



Avancerad Behandling: Pumpterapi

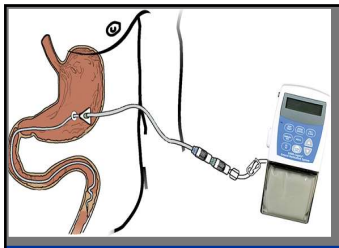
Per Odin, Professor, Head Division of Neurology, Lund University (Sweden)

1

Kontinuerlig dopaminerg stimulation för avancerad Parkinsonsjukdom



2



Pump-start: LCIG/LECIG

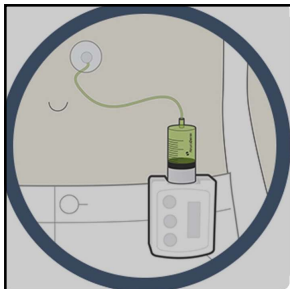


Att tänka på:

- Före start: Dagbok/PKG, L-dopa test, Neuropsykologi, rikligt med balanserad information
- PEG: Viktigt med erfaren gastroenterolog
- Monoterapi: I regel möjligt, men ibland fördelar med kombination, sätt ut DAg långsamt
- 16/24h terapi: Hos patienter med insomni: liberalt med 24h terapi
- Utbilda patient och anhöriga väl
- Efter utskrivning: Såväl firma som klinik bör vara lättillgängliga
- Täta kontakter i början av behandlingen

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3



Pump-start: Apomorfin



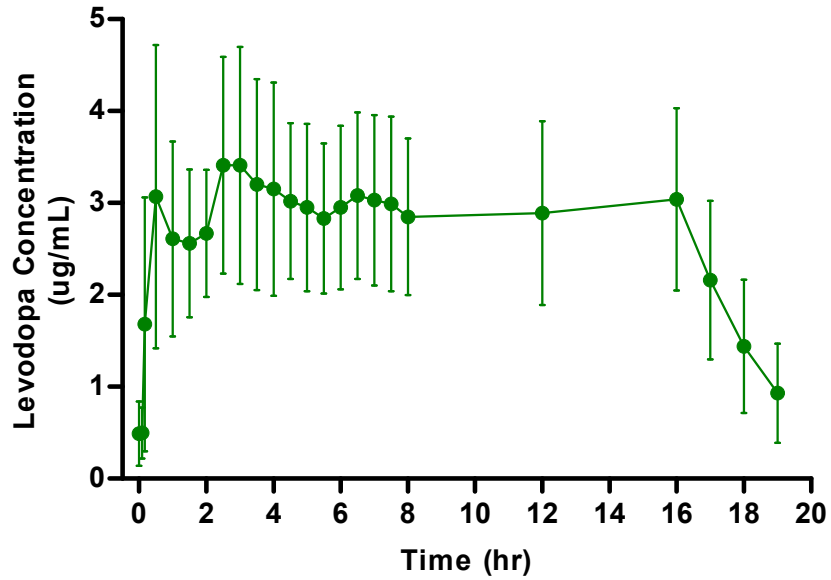
Att tänka på:

- Före start: Dagbok/PKG, Apomorfintest, Neuropsykologi, rikligt med balanserad information
- Monoterapi: Ibland möjligt, men i regel fördelar med kombination, i första hand med låg dos l-dopa
- 16/24h terapi: Hos patienter med insomni: pröva gärna 24h terapi
- Byt infusionsställe minst 1 gång per dag
- Utbilda patient och anhöriga väl, särskilt avseende hudvård
- Efter utskrivning: Såväl firma som klinik bör vara lättillgängliga
- Täta kontakter i början av behandlingen

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4

Profil av plasmakoncentrationen av levodopa över tid



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Nyholm D et al., 2013

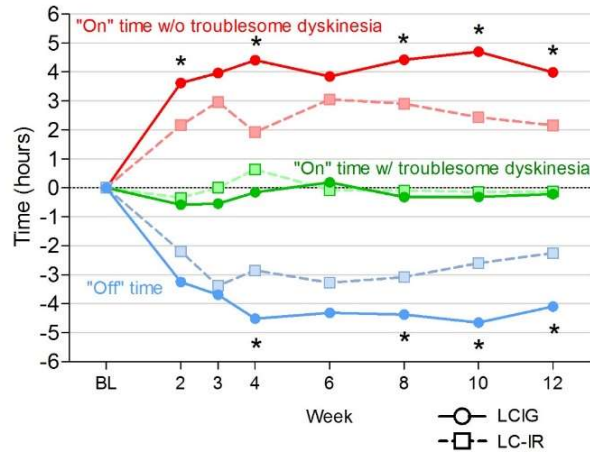
5

Effekt på motoriska symtom



6

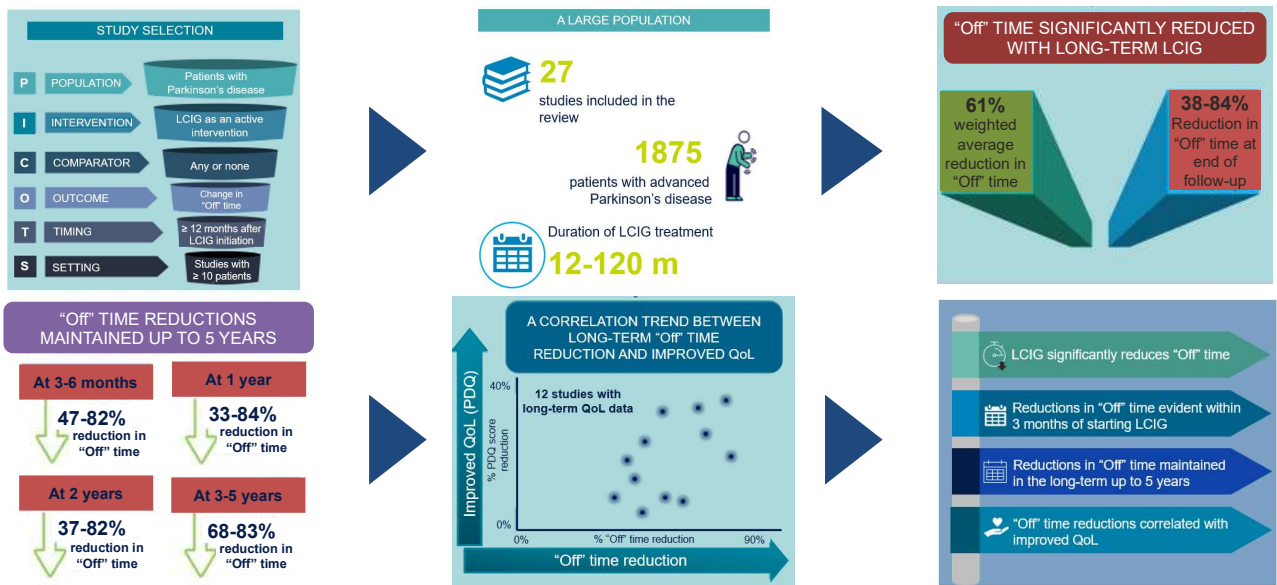
Förändring från baslinjen i "off"- och "on"-tid samt "on"-tid med/utan besvärande dyskinesi



Skånes universitetssjukhus

Olanow CW et al., 2014

7



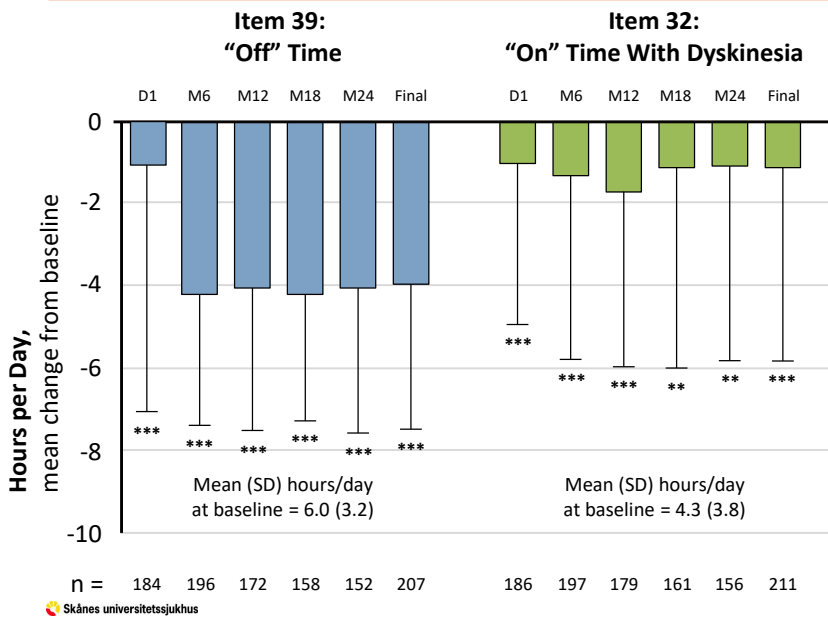
LCIG, levodopa carbidopa intestinal gel; QoL, quality of life

Antonini A, et al. *Adv Ther* 2021; 38: 2854–2890.

8



Slutliga långtidsresultat från GLORIA-registret



Genomsnittlig förändring från baslinjen av dagliga timmar i "off"-tid och "on"-tid med dyskinesi (modifierad UPDRS del IV)

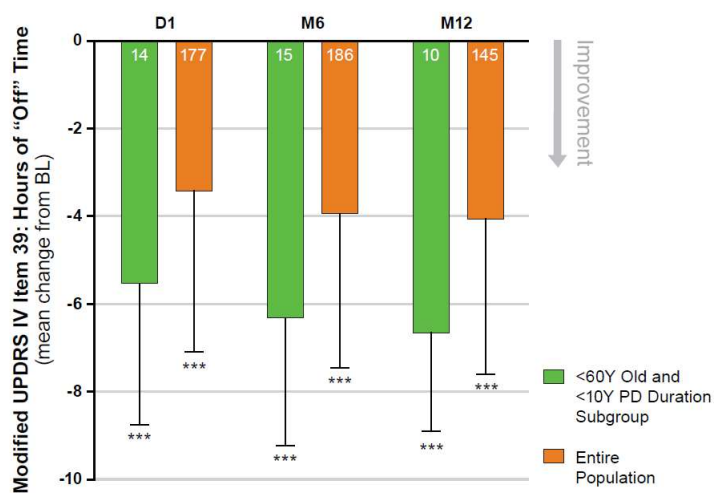
Antonini A et al., 2017

9



LORIA: post hoc-analys hos patienter i åldern <60 år och med en sjukdomsduration på <10 år

- Genomsnittlig förändring från baslinjen av dagliga timmar "off" tid (UPDRS IV: modifierad punkt 39)



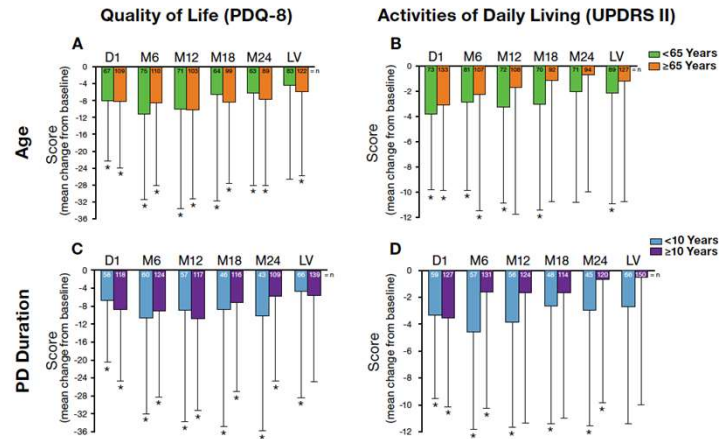
Antonini A et al., 2018

10

GLORIA: post hoc-analys hos patienter i åldern <60 år och med en sjukdomsduration på <10 år



- Genomsnittlig förändring från baslinjen i totalpoäng för PDQ-8 och UPDRS II: undergrupper för ålder och varaktighet



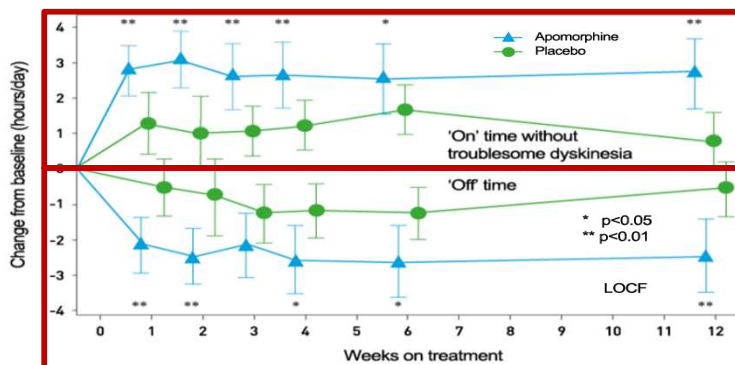
Error bars indicate standard deviation (SD). P-values from a paired t test indicate statistical significance compared to baseline at P<0.05 (*). D1 = discharge from hospital post-PEG-J placement; M = month; LV = last visit; PD = Parkinson's disease; PDQ-8 = Parkinson's Disease Questionnaire 8-item; UPDRS = Unified Parkinson's Disease Rating Scale

Skånes universitetssjukhus

Antonini A et al., 2018

11

Toledo: Huvudsakliga resultat



ON time without troublesome dyskinesia: treatment difference: 1.97 hours [95% CI: 0.69, 3.24; p=0.0008]

Primary endpoint: absolute change in OFF time from baseline to Week 12 derived from patient diaries

OFF time treatment difference -1.89 hours (95% CI: -3.16, -0.62; p=0.0025)

Number of observations
Apomorphine 53 52 52 52 52 52 53
Placebo 53 48 48 48 48 48

Safety and tolerability	APO (n=54)	Placebo (n=53)
At least one treatment-emergent AE (TEAE)	50 (92.6%)	30 (56.6%)
Most common TEAE (≥10% of patients)		
Skin nodules at infusion site	24 (44.4%)	0
Nausea	12 (22.2%)	5 (9.4%)
Somnolence	12 (22.2%)	2 (3.8%)
Skin erythema at infusion site	9 (16.7%)	2 (3.8%)
Dyskinesia	8 (14.8%)	0
Headache	7 (13.0%)	2 (3.8%)
Insomnia	6 (11.1%)	1 (1.9%)
Serious AEs	5 (9.3%)	2 (3.8%)

Patient Global Impression of Change: Favored apomorphine (p<0.0001)

Katzenschlager et al., 2018

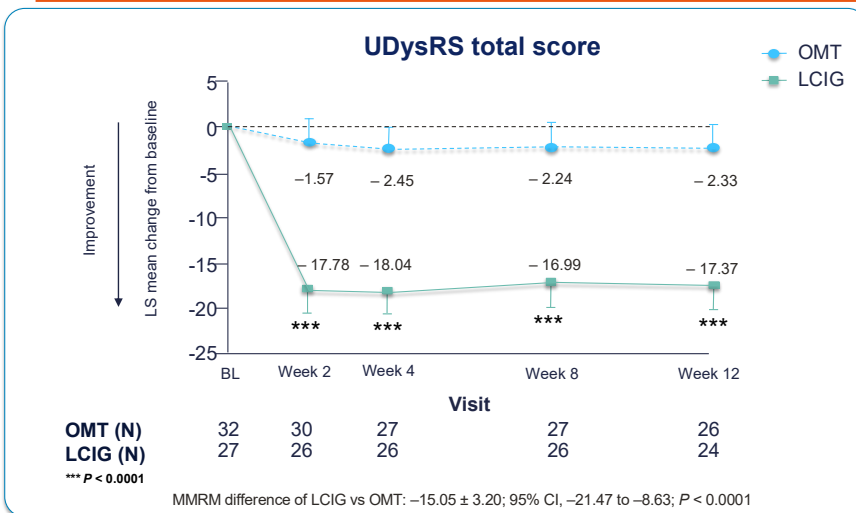
12

Effekt på dyskinesier



13

DYSCOVER-STUDIE: LCIG vs OMT-behandling minskade UDysRStotal-poängen signifikant redan vecka 2



The effect of LCIG on UDysRS total score was observed as early as week 2 and maintained to week 12

BL, baseline; LCIG, levodopa/carbidopa intestinal gel; LS, least squares; MMRM, mixed-effect model repeated measures; OMT, optimized medical treatment; UDysRS, Unified Dyskinesia Rating Scale; W, week. Skånes universitetssjukhus

Freire-Alvarez E, et al. *Mov Disord* 2021; 36:2615–2623.

14

Effekt på icke-motoriska symtom

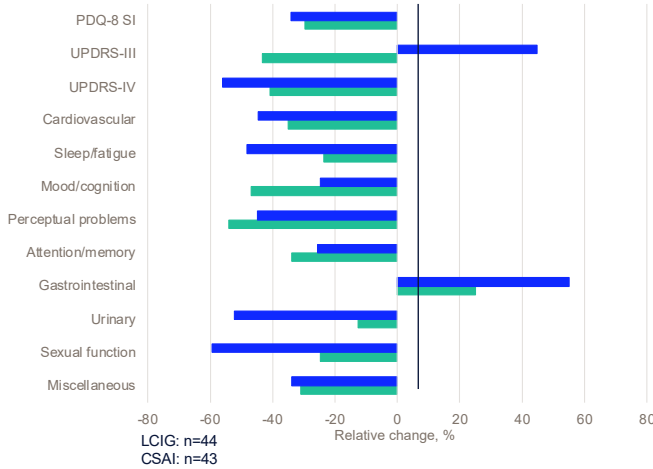


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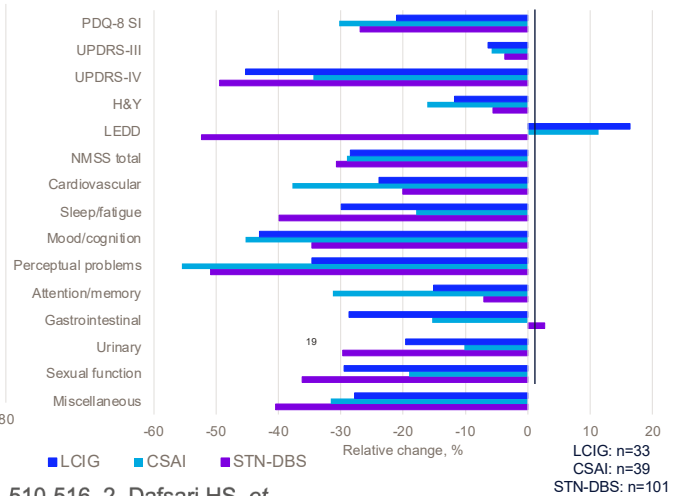
Eufinf 2 studien



EuroInf Observational Study¹



EuroInf 2 Observational Study²



1. Martinez-Martin P, *et al.* (2015) *Mov Disord*, 510-516. 2. Dafsari HS, *et al.* (2019) *Mov Disord*, 353-365..



16

Effekter på hälsorelaterad livskvalitet

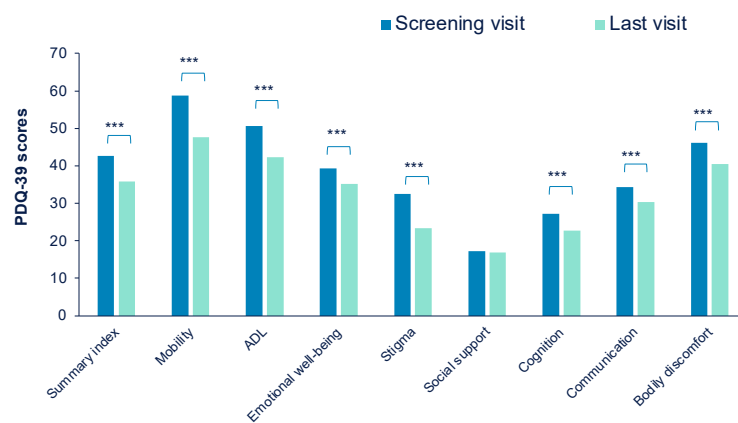


17

DAT kan avsevärt förbättra den individuella livskvaliteten



- Large international, prospective, 54-week, open-label LCIG study
 - Patients with PD and severe motor fluctuations despite optimized therapy
- 7 of 8 PDQ-39 domains (except social support) showed statistically **significant mean improvements** in patients receiving LCIG



*** $P < 0.001$; 1-sample t test.
PDQ-39, Parkinson's Disease Questionnaire-39; LCIG, levodopa-carbidopa intestinal gel.

Fernandez HH. *et al. Mov Disord* 2015; **30**: 500–509.

18

Biverkningar och komplikationer



19

Navigate PD: Vilka är biverkningarna och komplikationerna för LCIG/LECIG



Surgical/device-related complications	
Complication of device insertion	21.4–56.6% [4,41,66]
Procedural pain	17.7–29.7% [4,41,66]
Post-operative wound infection	10.4–21.0% [4,41,66]
Incision site erythema	9.4–18.9% [4,41,66]
Medical device site reaction	38.0% [66]
Device dislocation	34.7% [66]
Device occlusion	29.4% [66]
Device-related infection	21.3% [66]
Device connection issue	21.3% [66]
Device breakage	11.9% [66]
Unintentional removal of device by patient	10.6% [66]
Device leakage	
Procedural site reaction	
Post procedural discharge	8.3–10.9% [4,41,66]
Incision site pain	
Other	
Abdominal pain	30.7–34.2% [41,66]
Flatulence	16.2% [41]
Constipation	13.5–21.6% [4,41]
Nausea	13.5–29.7% [4,41]
Excessive granulation tissue	13.5–18.2% [41,66]
Fall	10.9% [41]
Dyskinesia	10.9% [41]
Insomnia	10.8–10.9% [4,41]
Anxiety	10.4% [41]

20

Navigate PD: Vilka är biverkningarna och komplikationerna för Apomorfinpump?



Table 3

The rate and frequency of the most common adverse events and complications associated with subcutaneous apomorphine.

	Relatively frequent ($\geq 10\%$)	Infrequent ($<10\%$ to $\geq 5\%$)	Rare ($<5\%$)
Administration/device-related complications			
Needle/injection-site pain	35.0% [35]		
Apomorphine-related complications			
Nodules	41–100.0% [23,32,36,65]		
Weight gain	60.0% [35]		
Neuropsychiatric AEs	36.4–44.0% [32,36]		
Daytime somnolence	31.0% [35]		
Nausea	4.0–18.2% [32,36]		
Orthostatic hypertension	16.0% [36]		
Mild sedation	13.6% [32]		
Coombs antiglobulin positive	12.5% [35]		
Hemolytic anemia		0.6–9.1% [35,23,32]	
Urinary urgency		8.0% [36]	
Abscess			1.6–4.0% [35,36]
Necrosis			0–4.0% [36,65]
Hyperlipidinous effect			4.0% [36]
Diarrhea			4.0% [36]

AE, adverse event.



Odin P et al., 2015

21

J Parkinsons Dis. 2020; 10(3): 935–944.

Published online 2020 Jul 28. Prepublished online 2020 Jul 15. doi: 10.3233/JPD-201978

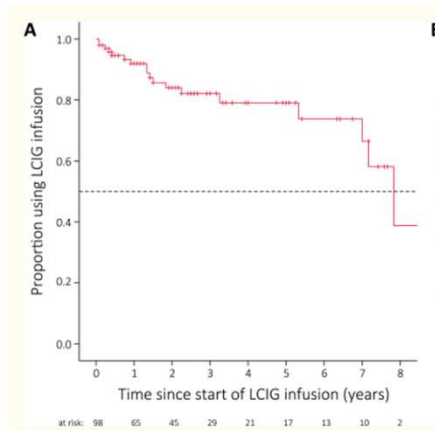
PMCID: PMC7458507

PMID: 32675420



Predictors of Time to Discontinuation of Levodopa-Carbidopa Intestinal Gel Infusion: A Retrospective Cohort Study

Harmen R. Moes,^{a,1,*} Jeremy W.M.J. Groenendaal-Laurenssen,^{b,1} Martje Drent,^a Gerrit Tissingh,^b and Teus van Laar^a



Reasons for discontinuation of LCIG infusion and causes of death during treatment

Reason for discontinuation	N=18
Device-related side effects	5
Effect less than expected by patient	5
Switch to DBS	4
Effect less than expected by clinician	2
Switch to CAI	1
Drug-related side effects of LCIG	1
Cause of death	N=7
LCIG-related	0
Device-related	0
Other (not specified)	5
Unknown	2


**98 patienter. Under en uppföljningstid på 2,6 år avbröt 8 LCIG och 7 avled.
Genomsnittlig behandlingstid: 7,8 år**

Moes et al., 2020

22

Neurological Sciences (2019) 40:1917–1923
https://doi.org/10.1007/s10072-019-03920-5

ORIGINAL ARTICLE



Continuous subcutaneous apomorphine infusion in Parkinson's disease: causes of discontinuation and subsequent treatment strategies

Enrica Olivola¹ · Alfonso Fasano^{2,3} · Sara Varanese⁴ · Francesco Lena¹ · Marco Santilli¹ · Cinzia Femiano¹ · Diego Centonze^{1,5} · Nicola Modugno¹

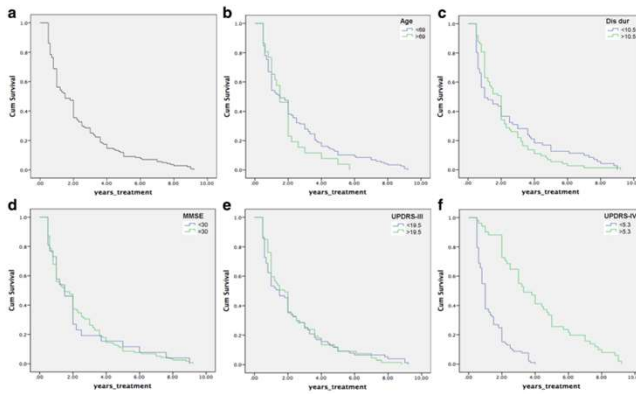
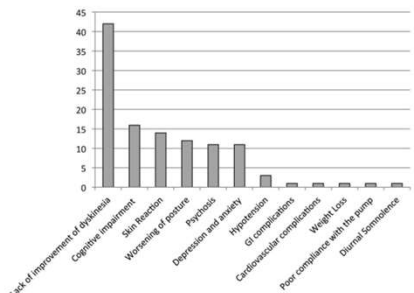


Fig. 1 Reasons for CSAI discontinuation




14 patienter som fått apomorfin i minst 6 månader

Olivola et al., 2019


23

SoS nationella riktlinjer Kostnad för avancerade behandlingar



- Beräknade behandlingarkostnader för ytterligare 500 patienter med avancerad vård under en 5-årsperiod

	Additional no. of patients	Cost for advanced treatment (M SEK)	Cost of standard of care (M SEK)	Difference (M SEK)
Apomorphine Infusion Pump	95	159	156	3
DBS	225	264	374	-109
Duodopa®	180	395	303	92
Total	500	818	833	-14



Swedish National Guidelines for Parkinson's Disease.
The Board of Health and Welfare, 2016

24

LECIG



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25

Movement Disorders

RESEARCH ARTICLE

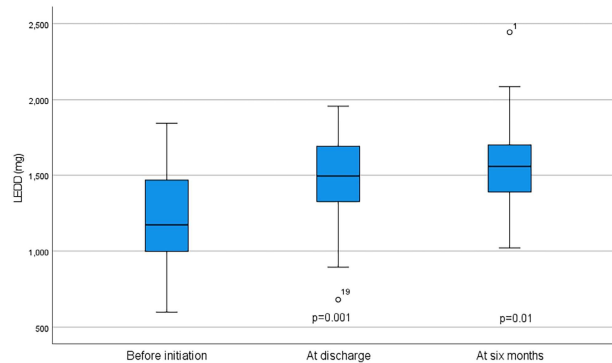
CLINICAL PRACTICE



LECIG

Levodopa-Entacapone-Carbidopa Intestinal Gel Treatment in Advanced Parkinson's Disease: A Single-Center Study of 30 Patients

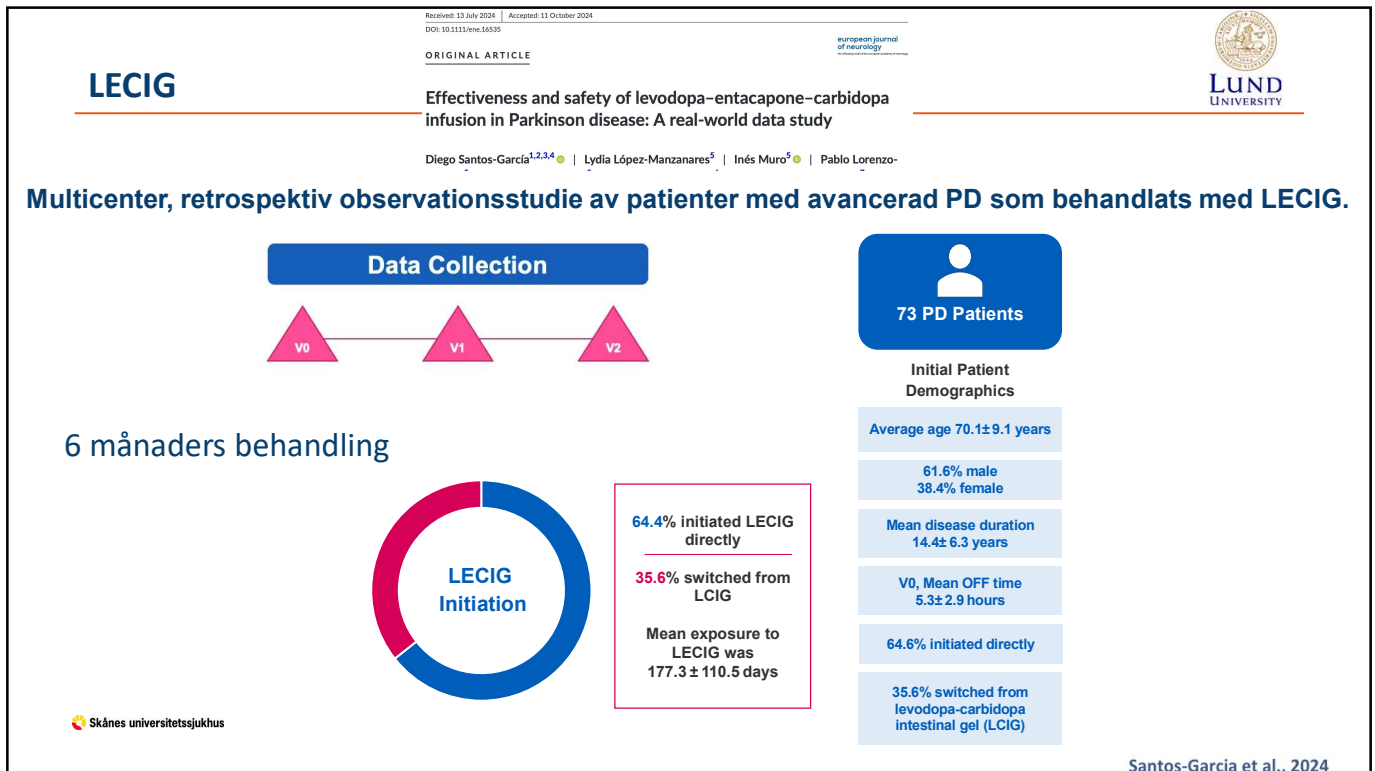
Vilij Viljajarju, MD,^{1,2*} Tuomas Mertsalmi, MD, PhD,^{1,2} K. Amande M. Pauls, MD, PhD,^{1,2} Maija Koivu, MD,^{1,2} Johanna Eerola-Rautio, MD, PhD,^{1,2} Marianne Udd, MD, PhD,¹ and Eero Pekkonen, MD, PhD^{1,2}



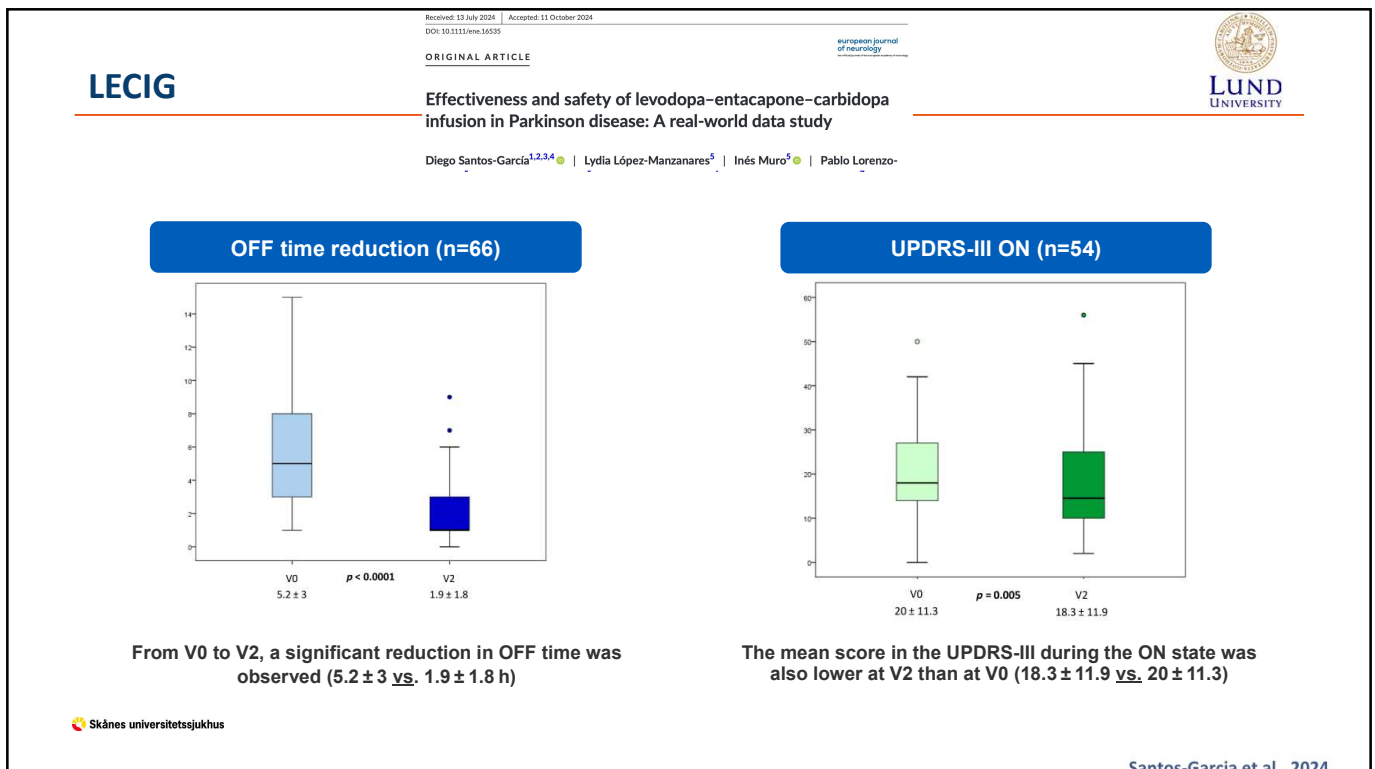
Viljajarju et al., 2023

Conclusions: LEDD seems to increase during the first months of LECIG treatment. When compared to studies on LCIG, safety profile of LECIG appears similar, but early discontinuation rate is higher than expected. However, long-term studies are lacking. Only clear advantage to LCIG appears to be the smaller LECIG pump size.

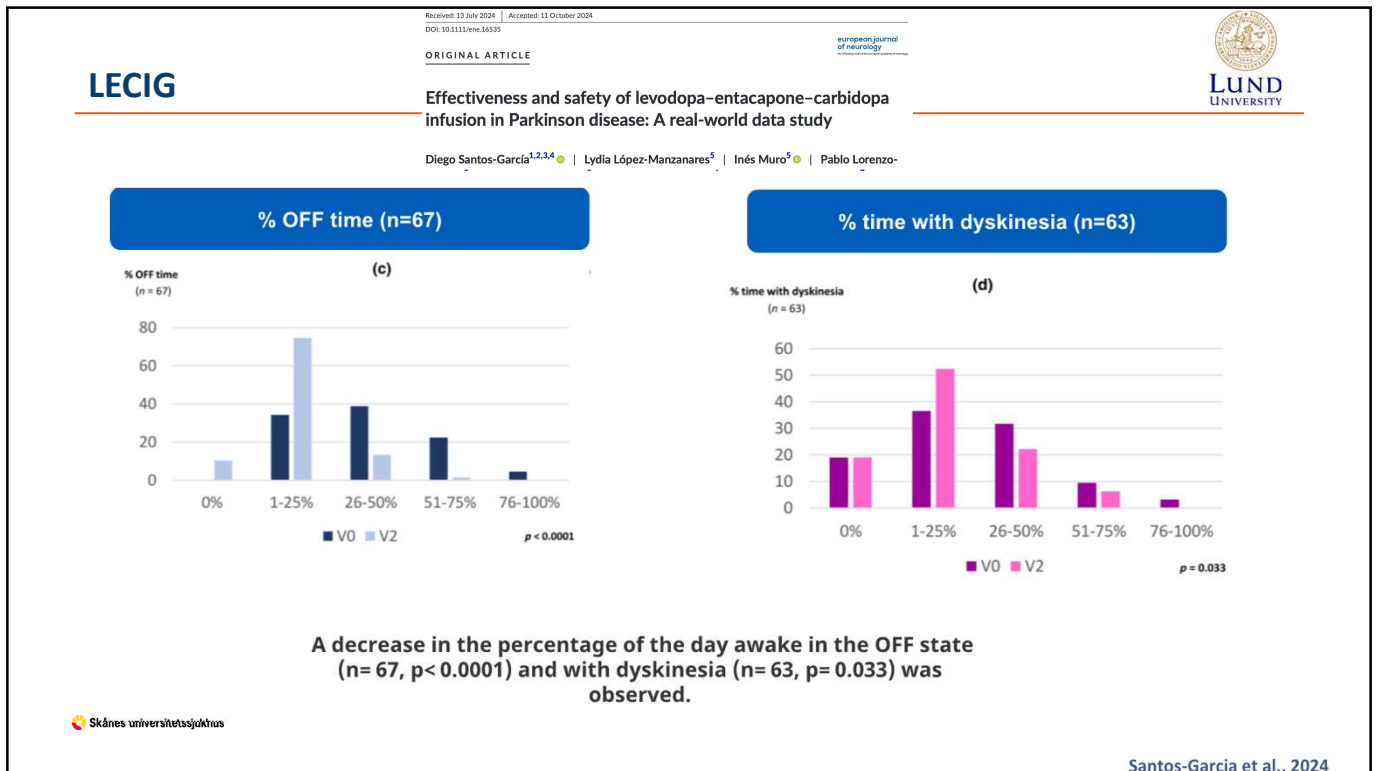
26



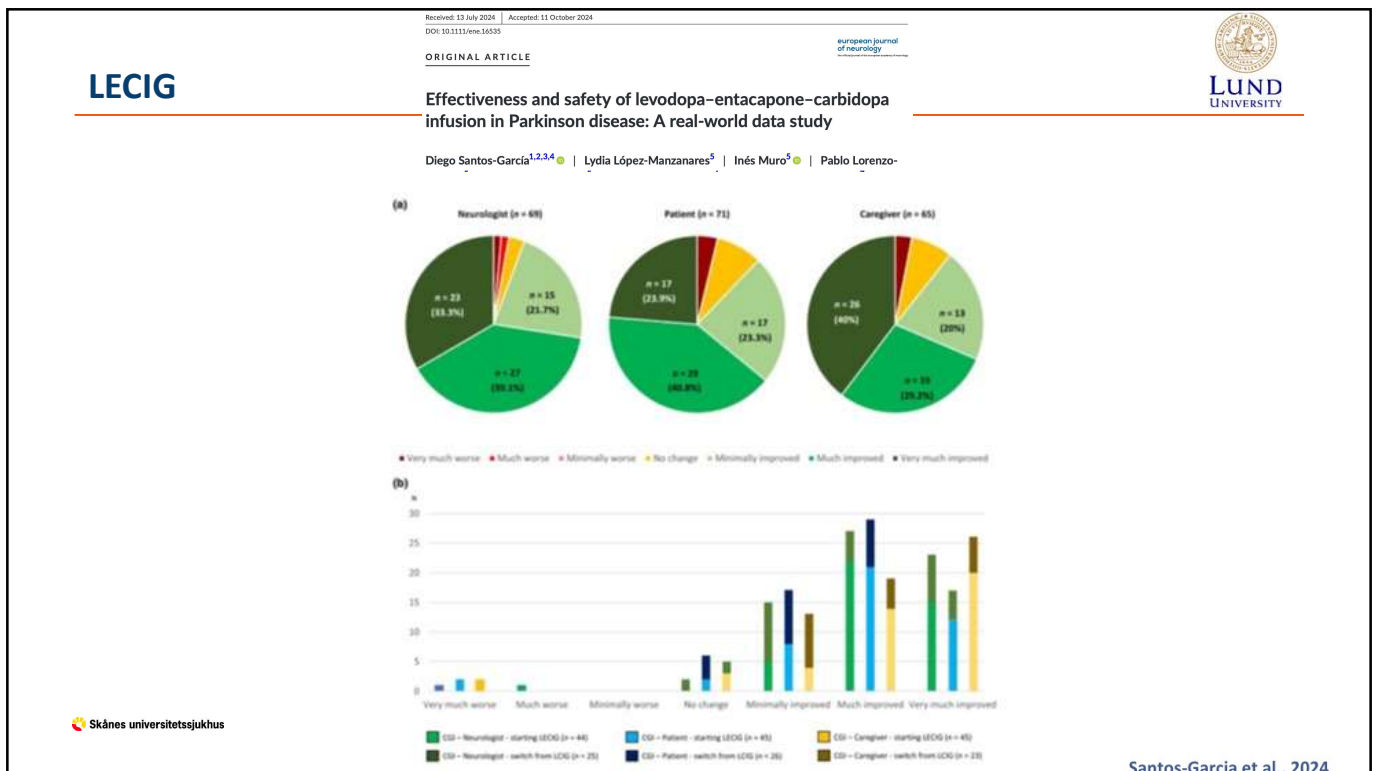
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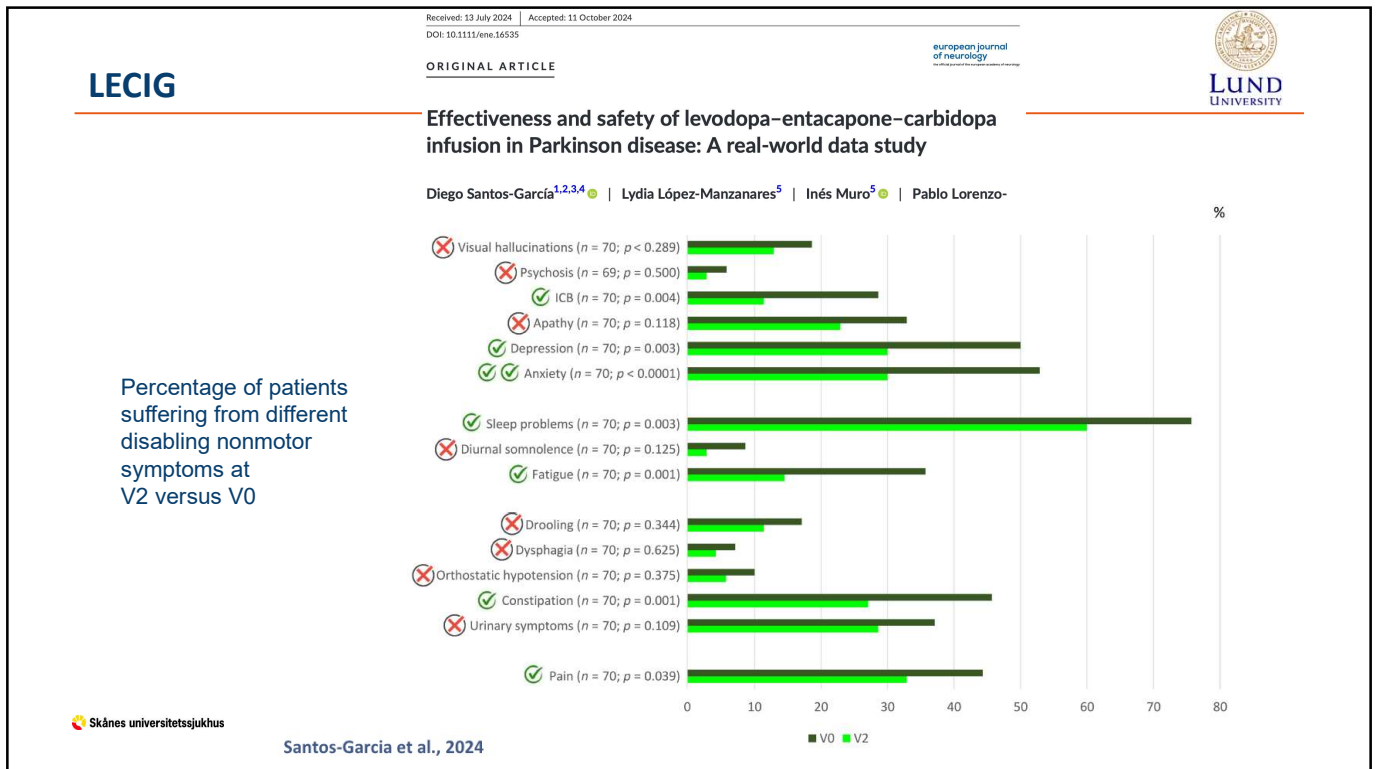
28



29



30



31

Received: 13 July 2024 | Accepted: 11 October 2024
DOI: 10.1111/ene.16535

ORIGINAL ARTICLE

European Journal of Neurology

LUND UNIVERSITY

LECIG

Effectiveness and safety of levodopa-entacapone-carbidopa infusion in Parkinson disease: A real-world data study

Diego Santos-García^{1,2,3,4} | Lydia López-Manzanares⁵ | Inés Muro⁵ | Pablo Lorenzo-

AEs collected by the neurologist in patients receiving LECIG from V1 (initiation LECIG) to V2 (follow-up visit; 177.3 ± 110.5 days, range = 7–476).

Adverse Event (AE)	n (number of patients)
Total AEs	54
Patients with at least one AE	36
Patients with at least one AE related to LECIG and/or the device	34
Patients with at least one AE leading to discontinuation	5
Deaths	1

AE leading to discontinuation
 Serious stoma infection (n=1)
 Acute urinary retention with urological complication (n=1)
 Psychosis (n=1)
 Dyskinesia (n=1)
 Ischemic colitis (n=1)

Due to severe stoma infection and acute renal failure during hospitalization.

Plasma Levels

Homocysteine

- A significant change was detected from V0 to V2 in the plasma levels of homocysteine (12.8 ± 4.0 mmol/L at V2 vs. 14.9 ± 4.6 mmol/L at V0, n= 15, p= 0.048)

B1 Vitamins

- No significant change was detected

B6 Vitamins

- No significant change was detected

B12 Vitamins

- No significant change was detected

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Santos-García et al., 2024

32

LECIG



Movement Disorders
CLINICAL PRACTICE

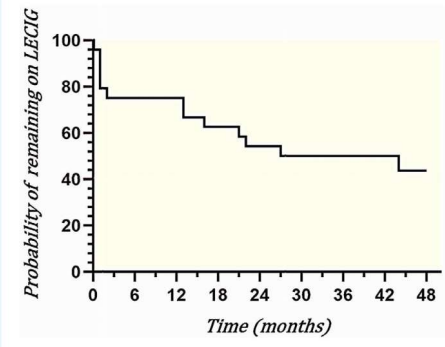
BRIEF REPORT



LUND
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A 4-Year Follow-Up of Levodopa-Entacapone-Carbidopa Intestinal Gel Treatment in Parkinson's Disease


Mezin Öthman, MD  and Dag Nyholm, MD, PhD 




Time (months)	Probability of remaining on LECIG (%)
0	100
3	85
6	80
12	75
18	65
24	55
30	50
36	48
42	45
48	45

Öthman et al., 2024


Conclusions: LECIG infusion is a viable treatment option for PD patients with motor fluctuations, for up to 4 years in our cohort.



33



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Uppdatering om infusionsbaserade behandlingar: Subkutan infusion av levodopa

34

Foslevodopa/Foscarbidopa (Produodopa) Översikt

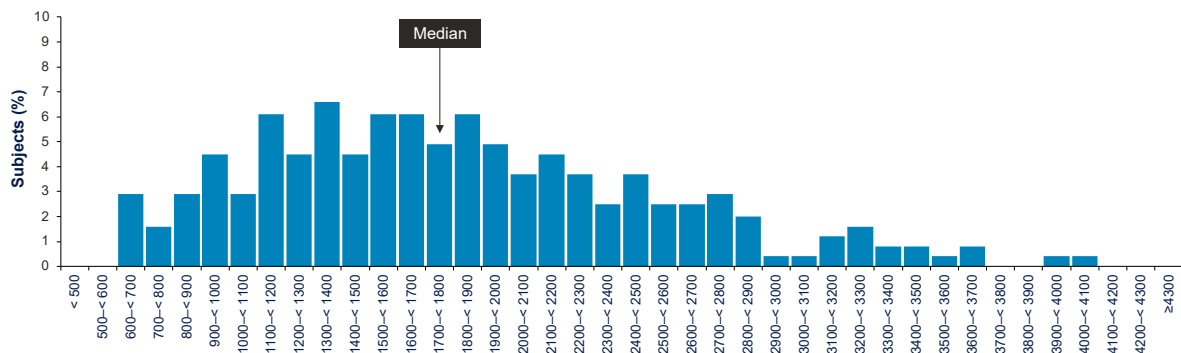


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Vyafuser™ pump CE-mark evaluation ongoing.

35

Study M15-741: Dosing



N	Minimum	10%	25%	Median	75%	90%	Maximum
244	600- < 700	900- < 1000	1200- < 1300	1700- < 1800	2200- < 2300	2700- < 2800	4000- < 4100

- The median modal total daily dose was between 1700 and 1800 mg LD equivalents/day
- The infusion rates most frequently prescribed ranged from approximately 0.30 mL/hr to 0.60 mL/hr, which deliver approximately 1200 to 2400 mg of LD equivalents per day

Modal (most frequent) daily dose, expressed in 100 mg intervals of LD equivalents, was obtained for each subject and was calculated from the actual infusion rates used in subjects and the duration of infusion. LD, levodopa.

AbbVie. Data on File (741).

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36

Study M15-741: Safety översikt



AE category, n (%)	All subjects N = 244
Any TEAE	230 (94.3)
Any serious TEAE	63 (25.8)
Any TEAE leading to death	3 (1.2)
Any TEAE leading to study drug discontinuation	64 (26.2)
Any severe TEAE	63 (25.8)
Any TEAE considered related to study drug	224 (91.8)
Any TEAE associated with product complaints	181 (74.2)

- After 12 months, the majority of TEAEs were non-serious and mild-to-moderate in severity
- The most common AEs of special interest were related to the infusion site
- Majority of infusion site AEs were non-serious, were mild-to-moderate in severity, and resolved with or without treatment
- Skin tolerability was assessed using the Infusion Site Evaluation Scale (notable skin reaction: numeric grade of 5, 6, or 7 and a letter grade of D, E, F, or G): 10.2% of subjects had at least 1 observation of numeric grade ≥ 5 and a letter grade $\geq D$

TEAE preferred terms, n (%)	All subjects N = 244
Infusion site erythema	127 (52.0)
Infusion site nodule	70 (28.7)
Infusion site cellulitis	56 (23.0)
Infusion site edema	47 (19.3)
Hallucination	42 (17.2)
Fall	41 (16.8)
Infusion site pain	38 (15.6)
Infusion site reaction	30 (12.3)
Anxiety	29 (11.9)
Infusion site abscess	27 (11.1)
Dizziness	25 (10.2)

Adverse events of special interest, n (%)	All subjects N = 244
Infusion site-related non-infection reactions	200 (82.0)
Infusion site-related infections	86 (35.2)
Falls and associated injuries	74 (30.3)
Hallucinations/psychosis	61 (25.0)
Weight loss	27 (11.1)
Somnolence	12 (4.9)
Polyneuropathy (narrow search)	8 (3.3)

AE, adverse event; TEAE, treatment-emergent adverse event.

Aldred J, et al. *Neurol Ther* 2023; 12:1937–1958 (incl. suppl.).



37

Nyckeln till framgång: god hudvård



- The majority of infusion site adverse events are **non-serious and mild to moderate** in severity

The **most common adverse events** of special interest were **related to the infusion site**



Infusion site **erythema** is the most frequently reported adverse event (51.2% of patients after 12 months of treatment)



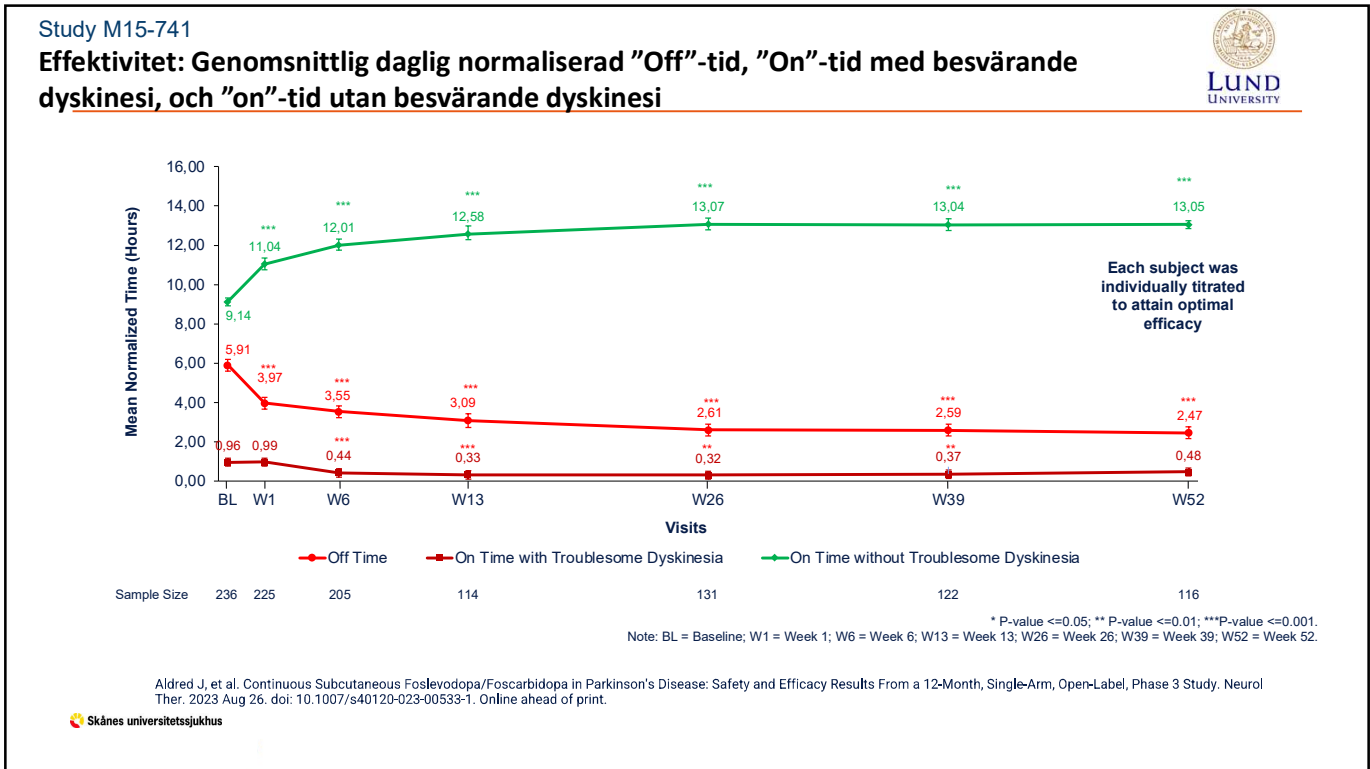
Risk of treatment discontinuation due to infusion site reaction can be reduced by **training strategies** like education on management of skin reactions and Home Health Nurse support

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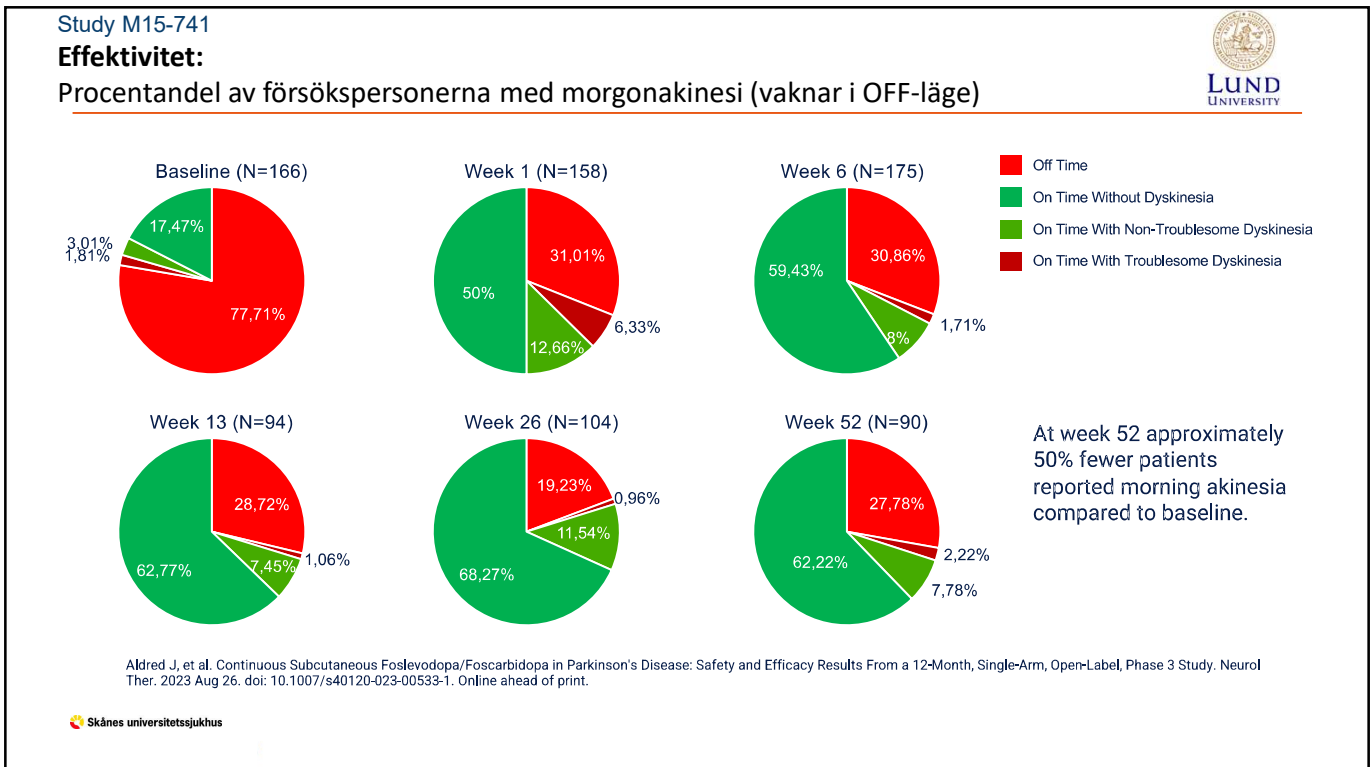
LDp/CDp, foslevodopa/foscarbidopa.



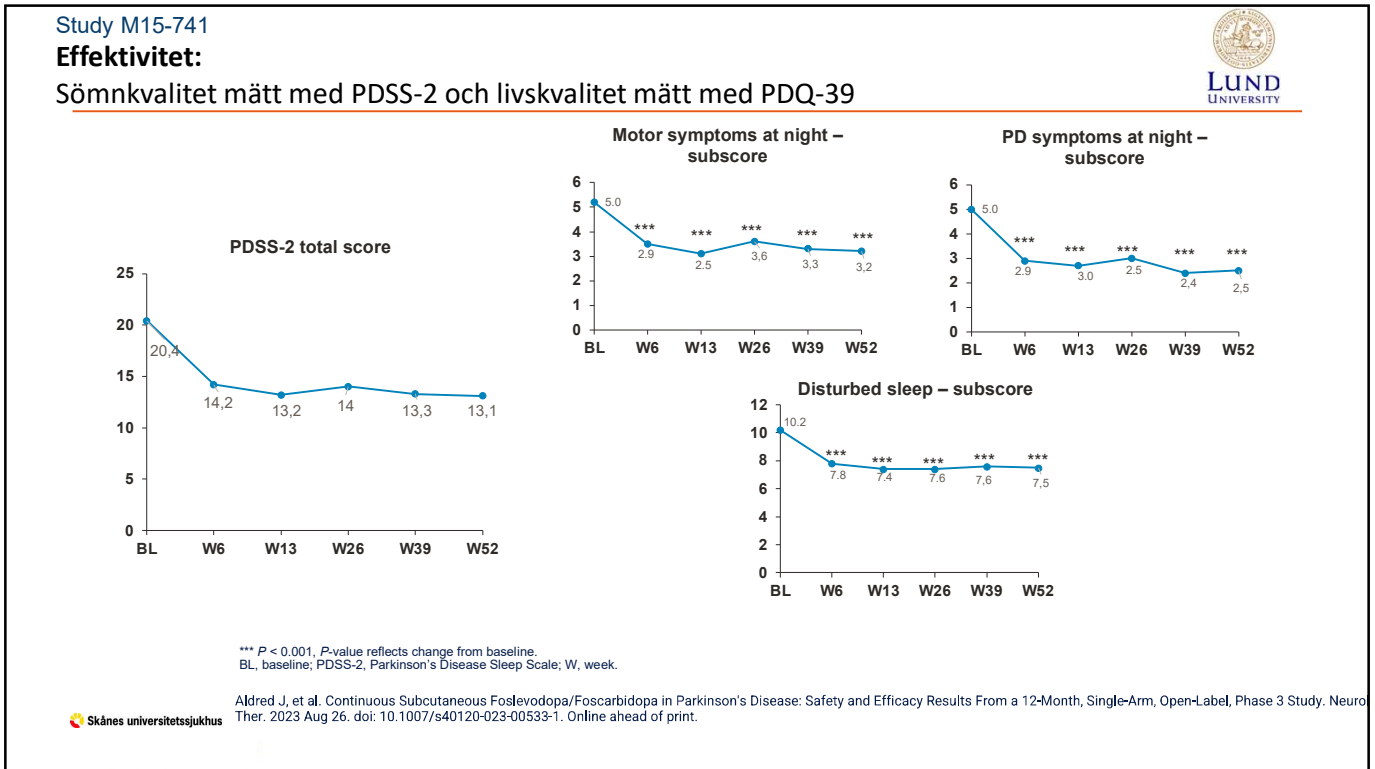
38



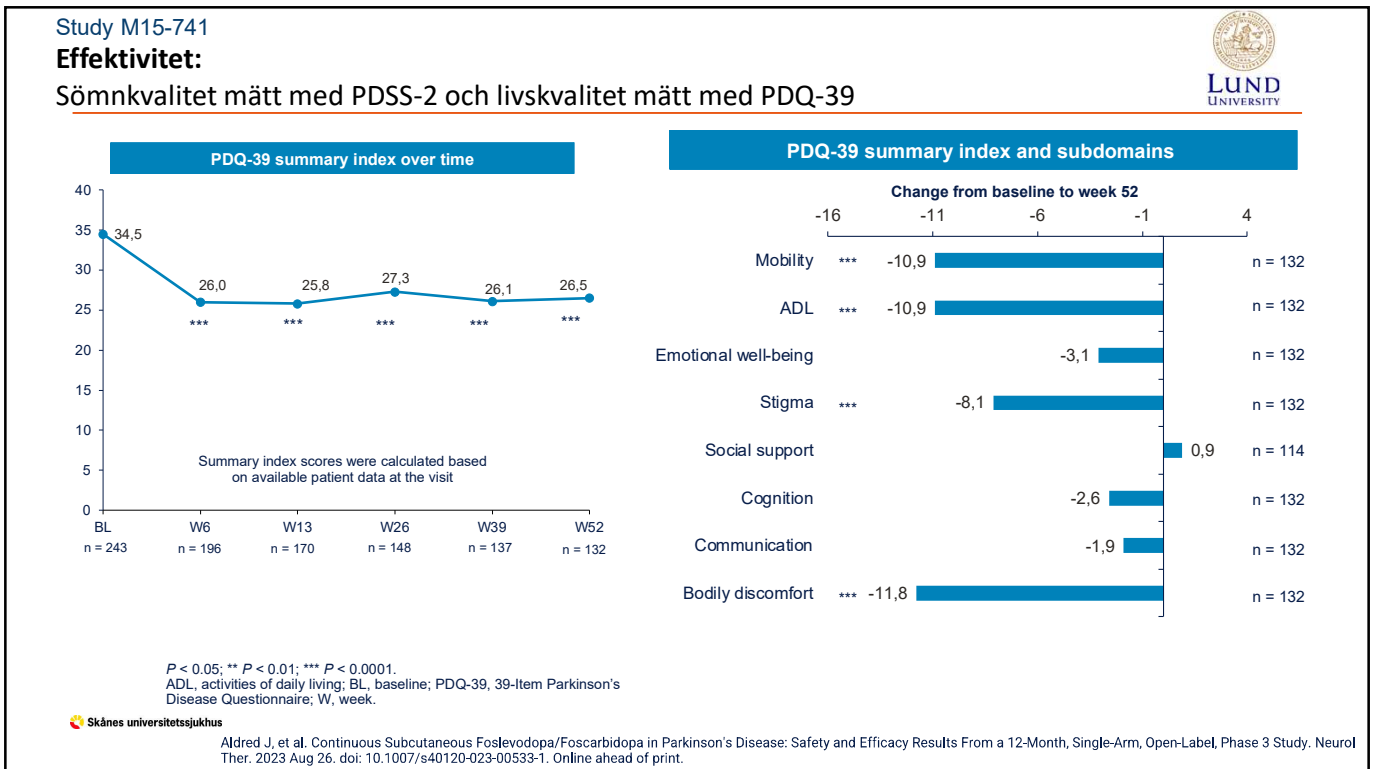
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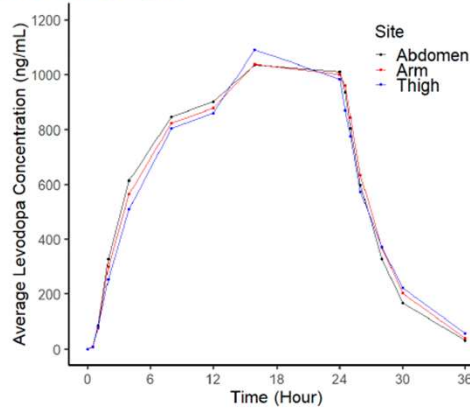


42

Resultat



Figure 2. Comparison of Mean Levodopa PK Profile following SC Infusion to Abdomen, Arm and Thigh



- LD and CD PK parameters following ABBV-951 infusion at different SC infusion sites are presented in Table 1.

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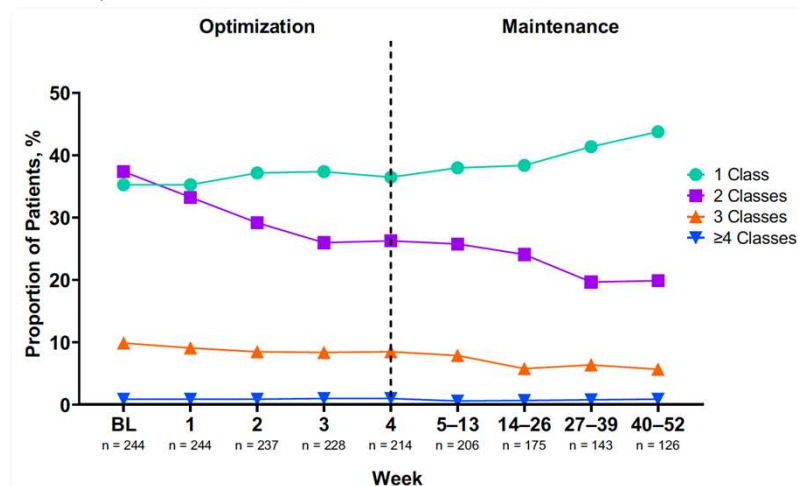
Rosebraugh et al., 2022

43

Resultat



Concomitant Medication Classes Other Than LD-Containing Medications and COMT Inhibitors
The proportion of patients using 2 or more classes of concomitant medications decreased through week 52, and a stable proportion of patients (above 25%) were treated with foslevodopa/foscarbidopa monotherapy during the maintenance period

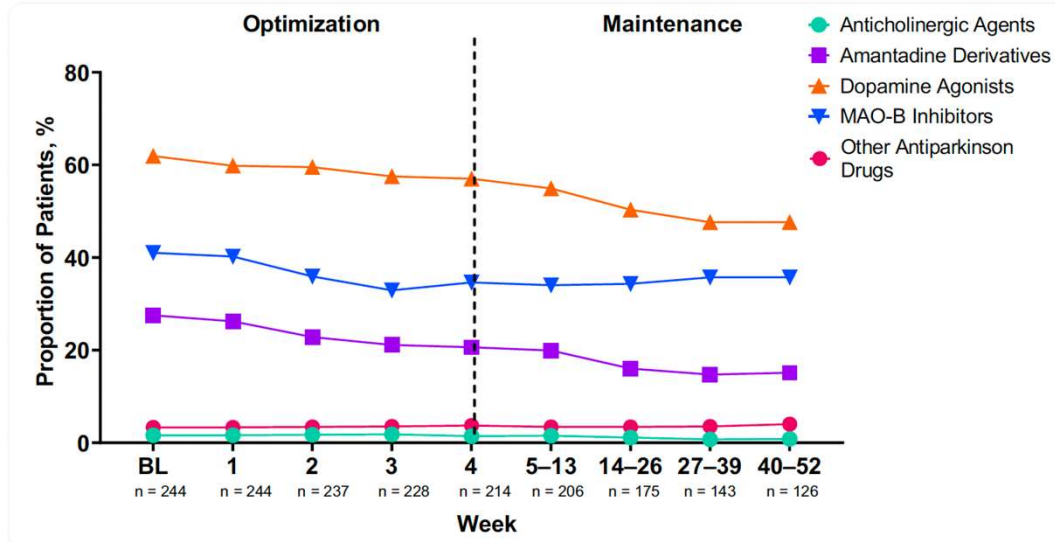


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Santos Garcia et al., 2022

44

Resultat



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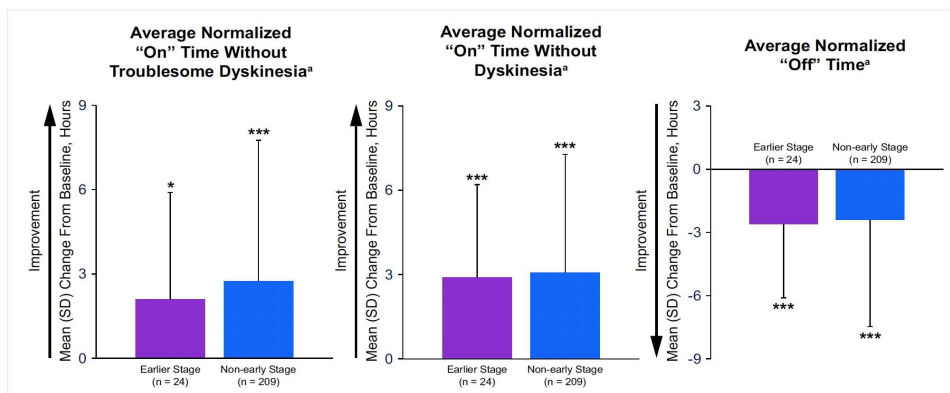
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45

Avancerade PD-terapier: Tidig användning hos unga patienter - Foslevodopa/Foscarbidopa



Figure 4. Improvement From Baseline to Final Available Visit in Motor Fluctuations in Patients With an Earlier Stage and a Non-Early Stage of aPD Treated With LDP/CDP CSCI in the Open-label Trial




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^aEarly stage here defined as aged ≤65 years, Hoehn and Yahr stage score ≤2 ["On" state], and time since motor fluctuations ≤3 years

Antonini et al., 2023

46



Pump-start: Foslevodopa/foskarbidopa




Att tänka på:

Före start: Dagbok/PKG, L-dopatest, Neuropsykologi, rikligt med balanserad information


- Monoterapi: I regel möjligt, men i regel fördelar med kombination
- 16/24h terapi: 24 h terapi regel, men 16 h kan övervägas
- Infusionsdos: Nytitrering kan bli nödvändig hos vissa patienter
- Vid behovsdos: Överväg Madopark Quick eller Apomorfinpenna
- Byt infusionsställe minst 1 gång per dag
- Utbilda patient och anhöriga väl, särskilt avseende hudvård; hygien!
- Efter utskrivning: Såväl firma som klinik bör vara lättillgängliga
- Täta kontakter i början av behandlingen

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47



5-2-1 kriterierna – Delphi consensus



5

times oral levodopa use per day

2

hours of the day with off-symptoms

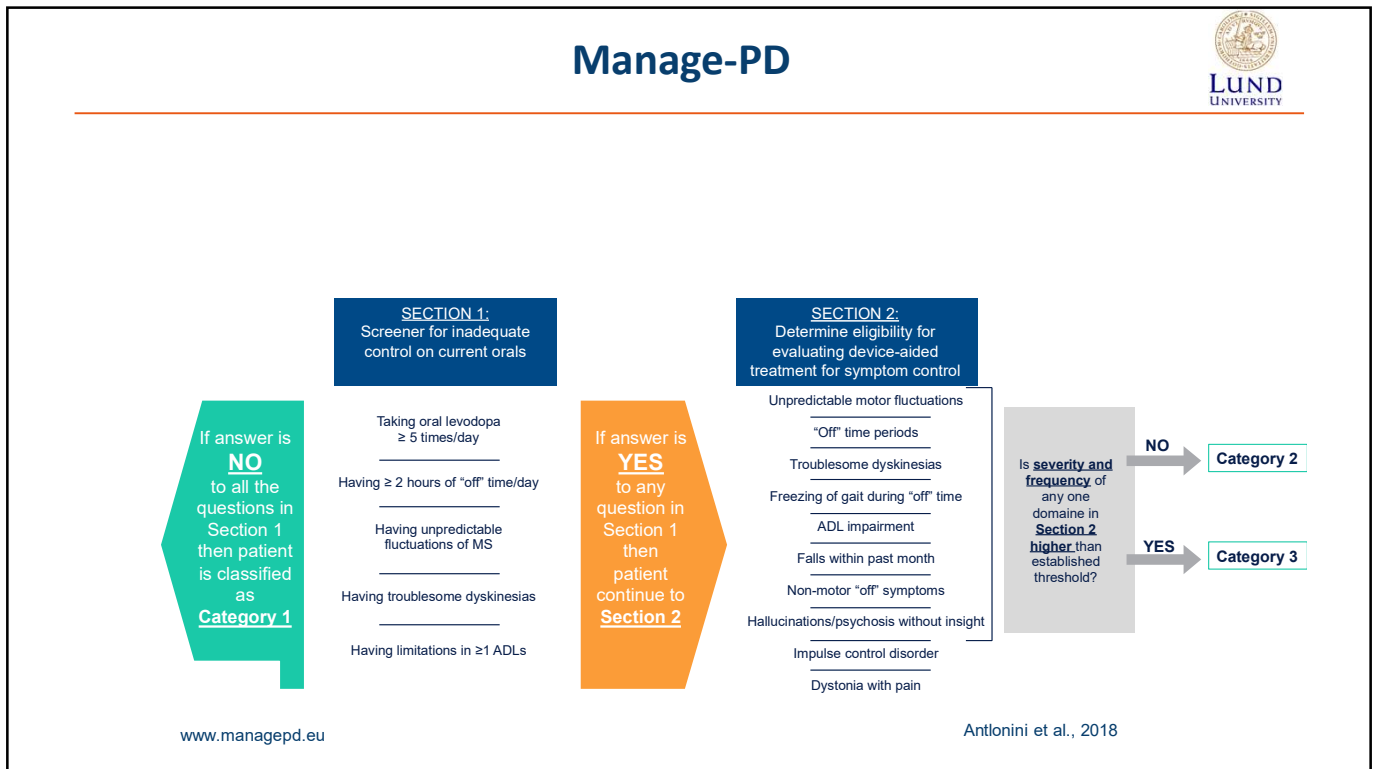
1

hour of the day with troublesome dyskinesia

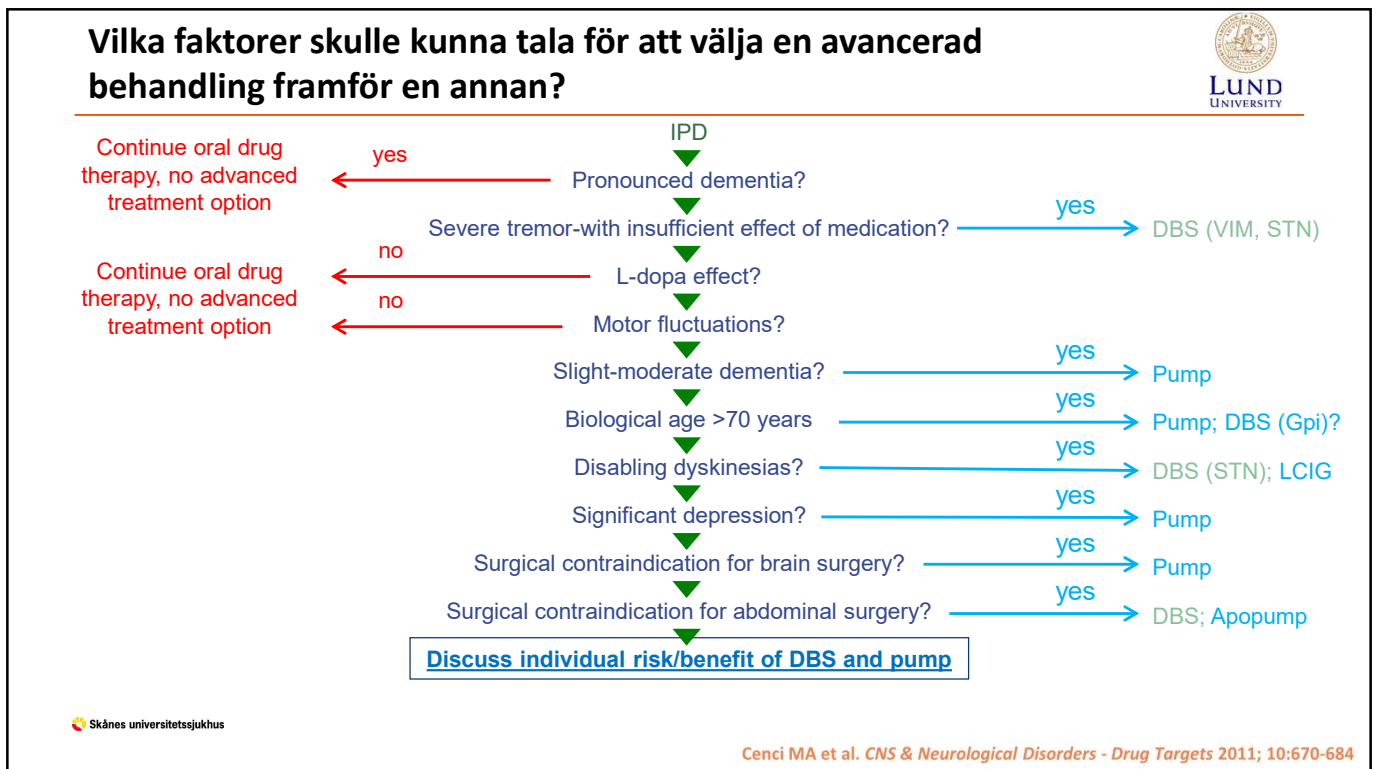
Skånes universitetssjukhus

Antonini et al. *Curr Med Res Opin* 2018; 34:2063-2073

48



49



50

Navigate PD: Faktorer som påverkar beslut om att använda en apparatstödd terapi framför en annan



Symptom	CSAI	STN-DBS	LCIG
Dyskinesias	+	++	+
Slight ongoing hallucinations	+/-	+/-	+/-
Drug-related hallucinations and/or delusions in patient history	+/-	+	+
Marked ongoing hallucinations/psychosis (delirium)	-	-	+/-
Impulse control disorders	-	+	+
Drug-related daytime somnolence	-	+/-	+/-
Maintenance insomnia	+	+	+
Mild cognitive impairment	+/-	+/-	+

*
*
*

++	Presence of symptom strongly supports decision to select
+	Presence of symptom supports decision to select
+/-	Presence of symptom requires further investigation
-	Presence of symptom discourages decision to select

*A different role for Produodopa?

51

Navigate PD: Faktorer som påverkar beslut om att använda en apparatstödd terapi framför en annan



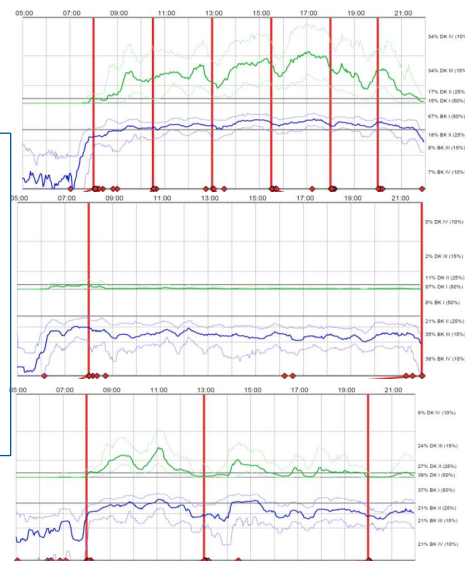
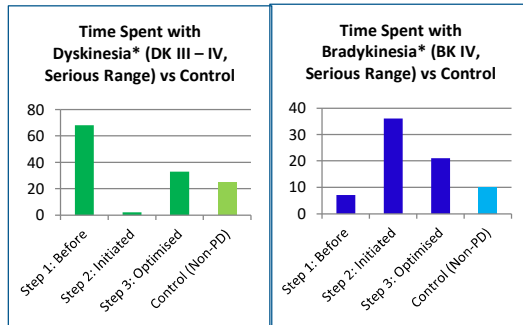
Symptom	CSAI	STN-DBS	LCIG
Dementia	-	-	+/-
Pronounced therapy-refractory depression	+	-	+
Non-motor fluctuations (eg, anxiety, pain, clouded thinking, apathy)	+	+	+
Dysphagia	+/-	-	+/-
Dysarthria	+	-	+
L-DOPA-unresponsive postural and gait problems, falls	+/-	-	+/-
Restless legs	+	+/-	+
Orthostatic hypotension	-	+/-	+/-

++	Presence of symptom strongly supports decision to select
+	Presence of symptom supports decision to select
+/-	Presence of symptom requires further investigation
-	Presence of symptom discourages decision to select

*A different role for Produodopa?

52

Monitorering av motoriska symtom som grund för optimering av pumpens effekt



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<http://www.globalkineticscorporation.com>



53

Sammanfattning



-Vid avancerad PD finns det betydande bevis för att pumpbaserade behandlingar kan förbättra:

- Motoriska symtom
- Icke-motoriska symtom
- Hälsorelaterad livskvalitet

-Selektion av patient och val av terapi av avgörande betydelse

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54



Stort Tack för er uppmärksamhet!