SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Quali peculiarità nel trattamento della malattia di Parkinson nell'anziano?

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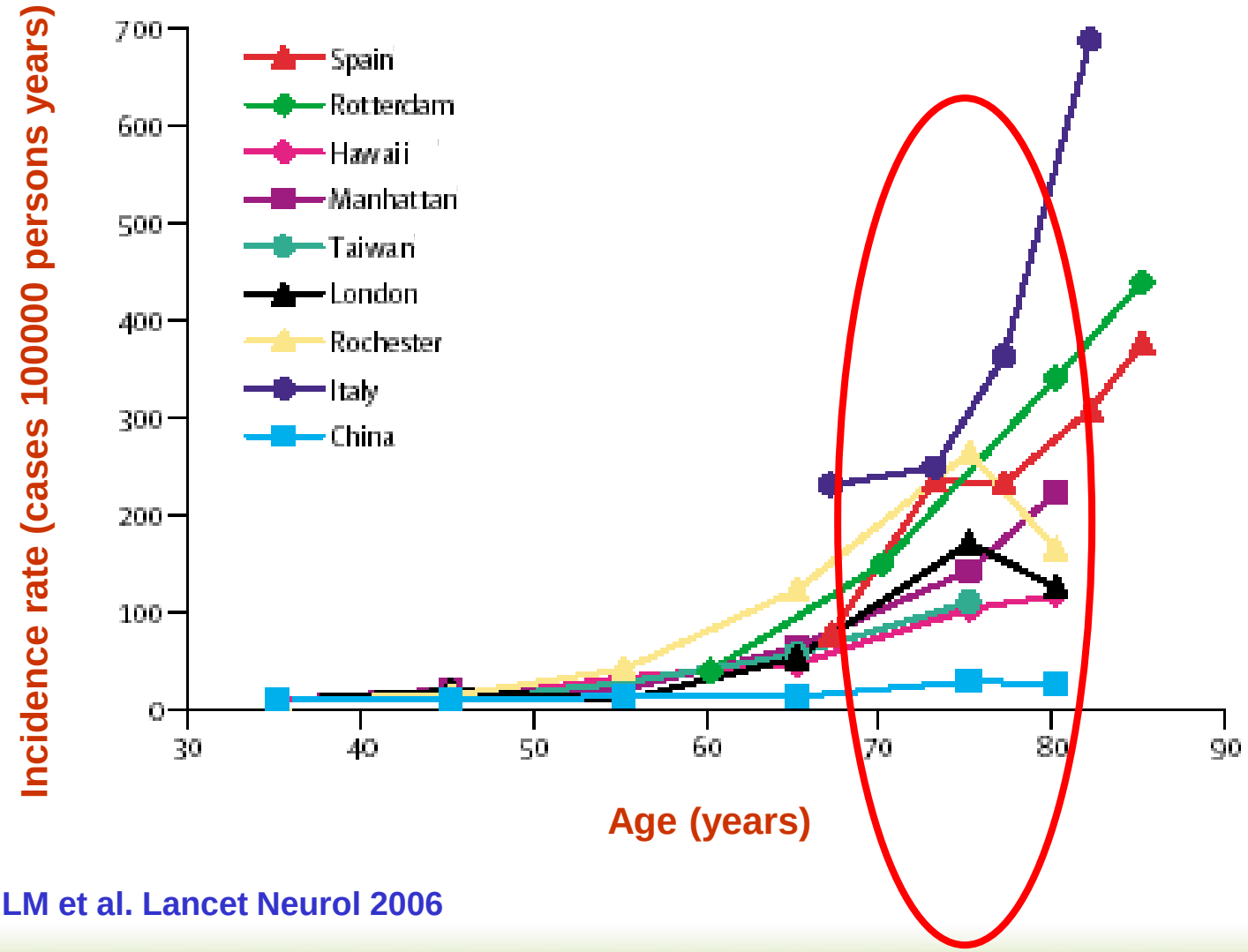
Dipartimento Geriatrico-Riabilitativo,
Ambulatorio della Fragilità

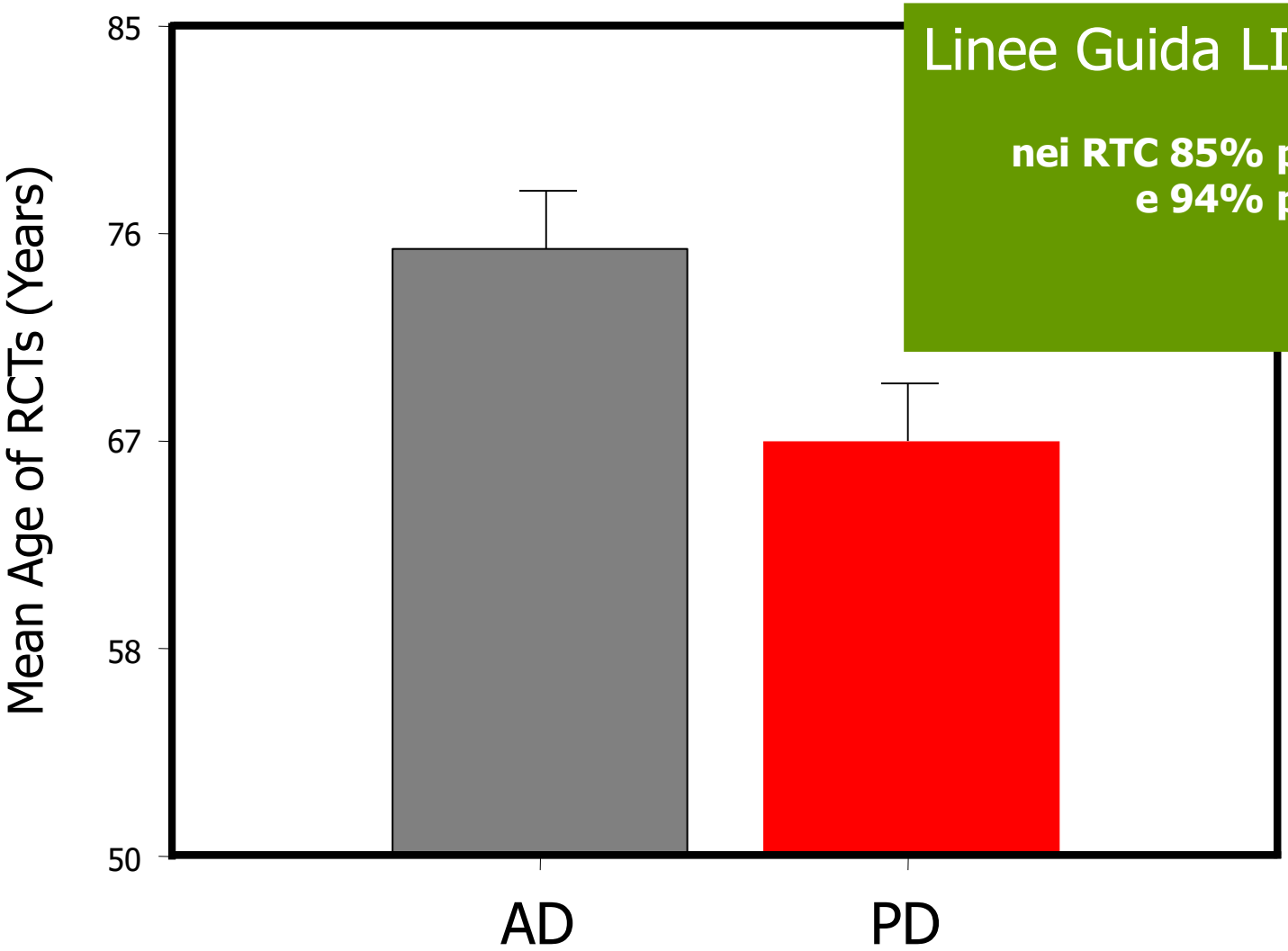
Azienda Ospedaliero-Universitaria di Parma

INCIDENZA DELLA MALATTIA DI PARKINSON



de Lau LM et al. Lancet Neurol 2006

Età media dei RCT nella Malattia di Parkinson e Alzheimer



Linee Guida LIMPE 2013:

nei RTC 85% pt < di 75 anni
e 94% pt < di 80 anni

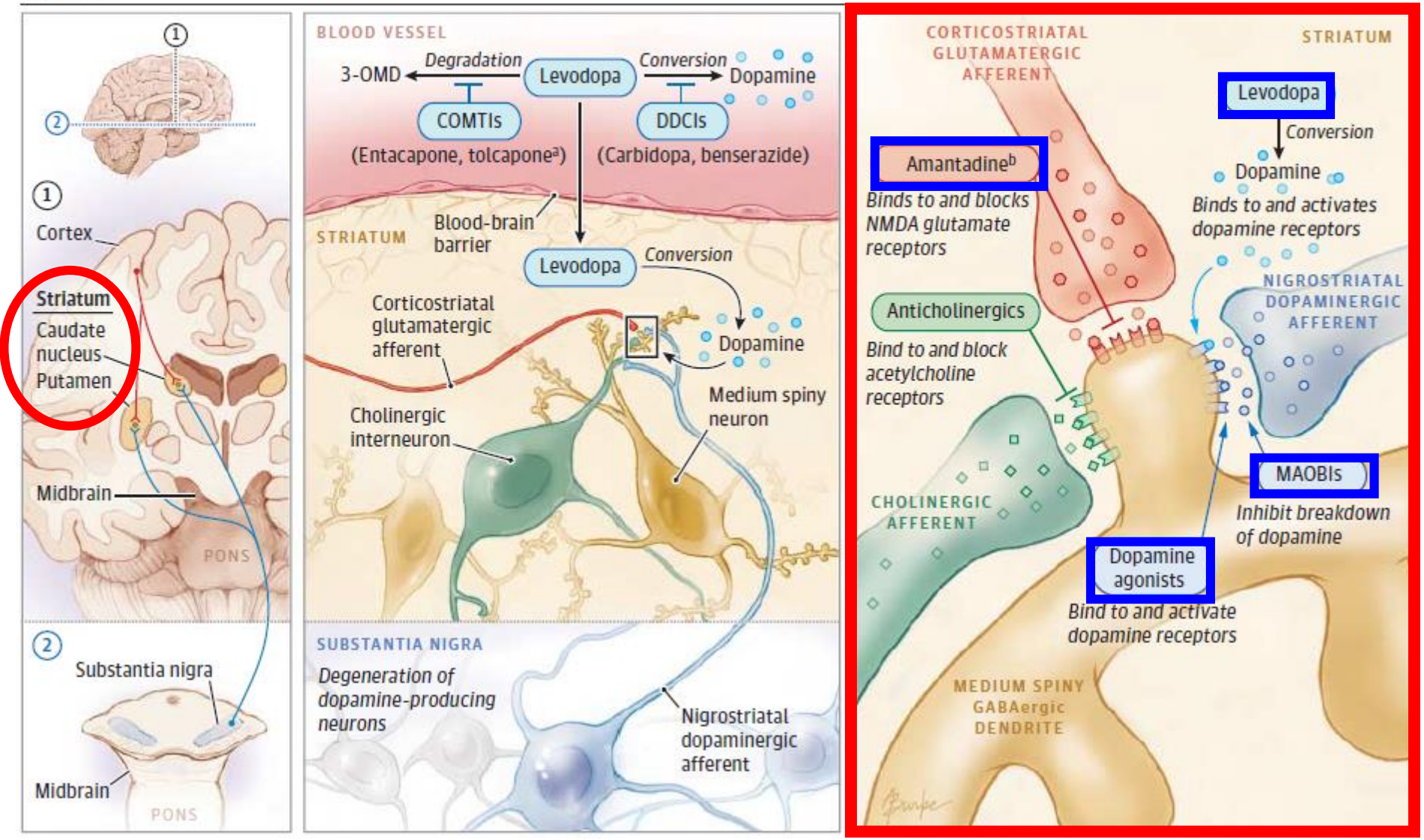
(*bias* dell'età)

Lauretani F, et al. Frontiers of Bioscience 2016 (in press)

Pharmacological Treatment of Parkinson's disease. A review

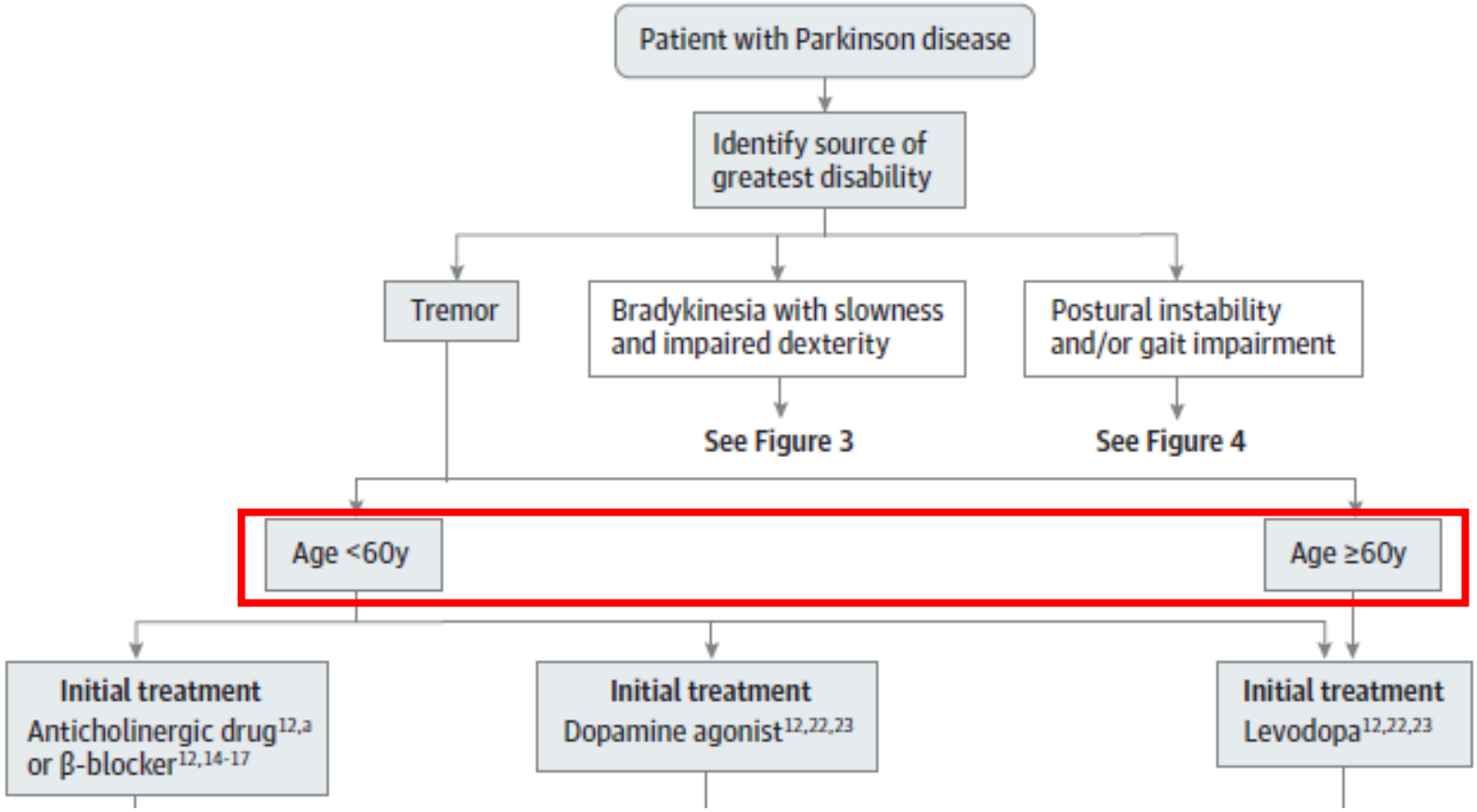
Connolly BS, Lang AE. JAMA 2014; 311:1670-83

Figure 1. Schematic Illustration of Neurologic Pathways Affected in Parkinson Disease and Sites of Action of Medications for the Treatment of Motor Symptoms



Pharmacological Treatment of Parkinson's disease. A review

Figure 2. Algorithm for the Treatment of Parkinson Disease With Tremor-Dominant Motor Symptoms



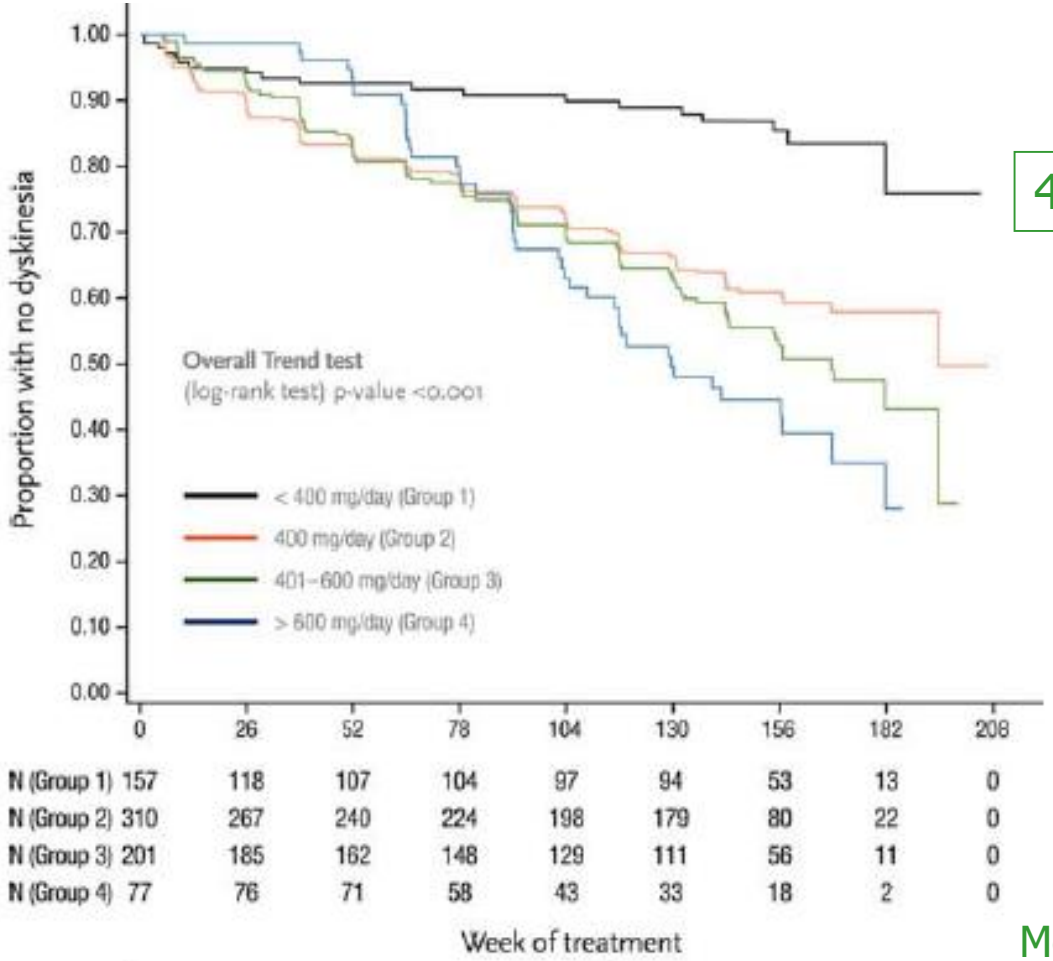
Connolly BS, Lang AE. JAMA 2014; 311:1670-83

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

Discinesie (compl. Motorie)



400 mg/die L-Dopa

Mov Disord. 2013 Apr 29

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

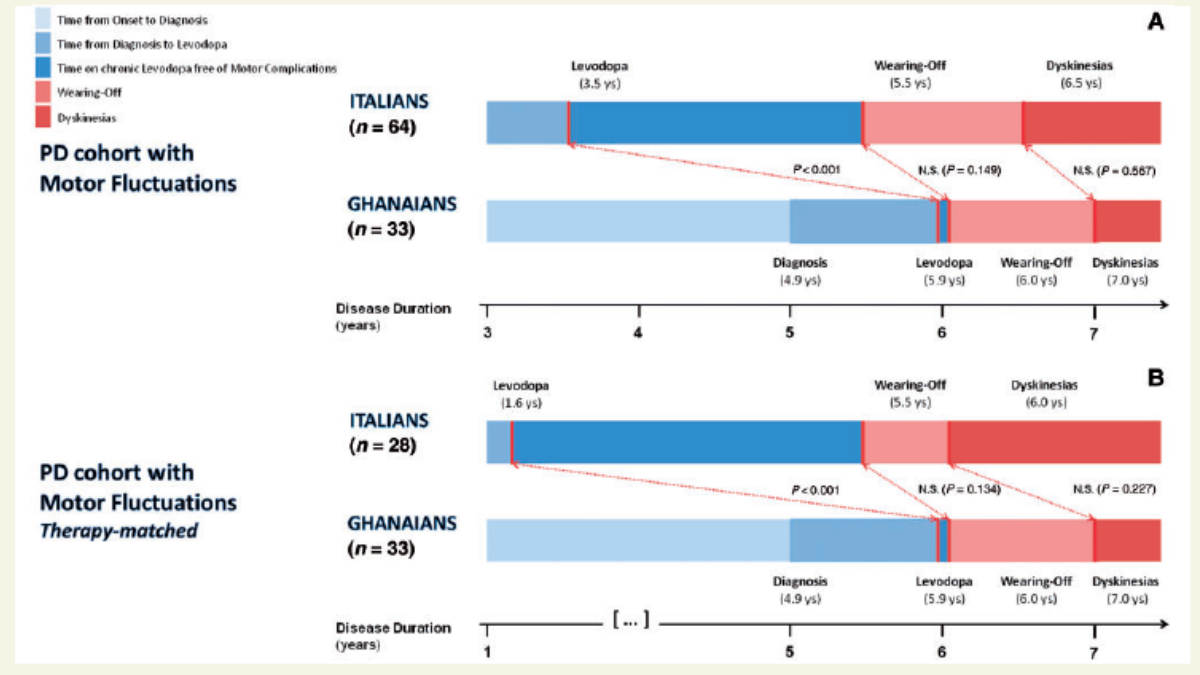


Table 4 Logistic regression analysis for predictors of motor complications

	Model prediction (AUC)[a]	
Set of variables[b,c]	Motor fluctuations	Dyskinesias
A + B + C	0.77[d]	0.79[e]
B + C + D	0.71	0.75
Model for motor fluctuations[d]	**OR (95%CI)**	***P*-value**
Levodopa dose (mg/kg)	1.33 (1.05–1.68)	**0.019**
Duration of levodopa at occurrence (years)	1.09 (0.80–1.48)	0.606
Disease duration at onset of motor fluctuations (years)	1.36 (1.01–1.83)	**0.040**
Model for dyskinesias[e]		
Levodopa dose (mg/kg)	1.19 (1.00–1.42)	**0.045**
Duration of levodopa at occurrence (years)	0.93 (0.73–1.18)	0.550
Disease duration at onset of motor fluctuations (years)	1.42 (1.07–1.87)	**0.014**

BRAIN
A JOURNAL OF NEUROLOGY

Cilia R,.....Pezzoli G. Brain 2014; 137: 2731-42

Parkinson's disease

Kalia and Lang

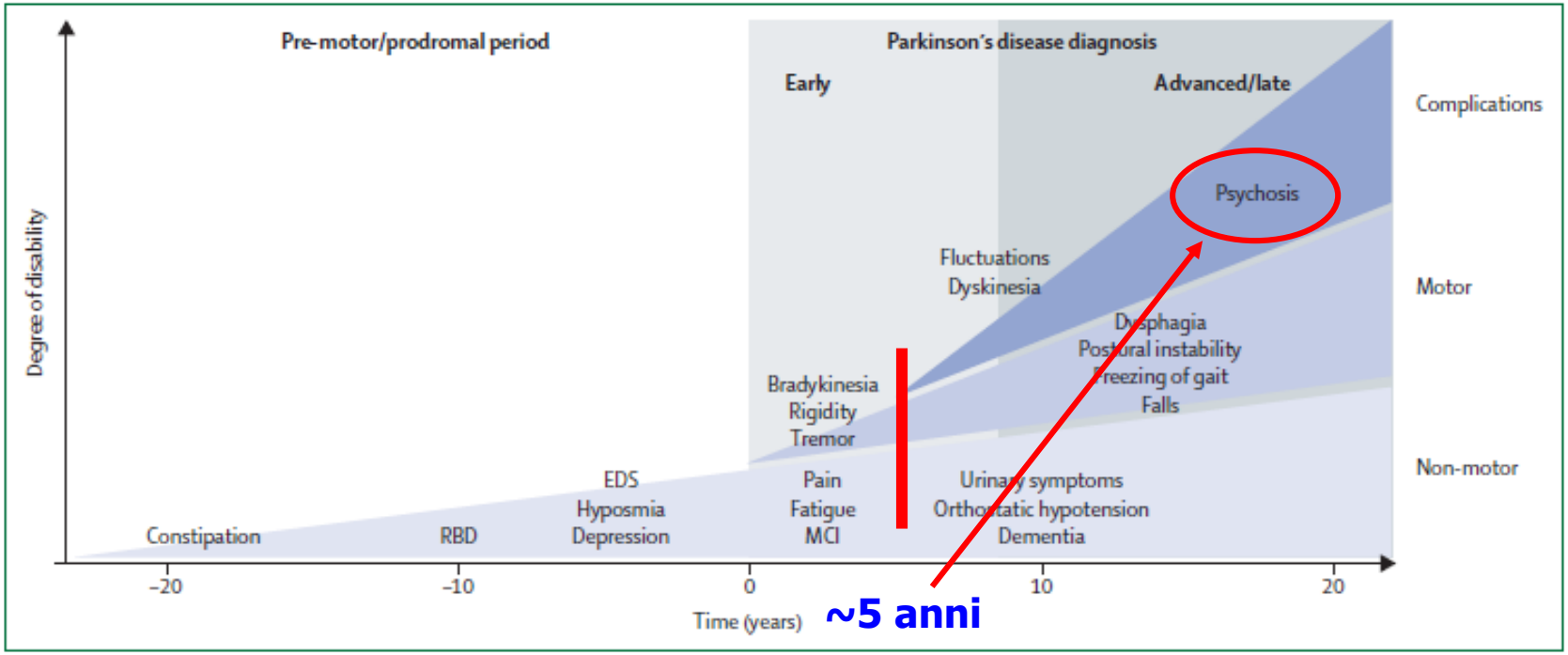
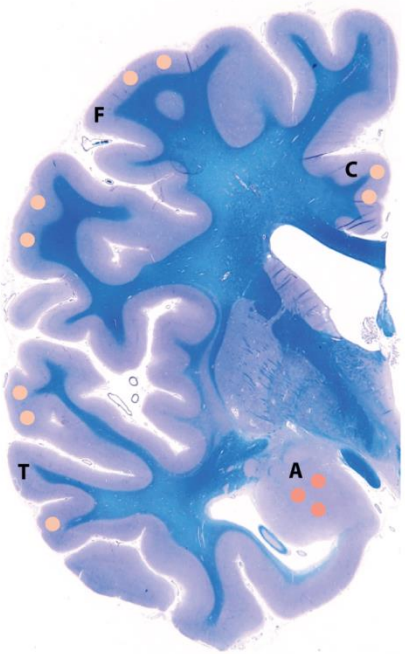
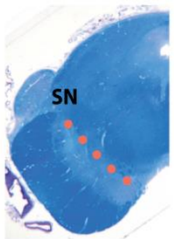
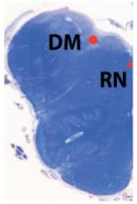


Figure 1: **Clinical symptoms and time course of Parkinson's disease progression**
Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

Kalia LV and Lang A, The Lancet 2015







BRAAK STAGES

Stages 5–6
Cingulate cortex (C)
Temporal cortex (T)
Frontal cortex (F)
Parietal cortex
Occipital cortex

Stage 4
Amygdala (A)
Nucleus of Meynert
Hippocampus

Stage 3
Substantia nigra
pars compacta (SN)

Stages 1–2
Dorsal motor nucleus
of vagus (DM)
Raphe nucleus (RN)
Locus coeruleus

With Complications (PD-D)

Aspecific non-motor symptoms, specific of the geriatric setting

-Memory Impairment
-Dysphagia with pneumonia
-Sleep Disorder
-Acute Delirium
-Nocturia

Disability: mean 7 yrs

Clinically Evident (PD)

Specific motor symptoms:

-Bradikinesia (plus at least):

-Rigidity
-Tremor
-Postural Instability

Frail: mean 10 yrs

Premotor Phase

Aspecific non-motor symptoms

-Hyposmia
-Costipation
-Orthostatic Hypotension
-Depression
-Articular pain
-Fatigue

Frail "in situ": mean 3-6 yrs

Shulman JM, et al. 2011.
Annu. Rev. Pathol. Mech. Dis. 6:193–222

(Lauretani F, et al. Arch Gerontol Geriatr. 2012)

Cosa condiziona la gestione dei sintomi motori della Malattia di Parkinson nell'età avanzata?

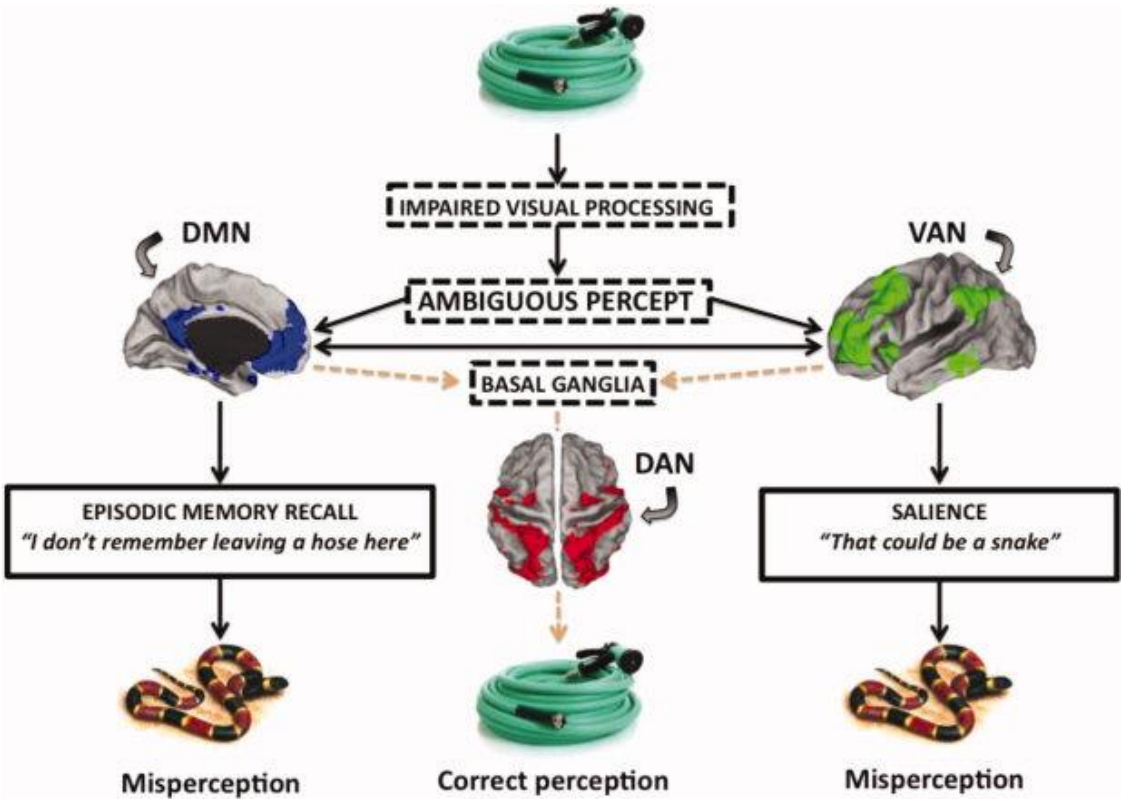
SINTOMI MOTORI

SINTOMI COGNITIVI e PSICOTICI

Il bilanciamento tra i sintomi motori e quelli cognitivi del paziente

Esempio di una mispercezione:

Visual misperceptions and hallucinations in Parkinson's disease: Dysfunction of attentional control networks?



Shine JM, et al. Mov Disord 2011; 26:2154-9

RESEARCH PAPER

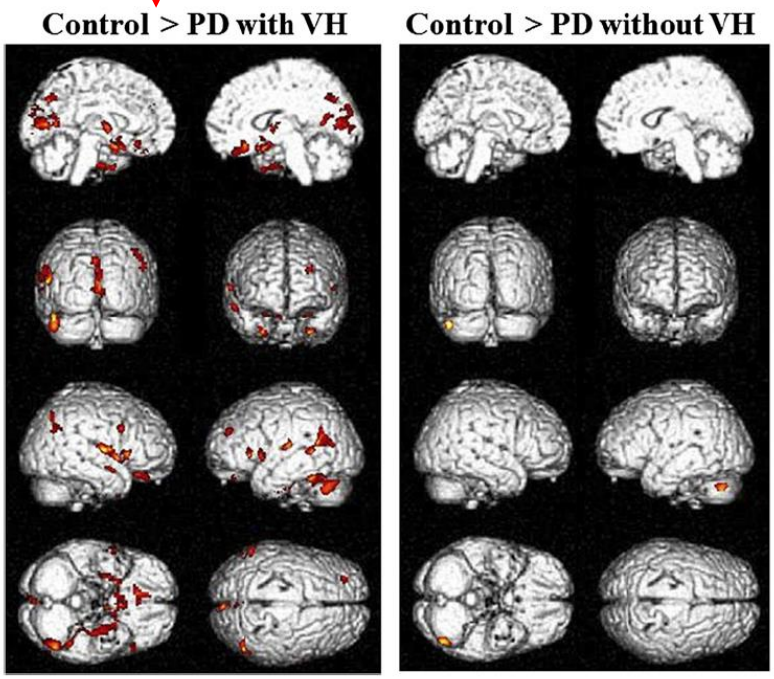
VH=Visual Hallucinations

Neuroanatomical substrates of visual hallucinations in patients with non-demented Parkinson's disease

Table 1 Demographic characteristics between PD with and without VH

	PD with VH	PD without VH	p Value
Participants	46	64	
Age (years)	71.3±5.9	70.7±5.7	NS
Number of female subjects	23	38	NS
Education (years)	8.3±5.1	8.4±5.2	NS
K-MMSE	25.2±3.0	25.7±2.9	NS
CCSI	6.5±2.5	6.1±2.5	NS
CDR	0.5±0.0	0.5±0.1	NS
VH-item score	4.3±3.6	0.0	<0.01
Parkinsonism duration (m)	3.3±3.0	2.8±3.0	NS
UPDRS III	24.1±10.4	21.6±11.0	NS
Levodopa equivalent dose	482.4±252.6	501.4±167.5	NS
Dopamine agonist (%)	20 (43.5)	32 (50.5)	NS
Anticholinergics (number)	2 (4.3)	1 (1.5)	NS
Total intracranial volume	1 641 021±126 794	1 625 539±203 716	NS

CCSI, cross-cultural smell identification; CDR, clinical dementia rating scale; K-MMSE, Korean version of the Mini-Mental State Examination; NS, not significant; PD, Parkinson's disease; UPDRS, Unified PD Rating Scale; VH, visual hallucination.



Conclusions The present study demonstrates that non-demented PD patients with VH exhibited a smaller volume in the frontal, temporal and thalamic areas as well as the SI, suggesting that PD hallucinators may have distinctive neuroanatomical bases relative to PD non-hallucinators.

J Neurol Neurosurg Psychiatry 2012; **83**: 1155-1161

Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression

Morgante L, Colosimo C, et al. on behalf of the **PRIAMO Study Group**

Table 4 Clinical factors associated with the development of psychosis over 24 months: final logistic regression model

Variable	Coefficient estimate	Wald χ^2	OR
Disease duration	0.13 (SE=0.05)	7.72 (p=0.006)	1.14 (1.04–1.26)
Prescribed dopamine—agonists	1.01 (SE=0. 50)	4.03 (p=0.045)	2.76 (1.02–7.42)
Age at disease onset	0.04 (SE=0.02)	2.80 (p=0.09)	1.04 (0.99–1.08)
Sleep disturbances (different from insomnia and RBD)	0.61 (SE=0.38)	2.58 (p=0.11)	1.83 (0.88–3.84)

Variables not presented were excluded by algorithm and therefore were considered not significant.
Coefficient estimate, Wald χ^2 and OR (95% Wald confidence limits) are reported variable by variable.
RBD, REM sleep behavioural disorder.

Domanda: I dopaminoagonisti possono essere considerati tutti uguali?

J Neurol Neurosurg Psychiatry 2012; 83:76-82

Original Investigation

Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated With Dopamine Receptor Agonist Drugs

Thomas J. Moore, AB; Joseph Glenmullen, MD; Donald R. Mattison, MD, MS

JAMA Intern Med 2014;174:1930-3

Table 1. Frequency of Medical Dictionary for Regulatory Activities Preferred Terms Identifying Impulse Control Disorder Events

Preferred Term	No. (%)[a]
Pathological gambling	628 (39.7)
Hypersexuality	465 (29.4)
Compulsive shopping	202 (12.8)
Gambling	186 (11.8)
Poriomania	125 (7.9)
Binge eating	122 (7.7)
Excessive masturbation	55 (3.5)
Compulsive sexual behavior	52 (3.3)
Kleptomania	41 (2.6)
Excessive sexual fantasies	26 (1.6)

[a] A case could contain more than 1 term.

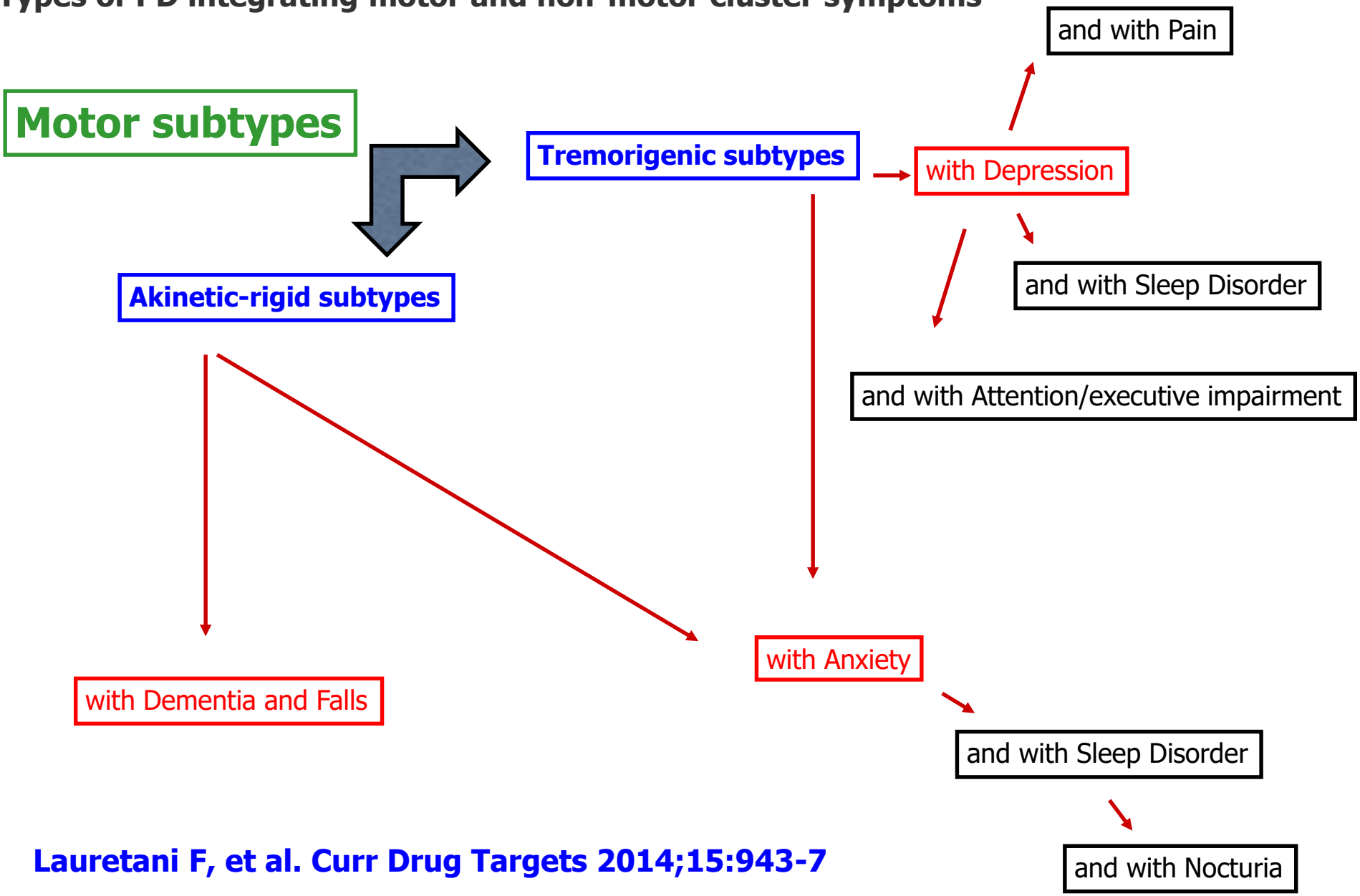
Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events

Drug	ICD Events, No.	All Events, No.	D_3 Selective	PRR[a]
Pramipexole	410	2095	Yes	455.9
Ropinirole	188	2414	Yes	152.5
Cabergoline	56	1592	No	62.9
Bromocriptine	30	613	No	86.1
Rotigotine	14	677	No	36.0
Apomorphine	12	605	No	34.5

Abbreviations: ICD, impulse control disorder; D_3, dopamine D_3 receptor; PRR, proportional reporting ratio.

[a] $P < .001$ for all drugs.

Types of PD integrating motor and non-motor cluster symptoms



Lauretani F, et al. Curr Drug Targets 2014;15:943-7

Treatment of the NMS according to cluster symptoms

anxiety + insomnia	→	Levodopa/ dopamine agonists
anxiety + RBD	→	Melatonin, Clonazepam
anxiety+ insomnia + nocturia	→	Rotigotine
depression + sleep disorder	→	Long-acting dopamine agonists (eg. Pramipexolo)
falls + cognitive impairment	→	Rivastigmine
anxiety (if “wearing-off”)	→	Levodopa/ dopamine agonists

Lauretani F, et al. Curr Drug Targets 2014;15:943-7

Treatment of the Depression according to cluster symptoms

depression + pain	→	Duloxetine
depression + anorexia	→	Mirtazapine
depression + resting tremor	→	Pramipexolo
depression + sleep disorder	→	Rotigotine
depression + dysexecutive syndrome	→	Venlafaxine

Lauretani F, et al. Curr Drug Targets 2014;15:943-7

RESEARCH ARTICLE

Three Simple Clinical Tests to Accurately Predict Falls in People With Parkinson's Disease

Mov Disord. 2013 Apr 15;28(5):655-62

TABLE 4. The predicted probability of falling, the actual number of falls sustained for each category of scores, and the likelihood ratios for each category of scores for the clinical prediction tool

Score: Sum of predictor weights	Probability of falling category	No. of individuals with this score	No. of individuals who fell	Predicted probability of falling, %	Actual probability of falling, %	Likelihood ratio (95% CI)
0	Low	43	8	17	19	0.16 (0.08–0.33)
2–6	Moderate	73	36	51	49	0.67 (0.48–0.99)
8–11	High	89	76	85	85	4.14 (2.47–6.96)

CI, confidence interval.

1. **Storia di cadute nell'anno precedente**
2. **Presenza di Freezing of gait (FOG)**
3. **Velocità del cammino a passo usuale di 1.1 m/sec**

Parkinson's disease with MCI and falls improve with AChEi?
A preliminary study report. Lauretani et al., Aging Clin Exp Res 2015

falls + cognitive impairment → **Inibitore acetilcolinesterasi**

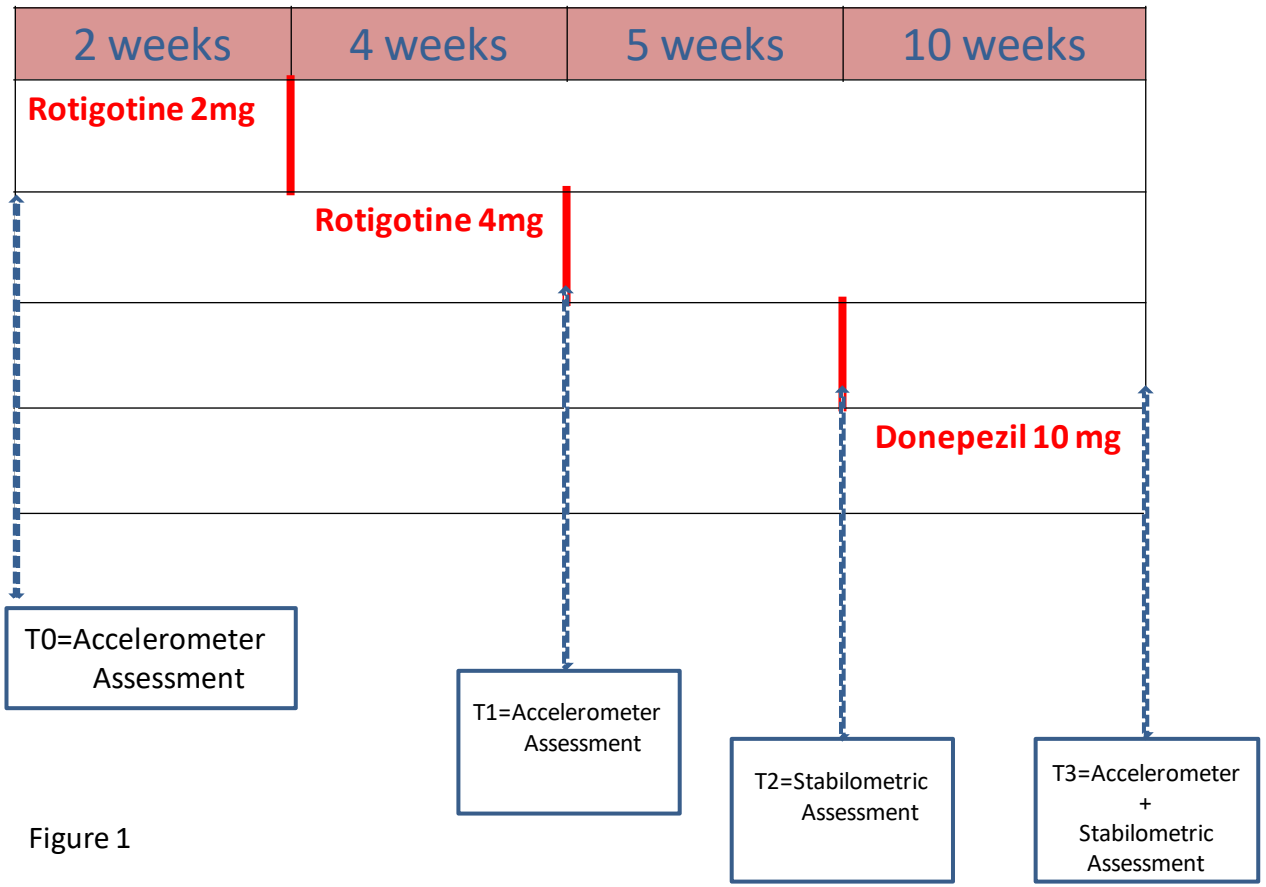
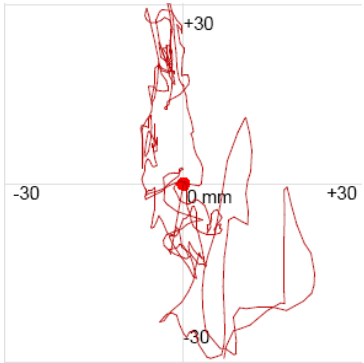
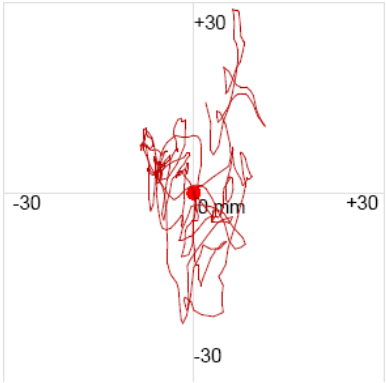


Figure 1

PRE-TRATTAMENTO



POST-TRATTAMENTO



Il tango argentino migliora la funzione motoria e l'equilibrio

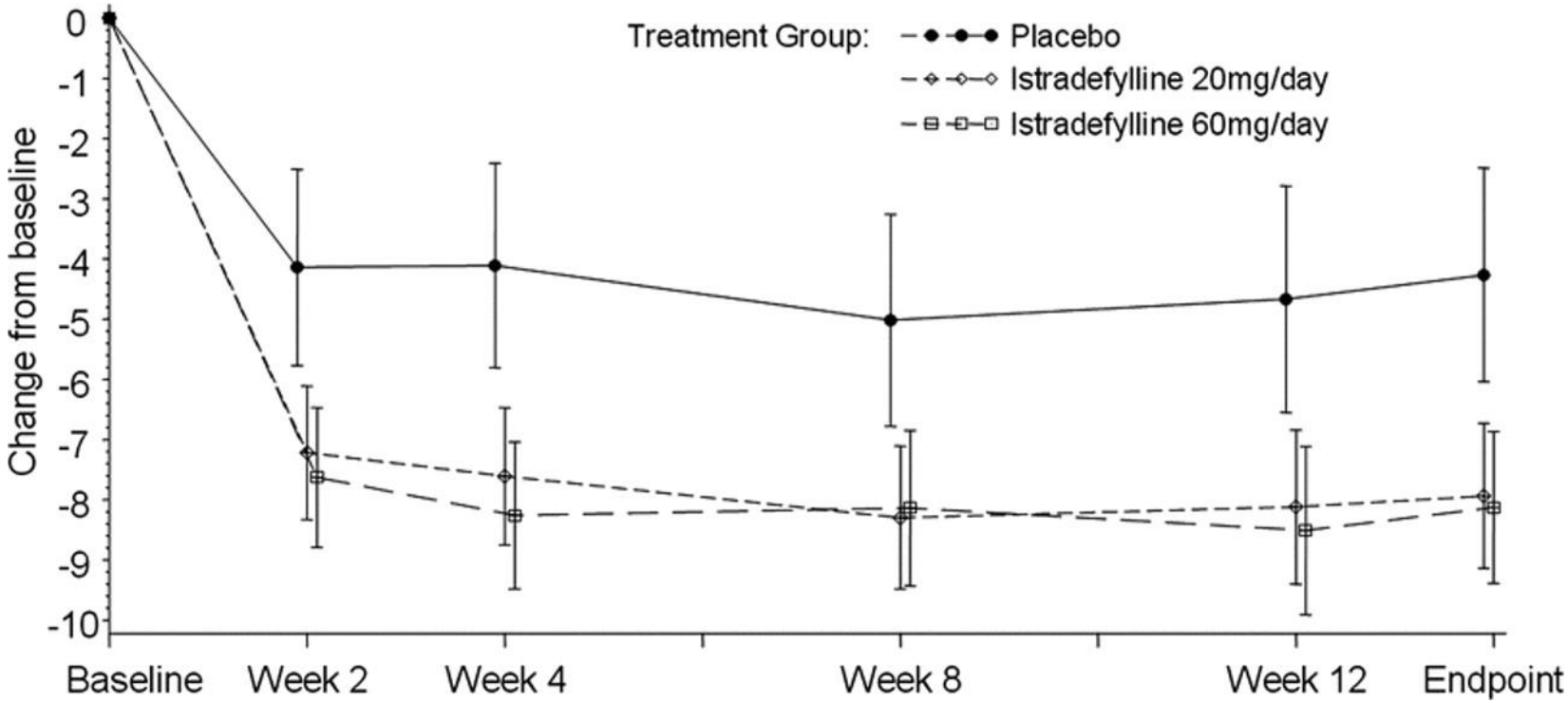
In seguito a ripetute segnalazioni degli effetti positivi del tango su pazienti parkinsoniani, ricercatori tedeschi hanno effettuato una metanalisi di 13 studi sugli effetti del tango argentino sulla funzione motoria e qualità di vita dei parkinsoniani.

È emerso che i pazienti che ballano il tango argentino, rispetto a gruppi di controllo che non hanno ballato, presentano un miglioramento del punteggio motorio sulla scala UPDRS (in media -0.62) e dell'equilibrio, ma non un miglioramento del freezing ovvero degli episodi in cui il malato sente di avere i piedi incollati al pavimento.

Lötzke D, et al. Argentine tango in Parkinson disease - a systematic review and meta-analysis. BMC Neurol. 2015 Nov 5;15:226. doi: 10.1186/s12883-015-0484-0.

A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease

by M. Stacy, D. Silver, T. Mendis, J. Sutton, A. Mori, P. Chaikin, and N. M. Sussman

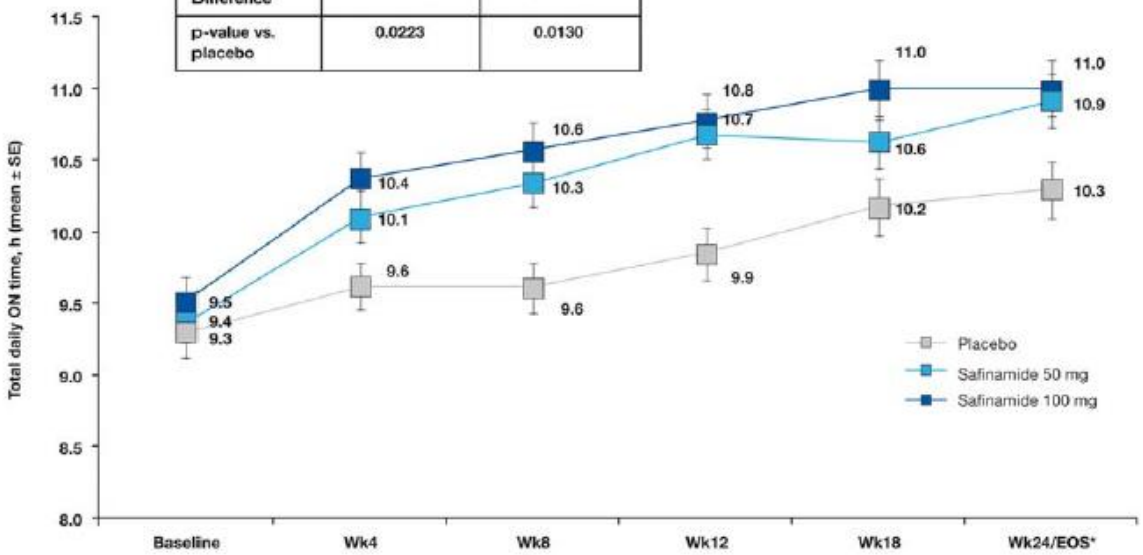


M. Stacy et al. Neurology 2008;70:2233-2240

AMERICAN ACADEMY OF NEUROLOGY®

Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease.

	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

FIG. 2. Primary endpoint. Mean change ± SE in *on* time with no or minor dyskinesia during the study (patient diary data). Using ANCOVA analysis (MMRM), all time points after baseline were statistically significant when compared with placebo, with the exception of safinamide 50 mg/day at week 18 ($P = 0.0974$). *$P < 0.05$ versus placebo. ANCOVA, analysis of covariance; MMRM, mixed model repeated measures; LS, least squares; CI, confidence interval; EOS, end of study; SE, standard error.

Borgohain R, et al. Study 018 Investigators. Mov Disord 2014; 29:1273-80

REVIEW

Basic Science Breaks Through: New Therapeutic Advances in Parkinson's Disease

Mov Disord. 2015 Sep 15;30:1521-7

Patrik Brundin, MD, PhD,[1*] Graham Atkin, PhD,[1] and Jennifer T. Lamberts, PhD[1,2]

Anti-leucemico: *Nilotinib* che degrada la α-syn

(Fenilbutirrato: Spazzino della α-syn nei neuroni in studi sull' animale)

Vaccinazione passiva

Vaccinazione attiva

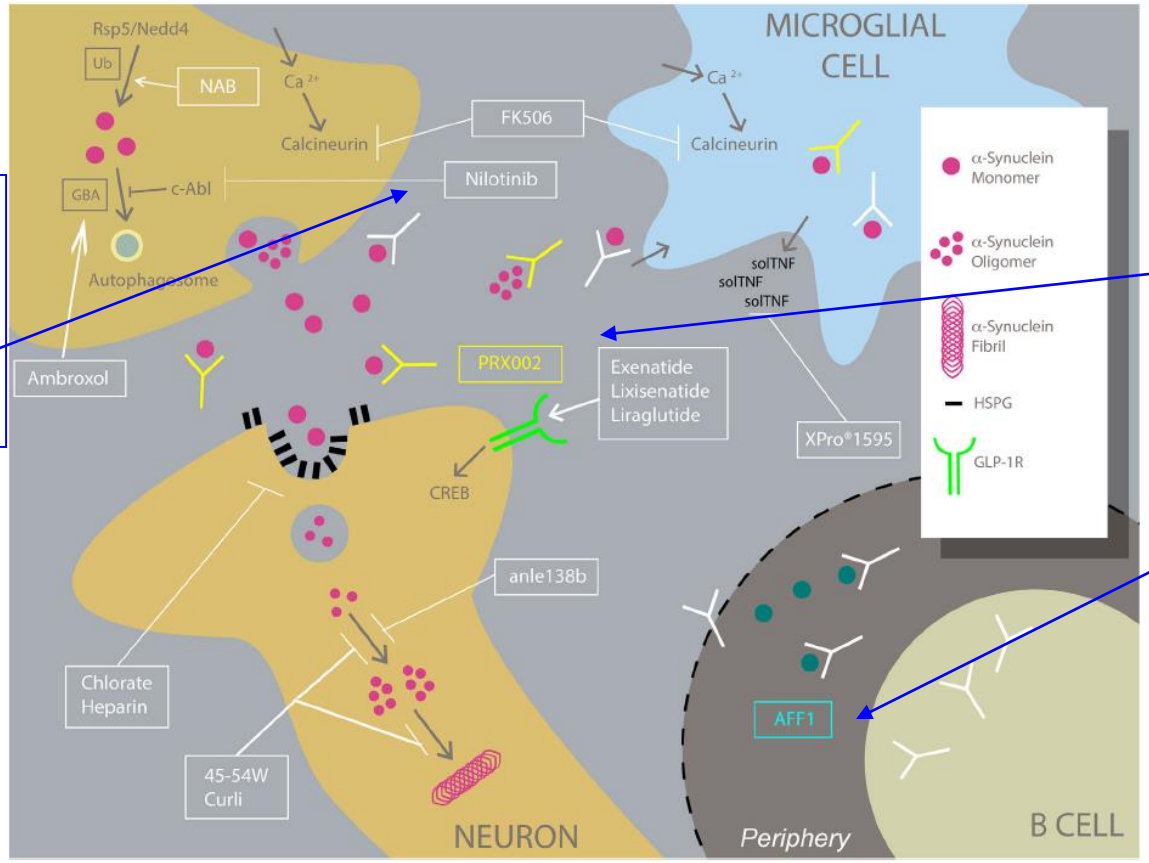


FIG. 1. Novel therapeutic strategies for Parkinson's disease (PD). New therapeutic approaches for the treatment of PD identified in basic research studies include active immunotherapy (AFF1); passive immunotherapy (PRX002); inhibition of α-Syn uptake (chlorate, heparin); inhibition of α-Syn oligomerization or fibrillation (anle138b, curli, 45-54W); stimulation of α-Syn degradation (ambroxol, NAB, nilotinib); calcineurin inhibition (FK506); soluble tumor necrosis factor (solTNF) inhibition (XPro1595); and glucagon-like peptide 1 receptor (GLP-1R) stimulation (exenatide, lixisenatide, liraglutide). CREB, cyclic adenosine monophosphate response element binding protein; GBA, glucocerebrosidase; HSPG, heparin sulfate proteoglycan; NAB, N-aryl-benzimidazole; Ub, ubiquitin. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Conclusioni

1. Differenziare bene i VD dai PD (DATSCAN pochissimi falsi negativi)

2. Bilanciamento tra sintomi motori e cognitivi, in particolare nel caso di presenza di allucinazioni e “mispercezioni”

3. Effettuare sempre una valutazione integrata motoria e cognitiva standardizzata

4. Differenziare le forme “tremorigene” da quelle “acinetico-rigide”

6. Trattamento basato sulla gestione a “cluster” dei sintomi

7. Identificare i pazienti ad elevato rischio di caduta

Grazie!!!

UNIVERSITÀ DEGLI STUDI DI PARMA
il mondo che ti aspetta

Prof. Gian Paolo Ceda

Prof. Marcello Maggio

La gestione della malattia di Parkinson in Italia

Come migliorare l'assistenza promuovendo l'informazione sulla patologia e una maggiore integrazione tra gli attori della filiera sanitaria

Roma, 18 novembre 2015
Senato della Repubblica – Sala Capitolare

28NOVEMBRE2015
GIORNATA NAZIONALE PARKINSON

DATSCAN per la diagnosi di PD (mediante analisi quantitativa)

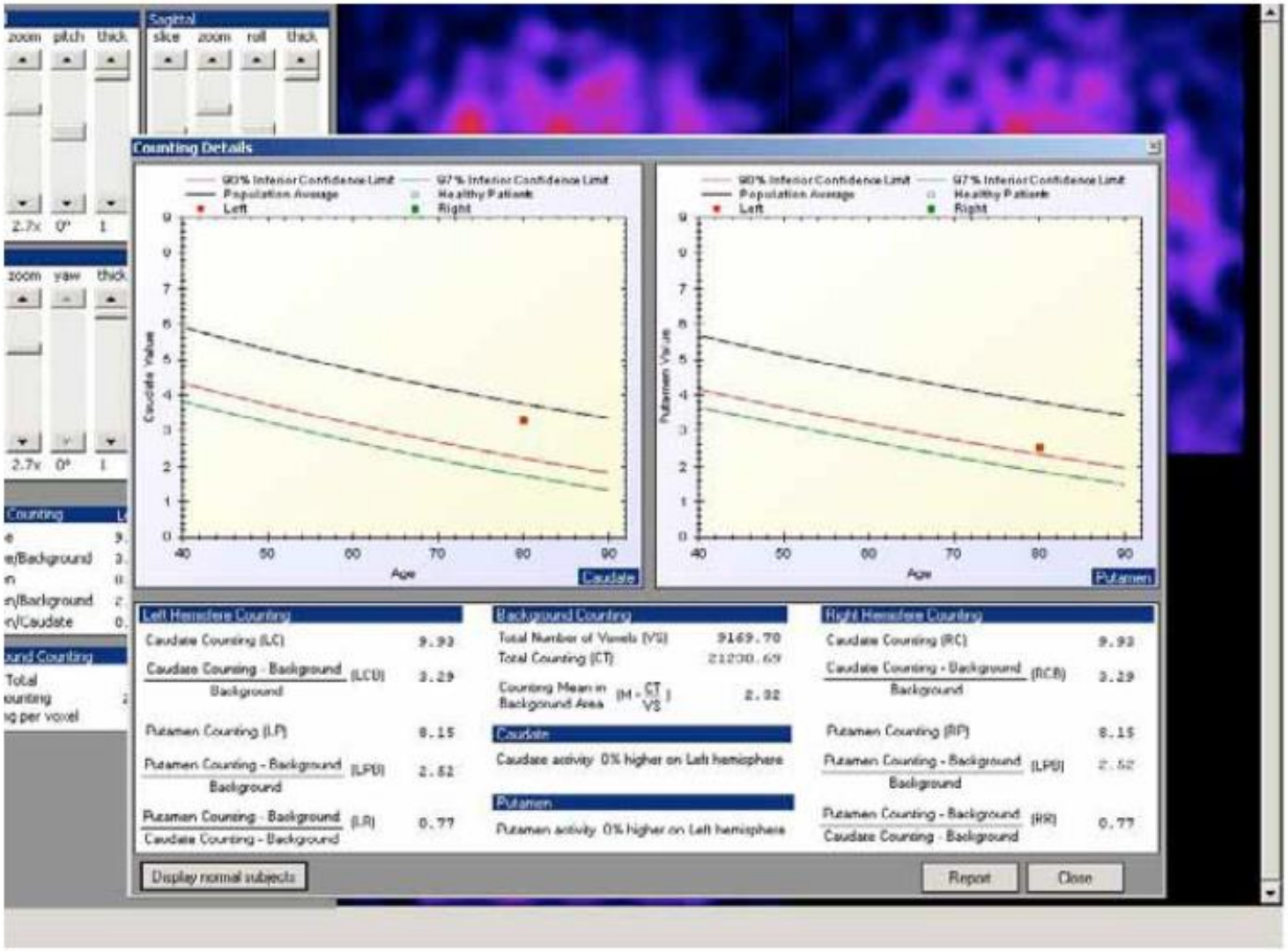


Fig. (3). Example of the SPECT images evaluation by using the Basal Ganglia software version 2.