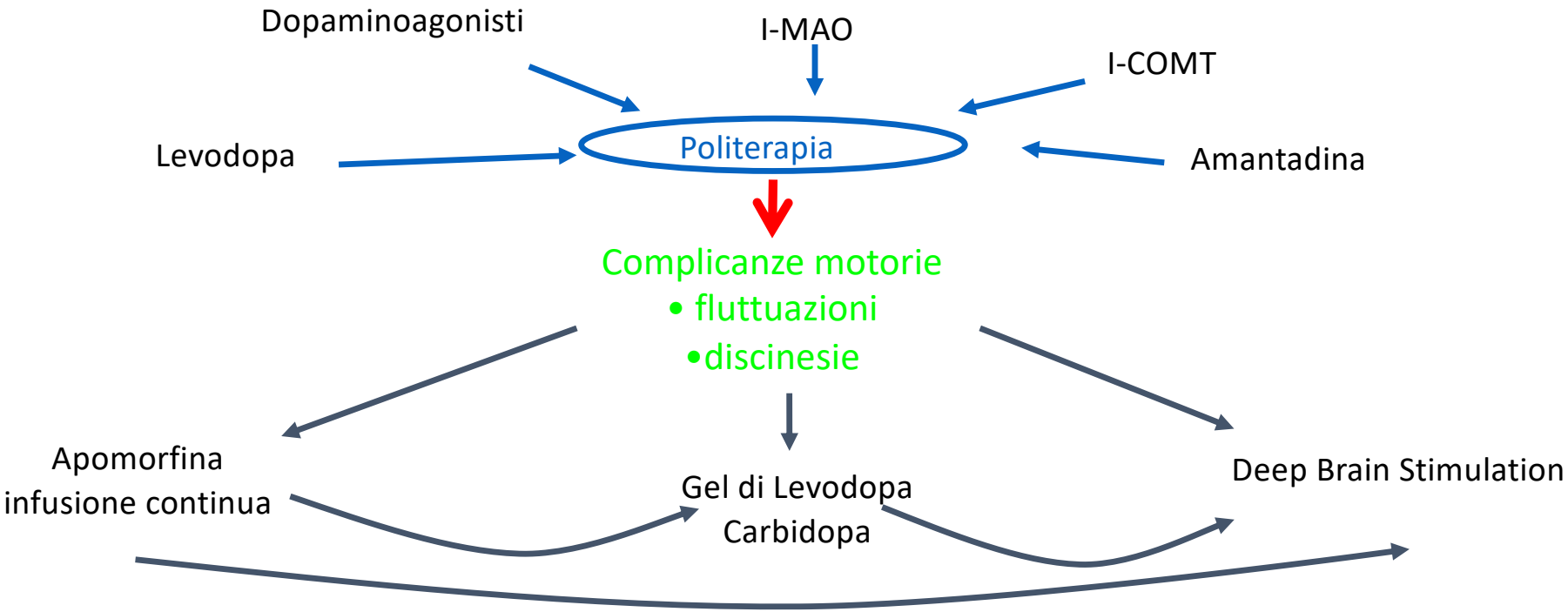
Angelo Antonini, A. Jon Stoessl, Leah S. Kleinman, Anne M. Skalicky, Thomas S. Marshall, Kavita R. Sail, Koray Onuk & Per Lars Anders Odin

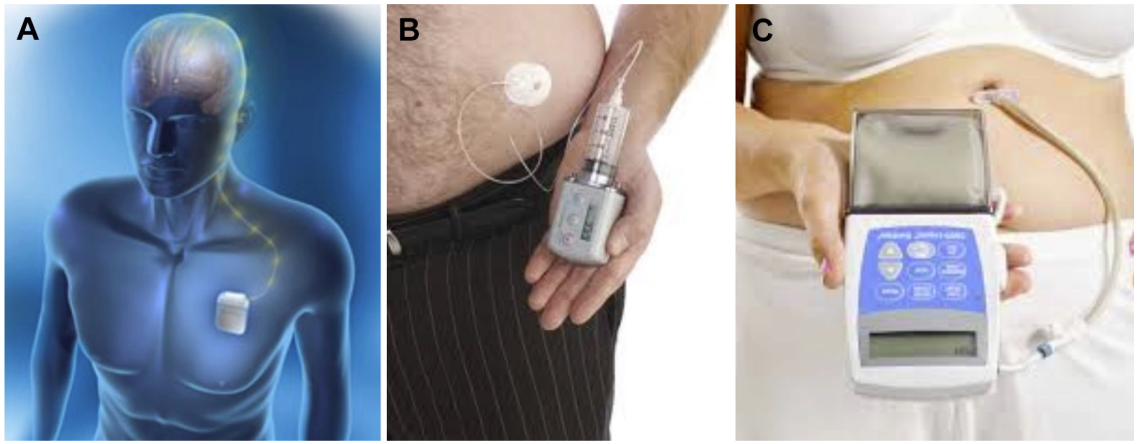
Application of simple criteria to identify advanced Parkinson's disease (PD) is important because early identification of advanced PD allows doctors to adjust treatment, leading to better symptom control and improved quality of life

5 – 2 – 1 CRITERIA

5 - taking levodopa by mouth at least five times a day;
2 - having at least 2 h of the day with 'Off' symptoms;
1 - having at least 1 h of troublesome, uncontrolled, muscle movements (dyskinesia)

- Fulfilling at least one of the '5-2-1 criteria' suggests advanced PD.
- Patients meeting at least one of the 5-2-1 criteria may also be candidates for advanced therapies:
    - Continuous infusion of levodopa–carbidopa intestinal gel
    - Continuous administration of subcutaneous apomorphine
    - Deep brain stimulation


Dopaminoagonisti
I-MAO
I-COMT
Levodopa
Politerapia
Amantadina
Complicanze motorie
• fluttuazioni
•discinesie
Apomorfina
infusione continua
Gel di Levodopa
Carbidopa
Deep Brain Stimulation

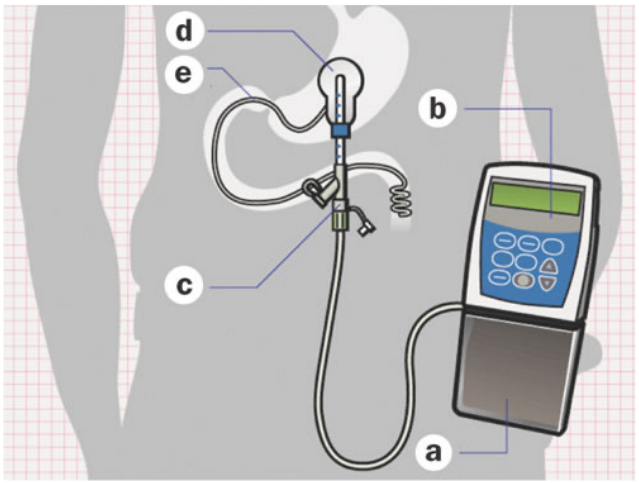

A
B
C

- Le terapie infusionali mirano a ridurre le complicanze motorie della terapia tramite il raggiungimento di una stimolazione dopaminergica continua

- La terapia chirurgica agisce invece attraverso il blocco funzionale di specifiche aree cerebrali coinvolte nella genesi dei sintomi parkinsoniani

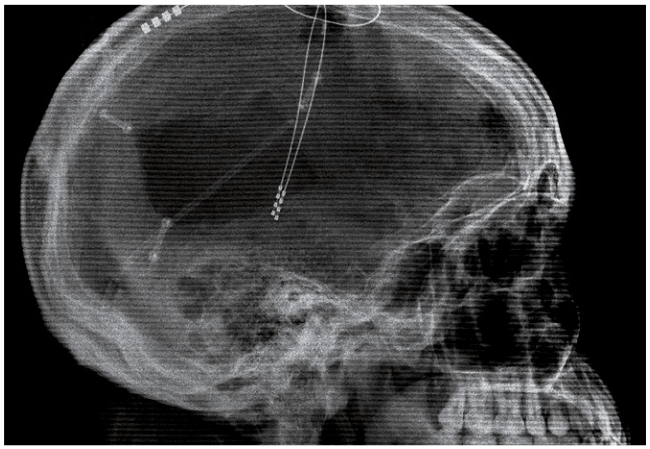
APOMORFINA

- Pazienti giovani
- Non motivati per terapie più invasive
- Assenza disturbi neuropsichiatrici
- Necessità caregiver



GEL LEVODOPA CARBIDOPA

- Età più avanzata
- Pazienti che non accettano il rischio chirurgico della DBS
- Compatibile con presenza di deficit cognitivo lieve-moderato
- Necessità caregiver

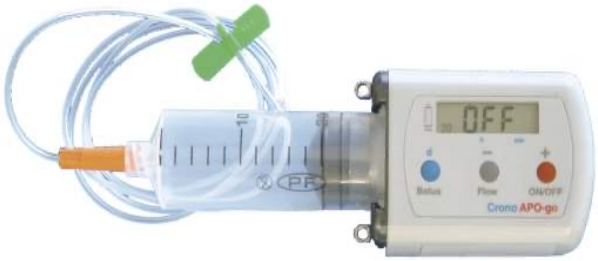


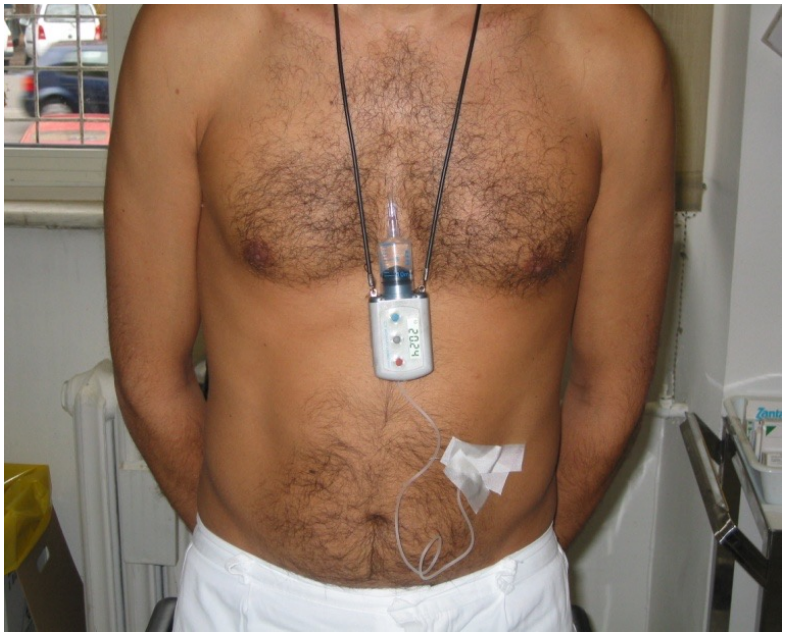
DEEP BRAIN STIMULATION

- Limite di età (~ 70 aa)
- Assenza deterioramento cognitivo o disturbi psichiatrici importanti
- Device compatibile con uno stile di vita “quasi normale”
- Consigliabile se il pz. accetta il rischio chirurgico

Infusione di apomorfina

- Potente dopaminoagonista
- Rapidità di azione: 11-13 min latenza effetto motorio
- Efficacia breve (50-60 min)





- Trattamento delle fasi avanzate di malattia tramite infusione sc continua per 12-15 ore /die
  - 4-8 mg/ora

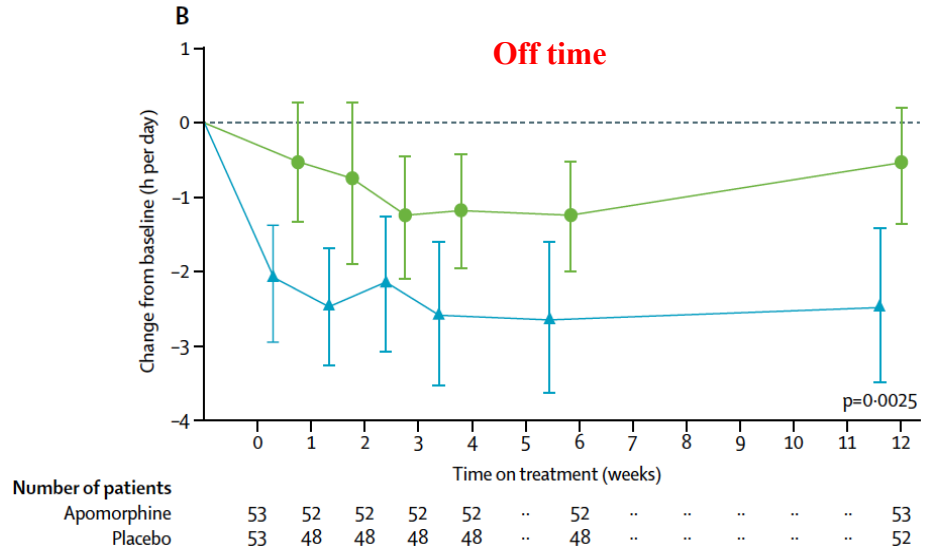
- **Riduzione fasi off ~ 60%**
- **Riduzione discinesie ~ 40%**

Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

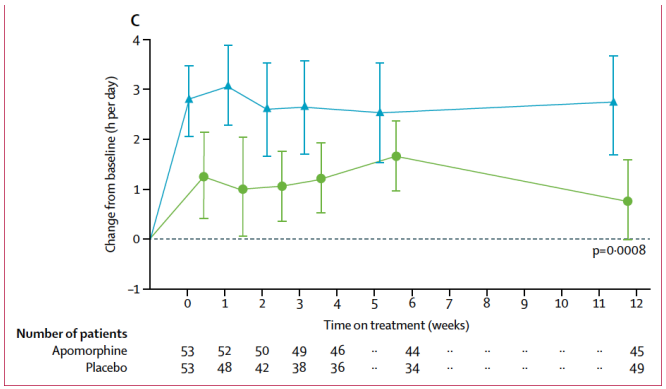
Regina Katzenschlager, Werner Poewe, Olivier Rascol, Claudia Trenkwalder, Günther Deuschl, K Ray Chaudhuri, Tove Henriksen, Teus van Laar, Kevin Spivey, Senthil Vel, Harry Staines, Andrew Lees

Lancet Neurol 2018; 17: 749–59

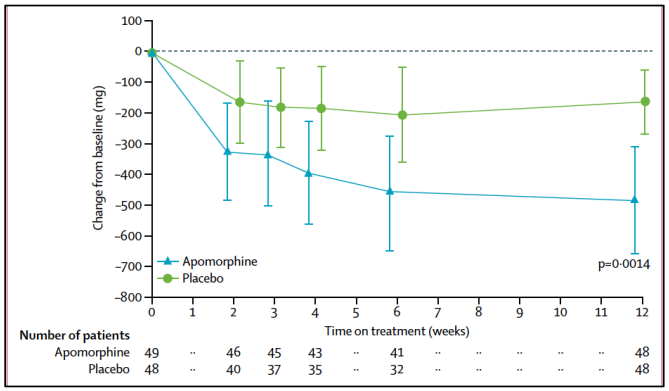
Off time



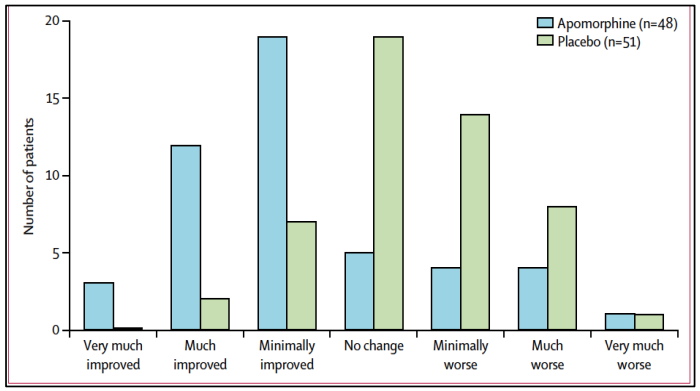
On without troublesome dyskinesia



LEDD

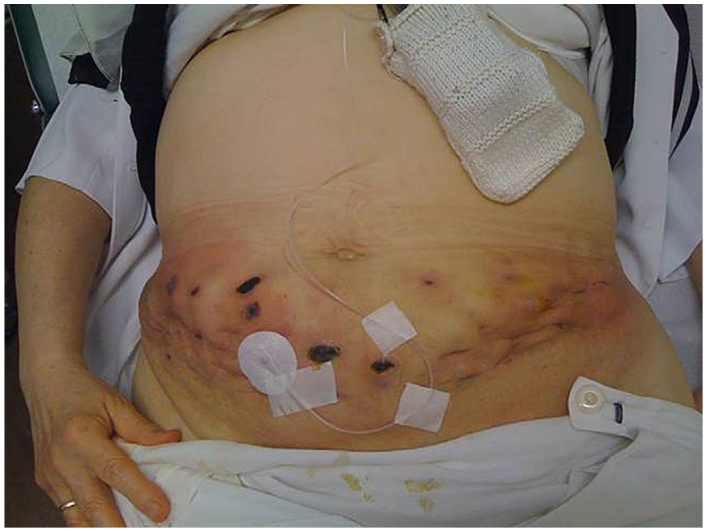


Patient Global Impression of Change



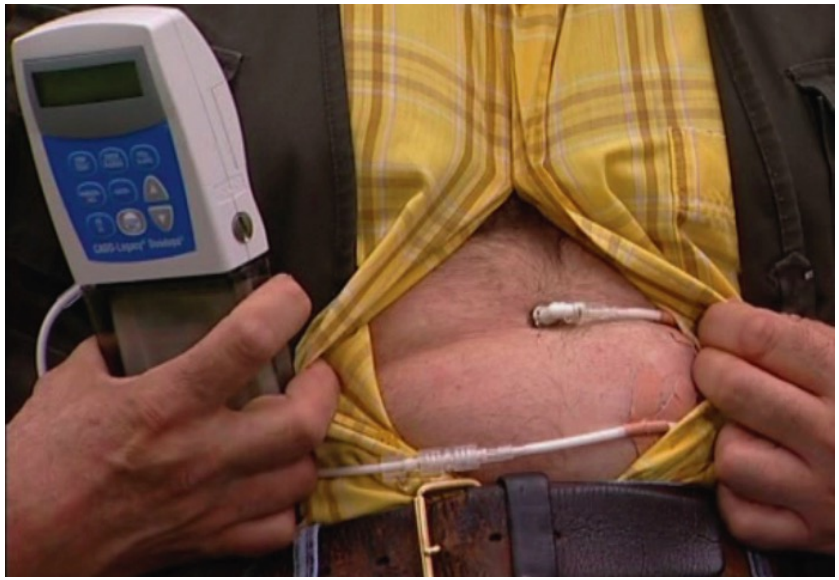
Effetti collaterali apomorfina

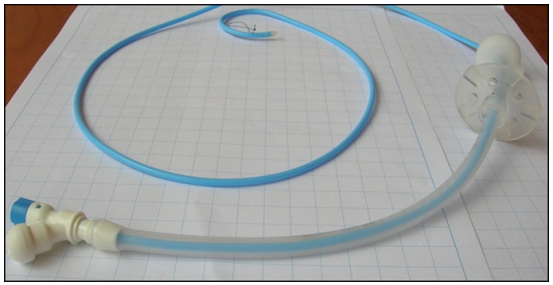
- nausea, vomito, sonnolenza, ipotensione (più frequenti)
- noduli sottocutanei in sede di iniezione (dolore, sovrainfezioni)
- priapismo
- anemia emolitica autoimmune (rara)



Infusione duodenale di gel di levodopa carbidopa

- Gel di levodopa/carbidopa (20/5 mg/ml)
- Sistema portatile di infusione
- Posizionamento di catetere a livello duodenale tramite gastrostomia percutanea endoscopica (PEG-J)
- Mantenimento di livelli plasmatici di levodopa più costanti
- Infusione per 12-16 ore/die
- Dose: 40-120 mg/ora
- Costo elevato



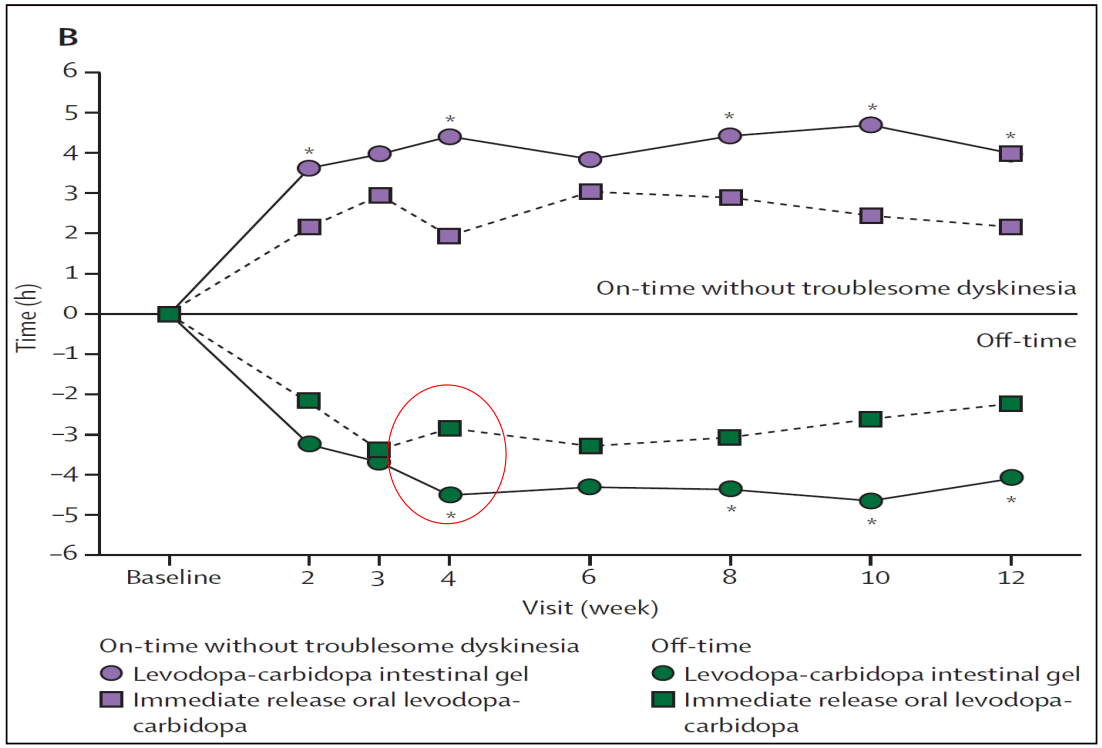


- **Riduzione fasi off ∼60%**
- **Riduzione discinesie ∼40%**

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

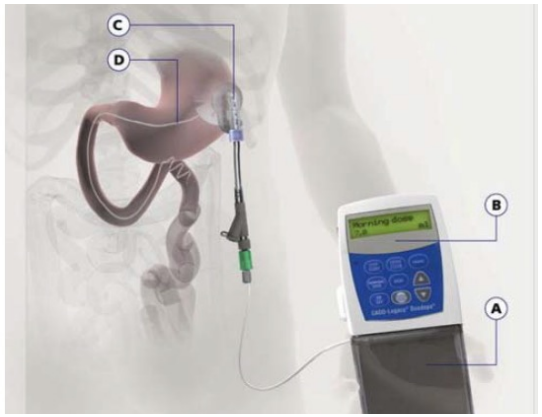
C Warren Olanow, Karl Kieburtz, Per Odin, Alberto J Espay, David G Standaert, Hubert H Fernandez, Arvydas Vanagunas, Ahmed A Othman, Katherine L Widnell, Weining Z Robieson, Yili Pritchett, Krai Chatamra, Janet Benesh, Robert A Lenz, Angelo Antonini, for the LCIG Horizon Study Group

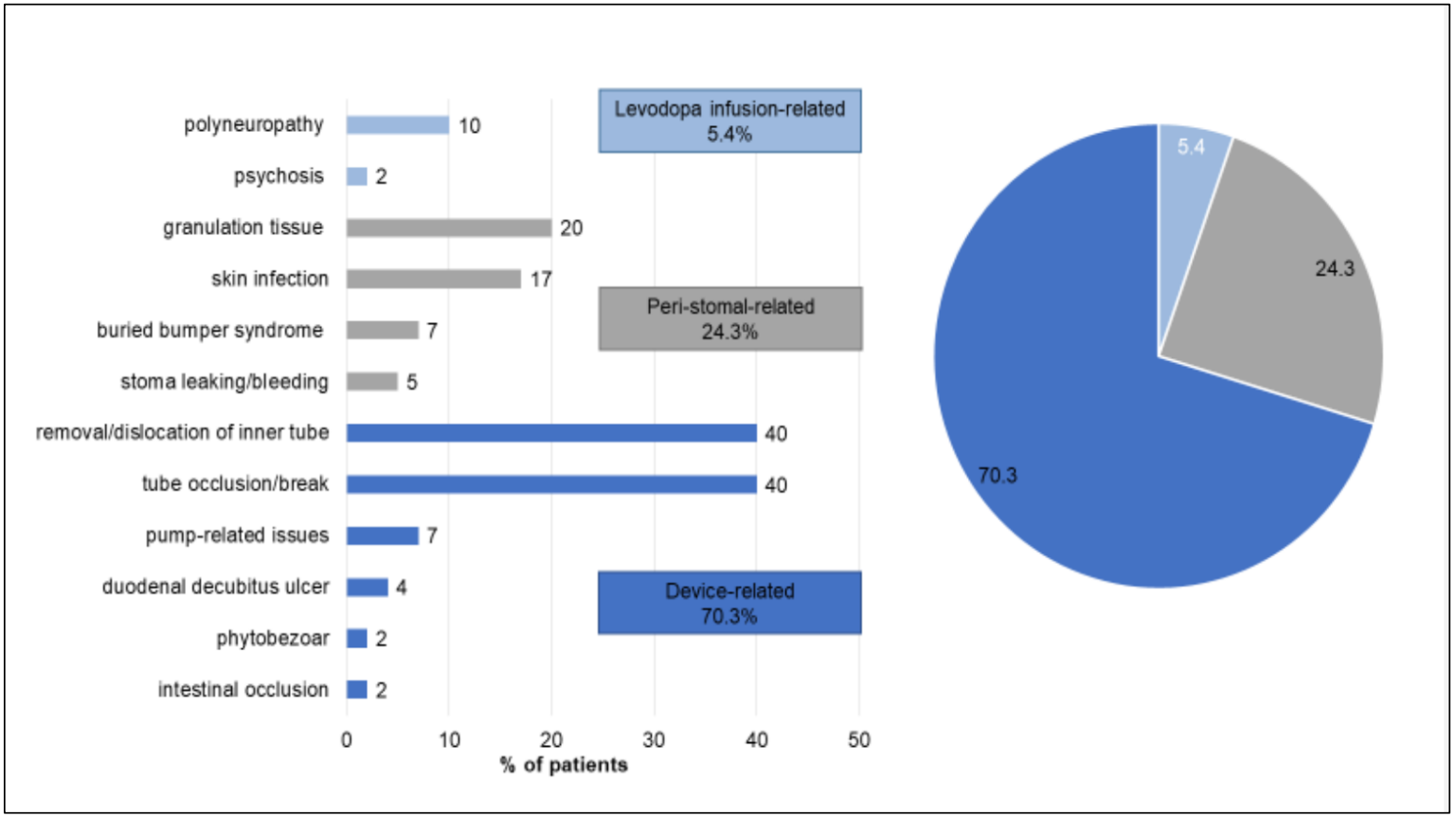
Lancet Neurol 2014; 13: 141–49



- **Off time** was **reduced by 4·04 h** from baseline
- This magnitude of benefit is greater than has been achieved with medical therapies assessed in double-blind studies in which there was **no increase in troublesome dyskinesia**, and is of **similar magnitude to** that reported with **deep brain stimulation** in open-label studies

Effetti collaterali Duodopa

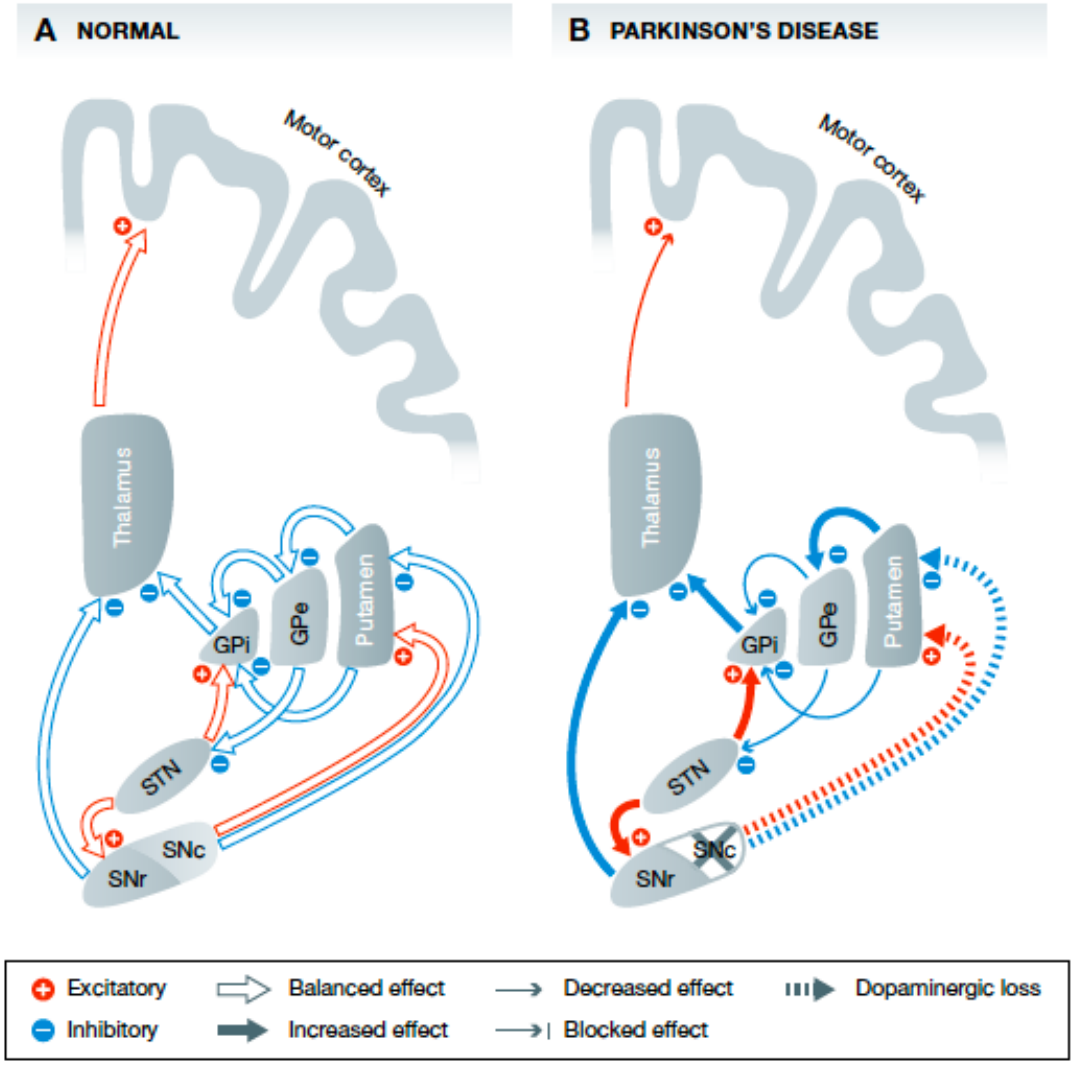




105 pazienti trattati con LCIG fino a 10 anni

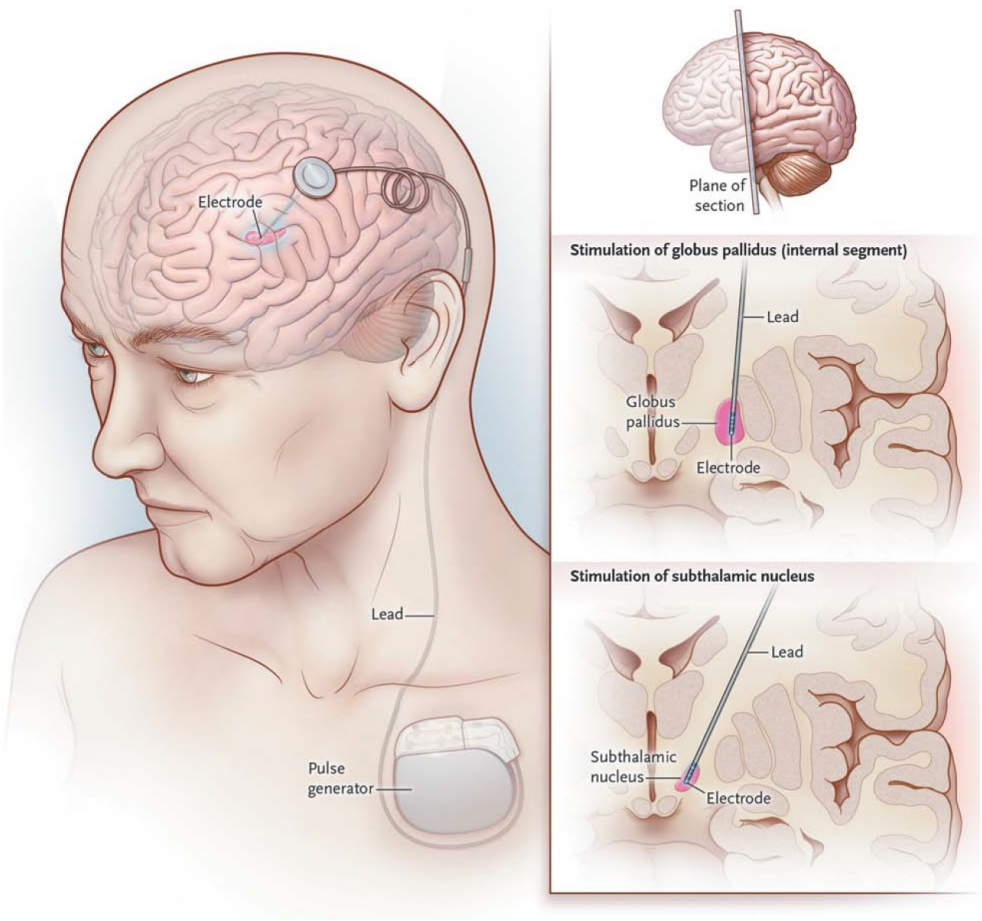
Artusi et al, 2019

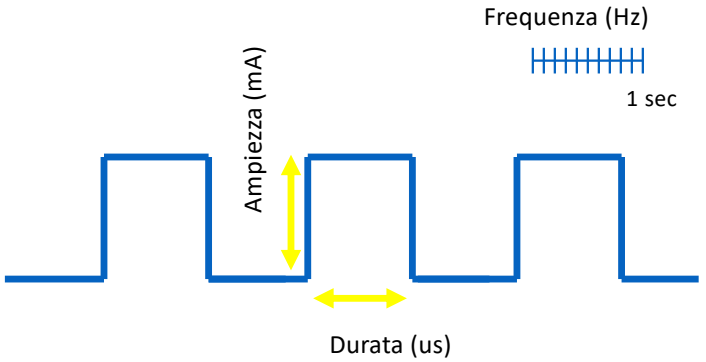
DBS

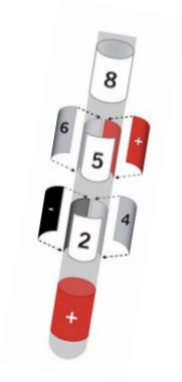


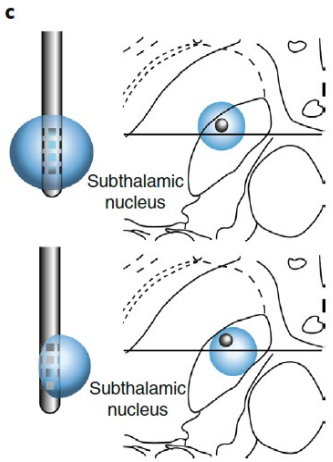
Jacobs et al., 2019

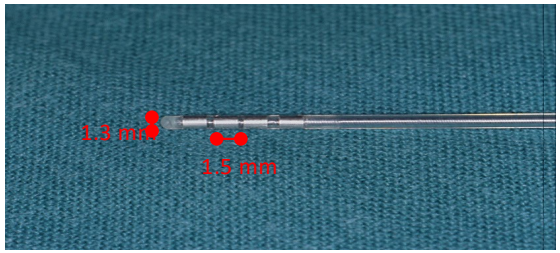
DBS











- **Riduzione fasi off ~60%**
- **Riduzione discinesie ~50%**

Contents lists available at ScienceDirect

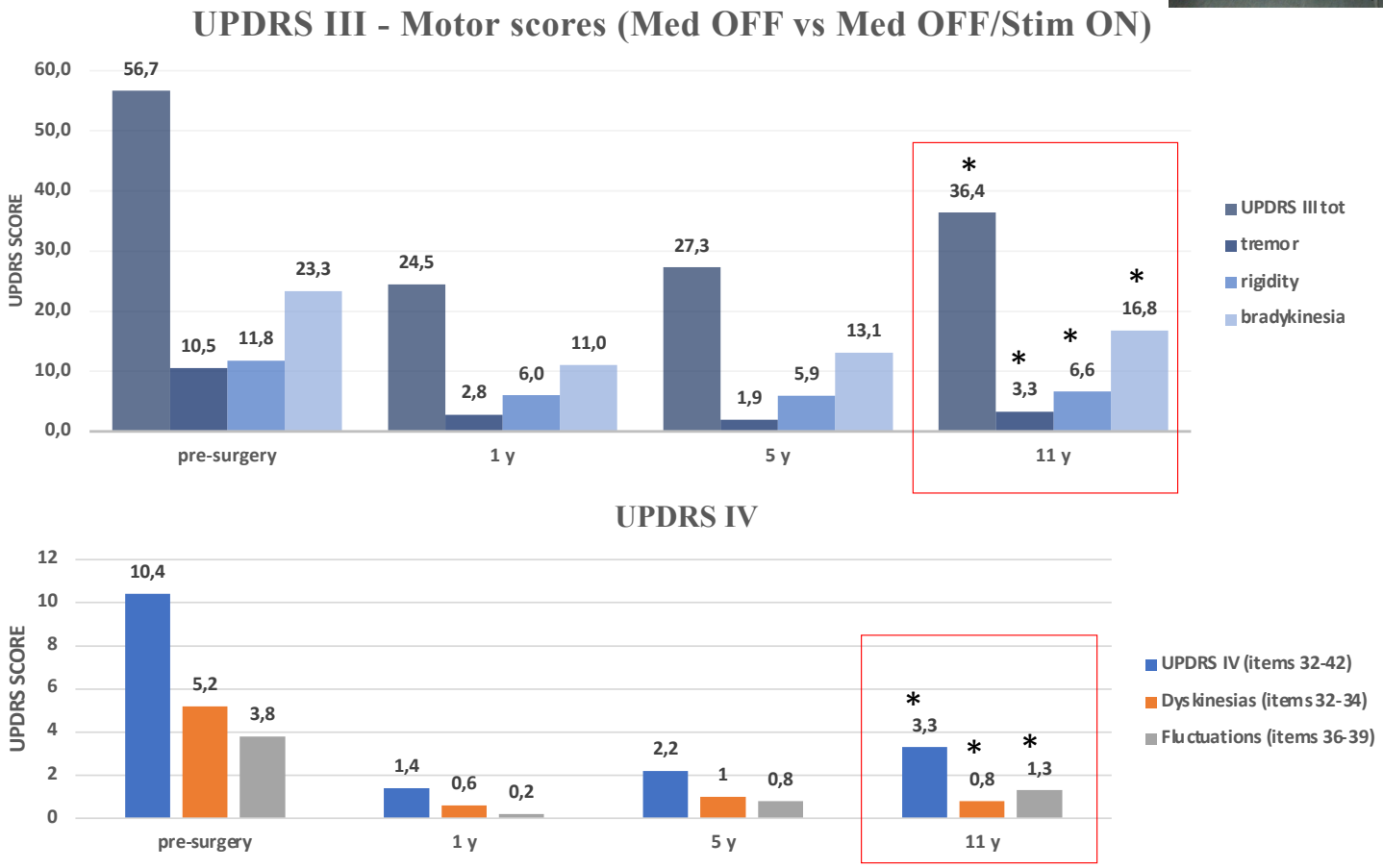
Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease?

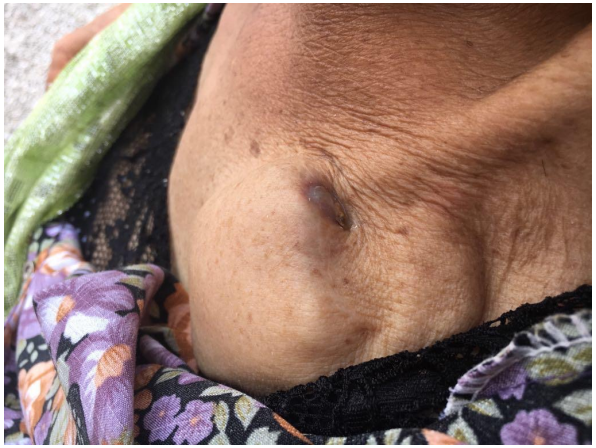
M.G. Rizzone [a], A. Fasano [b], A. Daniele [b], M. Zibetti [a], A. Merola [a], L. Rizzi [a], C. Piano [b], C. Piccininni [b], L.M. Romito [c], L. Lopiano [a,*], A. Albanese [b,c]

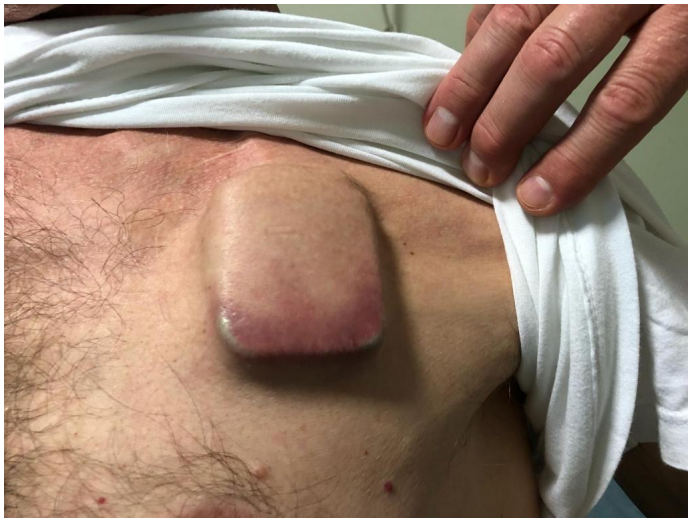
- **26 patients**
- **Mean Follow-up: 11 years**

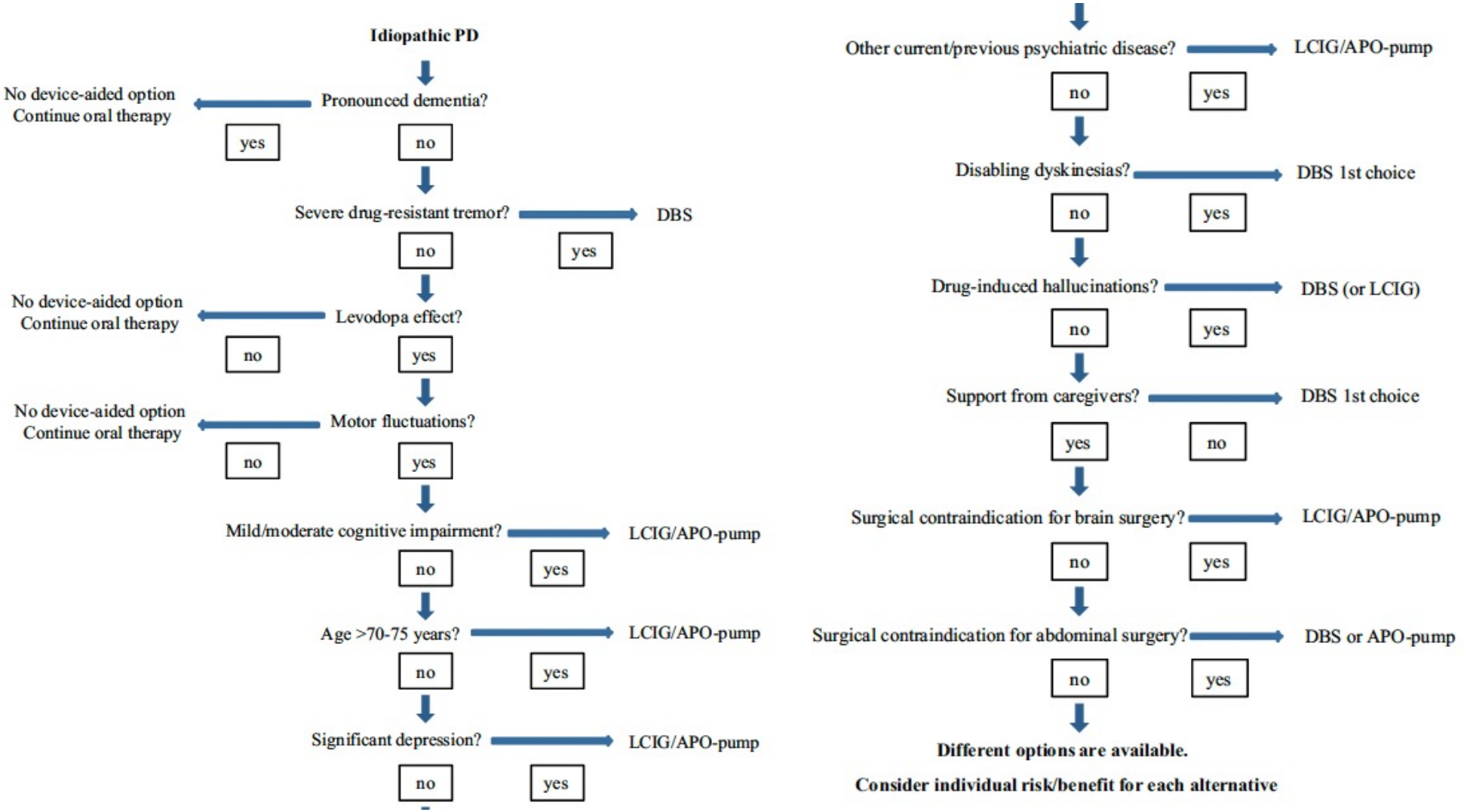


Effetti collaterali DBS

- Complicanze chirurgiche
  - Emorragie intracerebrali
  - Infezioni del sistema
- Dislocazione elettrodi
- Rotture cavi di connessione
- Effetti collaterali stimolo correlati
  - Contratture
  - Distonie
  - Parestesie
- Aumento di peso
- Disartria/ipofonia







E. Dietrichs et al., Acta Neurol Scand, 2017

Neurologia

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- Dr. ssa C. Ledda

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Grazie dell'attenzione

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