BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

VI Congresso Nazionale B&M
Nutrizione e Neurodegenerazione

SESSIONE III: RELATORI

- ***L'esperienza dell'infusione duodenale continua di levodopa/carbidopa***

Dr. Maurizio Zibetti
Dirigente Medico di I livello presso la II Divisione Universitaria di Neurologia dell'A.O, Città della Salute e della Scienza di Torino

MILANO | 11-12 MAGGIO | 2017

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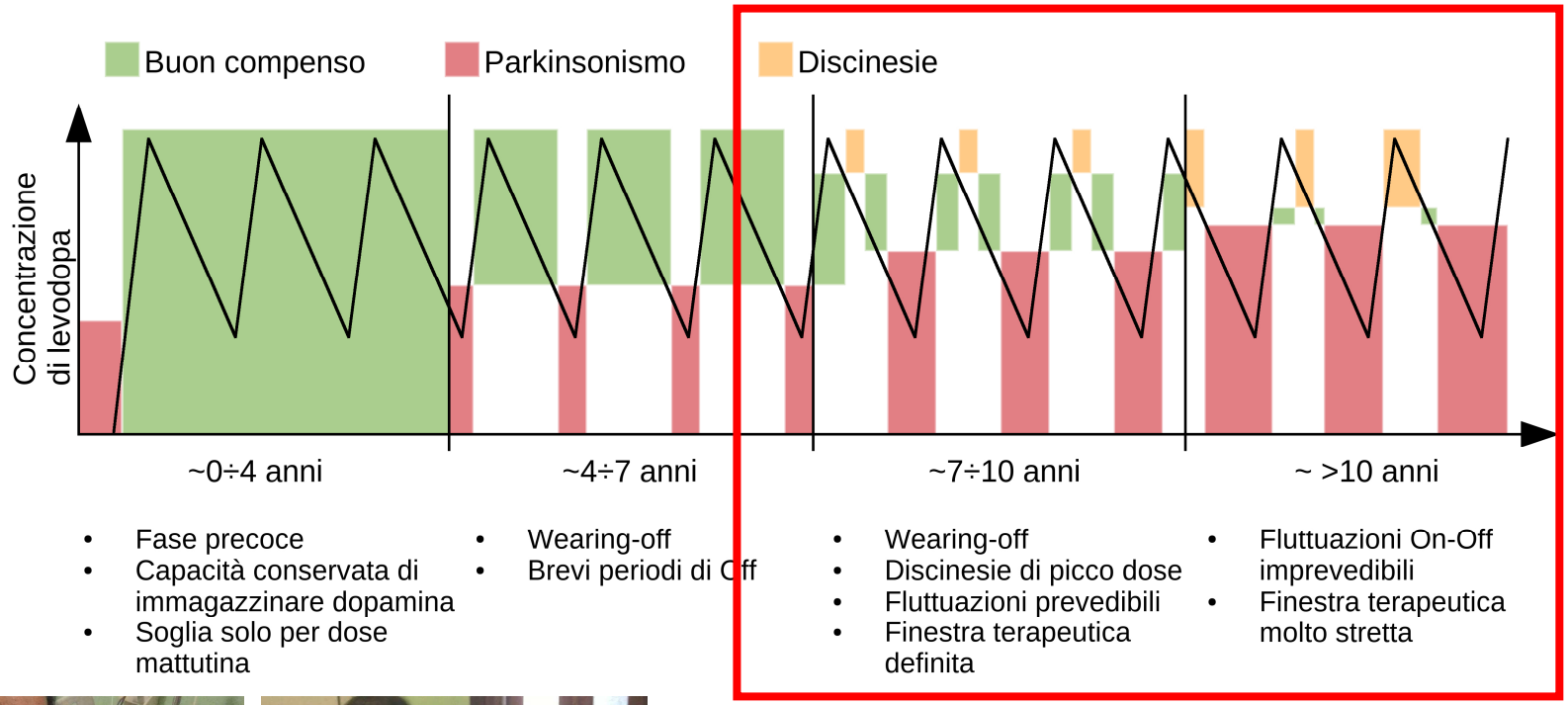
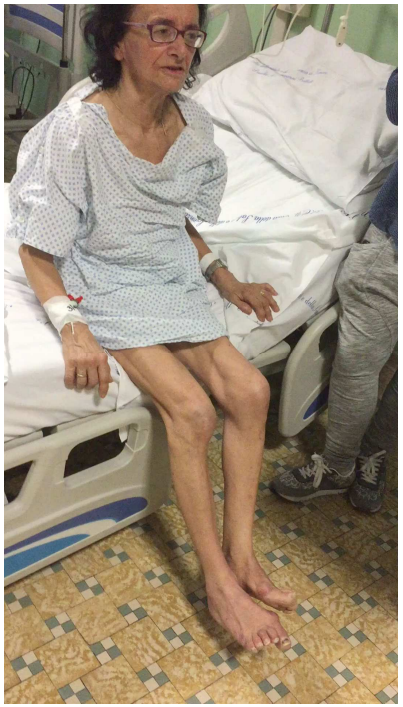
VENERDÌ 12 MAGGIO 2017

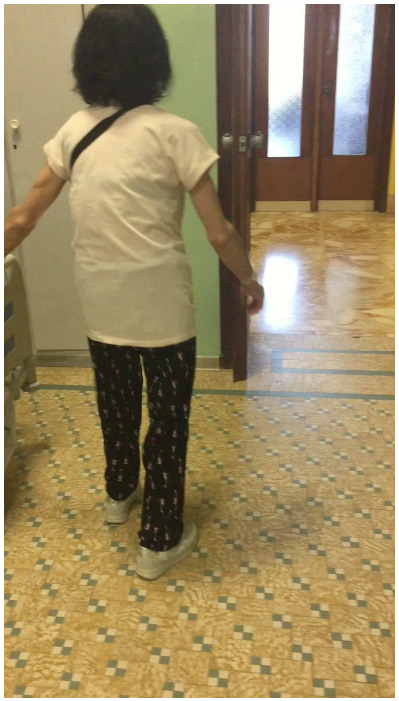
L'esperienza dell'infusione duodenale continua di levodopa/carbidopa

Maurizio Zibetti
Dipartimento di Neuroscienze
Città della salute e della Scienza di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino





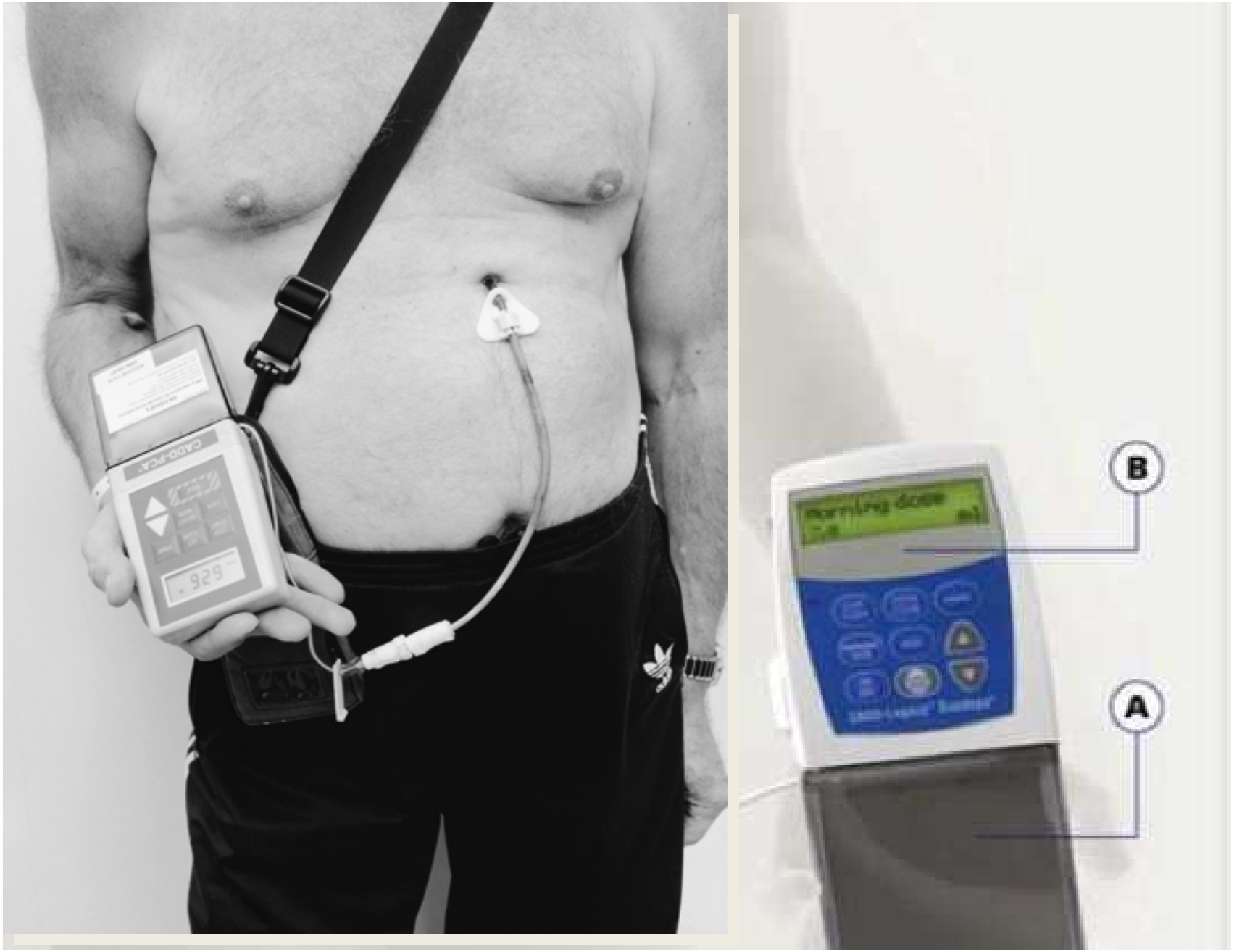


Malattia di Parkinson in fase avanzata

Outline

- Infusione LCIG
  - Studi RCT
  - Follow-up a lungo termine
  - Sintomi non motori
  - Effetti avversi
- Confronto LCIG-Apo-DBS

LEVODOPA CARBIDOPA INTESTINAL GEL INFUSION

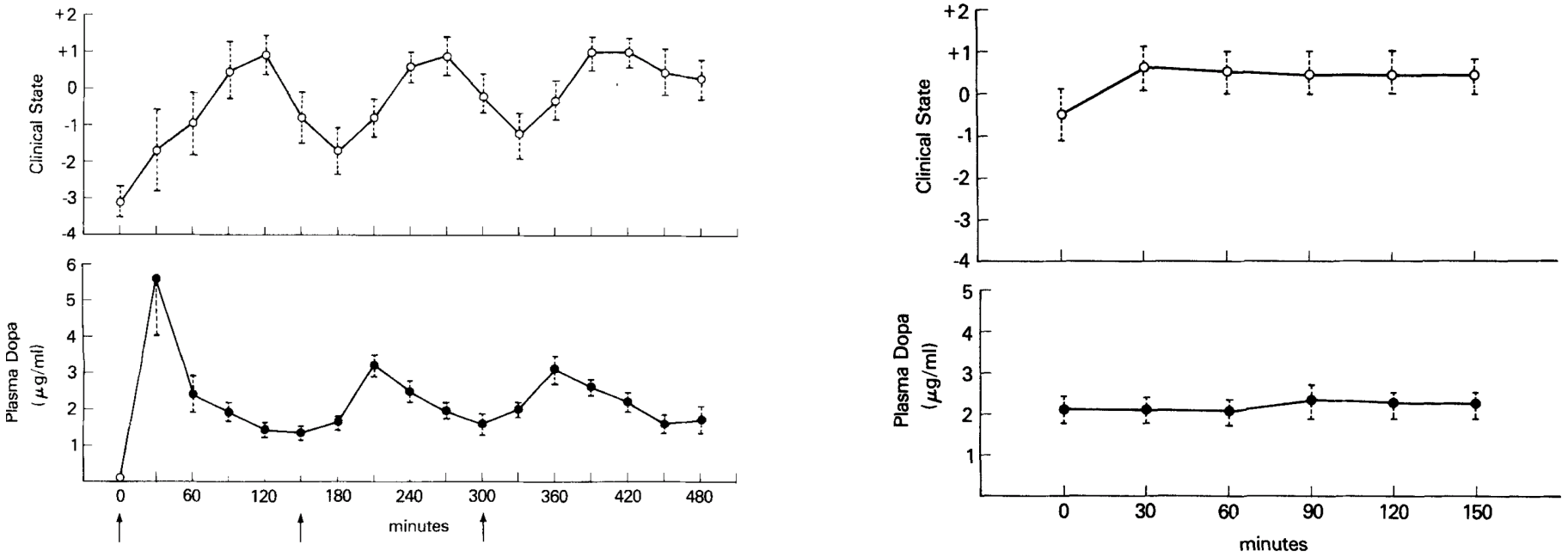


On-off response

Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients

IRA SHOULSON, M.D., GEORGE A. GLAUBIGER, M.D., Ph.D., and THOMAS N. CHASE, M.D.

NEUROLOGY 25: 1144-1148, December 1975



"A constant intravenous infusion of levodopa resulted in stable plasma dopa concentrations and virtual disappearance of motor fluctuations."

Duodenal Delivery of Levodopa for On-Off Fluctuations in Parkinsonism: Preliminary Observations

Roger Kurlan, MD, Allen J. Rubin, MD, Charlyne Miller, RN, MS, Leonor Rivera-Calimlim, MD, Allan Clarke, BS, and Ira Shoulson, MD

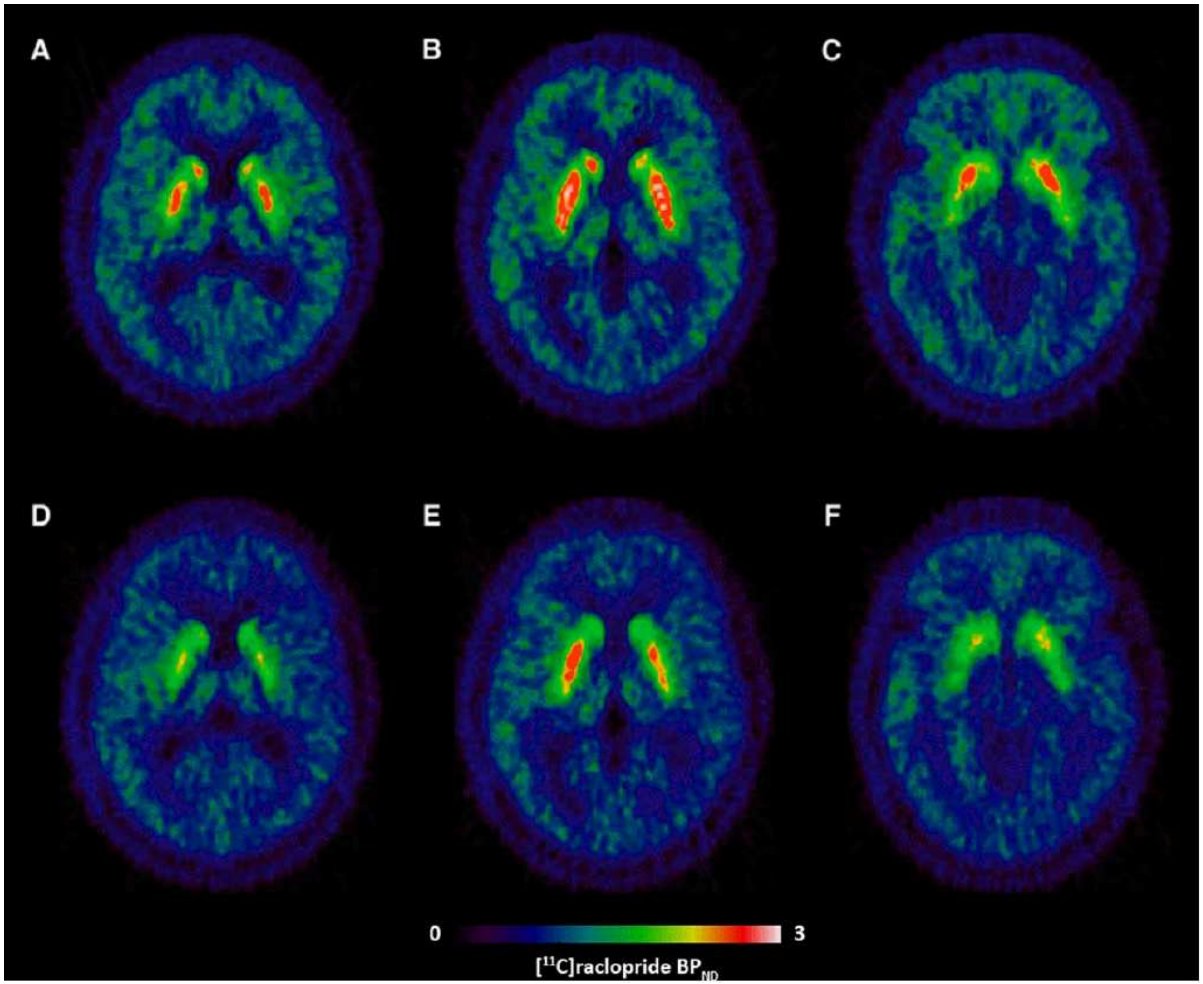
The pathogenesis of on-off motor fluctuations in parkinsonism remains incompletely understood, but slowed or erratic gastric emptying of orally administered levodopa may be involved. In 3 patients with resistant on-off fluctuations, direct duodenal continuous infusion of levodopa via a nasoduodenal tube resulted in a heightened therapeutic effect, including a reduction in motor fluctuations. In 1 of these patients, continuous duodenal levodopa infusion produced greater benefit than did intermittent duodenal levodopa administration. Direct duodenal delivery of levodopa lessens the problems with gastric emptying and may be suitable for long-term therapy in selected patients with resistant on-off motor fluctuations.

Kurlan R, Rubin AJ, Miller C, Rivera-Calimlim L, Clarke A, Shoulson I: Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. Ann Neurol 20:262–265, 1986

Sustained Striatal Dopamine Levels Following Intestinal Levodopa Infusions in Parkinson's disease patients

POLITIS ET AL

Movement Disorders, Vol. 32, No. 2, 2017



Our findings highlight the mechanisms underlying a possible superiority of LCIG infusions compared with conventional oral levodopa treatments in advanced PD patients with nonmotor and motor complications such as LIDs.

Lancet Neurol 2014; 13: 141–49

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

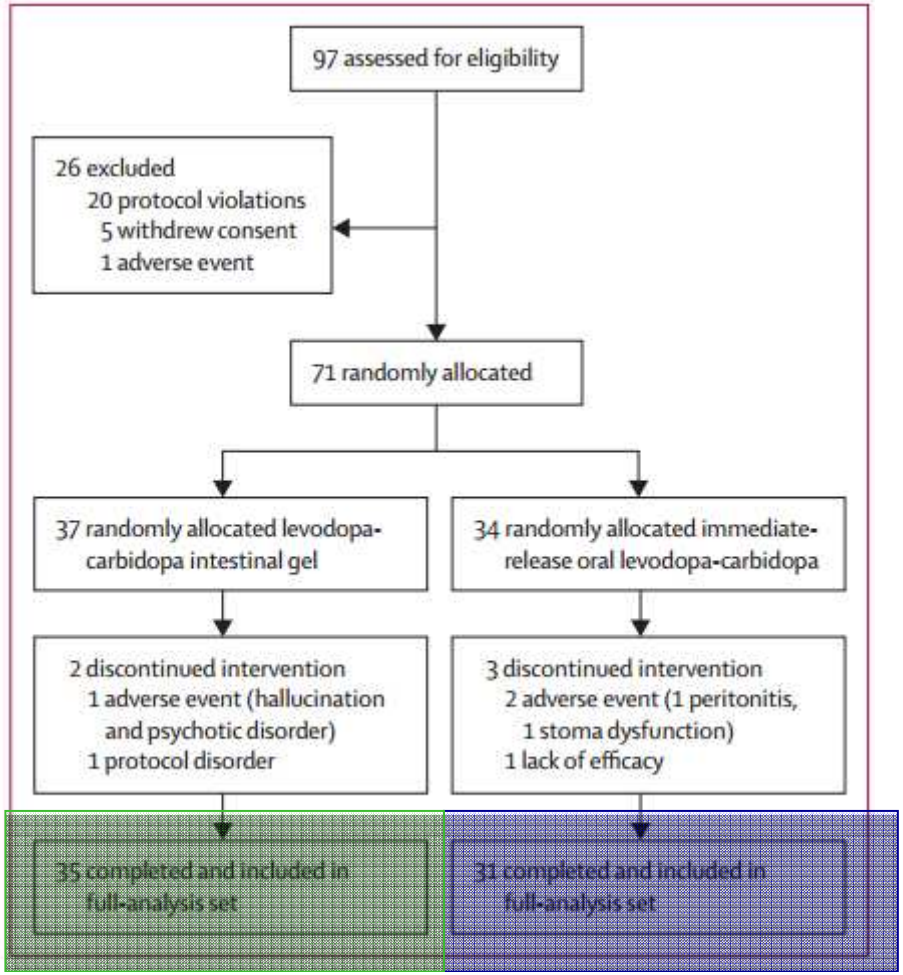
"26 centres in Germany, New Zealand and the USA"

PROTOCOL:

-12 weeks

-Random allocation to:

- **ORAL placebo**
- **LCIG placebo**



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

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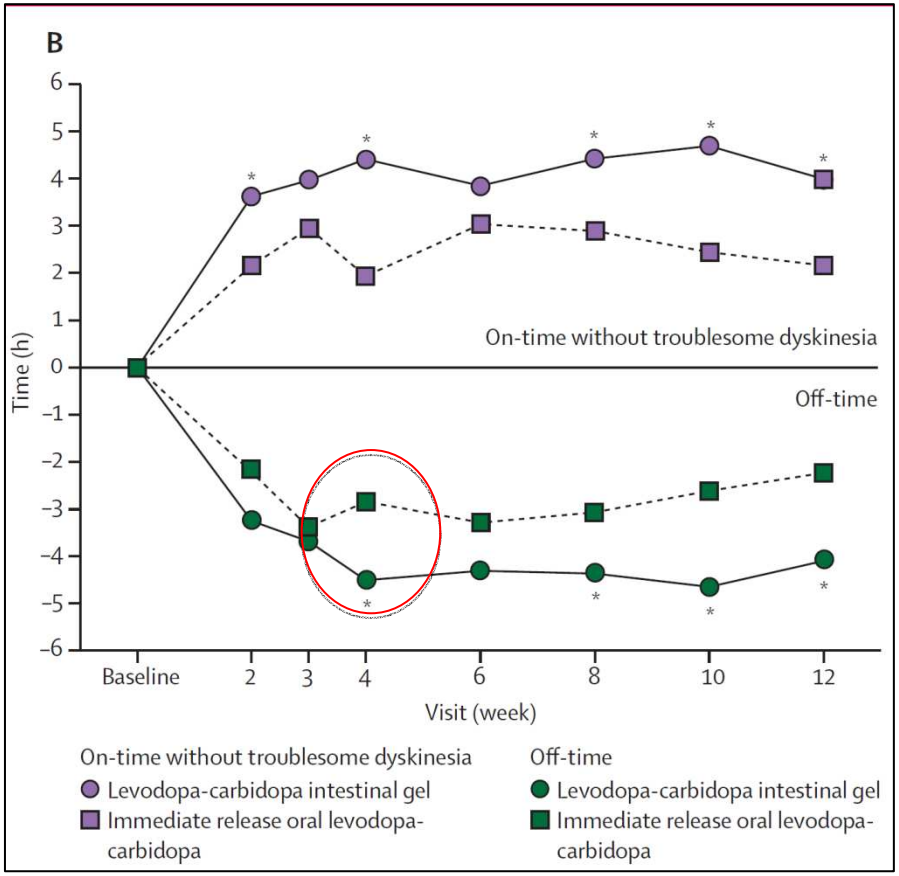
Lancet Neurol 2014; 13: 141–49



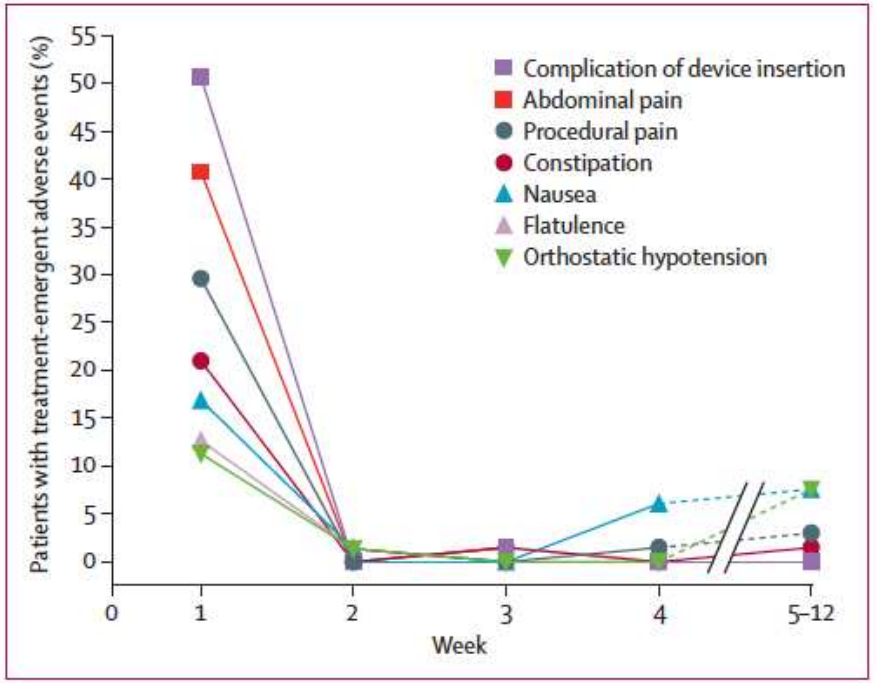
- **Off time in patients treated with levodopa-carbidopa intestinal gel was reduced by 4·04 h from baseline**

- **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**

Lancet Neurol 2014; 13: 141–49

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

	Levodopa-carbidopa intestinal gel (n=37)	Immediate-release oral levodopa-carbidopa (n=34)	Overall (n=71)
Any adverse event	35 (95%)	34 (100%)	69 (97%)
Serious adverse event	5 (14%)*	7 (21%)†	12 (17%)
Abdominal pain	19 (51%)	11 (32%)	30 (42%)
Nausea	11 (30%)	7 (21%)	18 (25%)
Procedural pain	11 (30%)	12 (35%)	23 (32%)
Device complications	34 (92%)	29 (85%)	63 (89%)
Intestinal tube	14 (38%)	12 (35%)	26 (37%)
Leakage	2 (5%)	1 (3%)	3 (4%)
Insertion	3 (8%)	1 (3%)	4 (6%)
Dislocation	8 (22%)	9 (26%)	17 (24%)
Occlusion	5 (14%)	4 (12%)	9 (13%)

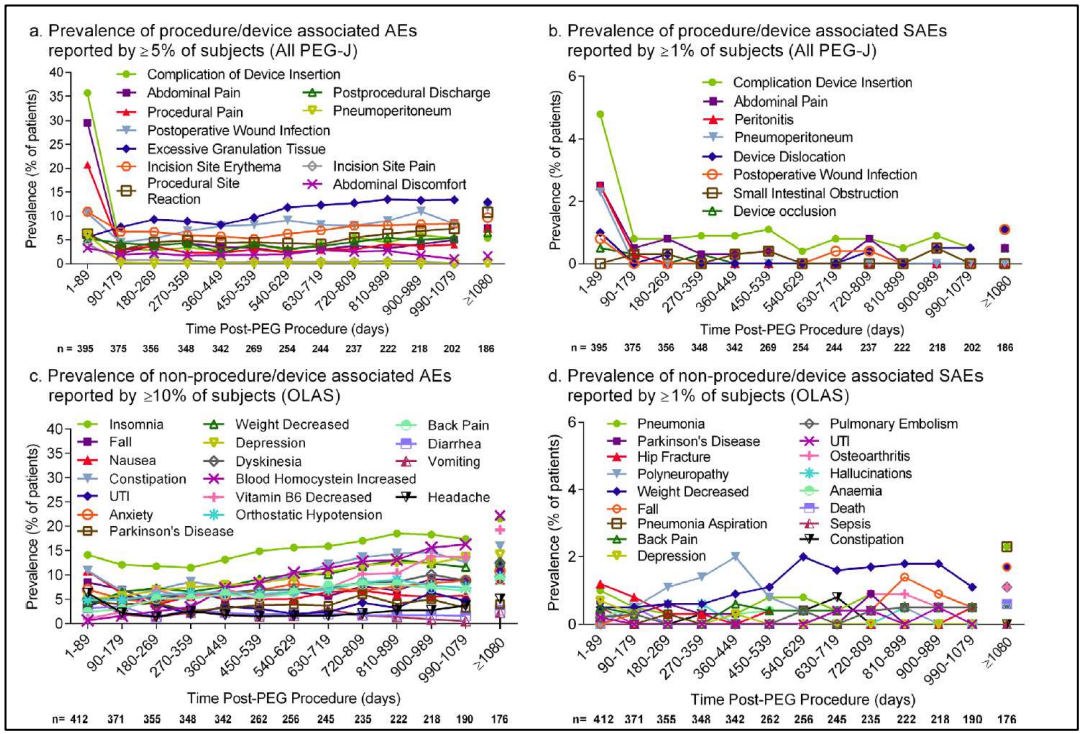


"Frequent device complications"

RESEARCH ARTICLE

Movement Disorders, Vol. 00, No. 00, 2015

Integrated Safety of Levodopa-Carbidopa Intestinal Gel From Prospective Clinical Trials



- **Procedure/device adverse events occurred in 300 patients (76%), and serious adverse events occurred in 68 (17%)**
- **Most frequently reported procedure/device adverse events and serious adverse events were complications of device insertion (41% and 8%) and abdominal pain (36% and 4%)**
- **Non-procedure/device adverse events occurred in 92% (379), with most frequently reported being insomnia (23%) and falls (23%)**
- **42% (171) had non-procedure/device serious adverse events, with most frequently reported being pneumonia (5%) and PD symptoms (2%)**
- **There were 34 treatment-emergent deaths (8.3%) in the overlapping data sets, 2 of which (0.5%) were considered "possibly related" to the treatment system.**

RESEARCH ARTICLE

Movement Disorders, Vol. 00, No. 00, 2015

Integrated Safety of Levodopa-Carbidopa Intestinal Gel From Prospective Clinical Trials

- **We have presented the largest, longest-term safety data set from prospective clinical studies for LCIG to date**

- **Given that conclusions regarding polyneuropathy, weight loss, and psychiatric symptoms were limited, further systematic surveillances of these are warranted**

- **Within the limitations of this analysis, procedure/device AEs were common, expected for the known risks associated with a PEG-J, and the most common cause of discontinuation**

- **This study suggests that despite the high incidence of patients with Aes, LCIG can be used in a safe and tolerable manner for the treatment of motor fluctuations that are inadequately controlled by other PD medications in levodopa-responsive patients with advanced PD**

Movement Disorders

Fernandez et al., 2015

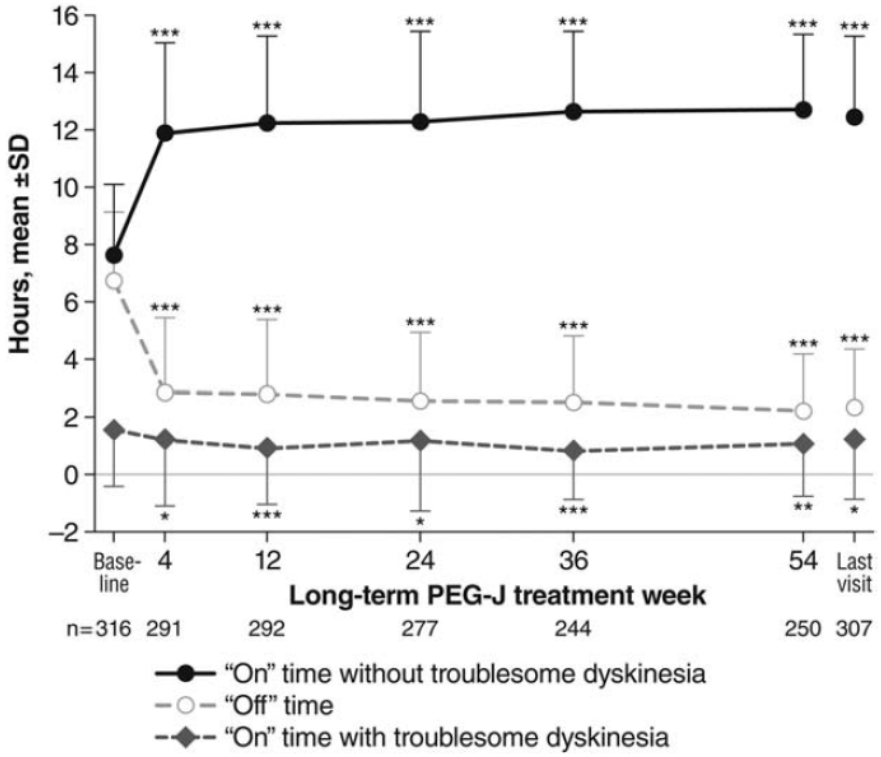
Official Journal of the Movement Disorder Society

RESEARCH ARTICLE

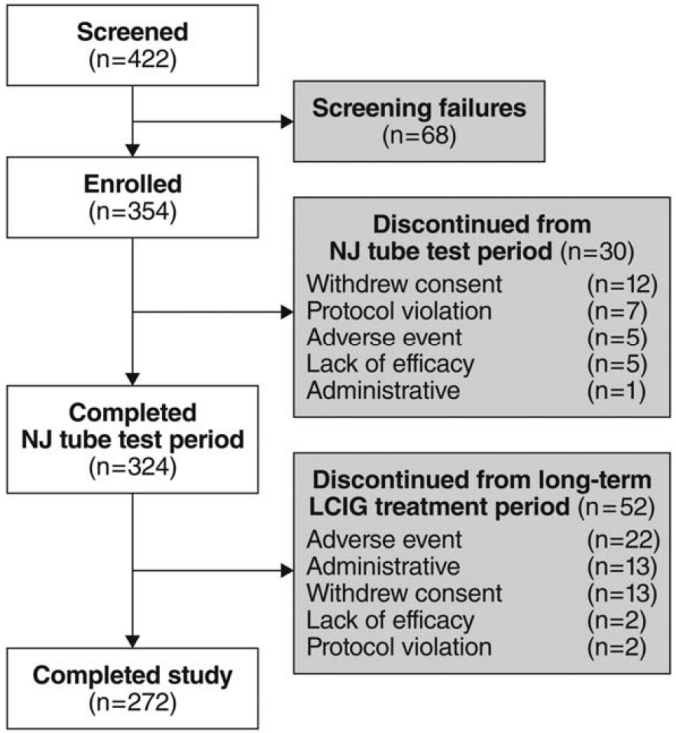
Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease: Final 12-Month, Open-Label Results

Hubert H. Fernandez, MD,[1*] David G. Standaert, MD, PhD,[2*] Robert A. Hauser, MD,[3] Anthony E. Lang, MD, FRCPC,[4] Victor S.C. Fung, PhD, FRACP,[5] Fabian Klostermann, PhD,[6] Mark F. Lew, MD,[7] Per Odin, MD, PhD,[8] Malcolm Steiger, MBBS, MD, FRCP,[9] Eduard Z. Yakupov, MD, PhD, DMSc,[10] Sylvain Chouinard, MD, FRCPC,[11] Oksana Suchowersky, MD, FRCPC, FCCMG,[12] Jordan Dubow, MD,[13] Coleen M. Hall, MS,[13] Krai Chatamra, PhD,[13] Weining Z. Robieson, PhD,[13] Janet A. Benesh, BSMT,[13] and Alberto J. Espay, MD, MSc[14]

Movement Disorders, Vol. 30, No. 4, 2015



B. Patient Disposition

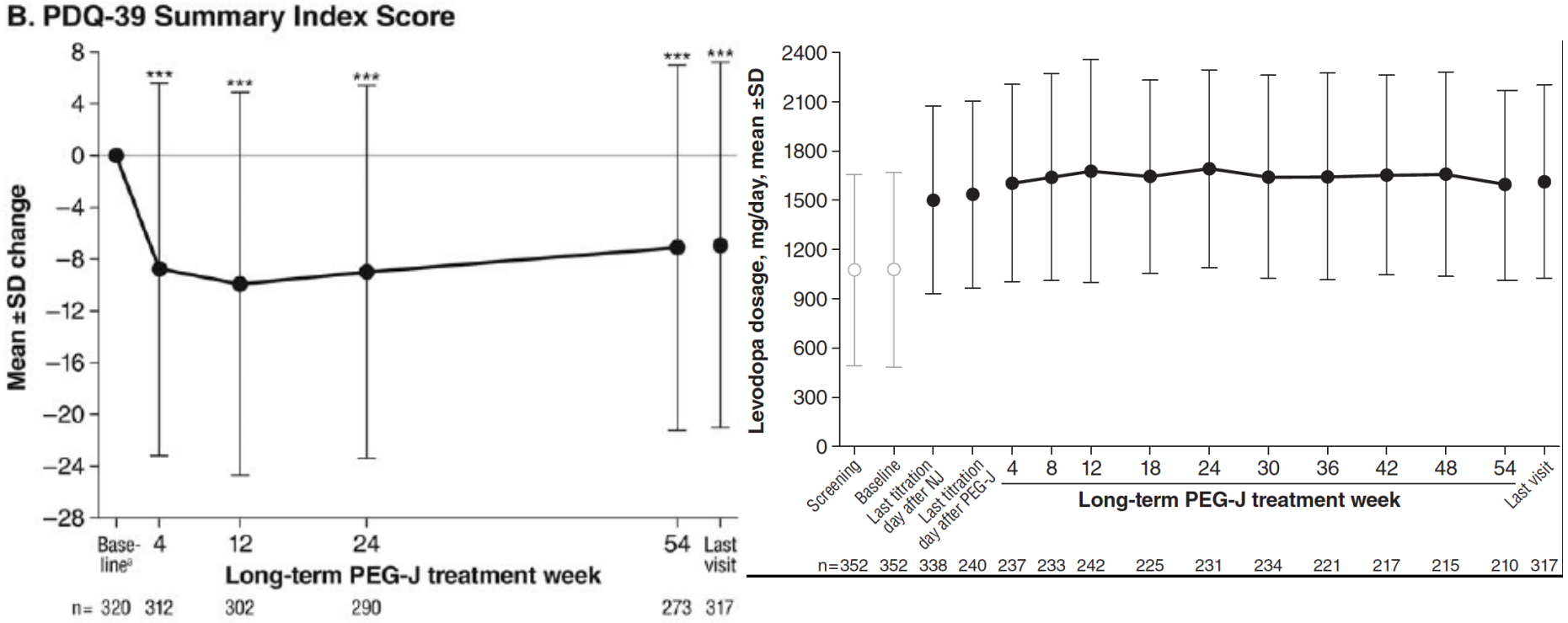


Movement Disorders
Official Journal of the Movement Disorder Society

Fernandez et al., 2015

RESEARCH ARTICLE

Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease: Final 12-Month, Open-Label Results



Real life cost and quality of life associated with continuous intraduodenal levodopa infusion compared with oral treatment in Parkinson patients

Christofer Lundqvist · Antonie Giæver Beiske · Ola Reiertsen · Ivar Sønbø Kristiansen

J Neurol (2014) 261:2438–2445

- **Continuous IDL is efficacious, but entails high costs.**
- **10 patients with advanced PD who switched from oral medication to IDL were assessed at baseline, 3, 6, 9 and 12 months follow-up.**
- **We used the UPDRS and Quality of Life (QoL) scores.**
- **Costs per quality adjusted life year (QALY) were estimated for conventional treatment prior to switch and for 1-year treatment with IDL.**

Table 5 Cost (2008 Norwegian kroner) during last 3 months prior to intraduodenal continuous levodopa infusion and during subsequent 3 months periods on this treatment, according to type of costs

	Baseline	3 months	6 months	9 months	12 months	Mean at fu
Travel costs	0.6 (0.6)	0.2 (0.5)	0.2 (0.3)	0.2 (0.3)	2.4 (4.7)	0.7 (1.4)
Health-related costs	54.2 (56.8)	37.3 (114.9)	19.5 (38.8)	15.7 (29.9)	15.7 (30.6)	22.1 (53.5)
Oral medication	6.4 (6.7)	0.1 (0.4)	0.2 (0.4)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
IDL	0.0 (0)	31.3 (96.3)	48.5 (96.3)	50.8 (96.3)	49.4 (96.3)	45.0 (96.3)
State pension	38.8 (40.7)	13.2 (40.7)	20.5 (40.7)	21.5 (40.7)	20.9 (40.7)	19.0 (40.7)
Planned study hospitalization	0.0 (0)	17.9 (55.1)	11.1 (22.0)	11.6 (22.0)	11.3 (22.0)	13.0 (30.3)
Total %	100 (104.8)	100 (307.9)	100 (198.6)	100 (189.6)	100 (194.8)	100 (222.7)

Real life cost and quality of life associated with continuous intraduodenal levodopa infusion compared with oral treatment in Parkinson patients

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Such individual variations need to be considered by policy makers and associated ethical challenges, such as which patient groups may be eligible for IDL, whether there should be a maximum permissible individual cost and how IDL should be paid for, should be discussed further.

There is little doubt, however, that IDL may substantially improve patients' lives.

Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes

Angelo Antonini [a,*], Ashley Yegin [b], Cornelia Preda [b], Lars Bergmann [b], Werner Poewe [c], on behalf of the GLORIA study investigators and coordinators

Parkinsonism and Related Disorders 21 (2015) 231e235

375 patients from 75 movement disorder centers in 18 countries

12-month interim outcomes of the first 172 included patients

Baseline patient demographics and disease characteristics.

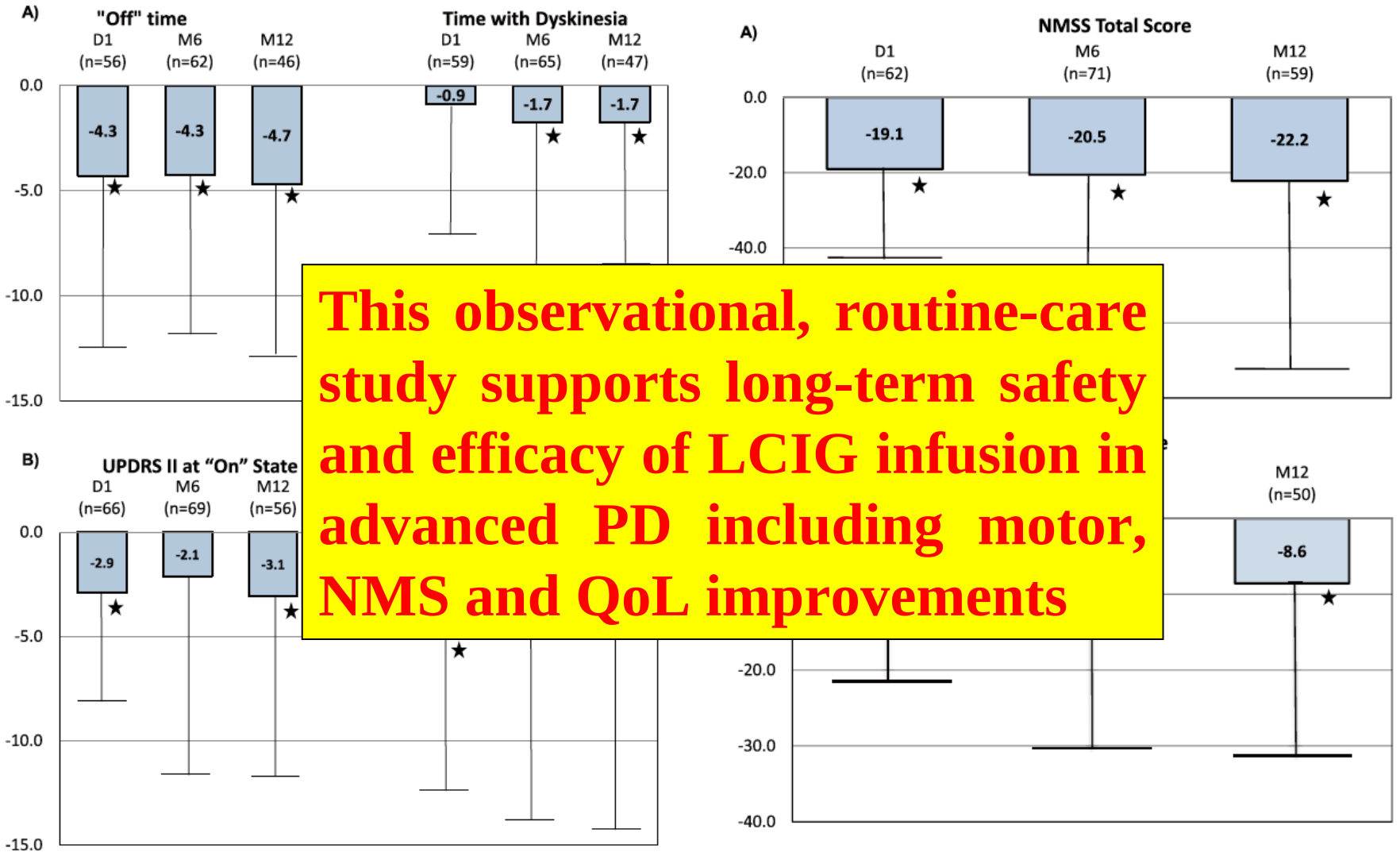
Demographics	
Gender	
Female	96 (55.8%)
Male	76 (44.2%)
Age (years)	66.5 ± 9.3
<65 years	60 (35.0%)
≥65 years	112 (65.0%)
Medical history	
Time since PD diagnosis (years)	12.6 ± 6.6
Hoehn and Yahr	2.8 ± 0.8
Dementia	20 (11.7%)
Impulse control disorder	26 (15.2%)
PD symptoms and QoL measures at baseline	
"Off" time (UPDRS item 39) hours/day	7.1 ± 3.5
Time with dyskinesia (UPDRS item 32) hours/day	5.2 ± 4.5
UPDRS II (activities of daily living) at "On" state	16.5 ± 10.7
UPDRS III (motor examination) at "On" state	26.5 ± 12.3
Non-Motor Symptoms Scale (NMSS total score)	75.3 ± 42.2
Quality of life (PDQ-8 total score)	48.6 ± 19.0
Previous PD medication as reported at baseline	
Levodopa	n (97.1%)
Total daily dose (mg)	884 ± 444
Dopamine agonist	n (64.5%)
COMT inhibitors	n (55.8%)
MAO-B inhibitors	n (33.1%)
Amantadine	n (22.7%)
Other oral medications	n (16.9%)

The mean ± standard deviation (SD) dose of orally-administered levodopa at BL was 884 ± 444 mg/day and a majority of patients was on one or more additional antiparkinsonian drugs, mainly COMT inhibitors and DAs (Table 1). At the start of LCIG, approximately half of the patients were using oral levodopa, and approximately 40% were using other anti-PD medications; these proportions decreased to approximately 25% for both oral levodopa and other anti-PD medications at M12. Primary reasons to start LCIG treatment were disabling "Off" periods and dyskinesias, pre-

NMS significant improvements in sub-scores for the **sleep/fatigue, gastrointestinal, and urinary domains**

Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes

Angelo Antonini [a,*], Ashley Yegin [b], Cornelia Preda [b], Lars Bergmann [b], Werner Poewe [c], on behalf of the GLORIA study investigators and coordinators



This observational, routine-care study supports long-term safety and efficacy of LCIG infusion in advanced PD including motor, NMS and QoL improvements

Movement Disorders
Vol. 22, No. 8, 2007, pp. 1145–1149

Duodenal Levodopa Infusion for Advanced Parkinson's Disease: 12-Month Treatment Outcome

Angelo Antonini, MD, PhD,[1]* Ioannis U. Isaias, MD,[1,2] Margherita Canesi, MD,[1]
Maurizio Zibetti, MD, PhD,[3] Francesca Mancini, MD,[4] Luigi Manfredi, MD,[4] Marco Dal Fante, MD,[4]
Leonardo Lopiano, MD, PhD,[3] and Gianni Pezzoli, MD[1]

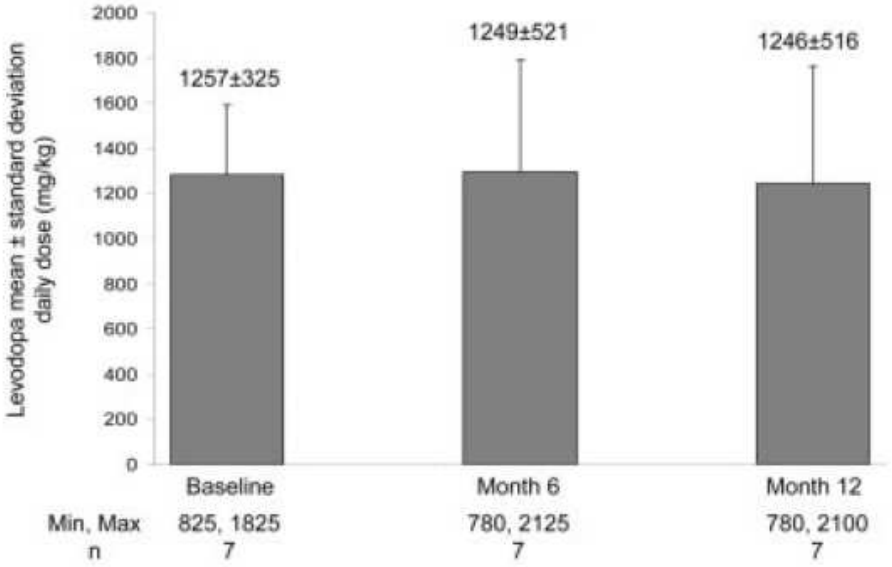


FIG. 1. Daily administered dose of levodopa. Baseline dose refers to total levodopa equivalents (levodopa + dopamine agonists), whereas 6- and 12-month dose refer to total infused levodopa.

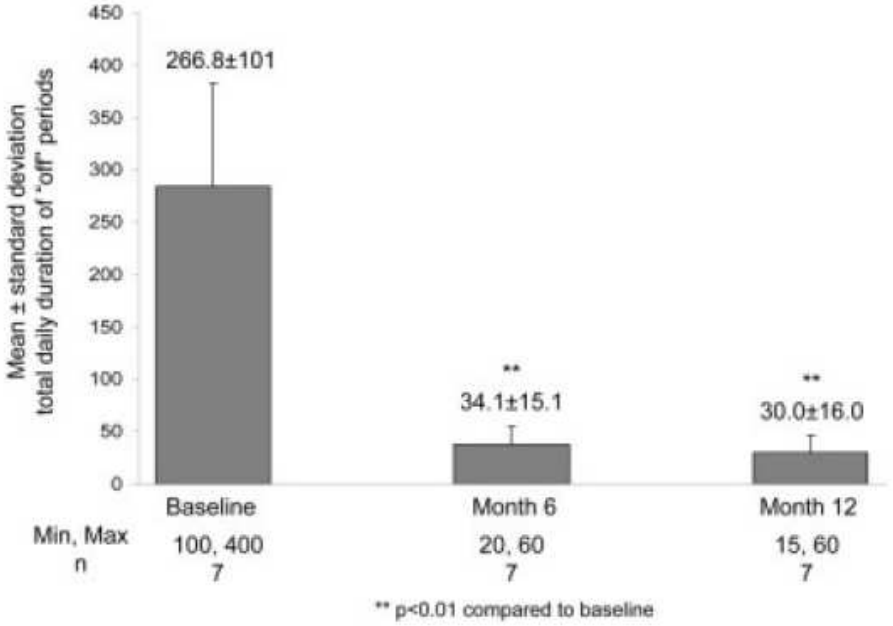


FIG. 2. Total daily duration (minutes) of moderate to severe "off" periods: observation period from 8:00 AM to 10:00 PM.

N° 444

FIRST ITALIAN EXPERIENCE WITH DUODENAL LEVODOPA/CARBIDOPA CONTINUOUS INFUSION

I.U.Isaias*, M.Zibetti, M.Canesi*, A. Cinquepalmi**, S.Ascione**, M.Barichella*, R.Cilia*, M.Zini*, M.Moroni, P.Piazzi, L.Lopiano**, G.Pezzoli*, A.Antonini***

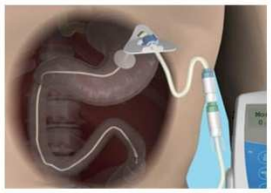
*Parkinson Institute Istituti Clinici di Perfezionamento, Milan, Italy; **Dipartimento di Neuroscienze Università di Torino

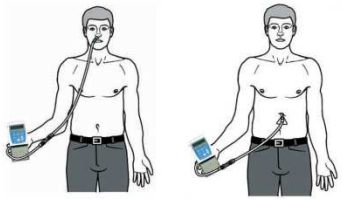
Objective:

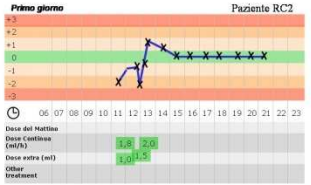
We report the first Italian experience in treating patients with Parkinson's Disease (PD) with duodenal levodopa infusion (Duodopa ®) resulting in continuous dopaminergic stimulation (CDS).

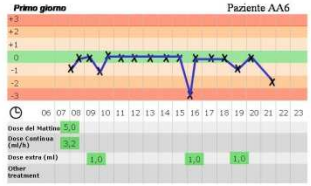
Methods

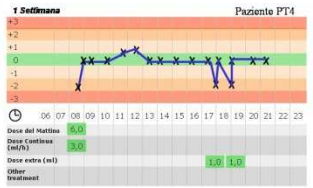
We treated with Duodopa five advanced PD patients with invalidating motor fluctuations, dyskinesia and "off" periods. The Unified Parkinson's Disease rating Scale (UPDRS) and the Parkinson's Disease Quality of Live Questionnaire (PDQ-39) were used to assess the clinical benefit of this new treatment.

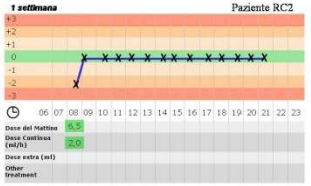


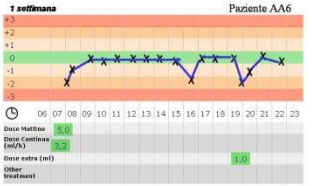


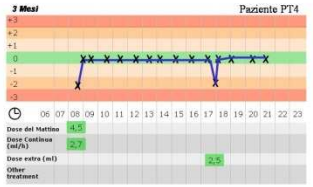


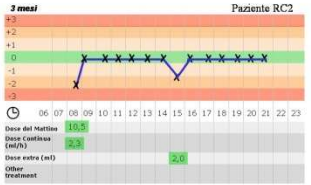


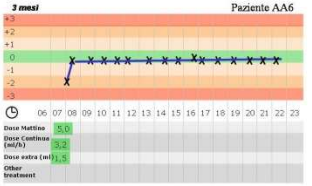












Results

Already after two weeks of continuous infusion patients reported a better overall quality of live and a reduction in "off" periods number and duration. Mean infusion rate was 88 mg/hour levodopa with infusion starting at 8AM and ending at 11PM.

PDQ-39 score was significantly decreased with a median summary index difference of 23,5%, calculated with the following formula: *sum of scores/4(max. score per question)x num. of questions*. The recurrence of "off"-periods was reduced from an average of 7 per day to 2. "Off"-periods were also easily stopped in a mean time of 40 min. by an an extra duodenal bolus of levodopa. An average of 2 (morning dose not included) levodopa duodenal extra-doses were needed during the day to recover from "off"-periods.

UPDRS parts I, II and IV showed a significant improvement of 16, 10 and 25% at "off" state and 12,5, 30 and 30% at "on" state; whereas improvement in part III was not significant (10%).

Conclusions

Keeping levodopa concentrations as constant as possible is the target for drug development. Earlier studies of intra-venous and enteral levodopa infusion have shown a milder and more predictable pattern of side effects.

Our results show, in accordance with earlier studies, that CDS can be achieved already after a few days and a therapeutic window can be identified even in very complicated PD patients. Moreover this technique provides lower median scores in all parts of the UPDRS, especially several important items like "off" time, walking and satisfaction with overall functioning as expressed by the PDQ-39.

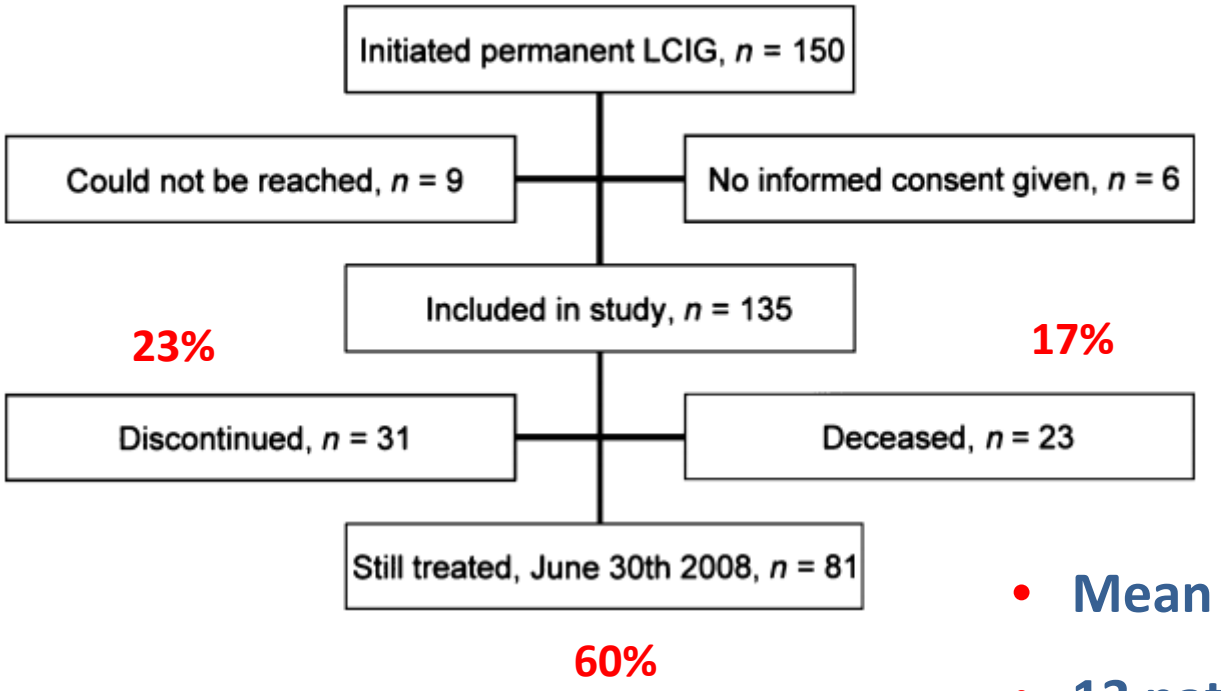
According to our preliminary experience Duodopa infusion should be consider, together with Deep Brain Stimulation and apomorphine infusion, as last-line therapy in treating PD.

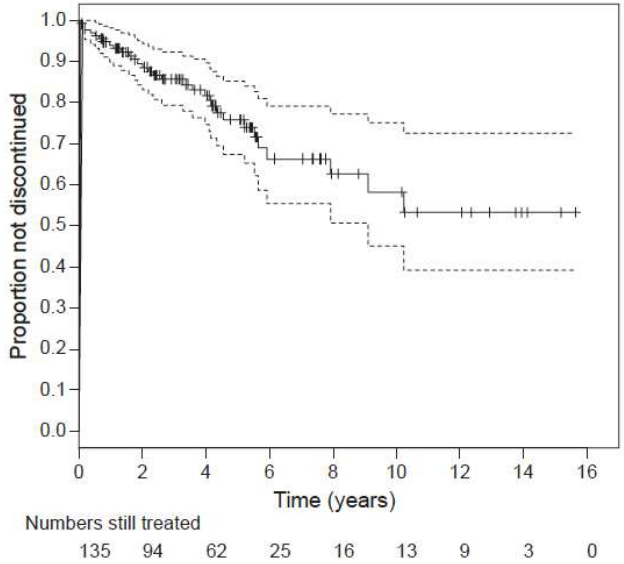
european journal of neurology
the official journal of the european academy of neurology

Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease

D. Nyholm[a], K. Klangemo[a] and A. Johansson[a,b]

European Journal of Neurology 2012, **19:** 1079–1085





- **Mean treatment duration: 8 y**
- **13 patients treated for ≥ 10 y**

european journal of neurology
the official journal of the european academy of neurology

Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: a 7-year experience

M. Zibetti[a], A. Merola[a], C. A. Artusi[a], L. Rizzi[a], S. Angrisano[a], D. Reggio[b], C. De Angelis[b], M. Rizzone[a] and L. Lopiano[a]

European Journal of Neurology 2014, **21:** 312–318

"59 patients - over 90% reported an improvement in their quality of life, autonomy and clinical global status"

"The most common adverse events were dislocation and kinking of the intestinal tube"

Patients (n = 39)	Great improvement	Moderate improvement	Slight improvement
Quality of life	17 (44%)	19 (48%)	3 (8%)
Autonomy	12 (30%)	20 (51%)	3 (8%)
Clinical global improvement	24 (62%)	11 (28%)	4 (10%)

Neurol Sci (2016) 37:1785–1792

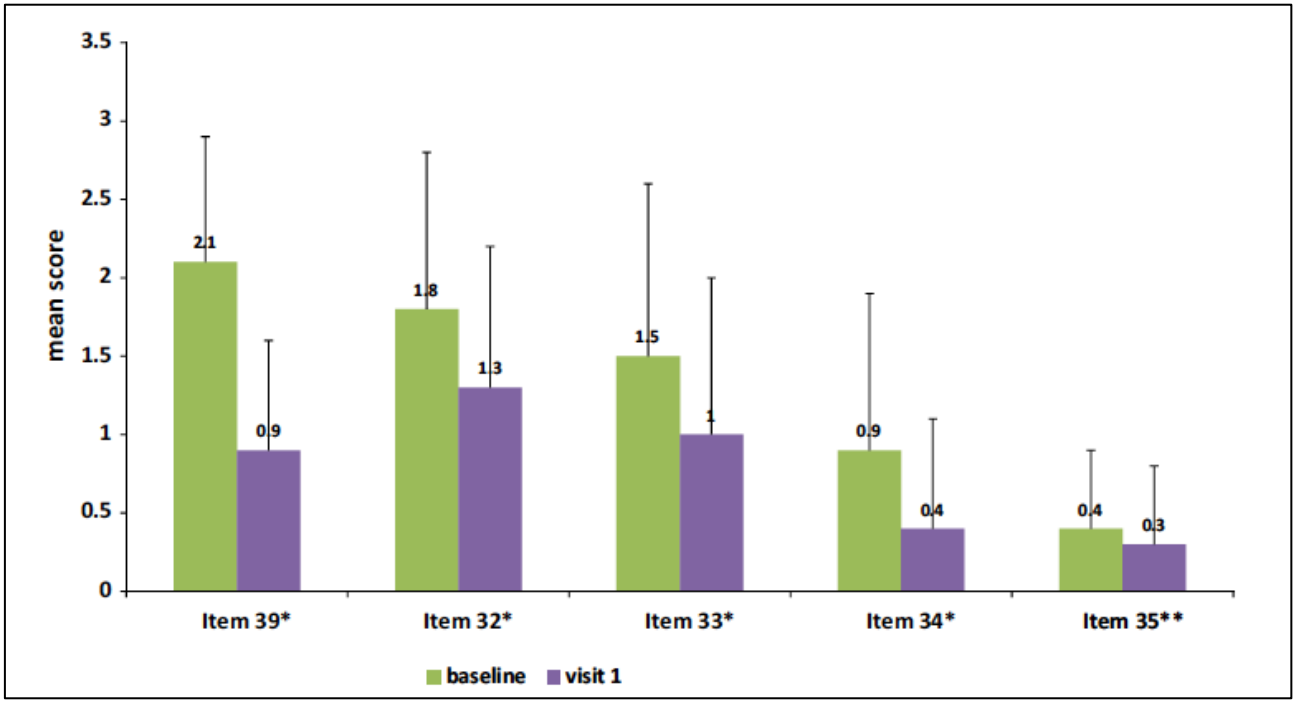
Motor outcomes in patients with advanced Parkinson's disease treated with levodopa/carbidopa intestinal gel in Italy: an interim analysis from the GREENFIELD observational study

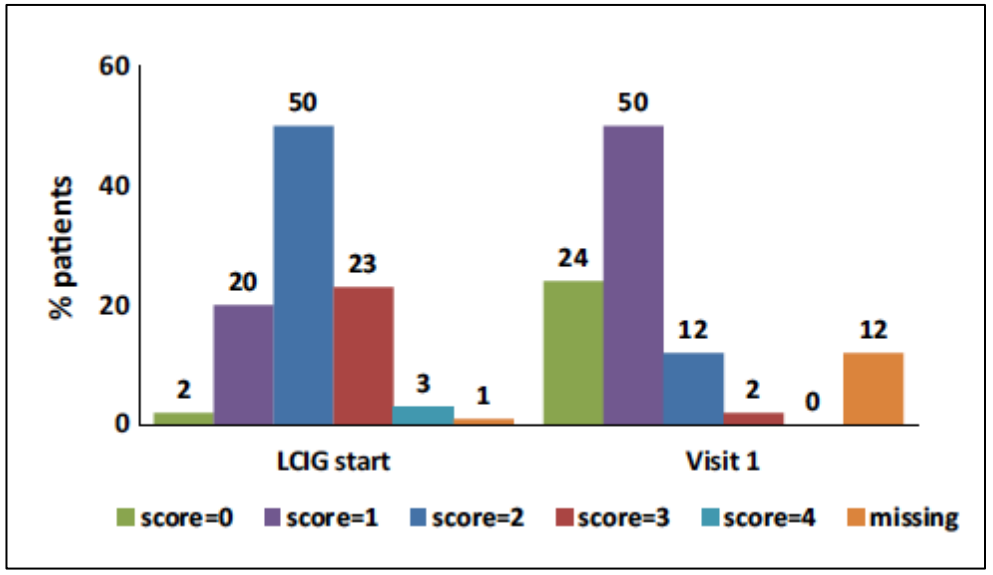
Leonardo Lopiano[1] · Nicola Modugno[2] · Pietro Marano[3] · Mariachiara Sensi[4] · Giuseppe Meco[5] · Antonino Cannas[6] · Graziano Gusmaroli[7] · Filippo Tamma[8] · Francesca Mancini[9] · Rocco Quatrale[10] · Anna Maria Costanzo[11] · Giuliana Gualberti[11] · Gabriella Melzi[11] · Umberto di Luzio Paparatti[11] · Angelo Antonini[12]

Table 2 Use of antiparkinsonian medications before and during LCIG at visit 1 among the 145 evaluable patients

Antiparkinsonian medications	Before LCIG start		At visit 1	
	N (%)	Daily dose, mean ± SD	*N* (%)	Daily dose, mean ± SD
Oral levodopa (mg)	140 (96.6 %)	812.17 ± 409.93	7 (5 %)—during the day 37 (26 %)—at night	307.0 ± 281.0 during the day 155.4 ± 75.3 at night
Dopamine agonists (mg)	93 (64.1 %)	6.38 ± 5.6	44 (30 %)	5.6 ± 3.8
COMT inhibitors (mg)	64 (44.1 %)	577.8 ± 336.8	17 (12 %)	255.9 ± 102.9
MAO inhibitors (mg)	21 (14.5 %)	2.33 ± 3.31	5 (3 %)	3.6 ± 4.0
Amantadine (mg)	25 (17.2 %)	190.6 ± 112.6	8 (6 %)	237.5 ± 91.6

148 patients from 14 Movement Disorder Centers in Italy with a mean LCIG treatment period of 1.38 ± 1.66 years





Proportion of waking day spent in OFF state according to UPDRS-Part IV Item 39 **Lopiano et al. 2016**

Acta Neurologica Scandinavica

Acta Neurol Scand DOI: 10.1111/ane.12483

ACTA NEUROLOGICA SCANDINAVICA

Improvement of dyskinesias with L-dopa infusion in advanced Parkinson's disease

Timpka J, Fox T, Fox K, Honig H, Odin P, Martinez-Martin P, Antonini A, Chaudhuri KR. Improvement of dyskinesias with L-dopa infusion in advanced Parkinson's disease.
Acta Neurol Scand: DOI: 10.1111/ane.12483.

J. Timpka[1], T. Fox[2], K. Fox[2], H. Honig[2], P. Odin[1,2], P. Martinez-Martin[3], A. Antonini[4], K. R. Chaudhuri[5]

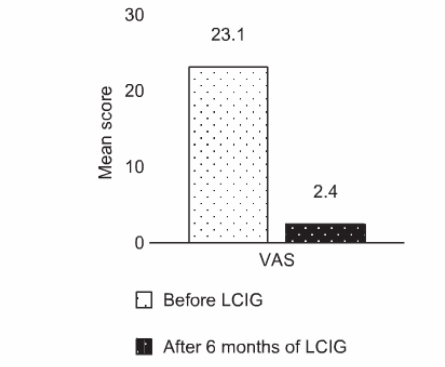
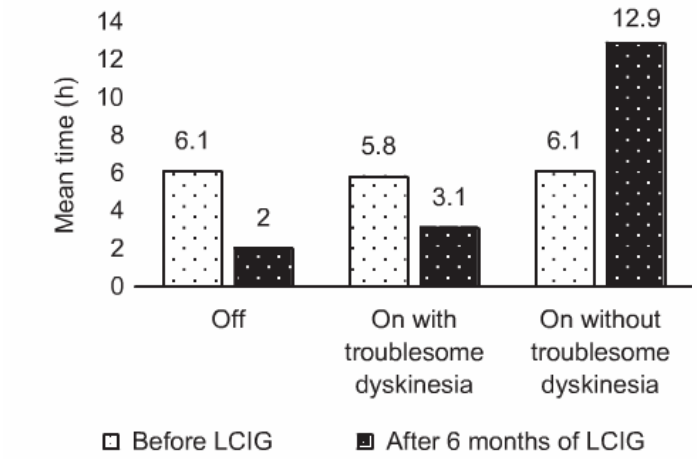
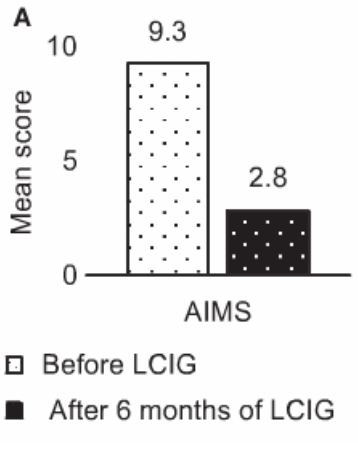
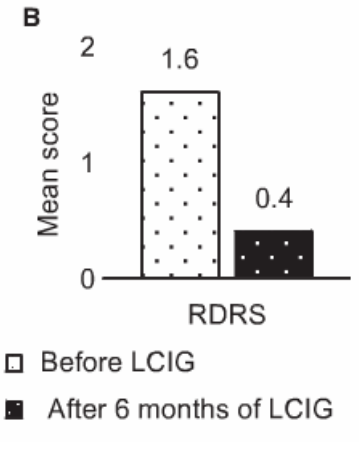


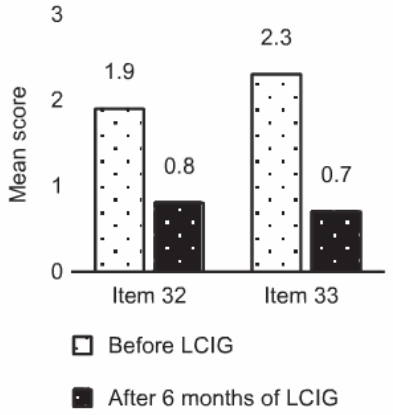
Figure 2. The VAS regarding intensity of dyskinesia.

9 patients – 6 months follow-up









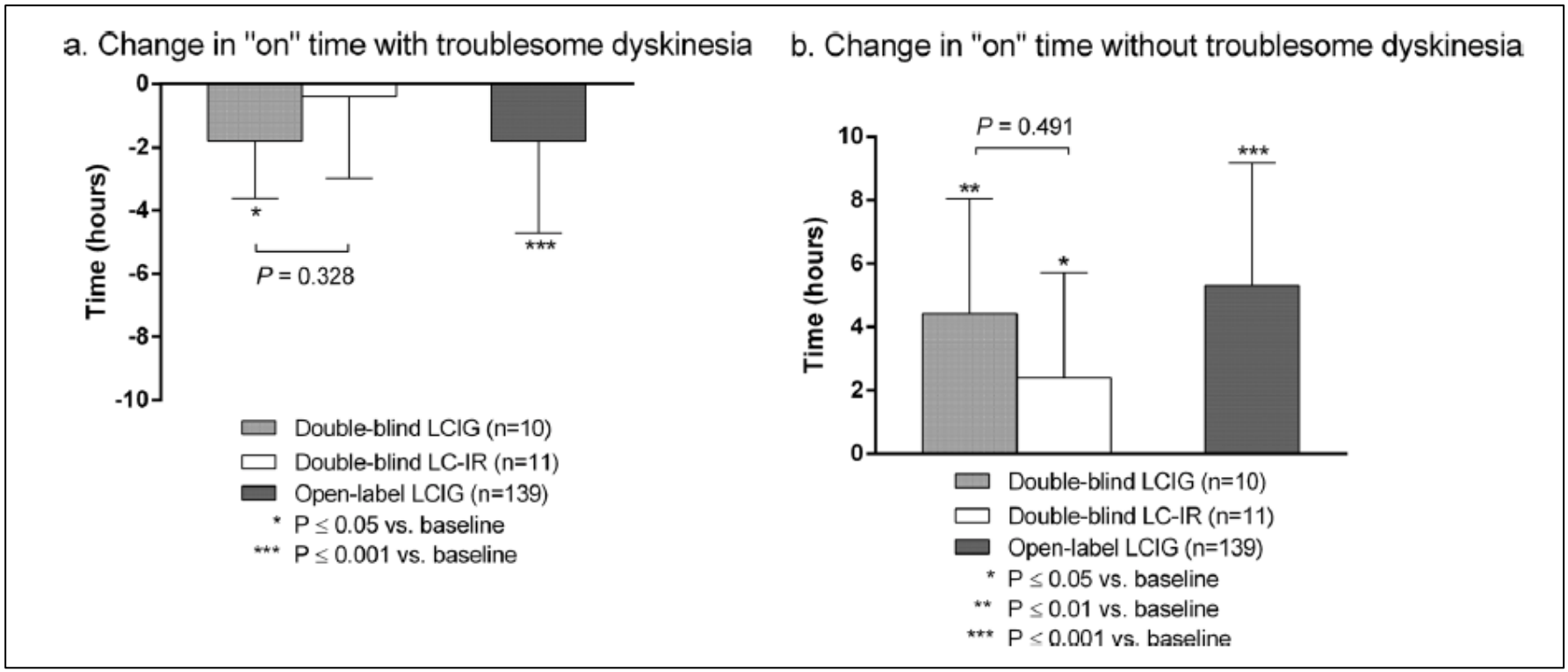
PD patients who reported **to spend at least 3 h per day in on with troublesome dyskinesia were included**

Timpka et al., 2015

Effect of Levodopa-Carbidopa Intestinal Gel on Dyskinesia in Advanced Parkinson's Disease Patients

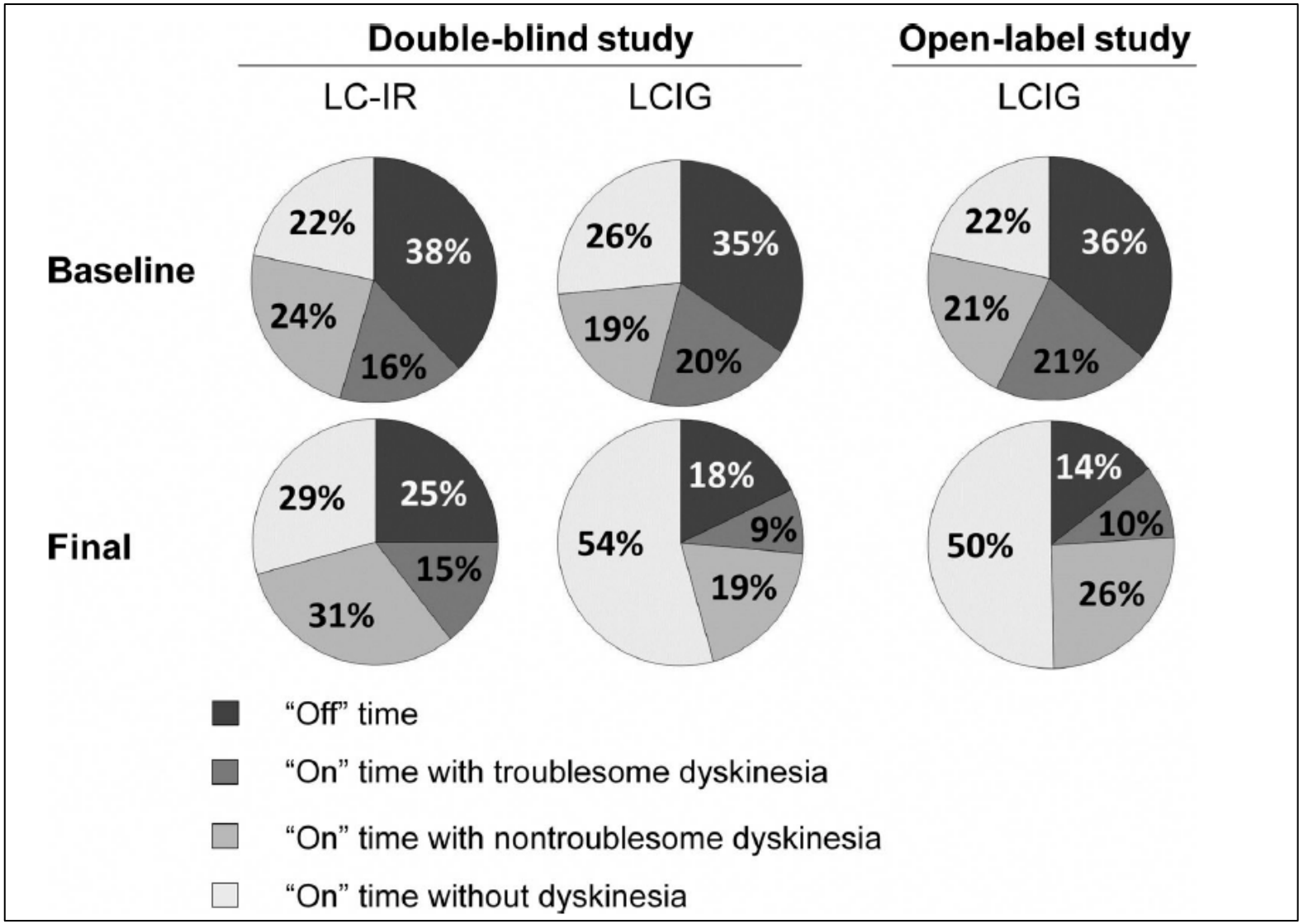
ANTONINI ET AL

Movement Disorders, Vol. 31, No. 4, 2016



Post hoc analyses of patient data from a 12-week, randomized, double-blind study and a 54-week open-label study were performed

Antonini et al., 2016


Double-blind study
Open-label study
LC-IR
LCIG
LCIG
Baseline
Final
22%
38%
24%
16%
26%
35%
19%
20%
22%
36%
21%
21%
29%
25%
31%
15%
54%
18%
9%
19%
50%
14%
10%
26%
"Off" time
"On" time with troublesome dyskinesia
"On" time with nontroublesome dyskinesia
"On" time without dyskinesia

Dyskinesias in Levodopa-Carbidopa Intestinal Gel Infusion Era: New Challenges, New Features

Maria-Jose Catalan et al.

Movement Disorders, Vol. 00, No. 00, 2017

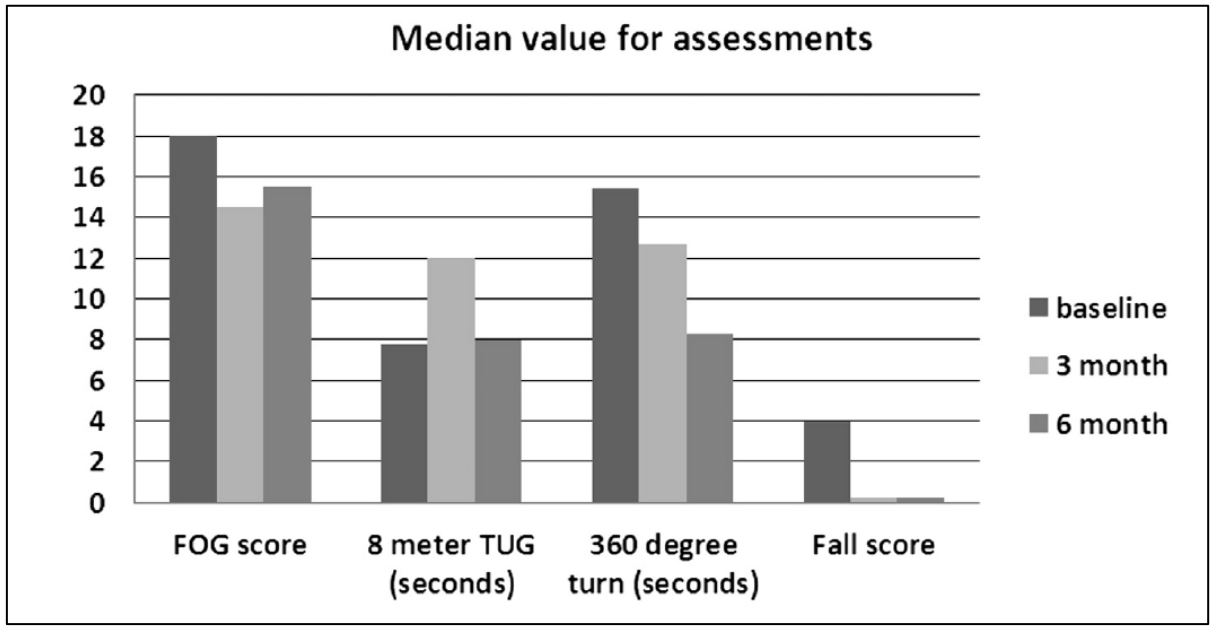
Jean 24

These cases suggest that continuous administration of levodopa in patients with advanced disease may develop drug-related dyskinesias with mixed characteristics of those described in the literature.

Parkinsonism and Related Disorders 21 (2015) 317–320

24 h Levodopa–carbidopa intestinal gel may reduce falls and "unresponsive" freezing of gait in Parkinson's disease

Florence C.F. Chang [a], David S. Tsui [a], Neil Mahant [a], Nigel Wolfe [a], Samuel D. Kim [a], Ainhi D. Ha [a], Melissa Drury [a], Jane M. Griffith [a], Victor S.C. Fung [a, b, *]



- **5 patients with disabling, unresponsive FOG were commenced on continuous 24h LCIG with the night-time rate at 50-80% of the daytime infusion rate**
- **Median turn time improved by 54%, fall frequency score reduced from 3 to 0 at 6 months, FOG questionnaire score improved by 14% and Timed Up- and -Go 8 m walk was unchanged**
- **24h LCIG therapy may reduce levodopa "unresponsive" FOG and associated falls. A larger prospective study is needed for confirmation**

Neurol Sci
DOI 10.1007/s10072-015-2234-x

BRIEF COMMUNICATION

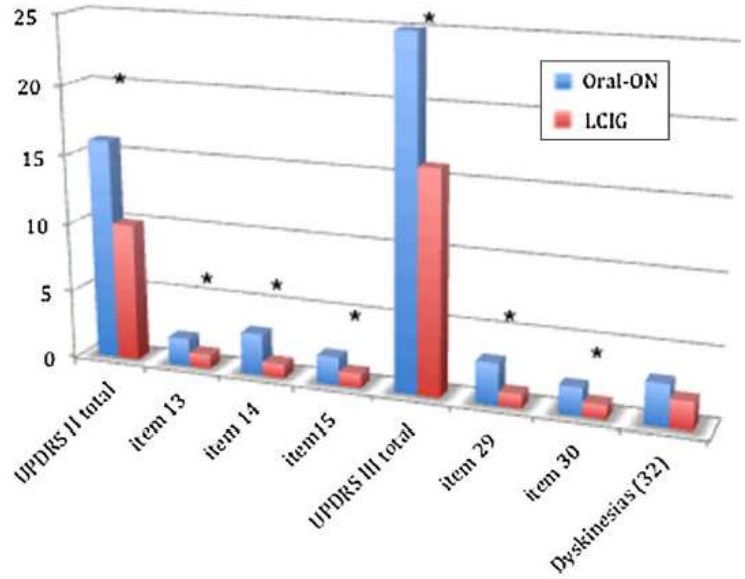
13 Falling
14 Freezing
15 Walking

Levodopa–carbidopa intrajejunal gel in advanced Parkinson disease with "on" freezing of gait

Giovanni Cossu[1] · Valeria Ricchi[1] · Manuela Pilleri[2] · Francesca Mancini[3] · Daniela Murgia[1] · Gianluigi Ricchieri[4] · Alessandra Mereu[5] · Maurizio Melis[1] · Angelo Antonini[2]

7 patients – 8/18 months LCIG infusion

29 Gait
30 Postural stability
32 Dyskinesia (duration)



Pt	Oral therapy				LCIG						
	LD	DAED	Entacapone ED	Oral LED	LD continuous infusion	LD morning dose	LD night dose	LD extra dose	Total LD	DAED	LCIG LED
1	1250	315	/	1565	1350	160	60	80	1650	105	1755
2	1200	210	160	1570	1080	150	60	40	1330	105	1435
3	600	315	/	915	570	140	60	60	830	/	830
4	500	105	150	755	675	160	60	50	945	/	945
5	900	160	270	1330	1440	140	60	/	1640	/	1640
6	600	210	/	810	720	140	60	/	920	105	1025
7	800	320	180	1300	720	120	60	50	950	200	1150

Terapia pre-Duodopa
Ropinirolo 8 mg RP
Stalevo 150 x 5
Madopar 200 + 50 ½ x 4
Sinemet 200+50 RM: 1 cp
LEDD: 1835

Duodopa 14 ore (ore 8 – 22)
Dose del mattino: 11 ml x 20 mg = 220
Dose di infusione: 5,4 ml/ora x 14 h x 20 mg/ml = 1512
~~Dose extra: 2 ml~~
Sinemet 200+50 RM: 1 cp
LEDD: 1932

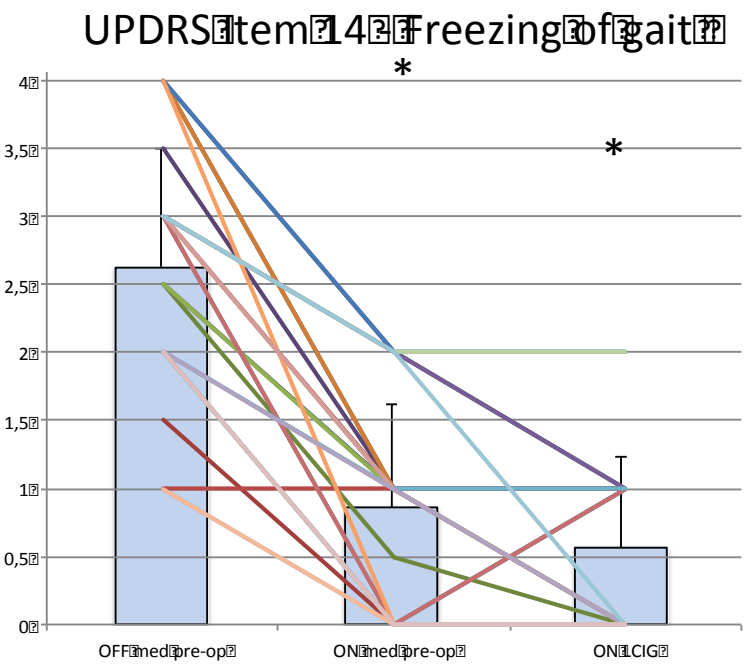
Duodopa 24 ore
~~Dose del mattino: 11 ml~~
Dose di infusione: 5,4 ml/ora x24 h x 20 mg/ml = 2592
~~Dose extra: 2 ml~~
~~Sinemet 200+50 RM: 1 cp~~
LEDD: 2592

M.C. anni 56 – MP esordita a 41 anni

Effects of intestinal Levodopa infusion on freezing of gait in advanced Parkinson disease

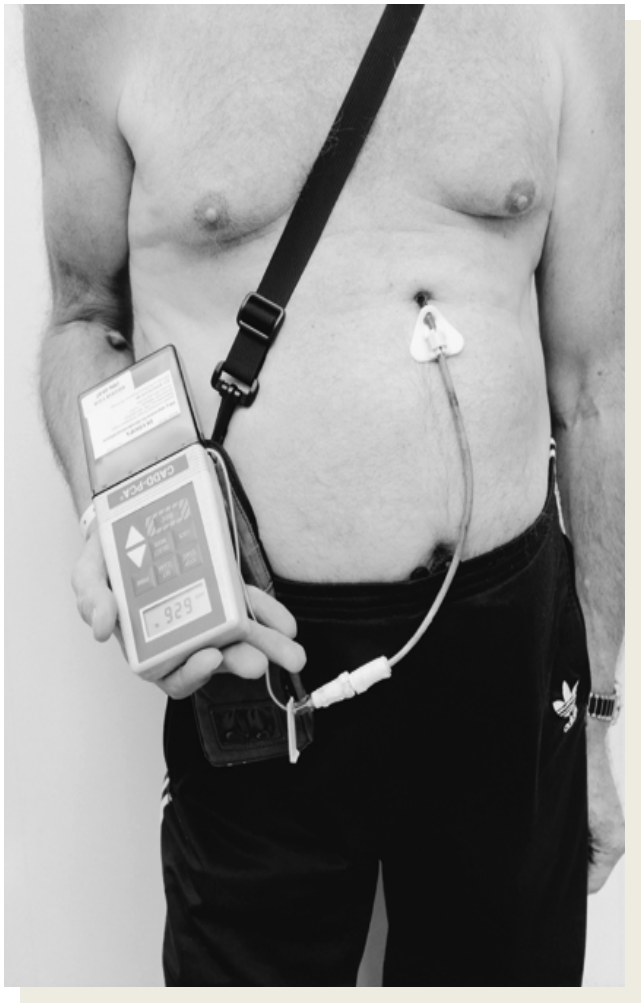
Maurizio Zibetti, Serena Angrisano, Francesca Dematteis, Carlo
Alberto Artusi, Alberto Romagnolo, Aristide Merola, Leonardo Lopiano. (**submitted**)

32 Patients treated with LCIG for a mean of 2.59±1.12 years



		Baseline	LCIG	P value
Gender (M/F)		22/10	-	-
Age at surgery, y		67.5 ± 6.9	-	-
Disease duration, y		14.0 ± 4.2	-	-
Motor complications duration, y		5.8 ± 3.2	-	-
UPDRS I		4.1 ± 2.4	-	-
UPDRS-II total	OFF med	24.9 ± 5.9	-	-
	ON med	13.3 ± 6.0	12.9 ± 6.9	0.953
UPDRS-II item 14 - FoG	OFF med	2.6 ± 0.9	-	
	ON med	0.9 ± 0.8	0.6 ± 0.7	**0.027**
UPDRS-III total	OFF med	46.3 ± 10.1	-	-
	ON med	23.5 ± 9.9	22.8 ± 13.4	0.695
UPDRS-III axial	OFF med	11.7 ± 3.4	-	-
	ON med	9.5 ± 5.0	9.3 ± 5.2	0.846
UPDRS-IV total		9.2 ± 2.5	6.1 ± 2.5	**0.001**
Dyskinesia duration		1.8 ± 1.0	1.4 ± 0.9	**0.021**
OFF period duration		2.1 ± 0.5	0.8 ± 0.5	**0.001**

DUODOPA



ON Oral LD

ON Duodopa

J Neurol
DOI 10.1007/s00415-017-8491-2

Published online: 19 April 2017

ORIGINAL COMMUNICATION

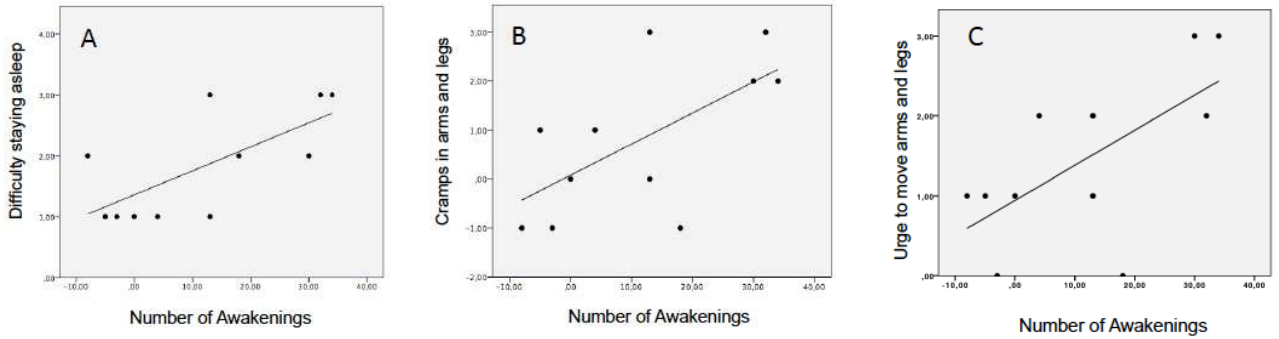
Springer

A polysomnographic study in parkinsonian patients treated with intestinal levodopa infusion

Maurizio Zibetti[1] · Alberto Romagnolo[1] · Aristide Merola[2] · Lorenzo Priano[1,3] · Elisa Montanaro[1] · Serena Angrisano[1] · Antonella Tribolo[1] · Alessandro Cicolin[1] · Leonardo Lopiano[1]

Eleven PD patients underwent PSG at baseline and after 3.8±1.2 months of LCIG treatment

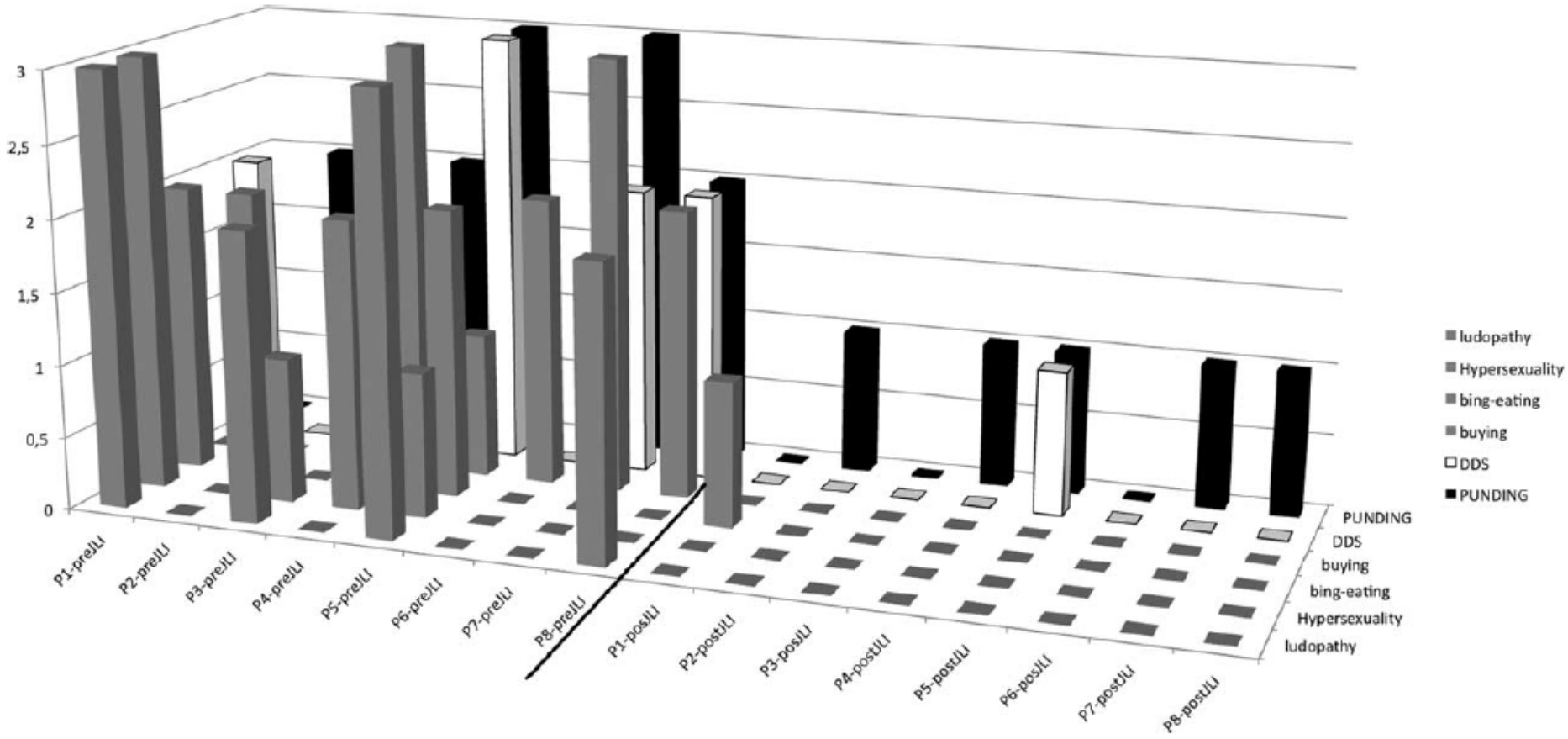
- Sleep quality improved in all patients
- PSG showed a **reduction of the number of awakenings** in sleep, a trend towards a lower Apnea-Hypopnea Index and no change in sleep latency, total sleep time and sleep efficiency
- There was a positive correlation between the number of awakenings and PDSS-2 scores for "**difficulty staying asleep**", "**muscle cramps of arms or legs**" and "**urge to move arms or legs**"
- Motor complications and activities of daily living improved with LCIG



Levodopa Infusion Improves Impulsivity and Dopamine Dysregulation Syndrome in Parkinson's Disease

María José Catalán, MD, PhD,[1*] Eduardo de Pablo-Fernández, MD,[1] Clara Villanueva, MD,[1] Servando Fernández-Diez, MD,[2] Teresa Lapeña-Montero, MD,[1] Rocío García-Ramos, MD, PhD[1] and Eva López-Valdés, MD, PhD[1]

Movement Disorders, Vol. 00, No. 00, 2013



Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome

J Neurol Neurosurg Psychiatry 2013;**0**:1–8.

Roberto Cilia, Chiara Siri, Margherita Canesi, Anna Lena Zecchinelli, Danilo De Gaspari, Francesca Natuzzi, Silvana Tesei, Nicoletta Meucci, Claudio Bruno Mariani, Giorgio Sacilotto, Michela Zini, Claudio Ruffmann, Gianni Pezzoli

Table 3 Differential features of PD patients with DDS according to clinical outcome

DDS	Total (n=35)	Remission (n=14)	Persisting (n=21)	p Values
Disease duration at DDS onset, years	10.9 (3.5)	10.3 (4.0)	11.4 (3.0)	0.4
Patient Follow-Up, years	3.2 (2.1)	3.8 (2.3)	3.5 (3.1)	0.77
Impulse Control Disorders (n (%))	23 (66)	12 (86)	11 (52)	0.07

(a) all patients on CAI persisted in their compulsive seeking of apomorphine boli and/or extra levodopa doses

(b) effective STN-DBS led to remission only in 4/7 cases

(c) DLI successfully relieved DDS in 4/5 patients (one patient relapsed after divorce and was lost at follow-up).

Quetiapine/Clozapine/Others†	12/8/3	4/6/0	8/2/3	N.S.
Clozapine (total %)	33%	60%	15%	0.04
Antidepressants (n (%))	11 (31)	5 (36)	6 (29)	0.71
SSRI/SNRI/TCA	8/3/0	4/1/0	5/2/0	N.S.
Mood stabilisers (n (%))	2 (6)	0 (0)	2 (9)	0.52
Psychological interventions (n (%))	6 (17)	3 (21)	3 (14)	0.65

Parkinsonism and Related Disorders xxx (2015) 1–4

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Short communication

Dopamine agonist withdrawal syndrome (DAWS) symptoms in Parkinson's disease patients treated with levodopa–carbidopa intestinal gel infusion

Paolo Solla [a, *, 1], Alfonso Fasano [b, 1], Antonino Cannas [a, 1], Cesare Salvatore Mulas [a], Maria Giovanna Marrosu [a], Anthony E. Lang [b, 2], Francesco Marrosu [a, 2]

Results: Within few days after DAs withdrawal, all 4 patients developed apathy, anhedonia and depression, despite the marked reduction of dyskinesias and the improvement of motor fluctuations after LCIG introduction. We unsuccessfully tried to manage these and other DAWS symptoms by increasing LCIG flow. Within 6 months, all patients spontaneously presented a slow but gradual improvement of DAWS symptoms, not requiring any further treatment strategy or LCIG discontinuation. *Conclusions:* To our knowledge, this is the first report describing the occurrence of DAWS symptoms in advanced PD patients after DAs withdrawal in LCIG and highlighting the difficulty of distinguishing postoperative effects from drug withdrawal symptoms. Therefore we wish to draw attention of clinicians to the risk of developing DAWS in advanced PD patients switched to LCIG monotherapy. In such cases, a rapid taper of DAs should be avoided.

LETTERS: PUBLISHED ARTICLE

Suicide and Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease

Paolo Solla,[1] Alfonso Fasano,[2] Antonino Cannas,*[1] and Francesco Marrosu[1]

[1]*Movement Disorders Center, Department of Neurology, Institute of Neurology, University of Cagliari, Cagliari, Italy*

[2]*The Edmond J. Safra Program in Parkinson's Disease, Movement Disorders Center, Toronto Western Hospital, Division of Neurology, University of Toronto, Canada*

Dear Editor:

Acta Neurologica Scandinavica

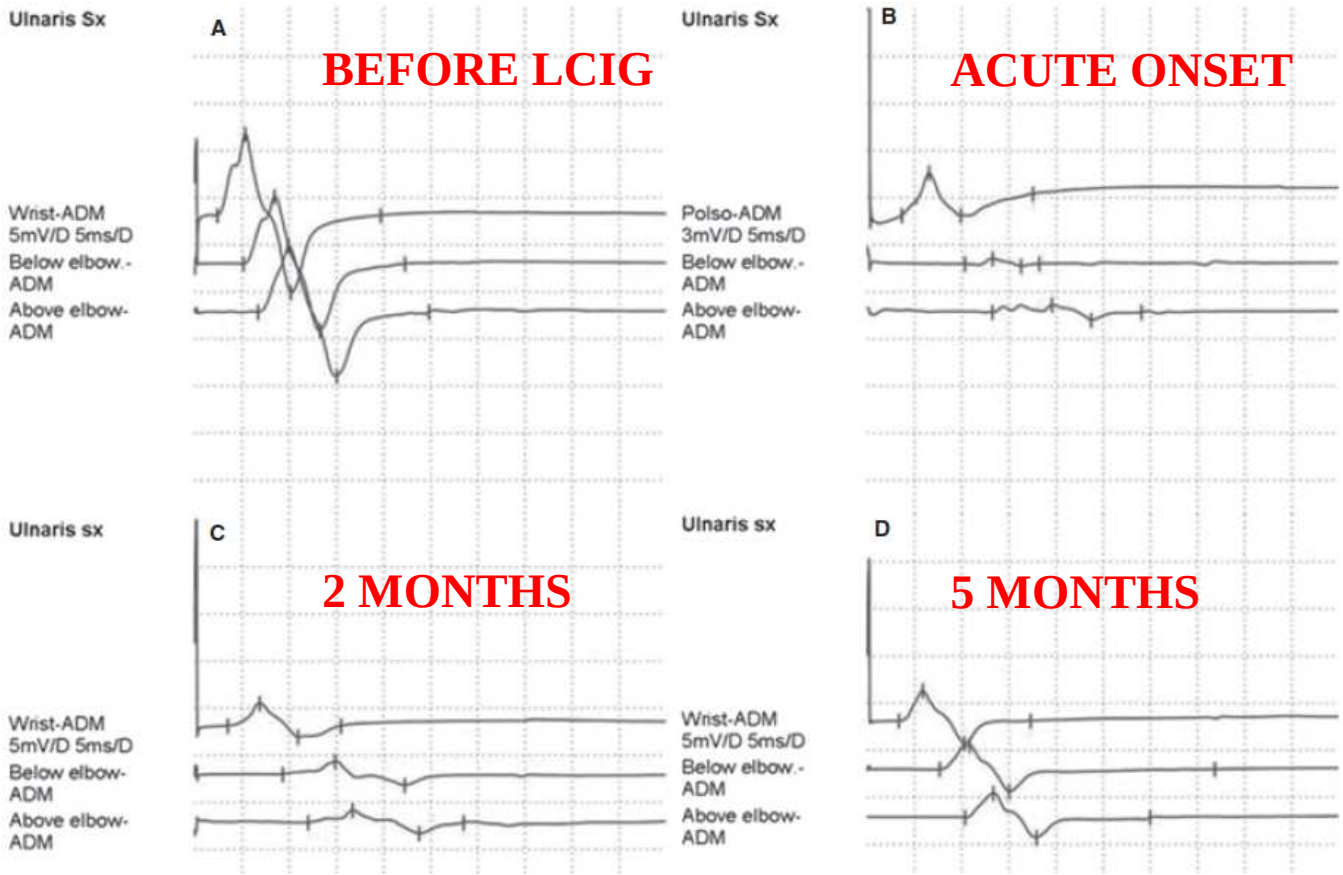
Acta Neurol Scand 2014: 129: e1–e5 DOI: 10.1111/ane.12164

Clinical Commentary

Prospective assessment of peripheral neuropathy in Duodopa-treated parkinsonian patients

A. Merola, M. Zibetti, M. G. Rizzone, M. Troiano, C. A. Artusi, S. Angrisano, D. Cocito, L. Lopiano

Department of Neuroscience, University of Turin, Torino, Italy

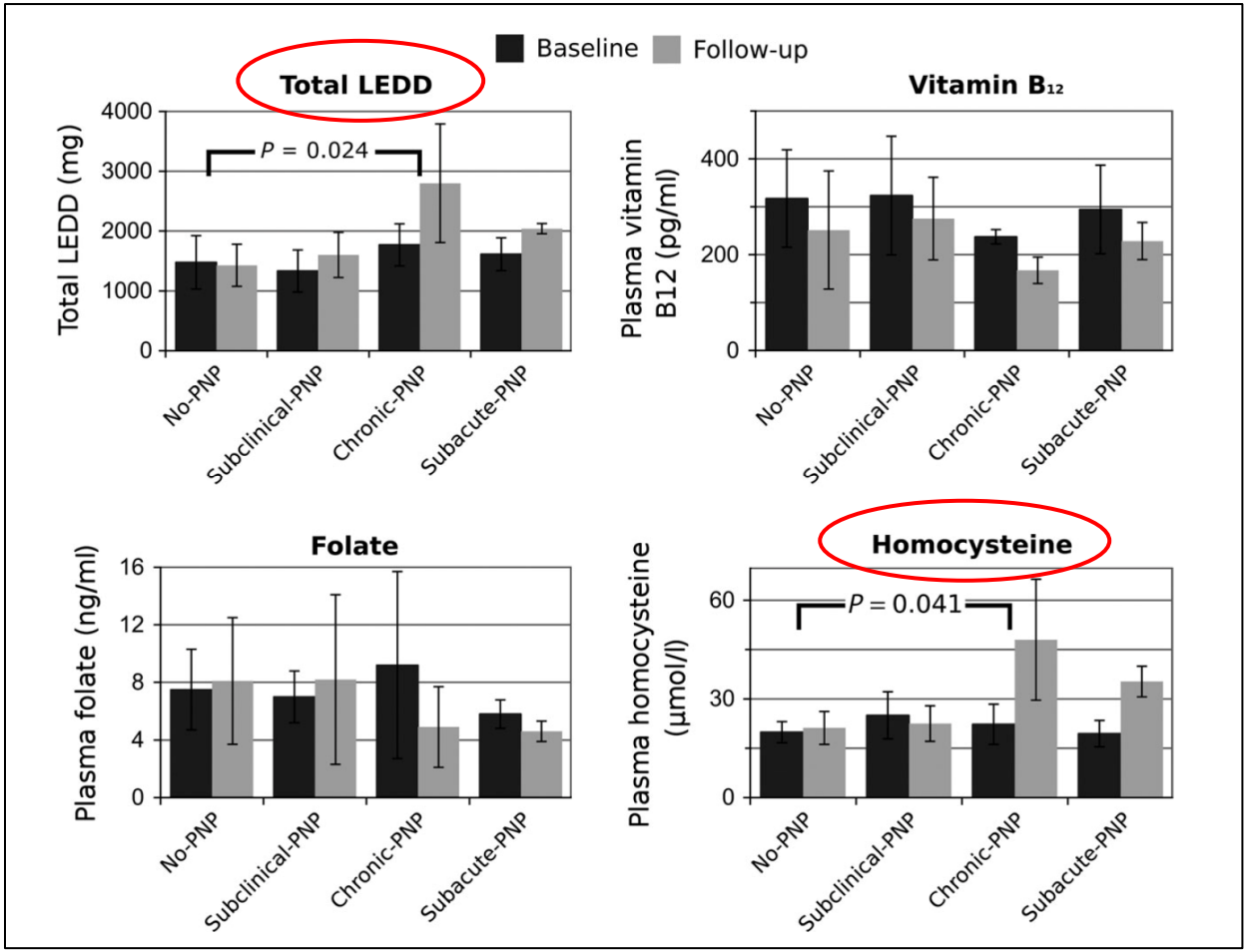


1 SUBACUTE PNP AFTER 4 MONTHS OF THERAPY

Peripheral neuropathy associated with levodopa–carbidopa intestinal infusion: a long-term prospective assessment

A. Merola*, A. Romagnolo*, M. Zibetti, A. Bernardini, D. Cocito and L. Lopiano

European Journal of Neurology 2015, **0:** 1–9



- **Higher levodopa daily dose and homocysteine levels were found in chronic PNP**
- **No correlations were observed with vitamin B12 and folate**
- **Serial clinical-electrophysiological evaluations are mandatory (risk of subacute PNP)**
- **No clear causative factors has been recognized in the subacute forms, whilst homocysteine-mediated neurotoxicity seems to underlie the pathogenesis of chronic forms**
- **Vitamin supplementation and regular clinical-electrophysiological assessments might be advised in chronic PNP**

european journal of neurology
the official journal of the european academy of neurology

PERIPHERAL NEUROPATHY ASSOCIATED WITH LEVODOPA-CARBIDOPA INTESTINAL INFUSION: A LONG-TERM PROSPECTIVE ASSESSMENT

Aristide Merola MD, PhD and Alberto Romagnolo MD, Maurizio Zibetti MD, PhD, Andrea Bernardini MD, Dario Cocito MD, Leonardo Lopiano MD, PhD

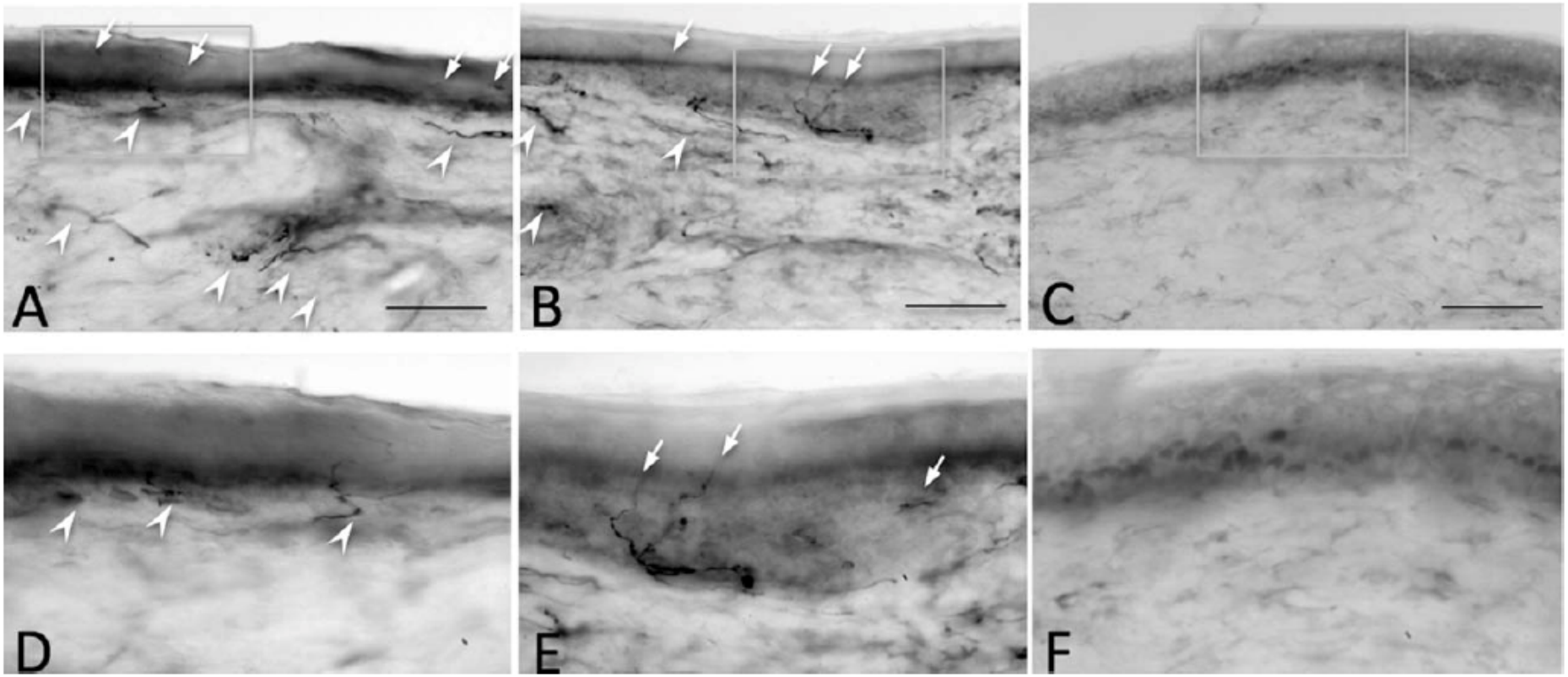
- Our findings confirm that **seriate clinical-electrophysiological evaluations** are mandatory in patients treated with LCIG, given the possible risk of subacute and chronic PNP.

- No clear causative factors were recognized in the subacute forms, while **homocysteine-mediated neurotoxicity** seems to underlie the pathogenesis of **chronic forms**.

LEVODOPA/CARBIDOPA INTESTINAL GEL THERAPY FOR ADVANCED PARKINSON DISEASE: AN EARLY TOXIC EFFECT FOR SMALL NERVE FIBERS?

GRAZIA DEVIGILI, MD, PhD, SARA RINALDO, Tch, CHRISTIAN LETTIERI, MD, and ROBERTO ELEOPRA, MD

MUSCLE & NERVE November 2016

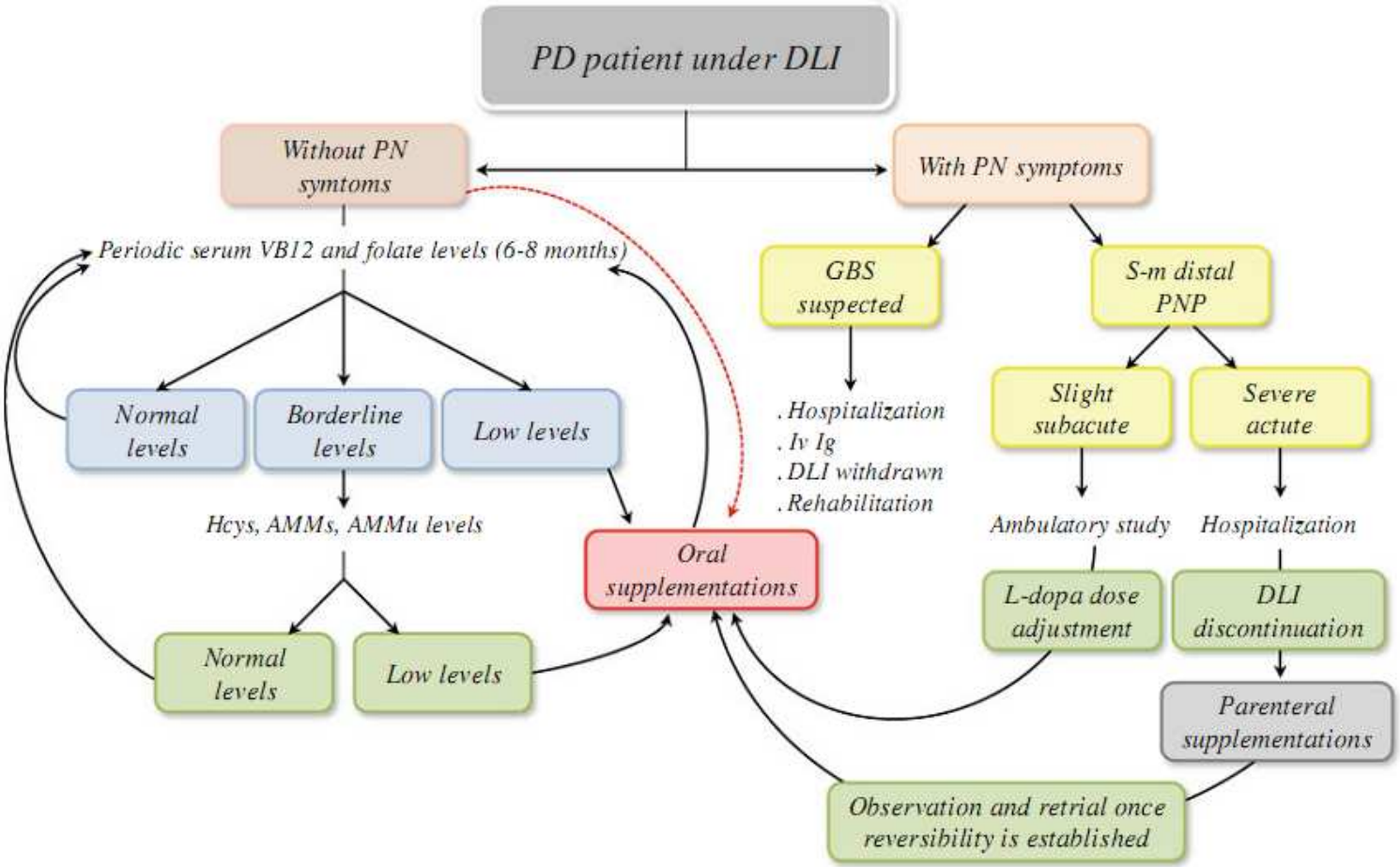


Polyneuropathy while on duodenal levodopa infusion in Parkinson's disease patients: we must be alert

Diego Santos-García · Raúl de la Fuente-Fernández · Francesc Valldeoriola · Antonio Palasí · Fátima Carrillo · Mónica Grande · Pablo Mir · Oriol De Fabregues · Jordi Casanova

J Neurol

Published online: 24 January 2012



Levodopa and neuropathy risk in patients with Parkinson disease: Effect of COMT inhibition

Parkinsonism and Related Disorders 27 (2016) 81–84

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Objective: **Our purpose was to determine whether the use of catechol-O methyltransferase-inhibitors (ICOMT) can reduce the risk of developing levodopa (LD)-induced neuropathy in Parkinson's disease (PD) patients.**

Methods: A multicentre study of 197 PD patients was performed. 144 were exposed to LD for more than three years (LELD group); 53 simultaneously assumed Entacapone for at least eighteen months (LELD_ ICOMT group).

Results: The prevalence of neuropathy in LELD patients was 19.4% whereas it was 5.7% in LELD_ICOMT group with a significant difference (p . 0.025). In LELD_ICOMT cohort the daily LD dose and serum VB12 levels were significantly higher (p < 0.0001), the serum Hcy levels were significantly lower (p . 0.001) compared to LELD group.

Conclusion: Our results suggest that ICOMT could have a protective effect on the development of Ldinduced neuropathy. Their action probably occurs through the metabolic rebalancing of the onecarbon- pathway cycle and is independent of the PD duration and severity and the duration of LD intake.

Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: clinical evidence and experience

Ther Adv Neurol Disord
2017, Vol. 10(3) 171–187
DOI: 10.1177/1756285616681280

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Relative contraindications, precautions and warnings	Absolute contraindications
• Noncompliance with noninvasive therapies • Pre-existing peripheral neuropathies • Previous or current dopamine dysregulation and punding • Moderate to severe dementia • Patient frailty (unable to support device weight) • Concurrent medications that may cause orthostatic hypotension • Well-controlled wide angle glaucoma • Administer with caution to patients to patients with severe CV or pulmonary disease, bronchial asthma, renal or hepatic or endocrine disease, history of peptic, ulcers, asthma, or convulsion	• Hypersensitivity to levodopa or carbidopa • Lack of levodopa response • Absolute or relative contraindications to abdominal surgery • Narrow angle glaucoma • Severe heart failure • Severe cardia arrhythmia • Acute stroke • Non selective-MAO inhibitors or selective MAO type A inhibitors • Conditions in which adrenergics are contraindicated, e.g. pheochromocytoma, hyperthyroidism and Cushing's syndrome. • Patients with suspicious undiagnosed skin lesions or a history of melanoma. • Inability of patient and caregiver to handle medication and device

Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection

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Table VII - Effects of LCIG infusion, DBS and subcutaneous apomorphine on different PD patient characteristics

	LCIG Infusion	DBS	Apomorphine
Age > 65-70 years	+++	-	-
Mild-moderate cognitive profile	+++	++	-
Severe cognitive profile	-	-	-
Reduction of OFF time	+++	+++	+++
Reduction of dyskinesia	++	+++	-/+
Improvement of axial symptoms	-/+	-	-
Complications of procedure	+++	++	-
Adverse events profile	+	-	+++

Functional Neurology 2012; 27(3): 147-154

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- Dr. A. Romagnolo
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Grazie dell'attenzione

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