5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 11

Current treatment in neurology (Level 1)

Parkinson's disease: Current treatment (medical and stimulation)

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Treatment of Parkinson´s Disease

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Disclosures

- Performed lectures with honorarium for AbbVie, Britannia, Lundbeck, Nordic Infucare, TEVA, UCB and Zambon
- Participated as an investigator in clinical studies performed by AbbVie and Britannia

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To improve Quality of Life

1. Start Therapy at diagnosis

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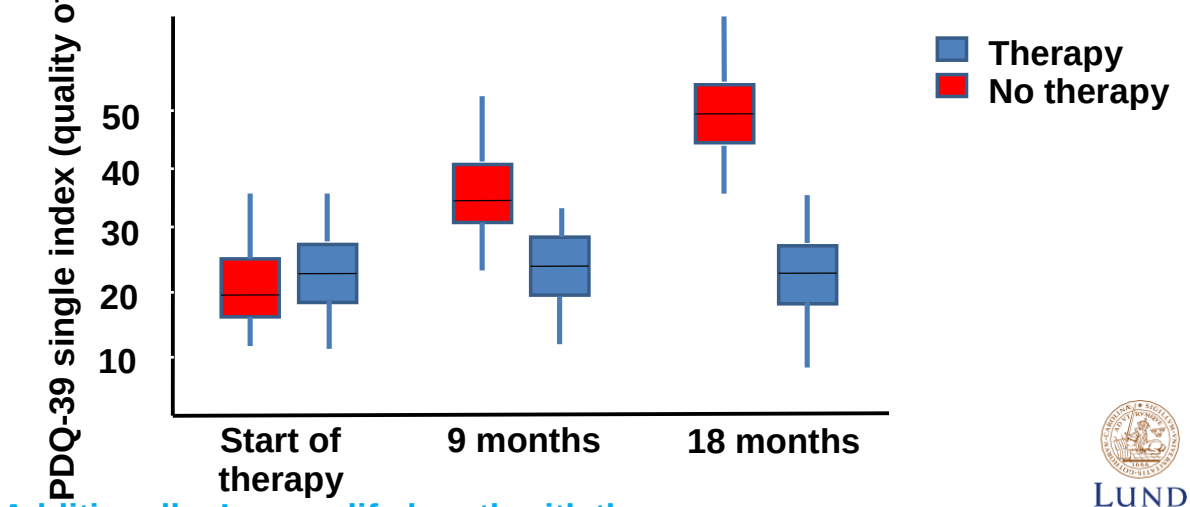
Start Therapy early

PD-Life (198 patients)



Additionally: Longer life length with therapy

Grosset et al., 2007

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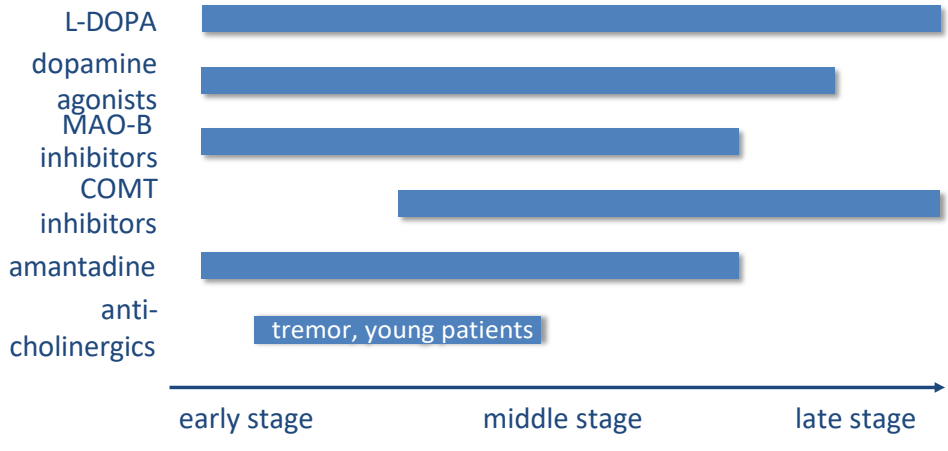
To improve Quality of Life

2. Treat motor symptoms effectively, but try to avoid motor fluctuations and dyskinesias

Use of Medication in PD



HrQoL: Relevance of motor complications and dyskinesias

- Significant negative effect of motor fluctuations ('wearing off') on HRQoL (according to most studies)
- Most severe effect: Nocturnal akinesia
- Effect of dyskinesias on HRQoL unclear;
- Relevance of dyskinesias for HRQoL probably depend on the severity of dyskinesias
- Severe dyskinesias impair quality of life

Pechevis M, et al., 2001
Chapuis S, et al., 2005

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Dominant NMS in early and late disease according to patients

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

Parkinson's Disease Symptoms: The Patient's Perspective

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

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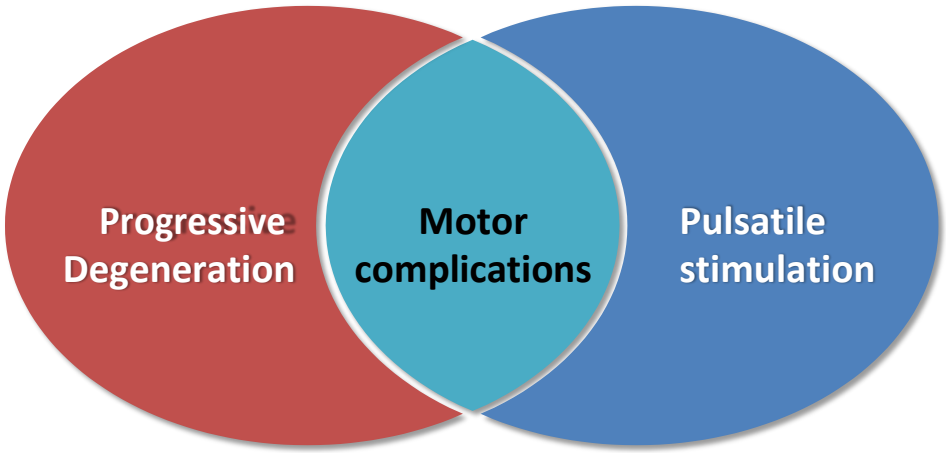
TABLE 3. *Rank of the 24 most bothersome PD related symptoms/conditions in 173 advanced patients with more than 6 yr of disease duration*

Rank	Symptom/condition	Total score	First choice %	Second choice %	Third choice %	3-Choice complaint prevalence (%)
1	Fluctuating response to medication	115	15.0	8.1	5.2	28.3
2	Mood	96	7.5	12.1	8.7	28.3
3	Drooling	85	10.4	6.9	4.0	21.4
4	Sleep	83	9.8	5.2	8.1	23.1
5	Tremor	67	8.1	5.2	4.0	17.3
6	Pain	60	6.4	5.8	4.0	16.2
7	Bowel problems	46	4.0	4.0	6.4	14.5
8	Urinary problems	40	2.9	5.2	4.0	12.1
9	Falls	39	4.0	4.0	2.3	10.4
10	Appetite/weight	36	2.3	4.6	4.6	11.6
11	Slowness	34	3.5	3.5	2.3	9.2
12	Fatigue	31	2.3	2.9	5.2	10.4
13	Sexual dysfunction	29	4.6	1.2	0.6	6.4
14	Hallucinations/delusions	26	2.3	2.9	2.3	7.5
–	Restless legs	26	1.7	2.9	4.0	8.7
–	Speech	26	1.2	3.5	4.6	9.2
17	Compulsive behavior	25	3.5	1.2	1.7	6.4
18	Handwriting	23	2.3	1.7	2.9	6.9
–	Loss of smell/taste	23	1.7	1.7	4.6	8.1
–	Sweating	23	1.2	2.9	4.0	8.1
21	Stiffness	22	1.2	3.5	2.3	6.9
–	Swallowing	22	0.0	4.6	3.5	8.1
23	Freezing	21	2.3	1.7	1.7	5.8
–	Memory	21	1.2	1.7	5.2	8.1

Politis et al., 2010

Two Key Factors Interact in the Development of Motor Fluctuations



Olanow et al., 2004

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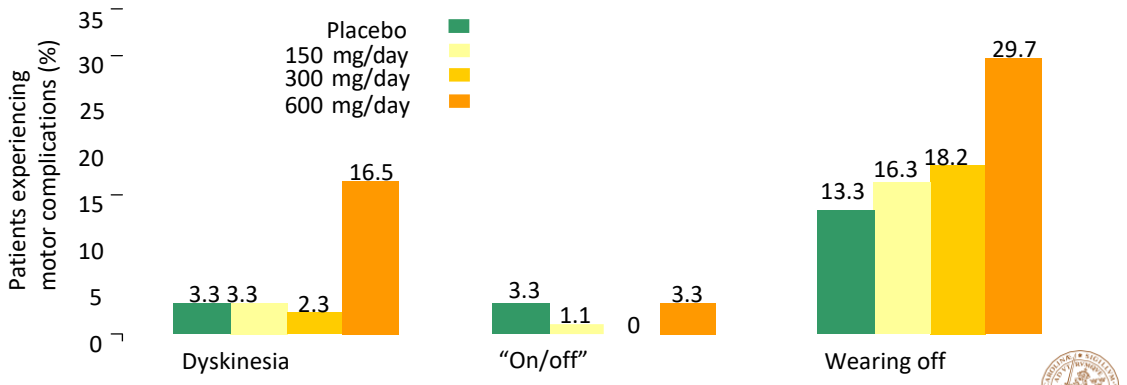
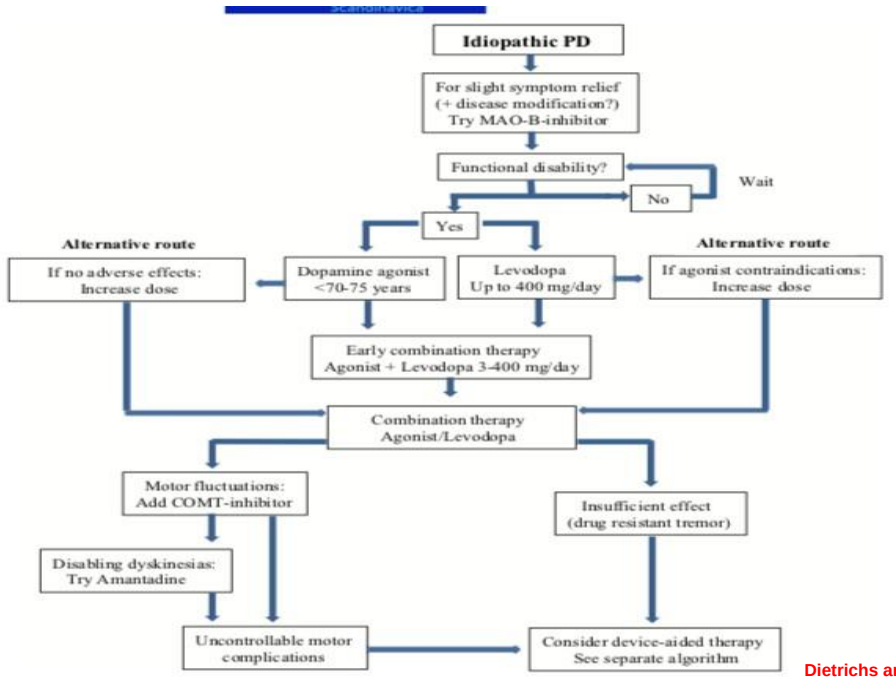
Results from the ELLDOPA trial showed a positive relationship between L-dopa dose and motor complications



ELLDOPA, Earlier vs Later LevoDOPA trial
The Parkinson Study Group. , 2004

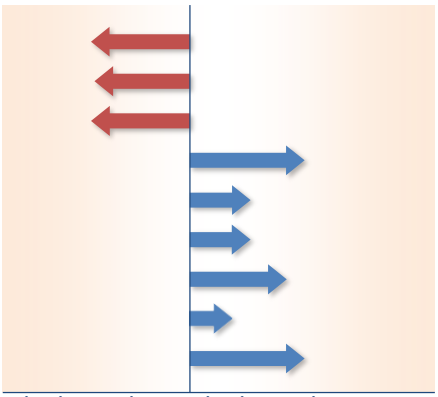


Dietrichs and Odin, 2017

Risk of Motor Complications and Other Side Effects

Dyskinesia
Motor fluctuations
Dopamine dysregulation syndrome
Oedema
Drowsiness
Impulse control disorders
Hallucinations
Nausea
Fibrosis*

*ergot agonists vs levodopa



Antonini et al., 2009

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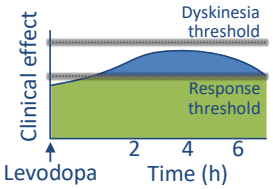
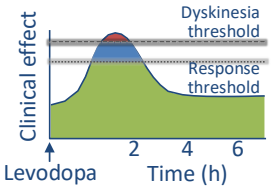
Increase in Fluctuations and Dyskinesias Due to Decreasing Duration of L-dopa

The therapeutic window gradually narrows

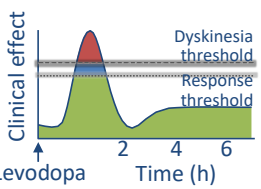
Risk of complications
Target response
Inadequate symptom control



- Smooth, extended duration of target clinical response
- Low incidence of dyskinesias



- Diminished duration of target response
- Increased incidence of dyskinesias

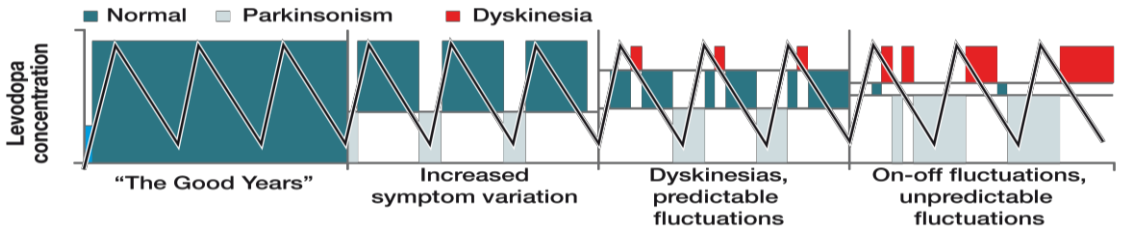


- Short duration of clinical response
- "On" time is associated with dyskinesias

After Obeso JA et al., 2009

Continuous Dopaminergic Stimulation

The therapeutic window gradually narrows



Establishing stable plasma levels from commencement of therapy onwards could reduce the development of fluctuations and dyskinesias.

Start non-oral therapies at the right time!

After Nyholm D et al., 2007

Motor Complications

Supreme principle in treatment of motor complications:

Adequate substitution of dopamine

with simultaneous

reduction in pulsatile dopaminergic stimulation of the striatum!

- fractionation of levodopa medication
- shortening of dosing intervals
- moderate decrease in individual doses
- combination with COMT and MAO inhibitors (increases LD bioavailability)
- combination of dopamine agonists, amantadine (additive active substances)
- continuous administration of levodopa / carbidopa or dopamine agonists (Apomorphine pump) bypassing gastric transit

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Parkinson Tremor: Therapy

	Classic Parkinson´s tremor	Rest and postural tremor of different frequency	Isolated action tremor
1	**Control of akinesia and rigidity** with dopaminergics or other antiparkinson drugs. When these core symptoms have been satisfactorily managed, the following steps are recommended **before L-dopa and agonists are increased**		
2	primidone	propranolol, primidone	propranolol, primidon
3	propranolol, clozapine	clozapine	topiramat, gabapentin
4	deep brain stimulation (STN, rarely VIM)	deep brain stimulation (STN, rarely VIM)	

dgn.org

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Newer Options: Safinamide

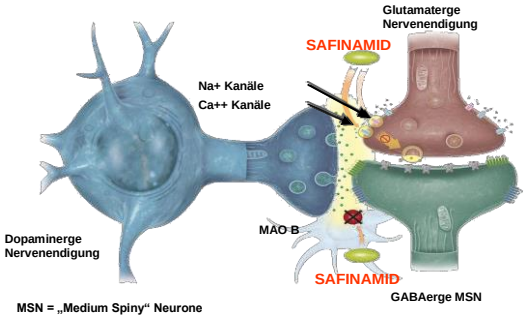
Dopaminergic

Monoaminooxidase B (MAO-B)

Non-dopaminergic:

Glutamate Release

- **Pharmaceutical form: tablet for once-daily oral administration in one of the following two doses:**
- **50 mg**
- **100 mg**



Caccia C. et al., Neurology 2006, 67

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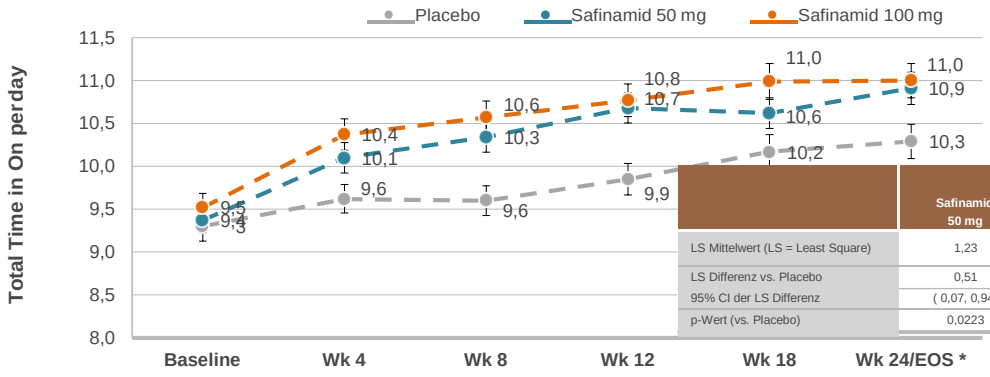
Newer Options: Safinamide



	Safinamid 50 mg	Safinamid 100 mg
LS Mittelwert (LS = Least Square)	1,23	1,28
LS Differenz vs. Placebo	0,51	0,55
95% CI der LS Differenz	(0,07, 0,94)	(0,12, 0,99)
p-Wert (vs. Placebo)	0,0223	0,0130

Study 016: Mean change of On-time

Borgohain R. et al., 2014

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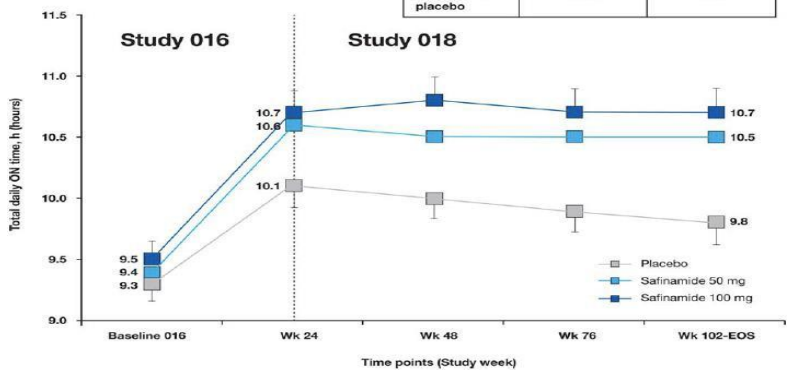
Newer Options: Safinamide

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



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Effect on ON time persist over further 18 month

Newer Options: Safinamide

Most patients (74%) had no or mild dyskinesias (DRS ≤ 4) at baseline, leaving little room for improvement.

Therefore, a post-hoc analysis of DRS data was performed on 242 patients who had moderate to severe dyskinesias when enrolled in study 016 (total DRS> 4).

	Placebo (n=69)	Safinamid 50 mg/Tag (n=78)	Safinamid 100 mg/Tag (n=74)
Dyskinesia Rating Scale (DRS)- value in month 24	7,0 ± 3,53	6,6 ± 3,54	6,4 ± 4,45
LS Diff vs. Placebo	0,0	**- 0,73**	**- 1,22**
p-Value vs. Placebo	N/A	0,1999	**0,0317**

Borgohain R. et al., 2014

National Guidlines

–

Support for management and leadership

112 pages

National Guidelines

Indicators and basis for assessments

145 pages

National Guidelines

Summary - with areas for improvemen

93 pages

Socialstyrelsen

Nationella riktlinjer för vård vid MS och Parkinsons sjukdom

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Swedish National Guidelines for PD

Priority levels

Priority 1-4	should be provided
Priority 5-7	can be provided
Priority 8-10	can in exceptional cases be provided
FoU	should be tested in clinical studies
Not do	

Evidence base or consensus

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

Swedish National Guidelines for PD

Treatment of Parkinson´s disease with motor complications in spite of optimized L-dopa therapy

Healthcare should:
-offer additional treatment with MAO-B inhibitors, dopamine agonists, or COMT inhibitors to people with Parkinson's disease with motor complications despite optimal treatment with levodopa (Priority 2).

Healthcare can:
-offer additional treatment with safinamide or amantadine to people with Parkinson's disease with motor complications despite optimal treatment with levodopa (Priorität 5).

Healthcare can in exceptional cases:
-offer change of treatment to long-acting L-dopa to people with Parkinson's disease with motor complications despite optimal treatment with levodopa (Priorität 10).

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

Future

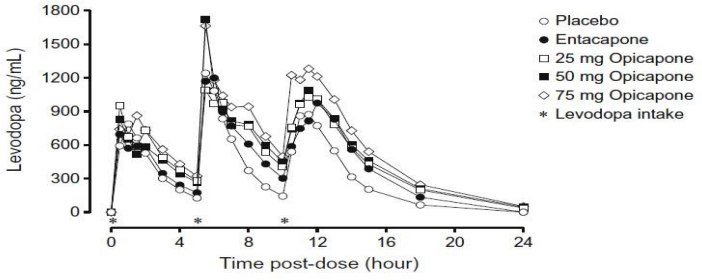
Description	Route	Status
Extended release LD-CD (IPX066)	oral	Approved
Gastro retentive LD-CD Accordion Pill	oral	Phase 3
Gastro retentive extended release LD-CD DM-1992	oral	Phase 2
LD-Entacapone-CD Intestinal Gel	intestinal	Approved/Sweden
Subcutaneous LD-CD	s.c.	Phase 2
Inhaled LD (CVT 301)	pulmonary	Phase 3
COMT-inibitor Opicapone	oral	Approved/ EMA
COMT-inhibitor ODM-104	oral	Phase 2
LD-CD Microtablets	oral	Approved / Sweden

New

Approved 2016
Available in two dosages
50 mg
25 mg

Administration at bedtime

Opicapone
A COMT inhibitor



Rocha et al., 2014

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Reduction of off time: Non-inferior to entacapone

Randomised, double-blind Controlled Trial N= 590

- Placebo
- 200 mg Entacapone
- 5 mg Opicapone
- 25 mg Opicapone
- 50 mg Opicapone

Treated for 14-15 weeks

Ferreira et al., 2015

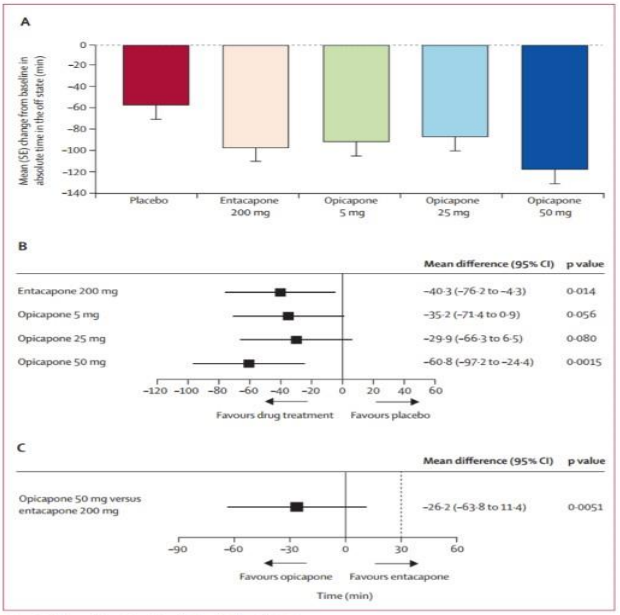
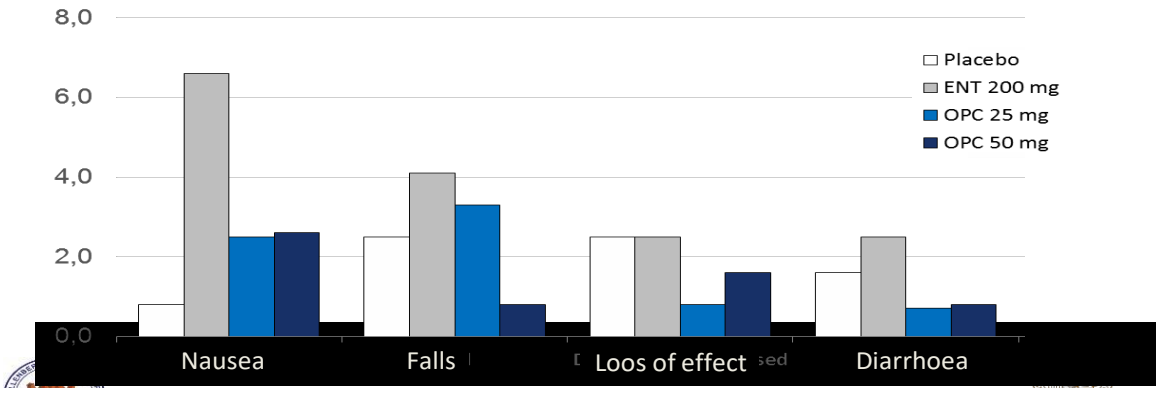


Figure 2: **Change from baseline in time in the off state**
(A) Mean (SE) change in absolute off time in the full analysis set (primary efficacy outcome). (B) Superiority test for the difference in mean change in absolute off time versus placebo in the full analysis set. (C) Non-inferiority test for the difference in mean change in absolute off time versus entacapone in the per-protocol set. The dashed line in (C) shows the non-inferiority margin.

Newer Options: Opicapone Opicapone vs Entacapone (Bipark I)

Opicapone is better tolerated than Entacapone



Ferreira et al., 2016

Rytary®

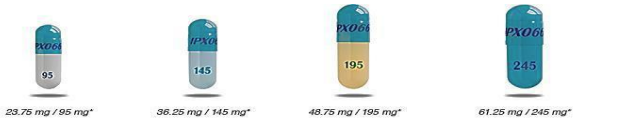
Available in different dosages:
23.75mg/95mg
36.25/145 mg
48.75/195mg
61.25mg/245mg

carbidopa: levodopa 1:4 ratio

New

Extended release CD-LD
IPX 066

oral/approved



New

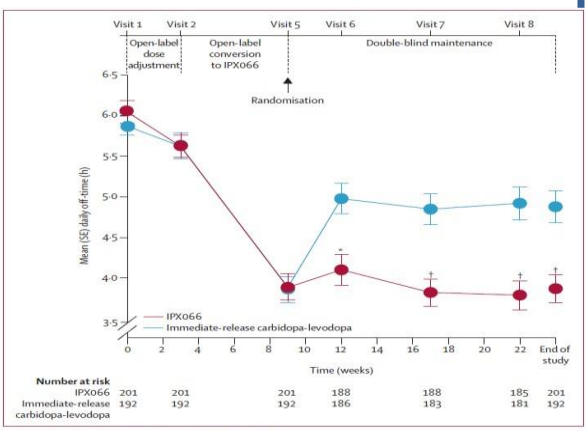


Figure 2: **Mean daily off-time throughout the study**
*p=0·0004 *vs* immediate-release carbidopa-levodopa group by ANCOVA. †p<0·0001 *vs* immediate-release carbidopa-levodopa group by ANCOVA.

Extended release CD-LD
IPX 066

ADVANCE-PD study:
Comparison IR vs ER

Hauser, Hsu, et al., 2013

Daily OFF -1.17 hrs

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New

LD-CD Microtablets

- For individualized dosing and dose fractionation
- Size: 3 mm diameter
- Used with dose dispenser MyFID
  - Memory, alarm and diary function
- Approved by Swedish MPA (LV) 2014, TLV 2016
- Recently approved by EMA 2016, reg in 13 EU countries

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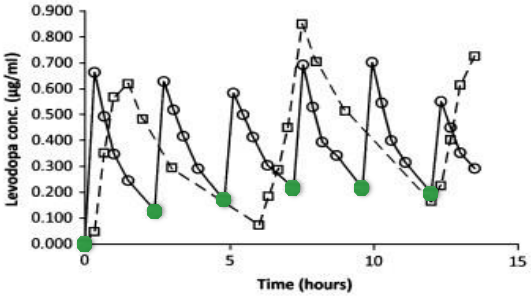
New



LD-CD Microtablets

6 daily doses of microtablets
versus 3 doses LDyCD/Entacapone

Nyholm et al., 2012
Nyholm et al., 2013

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Description	Route	Status
Apomorphine	s.c.	TOLEDO trial
Apomorphine dry powder (VR040)	pulmonary	Phase 2
Apomorphine (APL-130277, Cynapsus)	sublingual	Phase 3
Adenosine A2 receptor antagonists		
Istradefylline	oral	licensed in Japan 2013 Phase 3
Preladenant (A2a antagonist)	oral	stopped
Tozadenant (A2a antagonist)	oral	Phase 3 (TOZ-PD)
Caffeine (A2 rec antagonist)		CALM-PD retrospective analysis
Dyskinesia		
Amantadine ER ADS 5102	oral	Phase 2
Mavoglurant (mGlut5 rec modulator)	oral	stopped (SE)
OTHERS		
Pimavanserin (Nuplazid)	oral	PD psychosis, approved in USA, no effect on DA transmission
Oxycodone-naloxone	oral	pain in PD, no obstipation
Calcium-channel blocker		
Isradipine	oral	Phase III (STEADY-PD)/2018

To improve Quality of Life

3. Detect and treat motor fluctuations and dyskinesias effectively when they appear

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Use advanced therapies against motor complications when needed

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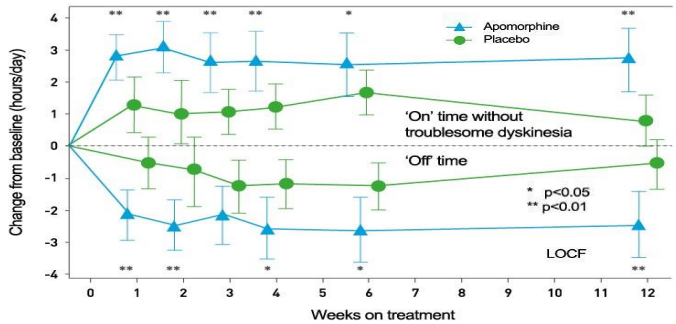
Main results

TOLEDO PROGRAMME



Number of observations

Apomorphine	53	52	52	52	52	52						53
Placebo	53	48	48	48	48	48						52

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)

Safety and tolerability	APO (n=54)	Placebo (n=53)
	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%)

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

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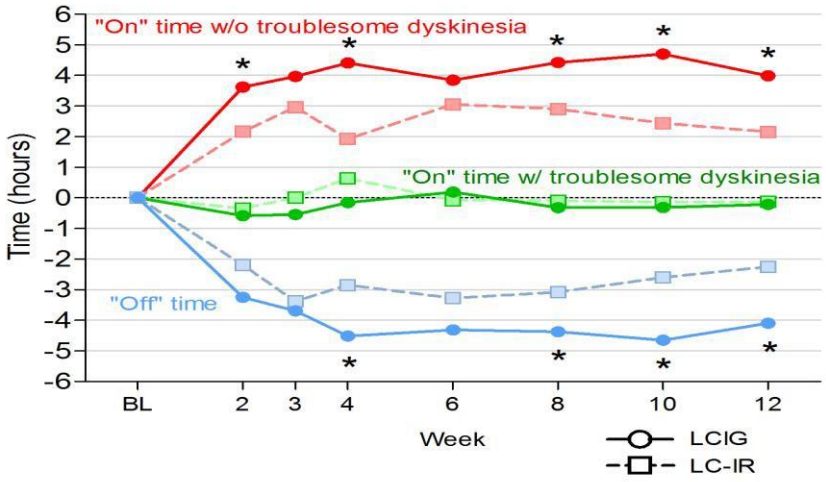
Katzenschlager et al., 2018

Change from Baseline in "Off" Time, "On" Time, "On" Time Without Troublesome Dyskinesia, and "On" Time With



S187.3.001 and 002

Olanow et al., 2013

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DBS versus best medical therapy: randomised, controlled trial comparing 6-month outcomes

- **255 patients with PD** (Hoehn and Yahr stage ≥2 while not taking medications); 25% were aged ≥70 years
- **Randomised to receive:**
  - Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (n=60) or globus pallidus (n=61)
  - Best medical therapy (BMT) (n=134)

Time	Best Medical Therapy (n = 134) Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Deep Brain Stimulation (n = 121) Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Best Medical Therapy Minus Deep Brain Stimulation Mean Difference (95% CI)	*P* Value[a]
On, h/d[b]								
Without troublesome dyskinesia	7.0 (2.9)	7.1 (3.3)	0 (–0.5 to 0.5)	6.4 (2.7)	10.9 (4.2)	4.6 (3.8 to 5.3)	–4.5 (–5.4 to –3.7)	<.001
With troublesome dyskinesia	4.2 (3.1)	3.9 (3.3)	–0.3 (–0.8 to 0.3)	4.4 (3.1)	1.8 (3.0)	–2.6 (–3.3 to –2.0)	2.3 (1.5 to 3.2)	<.001
Off, h/d[b]	5.6 (2.9)	5.7 (2.8)	0 (–0.4 to 0.5)	5.9 (2.6)	3.4 (3.1)	–2.4 (–3.1 to –1.8)	2.5 (1.7 to 3.2)	<.001
Asleep, h/d	7.1 (1.7)	7.3 (2.0)	0.3 (0 to 0.6)	7.3 (1.8)	7.7 (2.0)	0.4 (0 to 0.7)	–0.1 (–0.6 to 0.4)	.66

Abbreviation: CI, confidence interval.
[a] Test for the change scores from baseline to 6 months between the best medical therapy group and the deep brain stimulation group.
[b] "On" and "off" time are described in the "Study Procedures" section of the "Methods."

Weaver FM, et al. JAMA. 2009 Jan 7;301(1):63-73.

Results

- Patients who received DBS gained a mean of 4.6 h/d of **on time without troubling dyskinesia** compared with 0 h/d for patients who received BMT
- **Motor function improved** significantly (p<0.001) with DBS vs BMT
- Significant improvements in summary measure of **quality of life** (assessed with PDQ-39) with DBS vs BMT

Swedish National Guidelines for PD

Treatment conference before advanced Parkinson treatment

Healthcare should:

offer people receiving insufficient efficacy of oral, transdermal or intermittent subcutaneous drug treatment, an assessment at a treatment conference with people who have specialist knowledge about movement disorders and experience of all three advanced treatments for decisions about advanced Parkinson's Treatment (Priorität 2).

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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Swedish National Guidelines for PD

Healthcare should:

- offer DBS - that is treatment with continuous high-frequency electrode stimulation in the brain - in people who receive inadequate efficacy of oral, transdermal or intermittent subcutaneous drug treatment (Priority 1)
- offer treatment with pump-delivered L-dopa/carbidopa gel to people who receive inadequate efficacy of oral, transdermal or intermittent subcutaneous drug treatment (Priority 3)
- offer apomorphine pumps to people who receive inadequate efficacy of oral, transdermal or intermittent subcutaneous drug treatment (Priority 4)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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Table 3. Estimated Treatment Costs for additional 500 patients with advanced care in a 5-year horizon

	Additional no of patients	*Cost for avanced 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

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Review

Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program

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How do I recognize and refer for specialist assessment a patient in whom the dosage and adjustment of oral/transdermal therapies cannot further improve mobility and quality of life?

Non-invasive therapies may be judged insufficient when:

- QOL becomes inadequate due to motor fluctuations with or without dyskinesias
- The clinician and patient agree that non-invasive therapy alone is no longer effective

Adequate trial of noninvasive therapies includes:

L-DOPA and, unless contraindicated, dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors

Broadly, referral to a specialist should be considered if:

L-DOPA is required 5 times daily, although the number of doses is not relevant if tolerated by the patient and an adequate reduction in "off" time is achieved

Odin et al, Park Rel Dis 2015: 1133-1144.

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How do I recognize and refer for specialist assessment a patient in whom the dosage and adjustment of oral/transdermal therapies cannot further improve mobility and quality of life?

Individuals with > 1 to 2 h of "off" time during the awake part of the day despite optimized oral/transdermal medical management:

Should be considered candidates for device-based therapies. The severity and quality of a patient's "off" periods are equally important. Some patients with marked "off" symptoms should be considered for referral even if their overall "off" duration appears acceptable

Motor fluctuations accompanied by troublesome dyskinesias not controlled by addition of amantadine (100-400 mg/day,

if available), despite multiple attempts to achieve a patient acceptable response to non-invasive or transdermal therapies are usually considered an indication for referral for device-aided therapy

Odin et al, Park Rel Dis 2015: 1133-1144.

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Figure 2. Ranking of Clinically Important Motor, Non-motor and Functional Characteristics That Define a Patient Suspected to Have APD

Motor	Non-motor	Function
1. Moderate level of troublesome motor fluctuations	1. Mild level of dementia	1. Repeated falls* despite optimal treatment
2. At least 2 hours of the day with off symptoms	2. Non-transitory troublesome hallucinations	2. Needs help with ADLs at least some of the time
3. At least 1 hour of the day with troublesome dyskinesia	3. Moderate level of psychosis	3. Not able to perform complex tasks — most of the time
4. Moderate level of dyskinesia	4. Non-motor symptom fluctuations	4. Moderate impaired mobility
5. Troublesome dysphagia	5. Moderate level of nighttime sleep disturbances	
6. Daily oral levodopa doses "5 times a day"		

Severity definitions were provided by the panelists — **Mild:** Detectable to clinician but not interfering with daily life (not or minimally troublesome to the patient); **Moderate:** Detectable to clinician and Influences daily life (troublesome to the patient); **Severe:** Detectable to clinician and significantly influences daily life (very troublesome to the patient);*Repeated falls was defined as more than 1 fall.

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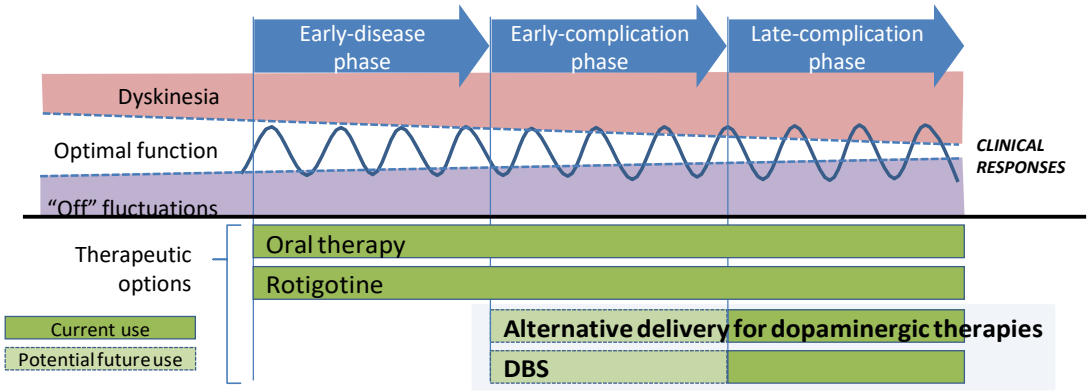
Device-Aided Therapies in PD: Selecting the Right Timing



Could initiating device-aided therapies at an earlier stage than current clinical practice be even more beneficial to some patients?

Adapted from Timpka J, *et al.* (2016) Mov Disord Clin Pract, 1-9.

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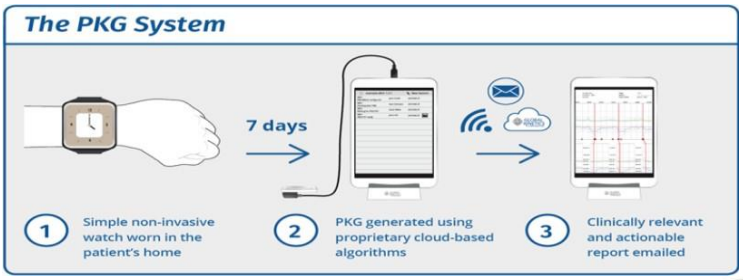
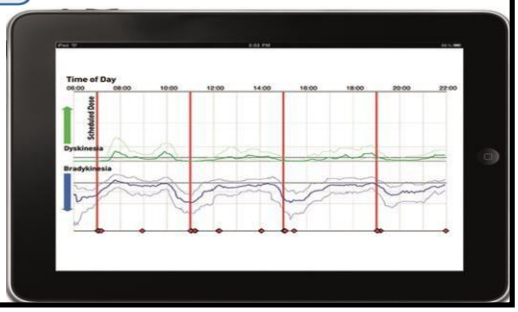
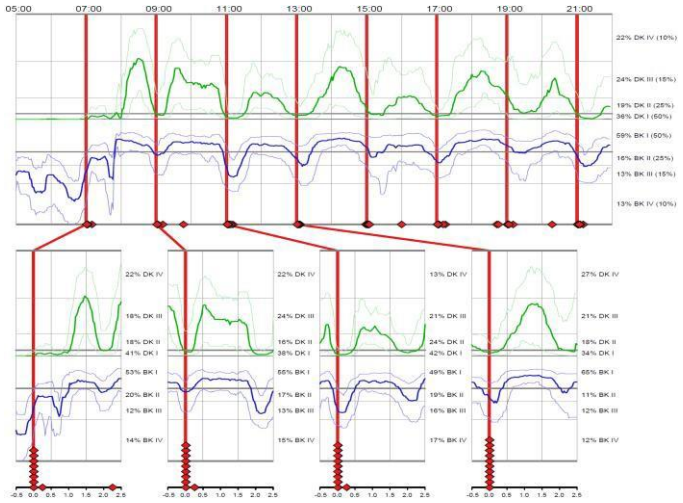
Monitoring PD: PKG





PKG: Indication for advanced therapy



- 8 doses L-dopa per day
- Oral medications causing peak dose DK
- BK with a number of unpredictable “off” periods
- Extreme fluctuations from “on” with BK IV to “off” DK IV

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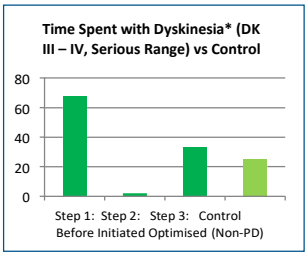
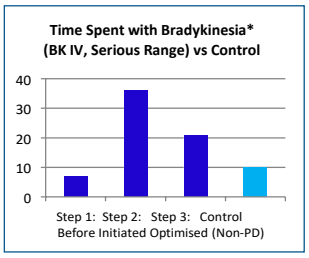
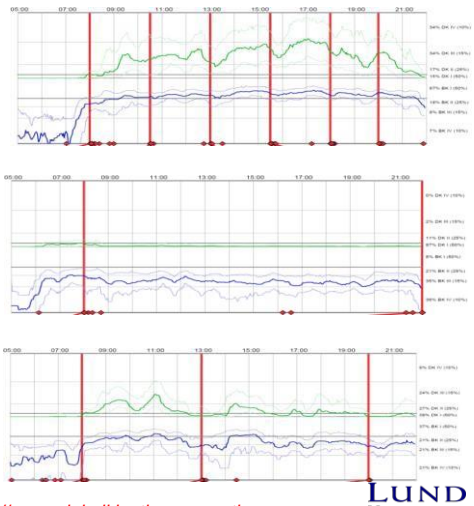
Monitoring PD: LCIG Effect







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To improve Quality of Life

4. Detect and treat non-motor symptoms

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Non-motor symptoms questionnaire

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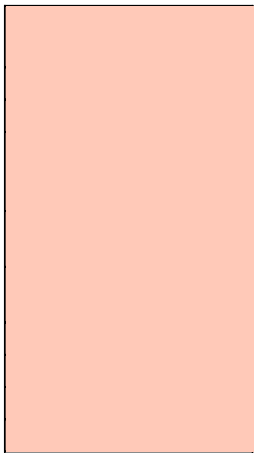
Faculty of Medicine



PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No		Yes	No
1. Dribbling of saliva during the daytime	☐	☐	16. Feeling sad, 'low' or 'blue'	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐	17. Feeling anxious, frightened or panicky	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐	18. Feeling less interested in sex or more interested in sex	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐	19. Finding it difficult to have sex when you try	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐	20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
6. Bowel (fecal) incontinence	☐	☐	21. Falling	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐	22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐	23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
9. Getting up regularly at night to pass urine	☐	☐	24. Intense, vivid dreams or frightening dreams	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐	25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐	26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐	27. Swelling of your legs	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐	28. Excessive sweating	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐	29. Double vision	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐	30. Believing things are happening to you that other people say are not true	☐	☐

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1984.

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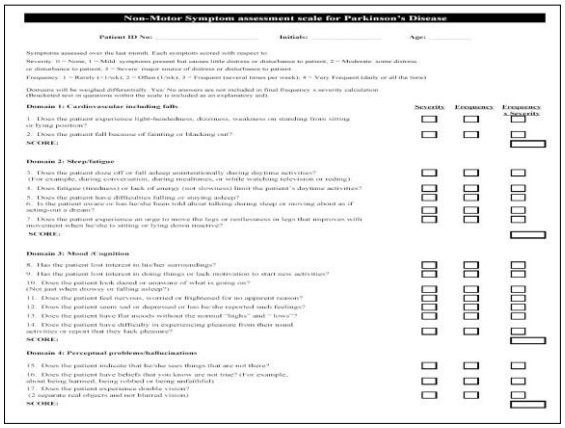
Chaudhuri et al, 2006

Non-motor symptoms scale (NMSS)

30 questions, 9 domains, degree x frequency



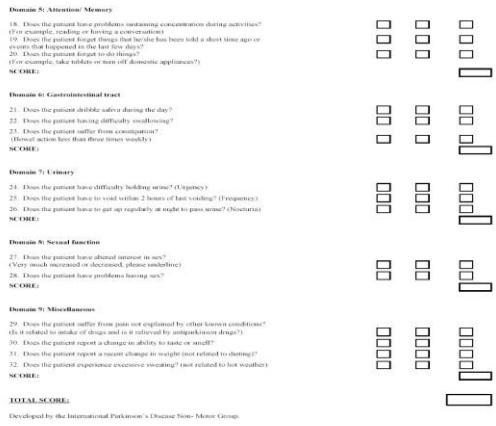
Non-Motor Symptom assessment scale for Parkinson's Disease

Patient ID No: Initials: Age:

Symptoms assessed over the last month. Each symptom scored with respect to:
Severity: 0 = None, 1 = Mild symptoms present but causes little distress or disturbance to patient, 2 = Moderate some distress or disturbance to patient, 3 = Severe major source of distress or disturbance to patient
Frequency: 1 = Rarely (<1/wk), 2 = Often (1/wk), 3 = Frequent (several times per week), 4 = Very Frequent (daily or all the time)

Domains will be weighed differentially. Yes/ No answers are not included in final frequency x severity calculation
(Bracketed text in questions within the scale is included as an explanatory aid)

	Severity	Frequency	Frequency x Severity
Domain 1: Cardiovascular including falls			
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading)	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Is the patient aware or has he/she been told about talking during sleep or moving about as if acting-out a dream?	☐	☐	☐
7. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐
Domain 3: Mood /Cognition			
8. Has the patient lost interest in his/her surroundings?	☐	☐	☐
9. Has the patient lost interest in doing things or lack motivation to start new activities?	☐	☐	☐
10. Does the patient look dazed or unaware of what is going on? (Not just when drowsy or falling asleep?)	☐	☐	☐
11. Does the patient feel nervous, worried or frightened for no apparent reason?	☐	☐	☐
12. Does the patient seem sad or depressed or has he/she reported such feelings?	☐	☐	☐
13. Does the patient have flat moods without the normal "highs" and "lows"?	☐	☐	☐
14. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	☐	☐	☐
SCORE:			☐
Domain 4: Perceptual problems/hallucinations			
15. Does the patient indicate that he/she sees things that are not there?	☐	☐	☐
16. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	☐	☐	☐
17. Does the patient experience double vision? (2 separate real objects and not blurred vision)	☐	☐	☐
SCORE:			☐



Domain 5: Attention/ Memory			
18. Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)	☐	☐	☐
19. Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?	☐	☐	☐
20. Does the patient forget to do things? (For example, take tablets or turn off domestic appliances?)	☐	☐	☐
SCORE:			☐
Domain 6: Gastrointestinal tract			
21. Does the patient dribble saliva during the day?	☐	☐	☐
22. Does the patient having difficulty swallowing?	☐	☐	☐
23. Does the patient suffer from constipation? (Bowel action less than three times weekly)	☐	☐	☐
SCORE:			☐
Domain 7: Urinary			
24. Does the patient have difficulty holding urine? (Urgency)	☐	☐	☐
25. Does the patient have to void within 2 hours of last voiding? (Frequency)	☐	☐	☐
26. Does the patient have to get up regularly at night to pass urine? (Nocturia)	☐	☐	☐
SCORE:			☐
Domain 8: Sexual function			
27. Does the patient have altered interest in sex? (Very much increased or decreased, please underline)	☐	☐	☐
28. Does the patient have problems having sex?	☐	☐	☐
SCORE:			☐
Domain 9: Miscellaneous			
29. Does the patient suffer from pain not explained by other known conditions? (Is it related to intake of drugs and is it relieved by antiparkinson drugs?)	☐	☐	☐
30. Does the patient report a change in ability to taste or smell?	☐	☐	☐
31. Does the patient report a recent change in weight (not related to dieting)?	☐	☐	☐
32. Does the patient experience excessive sweating? (not related to hot weather)	☐	☐	☐
SCORE:			☐
TOTAL SCORE:			☐

Developed by the International Parkinson's Disease Non- Motor Group.

Correlation of total NMSS score and HrQoL

NMSS-Study 1	PDQ-8	NMSS-Study 2	PDQ-39	EQ-5D
	n = 242		n = 411	
Age	-0.03†	Age	0.05†	-0.13†
PD Duration	0.26	PD Duration	0.34	-0.33
H&Y staging	0.41	H&Y staging	0.51	-0.53
UPDRS_3	0.46	SCOPA-Motor Exam	0.47	-0.59
UPDRS4_Dysk&Fluct	0.36	SCOPA-Motor Compl.	0.53	-0.47
FAB_Total	-0.39	SCOPA-Cognition	-0.41	0.34
NMS Scale	0.70	NMS Scale	0.70	-0.57
NMS Quest	0.63	SCOPA-Autonomic	0.61	-0.49
Fatigue_VAS	-0.40	PDSS	-0.49	0.41

Mov Disord 2007; 22: 1901-1911

Neurology 2009; 73: 1584-1591

RESEARCH ARTICLE

The Impact of Non-Motor Symptoms on Health-Related Quality of Life of Patients with Parkinson's Disease

Pablo Martinez-Martin, MD, PhD,[1,2*] Carmen Rodriguez-Blazquez, BS,[1] Monica M. Kurtis, MD,[3] K. Ray Chaudhuri, MD, FRCP, DSC,[4,5] on Behalf of the NMSS Validation Group

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[2]Scientific Management, Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain
[3]Movement Disorders Unit, Department of Neurology, Ruber International Hospital, Madrid, Spain
[4]National Parkinson Foundation Centre of Excellence, Kings College Hospital, London, United Kingdom
[5]Department of Neurology, University Hospital Lewisham, Kings College, London, United Kingdom

Martinez-Martin et al., 2010

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TABLE 3. Percentage of patients reporting each non-motor symptom as measured by the NMSS

Items	Patients* N	Patients* %
1. Light-headedness	167	40.6
2. Fainting	38	9.2
3. Daytime sleepiness	195	47.4
4. Fatigue	271	65.9
5. Difficulty falling asleep	207	50.4
6. Restless legs	131	31.9
7. Lost interest in surroundings	141	34.3
8. Lack motivation	179	43.6
9. Feel nervous	208	50.6
10. Seem sad	204	49.6
11. Flat mood	132	32.1
12. Difficulty experiencing pleasure	121	29.4
13. Hallucinations	72	17.5
14. Delusions	40	9.7
15. Double vision	72	17.5
16. Concentration	222	54.0
17. Forget things or events	209	50.9
18. Forget to do things	172	41.8
19. Saliva	178	56.7
20. Swallowing	121	29.4
21. Constipation	202	49.1
22. Urgency	224	54.5
23. Frequency	224	54.5
24. Nocturia	281	68.4
25. Altered interest in sex	135	32.8
26. Problems having sex	115	28.0
27. Pain	162	39.4
28. Taste or smell	171	41.6
29. Weight change	122	29.7
30. Excessive sweating	125	30.4

*Patients scoring 1 or more points on the NMSS.

TABLE 4. Correlations of NMSS, SCOPA-Motor, and HRQL measures

	PDQ-39 SI	EQ-5D Index	EQ-5D VAS
NMSS total score	0.70	−0.57	−0.37
Cardiovascular	0.26	−0.26	−0.14
Sleep/fatigue	0.58	−0.49	−0.34
Mood/apathy	0.57	−0.47	−0.33
Perceptual problems/hallucinations	0.36	−0.33	−0.19
Attention/memory	0.43	−0.27	−0.23
Gastrointestinal	0.38	−0.40	−0.21
Urinary	0.41	−0.32	−0.19
Sexual dysfunction	0.14	−0.12	−0.06 (n.s.)
Miscellaneous	0.42	−0.42	−0.22
Number of non-motor symptoms	0.63	−0.61	−0.42
SCOPA-motor	0.58	−0.67	−0.40
Motor examination	0.43	−0.58	−0.37
Activities of daily living	0.58	−0.64	−0.33
Motor complications	0.50	−0.47	−0.28

Spearman's rank correlation coefficient, all significant at a $P < 0.0001$ level, except n.s.: not significant.
SCOPA, scales for outcomes in Parkinson's disease; EQ-5D, EuroQol five dimensions; PDQ-39, Parkinson's disease questionnaire-39 items; NMSS, non-motor symptoms scale; VAS, visual analogue scale.

Martinez-Martin et al., 2010

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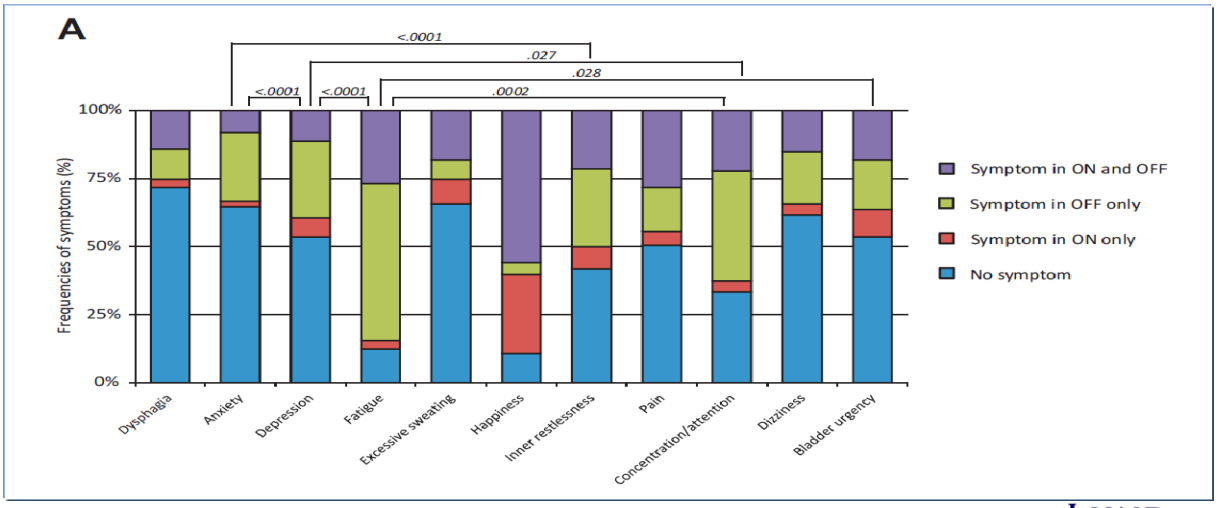
Non-motor fluctuations



Storch et al., 2012

EuroInf: A Multicenter Comparative Observational Study of Apomorphine and Levodopa Infusion in Parkinson's Disease

Pablo Martinez-Martin, MD, PhD,[1] Prashanth Reddy, MBBS, MRCP,[2] Regina Katzenschlager, MD,[3] Angelo Antonini, MD, PhD,[4] Antoniya Todorova, MD, PhD,[2] Per Odin, MD, PhD,[5] Tove Henriksen, MD,[6] Anne Martin, BSc,[2] Daniela Calandrella, MD,[4] Alexandra Rizos, MSc,[2] Narissah Bryndum, RN,[6] Arne Glad, RN,[6] Haidar Salimi Dafsari, MD,[7] Lars Timmermann, MD,[7] Georg Ebersbach, MD,[8] Milica G. Kramberger, MD, PhD,[9] Michael Samuel, MD, FRCP,[2] Karoline Wenzel, MD,[10] Volker Tomantschger, MD,[11] Alexander Storch, MD,[12] Heinz Reichmann, MD,[12] Zvezdan Pirtosek, MD, PhD,[9] Maja Trost, MD, PhD,[9] Per Svenningsson, MD, PhD,[13] Sven Palhagen, MD,[13] Jens Volkmann, MD, PhD,[14] and K. Ray Chaudhuri, MD, DSc[2]*

TABLE 1. Descriptive and comparative statistics at baseline and follow-up for each group of treatment

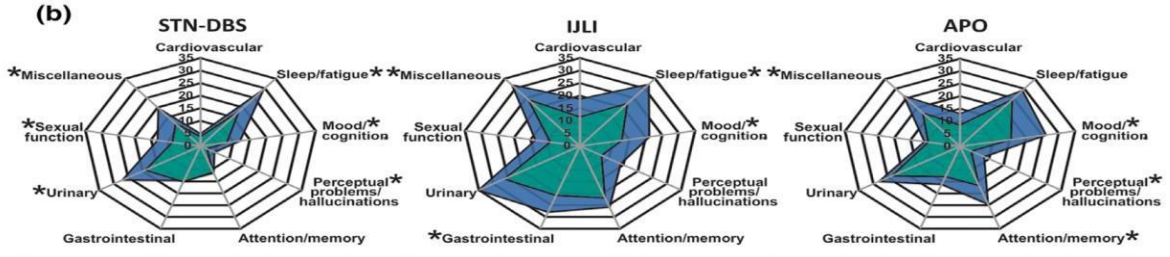
	Intrajejunal Levodopa Infusion					Apomorphine Infusion				
	Baseline		Follow-up			Baseline		Follow-up		
	Mean	SD	Mean	SD	*P* Value	Mean	SD	Mean	SD	*P* Value
UPDRS part 3[a]	27.29	12.28	15.07	10.37	<0.0001	30.79	10.40	17.46	8.08	<0.0001
UPDRS part 4[a]	9.93	3.29	4.36	3.07	<0.0001	10.02	4.68	5.93	3.35	<0.0001
NMSS domains										
Cardiovascular	3.36	3.69	1.86	2.67	0.0076	3.19	4.57	2.07	2.49	0.23
Sleep/fatigue	16.68	10.97	8.64	8.26	<0.0001	16.98	10.12	12.98	10.13	0.024
Mood/apathy	15.79	12.85	11.89	13.04	0.021	18.81	18.00	9.98	10.17	0.0003
Perceptual/hallucinations	3.54	5.54	1.95	4.51	0.010	3.02	5.18	1.40	3.14	0.003
Attention/memory	10.20	9.35	7.60	8.68	0.011	8.77	8.24	5.79	6.35	0.003
Gastrointestinal	9.48	7.68	4.25	4.80	<0.0001	6.21	5.82	4.65	5.49	0.003
Urinary	11.5	10.42	5.48	5.78	0.0001	9.07	7.40	7.93	8.03	0.002
Sexual functioning	5.73	7.93	2.32	4.12	0.014	2.56	5.29	1.93	3.59	0.18
Miscellaneous	14.66	9.25	9.68	7.87	0.0008	13.77	10.94	9.49	8.15	0.50
NMSS total score	90.95	45.00	53.66	38.67	<0.0001	82.37	49.54	56.21	32.21	0.0007
PDQ-8 summary index[a]	48.58	14.62	31.96	14.89	<0.0001	49.85	16.59	35.03	18.00	<0.0001

Martinez-Martin et al, 2015

EuroInf 2: Subthalamic Stimulation, Apomorphine, and Levodopa Infusion in Parkinson's Disease

Haidar S. Dafsari, MD,[1,2*] Pablo Martinez-Martin, MD, PhD,[3] Alexandra Rizos, MSc,[2] Maja Trost, MD,[4] Maria Gabriela dos Santos Ghilardi, MD,[5] Prashanth Reddy, MD/PhD,[2] Anna Sauerbier, MD,[2,6] Jan Niklas Petry-Schmelzer, MD,[1] Milica Kramberger, MD,[4] Robbert W. K. Borgemeester, MD,[7] Michael T. Barbe, MD,[1] Keyoumars Ashkan, MD, PhD,[2] Monty Silverdale, MD, PhD,[8] Julian Evans, MD, PhD,[8] Per Odin, MD, PhD,[9,10] Erich Talamoni Fonoff, MD, PhD,[5,11] Gereon R. Fink, MD,[1,12] Tove Henriksen, MD, PhD,[13] Georg Ebersbach, MD,[14] Zvezdan Pirtošek, MD, PhD,[4] Veerle Visser-Vandewalle, MD, PhD,[15] Angelo Antonini, MD, PhD,[16,17] Lars Timmermann, MD,[1,18] and K. Ray Chaudhuri, MD, PhD,[2,6*]
on behalf of EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson's Disease Study Group

Dafsari et al., 2019



Dafsari et al., 2019

Original cohort	Relative change			Effect size (CI)		
	STN-DBS	IJLI	APO	STN-DBS	IJLI	APO
PDQ-8 SI	−26.9	−21.1	−30.3	*0.58* (0.37 to 0.79)	*0.55* (0.17 to 0.92)	*0.76* (0.40 to 1.12)
UPDRS-III	−3.7	−6.4	−5.8	0.10 (−0.10 to 0.30)	0.19 (−0.16 to 0.54)	0.13 (−0.19 to 0.45)
UPDRS-IV	−49.4	−45.3	−34.4	**0.85** (0.62 to 1.08)	**1.20** (0.74 to 1.65)	**0.80** (0.41 to 1.18)
H&Y	−5.6	−11.8	−16.1	0.19 (−0.01 to 0.39)	*0.61* (0.23 to 0.98)	*0.74* (0.38 to 1.10)
LEDD	−52.3	16.4	11.3	**1.18** (0.92 to 1.43)	0.34 (−0.03 to 0.70)	0.27 (−0.07 to 0.61)
NMSS total score	−30.7	−28.5	−29.0	*0.59* (0.38 to 0.80)	*0.67* (0.27 to 1.06)	0.47 (0.13 to 0.80)
Cardiovascular	−20.0	−23.9	−37.8	0.09 (−0.11 to 0.29)	0.25 (−0.11 to 0.61)	0.23 (−0.10 to 0.55)
Sleep/fatigue	−39.9	−29.9	−17.9	*0.64* (0.43 to 0.86)	0.45 (0.08 to 0.81)	0.18 (−0.14 to 0.50)
Mood/cognition	−34.6	−43.0	−45.3	0.21 (0.01 to 0.41)	*0.50* (0.12 to 0.87)	0.46 (0.12 to 0.79)
Perceptual problems/hallucinations	−50.9	−34.6	−55.5	0.29 (0.09 to 0.49)	0.23 (−0.13 to 0.59)	0.35 (0.02 to 0.67)
Attention/memory	−7.1	−15.1	−31.3	0.05 (−0.15 to 0.25)	0.19 (−0.17 to 0.54)	0.39 (0.05 to 0.71)
Gastrointestinal	2.7	−28.7	−15.4	0.03 (−0.17 to 0.23)	0.35 (−0.02 to 0.71)	0.21 (−0.12 to 0.53)
Urinary	−29.7	−19.6	−10.2	0.36 (0.15 to 0.56)	0.30 (−0.06 to 0.66)	0.20 (−0.12 to 0.52)
Sexual function	−36.2	−29.5	−19.1	0.25 (0.05 to 0.45)	0.19 (−0.17 to 0.54)	0.10 (−0.22 to 0.42)
Miscellaneous	−40.5	−27.8	−31.6	*0.55* (0.34 to 0.76)	0.42 (0.05 to 0.78)	0.46 (0.12 to 0.79)

Dafsari et al., 2019

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Swedish National Guidelines for PD

Medical treatment of Parkinson dementia

Healthcare should:

offer people with Parkinson dementia treatment with acetylcholine inhibitors (Priority 4).

offer people with Parkinson dementia treatment with memantine (Priority 9)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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Swedish National Guidelines for PD

Treatment of depression in Parkinson´s disease

Healthcare should:

- offer medical treatment with SNRI in people with depression and Parkinson´s disease (Priority 3)
- offer medical treatment with TCA or cognitive behavioural therapy in people with depression and Parkinson´s disease (Priority 4)

Healthcare should in exceptional cases:

-offer medical treatment with SSRI in people with depression and Parkinson´s disease (Priority 8)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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Symptoms and treatments that are not part of the central recommendations

- treatment with anticholinergics in PD tremor (Priority 8)
- non-dopaminergic treatment of Parkinson tremor (Priority 9)
- treatment with apomorphine pen in ”off” fluctuations (Priority 4)
- treatment of psychotic symptoms with clozapine (Priority 3), quetiapine (Priority 7) or olanzapine (Priority: not do)
- treatment of severe siallorea with botulinum toxine (Priority 4)
- treatment of anhedonia (R & D), treatment of fatigue (R & D); treatment of daytime sleepiness (R & D)
- treatment of overactive bladder with peripherally acting anticholinergic agents (Priority 6)
- treatment of overactive bladder with botulinum toxine in the bladder wall (Priority 7)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

Symptoms and treatments that are not part of the central recommendations

- treatment of orthostatic hypotension with Droxidopa (Priority 8)
- treatment of orthostatic hypotension with Midodrine (Gutron) (Priority 3)
- treatment of orthostatic hypotension with Fludrocortisone (Astonin) (Priority 5)
- treatment of orthostatic hypotension with Etilefrine (Effortil) (Priority 3)
- treatment of orthostatic hypotension with Norepinephrine-Infusion (R & D)
- Treatment of impulse control symptoms which remain in spite of optimized dopaminergic treatment with CBT (Priority 8)
- Treatment of impulse control symptoms which remain in spite of optimized dopaminergic treatment with Naltrexone (Priority 9)
- Treatment of severe dysphagia with PEG (Priority 3)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

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To improve Quality of Life

5. Live an active life: Regular physical activity

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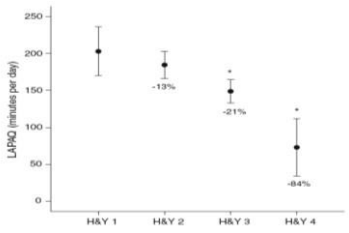
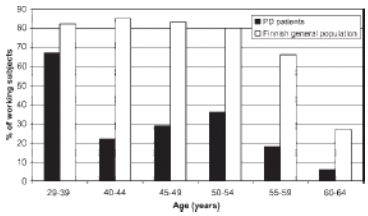
Medication and DBS does not solve everything

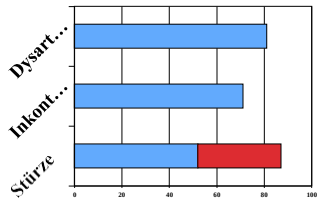
Reduced Activity



Stop working

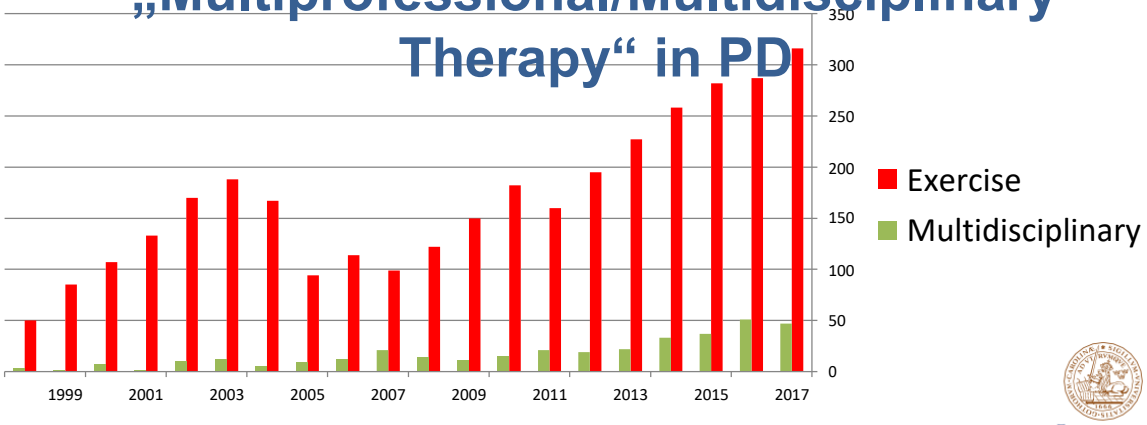


Severe Handicap



1. van Nimwegen et al J Neurol 2011, 2. Martikainen et al. Mov Disord 2008, 3. Hely et al. Mov Disord 2008

Publications on „Exercise/Physical Therapy“ and „Multiprofessional/Multidisciplinary Therapy“ in PD



Source: PubMed

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Result of larger Studies (>100) on activating Therapy in PD

Autor	Methode	n	Dosis [h]	Dauer [w] (f/u)	Akt. Komp.	QuOL	Motor scores	ADL	Falls
Clarke et al JAMA Neurol 2016	Ergo/Physio	762	4	8 (56)	-	-		-	
Sturkenboom et al Lancet Neurol 2014	Ergo	191	16	10 (26)	-			+	
Canning et al Neurology 2014	Physio	231	78	26 (0)	-	+	+	+	-
Li et al NEJM 2012	Tai Chi	195	48	24 (12)	+	+	+		+
Goodwin et al JNNP 2011	Physio	130	10	10(10)	-	-	+	-	-
Nieuwboer et al JNNP 2007	Cueing	153	4,5	3(6)	-	-	+	-	

= primary outcome

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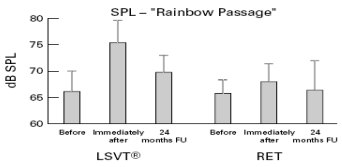
Principles of therapy LSVT LOUD, LVST BIG



Focus: Amplitude
(Voice or movement)
Goal
„Recalibration“

Therapy intensity:
Individual therapy
4 weeks
4 times a week
50 min per session
No "long-term therapy"

Ramig et al. 2001, Ebersbach et al. 2010

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Swedish National Guidelines for PD

Multidisciplinary team management in Parkinson´s disease

Healthcare should:

Offer people with Parkinson´s disease care by a multidisciplinary team (Priority 3).

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

Swedish National Guidelines for PD

Team Rehabilitation in Parkinson´s disease

Healthcare should:

Offer continuous team rehabilitation for persons with Parkinson´s disease and reduced functional capacity (Priority 4)

Swedish National Guidelines for PD, 2016
Swedish Board of Health and Welfare

Summary

For best benefit on health related quality of life

-Start therapy at diagnosis

-Treat motor symptoms effectively, but try to avoid motor complications and dyskinesias

-Treat motor complications and dyskinesias effectively, when they appear

-Detect and treat non-motor symptoms

-Live an active life: regular physical activity