Terapia della malattia di Parkinson

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Evoluzione della terapia per la M. di Parkinson "Levodopa Story"

A. Carlsson

G. Cotzias

O. Hornykiewcz

Marcato beneficio con alte dosi orali di levodopa (b)

Introduzione di formulazioni di levodopa controlled-release

Introdotti DA agonisti

Inibitori MAOb

1960 *1970* *1980* *1990*

Perdita di dopamina striatale identificata nella MP (a)

Introdotti inibitori DDC†

Introdotti inibitori COMT‡

†Dopa decarbossilasi

‡Catecol-O-metil transferasi

a) Ehringer et al 1960
b) Cotzias et al 1967

Levels of recommendation for the treatment of early PD

Therapeutic interventions	Symptomatic control of parkinsonism	Prevention of motor complications
• Levodopa	Effective (level A)	Not applicable
• Levodopa CR	Effective (level A)	Ineffective (level A)
• Apomorphine	Not used	Not used
• Bromocriptine	Effective (level B)	Effective (level B)
• Cabergoline	Effective (level B)	Effective (level A)
• Dihydroergocryptine	Effective (level A)	No recommendation
• Lisuride	Effective (level B)	Effective (level C)
• Pergolide	Effective (level A)	Effective (level B)
• Piribedil	Effective (level C)	No recommendation
• Pramipexole	Effective (level A)	Effective (level A)
• Pramipexole CR	Effective (level A)	Not available
• Ropinirole	Effective (level A)	Effective (level A)
• Ropinirole CR	Effective (level A)	No recommendation
• Rotigotine	Effective (level A)	No recommendation

Ferreira J. J. et al European Journal of Neurology 2013, 20: 5–15

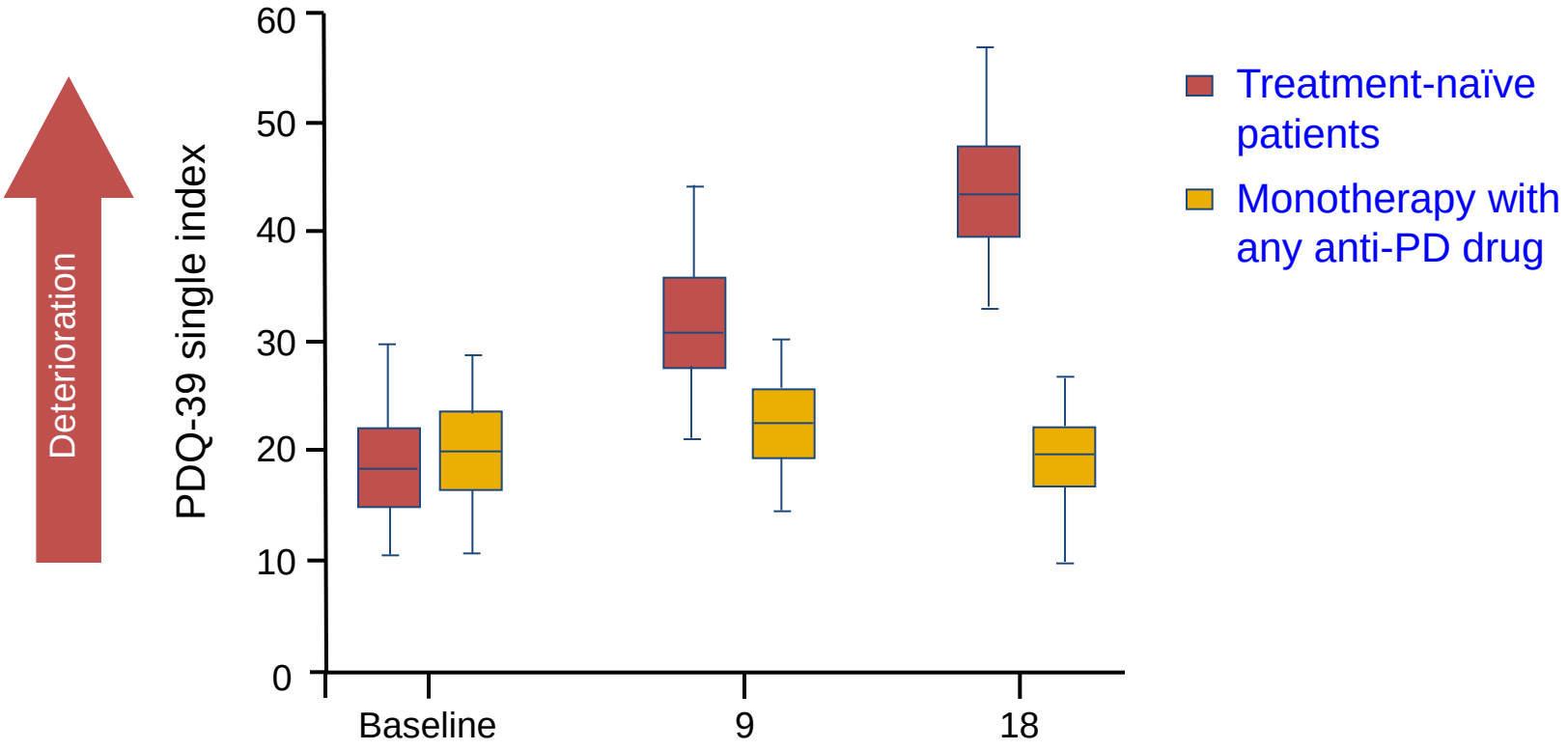
Levels of recommendation for the treatment of early PD

Therapeutic interventions	Symptomatic control of parkinsonism	Prevention of motor complications
• Selegiline	Effective (level A)	Ineffective (level A)
• Rasagiline	Effective (level A)	No recommendation
• Entacapone	No recommendation	Ineffective (level A)
• Tolcapone	No recommendation	No recommendation
• Amantadine	Effective (level B)	No recommendation
• Anticholinergics	Effective (level B)	No recommendation
• Rehabilitation	No recommendation	No recommendation
• Surgery	Not used	Not used

Ferreira J. J. et al European Journal of Neurology 2013, 20: 5–15

To treat or not to treat?

PD-LIFE: multi-centre prospective audit-based study, on-going, N=198



Treatment-naïve PD patients have significantly worse QoL than those receiving treatment

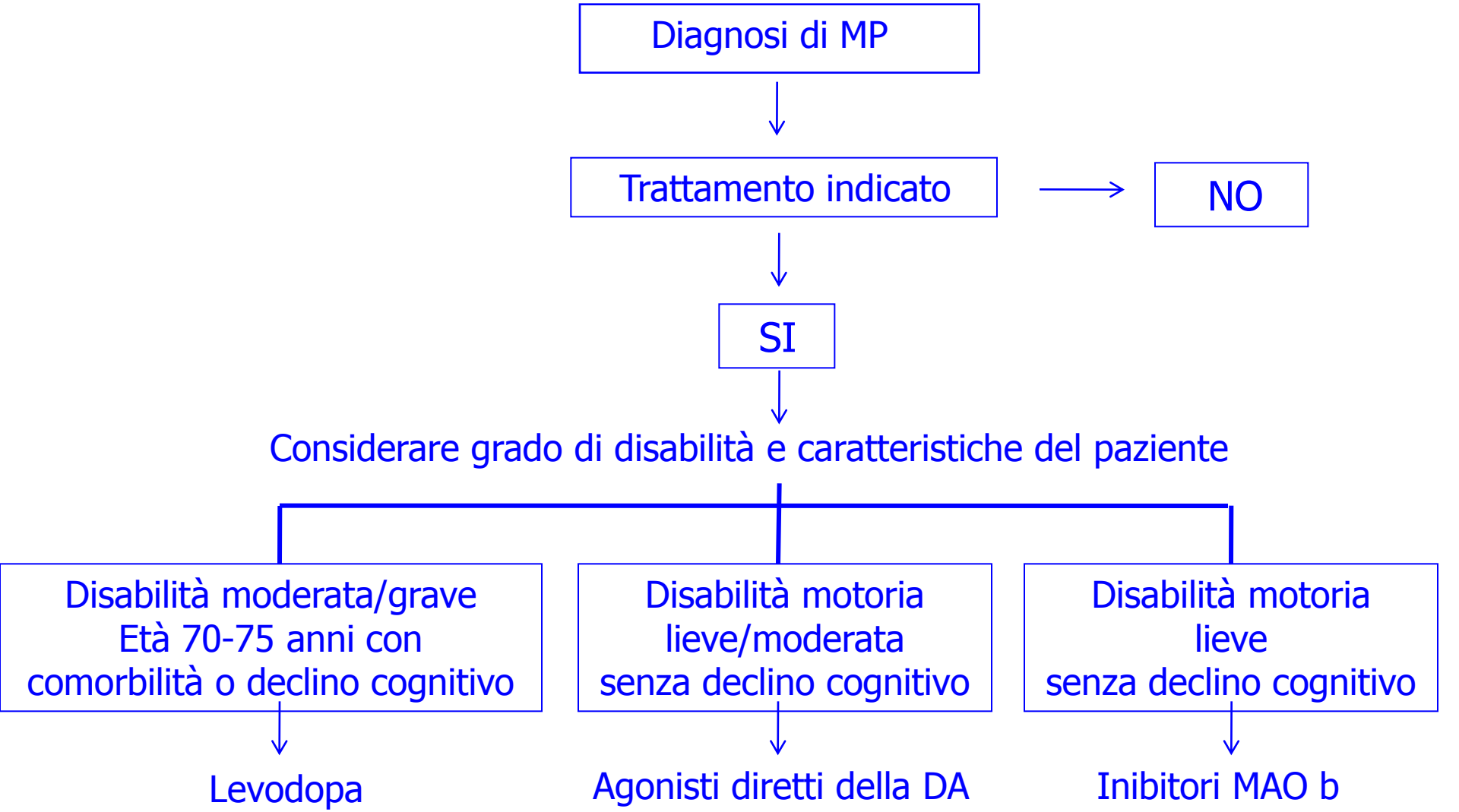
Grosset. et al JNNP 2007; 78 (5): 465

Obiettivi del trattamento iniziale della malattia di Parkinson

- **Gravità della malattia**
  - **grado di alterazione funzionale**
  - **impatto sulla qualità della vita**

- **Età della persona con Parkinson**
  - **comorbidità**
  - **rischio di effetti collaterali acuti**
  - **rischio di complicazioni a lungo termine**

Trattamento della Malattia di Parkinson iniziale



Mod Schapira 2007

TERAPIA FARMACOLOGICA DELLA M. DI PARKINSON: UN GIOCO A 3

DOPAMINO AGONISTI

Pramipexolo IR e ER

Ropinirolo IR e ER

Rotigotina

Cabergolina

Pergolide

Apomorfina

L-DOPA

IR(±ICOMT)

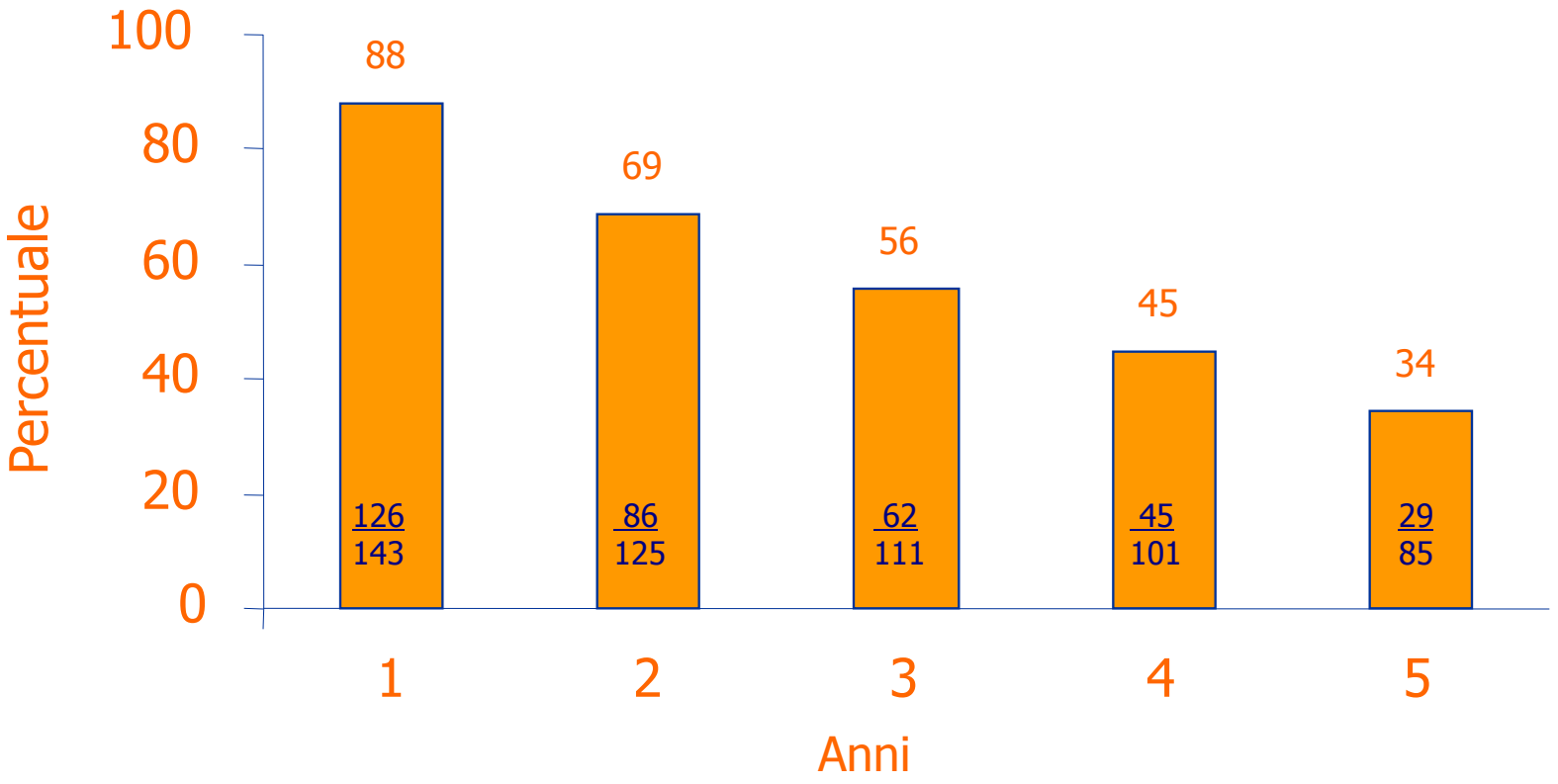
CR

I-MAO-B

Rasagilina

Selegilina

Monoterapia con Dopamino Agonisti

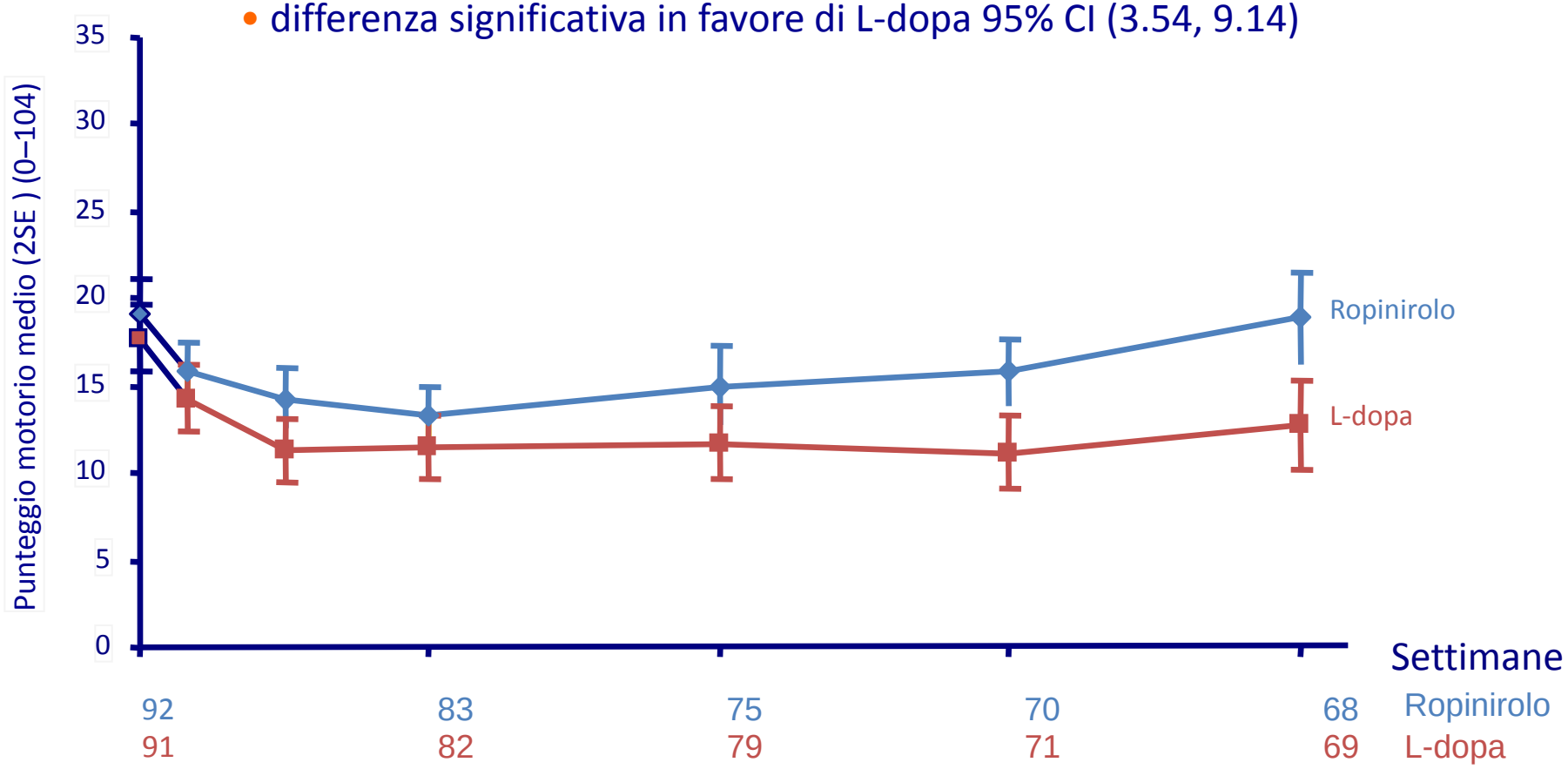


(Rascol, NEJM, 2000)

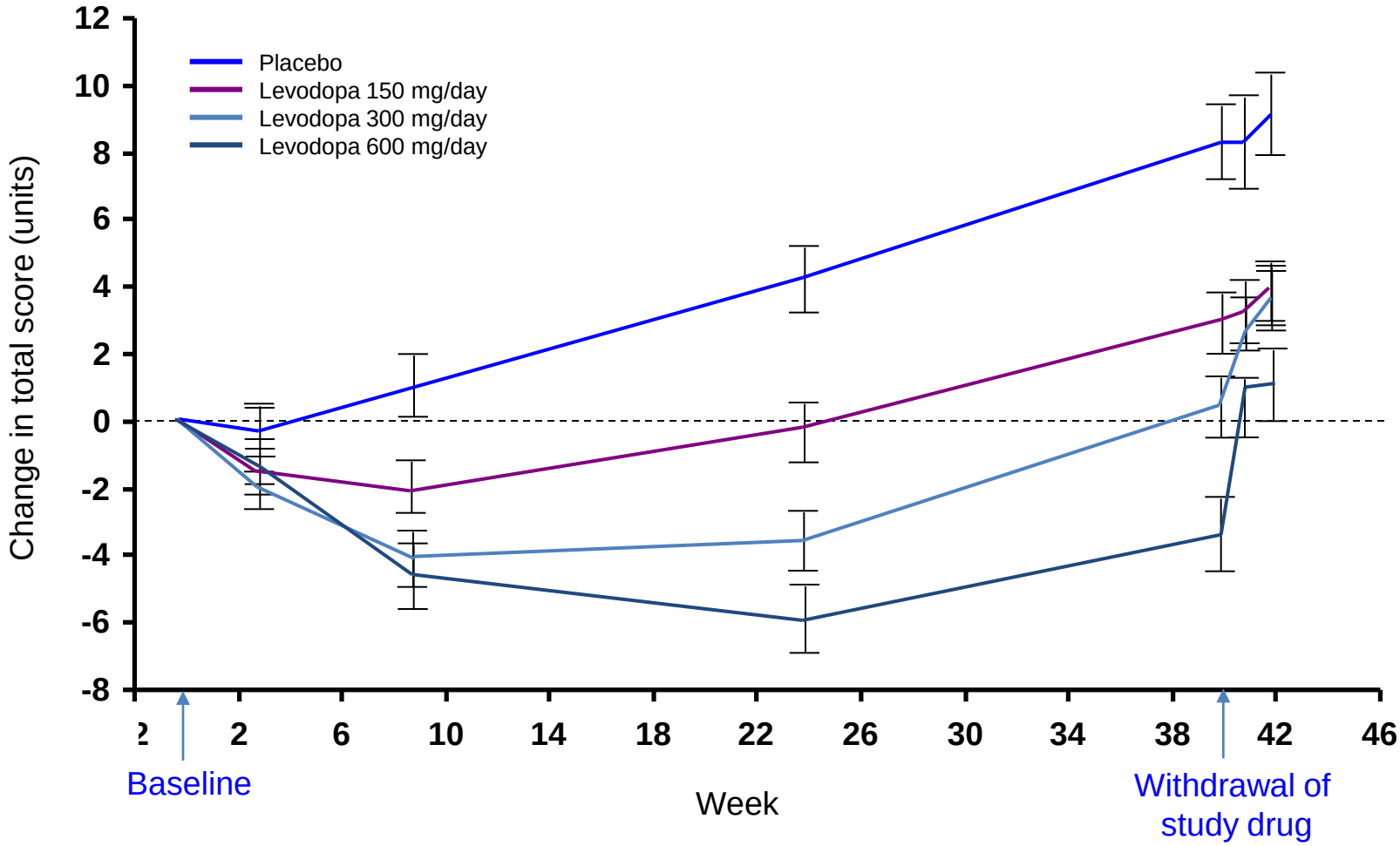
REAL-PET

Variazione nel punteggio motorio UPDRS

- differenza significativa in favore di L-dopa 95% CI (3.54, 9.14)



ELLDOPA



Parkinson Study Group. N Engl J Med 2004; 351: 2498

ELLDOPA: complicanze motorie in pazienti con MP iniziale dopo 9 mesi – n° (% pazienti)

		Levodopa			
	Placebo n = 90	150 mg/die n = 92	300 mg/die n = 88	600 mg/die n = 91	P
Discinesie	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	< 0,001
Wearing off	12 (3.3)	15 (16.3)	16 (18.2)	27 (29.7)	0,06

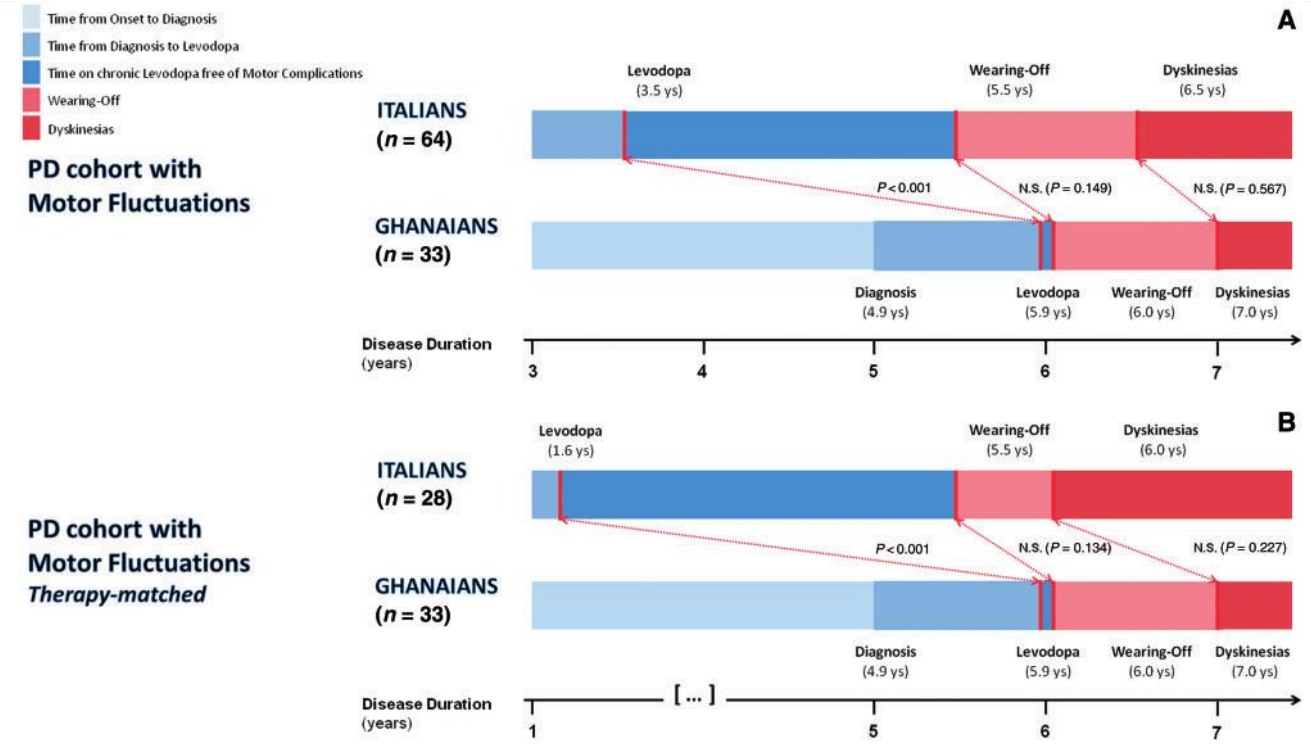
Parkinson Study Group. N Engl J Med 2004; 351: 2498 – 2508
Fahn & Parkinson Study Group. J Neurol 2005; 252(Suppl 4): IV/37

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]



ORIGINAL CONTRIBUTION

Arch Neurol. 2005;62:601-605

Sex Differences in Clinical and Genetic Determinants of Levodopa Peak-Dose Dyskinesias in Parkinson Disease

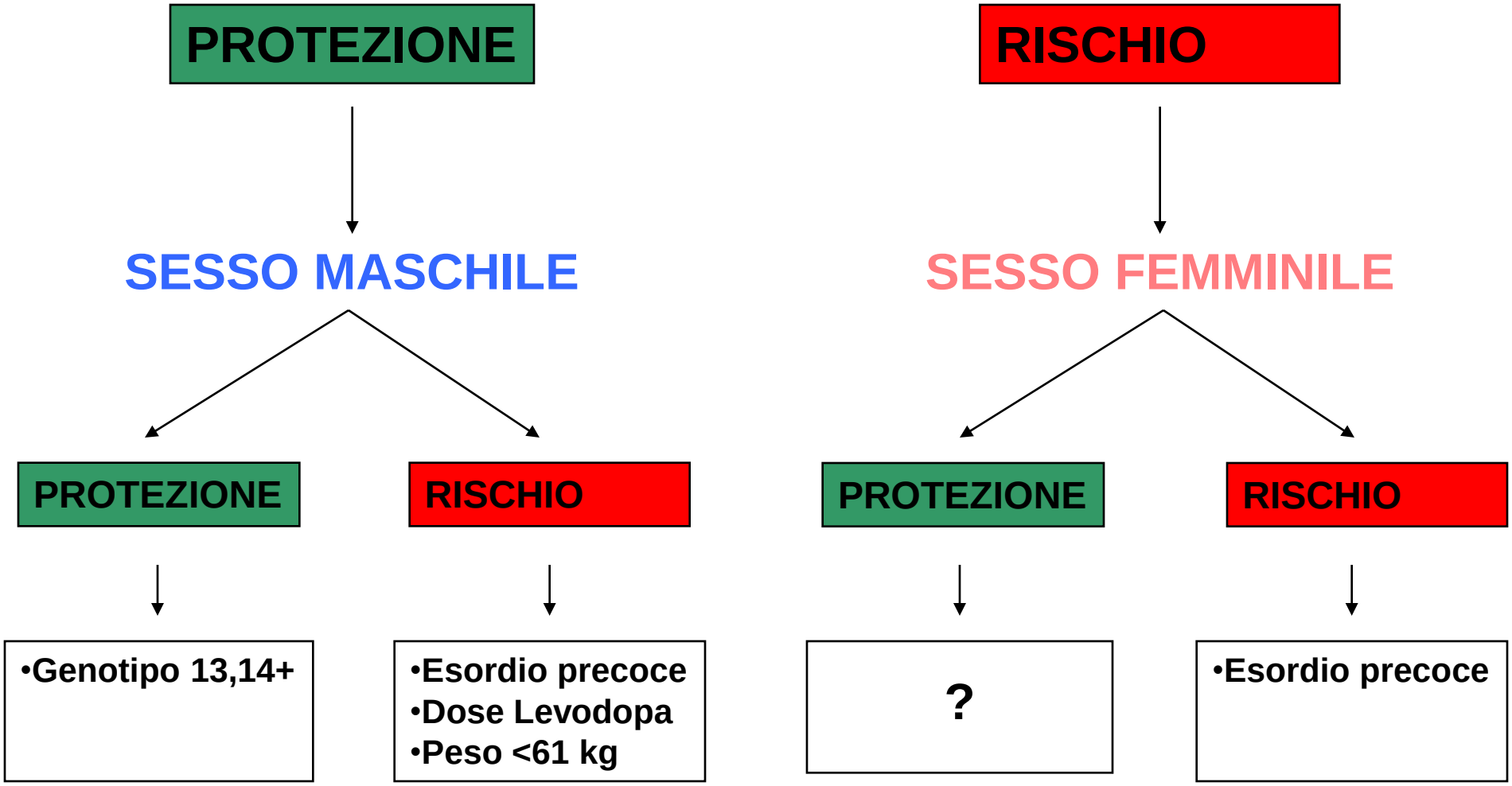
An Exploratory Study

Mario Zappia, MD; Grazia Annesi, PhD; Giuseppe Nicoletti, MD; Gennarina Arabia, MD; Ferdinanda Annesi, PhD; Demetrio Messina, MD; Pierfrancesco Puglisi, MD; Patrizia Spadafora, PhD; Patrizia Tarantino, PhD; Sara Carrideo, PhD; Donatella Civitelli, PhD; Elvira V. De Marco, PhD; Innocenza C. Cirò-Candiano, PhD; Antonio Gambardella, MD; Aldo Quattrone, MD

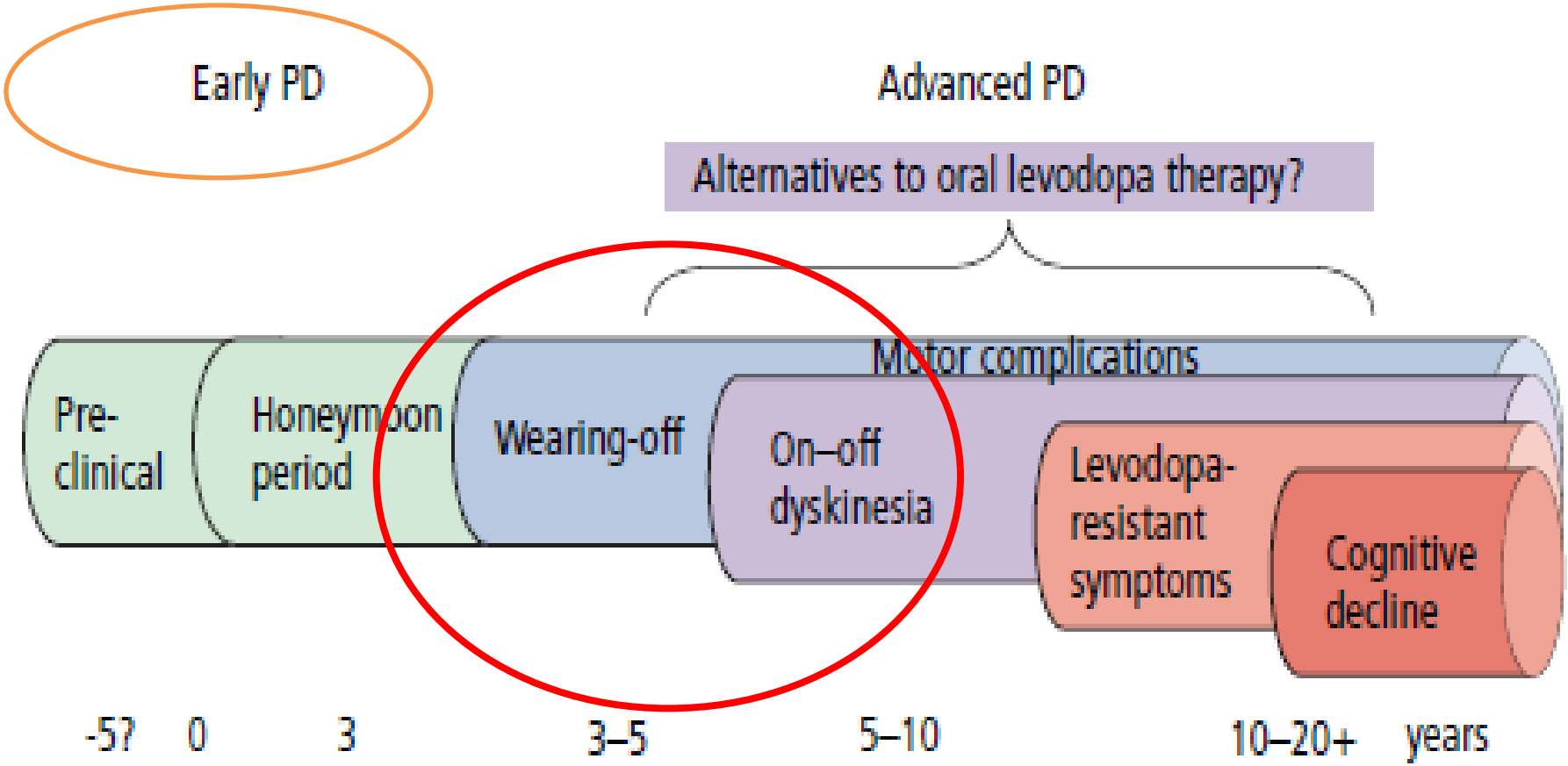
Table 3. Multivariate Logistic Regression Analysis for the Risk of Peak-Dose Dyskinesias

Group	OR (95% CI)	*P* Value
Total sample		
Female sex	3.294 (1.759-6.166)	<.001
Earlier age at onset of PD	1.053 (1.017-1.089)*	.003
Longer duration of levodopa treatment	1.098 (1.019-1.185)†	.02
Higher levodopa dose	1.001 (1.000-1.003)†	.02
Men		
Earlier age at onset of PD	1.082 (1.034-1.134)*	.001
CA_n-STR genotype 13,14+‡	0.339 (0.137-0.839)	.02
Higher levodopa dose	1.002 (1.000-1.003)†	.03
Weight ≤61 kg	7.637 (1.359-42.925)	.02
Women		
Earlier age at onset of PD	1.072 (1.018-1.129)*	.008

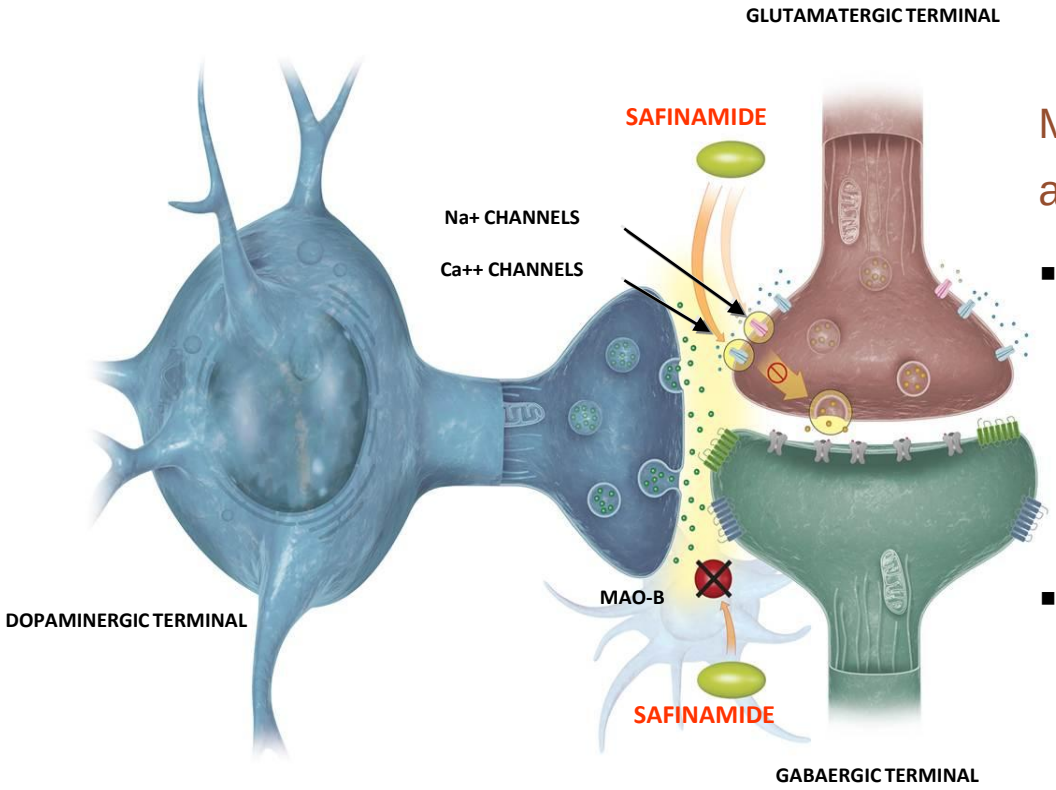
PROFILI CLINICO-GENOMICI DI RISCHIO PER DISCINESIE NELLA MALATTIA DI PARKINSON



Evoluzione della M. Parkinson



Siti d'azione di safinamide per il trattamento di sintomi motori nella MP



MSN = Medium Spiny Neurons

Multiple pharmacological systems are affected by safinamide, involving:

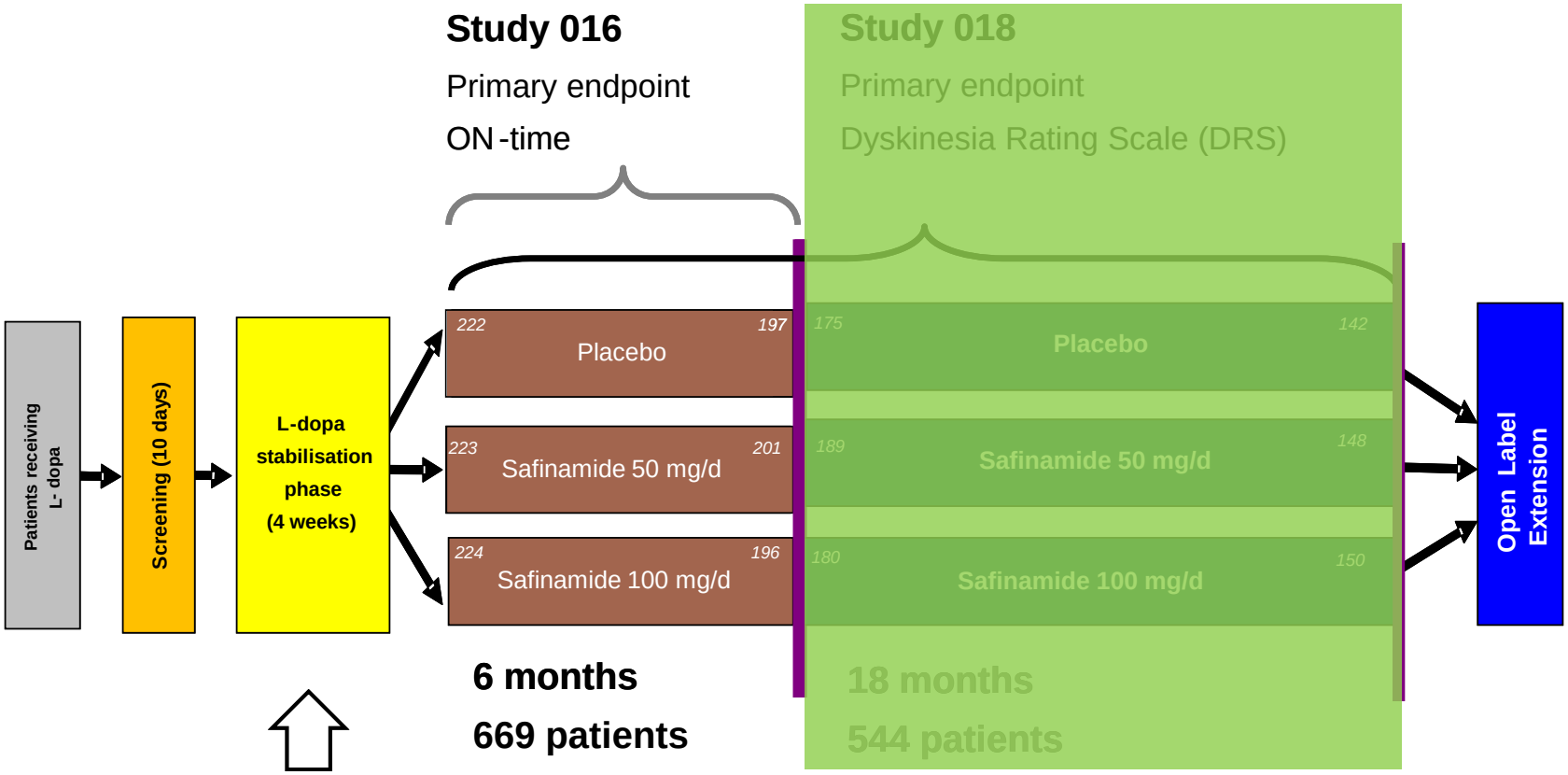
- **Non dopaminergic targets**
  - ***Sodium channels*** *blockade*
  - ***Calcium channels*** *modulation*
  - *Overactive* ***Glutamate*** *release inhibition*
- **Dopaminergic targets**
  - *Monoamine oxidase B (MAO-B)*

Safinamide represents the unique option for dopaminergic and non dopaminergic treatment in PD

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

Study 016-018: Design

(double-blind, placebo controlled study through 2 years)



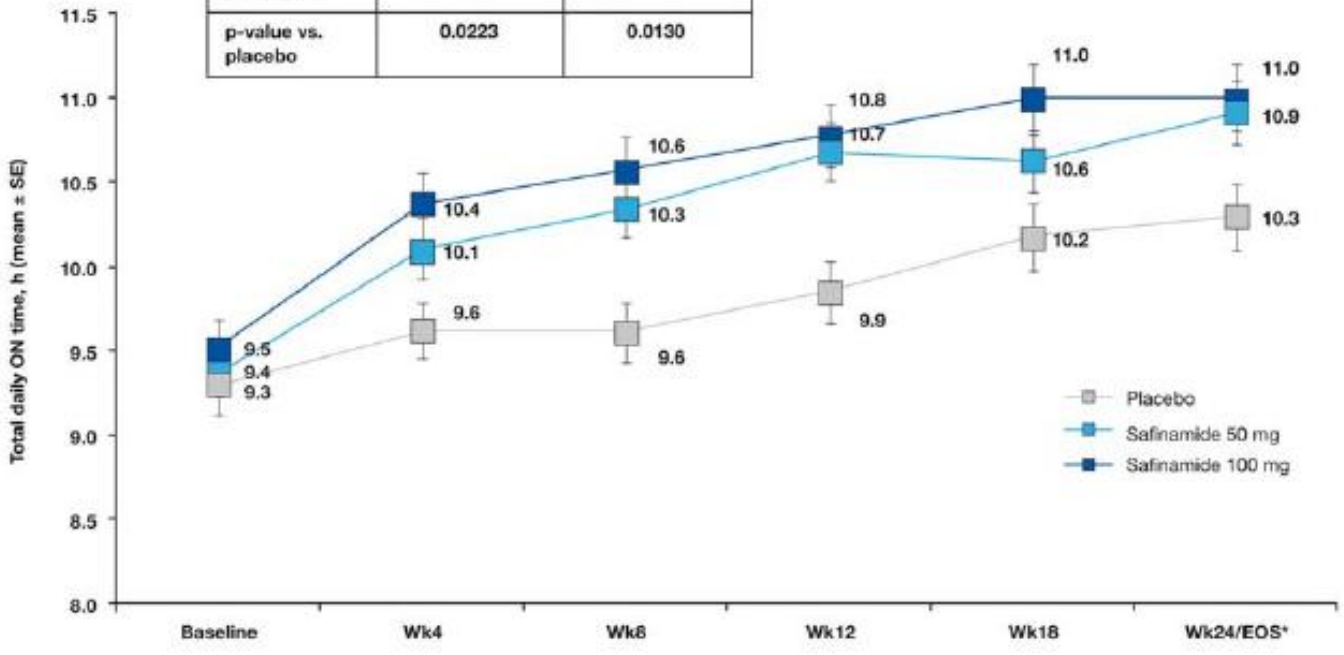
Optimize levodopa dose; continue **other PD medications**

Once a day
In the morning

Studio 016: variabili di efficacia

(mean change in total daily ON* time)

	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

Borgohain et al, Mov Disord 2014;29: 229-234

Studio 016: Variazioni all'end-point

(patient-recorded functional status, UPDRS scores, overall clinical status, PDQ-39, depression scores)

	Placebo (n = 222)		Safinamide 100 mg/day (n = 224)				Safinamide 50 mg/day (n = 223)			
Parameter	Baseline	Change from baseline	Baseline	Change from baseline	*P* (vs placebo)	95% CI	Baseline	Change from baseline	*P* (vs placebo)	95% CI
Patient-related outcomes										
PDQ-39										
Total score	230 (109.8)	−11.9	229 (124.1)	−28.4	0.0360	−31.9 to −1.1	225 (110.5)	−16.4	0.5603	−20.0 to 10.9
Mobility	41.8 (22.20)	−3.5	40.4 (25.81)	−5.5	0.2067	−5.0 to 1.1	42.0 (23.24)	−5.9	0.1186	−5.5 to 0.6
Activities of daily living	37.0 (21.85)	−1.5	36.5 (23.66)	−4.2	0.0940	−5.7 to 0.5	37.0 (22.42)	−5.1	0.0256	−6.6 to −0.4
Emotional well-being	30.4 (18.29)	−1.7	30.8 (18.86)	−5.1	0.0116	−6.0 to −0.8	31.1 (19.70)	−2.4	0.6123	−3.3 to 1.9
Stigma	31.4 (25.51)	−2.5	31.0 (26.16)	−2.9	0.8151	−3.9 to 3.1	29.2 (25.66)	−3.9	0.4267	−4.9 to 2.1
Social support	9.8 (16.70)	−0.2	11.2 (17.94)	0.1	0.9684	−2.8 to 2.7	9.5 (16.17)	1.8	0.2498	−1.1 to 4.3
Cognition	24.8 (17.58)	−0.5	23.7 (17.71)	−1.6	0.3775	−3.6 to 1.3	22.6 (16.12)	0.7	0.3081	−1.2 to 3.7
Communication	25.9 (20.80)	−1.1	26.8 (22.33)	−4.4	0.0361	−6.4 to −0.2	27.6 (20.90)	−2.6	0.3425	−4.6 to 1.6
Bodily discomfort	28.8 (21.99)	0.2	28.0 (21.43)	−3.5	0.0159	−6.8 to −0.7	26.5 (20.06)	1.3	0.4937	−2.0 to 4.1
GRID-HAM-D										
Total score	5.9 (3.70)	−0.3	6.0 (3.54)	−0.8	0.0731	−1.0 to 0.0	6.0 (3.70)	−0.5	0.3922	−0.8 to 0.3

Borgohain et al, Mov Disord 2014;29: 229-234

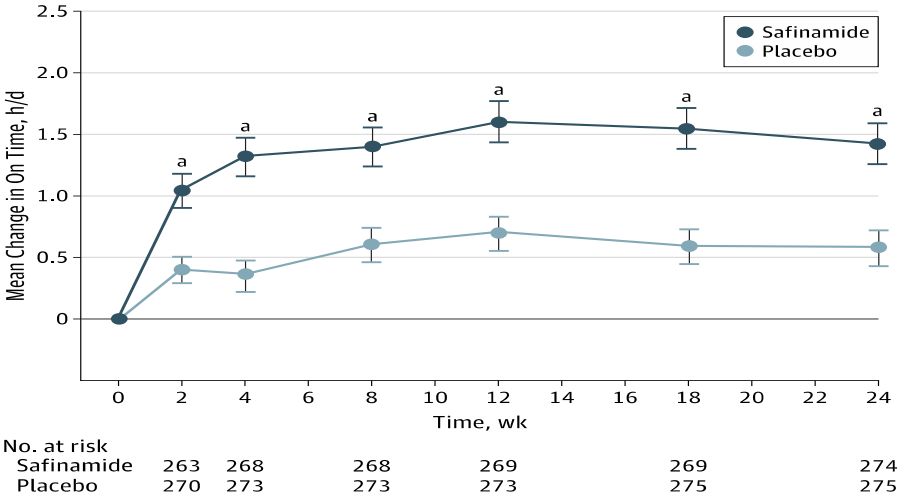
JAMA Neurology | Original Investigation | CLINICAL TRIAL

Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations

A Randomized Clinical Trial

Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci; Susan H. Fox, MBChB, MRCP(UK), PhD; Robert A. Hauser, MD, MBA; Joseph Jankovic, MD; Wolfgang H. Jost, MD, PhD; Christopher Kenney, MD; Jaime Kulisevsky, MD; Rajesh Pahwa, MD; Werner Poewe, MD; Ravi Anand, MD

Figure 2. Change in "On" Time Without Troublesome Dyskinesia During Double-blind Treatment in the Intention-to-Treat Population (Last Observation Carried Forward)



Results are based on patient diary data. "On" time indicates when patients experience relief of parkinsonian motor features. Error bars indicate SE.

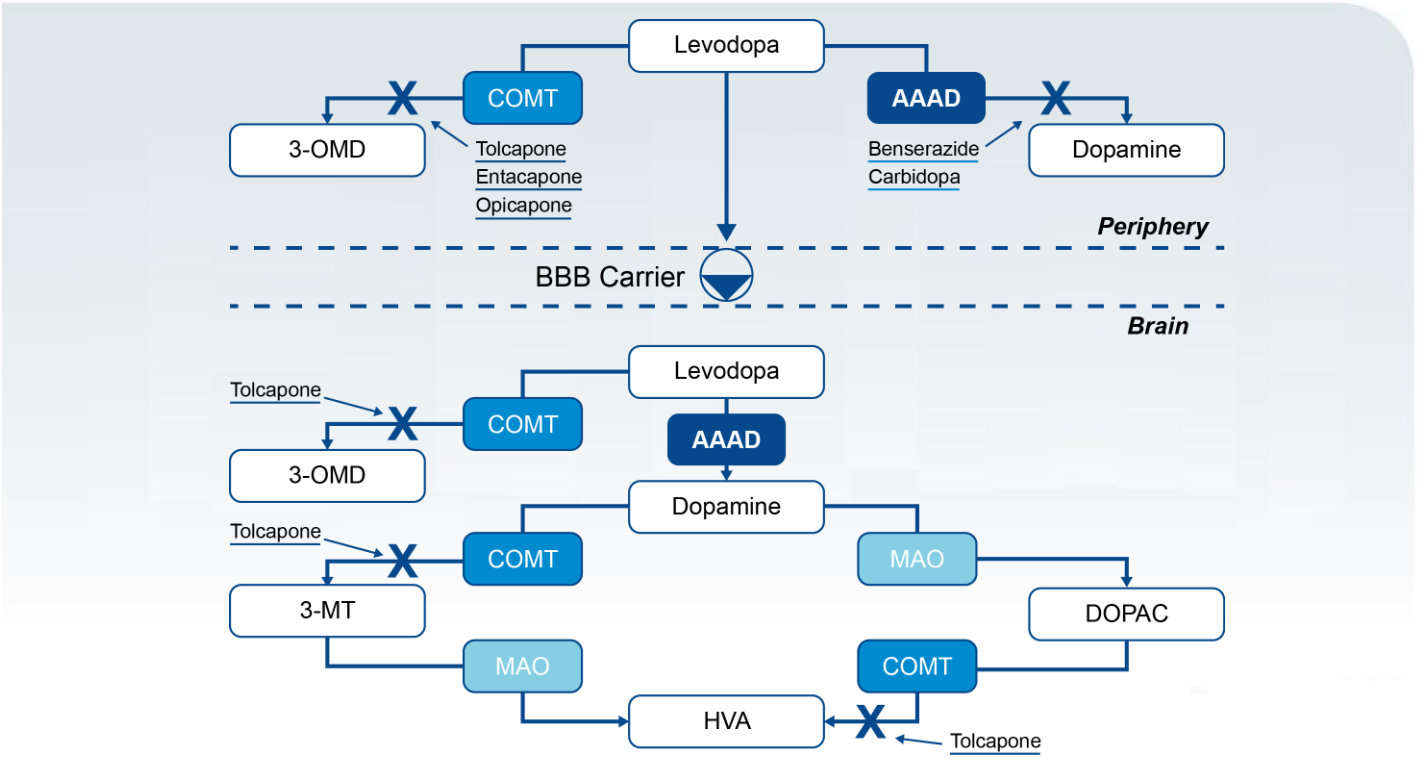
[a] $P < .001$ (unpaired, 2-sample t test).

Schapira, 2017

Nuovi farmaci per trattare i sintomi motori della MP

Farmaci dopaminergici

Levodopa: metabolismo



JAMA Neurology | Original Investigation | CLINICAL TRIAL

Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations

A Randomized Clinical Trial

Andrew J. Lees, MD; Joaquim Ferreira, MD; Olivier Rascol, MD; Werner Poewe, MD; José-Francisco Rocha, BSc; Michelle McCrory, MSc; Patricio Soares-da-Silva, MD; for the BIPARK-2 Study Investigators

eTable 2. Change From Baseline to End Point of the Different On-Time Variables

Parameter	Placebo (N=167)	OPC 25mg (N=169)	OPC 50mg (N=171)
ON time without dyskinesia or with non-troublesome dyskinesia (minutes)			
LS Mean change from baseline	48.1	84.1	85.6
LS mean difference vs placebo (95%CI)		36.0 (15.6, 56.3), 0.009	37.4 (17.2, 57.7), 0.009
P value vs placebo		0.005	0.005
ON time with troublesome dyskinesia (minutes)			
LS Mean change from baseline	11.2	19.4	25.6
LS mean difference vs placebo (95%CI)		8.2 (-15.1, 31.5)	14.4 (-8.9, 37.8)
P value vs placebo		0.49	0.226

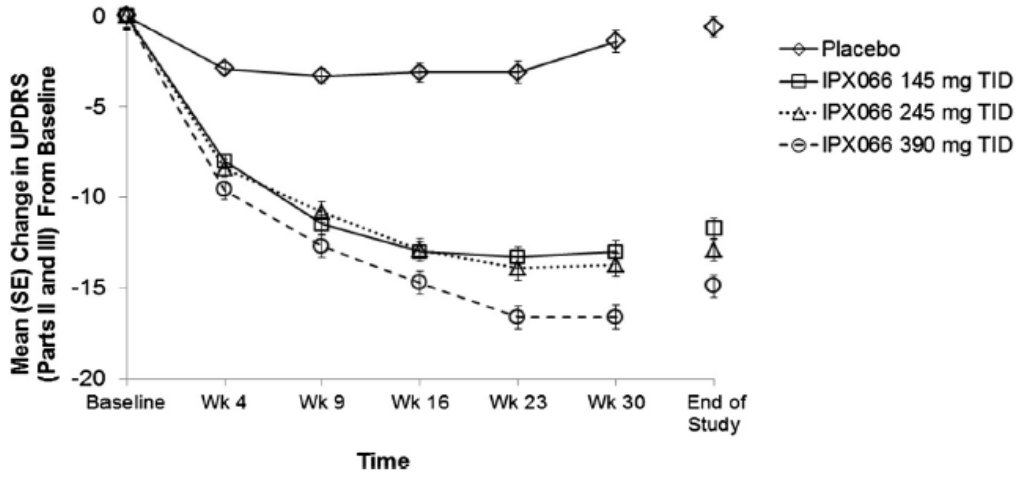
Lees, 2017

Nuove formulazioni di Levodopa

- Duodopa
- **IPX066**
- **CVT-301**
- **ND0612**
- **XP21279**

IPX066

- Capsula orale
- Contiene parti che dissolvono in tempi differenti
- Consente sia un rilascio immediato sia ritardato
- Consente una riduzione della frequenza di somministrazione



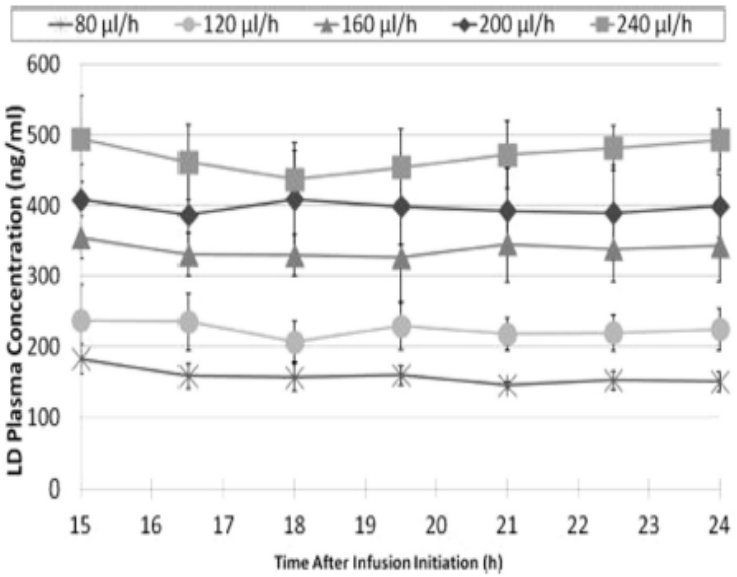
Pathwa, Park Rel Dis 2013

CVT-301

- Formulazione di levodopa inalata
- Evita l'assorbimento GI
- Assicura un assorbimento rapido, quasi immediato,
- Può essere usato come farmaco "rescue"
- Per alleviare periodi off improvvisi e imprevedibili
- Studio di fase 2-a positivo (24 pazienti)
- Studio di fase 2-b in corso

ND 0612

- Formulazione di levodopa liquida
- Evita l'assorbimento GI
- Somministrazione continua sc mediante una micropompa patch
- Consente livelli stabili di levodopa
- Trial fase 1 concluso
- Livelli di levodopa clinicamente ottenuti e mantenuti
- Studi di fase 2 iniziati

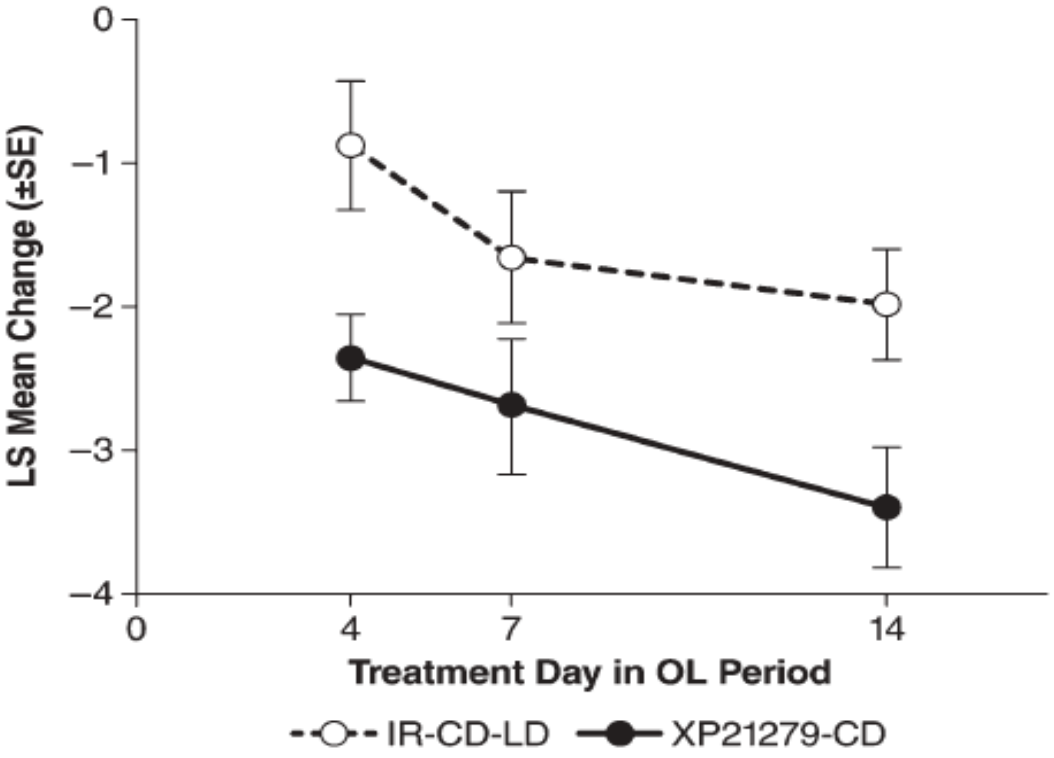


Caraco Y et al, Mov Disord, 2013

RESEARCH ARTICLE

Double-Blind Study of the Actively Transported Levodopa Prodrug XP21279 in Parkinson's Disease

Peter A. LeWitt, MD, MMSc,[1,2*] F. Jacob Huff, MD,[3] Robert A. Hauser, MD, MBA,[4] Dan Chen, MD, PhD,[3] Dmitri Lissin, MD,[3] Katie Zomorodi, PhD,[3] and Kenneth C. Cundy, PhD[3]



Nuove formulazioni di apomorfina

- VR040

  Formulazione di apomorfina inalata

  Può essere usato come farmaco “rescue”

  Studio di fase 2 completati:

  - assorbimento rapido

  - tempo medio per migliorare un periodo off 10 min

Grosset, Acta Neurol Scand 2013: 128, 166-171

Antagonisti del Recettore A2A dell'Adenosina

- A2A R Situati nel Caudato e Putamen, Potenziano la "via indiretta"
- I loro antagonisti inibiscono la "via indiretta" con conseguente riduzione degli OFF
- **Istradefillina** (in commercio in Giappone ed USA)
  - RCT 373 pz, 20-40 mg / d
  - In Add-on nei pazienti con fluttuazioni motorie: riduzione degli OFF
  - Open label extension: efficacia mantenuta a 12 m
  - EA: Discinesie

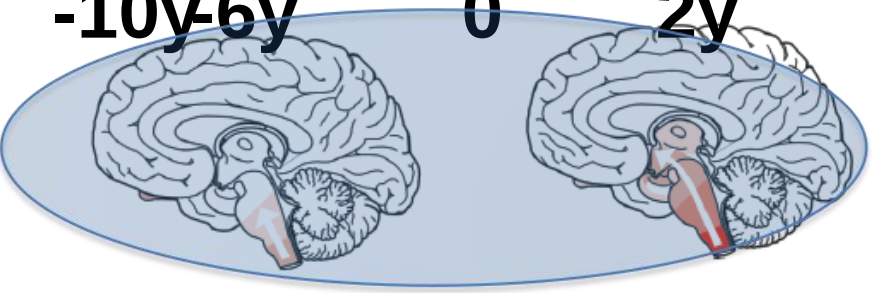
  Mizuno et al., 2013; Kondo et al., 2015
- **Preladenant** (non utilizzato)
  - 2 o 5 mg / d
  - Risultati contrastanti (Preladenant non superiore al placebo)
- **Tozadenant**

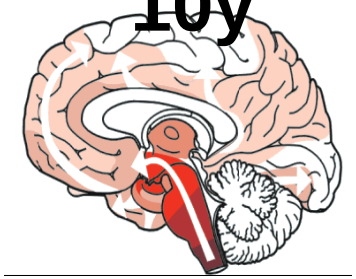
  Hauser et al., 2014; 2015
  - Trial fase II in 403 pz: 120 e 180 mg / d
  - Riduzione degli OFF
  - Trial di fase III (in corso)
  - AE: discinesie, nausea e vertigini

  NCT02453386

Drugs Targeting alfa-synuclein

-10y -6y 0 2y 5y 10y 15y





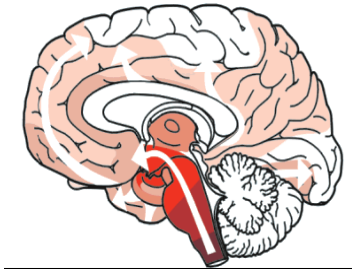
Olfactory loss
RBD, constipation
anxiety, depression

Markers:
Genetic mutations,
CSF alpha-synuclein ,
imaging abnormalities

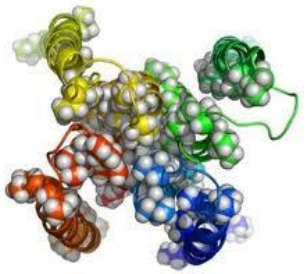
Bradykinesia,
Rigidity,
Rest-tremor,
(+/- non-motor-symptoms)

Motor complications:
Wearing off/dyskinesias,
gait and balance problems,
axial deformities,
dysarthria/dysphagia

Non-motor symptoms:
cognitive decline/ dementia, psychosis,
autonomic dysfunction,
sleep–wake dysregulation



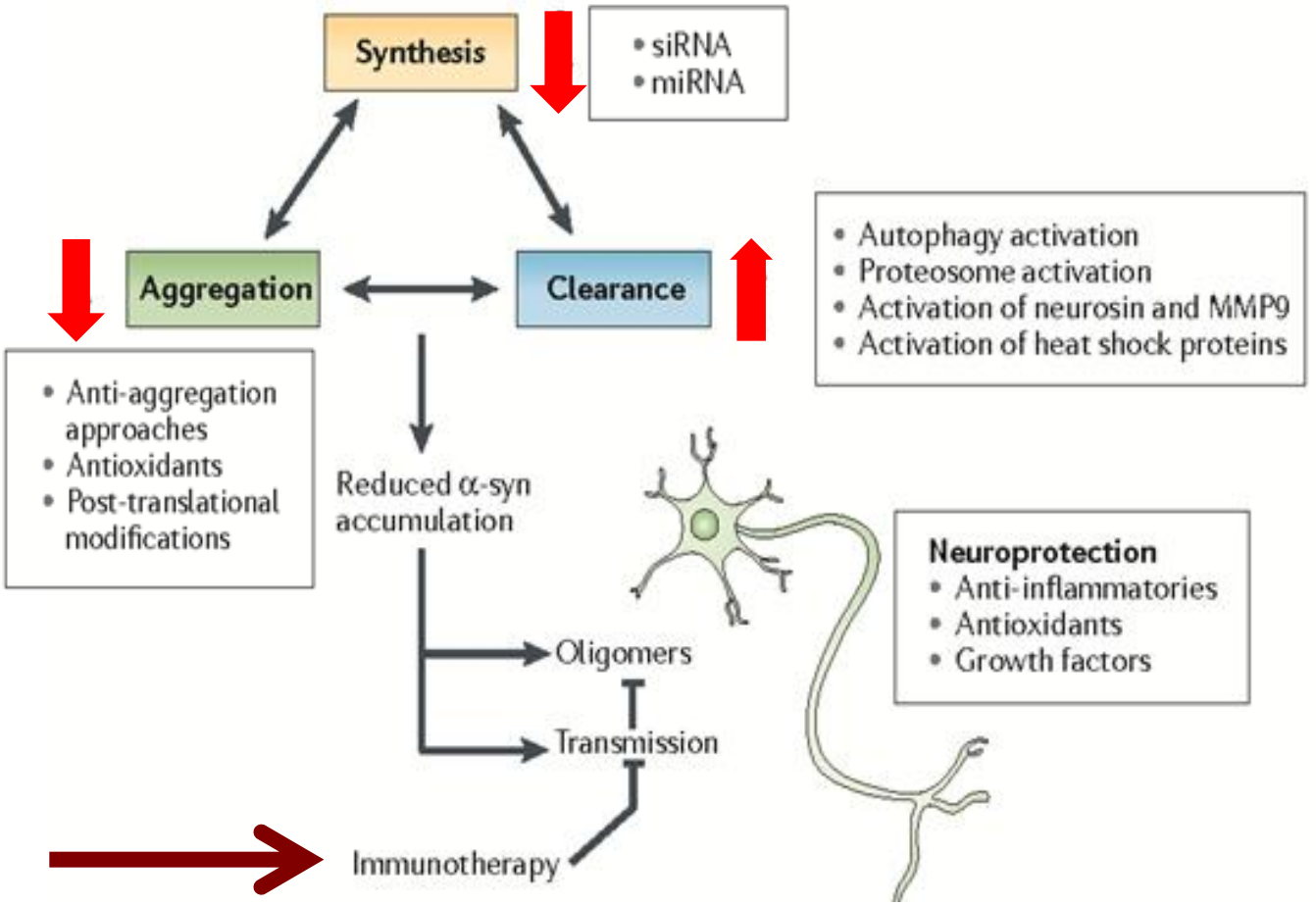
Strategie Terapeutiche per Impedire l'Aggregazione e Propagazione dell'Alfa-Sinucleina



-L'aggregazione di αSYN è stata correlata alla patogenesi della MP da una serie di evidenze scientifiche

- I composti tossici sembrerebbero essere oligomeri e piccole fibrille, mentre i corpi di Lewy sembrerebbero il risultato di una risposta compensatoria

–αSYN si propagherebbe in maniera simil-prionica



Alfa-synuclein – Disease modifying

www.clinicaltrials.gov

Drug	Action	Phase	Outcome
PRX002	antibodies that target α-synuclein	1-PD	Safety, pharmacokinetics
AFFITOPE PD03A	active immunization	1-PD	Safety, pharmacokinetics

IMMUNOTERAPIA ANTI ALFA-SINUCLEINA NELLA MP ?

Valutazione in corso in un Trial di fase I in pazienti con MP

- Studio AFF01: RCT fase I per indagare la sicurezza ed efficacia di due dosaggi di vaccino PD03A in pazienti conMP
- Immunizzazione attiva: produzione di anticorpi anti **αSYN**
- 36 pazienti (2 gruppi trattamento, 1 placebo)
- Durata 52 settimane con immunizzazione basale e dopo 36 settimane

PDTA

- Riconoscimento dell’eccellenza
- Centri Parkinson in rete
- Coinvolgimento MMG
- Approccio multidisciplinare
- Integrazione assistenza e ricerca