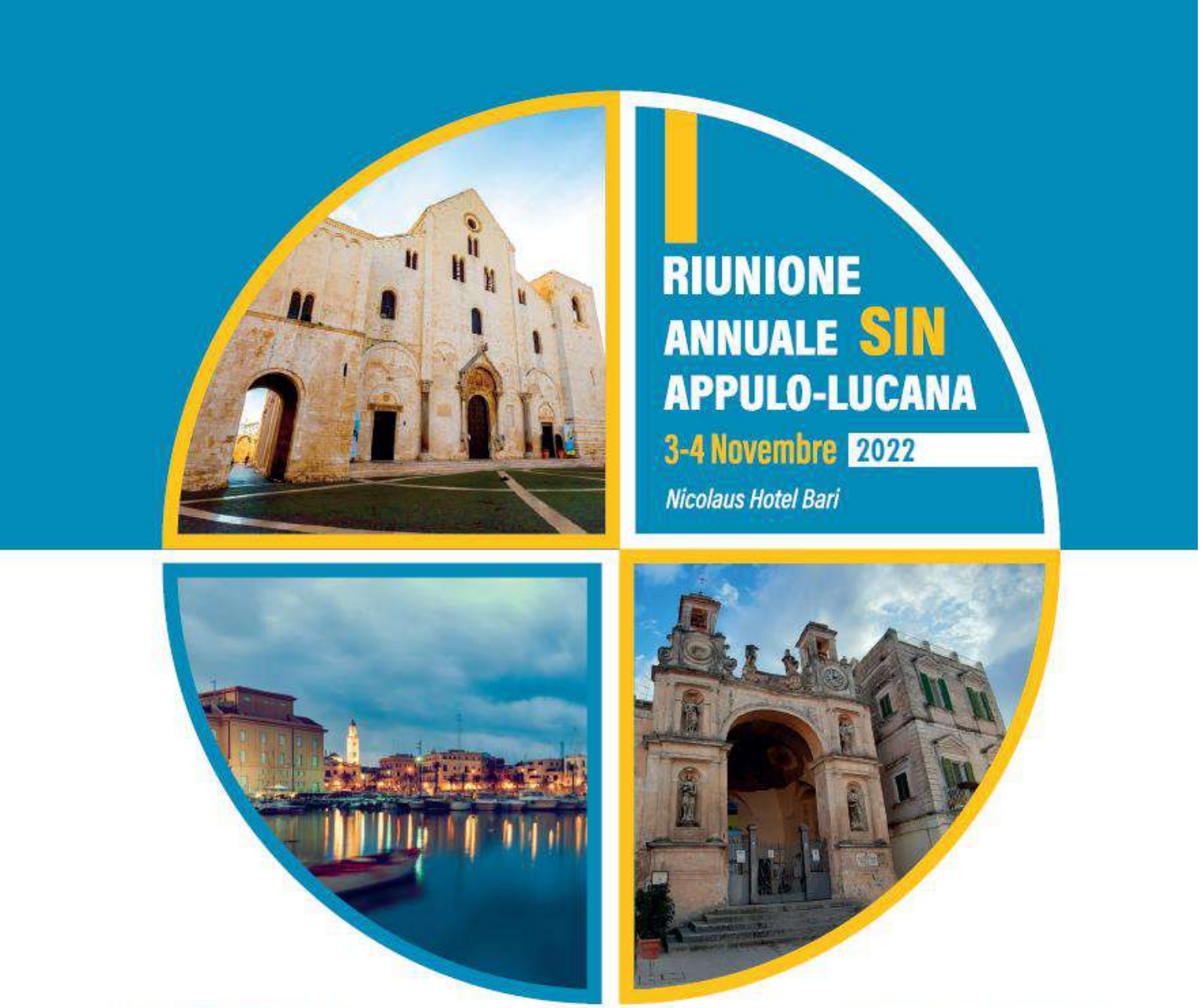
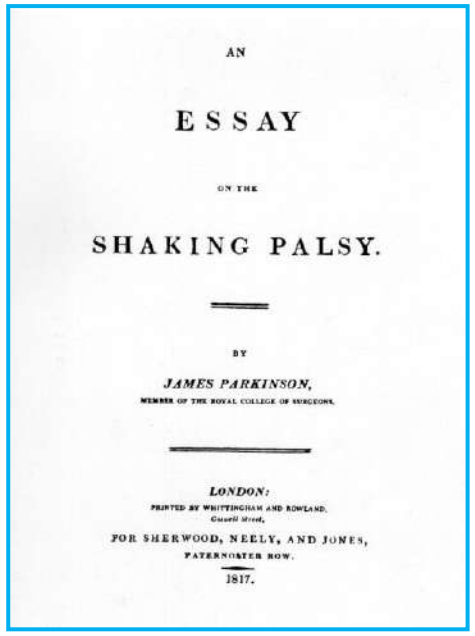


Impatto delle fluttuazioni motorie e non motorie sulla qualità di vita nei pazienti con malattia di Parkinson in fase intermedia

Giovanni Iliceto
UOC Neurofisiopatologia
AOU Policlinico Bari

Progressione della M. di Parkinson


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

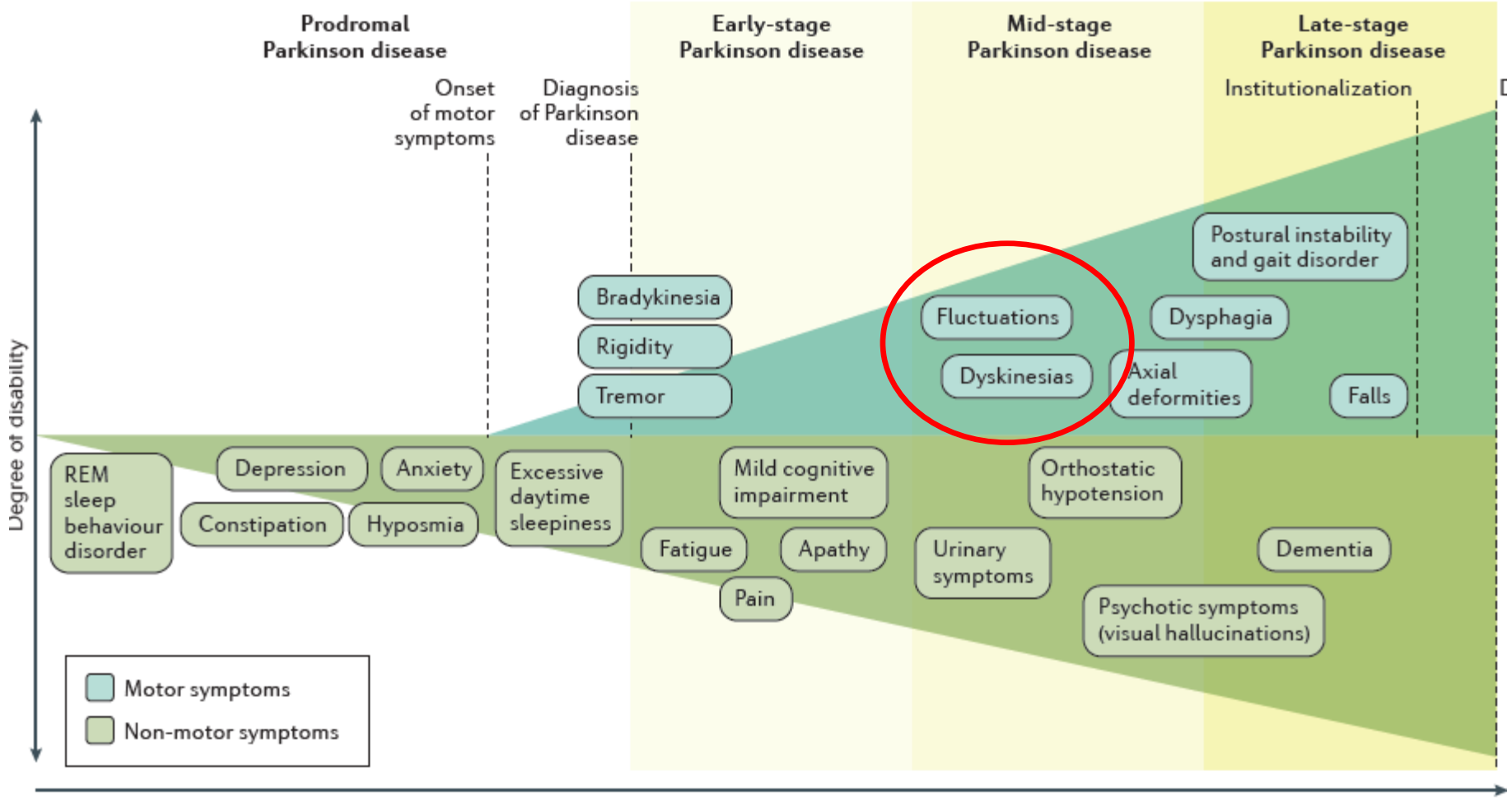
LONDON:

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

James Parkinson (1817)



Poewe W, Nature Reviews 2017

Complicanze motorie correlate all'uso della L-dopa

Fluttuazioni motorie

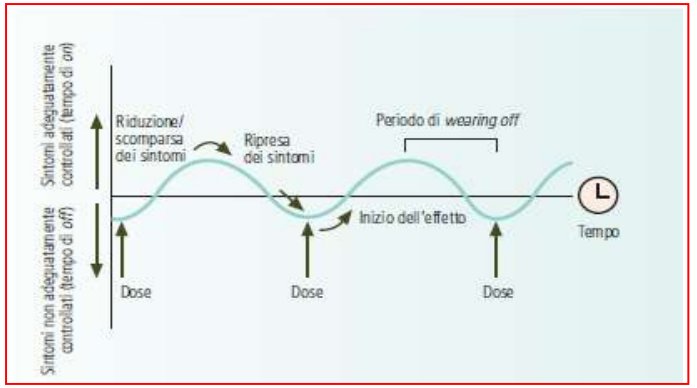
- Prevedibili: *Wearing-off*
  On-off

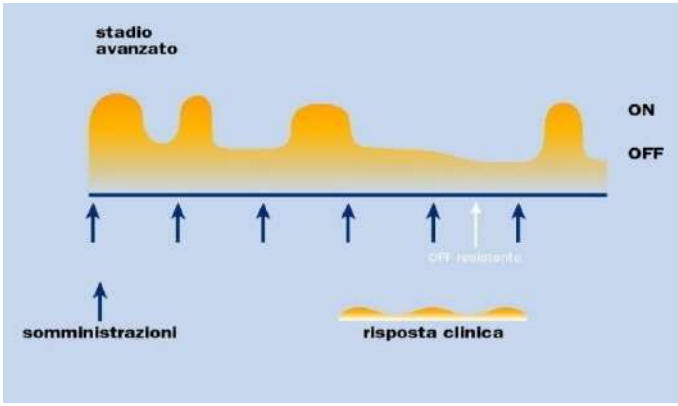
- Non prevedibili: *On-off*
- Ritardo dell'on
- Off resistente

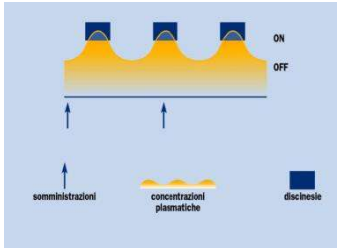
Movimenti involontari

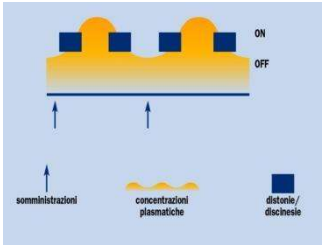
Discinesie da picco

- Discinesie inizio-fine dose
- Distonia off (al risveglio, di fine dose)

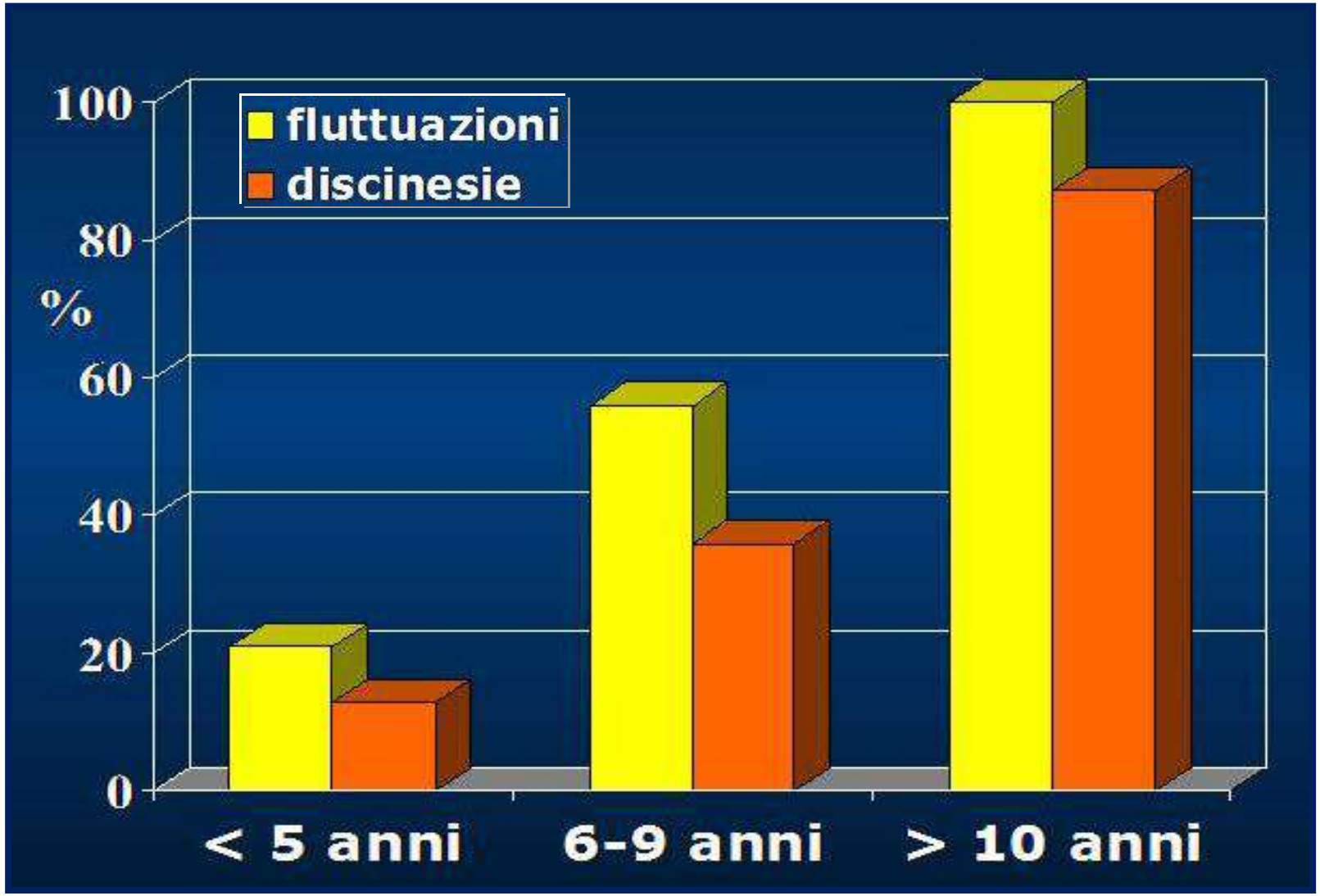








Prevalenza delle fluttuazioni motorie e discinesie in pazienti trattati con L-dopa



Schrag and Quinn, Brain 2000

CAUSE DELLE COMPLICANZE MOTORIE CORRELATE ALLA TERAPIA CON L-DOPA

"Limiti" farmacocinetici della Levodopa

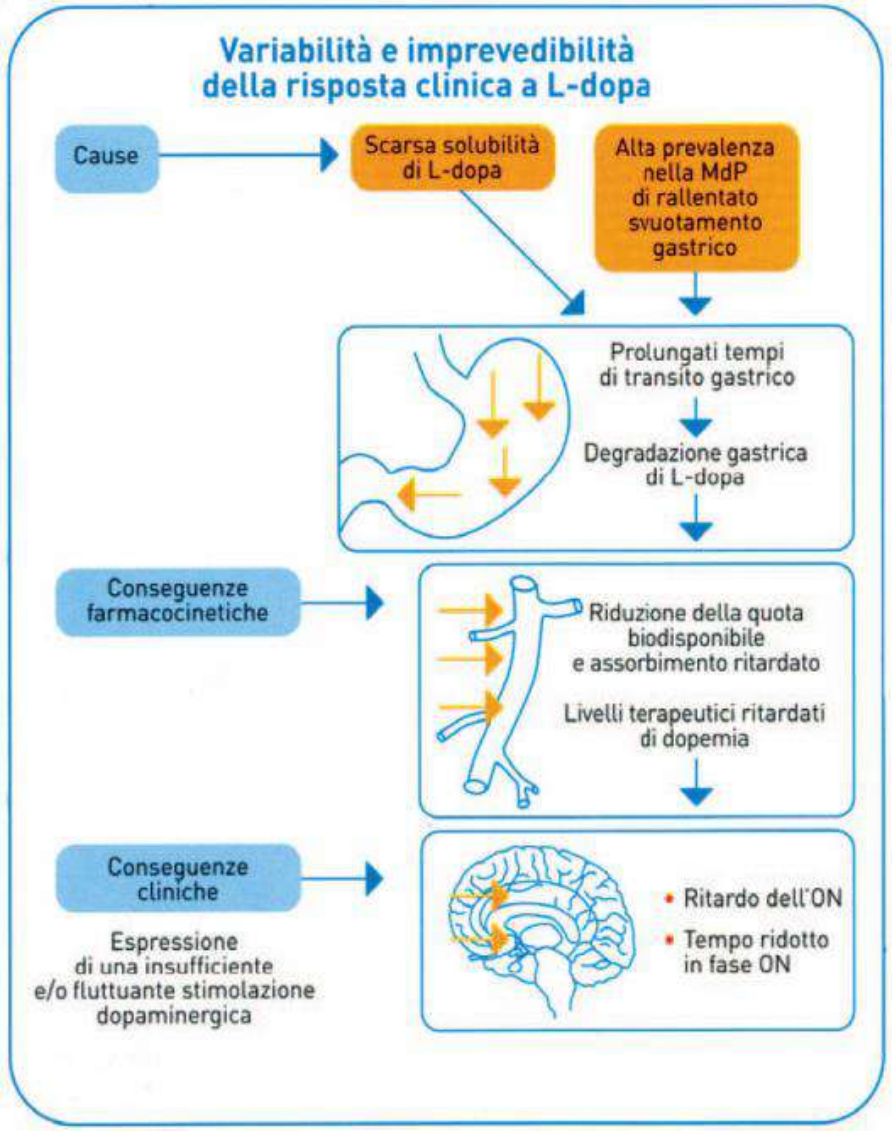
- Assorbimento solo nel terzo prossimale del piccolo intestino
- Assorbimento dipendente dallo svuotamento gastrico

- Ostacoli periferici all'assorbimento (infezione da *HP* e la *SIBO)*

- Breve emivita plasmatica (90-120 min)

- Competizione nel passaggio barriere (intestinale ed ematoencefalica)

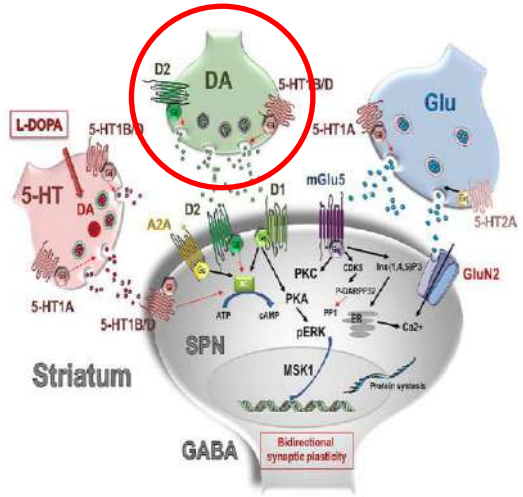
Livelli plasmatici variabili e fluttuanti



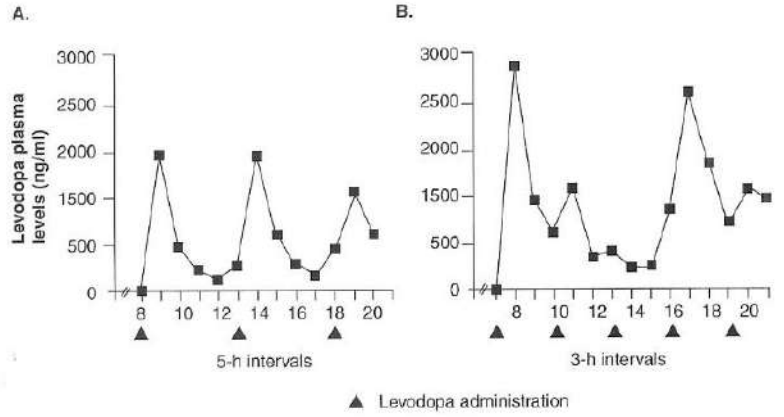
CAUSE DELLE COMPLICANZE MOTORIE CORRELATE ALLA TERAPIA CON L-DOPA

- **Fattori farmacocinetici** *Breve emivita plasmatica Levodopa, variabilità assorbimento, competizione per trasporto attraverso BEE*

- **Denervazione dopaminergica presinaptica** con riduzione della "capacità di storage" della dopamina
  Le fluttuazioni dei livelli plasmatici della levodopa dovute alla breve emivita del farmaco non possono più essere "tamponate"



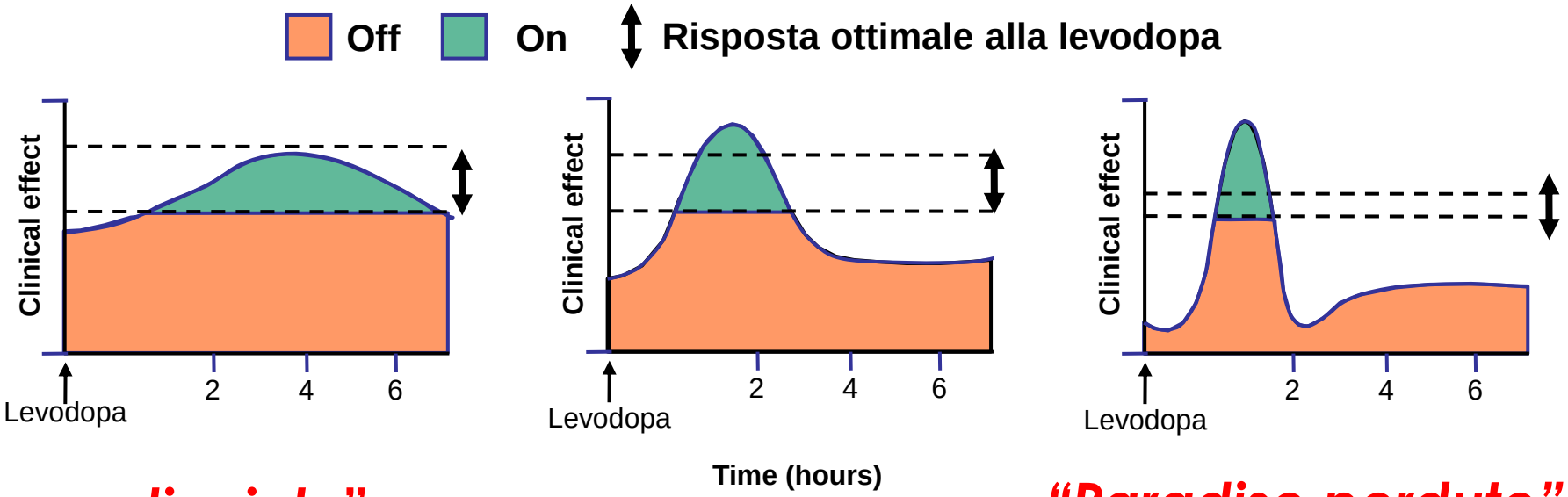
- - Livelli plasmatici variabili e fluttuanti
  - Livelli cerebrali di dopamina fluttuanti
  - Stimolazione dopaminergica pulsatile



- **Modificazioni farmacodinamiche** del recettore post-sinaptico

Risposta alla Levodopa e progressione della malattia

- **Riduzione progressiva della durata d'azione della L-Dopa**
- **Graduale riduzione della finestra terapeutica della L-Dopa**
  intervallo tra la dose di farmaco che produce effetti antiparkinsoniani e quella che induce movimenti involontari



"Luna di miele"

Fase iniziale

- **Risposta motoria di lunga durata**
- **Bassa incidenza di discinesie**

Fase intermedia

- **Risposta motoria di breve durata**
- **Aumentata incidenza di discinesia**

"Paradiso perduto"

Fase avanzata

- **Risposta motoria di breve durata**
- **Periodi "on" associati a discinesie**

Obeso et al, 2000

Complicanze motorie - Fattori di rischio

Malattia

- Durata di malattia / Gravità di malattia
- Esordio giovanile (< 40-50 aa)
- Gentotipo (parkina, Pink1....)
- Fenotipo clinico: *PD rigido-bradicinetico > PD tremorigeno*

Trattamento

- Dose giornaliera di L-dopa (>400 mg/die; 6-8 mg/kg/die)
- Emivita ($t_{1/2}$) farmaci DA

Fattori individuali

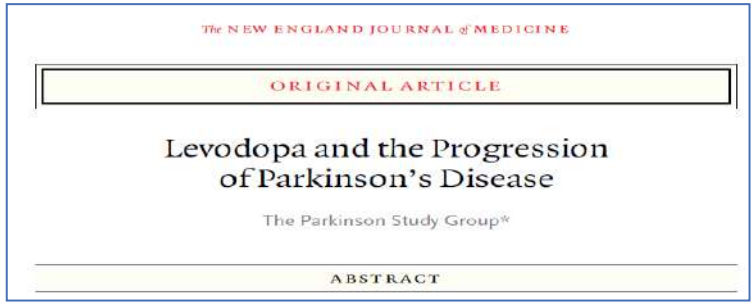
- Peso corporeo
- Sesso (F > M)
- Consumo di caffè
- Aderenza allo schema terapeutico
- Fattori locali gastro-intestinali *(svuotamento gastrico, HP, SIBO, stipsi...)*

How to treat: the relevance of dosage

The ELLDOPA Study

Motor complications may emerge after only 40 weeks of therapy:

ELLDOPA trial - 361 Patients with PD (HY stage < 3)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levodopa and the Progression of Parkinson's Disease

The Parkinson Study Group*

ABSTRACT

N Engl J Med 2004

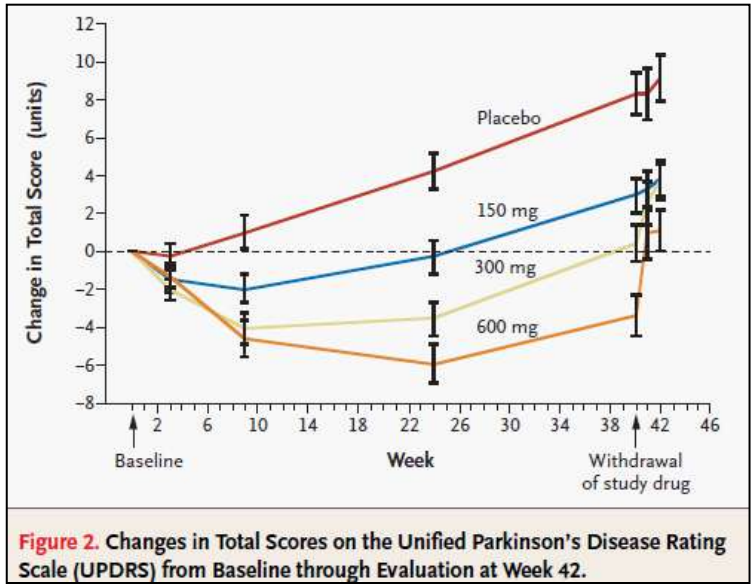
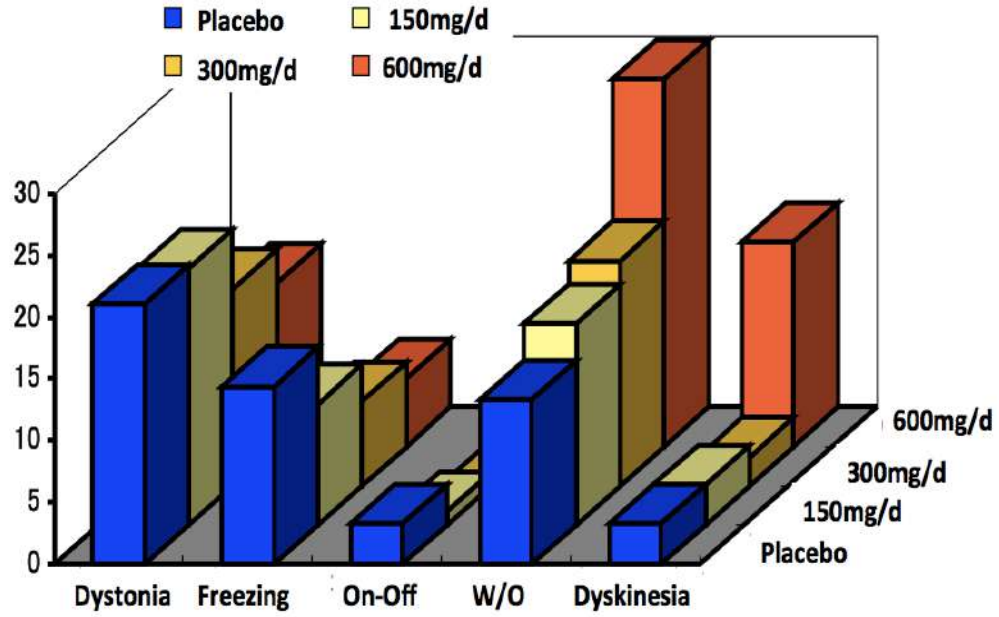


Figure 2. Changes in Total Scores on the Unified Parkinson's Disease Rating Scale (UPDRS) from Baseline through Evaluation at Week 42.

"higher doses of L-dopa were associated with increases in dyskinesia and wearing-off"



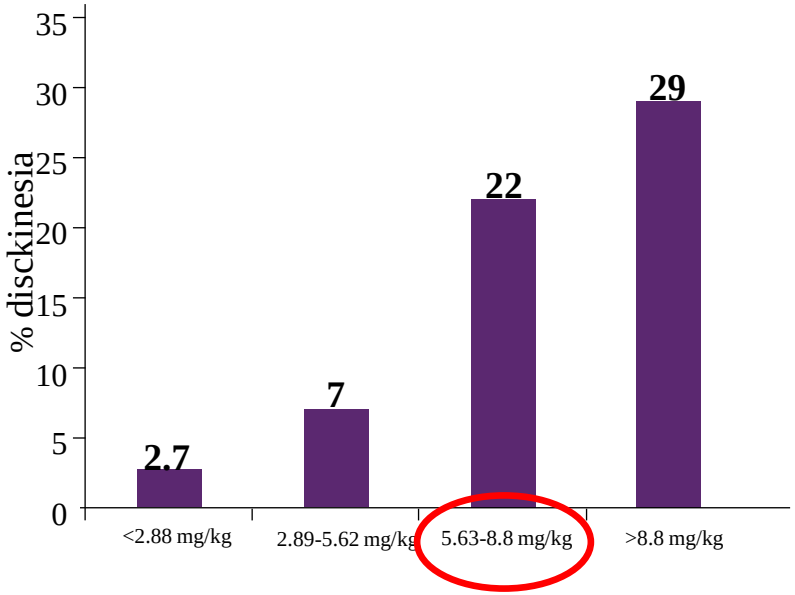
Il dosaggio di l-dopa è un fattore predittivo per lo sviluppo di discinesie e wearing-off

RESEARCH ARTICLE

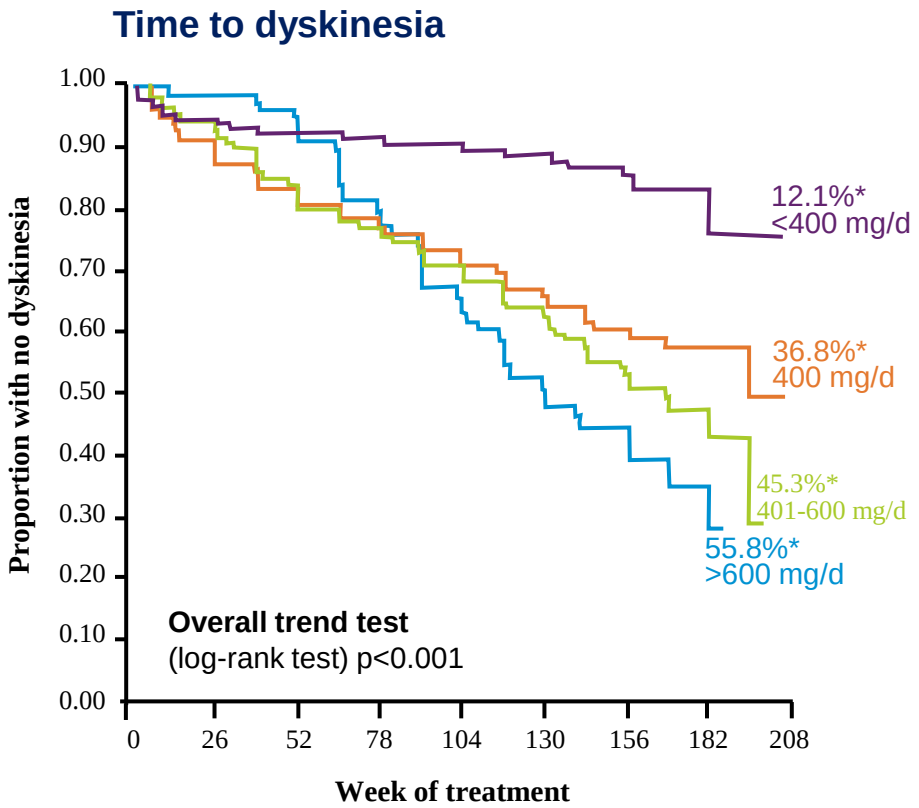
Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

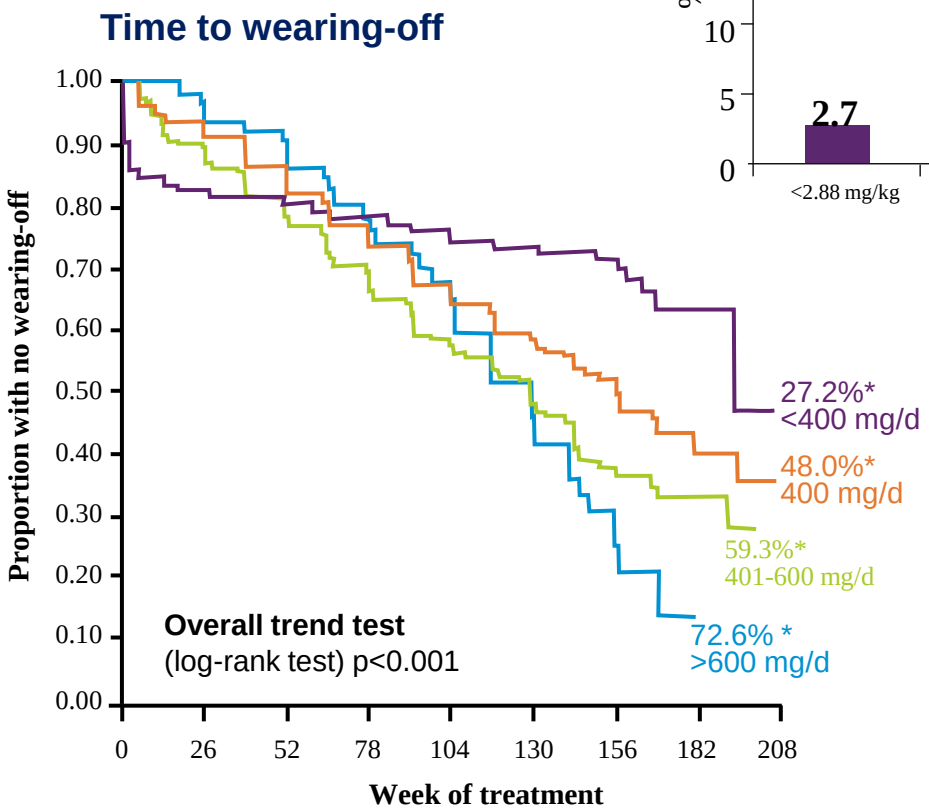
C. Warren Olanow, MD, FRCPC,[1,2]* Karl Kieburtz, MD, MPH,[3] Olivier Rascol, MD, PhD,[4] Werner Poewe, MD,[5] Anthony H. Schapira, MD, DSc, FRCP, FMedSci,[6] Murat Emre, MD,[7] Helena Nissinen, MD, PhD,[8] Mika Leinonen, MSci,[9] Fabrizio Stocchi, MD, PhD,[2] for the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators

Movement Disorders, Vol. 28, No. 8, 2013



Sharma JC, Park Rel Dis 2006





doi:10.1093/brain/awu195 Brain 2014: 137; 2731–2742 | 2731

BRAIN
A JOURNAL OF NEUROLOGY

The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa

Roberto Cilia,[1] Albert Akpalu,[2] Fred Stephen Sarfo,[3] Momodou Cham,[4] Marianna Amboni,[5,6] Emanuele Cereda,[7] Margherita Fabbri,[8] Patrick Adjei,[2] John Akassi,[3] Alba Bonetti[1] and Gianni Pezzoli[1]

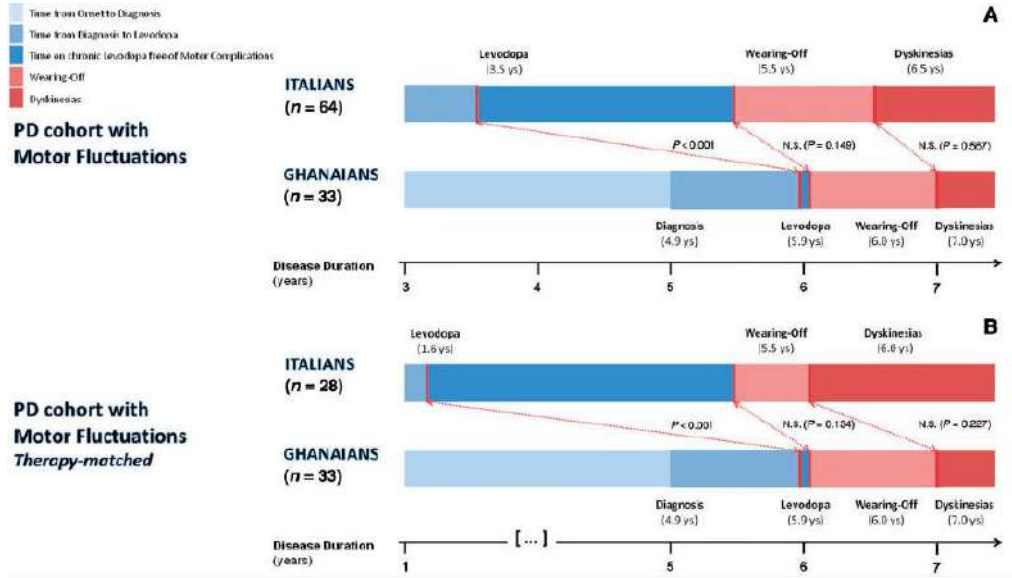
Although levodopa therapy was introduced later in Ghana, disease duration at the occurrence of motor fluctuations and dyskinesias was similar in the two populations.

Motor fluctuations and dyskinesias are not associated with the duration of levodopa therapy, but rather with longer disease duration and higher levodopa daily dose

In multivariate analysis:
- disease duration
- levodopa daily dose (mg/kg)

were associated with motor complications

- 4-year multicentre study
- To investigate whether the occurrence of motor complications is primarily related to the duration of levodopa therapy or to disease-related factors
- Cohort of 91 PD patients in a sub-Saharan African country (Ghana), compared to 2282 consecutive Italian patients recruited during the same period



Terms used to describe “Off” states in PD due to levodopa therapy

Motor Fluctuations/“Offs”
• Wearing off or end-of-dose deterioration
• On-Off phenomenon/Sudden “off”/Random “off”
• Yo-yo-ing
• Early morning akinesia/bradykinesia
• Delayed “on”
• Dose failure or No “on”
• Weak response at the end of day

Non-motor “offs”
• Sensory “off”
• Behavioral “off”
• Non-motor “off”
• Non-motor fluctuations

Adapted from *Stocchi* and *Fahn*

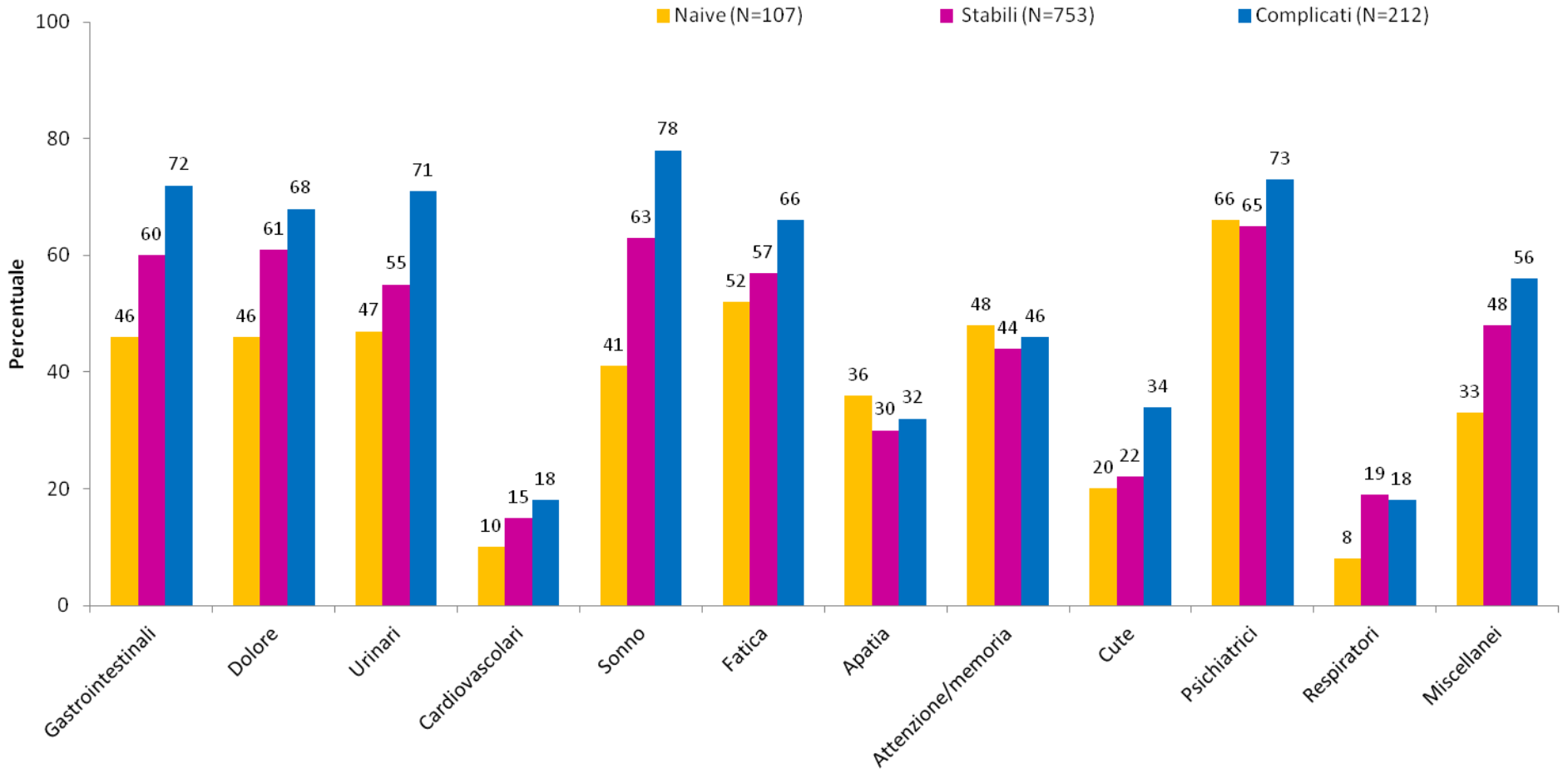
Sintomi non-motori (NMS) della Malattia di Parkinson

Sintomi Neuropsichiatrici	• Depressione, apatia, ansia, anedonia, deficit dell'attenzione, allucinazioni • Delusione, demenza, comportamento ossessivo
Disturbi del sonno	• Gambe senza riposo, movimenti periodici degli arti, disordini REM • Eccessiva sonnolenza diurna, sogni vividi, movimenti non-REM correlati, insonnia
Sintomi autonomici	• Disturbi della vescica, urgenza, nicturia, frequenza, sudorazione • Ipotensione ortostatica (OH), cadute correlate a OH • Disfunzioni sessuali, ipersessualità, impotenza erettile
Sintomi gastrointestinali (sovrapposizione con gli autonomici)	• Perdita di saliva, ageusia, disfagia/soffocamento, reflusso, vomito, • Nausea, costipazione, svuotamento insoddisfacente dell'intestino, incontinenza fecale
Sintomi sensoriali	• Dolore, parestesia, disturbi dell'olfatto
Altri sintomi	• Fatigue, diplopia, visione offuscata, seborrea, perdita di peso

Chaudhuri K R et al. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment Lancet Neurol 2009;8:464-74.

PRIAMO Study: prevalenza dei NMS a seconda dello stadio della Malattia di Parkinson

I sintomi non motori sono comuni in tutti gli stadi della Malattia di Parkinson



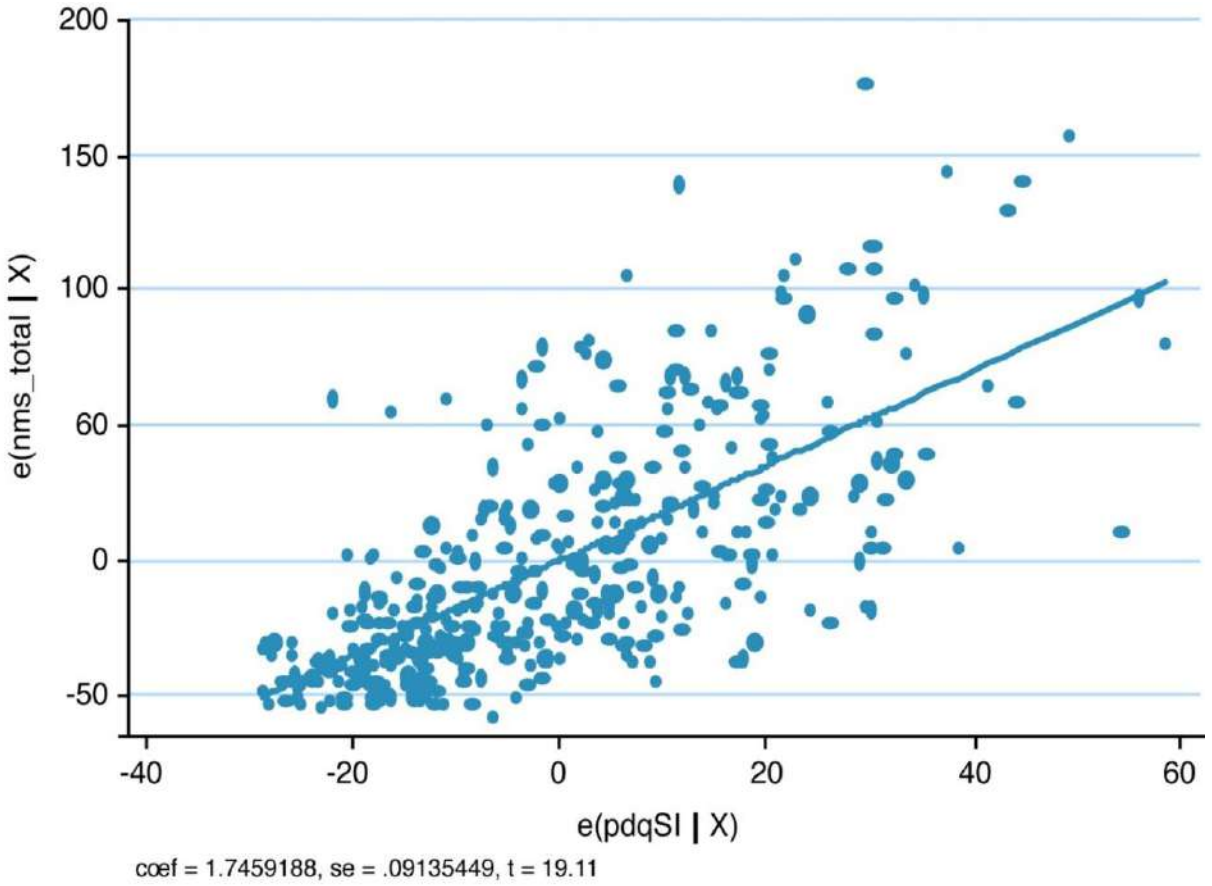
Adattata da Barone et al. Mov. Disorders 2009

PaRkInson And non Motor symptOms

Alti punteggi NMS sono associati ad un peggioramento della qualità di vita

Scala NMS
e PDQ-39

Il peso dei sintomi non motori mostra una robusta correlazione con il deterioramento della qualità di vita



Martinez-Martin P, et al. Neurology 2009;73:1584-91.

Non-motor symptoms and their relationship to the on/off state

Non-motor symptoms and their relationship to the on/off state.

NMS category	Relationship to motor OFF/ON	Response to dopaminergic treatment
Neuropsychiatric		
Depression	OFF > ON	Yes
Apathy	OFF > ON	Limited
Fatigue	OFF > ON	Limited
Panic attacks	OFF > ON	Yes
Anxiety	OFF > ON	Yes
Decline in cognitive performance	OFF > ON	Yes
Drowsiness	OFF > ON	Yes
Decline in attention	OFF > ON	Yes
Impulse control behavior[a]	ON > OFF	Yes with dose reduction
Autonomic		
Lightheadedness	OFF > ON	Limited
Abdominal pain and bloating	OFF	Yes
Constipation	OFF > ON	Yes
Urinary urgency	OFF > ON	Yes
Sweating	OFF > ON	Limited
Swallowing dysfunction	OFF > ON	Limited
Stridor	OFF	Yes
Sensory symptoms		
Diffuse pain	OFF > ON	Yes
Neuralgic pain	OFF > ON	Yes
Dysesthesia	OFF > ON	Yes
Visual disturbances	OFF > ON	Limited
Restless legs syndrome	OFF	Yes

[a] Can occur as medication ON peak effect. Adapted from Martinez-Fernandez et al. [9] and Storch et al. [15].

KL Chou, Parkinsonism and Related Disorders 2018

Fluttuazioni neuropsichiatriche

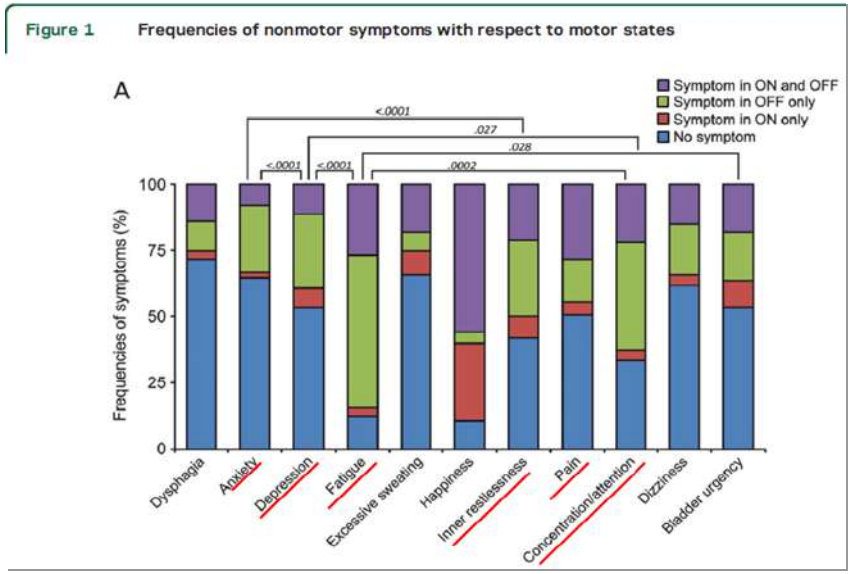
Patterns of NMS fluctuations are heterogeneous and complex, but psychic NMS fluctuate more frequently and severely.
NM symptoms shown to be worse or declared only/exclusively during off periods:

- Fatigue, Apathy
- Depression
- Anxiety
- Inner restlessness
- Lack of concentration
- Pain

Nonmotor fluctuations in Parkinson disease
Severity and correlation with motor complications

Alexander Storch, MD
Christine B. Schneider, MD
Martin Wolz, MD
Yannic Stürwald
Angelika Nebe, MD
Per Odin, MD, PhD
Andreas Mahler, MD
Gerd Fuchs, MD
Wolfgang H. Jost, MD
K. Ray Chaudhuri, DSc, MD
Rainer Koch, MD, PhD
Heinz Reichmann, MD, PhD
Georg Ebersbach, MD

Neurology 2013



REVIEW

Check for updates

Frequency of Mood and Anxiety Fluctuations in Parkinson's Disease Patients With Motor Fluctuations: A Systematic Review

Rachel M. J. van der Velden, BSc,[1] Martijn P. G. Broen, MD, PhD,[2] Mark L. Kuijf, MD, PhD,[2] and Albert F. G. Leentjens, MD, PhD[1]*

[1] *Department of Psychiatry, Maastricht University Medical Center, Maastricht, the Netherlands*
[2] *Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands*

Movement Disorders, 2018

A systematic literature search in PubMed, Medline, and the Cochrane Library. This search yielded 10 studies, of which 9 were included after quality assessment

TABLE 2. Overview of quality scores and reported frequencies of fluctuations in anxiety, depressive symptoms, panic, or mood in the included studies

Study	Quality score (n)	Anxiety fluctuations (%)	Depressive symptoms fluctuations[a] (%)	Panic fluctuations (%)	Mood fluctuations (%)
Girotti et al, 1986[27]	14	57.1	71.4		
Nissenbaum et al, 1987[23]	16	[illegible]	[illegible]		77.4
Vazquez et al, 1993[25]	16			54.5	
Richard et al, 2001[20]	16	44.0			44.0
Raudino et al, 2001[26]	15	10.5	7.9		
Witjas et al, 2002[21]	16	66.0	38.0	18.0	
Richard et al, 2004[24]	17	20.0			55.0
Pontone et al, 2011[15]	16	22.9	14.6		15.6
Storch et al, 2013[12]	16	[illegible]	[illegible]		
Weighted mean		35.4	34.9	37.1	X[a]

Fluttuazioni neuropsichiatriche

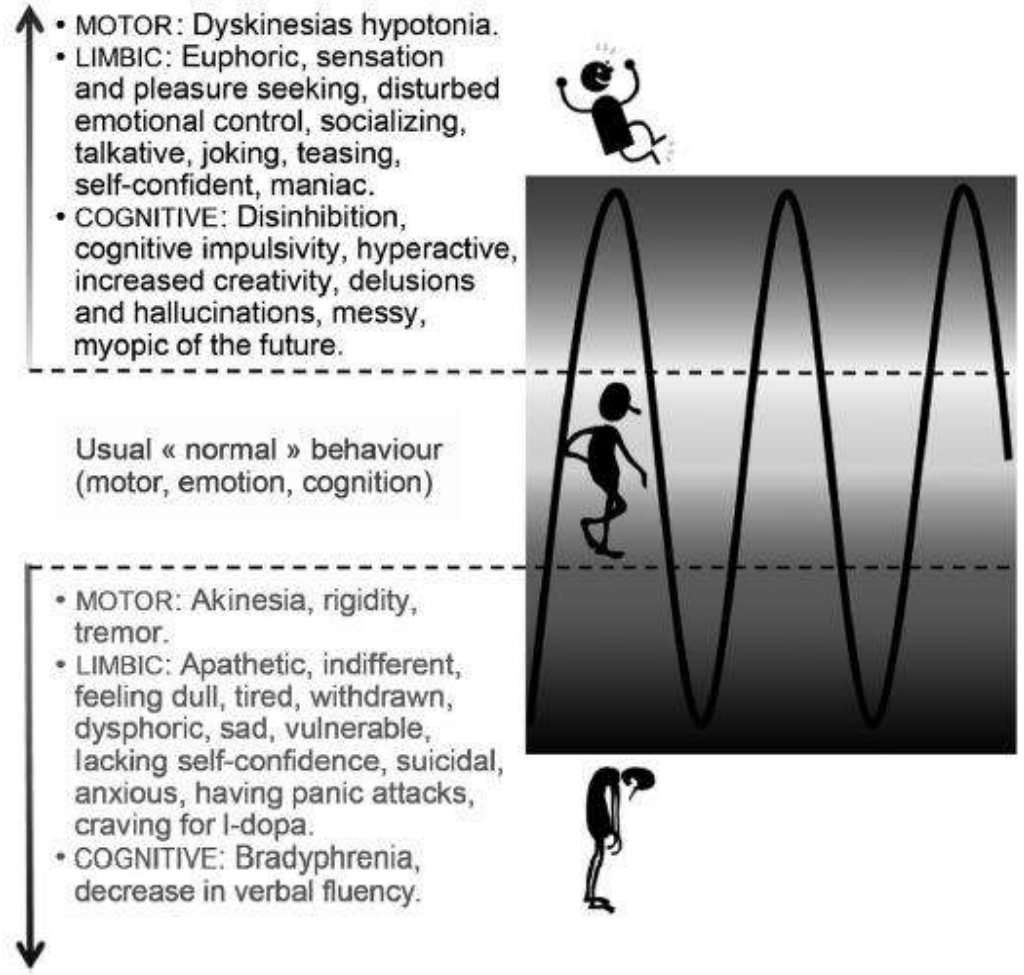
NONMOTOR SERIES: REVIEW

Mov Dis 2016

The Hidden Sister of Motor Fluctuations in Parkinson's Disease:
A Review on Nonmotor Fluctuations

Raul Martínez-Fernández, MD,[1]* Emmanuelle Schmitt, MSc,[2] Pablo Martinez-Martin, MD, PhD,[3] and Paul Krack, MD, PhD[4]

- Rappresentano le più frequenti fluttuazioni non-motorie
- Presenti nel 50% dei pazienti con NMS
- Le fluttuazioni dell' umore/ansia sono quelle con il maggior impatto negativo sulla qualità della vita



Esiste un consenso sulla definizione di “off” ?

• I termini "on" e "off" , introdotti da Marsden , sono stati utilizzati per più di 40 anni per descrivere, nei pazienti con malattia di Parkinson in fase avanzata, l’alternanza di fasi di buona **funzione motoria** *("on")* e di fasi di **immobilit**à *("off“)*

• Tuttavia, a distanza di oltre 40 anni non esiste un consenso sulla definizione degli “off”, che includono **sintomi motori e non motori**

• Quanto devono essere gravi i sintomi per poter definire un “off” ?

Esiste un consenso sulla definizione di “off” ?

- I termini "on" e "off" implicano l'esistenza di solo due stati estremi: buona mobilità e grave disabilità
- Spesso i neurologi non considerano il wearing-off come un vero “off “ oppure usano il termine “off” solo in situazioni particolarmente severe
- Spesso nella definizione di “off” i sintomi non-motori non vengono presi in considerazione
- Il termine “off” viene quindi diversamente interpretato dai neurologi e dai pazienti
- In realtà i pazienti presentano un ampio spettro di gravità “off”
- Bisogna considerare anche le sensazioni soggettive del paziente che possono invece non essere facilmente percepite dal neurologo


ARTICLE IN PRESS

Parkinsonism and Related Disorders xxx (2018) 1–8

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

2018

Review article

The spectrum of "off" in Parkinson's disease: What have we learned over 40 years?

Kelvin L. Chou [a, b, *], Mark Stacy [c], Tanya Simuni [d], Janis Miyasaki [e], Wolfgang H. Oertel [f, g], Kapil Sethi [h], Hubert H. Fernandez [i], Fabrizio Stocchi [j]

Practical definition of "off" that more broadly captures the **full spectrum of "off"**, including severity and complexity, and recognizes the functional impact of "off" symptoms

Practical definition of OFF

- **OFF is a change in the clinical state of a PD patient where motor and/or non-motor symptoms appear or worsen and result in *functional disability***

- *The combination and severity of these symptoms are unique for each patient and improve with PD therapy*.

- Previous terms used to describe various OFF states, including but not limited to wearing off, on-off phenomenon, early morning akinesia, delayed on, dose failures and off period dystonia, are all part of OFF as defined above.

REVIEW

CME

Classification of levodopa-related motor fluctuations in PD

Motor and Nonmotor Complications of Levodopa: Phenomenology, Risk Factors, and Imaging Features

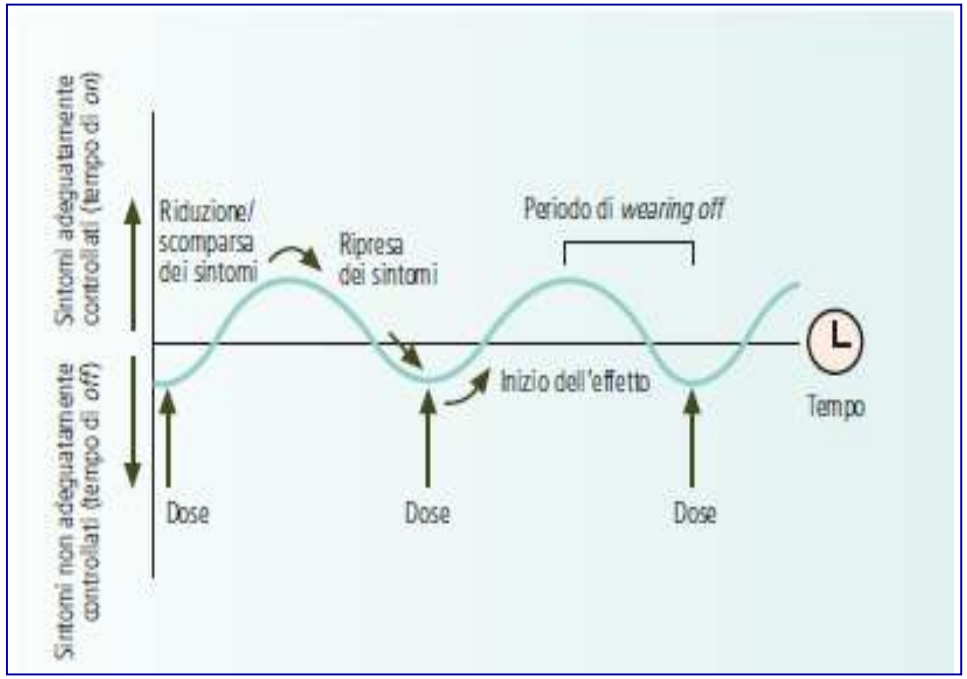
K. Ray Chaudhuri, DSc,[1]* Werner Poewe, PhD,[2] and David Brooks, DSc[3]

Mov Dis 2018

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	

Wearing-off

"La ricomparsa generalmente prevedibile di sintomi motori e non motori che precede l'assunzione della successiva dose programmata e scompare con il trattamento"



F.Stocchi. Pharmacother 2006

Il fenomeno è prevedibile da parte del paziente ed è strettamente legato ai livelli plasmatici di levodopa

Il riemergere dei sintomi non motori spesso può precedere il riemergere dei sintomi motori

- **I pazienti non riconoscono il "wearing-off'**
- **I medici non riconoscono il "wearing-off'**
- **Il "wearing-off' può essere presente anche in pazienti apparentemente «stabili»**
- **influenza l'outcome della malattia**

Review

European Neurology

Eur Neurol 2010;63:257–266
DOI: 10.1159/000300647

When Do Levodopa Motor Fluctuations First Appear in Parkinson's Disease?

Fabrizio Stocchi[a] Peter Jenner[b] Jose A. Obeso[c]

Scale per la valutazione della severità delle fluttuazioni (motorie > non-motorie)

- Wearing-off Questionnaire (WOQ-32, 19, 9)
- UPDRS – part IV
- MDS UPDRS – part IV
- Treatment Response Scale (TRS)
- PD Diary
- CAPSIT-PD
- Dispositivi mobili (giroscopi, accelerometri, etc)

Tools for the assessment of NMF

- **NOn-MOtor Fluctuation Assessment (NOMOFA).**

  A patient-rated questionnaire that captures the presence and severity of non-motor fluctuations

  validated 2021 Mov Dis

RESEARCH ARTICLE *Mov Dis 2021*

Non-Motor Fluctuations in Parkinson's Disease: Validation of the Non-Motor Fluctuation Assessment Questionnaire

Galit Kleiner, MD,[1,2*] Hubert H. Fernandez, MD,[3] Kelvin L. Chou, MD,[4] Alfonso Fasano, MD, PhD,[5,6] Kevin R. Duque, MD,[7] Diana Hengartner, MD,[3] Albie Law, BA, CCRA,[1,2] Adam Margolius, MD,[3] Yu-Yan Poon, RN,[5] Michel Sáenz Farret, MD,[5] Philip Saleh, MD, MSc,[1,2] Joaquin A. Vizcarra, MD,[7] Glenn T. Stebbins, PhD,[8] Alberto J. Espay, MD, MSc,[7] and PSG NoMoFA Study Group

- **Non-Motor Symptoms Questionnaire for PD (NMSQuest)**

- **Non-Motor Symptoms Scale (NMSS)**

- **Ardouin Scale for Behavioral Assessment in PD**

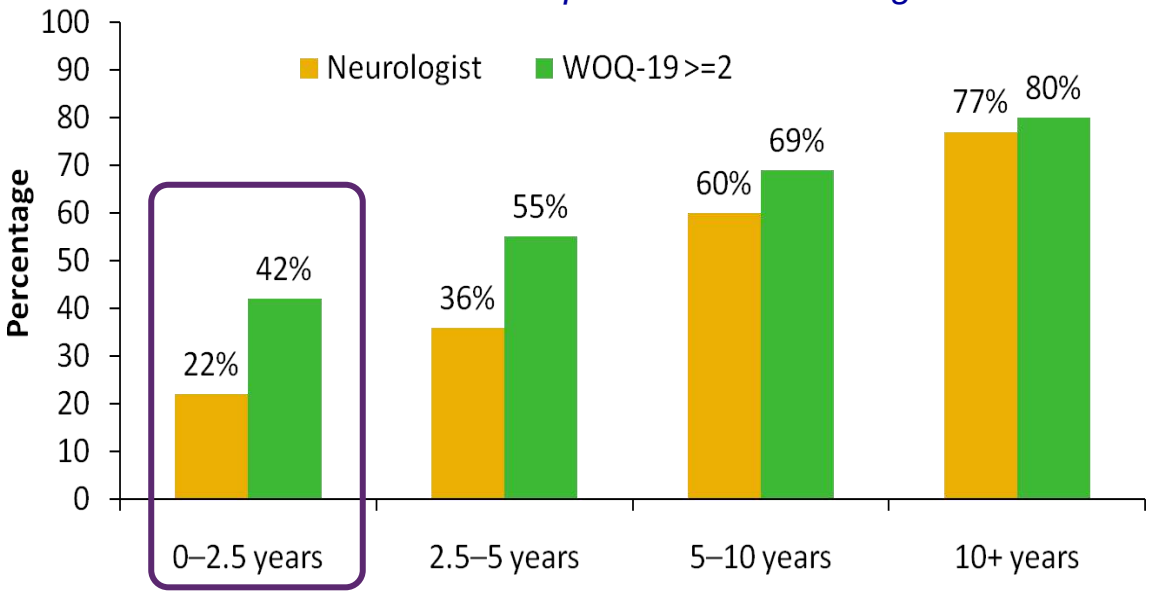
  Evaluates hypo- and hyperdopaminergic behaviors and allows to detect and quantify neuropsychiatric fluctuations by evaluating OFF-drug dysphoria and ON-drug euphoria

Identificazione del wearing-off: neurologi verso WOQ-19
DEEP study – risultati

Parkinsonism & Related Disorders 2014

617 PD pz 37 da centri italiani; durata media di malattia 8 ys
Cut-off positività al WOQ-19: ≥ 2
(2 sintomi che migliorano con l'assunzione di una successiva dose di levodopa)

Percentuale di pazienti con Wearing-off



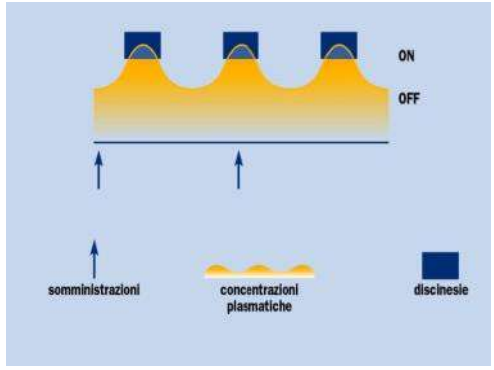
WOQ-19 (*Wearing Off Questionnaire-19*)

Sintomo	Presente	Migliora con la dose successiva
1. Tremori	☐	☐
2. Difficoltà nell'eloquio	☐	☐
3. Ansia	☐	☐
4. Ipersudorazione	☐	☐
5. Cambiamenti di umore	☐	☐
6. Debolezza	☐	☐
7. Problemi di equilibrio	☐	☐
8. Lentezza nei movimenti	☐	☐
9. Ridotta destrezza	☐	☐
10. Intorpidimento	☐	☐
11. Rigidità generale	☐	☐
12. Attacchi di panico	☐	☐
13. Mente annebbiata	☐	☐
14. Disturbi addominali	☐	☐
15. Crampi muscolari	☐	☐
16. Difficoltà nell'alzarsi dalla sedia	☐	☐
17 Sensazione di caldo o di freddo	☐	☐
18. Dolore	☐	☐
19. Anomala sensazione di dolore	☐	☐

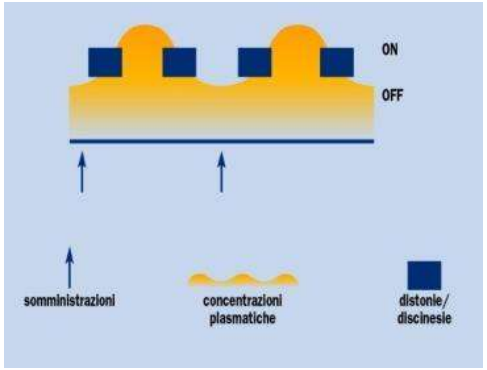
- 57 % pazienti presentava *wearing-off* secondo giudizio clinico
- 67 % pazienti presentava wearing-off secondo il WOQ-19

Complicanze motorie
Discinesie

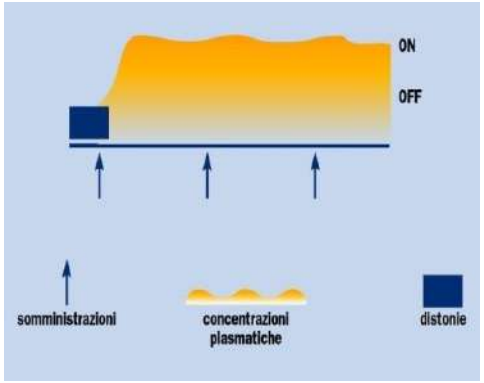
- **Caratteristiche cliniche:** movimenti coreici, ballici, distonia, pattern misti
- **Distribuzione corporea**: generalmente cominciano dal lato più affetto dalla malattia ma possono interessare il tronco, il distretto cranico e la muscolatura respiratoria
- **Rapporto temporale** con assunzione della Levodopa



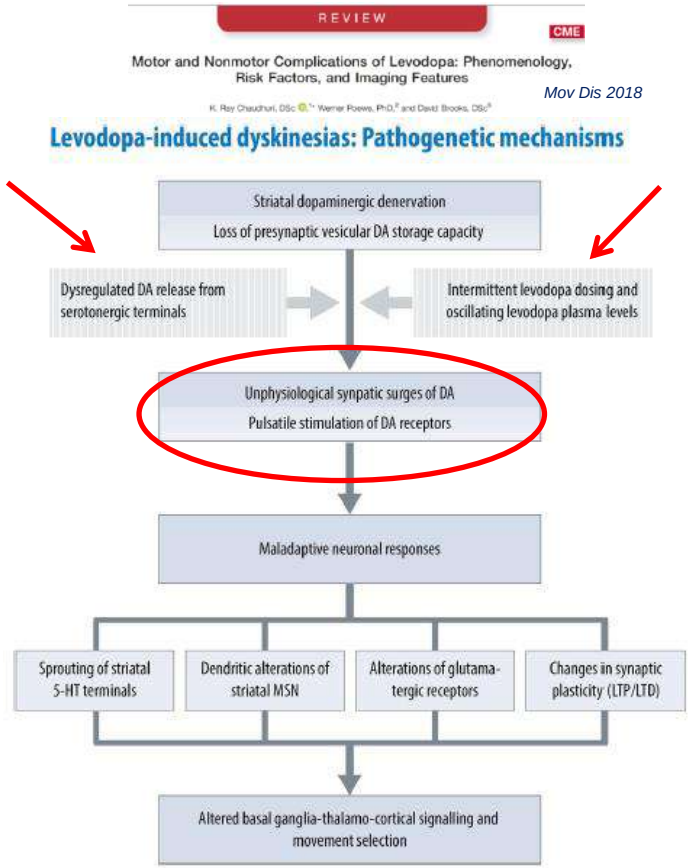
Discinesie da picco



Discinesie inizio-fine dose



Distonia off



IL PUNTO DI VISTA DEL PAZIENTE IN FASE INTERMEDIO/AVANZATA

Movement Disorders
Vol. 25, No. 11, 2010, pp. 1646–1651

Parkinson's Disease Symptoms: The Patient's Perspective

Marios Politis, MD, MSc,[1,2*] Kit Wu, MRCP,[1,2] Sophie Molloy, MD,[3] Peter G. Bain, MD, FRCP,[3] K. Ray Chaudhuri, MD, FRCP, DSc,[4] and Paola Piccini, MD, PhD, FRCP,[1,2]

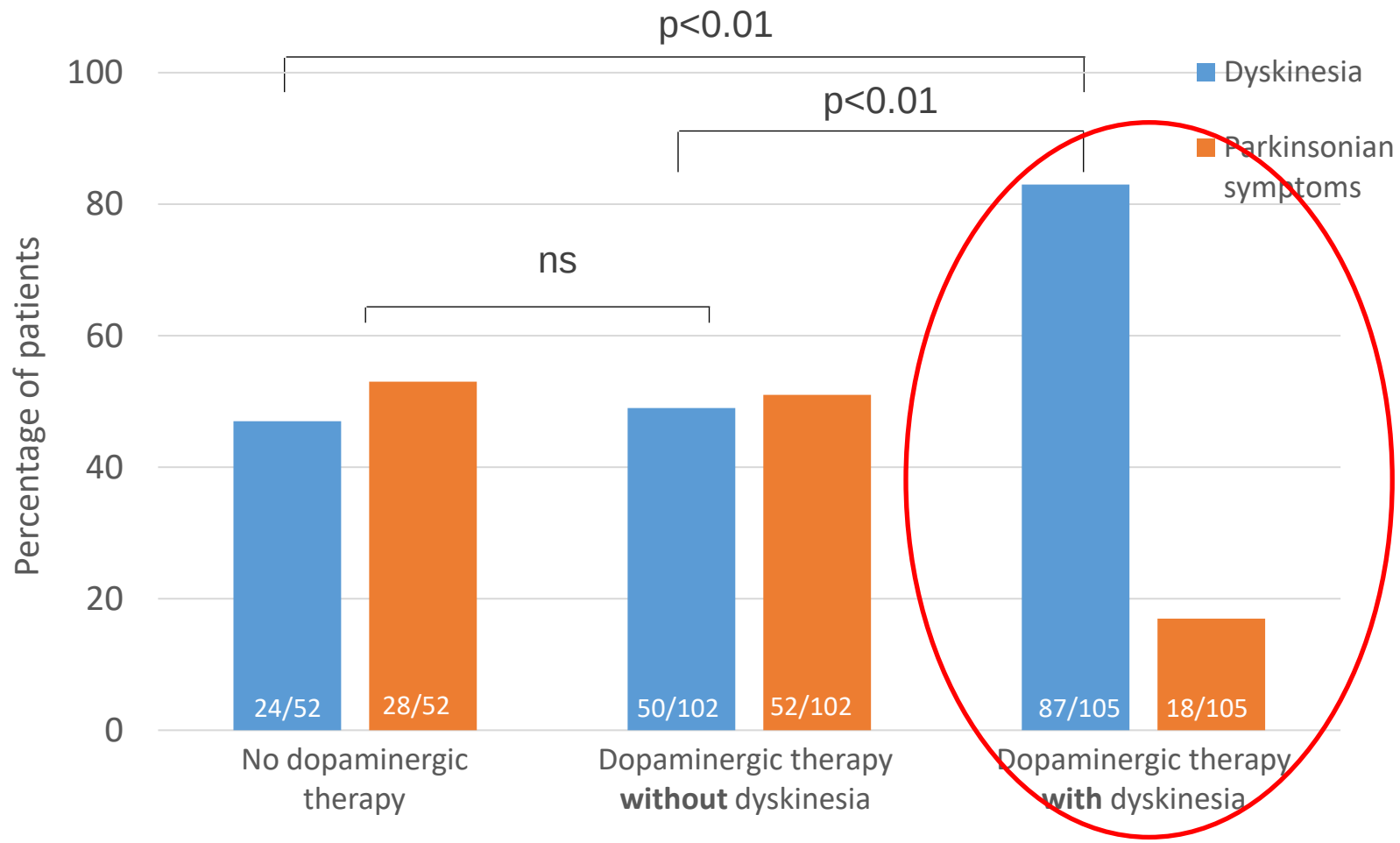
Movement Disorders 2010

TABLE 3. *Rank of the 24 most bothersome PD related symptoms/conditions in 173 advanced patients with more than 6 yr of disease duration*

Rank	Symptom/condition	Total score	First choice %	Second choice %	Third choice %	3-Choice complaint prevalence (%)
1	Fluctuating response to medication	115	15.0	8.1	5.2	28.3
2	Mood	96	7.5	12.1	8.7	28.3
3	Drooling	85	10.4	6.9	4.0	21.4
4	Sleep	83	9.8	5.2	8.1	23.1
5	Tremor	67	8.1	5.2	4.0	17.3
6	Pain	60	6.4	5.8	4.0	16.2
7	Bowel problems	46	4.0	4.0	6.4	14.5
8	Urinary problems	40	2.9	5.2	4.0	12.1
9	Falls	39	4.0	4.0	2.3	10.4
10	Appetite/weight	36	2.3	4.6	4.6	11.6
11	Slowness	34	3.5	3.5	2.3	9.2
12	Fatigue	31	2.3	2.9	5.2	10.4
13	Sexual dysfunction	29	4.6	1.2	0.6	6.4
14	Hallucinations/delusions	26	2.3	2.9	2.3	7.5

Patients' perspective depends on disease stage and personal experience

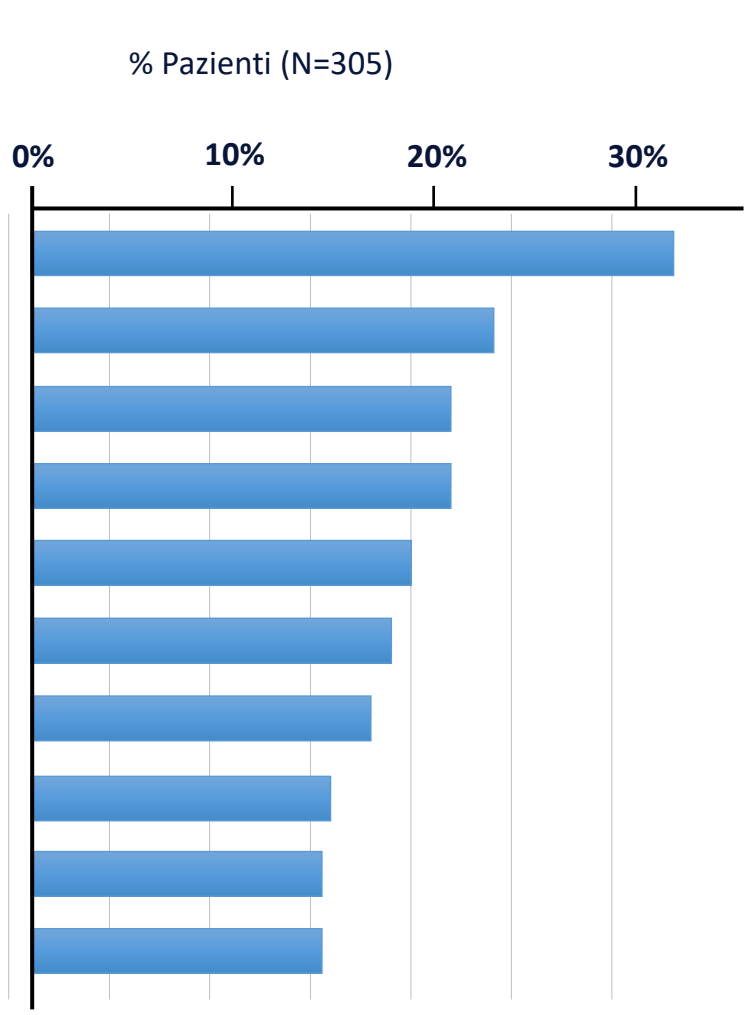
"If you had to choose, would you prefer dyskinesia or parkinsonian symptoms?"



Adapted from Hung SW et al. J Neurol Neurosurg Psychiatry 2010;81:1112–5

La prospettiva del paziente: l'OFF è limitante su molte attività della vita quotidiana

Attività classificate come **più fastidiose** perchè **più limitate durante l'OFF**



OR, odds ratio.

Risultati di una survey in pazienti con MP avanzata con fluttuazioni motorie/wearing-off con LD

Le due più importanti preferenze del paziente per un trattamento erano:

- **Durata dell' "ON"** (aumento di 1h/die; OR, 1.40)
- **Prevedibilità dell'OFF"** (entro 30 min; OR, 1.42)

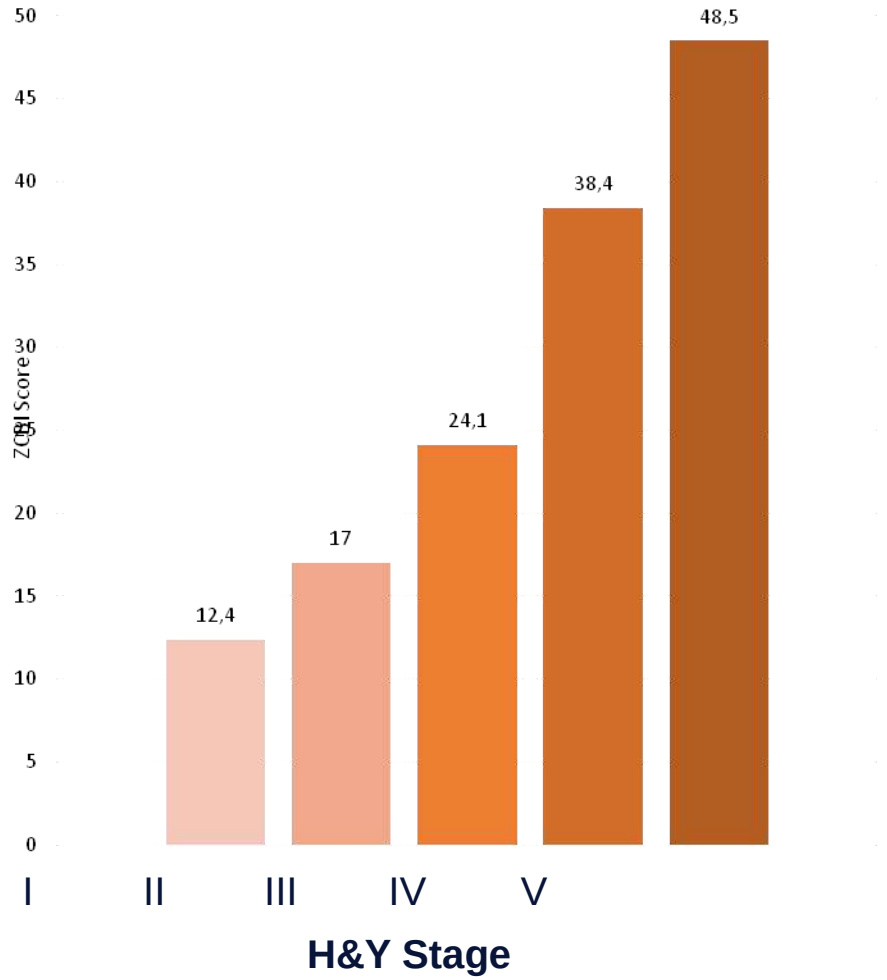
HRQL score was significantly lower for 'off time' (0.37) than for 'on time' (0.60).

Kerr C, et al. (2016) Qual Life Res, 1505-1515.

Anche il disagio del caregiver cresce proporzionalmente con la progressione di malattia

Studio osservazionale su 289 pazienti con MP e i loro caregivers

- I caregivers avevano più ansia e depressione della popolazione normale
- Il caregiver burden aumentava e la QoL si riduceva in funzione della gravità di malattia
- L'aumento del burden del caregiver si accompagna ad un peggioramento dell'ansia e depressione



Martinez-Martin, et al. (2008) Mov Disord, 1673-1680.

PD equally impacts on patients and caregivers QoL

ORIGINAL ARTICLE

2016 WILEY Acta Neurologica Scandinavica

Quality-of-life perception by Parkinson's disease patients and caregivers

Y. Balash[1,2] | A. D. Korczyn[1,2] | J. Knaani[1] | A. A. Migirov[1] | T. Gurevich[1,2,3]

- 12 PD patient-CG pairs
- PD QoL Questionnaire (PDQ-39)
- The Scale of Quality of Life of Care-Givers (SQLC)
- The Multidimensional Caregiver Strain Index (MCSI)

Agreements for QoL items were strong and comparable for the total scores of the PDQ-39, SQLC and MCSI questionnaires

	Average scores ± SD		Average agreement ± SD
	PD	CG	
QoL of PD patients assessed according to PDQ-39 scores	45.2 ± 24	46.3 ± 28.1	75.4 ± 14%
QoL of spouse/partners assessed according to SQLS scores	46.2 ± 7.2	45.3 ± 6.7	78.1 ± 14.1%
Strain of spouse/partners assessed according to MCSI scores	12.6 ± 5.6	13.1 ± 13.2	78.2 ± 14.3%

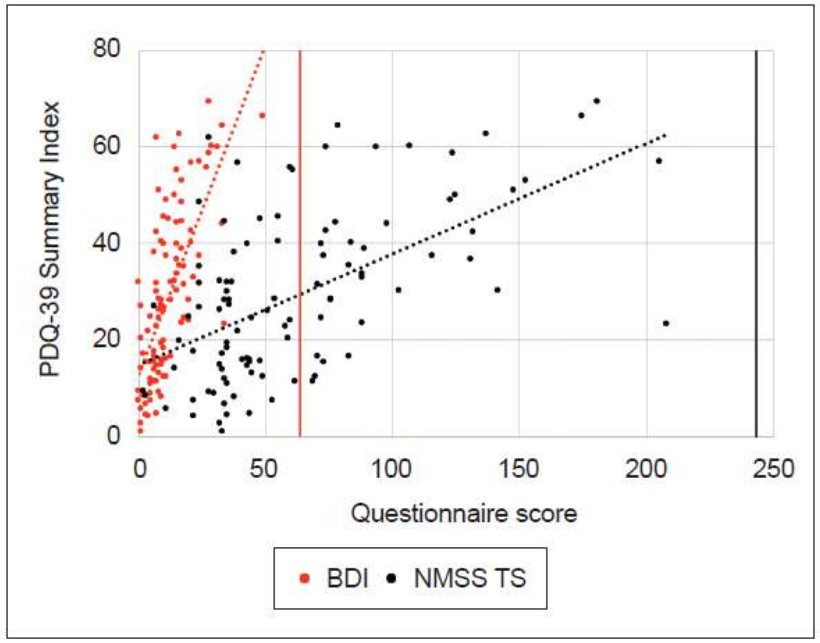
JMD
https://doi.org/10.14802/jmd.20079 / J Mov Disord 2021;14(1):42-52
pISSN 2005-940X / eISSN 2093-4939

ORIGINAL ARTICLE

Health-Related Quality of Life for Parkinson's Disease Patients and Their Caregivers

Michal Lubomski,[1,2,3] Ryan L. Davis,[2*] Carolyn M. Sue[1,2*]

103 PD patients were compared with 81 caregivers.



Strong positive correlations between **health-related quality of life** (PDQ-39) and **depression** severity (BDI) and **non-motor symptoms** (NMSS TS) in PD

PD patients perceived their health to decline by 12% more than their caregivers did over a 1-year period

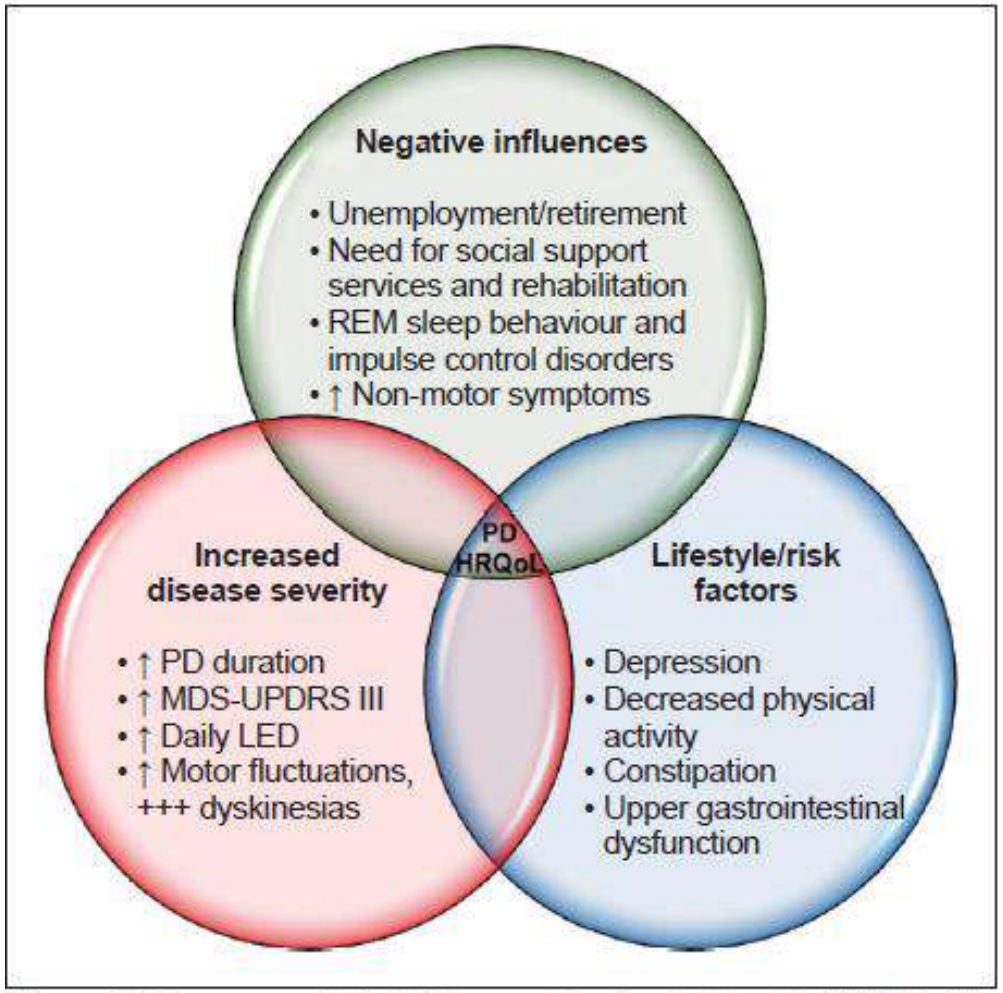


Figure 3. Summary of the influences leading to impaired HRQoL in PD. HRQoL: health-related quality of life, PD: Parkinson's disease, MDS UPDRS-IIII: Movement Disorder Society–Unified Parkinson's Disease Rating Scale–Part III, LED: levodopa equivalent dose.

Parkinsonism and Related Disorders 19 (2013) 1130–1135

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Reasons driving treatment modification in Parkinson's disease: Results from the cross-sectional phase of the REASON study

Michele Tinazzi[a], Giovanni Abbruzzese[b], Angelo Antonini[c], Roberto Ceravolo[d], Giovanni Fabbrini[e], Patrizia Lessi[f], Paolo Barone[g,*], On behalf of the REASON Study Group[1]

Neurol Sci (2015) 36:935–943
DOI 10.1007/s10072-014-2060-6

ORIGINAL ARTICLE

Clinical variables associated with treatment changes in Parkinson's disease: results from the longitudinal phase of the REASON study

Giovanni Abbruzzese · Paolo Barone · Roberto Ceravolo · Giovanni Fabbrini · Patrizia Lessi · Alessandra Ori · Lucia Simoni · Michele Tinazzi · Angelo Antonini

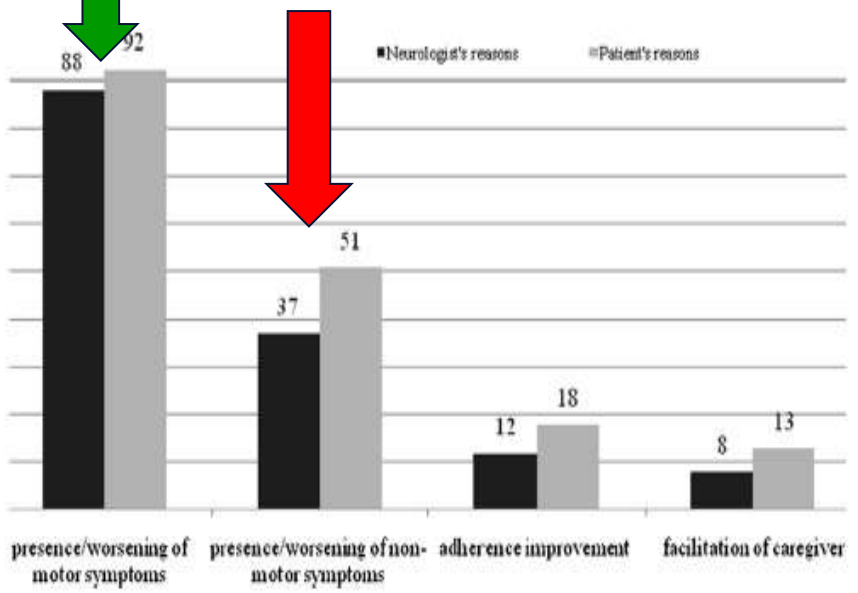


Fig. 1. Rates of neurologist's reasons driving to APD therapy and patient's causes of dissatisfaction with ongoing APD therapy at baseline: the REASON study.

775 PD patients
51 % early PD (HY 1-2)
49 % advanced PD (HY 2.5-4)

- Il motivo principale per il cambio terapia da parte dei neurologi era la presenza/peggioramento dei sintomi motori nell'88% dei casi
- I SNM erano motivo di insoddisfazione verso il trattamento per il 51% dei pazienti ma solo il 37% dei neurologi considerava questi ultimi un valido motivo per il cambio terapia

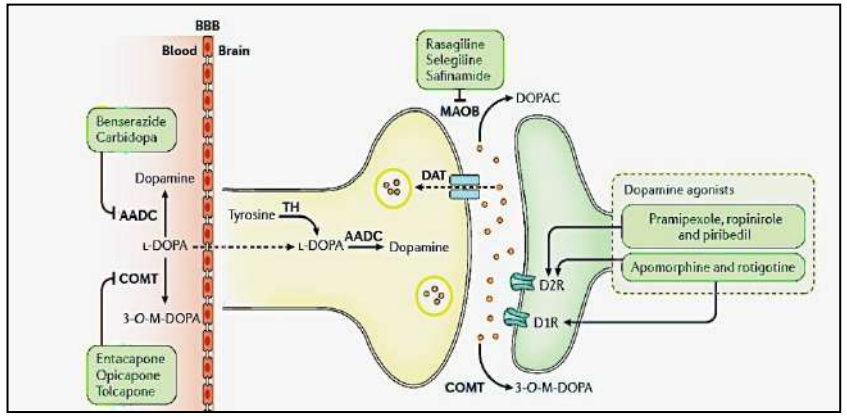
Evoluzione dei sintomi non motori nella M. Parkinson

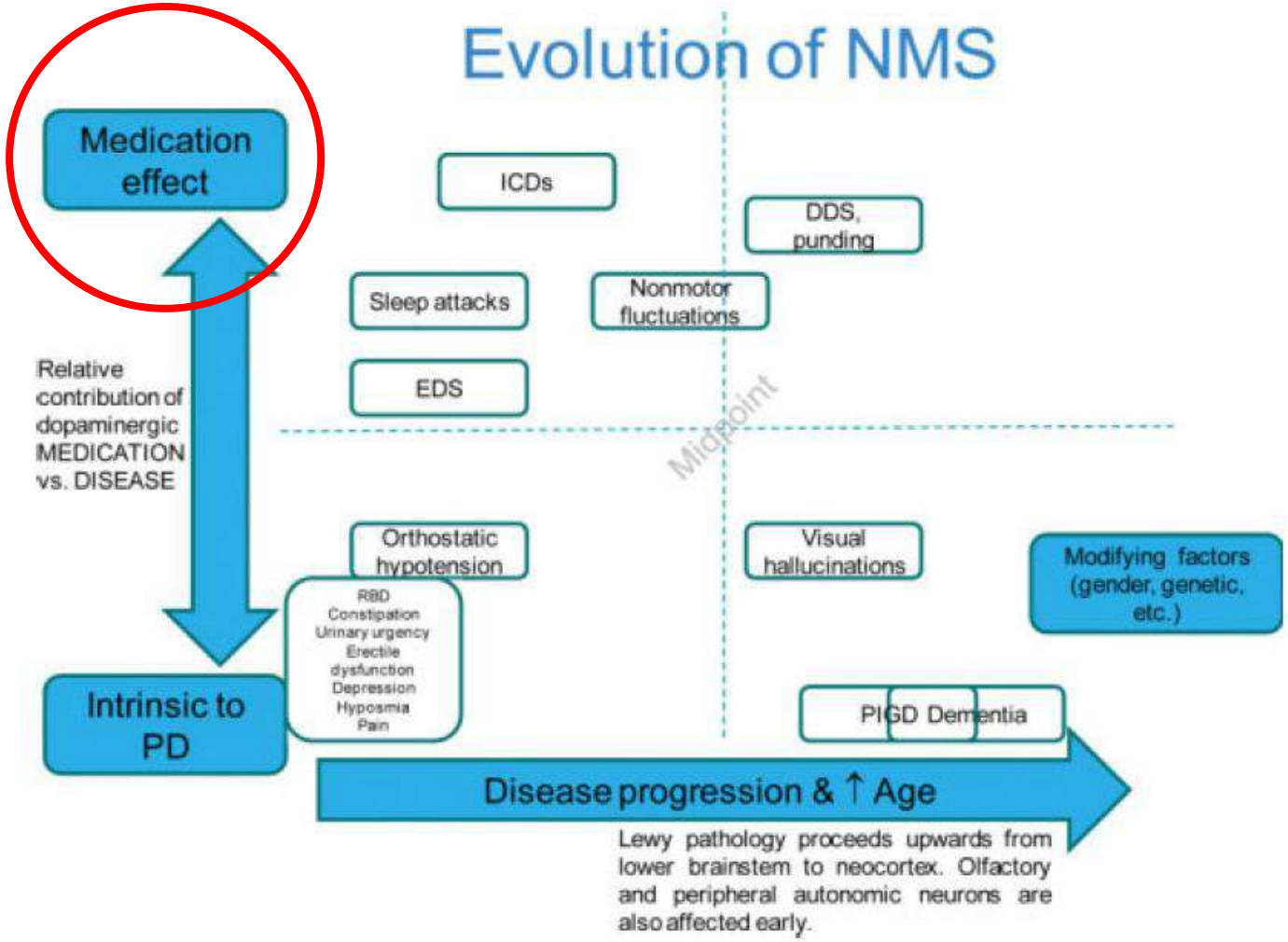
Movement Disorders
Vol. 25, Suppl. 1, 2010, pp. S123–S130

The Nonmotor Symptoms of Parkinson's Disease—An Overview

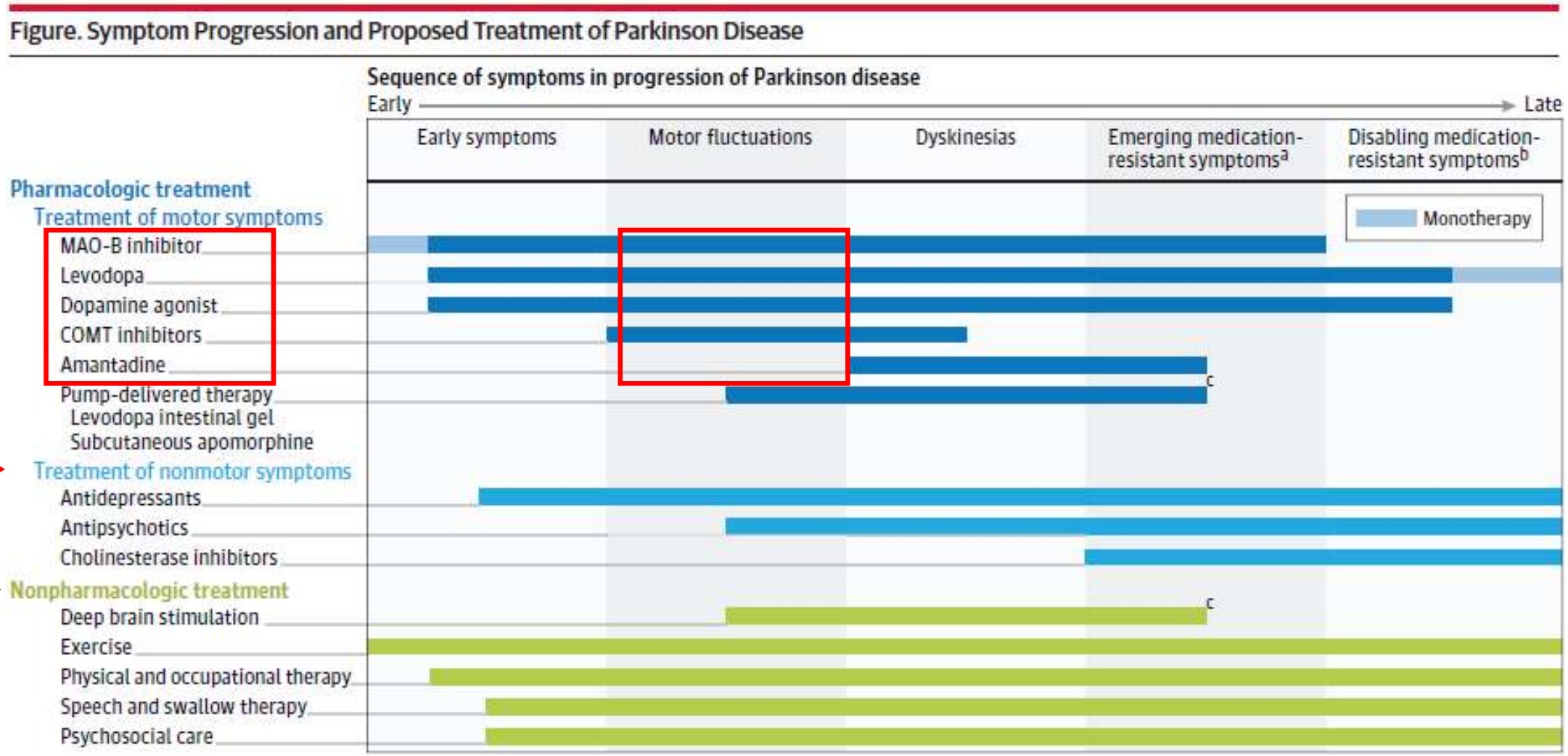
Shen-Yang Lim, MBBS, FRACP[1,2] and Anthony E. Lang, MD, FRCPC[1]*

[1]*Movement Disorders Centre, Toronto Western Hospital, Ontario, Canada*
[2]*Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*





Terapia nelle diverse fasi della M. Parkinson



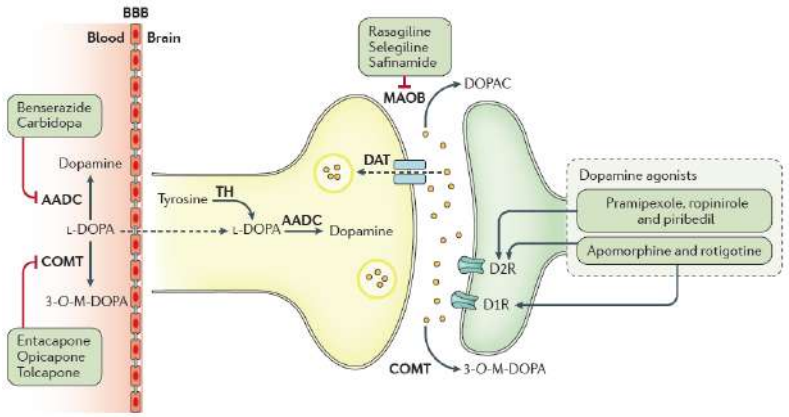
Okun S, Jama 2017

Svantaggi della manipolazione della LDopa

Aumento singola dose	Frazionamento dose giornaliera	Preparazioni a Rilascio Modificato
↓	↓	↓
Incremento dei picchi plasmatici	*Riduzione dei livelli plasmatici*	*Assorbimento irregolare e ritardato*
↓	↓	↓
Discinesie da picco	**Ridotto effetto/durata della singola dose; Possibili "no-on"**	**Delayed "on" Possibili "no-on"**

F. Stocchi

DA agonisti nella M. di Parkinson



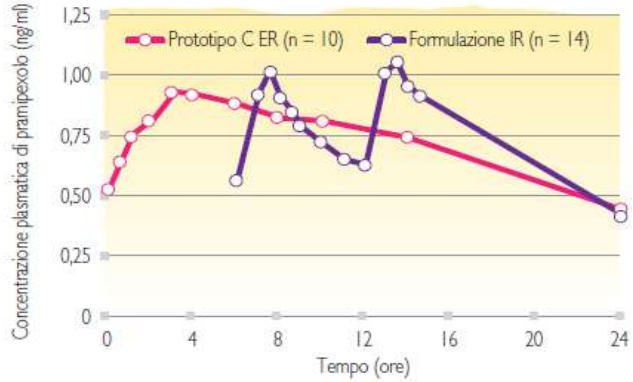
	D2/D3 receptor affinity	D1 receptor affinity	NE receptor affinity	5-HT_{2B} receptor affinity	Half-life (h)
Ergot agonists					
Bromocriptine	D2	–	+	+/–	3–6
Cabergoline	D3>D2	–	+	+	65
Dihydroergocriptine	D2	+/–	+	+	12–16
Lisuride	D2	–	+	+*	2–3
Pergolide	D3>D2	+	+	+	15–20
Non-ergot agonists					
Apomorphine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

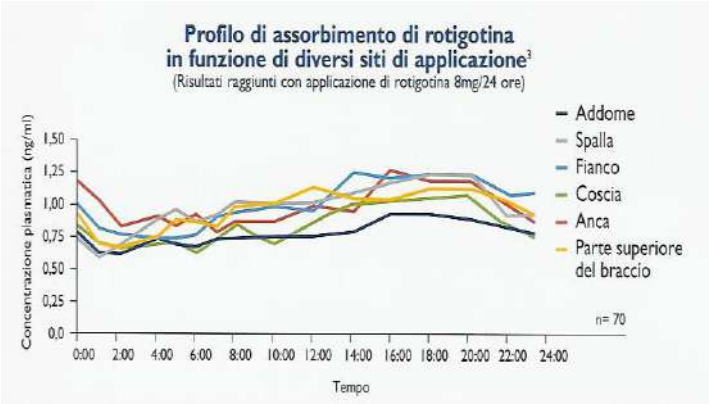
Table 1: Pharmacological properties of the dopamine agonists

Ropinirolo

Pramipexolo

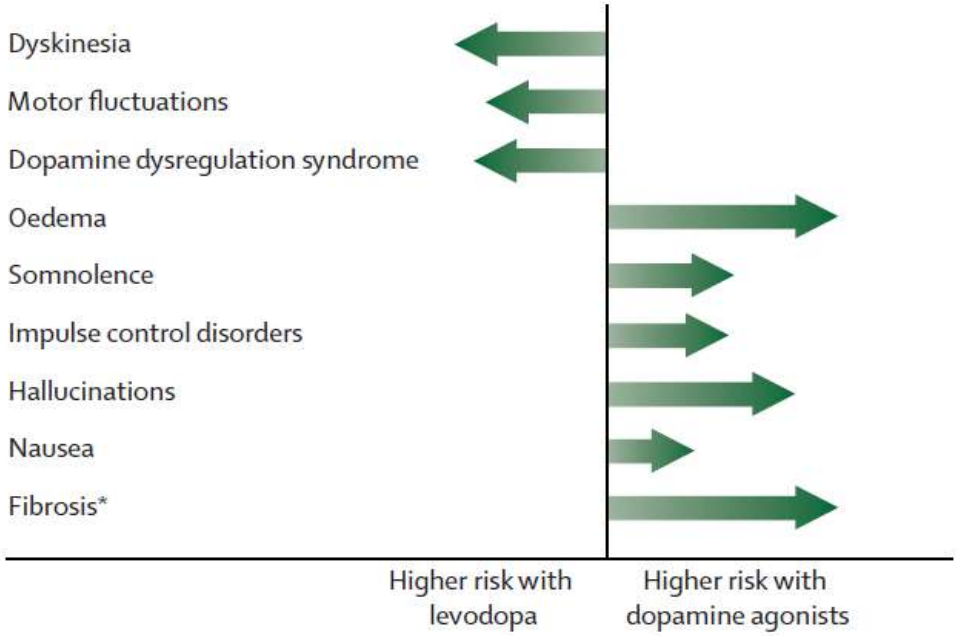


Rotigotina



DA agonisti - Effetti collaterali

- **Periferici**:
  - nausea, vomito
  - ipotensione ortostatica
  - edemi periferici
  - reazioni cutanee in sede di posizionamento del cerotto (rotigotina)
  - Reazioni fibrotiche (ergot-derivati)



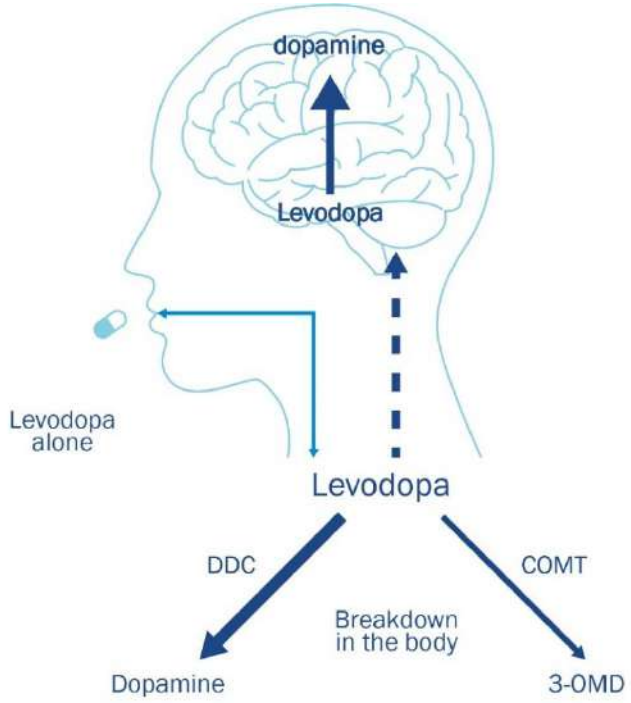
- **Centrali**:
  - sonnolenza/attacchi improvvisi di sonno
  - psicosi dopaminergica
    - allucinazioni
    - episodi confusionali
    - deliri
  - disturbi del controllo degli impulsi
    - gioco d'azzardo patologico
    - ipersessualità
    - iperfagia
    - shopping compulsivo
    - punding
  - sindrome da disregolazione dopaminergica (auto-somministrazione di farmaci dopaminergici e dipendenza da questi)

A reassessment of risks and benefits of dopamine agonists in Parkinson's disease

Angelo Antonini, Eduardo Tolosa, Yoshikuni Mizuno, Mitsutoshi Yamamoto, Werner H Poewe

Lancet Neurol 2009; 8: 929–37

Optimising levodopa through DDCI + COMT inhibition



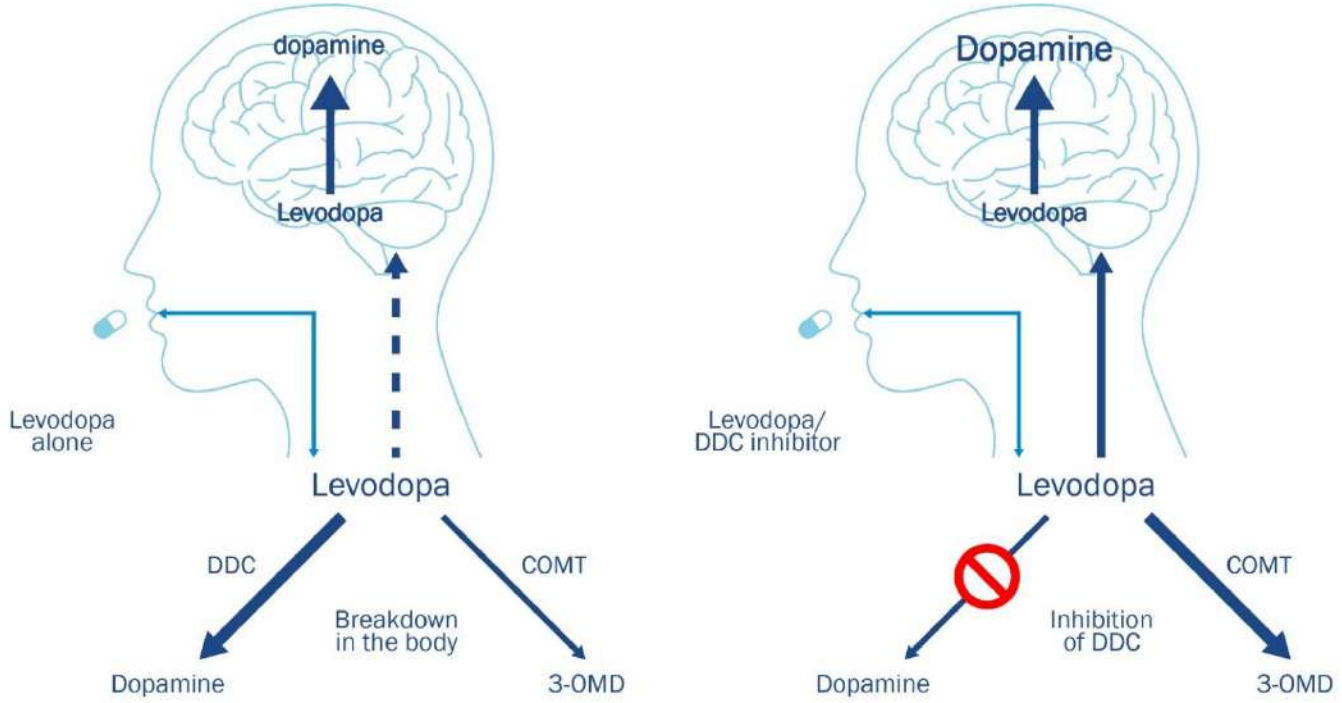
Adapted from Schapira AVH, 2007[1]

Large amount of dopamine formed in periphery

COMT, catechol-O-methyltransferase;
DDC, dopa-decarboxylase;
3-OMD, 3-O-methyldopa

1. Schapira AVH. Chapter 71 – Parkinson's Disease. In: Neurology and Clinical Neuroscience. 1st edn. Mosby, 2007:927–60; 2. Tuite P et al. New treatment modalities in Parkinson's disease. In: Scientific Basis for the Treatment of Parkinson's Disease. 2nd edition. Informa Healthcare, 2004

Optimising levodopa through DDCI + COMT inhibition



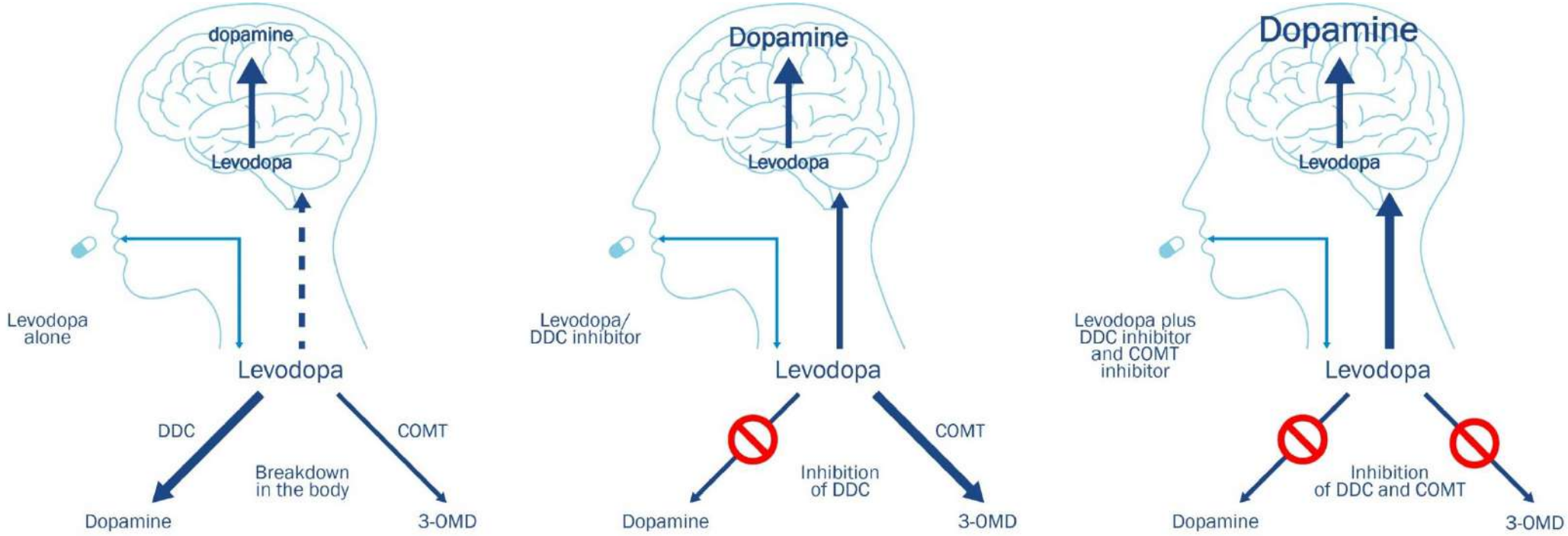
Adapted from Schapira AVH, 2007[1]

Significantly greater entry of levodopa into the brain with DDC inhibition

COMT, catechol-O-methyltransferase;
DDC, dopa-decarboxylase;
3-OMD, 3-O-methyldopa

1. Schapira AVH. Chapter 71 – Parkinson's Disease. In: Neurology and Clinical Neuroscience. 1st edn. Mosby, 2007:927–60; 2. Tuite P et al. New treatment modalities in Parkinson's disease. In: Scientific Basis for the Treatment of Parkinson's Disease. 2nd edition. Informa Healthcare, 2004

Optimising levodopa through DDCI + COMT inhibition



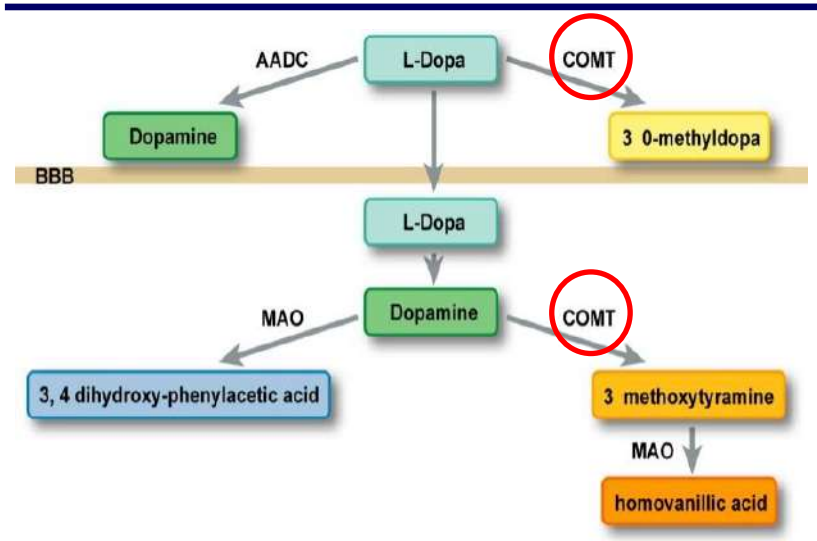
Adapted from Schapira AVH, 2007[1]

30–50% reduction in plasma variability with dual inhibition[2]

COMT, catechol-O-methyltransferase;
DDC, dopa-decarboxylase;
3-OMD, 3-O-methyldopa

1. Schapira AVH. Chapter 71 – Parkinson's Disease. In: Neurology and Clinical Neuroscience. 1st edn. Mosby, 2007:927–60; 2. Tuite P et al. New treatment modalities in Parkinson's disease. In: Scientific Basis for the Treatment of Parkinson's Disease. 2nd edition. Informa Healthcare, 2004

Inibitori Enzimatici - iCOMT



- **Entacapone** (periferico)
- **Opicapone** (periferico)
- **Tolcapone** (periferico e **centrale**)

Effetti collaterali

- Correlati al potenziamento dell' effetto della levodopa
- Specifici:
  - Diarrea con entacapone (10-20% da 2 a 4 mesi dopo l'inizio; regredisce nel 50% dei casi)
  - Rischio di epatotossicità con Tolcapone

Efficacia clinica:

Tolcapone ≥ Opicapone >> Entacapone

Profilo di sicurezza:

Opicapone >> Entacapone & Tolcapone

Facilità di utilizzo:

Opicapone >> Entacapone & Tolcapone

Uno dei polimorfismi del gene che codifica le COMT, Val (158/108) Met, influenza l'attività enzimatica e di conseguente l'efficacia terapeutica dell' iCOMT.

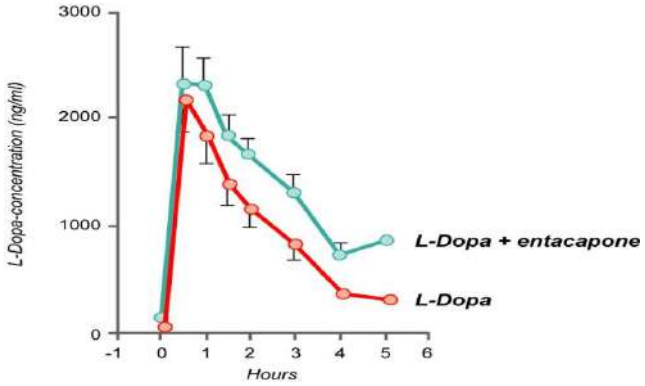
L'attività delle COMT è ridotta in soggetti omozigoti Met/Met

iCOMT

ENTACAPONE

Inibitore periferico reversibile, con un'emivita plasmatica di 1,5 ore.

Aumenta l'emivita della L-dopa, senza aumentare la Cmax.

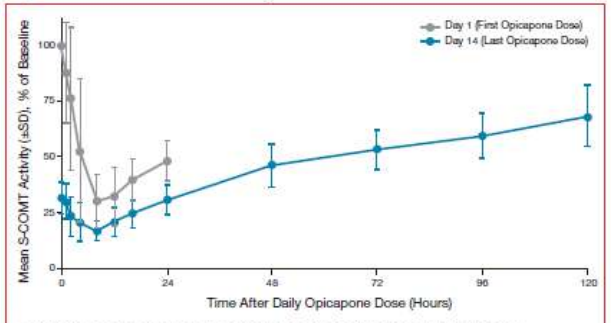


OPICAPONE

L'inibizione delle COMT si mantiene > 65% sull'arco delle 24 ore

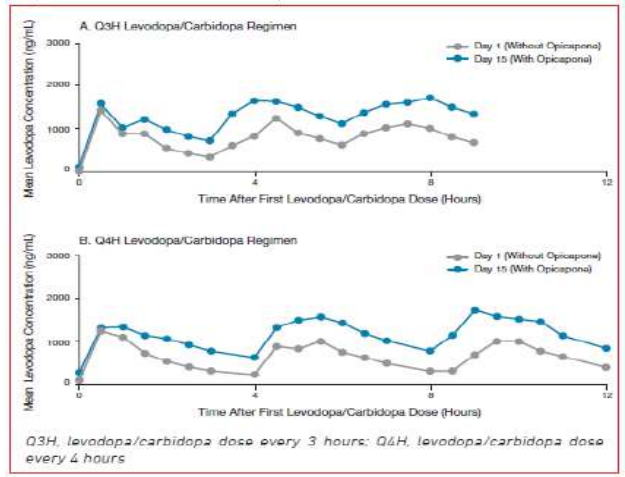
L'attività delle COMT ha impiegato circa 5 giorni per tornare ai livelli basali

Figure 1. Mean S-COMT Activity



S-COMT, soluble catechol-O-methyltransferase; SD, standard deviation

Figure 2. Mean Plasma Levodopa Concentrations



Q3H, levodopa/carbidopa dose every 3 hours; Q4H, levodopa/carbidopa dose every 4 hours

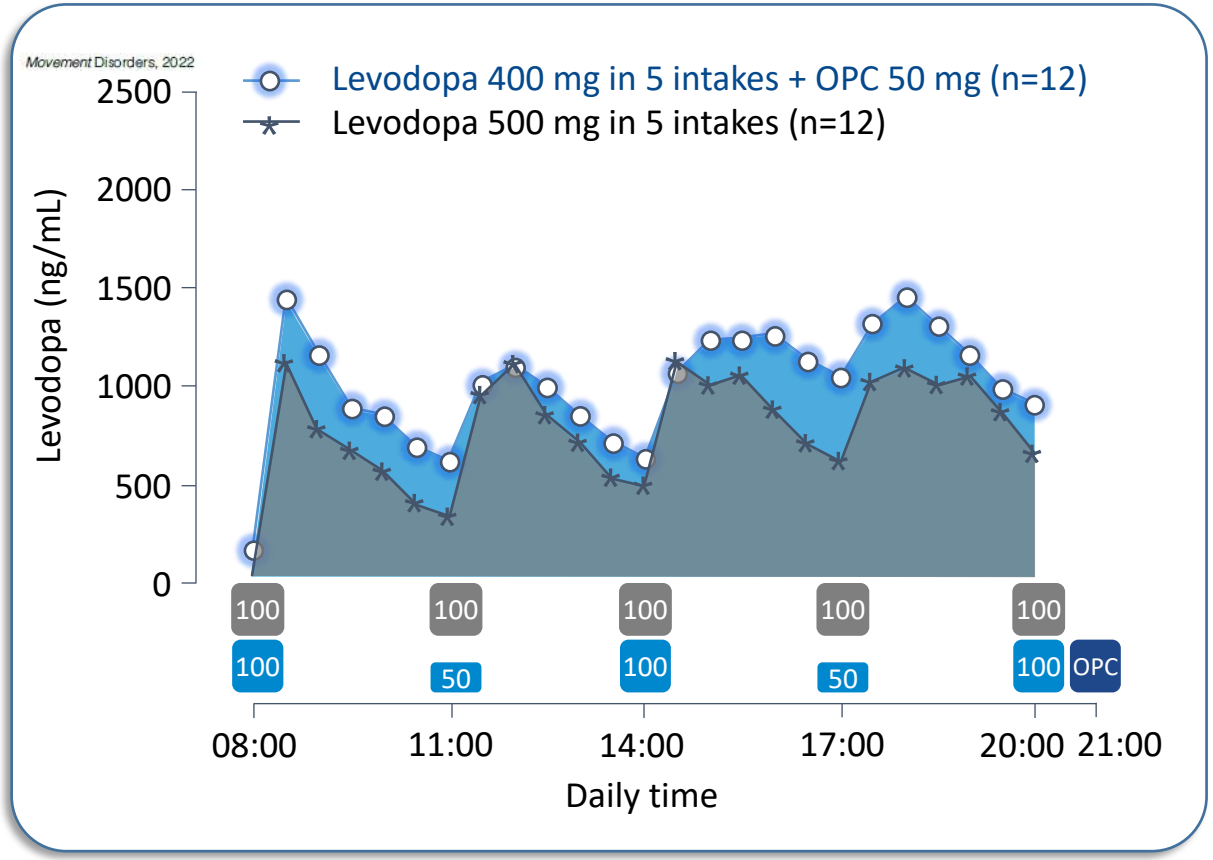
G Loewen et al,2020

Levodopa pharmacokinetics (primary endpoint)
Daily levodopa 400 mg in 5 intakes + opicapone 50 mg

RESEARCH ARTICLE

Effect of Opicapone on Levodopa Pharmacokinetics in Patients with Fluctuating Parkinson's Disease

Joaquim J. Ferreira, MD, PhD,[1,2*] Werner Poewe, MD,[3] Olivier Rascol, MD, PhD,[4] Fabrizio Stocchi, MD, PhD,[5] Angelo Antonini, MD, PhD,[6] Joana Moreira, PharmD,[7] Bruno Guimarães, BSc,[7] José-Francisco Rocha, BSc,[7] and Patrício Soares-da-Silva, MD, PhD[7,8,9]



C_{max}, maximum plasma concentration; $C_{max,max}$, maximum C_{max} observed; C_{min}, minimum observed plasma concentration; $C_{min,min}$, minimum C_{min} observed; FI, fluctuation index; GMR, geometric mean ratio; LD/CD, levodopa/carbidopa; OPC, opicapone

Ferreira JF et al. Mov Disord 2022 Aug 31; doi.org/10.1002/mds.29193

RESEARCH ARTICLE

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Levodopa pharmacokinetics (primary endpoint)

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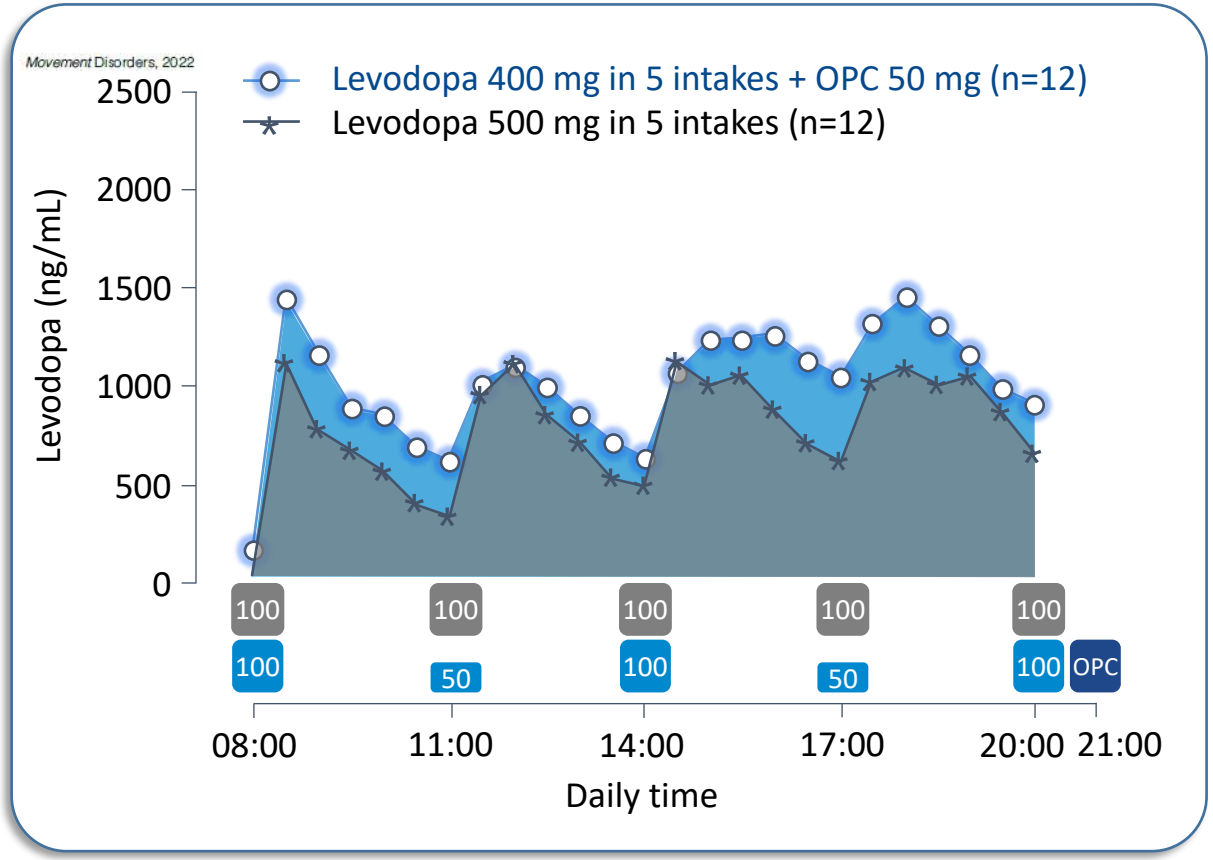

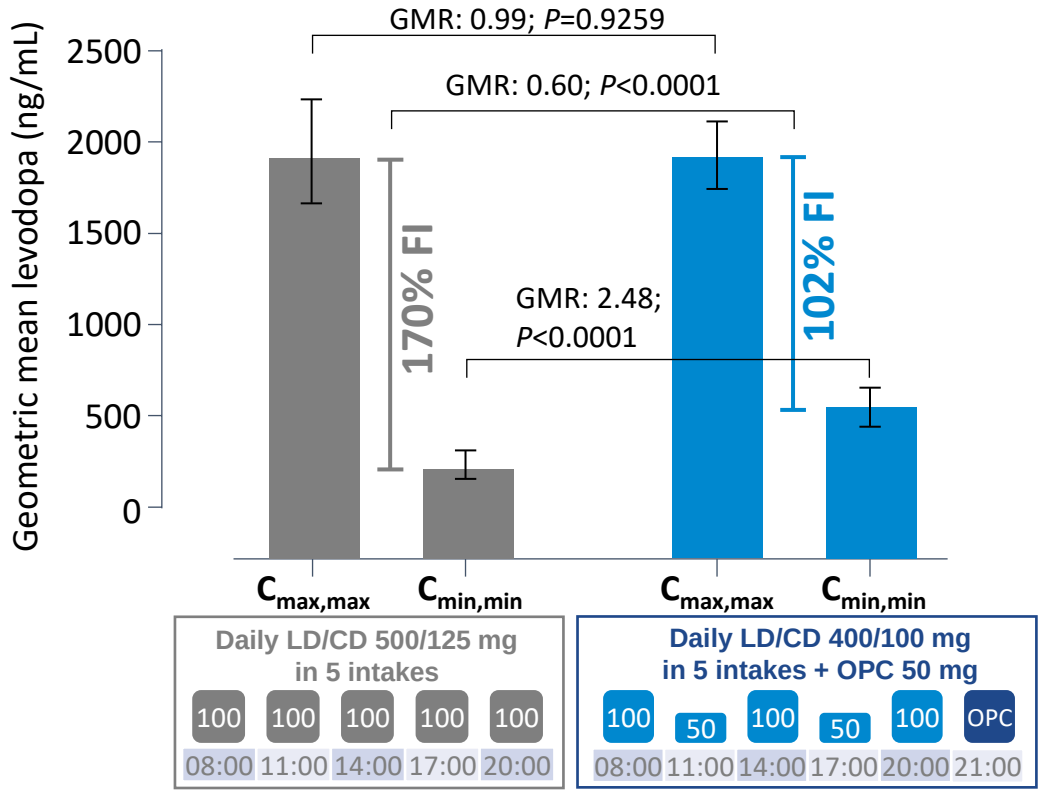

For C_{max} n=12, FI n=12, C_{min} n=11

C_{max}, maximum plasma concentration; $C_{max,max}$, maximum C_{max} observed; C_{min}, minimum observed plasma concentration; $C_{min,min}$, minimum C_{min} observed; FI, fluctuation index; GMR, geometric mean ratio; LD/CD, levodopa/carbidopa; OPC, opicapone

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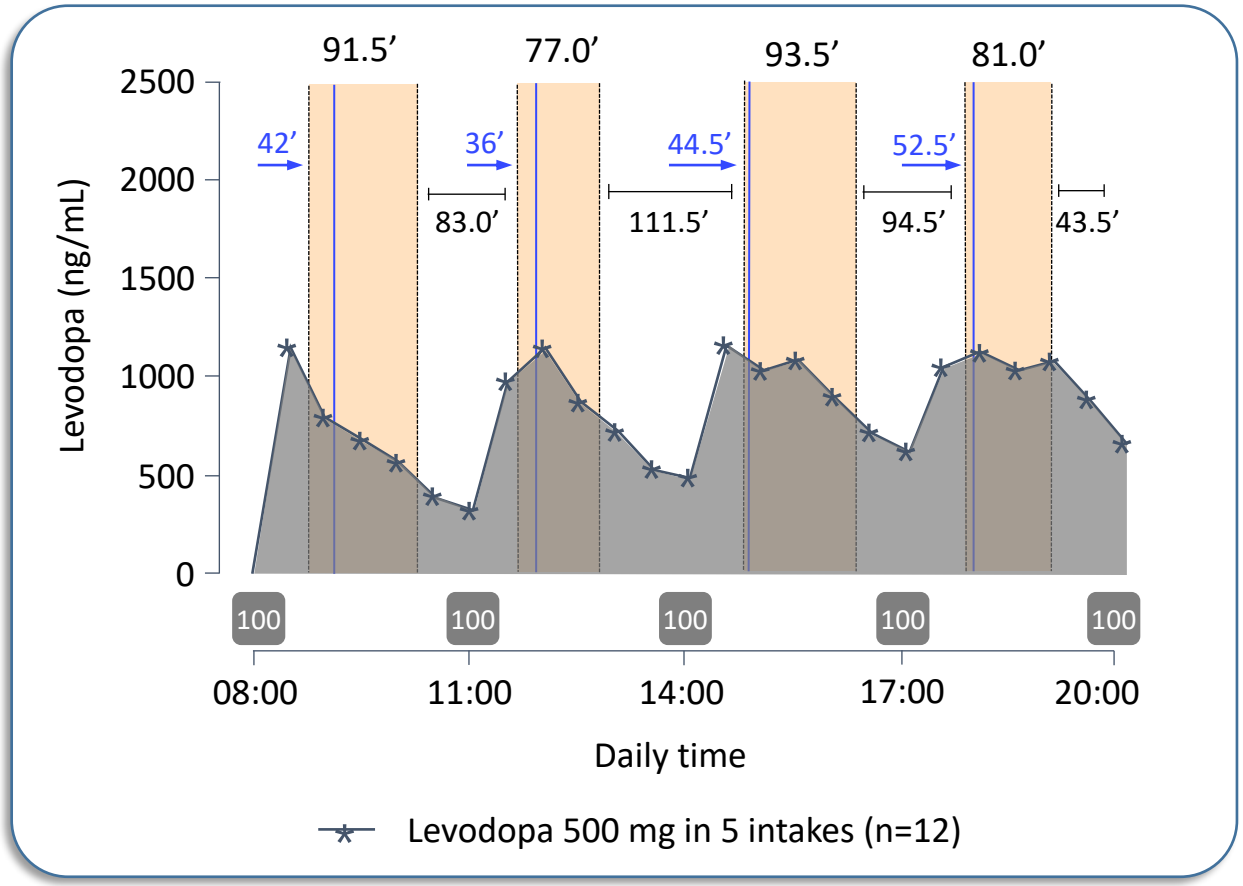
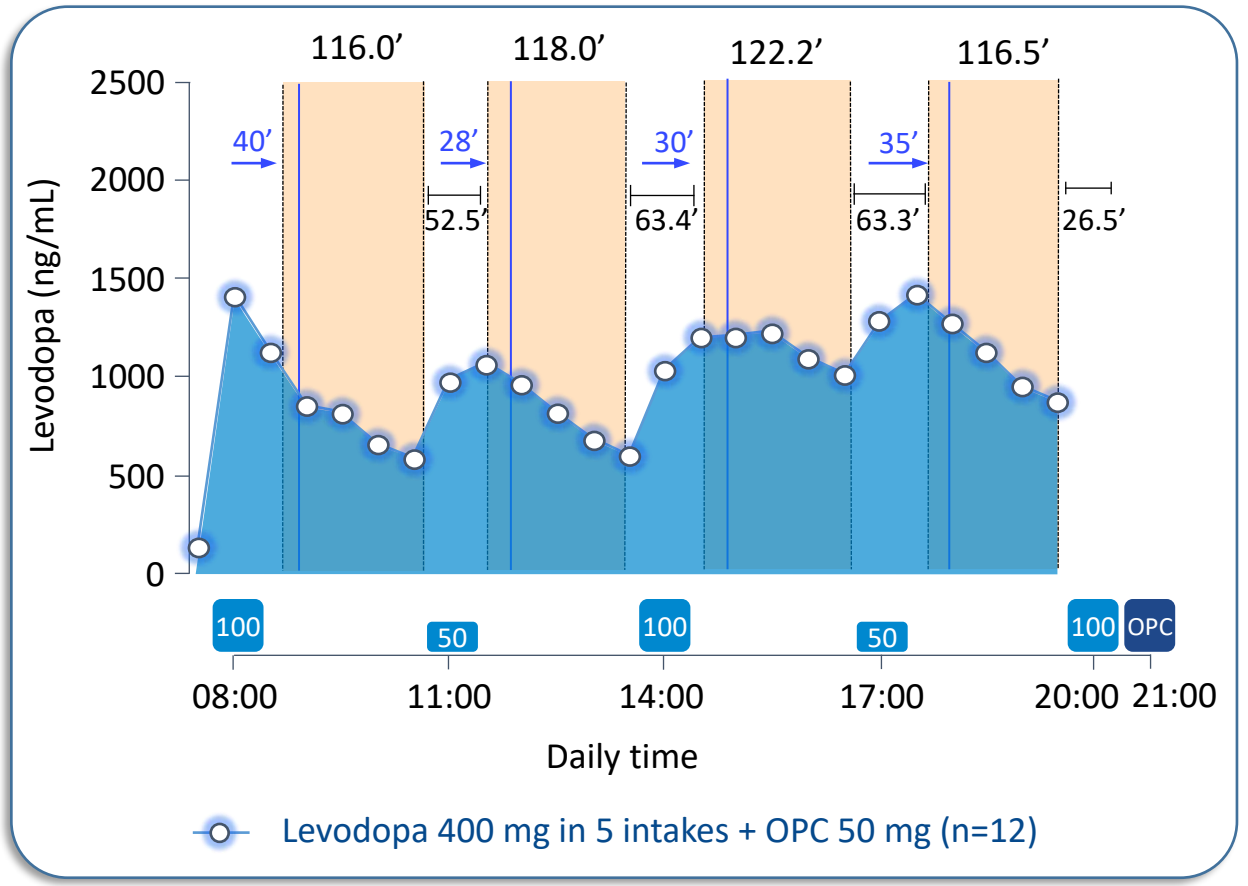
Clinical outcomes (secondary endpoint)

Daily levodopa 400 mg in 5 intakes + opicapone 50 mg





CD, carbidopa; LD, levodopa; OPC, opicapone

Ferreira JF et al. Mov Disord 2022 Aug 31; doi.org/10.1002/mds.29193

Opicapone e sintomi non motori

brain sciences

2022

MDPI

Article

Opicapone Improves Global Non-Motor Symptoms Burden in Parkinson's Disease: An Open-Label Prospective Study

Diego Santos García [1,2,*], Gustavo Fernández Pajarín [3], Juan Manuel Oropesa-Ruiz [4], Francisco Escamilla Sevilla [5], Raúl Rashid Abdul Rahim López [6] and José Guillermo Muñoz Enríquez [7]

Chaudhuri *et al. BMC Neurology* (2022) 22:88
https://doi.org/10.1186/s12883-022-02602-8

BMC Neurology

2022

STUDY PROTOCOL Open Access

Opicapone versus placebo in the treatment of Parkinson's disease patients with end-of-dose motor fluctuation-associated pain: rationale and design of the randomised, double-blind OCEAN (OpiCapone Effect on motor fluctuations and pAiN) trial

K. Ray Chaudhuri[1*], Per Odin[2], Joaquim J. Ferreira[3], Angelo Antonini[4], Olivier Rascol[5], Mónica M. Kurtis[6], Alexander Storch[7], Kirsty Bannister[8], Patrício Soares-da-Silva[9,10], Raquel Costa[9], Diogo Magalhães[9] and José Francisco Rocha[9]

International Parkinson and Movement Disorder Society
–MEETING ABSTRACTS–

The OASIS (OpicApone in Sleep dISorder) study in Parkinson's disease: design and rationale of an open-label, single-arm, pilot trial

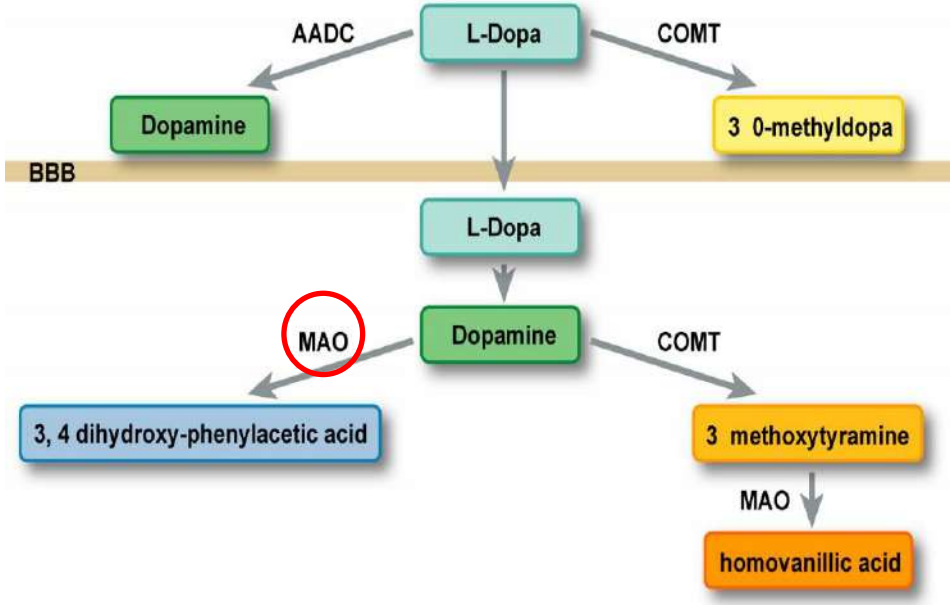
R. Costa, C. Trenkwalder, J. Ferreira, D. Magalhães, J. Rocha, P. Soares-da-Silva (Coronado, Portugal)

Meeting: MDS Virtual Congress 2021

ABSTRACT NUMBER: 376

Inibitori Enzimatici – iMAO-B

- **Selegilina** (irreversibile)
- **Rasagilina** (irreversibile)
- **Safinamide** (reversibile)



Effetti collaterali

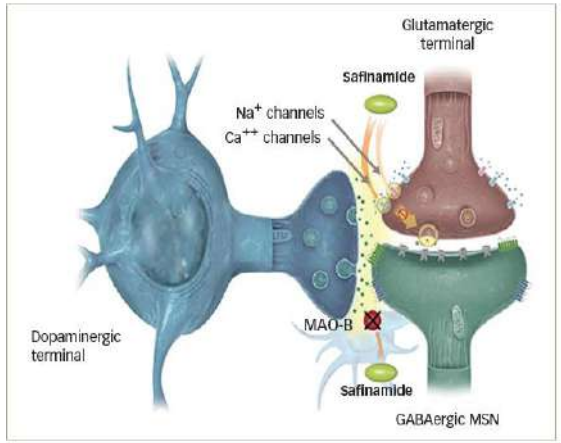
- Correlati al potenziamento dell'effetto della levodopa
- Selegelina: *i suoi metaboliti, derivati della l-methamphetamina, sono stati associati a possibili effetti collaterali cardiaci e neuropsichiatrici in alcuni pazienti*
- Metabolismo epatico (controindicati in pazienti con epatopatia moderata/severa)
- Interferenza con antidepressivi *Triciclici e SSRI* e *vasocostrittori* (rischio teorico di sindrome serotoninergica)

iMAO-B – Safinamide

Duplice **meccanismo d'azione**:

- inibizione delle MAO-B altamente selettiva e reversibile

- modulazione del rilascio eccessivo del glutammato tramite il blocco stato-dipendente dei canali del Sodio e la modulazione dei canali del Calcio



meno discinesie

miglioramento del dolore

stabilizzazione dell' umore

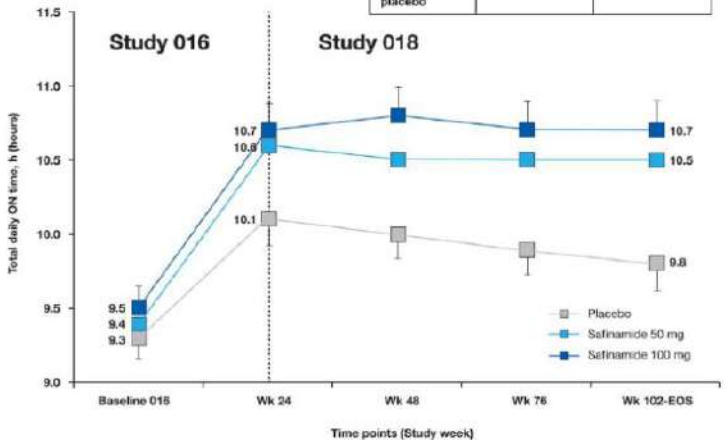
Movement Disorders, Vol. 29, No. 10, 2014

RESEARCH ARTICLE

Two-Year, Randomized, Controlled Study of Safinamide as Add-on to Levodopa in Mid to Late Parkinson's Disease

Rupam Borgohain, DM,[1*] Jozsef Szasz, MD,[2] Paolo Stanzione, MD,[3] Chandrashekhar Meshram, DM,[4] Mohit H. Bhatt, DM,[5] Dana Chirilineau, MD,[6] Fabrizio Stocchi, MD,[7] Valentina Lucini, MD,[8] Rodolfo Giuliani, MD,[8] Emma Forrest, PhD,[8] Patricia Rice, PhD,[9] Ravi Anand, MD,[10] and the Study 018 Investigators[11]

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



C Warren Olanow[1] and Fabrizio Stocchi[2]

European Neurological Review, 2016;11(Suppl. 2): 2–15

Safinamide e sintomi non motori

Journal of Neural Transmission (2020) 127:1143–1152
https://doi.org/10.1007/s00702-020-02218-7

2020

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Effects of safinamide on pain in Parkinson's disease with motor fluctuations: an exploratory study

Christian Geroin[1] · Ilaria A. Di Vico[1] · Giovanna Squintani[2] · Alessia Segatti[2] · Tommaso Bovi[2] · Michele Tinazzi[1]

Neurological Sciences (2022) 43:357–364
https://doi.org/10.1007/s10072-021-05324-w

2022

ORIGINAL ARTICLE

Effects of safinamide on non-motor, cognitive, and behavioral symptoms in fluctuating Parkinson's disease patients: a prospective longitudinal study

Rosa De Micco[1] · Sara Satolli[1] · Mattia Siciliano[1,2] · Antonio De Mase[1] · Alfonso Giordano[1] · Gioacchino Tedeschi[1] · Alessandro Tessitore[1]

brain sciences

2021

MDPI

Article

Safinamide Improves Non-Motor Symptoms Burden in Parkinson's Disease: An Open-Label Prospective Study

Diego Santos García [1,*], Carmen Labandeira Guerra [2], Rosa Yáñez Baña [3], Maria Icíar Cimas Hernando [4], Iria Cabo López [5], Jose Manuel Paz Gonález [1], Maria Gemma Alonso Losada [2], María José González Palmás [5] and Cristina Martínez Miró [1]

brain sciences

2021

MDPI

Article

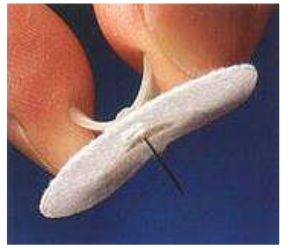
SURINPARK: Safinamide for Urinary Symptoms in Parkinson's Disease

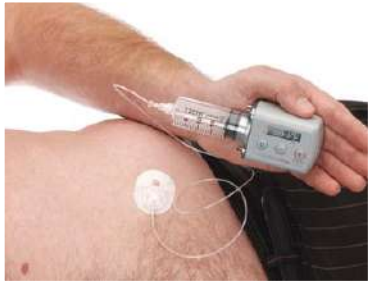
Ana Gómez-López [1,*], Arantxa Sánchez-Sánchez [1], Elena Natera-Villalba [1], Victoria Ros-Castelló [1], Álvaro Beltrán-Corbellini [1], Samira Fanjul-Arbós [1,2], Isabel Pareés Moreno [1,2], José Luis López-Sendon Moreno [1,2], Juan Carlos Martínez Castrillo [1,2] and Araceli Alonso-Canovas [1,2]

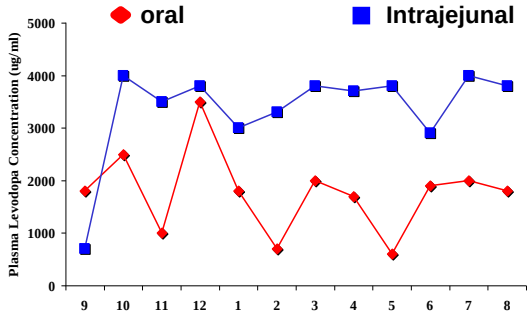
Terapie avanzate

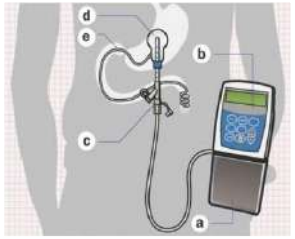
Device-aided therapies

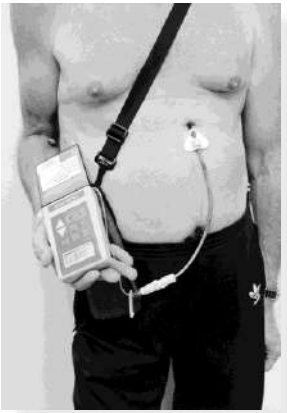
- Infusione sottocutanea di Apomorfina
- Infusione intradigiunale di Levodopa-Carbidopa gel
- DBS (subtalamo, pallido)
- MRgFUS

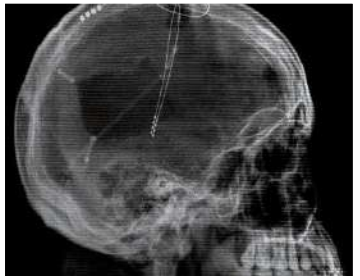












RIABILITAZIONE NELLA M. PARKINSON
ETEROGENEITÀ DEGLI APPROCCI

TERAPIA FISICA (EBM)

- Cues strategies
- Treadmill training
- Dual Task Training
- Movement and attentional strategies
- Aerobic and muscle strength activities
- Stretching exercises
- *Action observation and Motor Imagery training*
- *Motor-cognitive combined approach (Exergaming and Virtual reality)*

TERAPIE NON CONVENZIONALI

2014

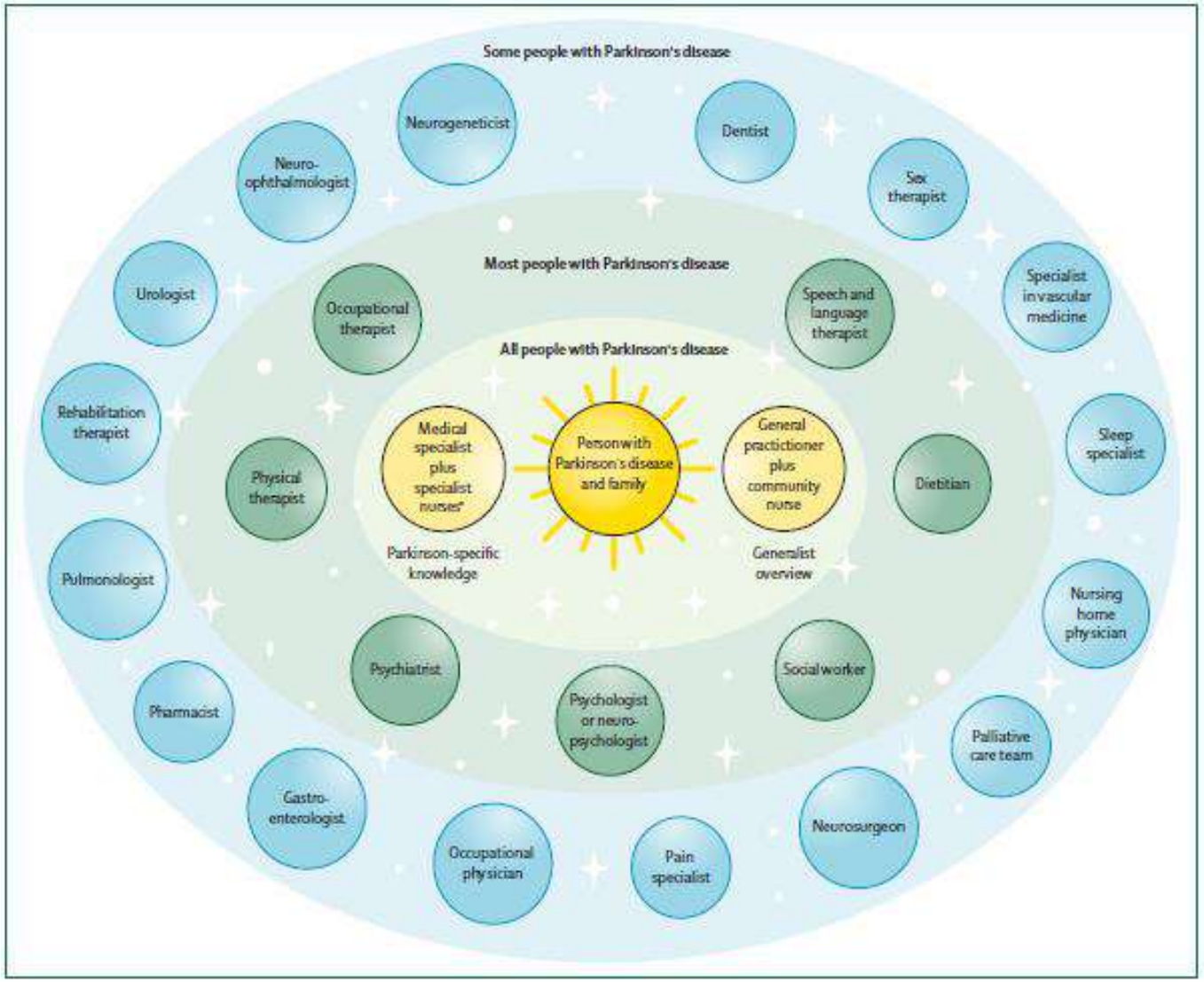
- Martial art: Tai-Chi
- Dance
- Nordic Walking
- *Yoga*
- *AFA*
- *Relaxation exercises*

Figure professionali coinvolte nella cura multidisciplinare per le persone con malattia di Parkinson

Parkinson's disease

Bastiaan R Bloem, Michael S Okun, Christine Klein

Lancet 2021; 397: 2284–303



Bastiaan R Bloem , Lancet 2021

Conclusioni

- Le fluttuazioni motorie e non motorie rappresentano uno dei maggiori fattori di disabilità nella vita dei pazienti con malattia di Parkinson

- Possono apparire anche molto precocemente nel corso della malattia e contribuiscono significativamente al deterioramento della qualità di vita → importanza del riconoscimento precoce

- Le fluttuazioni non motorie, percepite come "molto disabilitanti" da parte del paziente, non sempre inducono il neurologo a modificare il trattamento

Conclusioni

- Le funzioni motorie e i disturbi psichici (> depressione) sono quelli che impattano maggiormente sulla QoL
- Anche la qualità della vita del caregiver viene influenzata negativamente tanto che anche lo stato di salute può essere compromesso
- Importanza dell‘ ottimizzazione del trattamento in quanto ciò può avere un impatto positivo sull’ indipendenza dei pazienti nelle attività della vita quotidiana e sulla loro sopravvivenza
- Nella scelta della strategia terapeutica delle fluttuazioni motorie/non-motorie considerare:
  - caratteristiche individuali del paziente

    frequenza e gravità degli episodi di OFF, età, stile di vita e comorbidità
  - caratteristiche del farmaco

    efficacia, tollerabilità, via di eliminazione, interazioni farmacologiche, facilità d'uso, accessibilità e costo