EXTENDING CHOICE

CONNECTING EXPERTS IN PD

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Parkinson's Disease Education Day 2023

June 2023

GB_XAD_709

EXTENDING CHOICE
CONNECTING EXPERTS IN PD

BROUGHT TO YOU BY ZAMBON UK

Practical Management of Complex Patients in Parkinson's

Ms Miriam Parry

Parkinson's Disease Nurse Consultant,
Kings College Hospital NHS Trust

As presented in May 2023 (GB_XAD_679)

King's College Hospital NHS Foundation Trust | South London and Maudsley NHS Foundation Trust | Guy's and St Thomas' NHS Foundation Trust | Lewisham and Greenwich NHS Trust | NIHR National Institute for Health and Care Research | مستشفى كينغز كوليدج لندن King's College Hospital London

Complex Phase of Parkinson's Disease

Miriam Parry
Parkinson's Disease Nurse Consultant
Parkinson's Foundation Centre of Excellence
King's College Hospital, King's College London, London, UK

Royal College of Physicians 24 May 2023

Parkinson's Foundation CENTER OF EXCELLENCE | King's College London | Europar

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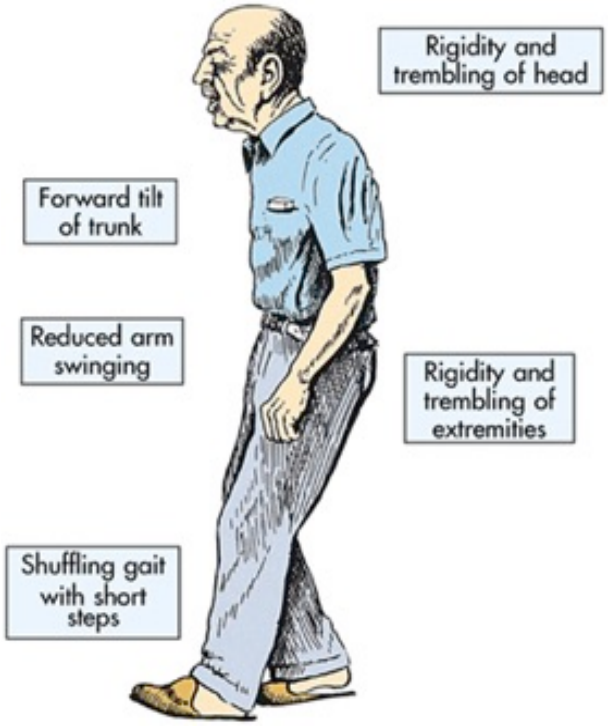
Advisory board

- Britannia Pharmaceuticals
- Syneos Health

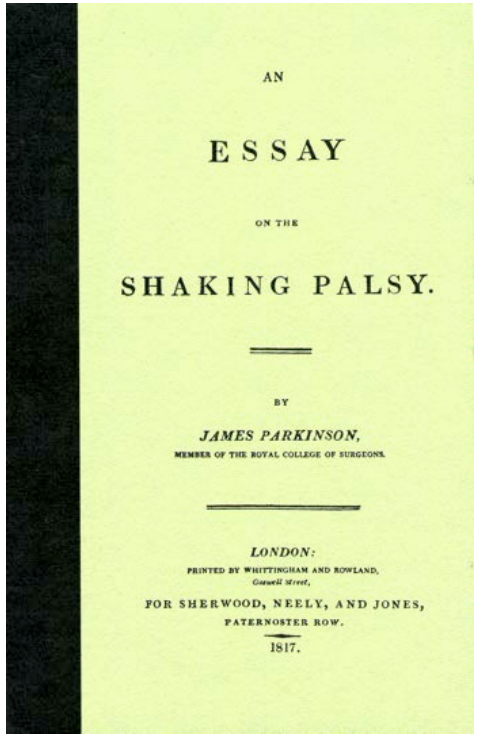
Aim of Session

- To increase your knowledge and understanding of the complex phase of Parkinson's
- To better understand the needs of people living with Parkinson's & caring for people with Parkinson's at the complex phase
- To identify challenges associated with the symptoms of Parkinson's, the side effects of the medication
- To learn about the resources available to improve the quality of life for people with Parkinson's and their carers

Dr James Parkinson recognised a mixture of a Motor symptoms & Non-Motor Symptoms



Prodromal Parkinson's: Pain


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Described

- Pain
- Sleep dysfunction
- Dysautonomia
- Constipation
- Delusion

Modern concept of Parkinson's is that it is a syndromic condition

Calne DB. Is 'Parkinson's disease' one disease? J Neurol Neurosurg Psychiatry 1989; 52 (Suppl):18–21.
Weiner WJ. There is no Parkinson disease. Arch Neurol 2008; 65:705–708.


J Neural Transm
DOI 10.1007/s00702-016-1667-6

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Parkinson's: a syndrome rather than a disease?

Nataliya Titova[1] · C. Padmakumar[2] · Simon J. G. Lewis[3] · K. Ray Chaudhuri[4,5]

Clinical subtypes and genetic heterogeneity: of lumping and splitting in Parkinson disease

Rainer von Coelln and Lisa M. Shulman

POINTS OF VIEW

The Parkinson's Complex: Parkinsonism Is Just the Tip of the Iceberg

J. William Langston, MD

Titova N et al. J Neural Transm (Vienna) 2017;124(8):907-14
Chaudhuri KR et al. Parkinsonism Rel Disord 2011;17:717-23
Langston JW. Ann Neurol 2006 Apr;59(4):591-6

Disease progression in Parkinson's is complex

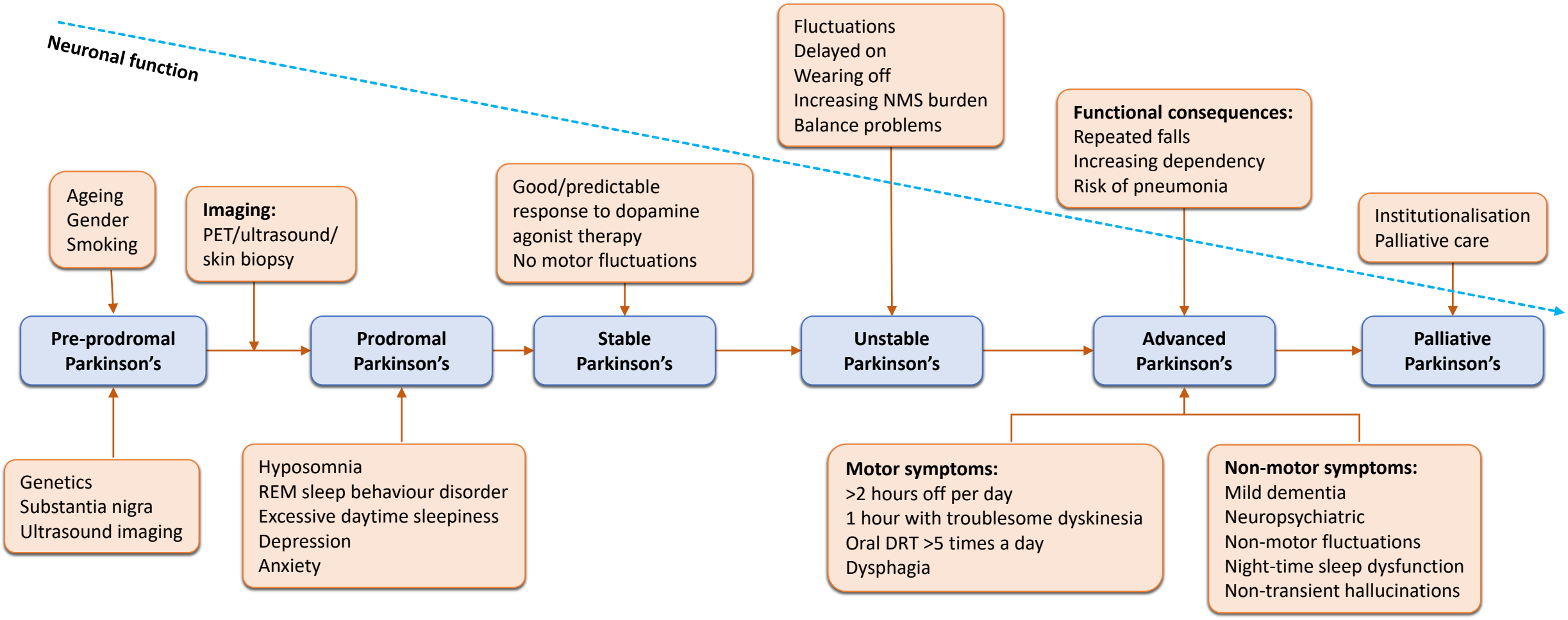


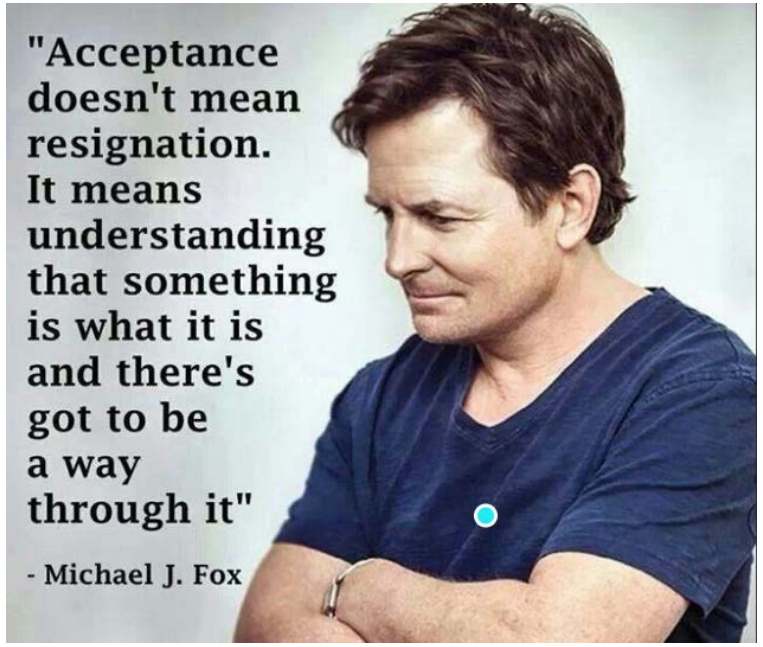
Figure adapted from Titova and Chaudhuri 2018

DRT, dopamine replacement therapy; NMS; non-motor symptoms; PET, positron emission tomography; REM, rapid eye movement.

Titova N and Chaudhuri KR. *Med J Aust*. 2018;208:404–9.

Complex Parkinson's Disease is defined as:

- Treatment is unable to consistently control motor symptoms
- Development of uncontrollable dyskinesia
- Treatment is unable to consistently control non-motor symptoms
- Symptoms impact on quality of life



What is QOL?

HRQOL means the perception and evaluation, by patients themselves, of the impact caused on their lives by the disease and its consequences.

Martinez-Martin, 1998

Why is it relevant?

- In chronic diseases lacking cure
  - Improving patients' QOL is the main objective of caring
- Unique information, coming directly from patients
  - Cannot be obtained through any clinical method
- A complement to clinical evaluation
  - Focused on aspects of interest for patients
- Helps understand discrepancies doctor-patient
  - Not equivalent to clinical measures

HRQOL, health-related quality of life.

Martínez-Martín P. (1998) J Neurol, S2-S6.

Health related quality of life (HRQoL) is decreased in Parkisnon's patients compared to general population

Due to the disabling symptoms of PD the patients have a lower health related quality of life than the general population (measured as EQ-5D utility)[1)]

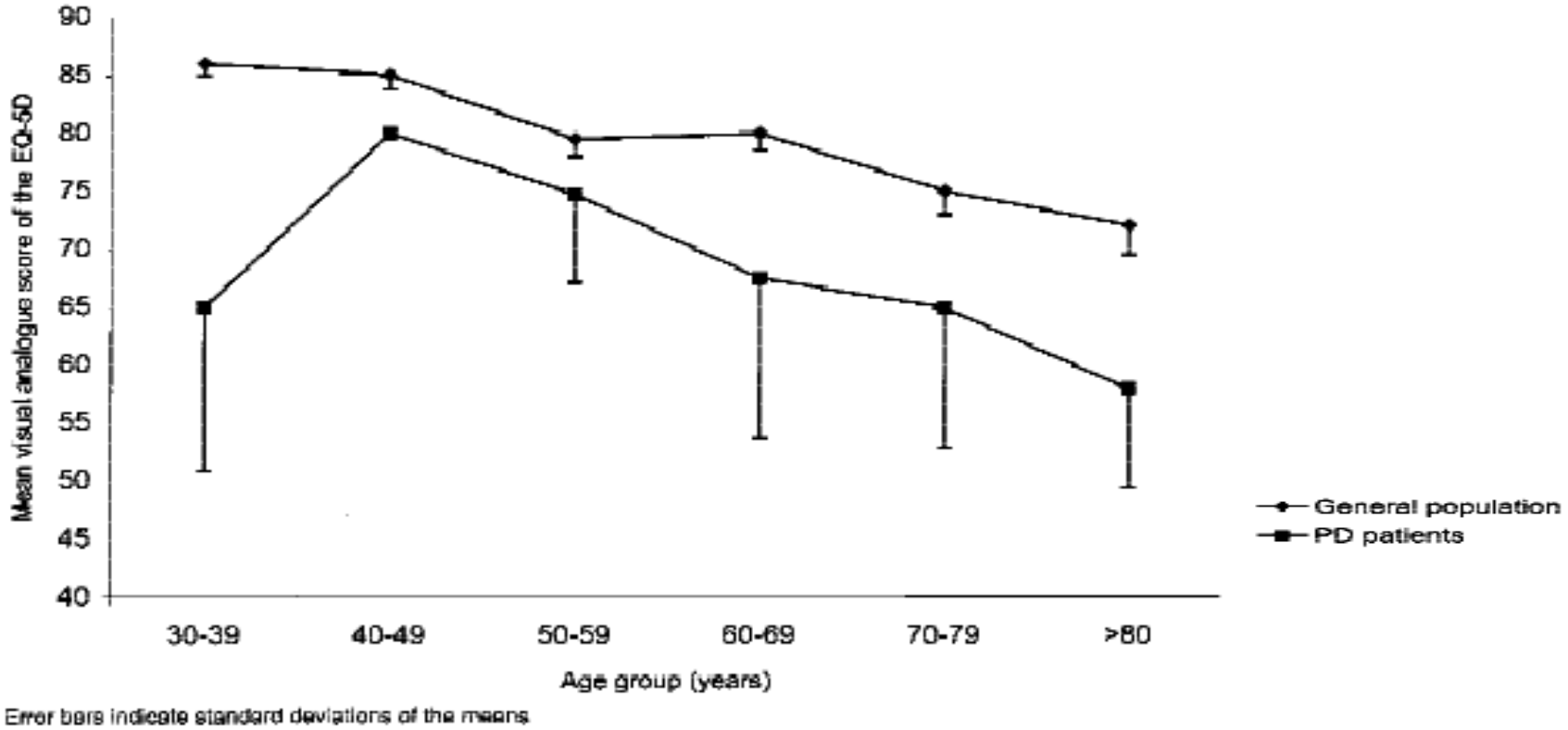
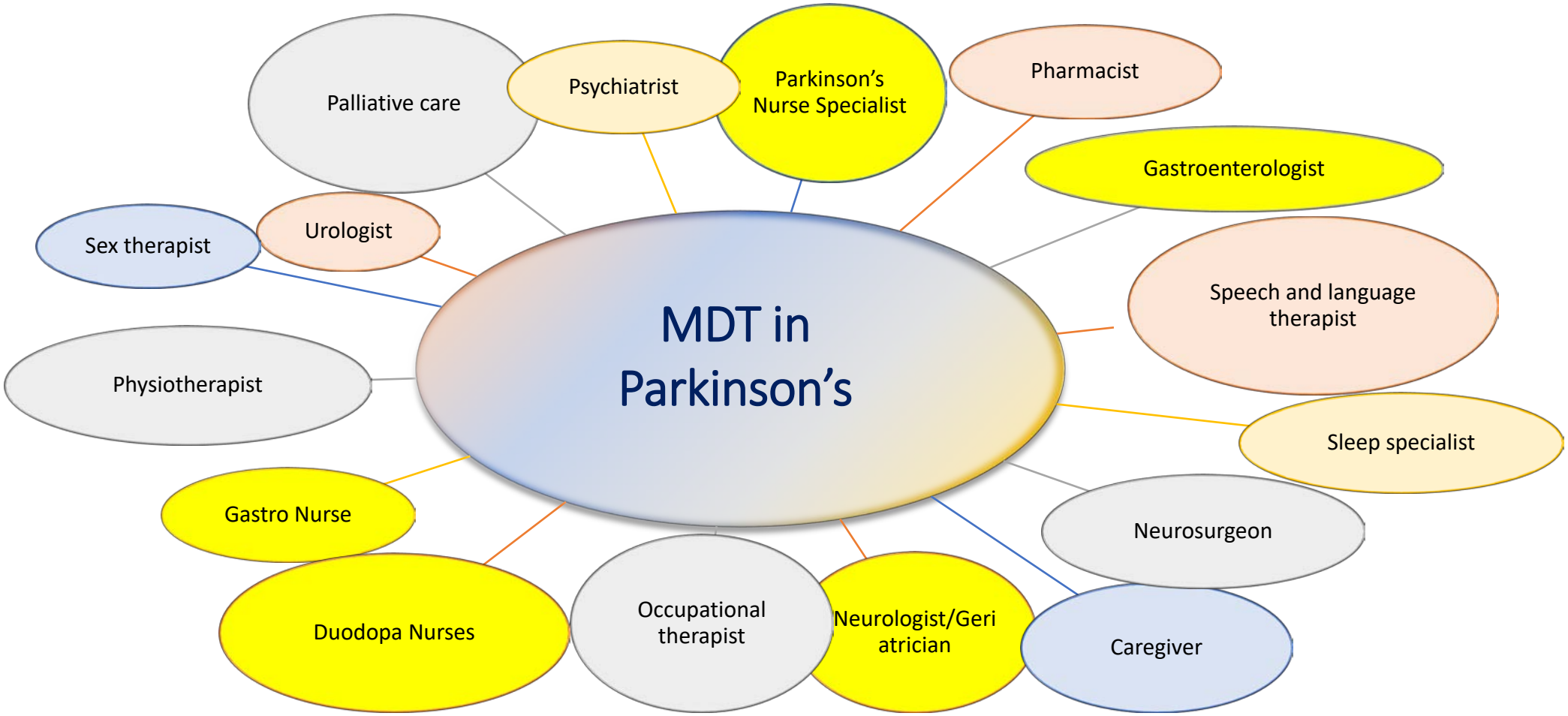


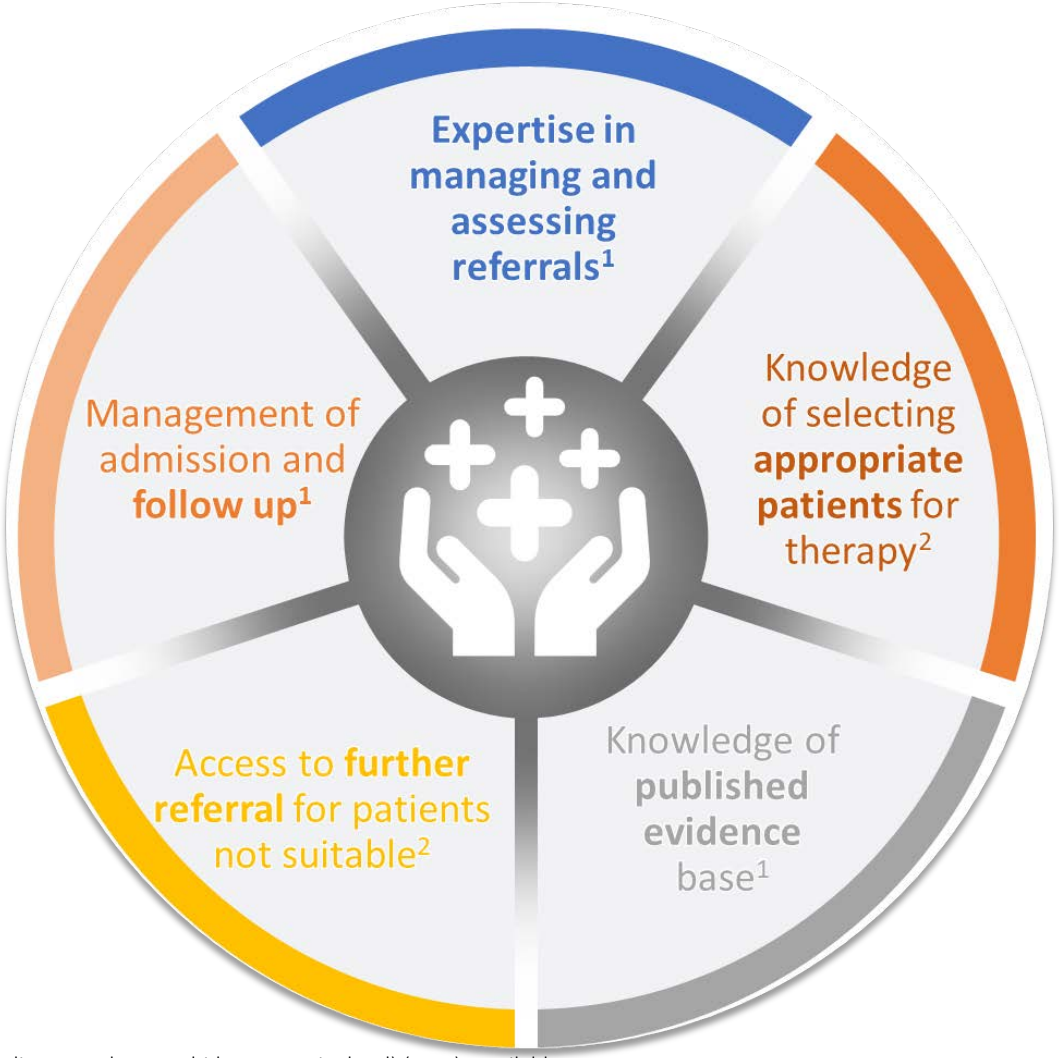
Fig. 1
Mean visual analog scales scores of patients with Parkinson's disease as compared with norms from the general population.

[1] Schrag A. Mov Dis. 2000

Specialist requirements for improving QoL in Parkinson's patients at KCH



Expertise & experienced movement disorders MDT

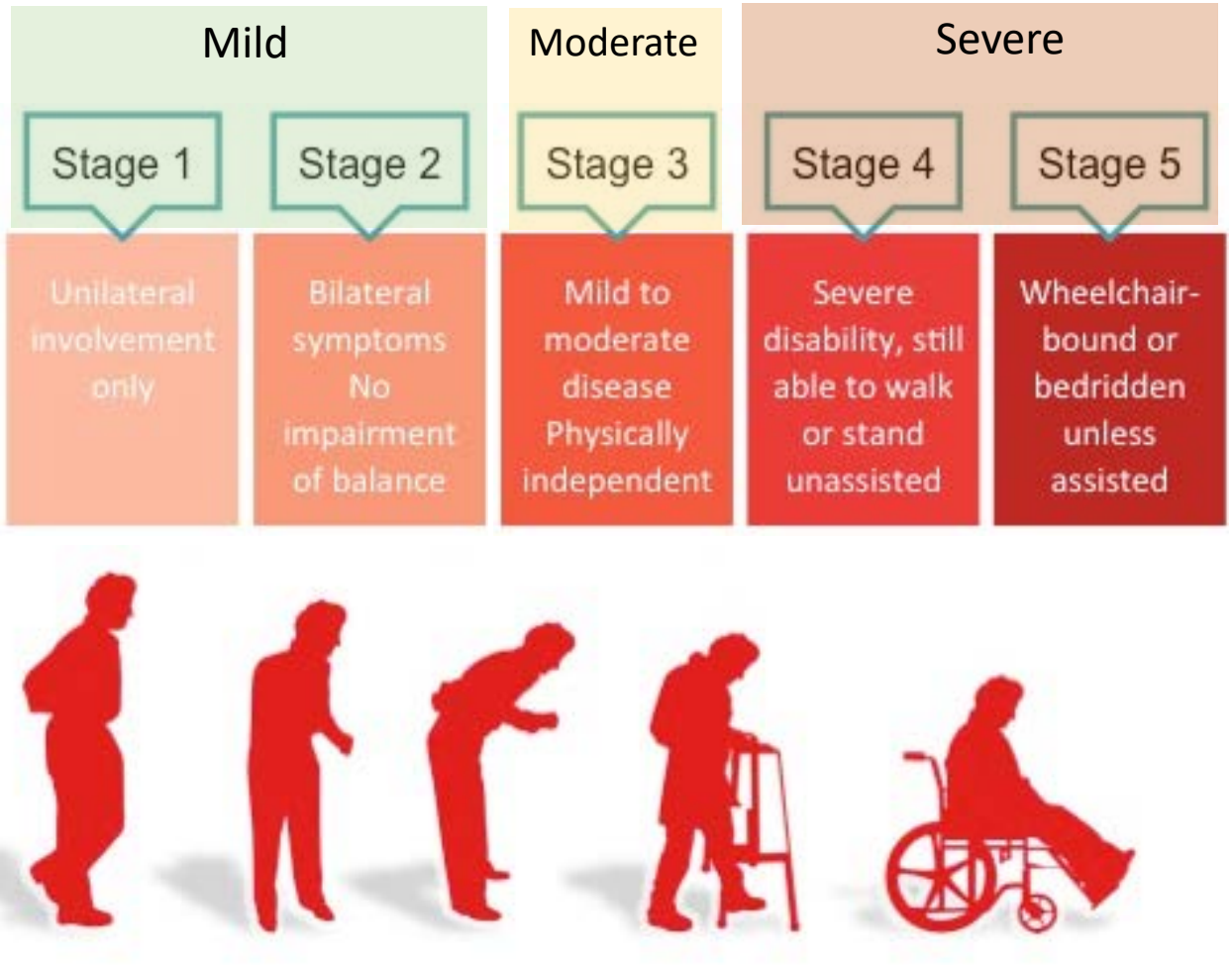


MDT, multidisciplinary team; KCH, King's College Hospital.
1. Information courtesy of M.Parry; 2. NHS England. Clinical Commissioning Policy: Levodopa-Carbidopa Intestinal Gel) (LCIG). Available at https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/07/d04-p-e.pdf Accessed: August 2022.

Hoehn and Yahr Scale Staging

Margaret M. Hoehn

Melvin D. Yahr

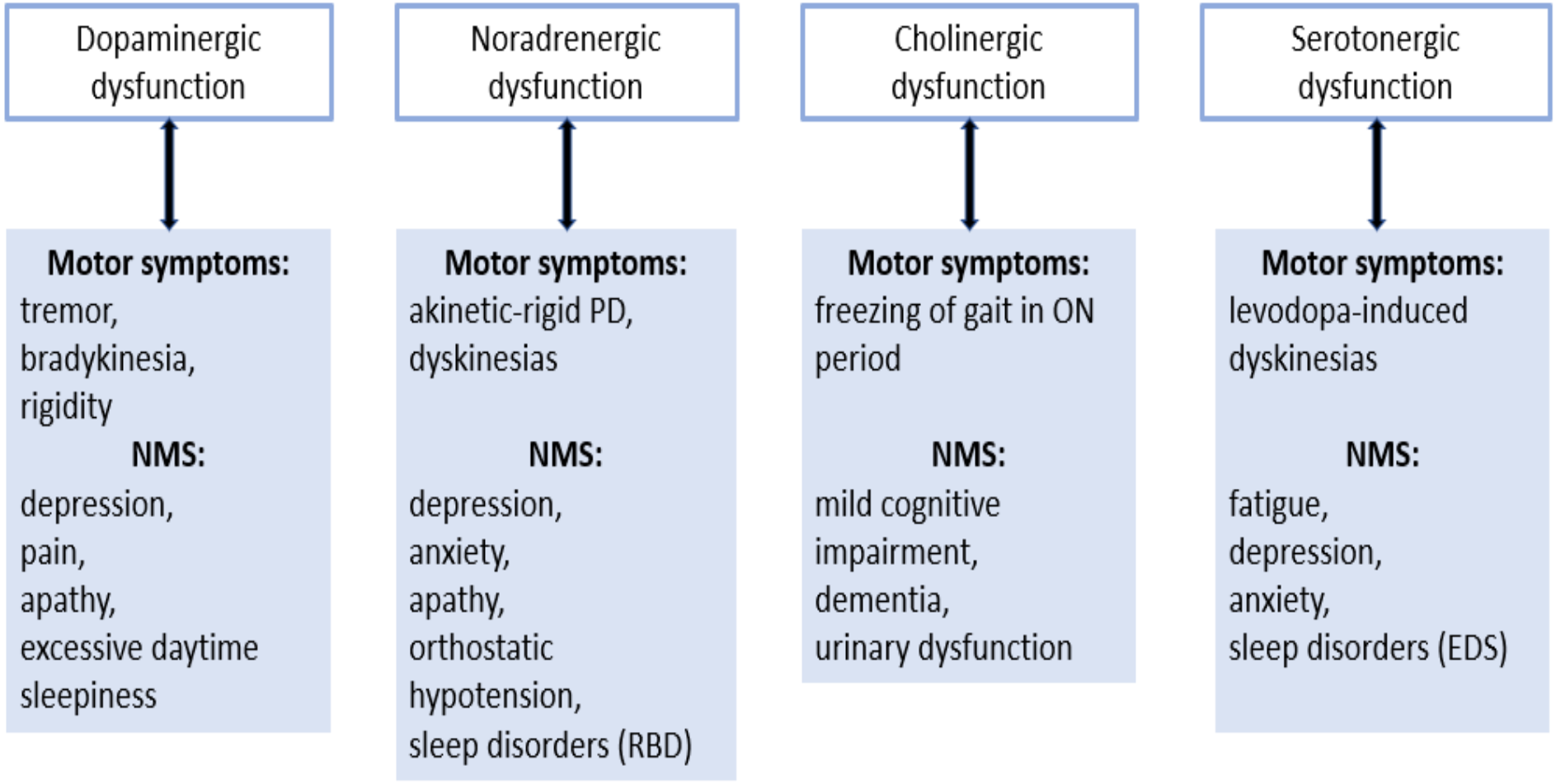


Hoehn and Yahr. Neurology 1967; 17: 427-442

DOI: 10.18454/ACEN.2017.4.1

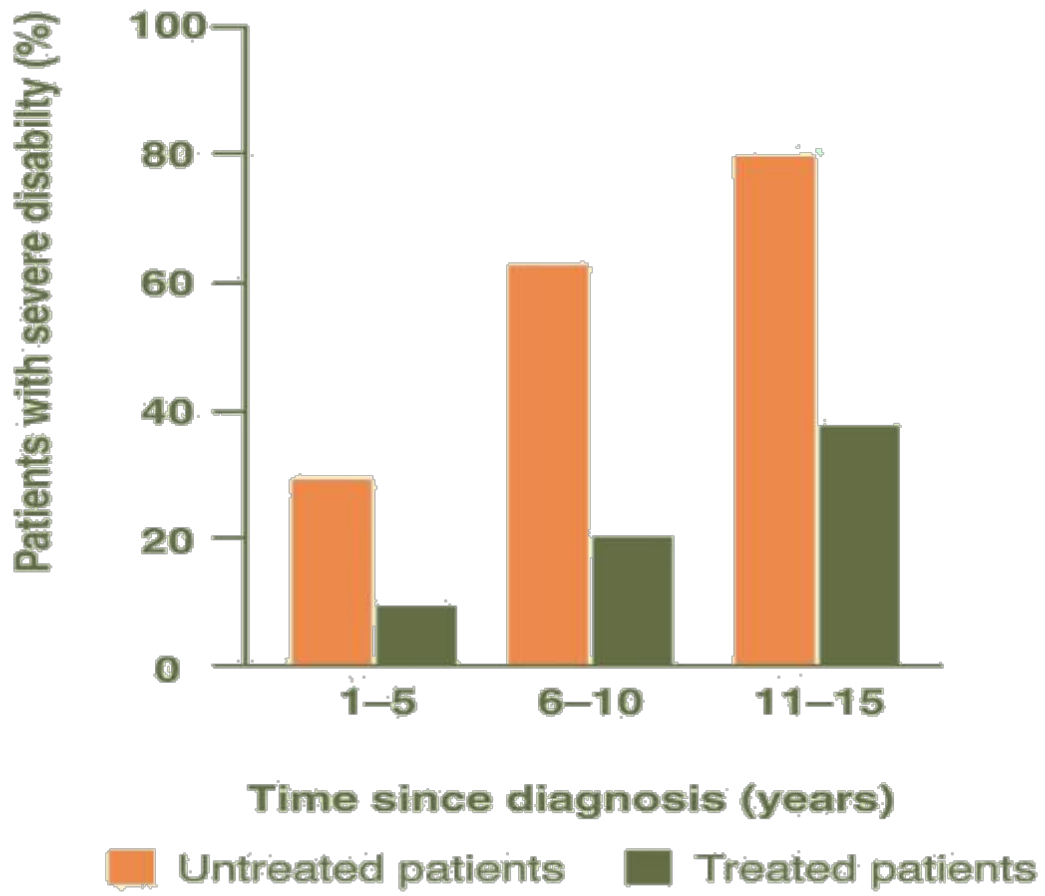
Non-motor symptoms of Parkinson's disease: the submerged part of the iceberg

Natalia V. Titova[1], K. Ray Chaudhuri[2]



Titova N and Chaudhuri KR. Annals of Clinical and Experimental Neurology 2017;11(4)

Unique benefits of Levodopa

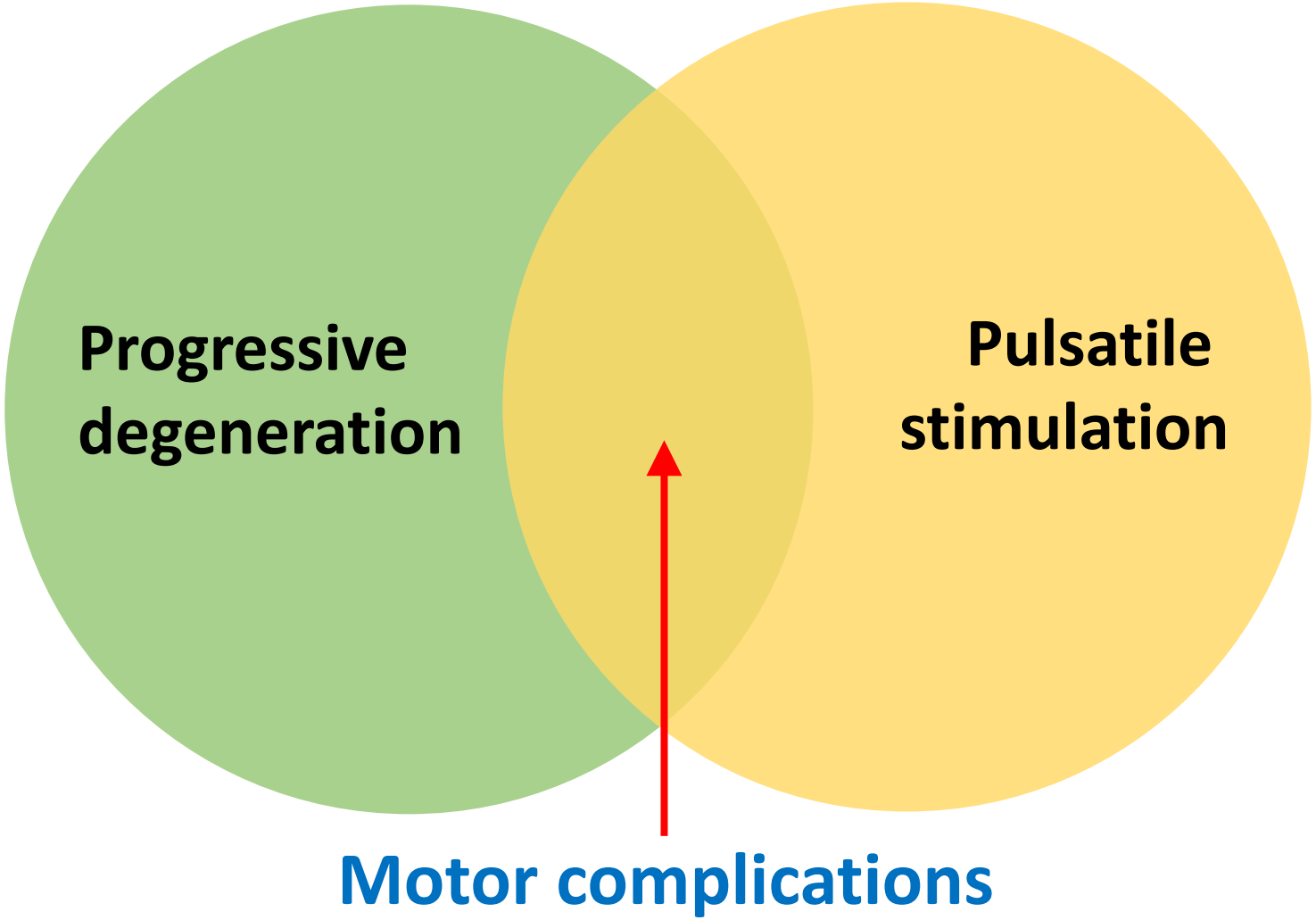


- ✓ Provides antiparkinsonian benefit over the course of the disease
- ✓ Well tolerated

"Levodopa is currently the most effective antiparkinsonian drug and all PD patients eventually require it"

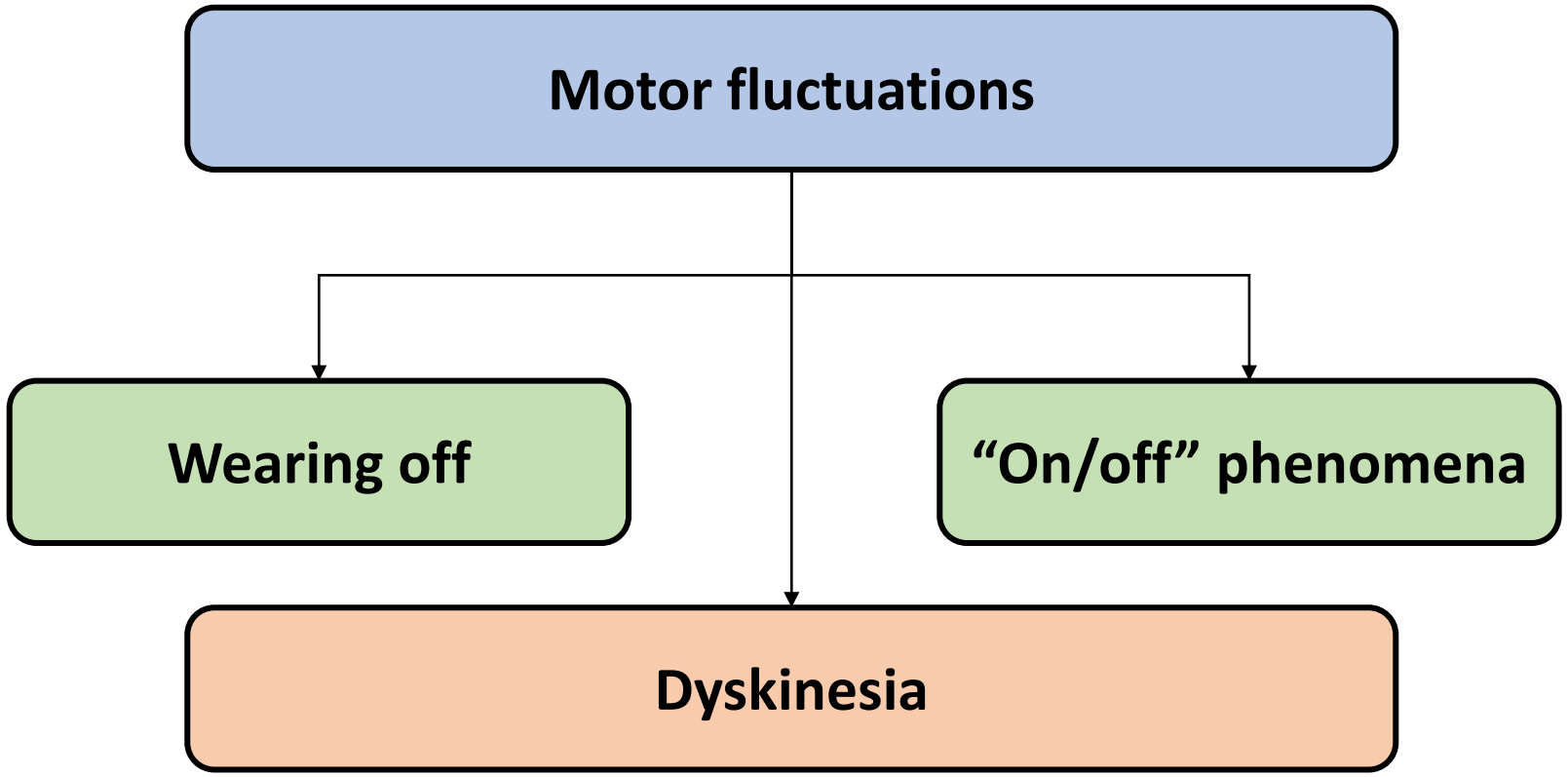
Agid et al 2002

Two key factors interact in the development of motor complications



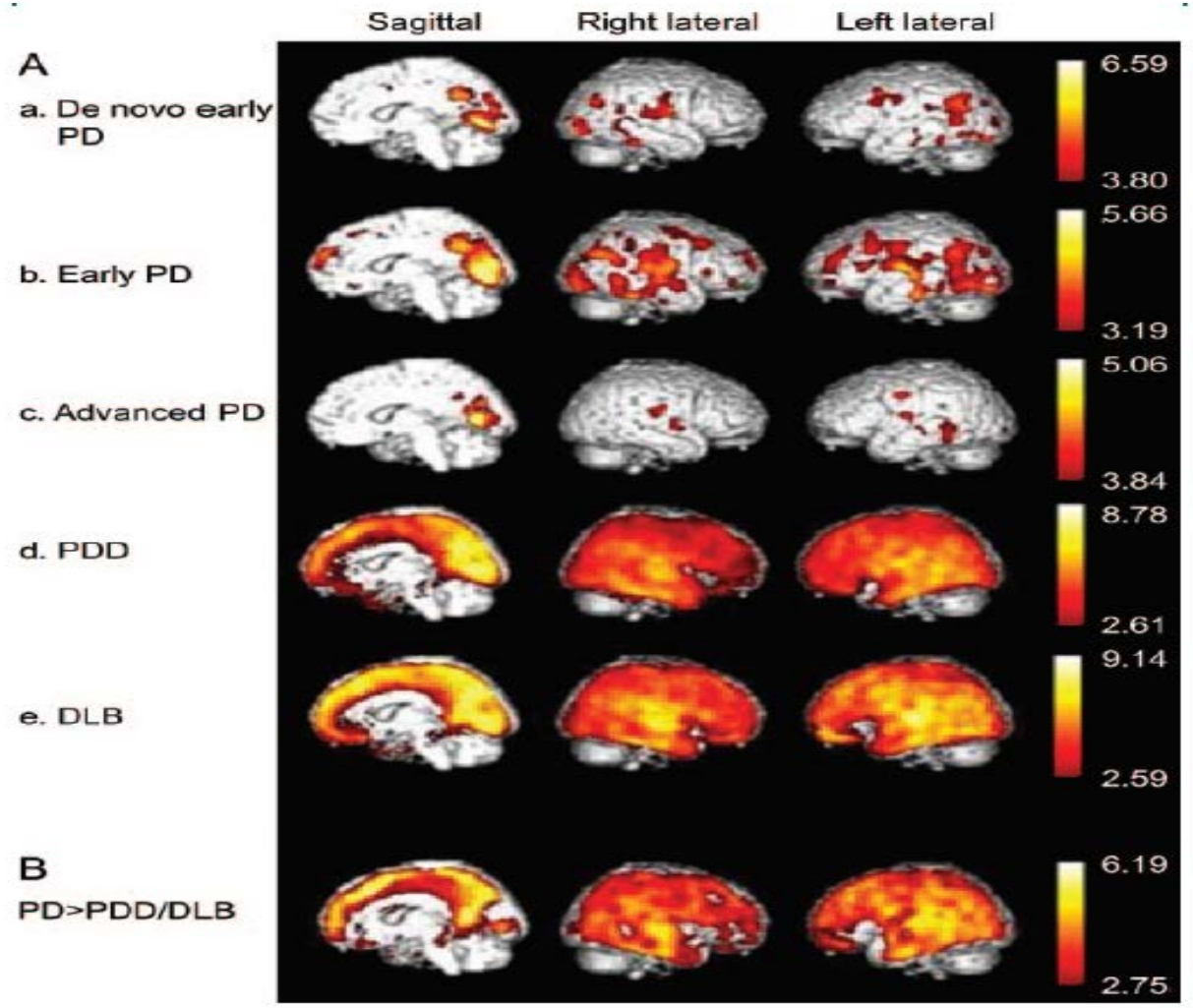
1. Olanow CW et al. Nat Clin Pract Neurol 2006;2:382–92.
2. Stocchi F et al. Neurology 2004;62 (Suppl1):S56–S63. 3. Olanow CW et al. Mov Disord 2004;19:997–1005.

Motor complications associated with Parkinson's disease



Olanow CW et al. Nat Clin Pract Neurol 2006;2:382–92.

Figure 1 Cortical k_3 declines in each group compared with healthy controls



Shimada et al. Neurology 2009;73(4):273-8

npj | Parkinson's Disease

www.nature.com/npjparkd

REVIEW ARTICLE OPEN

Non-oral dopaminergic therapies for Parkinson's disease: current treatments and the future

K Ray Chaudhuri[1,2], Mubasher A Qamar[1,2], Thadshani Rajah[1,2], Philipp Loehrer[1,2,3], Anna Sauerbier[1,2], Per Odin[4,5] and Peter Jenner[6]

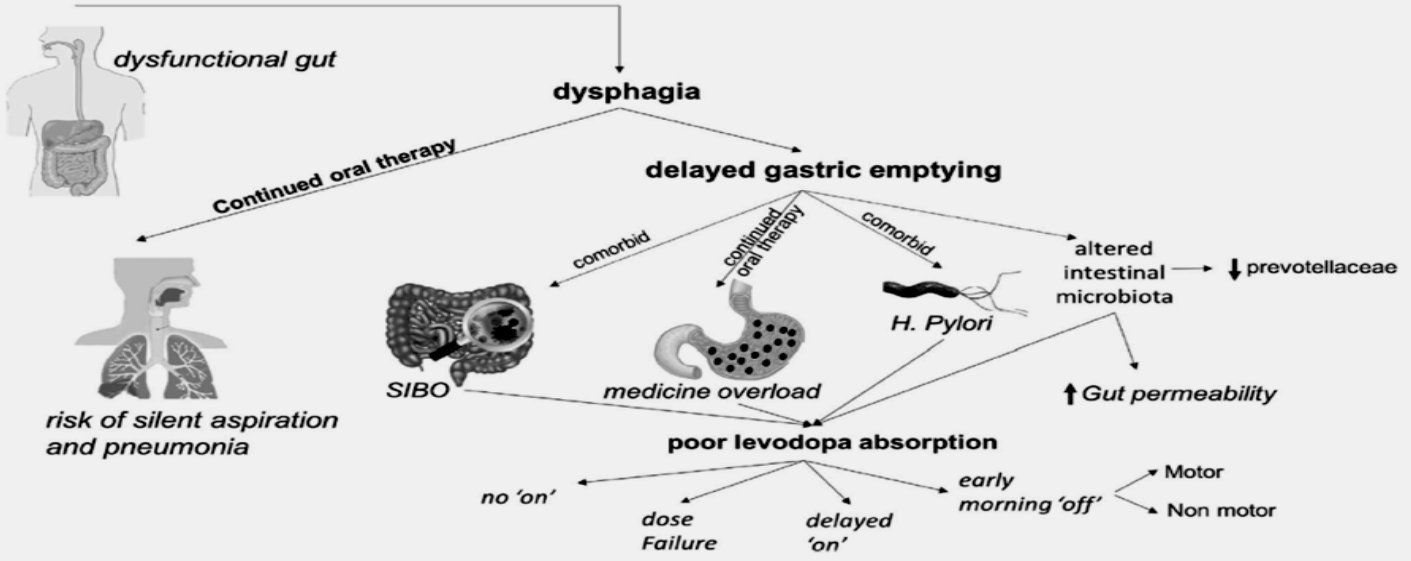
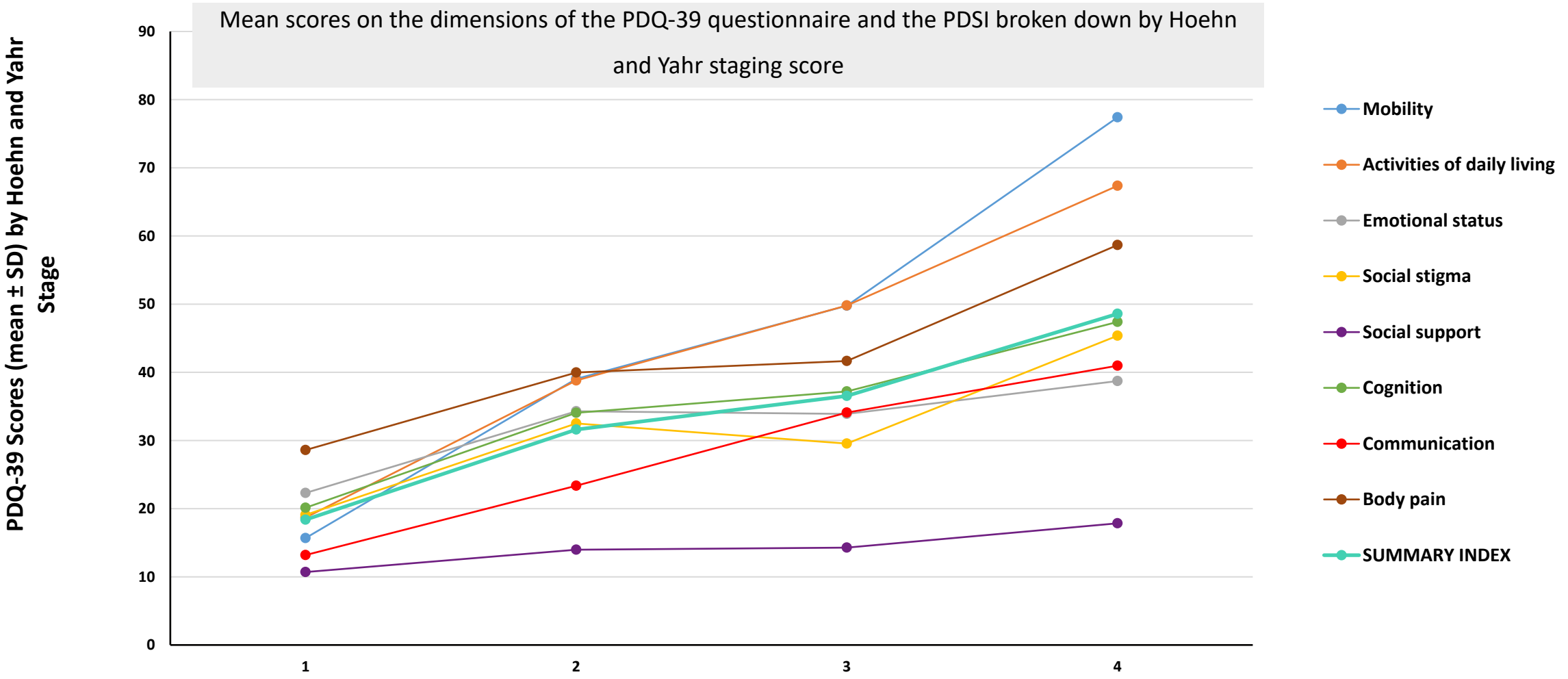


Figure 1. The problems of oral therapy in Parkinson's disease in relation to various pathologies within the upper gastrointestinal system. Poor levodopa absorption could be the chief cause of many variants of levodopa-induced motor fluctuations. *H. Pylori, Helicobacter pylori*; SIBO, small intestine bacterial overgrowth.

Patient QoL declines steadily with disease progression across all PDQ-39 domains



PDQ-39: 39-item Parkinson's Disease Questionnaire. [a] n = 33; [b] n = 56; [c] n = 20; [d] n = 18.

Adapted from Jenkinson C, et al. Age Ageing 1997;26(5):353–7.

From early to complex/advanced Parkinson's: Symptom manifestation increases

Progression of Parkinson's

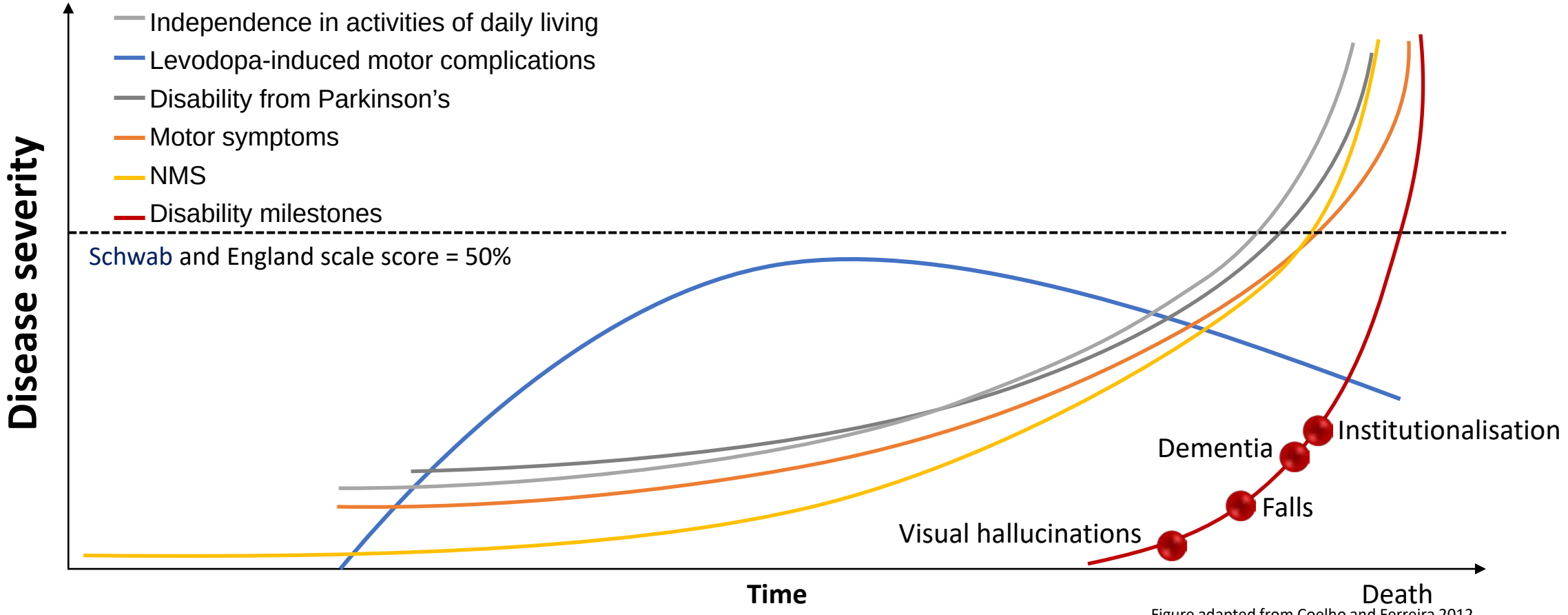


Figure adapted from Coelho and Ferreira 2012

NMS, non-motor symptoms.

Coelho M and Ferreira JJ. Nat Rev Neurol 2012;8:435–42.

Troublesome symptoms: the patient's perspective

Ranking of the 10 most bothersome symptoms in 173 patients with advanced PD of more than 6 years duration

Rank	Symptom/condition	Total score
1	Fluctuating response to medication	115
2	Mood	96
3	Drooling	85
4	Sleep	83
5	Tremor	67
6	Pain	60
7	Bowel problems	46
8	Urinary problems	40
9	Falls	39
10	Appetite/weight	36

Adapted from Politis et al. Mov Disord 2010;25(11):1646-51

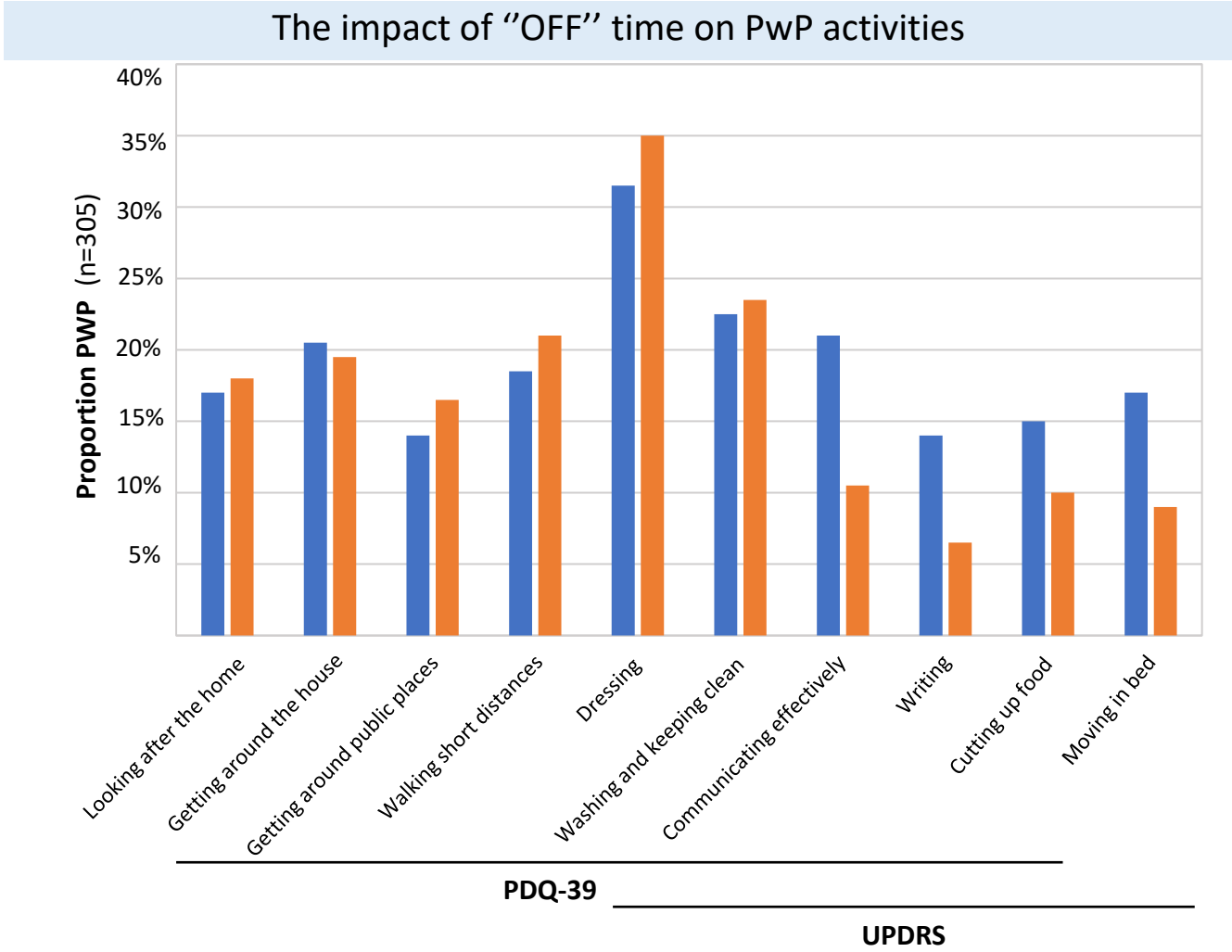
HRQoL in Parkinson's: The impact of "OFF" time on daily life

305 patients with Parkinson's across UK, France, Spain and Italy completed an online survey to explore:

1. **The impact of "OFF" time** on HRQoL

2. **Daily functioning** in people with Parkinson's (PwP) **relative to "ON" time**

Real-world evidence is collected outside of controlled clinical trials and has inherent limitations, including a lesser ability to control for confounding factors.

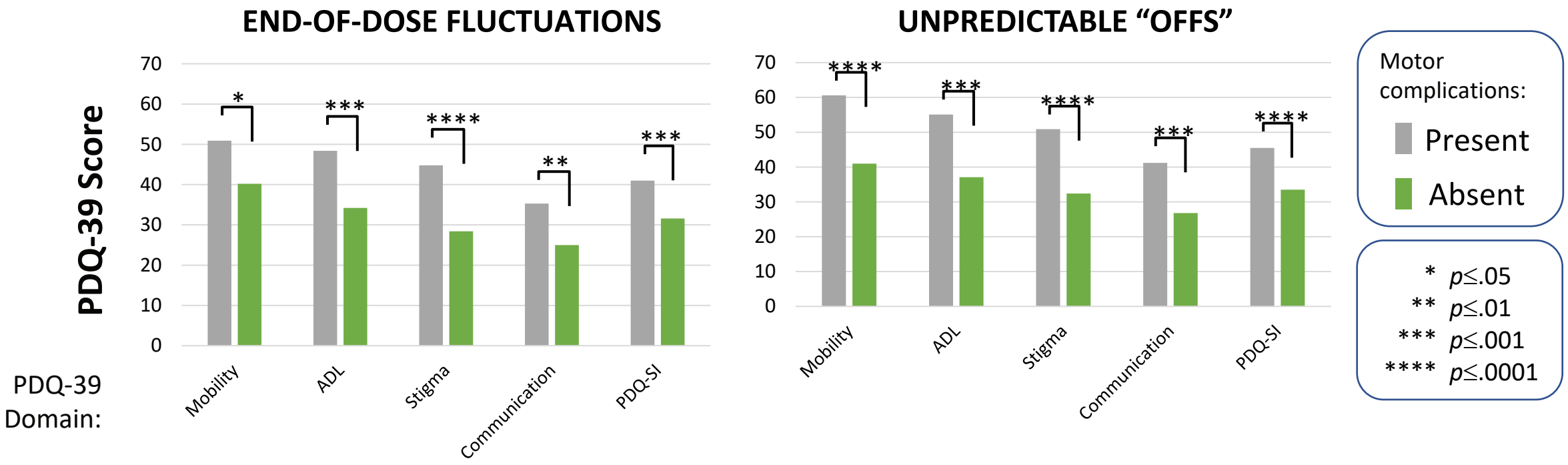


HRQoL, health related quality of life; PDQ-39, Parkinson's disease 39 Item Questionnaire; PwP, people with Parkinson's; UPDRS, Unified Parkinson's Disease Rating Scale. Kerr C, et al. Qual Life Res. 2016;25:1505–15.

Figure adapted from Kerr 2016

Motor complications diminish QoL, most strongly affect mobility, ADL, communication and stigma

143 patients with PD evaluated on Hoehn & Yahr scale, UPDRS and PDQ-39



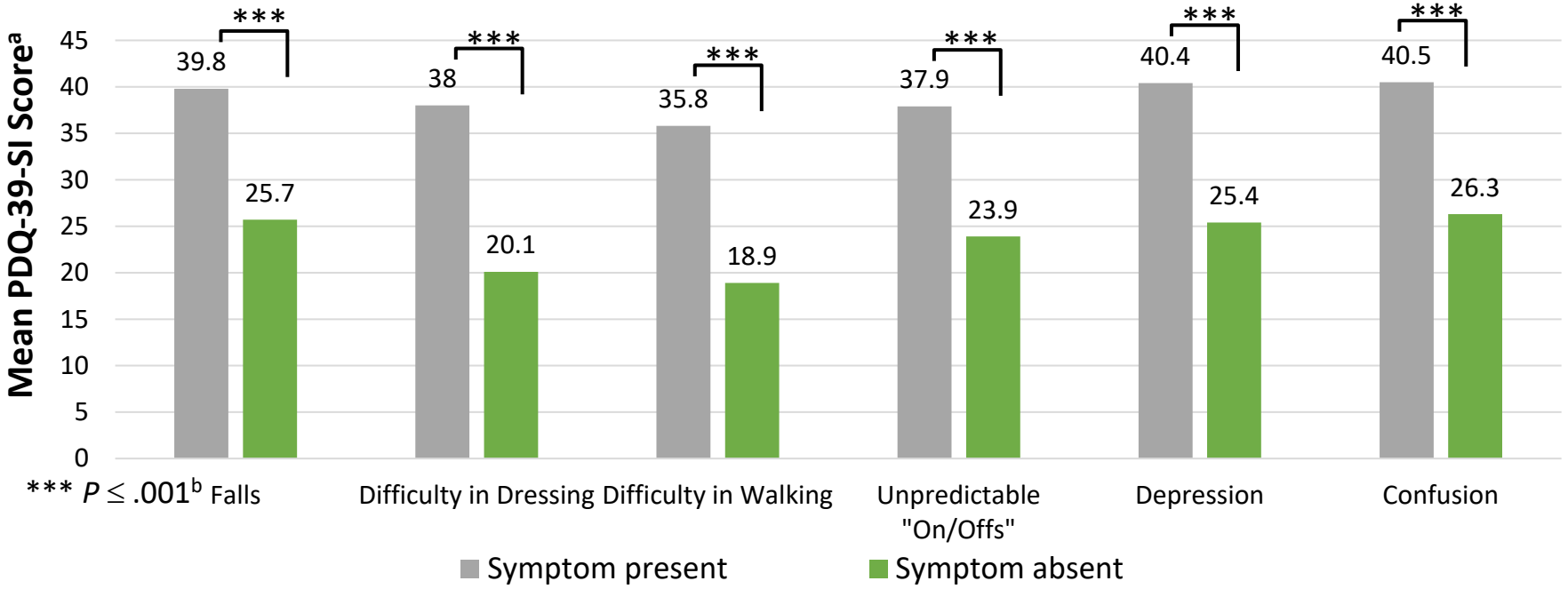
Motor fluctuations did **not** significantly affect the four other PDQ-39 domains (emotional wellbeing, cognition, social support, and bodily discomfort)

ADL, Activities of Daily Living; PDQ-SI, Parkinson's Disease Questionnaire Summary Index; UPDRS, Unified Parkinson's Disease Rating Scale. All p values were significant.
Chapuis S, et al. Movement Disord 2005;20(2):224–30.

Symptoms Impact on QOL in Parkinson's

130 patients with PD in the United Kingdom completed a booklet of questionnaires, including the PDQ-39

- Mean (SD) age: **66.7** (8.52)
- Mean (SD) number of years of illness: **12.1** (7.94)

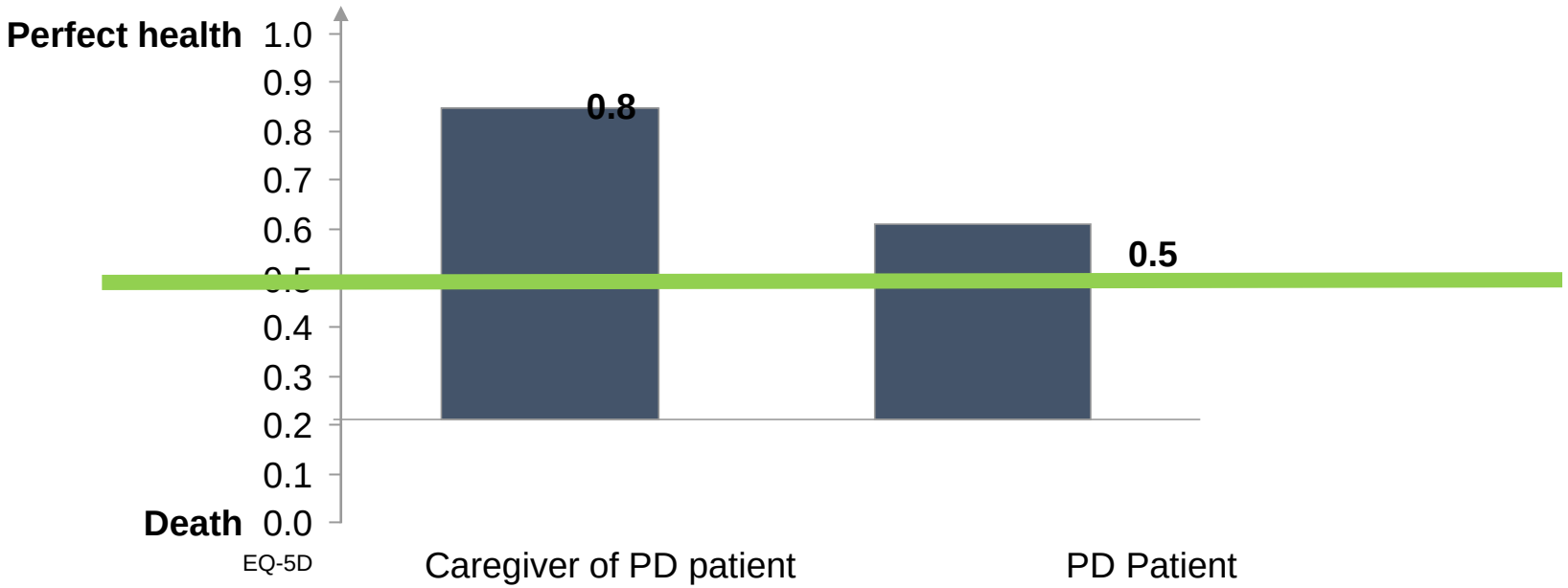


Contributions of physical, medication-related, and cognitive/psychiatric symptoms to QOL can be significant

SD, standard deviation. a Range, 0-100; higher scores reflect poorer QOL. b One-way analysis of variance with Bonferroni correction; significance set at P ≤ .0017.
Rahman S, et al. Mov Disord 2008;23(10):1428–34.

Health related quality of life (HRQoL) is affected in both the patient and their carer

- PD severely impacts upon patients' quality of life
- Disability and disease severity also have an impact on carer burden and mental aspects of the caregivers' HRQoL



Martinez-Martin P. Movement Disorders 2007

HRQoL in Parkinson’s: The impact on the patient and the caregiver

- With disease progression in Parkinson’s , patients require more assistance in their everyday lives, often delivered by caregivers
- In a study looking at the patient and caregiver characteristics associated with caregiver burden in Parkinson's in the palliative stage, caregiver burden is defined as the perception of strain and stress resulting from a perceived obligation to provide care for their loved one with Parkinson’s
- **Studies have shown that several patient characteristics in Parkinson’s contribute to higher rates of caregiver burden**
- The greatest predictors being disease severity and the presence of non-motor symptoms, especially neuropsychiatric disturbances

HRQoL, health related quality of life.

1.Grün G, et al. JAMDA. 2016;17:626–32; 2. Macchi ZA, et al. Ann Palliat Med. 2020;9:24–33.

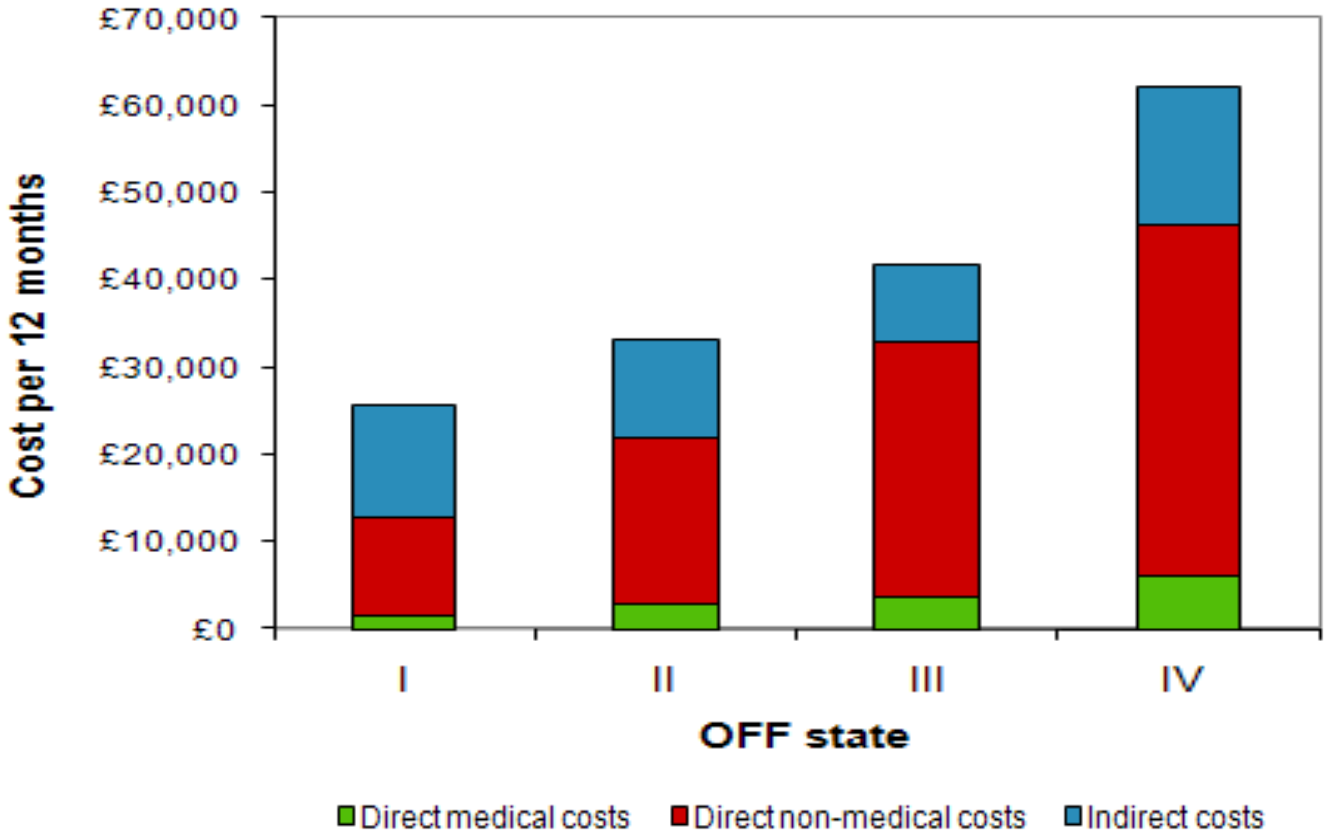
Factors which may influence caregiver burden

- Parkinson's patients are dependent on personal care[1]
- Mainly provided by a female member of family[2]
- Motor impairment[3]
- Neurocognitive symptoms[3]
- Neuropsychiatric symptoms[3]
- Behavioural issues[3]
- Autonomic nerves system disorders[2]
- Bladder and bowel management[2]
- Sleep disturbances[3]

- Restriction in time for personal needs[3]
- Lack of family time[1]
- No time for leisure and social activities[1]
- Occupational limitation[4]
- Costs[3]
- Lack of social support[3]
- Impairment of sleep[3]
- Depression and anxiety[1,3]
- Other health issues[1,3]

1. Schrag A, et al. Parkin Rel Disord. 2006;12:35–45; 2. Grün G, et al. JAMDA. 2016;17:626–32;
3. Mosley RE, et al. J Geriatr Psychiatry Neurol. 2017;30:235–52; 4. Dowding CH, et al. Drugs Aging. 2006;23:693–721.

Association between cost types and progression in disease severity



- Mean annual total costs increase according to the time spent in OFF
- The cost of care accounts for more than 85% of the total costs at all stages of OFF

Note:

Calculation did not include

- direct medical care costs for medication and home medical care
- direct non medical care costs for transportation to visits and
- indirect costs for sick leave and retirement due to PD

Findley et al. Journal of Medical Economics 2011

Clinical benefit of MAO-B and COMT inhibition in Parkinson's disease: practical considerations

Martin Regensburger, Chi Wang Ip, Zacharias Kohl, Christoph Schrader, Peter P. Urban, Jan Kassubek & Wolfgang H. Jost

Journal of Neural Transmission (2023) | Cite this article

Substance	Label (EMA)	Dosing	Approx. half-life of enzymatic inhibition	Main side effects	Caveats
MAO-B inhibitors					
Selegiline	Monotherapy, or combination with levodopa/DDCI	5 mg or 10 mg OD in the morning	14 days	Insomnia, bradycardia, hypotension, nausea	Multiple interactions and contraindications (see text)
Rasagiline	Monotherapy, or combination with levodopa/DDCI in end-of-dose fluctuations	1 mg OD in the morning	14 days	Nausea, light-headedness, headache, insomnia	Contraindication in combination with other MAO inhibitors and pethidine; increased caution in combination with other serotonergic compounds
Safinamide	Combination with a stable dose of levodopa/DDCI ± other PD drugs in mid-to late-stage fluctuating patients	50 mg OD in the morning, increase to 100 mg OD after 2 weeks as needed	22 h	Dyskinesia, hallucinations, nausea	Contraindication in combination with other MAO inhibitors and pethidine, severe hepatic impairment, certain eye diseases. Increased caution in combination with other serotonergic compounds
COMT inhibitors					
Tolcapone	Idiopathic PD with motor fluctuations, non-responsive to or intolerant of other COMT inhibitors in combination with levodopa/DDCI	100 mg TID or 200 mg TID	3–4 h	Diarrhea, urine discoloration, dyskinesia	Third line COMT substance. Strict vigilance for liver injury by liver function tests every 2 weeks for 1 year, every 4 weeks for subsequent 6 months and every 8 weeks thereafter
Entacapone	PD with end-of-dose motor fluctuations in combination with levodopa/DDCI	200 mg with each levodopa/DDCI dose	2–3 h	Diarrhea, urine discoloration, dyskinesia	Contraindication in combination with *non-selective* MAO inhibitors, in hepatic impairment and previous neuroleptic malignant syndrome
Opicapone	Combination with levodopa/DDCI in end-of-dose fluctuations	50 mg OD in the evening	4 days	Dyskinesia	Contraindication in combination with MAO inhibitors other than those used for PD, previous neuroleptic malignant syndrome

Early motor fluctuation (wearing off)

*provided no contraindications and ensure treatment is personalised to person with Parkinson's

Wearing off features &/or Good cognition/ mild cognitive impairment

Adjust Levodopa + carbidopa or benserazide (IR,CR)

Add Dopamine agonist PR/MR
- Oral,
- Transdermal

If not given already

Add MAO-B inhibitor
- Rasagiline,
- Safinamide,

Selegiline (2nd line choice)

If not given already

Add COMT Inhibitor
- Entacapone,
- Opicapone,

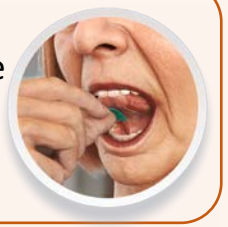
Tolcapone (2nd line choice)

If not given already

Worsening of motor fluctuations: all above options & considering that **Amantadine** is the only one that can improve both dyskinesia and off time Consider on demand device-aided therapies

Inhaled L-Dopa

Sublingual Apomorphine



Apo-go pen S/C

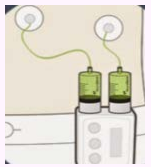
Oral dispersible L-dopa

Severe motor fluctuation: consider second-line **device-aided therapies** if no dementia*

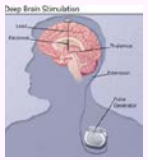
L-dopa/carbidopa intra-jejunal continues infusion

Apomorphine S/C continues infusion

L-dopa S/C continues infusion



Deep Brain Stimulation (Gpi, STN)



Why Should We Differentiate APD?

Effective management

Timely involvement of MDSs

Uniformity in evaluation

Timely treatment options

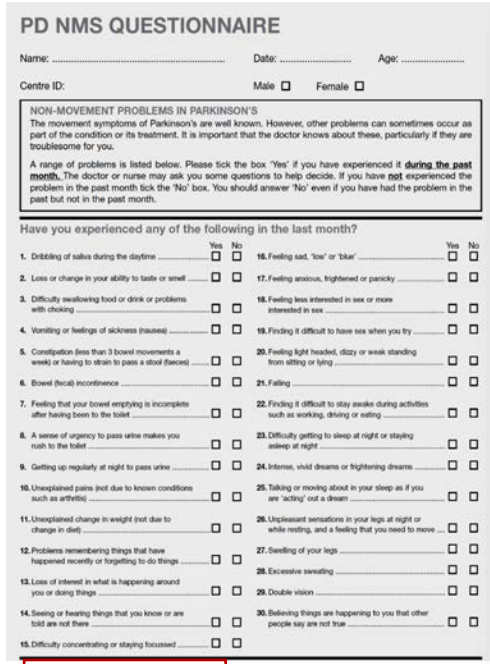
Key desired features of a specific APD screening tool:

- **Comprehensive** patient assessment (motor, non-motor, and functional symptoms)
- **Ease of use** (brevity and simplicity of screening items)
- **Uniformity of use** across all levels of specialty (general neurologists and MDSs)

MDS, movement disorder specialist

1. Antonini A, et al. (2011) J Neurol, 579-585; 2. Alves G, et al. (2008) J Neurol, 18-32; 3. Braak H, et al. (2003) Neurobiol Aging, 197-211; 4. Goetz CG, et al. (2004) Mov Disord, 1020-1028; 5. Kulisevsky J, et al. (2013) Neurología, 503-521; 6. Kulisevsky J, et al. (2013) Neurología, 558-583.

Comprehensive Clinical Assessment of Symptoms in PD


PD NMS QUESTIONNAIRE

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

Centre ID: Male ☐ Female ☐

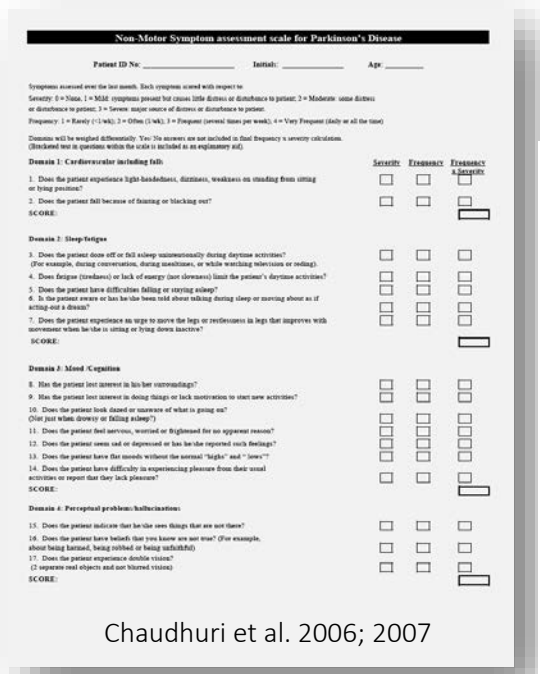
NON-MOVEMENT PROBLEMS IN PARKINSON'S

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
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (fecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐


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).

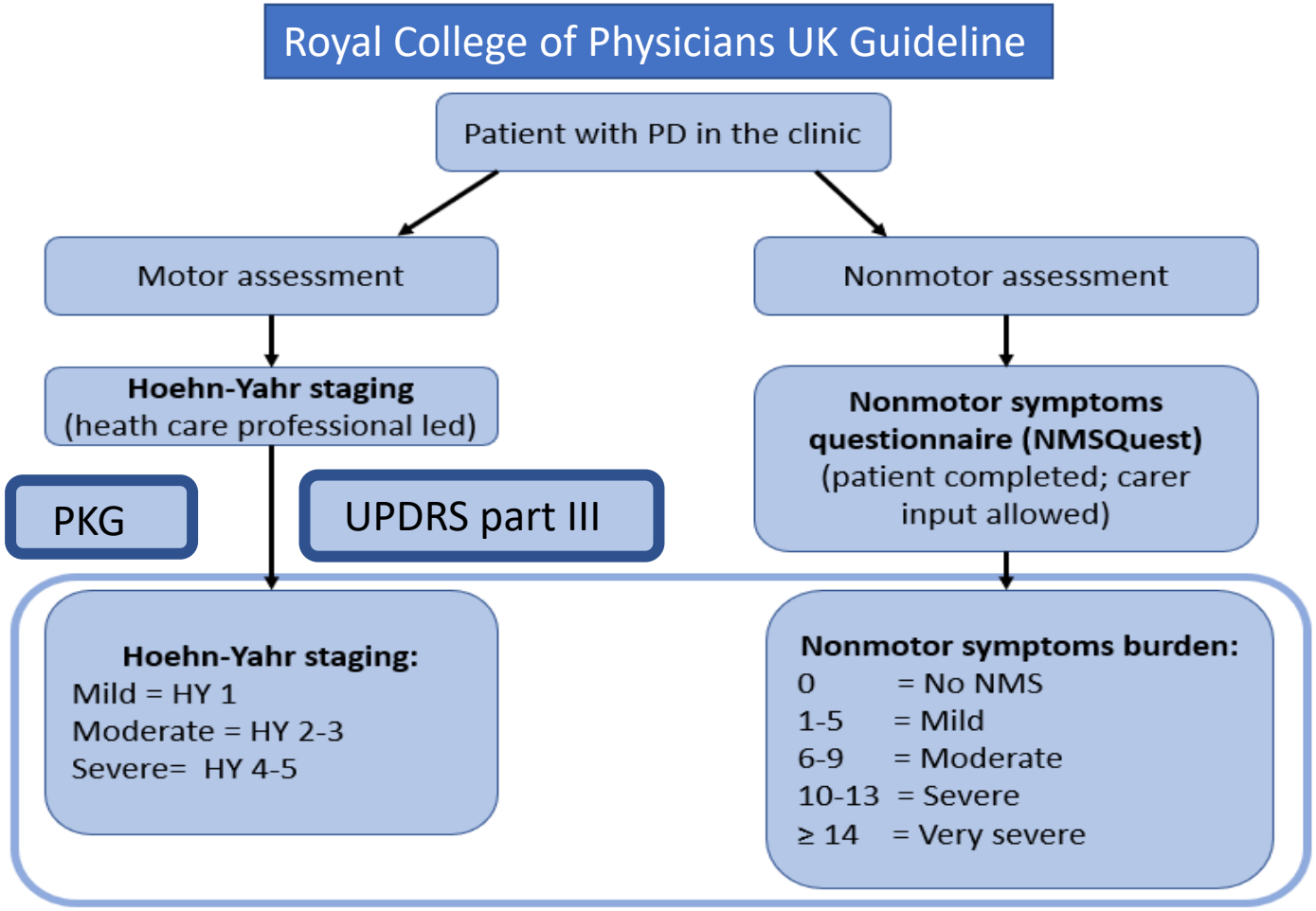
	Severity	Frequency	Frequency x Severity
Domain 1: Cardiovascular including fall:			
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
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/hallucination:			
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:			☐

Chaudhuri et al. 2006; 2007

Hoehn and Yahr Scale

1. **Unilateral involvement only usually with minimal or no functional disability**
2. **Bilateral or midline involvement without impairment of balance**
3. **Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent**
4. **Severely disabling disease; still able to walk or stand unassisted**
5. **Confinement to bed or wheelchair unless aided**

Hoehn and Yahr. Neurology 1967; 17: 427-442



Sauerbier et al 2016

MDS, movement disorder specialist

1. Antonini A, et al. (2011) J Neurol, 579-585; 2. Alves G, et al. (2008) J Neurol, 18-32; 3. Braak H, et al. (2003) Neurobiol Aging, 197-211; 4. Goetz CG, et al. (2004) Mov Disord, 1020-1028; 5. Kulisevsky J, et al. (2013) Neurología, 503-521; 6. Kulisevsky J, et al. (2013) Neurología, 558-583.

Delphi Panel Building Consensus on APD

Characteristics That Define a Patient With APD

Motor

1. Moderate level of troublesome motor fluctuations
2. At least 2 hours of the day with "off" symptoms
3. At least 1 hour of the day with troublesome dyskinesia
4. Moderate level of dyskinesia
5. Troublesome dysphagia
6. Daily oral levodopa doses 5 times a day

Non-Motor

1. Mild level of dementia
2. Non-transitory troublesome hallucinations
3. Moderate level of psychosis
4. Non-motor symptom fluctuations
5. Moderate level of nighttime sleep disturbances

Function

1. Repeated falls (more than 1 fall) despite optimal treatment
2. Needs help with ADL at least some of the time
3. Not able to perform complex tasks—most of the time
4. Moderate impaired mobility

Antonini A, et al. (2015) 19th International Congress of Parkinson's Disease and Movement Disorders. San Diego, CA, USA. Poster 1186.

Delphi Panel Building Consensus on APD

Most Salient Characteristics of Patients with APD Eligible for Device-Aided Treatments

Motor

- Troublesome dyskinesia and “off” periods
- ≥ 2 hours of “off” time
- “Off” period postural instability
- Dystonia with pain
- Freezing of gait during “off” periods

Non-Motor

- Nighttime sleep disturbances

Function

- Limited ADL

Antonini A, et al. (2015) 19th International Congress of Parkinson’s Disease and Movement Disorders. San Diego, CA, USA. Poster 1186.

Practical Guidance on Device-aided Management of PD: Recognizing Patients Who Are Failing Oral Therapies

Motor Complications	• > 1-2 h “off” time during waking hours, despite optimized oral therapy • Patients with marked “off” symptoms, regardless of “off” duration • Motor fluctuations accompanied by troublesome dyskinesias not controlled by addition of Amantadine[a], despite multiple attempts to achieve a response
Inadequate QoL	• QOL becomes inadequate due to motor fluctuations and the clinician/patient agree that oral therapy is no longer effective • Adequate trial of oral therapies should include levodopa and, unless contraindicated, dopamine agonists, MAO-B inhibitors, and COMT inhibitors
Frequency of Oral therapies	• Levodopa is required > 5 times daily • Number of doses is not relevant if tolerated by the patient and an adequate reduction in “off” time is achieved

MAO-B, monoamine oxidase-B; COMT, catechol-O-methyltransferase.
a Amantadine is not currently indicated for the treatment of dyskinesia.
Odin P, Chaudhuri KR, et al. (2015) Parkinsonism Relat Disord, 1133-1144.

Parkinsonism & Related Disorders
Volume 109, April 2023, 105359

Timely referral for device-aided therapy in Parkinson's disease. Development of a screening tool

Harmen R. Moes [a], Jolien M. ten Kate [a], Axel T. Portman [b], Barbera van Harten [c], Mirjam E. van Kesteren [d], Tjeerd Mondria [e], Gerton Lunter [f], Erik Buskens [f], Teus van Laar [a]

Highlights

- The estimated prevalence of eligibility for referral for DAT is relatively low (6.6%).
- Patient and treatment characteristics are predictive of eligibility for referral.
- A new screening tool was composed encompassing three patient factors.
- The new tool can accurately screen for eligibility for referral for DAT.
- The tool outperforms other tools by having a high positive-predictive value.

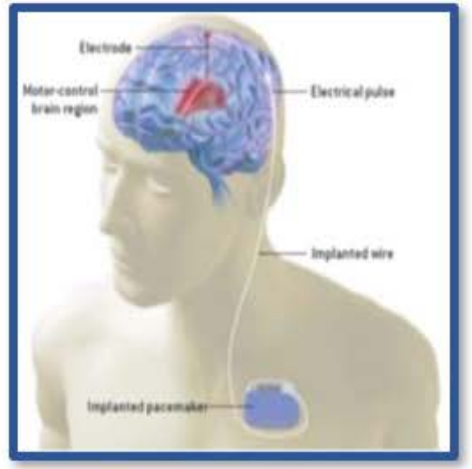
Non-oral therapies

Rotigotine transdermal patch

Subcutaneous apomorphine

Intrajejunal levodopa-carbidopa

Deep Brain Stimulation



Clinical Considerations in Advanced Therapy Patient Selection

Patients with dyskinesia and motor fluctuations that can no longer be controlled by oral medication

	Apomorphine	LCIG	DBS
Age	No age limitation (caveat: hallucinations and psychosis in patients aged > 70 years)[1]	**No age limitation[1]**	Patients should not be older than 70 years[1]
Psychiatric status	No limitation; however, careful monitoring is advisable[1]	**No limitation, but treat patients with past/current psychosis with caution[1,2]**	No psychiatric medical history[1]
Cognitive impairment	No or mild cognitive impairment[1]	**No limitation, nurse/caregiver support advisable in case of suspected or diagnosed dementia**	No cognitive impairment (MMSE > 24) [1]
Follow-up treatment	Technical adjustments by patients or caregiver possible, regular check by physician[1]	**Technical adjustments by patients or caregiver possible, regular check by physician[1]**	Technical adjustments only by physician[1]

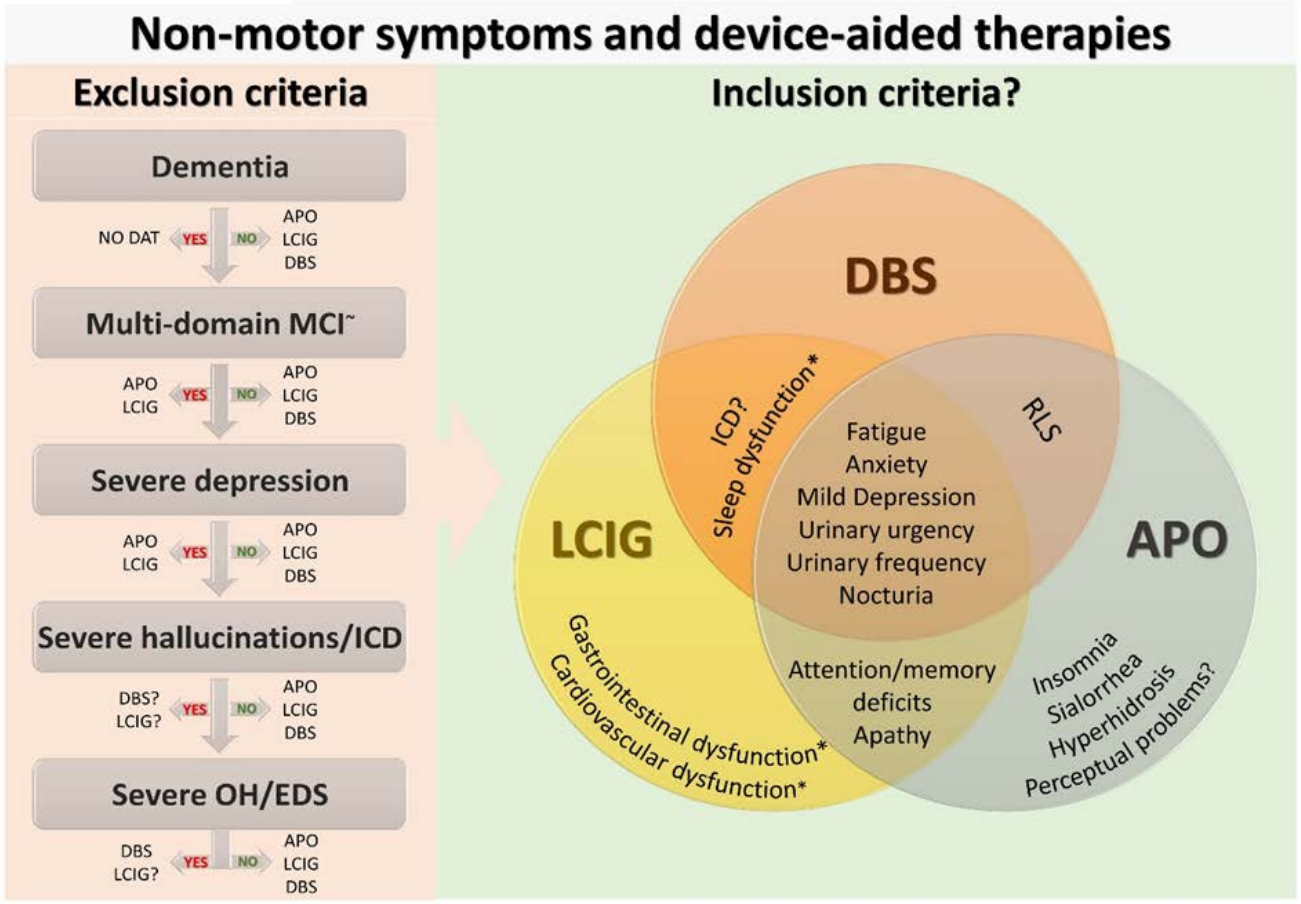
Journal of Personalized Medicine

MDPI

Viewpoint

Personalised advanced therapies in Parkinson's disease: the role of non-motor symptoms profile

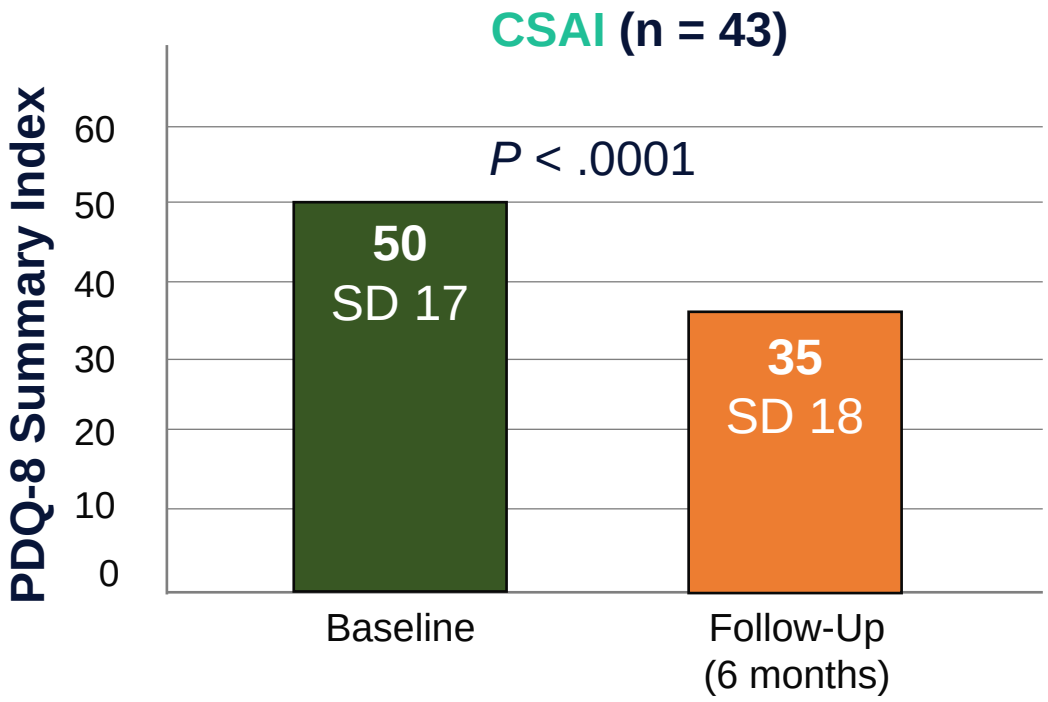
Valentina Leta[1,2,†], Haidar Dafsari[3,†], Anna Sauerbier[1,2,3], Vinod Metta[1,2], Nataliya Titova[4,5], Lars Timmermann[6], Keyoumars Ashkan[7], Michael Samuel[2], Eero Pekkonen[8], Per Odin[9], Angelo Antonini[10], Pablo Martinez-Martin[11], Miriam Parry[1,2], Daniel J van Wamelen[1,2,12] and K Ray Chaudhuri[1,2,*]

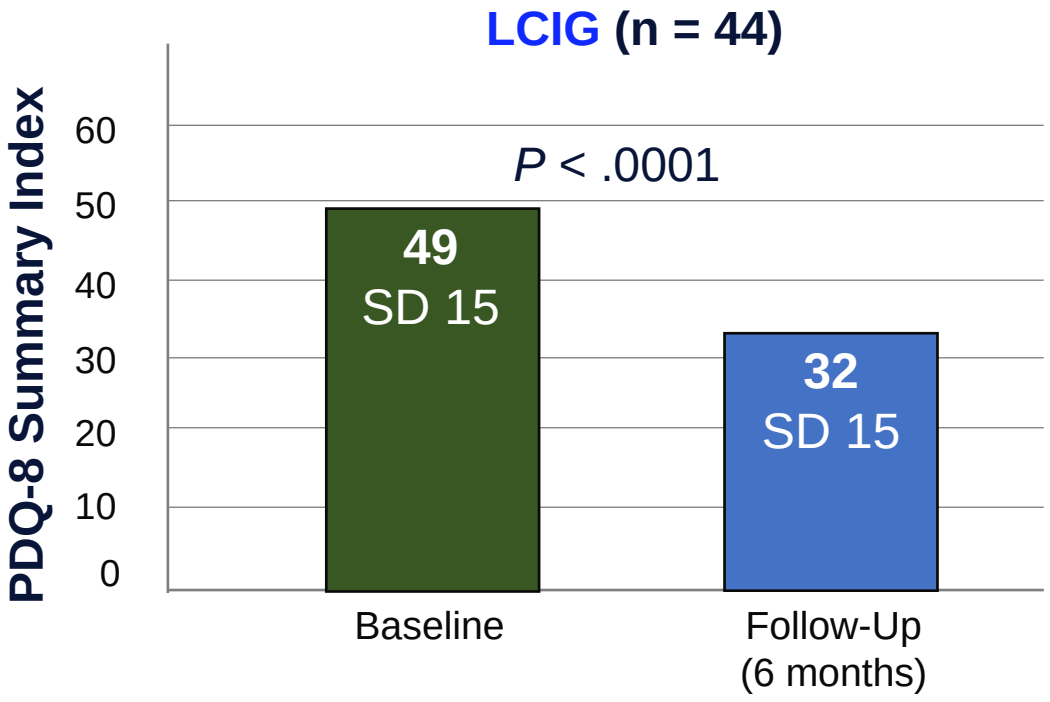


APO: Subcutaneous apomorphine infusion
LCIG: Levodopa-carbidopa intestinal gel infusion
DBS: Subthalamic deep brain stimulation

J. Pers. Med. **2021**, *11*, 773. https://doi.org/10.3390/jpm11080773

EuroInf: a 6-Month, Open-Label, Prospective, Observational, Multi-center Study Comparing Apomorphine and LCIG



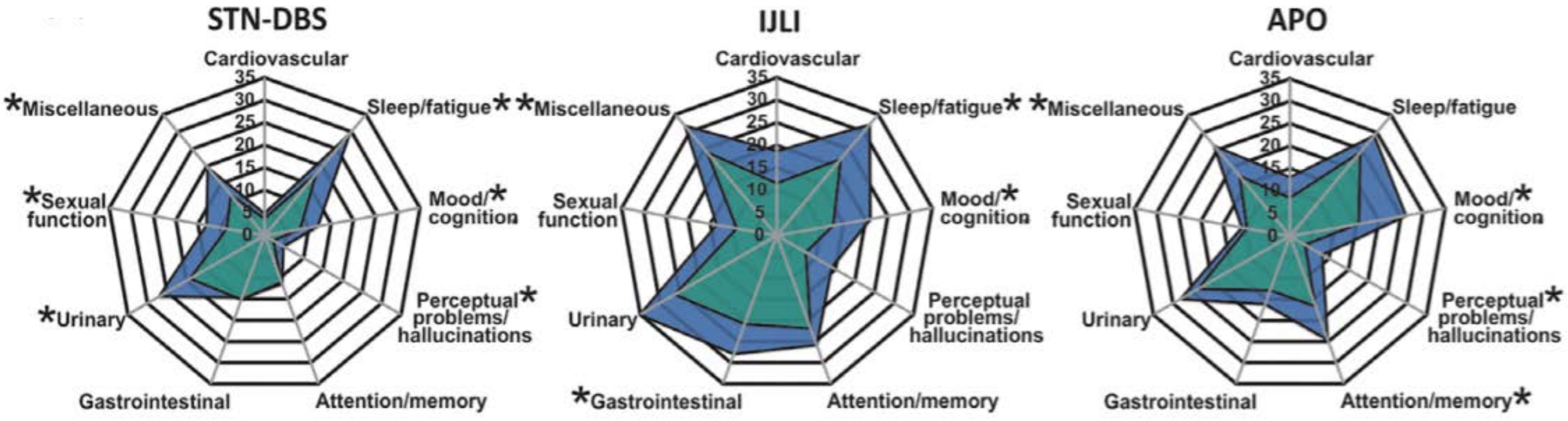


CSAI-treated patients showed a 30% relative reduction in PDQ-8 Summary Index score (effect size: 0.89)

LCIG-treated patients showed a 34% relative reduction in PDQ-8 Summary Index score (effect size: 1.14)

PDQ-8, Parkinson's Disease Questionnaire-8. Martinez-Martin P, Reddy P, Katzenschlager R, Antonini A, Todorova A, Odin P, Henriksen T, Martin A, Calandrella D, Rizos A, Bryndum N, Glad A, Dafsari HS, Timmermann L, Ebersbach G, Kramberger MG, Samual M, Wenzel K, Tomantschger V, Storch A, Pirtošek Z, Trost M, Svenningsson P, Palhagen S, Volkmann J, Chauduri KR. (2015) Mov Disord, 510-516.

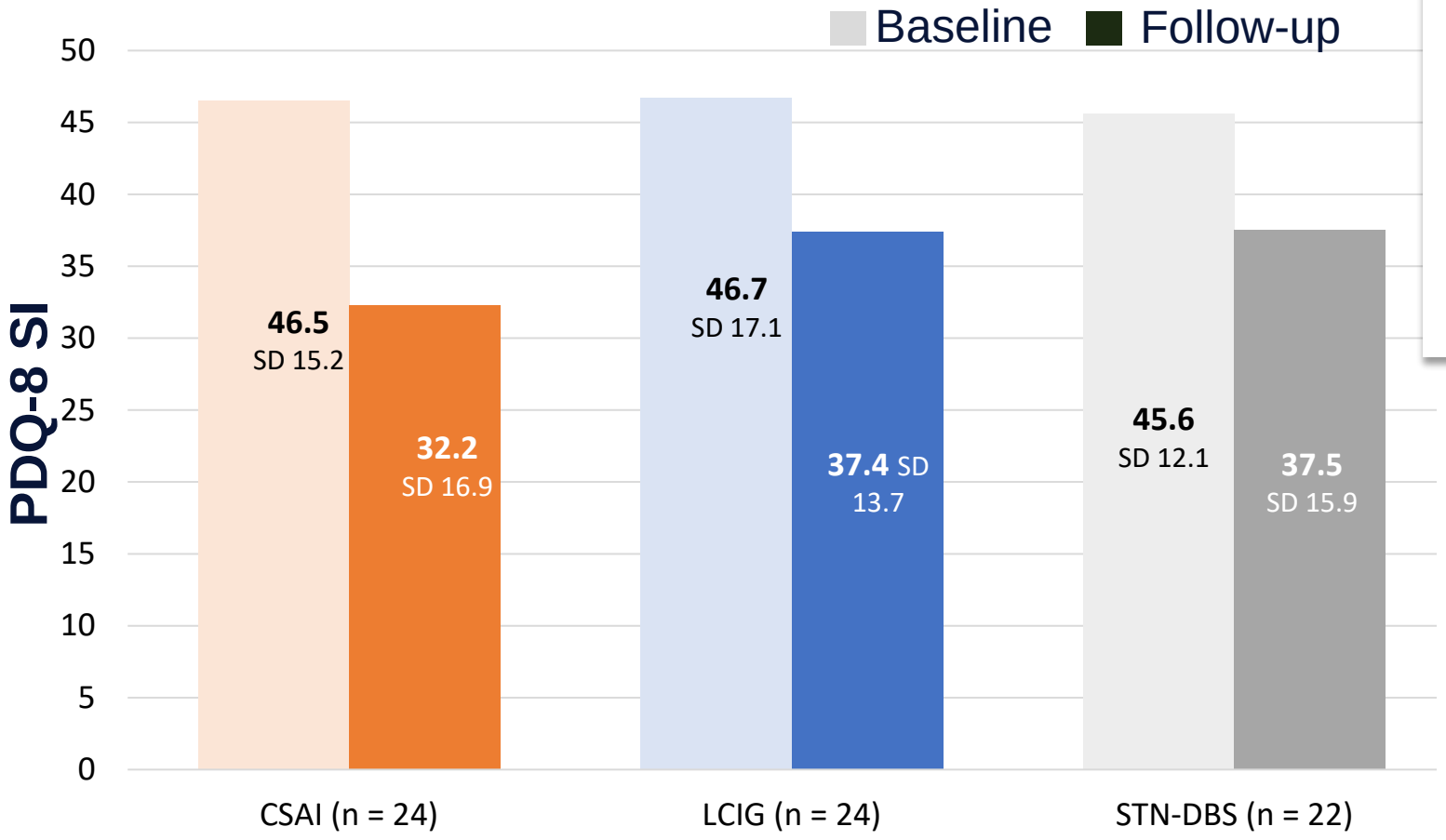
Advanced therapies



Dafsari et al. Mov Disord. 2019;34(3):353-365.

APO: apomorphine infusion IJLI: intrajejunal levodopa infusion STN-DBS: subthalamic deep brain stimulation

EuroInf 2: Real-Life, Multi-center, International, Non-Randomized Contrast and Comparison of Device-Aided Therapies



RESEARCH ARTICLE

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

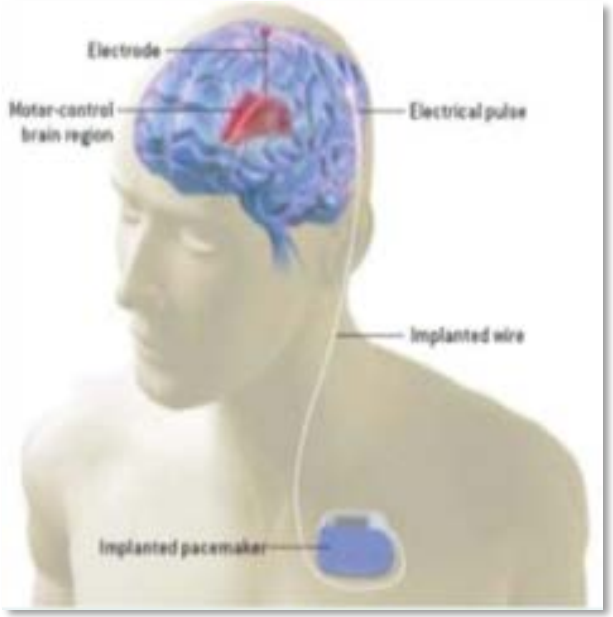
Haidar S. Dafsari, MD,[1,2*] Pablo Martinez-Martin, MD, PhD,[3] Alexandra Rizos, MSc,[2] Maja Trost, MD,[4] Maria Gabriela dos Santos Ghilardi, MD,[5] Prashanth Reddy, MD/PhD,[2] Anna Sauerbier, MD,[2,6] Jan Niklas Petry-Schmelzer, MD,[1] Milica Kramberger, MD,[4] Robbert W. K. Borgemeester, MD,[7] Michael 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

Improvement at follow-up was significant for all therapies (P ≤ .05); however, sample sizes in the matched sub-cohort are small.

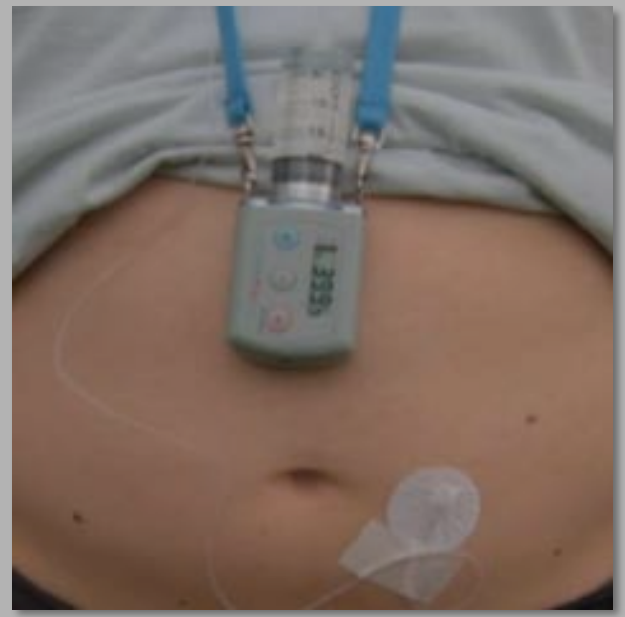
SI, summary index. Dafsari HS, Martinez-Martin P, Rizos A, Trost M, Dos Santos Ghilardi MG, Reddy P, Sauerbier A, Petry-Schmelzer JN, Kramberger M, Borgemeester RWK, Barbe MT, Ashkan K, Silverdale M, Evans J, Odin P, Fonoff ET, Fink GR, Henriksen T, Ebersbach G, Pirtošek Z, Visser-Vandewalle V, Antonini A, Timmermann L, Ray Chaudhuri K; EUROPAR and the International Parkinson and Movement Disorders Society Non-Motor Parkinson's Disease Study Group. (2019) Mov Disord, 353-365.

Advanced Therapies and QOL in Parkinson's

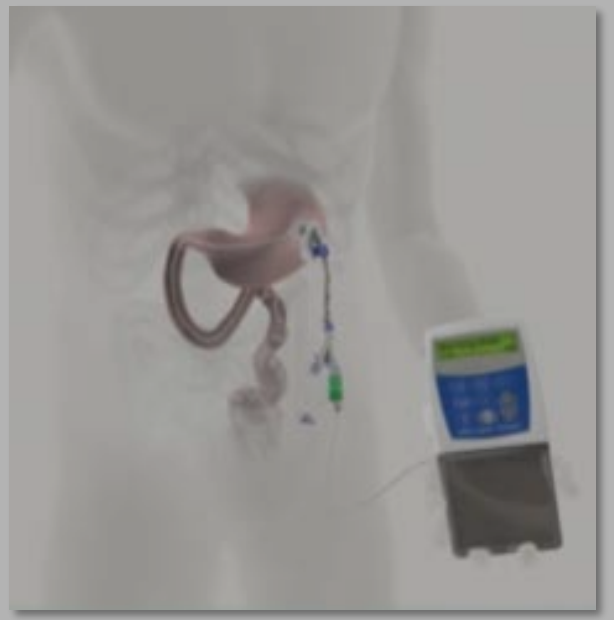
Deep Brain Stimulation (DBS)



Continuous Subcutaneous Apomorphine Infusion (CSAI)

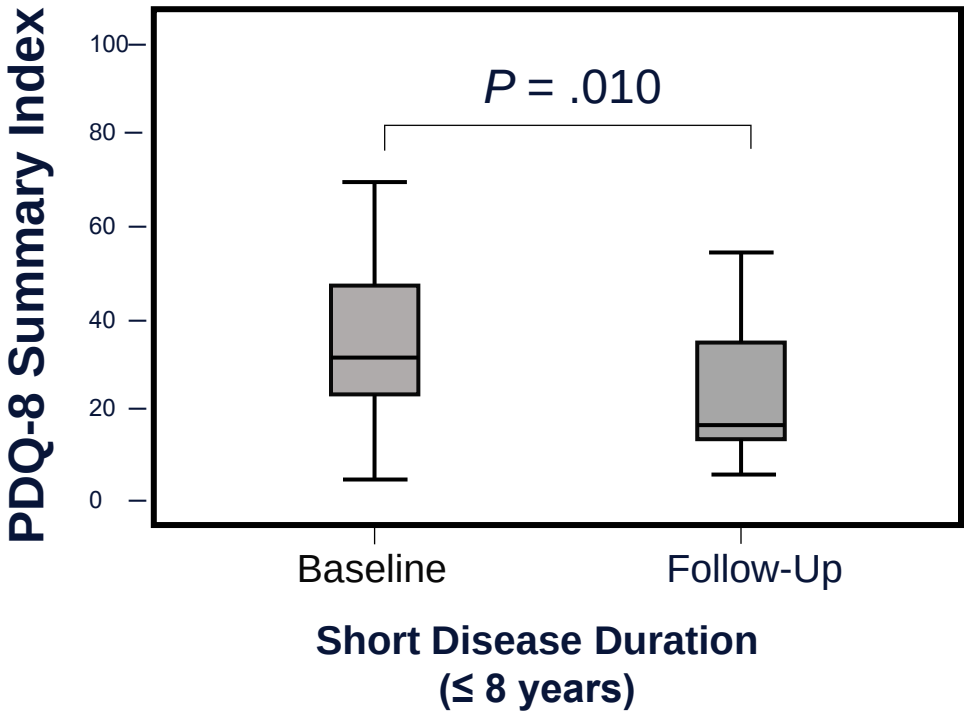


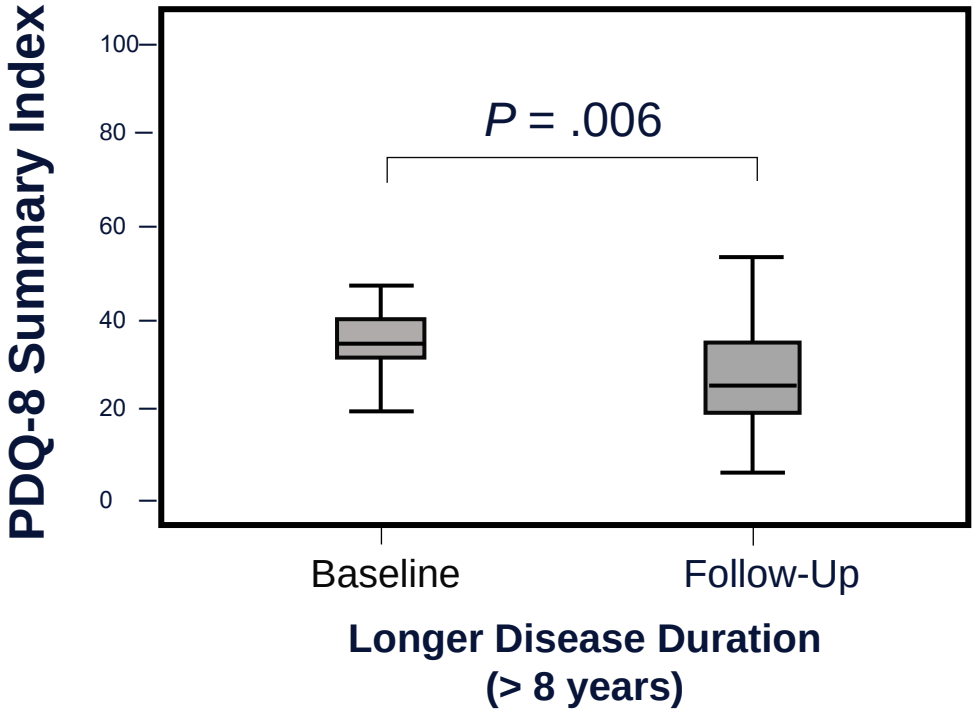
Levodopa-Carbidopa Intestinal Gel (LCIG)



Subthalamic Neurostimulation for Patients Aged ≥ 61 Years With PD

QOL in patients aged ≥ 61 years with short and longer disease duration





STN-DBS in patients aged ≥ 61 years significantly improved QOL, irrespective of PD duration

Dafsari HS, Reker P, Silverdale M, Reddy P, Pilleri M, Martinez-Martin P, Rizos A, Perrier E, Weiß L, Ashkan K, Samuel M, Evans J, Visser-Vandewalle V, Antonini A, Chaudhuri KR, Timmermann L; EUROPAR and the IPMDS Non-Motor PD Study Group. (2017) Neuromodulation, 532-540.

DBS Safety: Overview From a Meta-Analysis

Reported common AEs associated with STN-DBS in 778 patients across 29 studies from 1993 to 2004

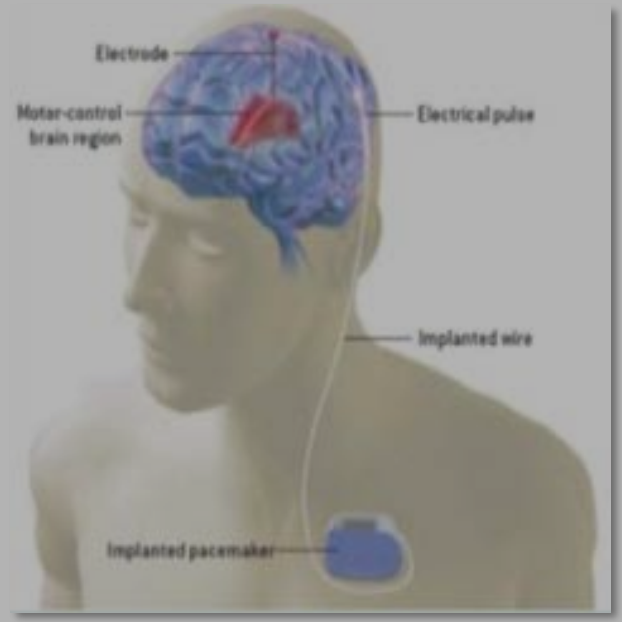
Surgery	Device	Stimulation
• Transient confusion (15.6%) • Intracranial hemorrhage (3.9%) • Infection (1.7%) • Seizure (1.5%) • Miscellaneous (3.3%) • Pulmonary embolus (0.3%)	• Electrode/wire replacement (4.4%) • Device dysfunction (3.0%) • Infection (1.9%) • Migration (1.5%)	• Dysarthria (9.3%) • Weight gain (8.4%) • Depression (6.8%) • Eyelid-opening apraxia (3.6%) • Stimulation-induced dyskinesia (2.6%) • Manic episodes (1.9%) • Miscellaneous motor (4.0%) • Miscellaneous psychiatric (3.5%)

Overall cumulative incidence of AEs directly related to DBS was ≈ 11% but was highly variable across studies.

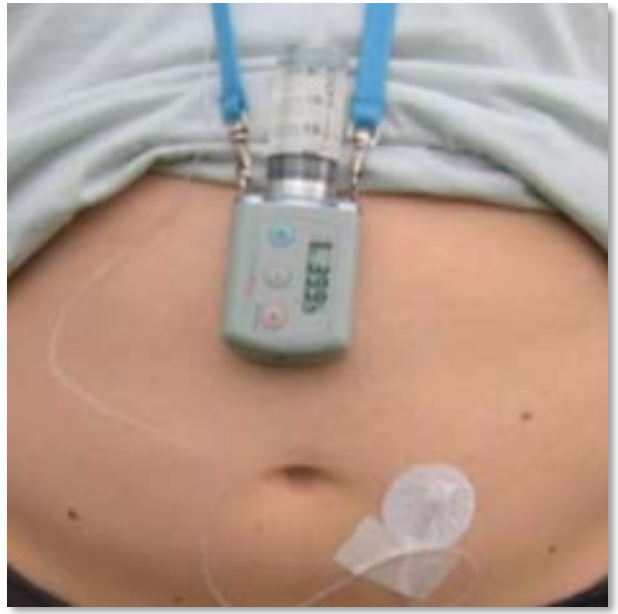
Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G. (2006) Mov Disord, S290-S304.

Advanced Therapies and QOL in Parkinson's

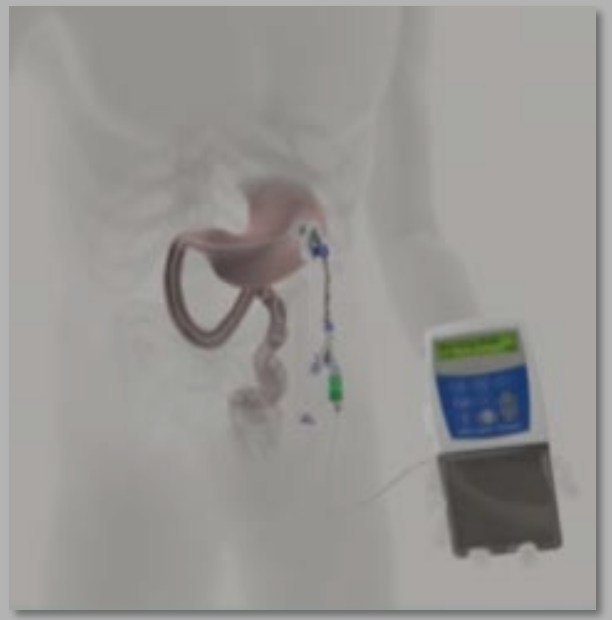
Deep Brain Stimulation (DBS)



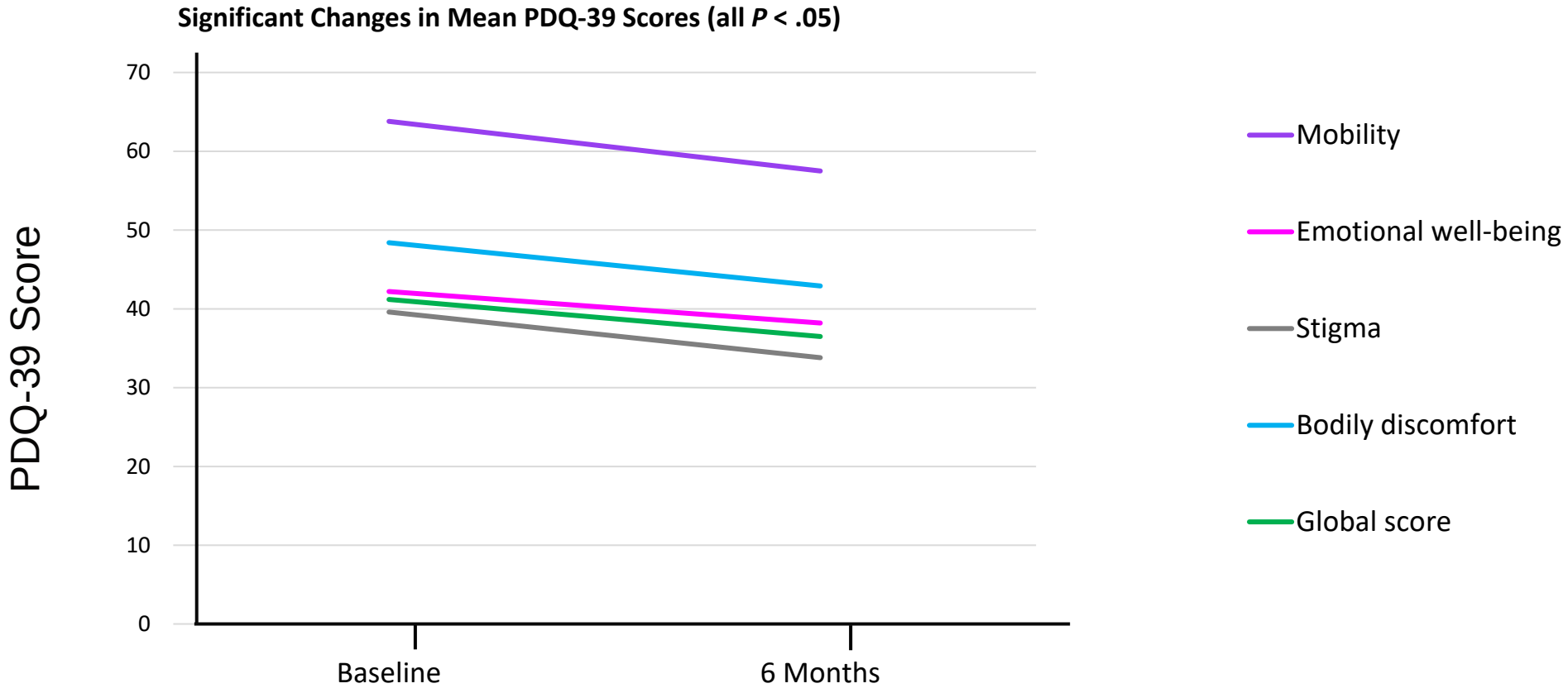
Continuous Subcutaneous Apomorphine Infusion (CSAI)



Levodopa-Carbidopa Intestinal Gel (LCIG)



OPTIPUMP Study: QOL in PD Improved by CSAI



Drapier S, Eusebio A, Degos B, Vérin M, Durif F, Azulay JP, Viallet F, Rouaud T, Moreau C, Defebvre L, Fraix V, Tranchant C, Andre K, Courbon CB, Roze E, Devos D..(2016) J Neurol, 1111-1119.

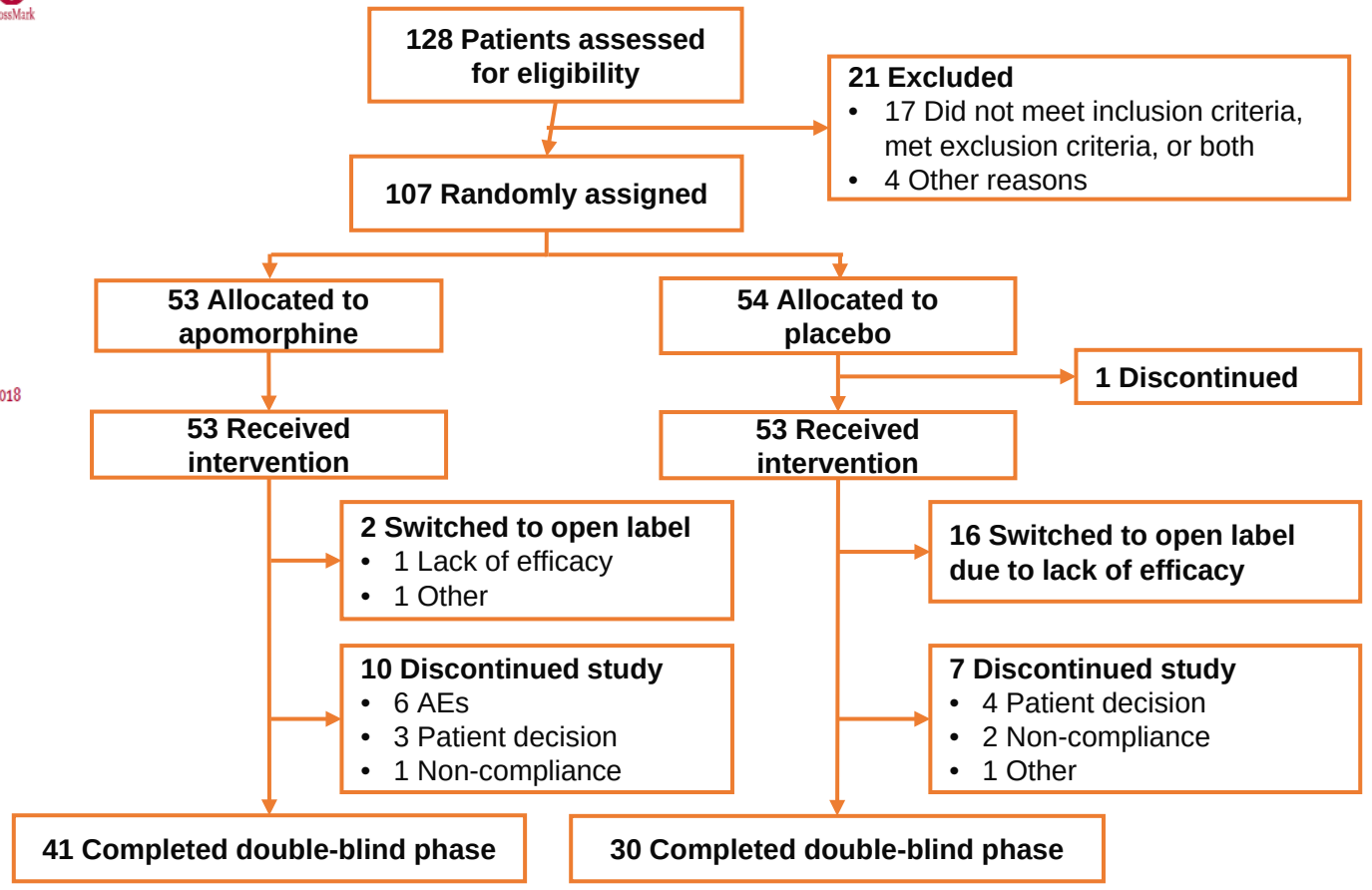
TOLEDO: Multicenter, Parallel-Group, Double-Blind, Placebo-Controlled, Phase 3 Study

Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

Regina Katzenschlager, Werner Poewe, Olivier Rascol, Claudia Trenkwalder, Günther Deuschl, K Ray Chaudhuri, Tove Henriksen, Teus van Laar, Kevin Spivey, Senthil Vel, Harry Staines, Andrew Lees

Summary

Background Subcutaneous apomorphine infusion is a clinically established therapy for patients with Parkinson's Lancet Neurol 2018



Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Chaudhuri KR, Henriksen T, van Laar T, Spivey K, Vel S, Staines H, Lees A. (2018) Lancet Neurol, 749-759.

Safety and Tolerability of CSAI in the Treatment of PD

Characteristic, n (%)	CSAI (n = 54)	Placebo (n = 53)
≥ 1 TEAE	50 (93)	30 (57)
TEAEs in ≥ 10% of patients		
Skin nodules	24 (44)	0
Nausea	12 (22)	5 (9)
Somnolence	12 (22)	2 (4)
Skin erythema	9 (17)	2 (4)
Dyskinesia	8 (15)	0
Headache	7 (13)	2 (4)
Insomnia	6 (11)	1 (2)
Serious TEAEs	5 (9)	2 (4)

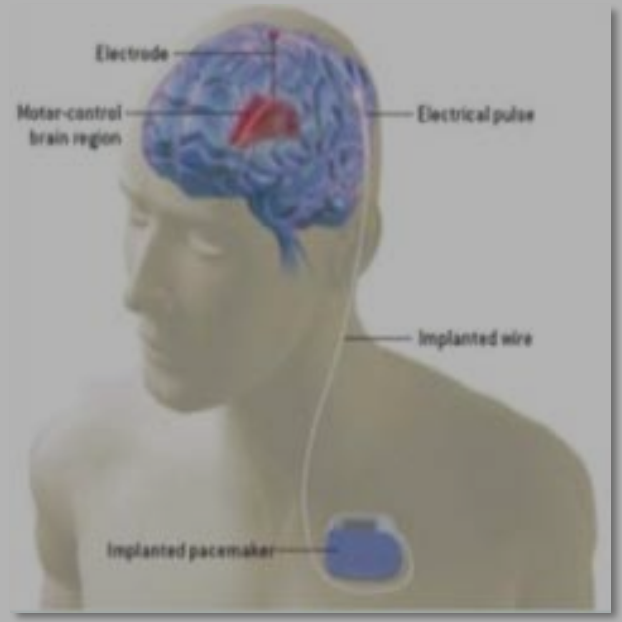
- ***CSAI was well tolerated without any unexpected safety signals***
- ***6 Patients withdrew from the CSAI group***

TEAE, treatment-emergent adverse event.

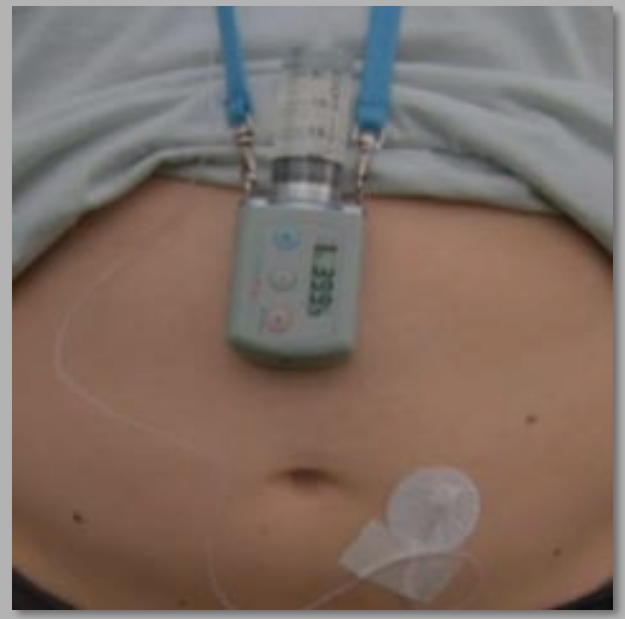
Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Chaudhuri KR, Henriksen T, van Laar T, Spivey K, Vel S, Staines H, Lees A. (2018) Lancet Neurol, 749-759.

Advanced Therapies and QOL in Parkinson's

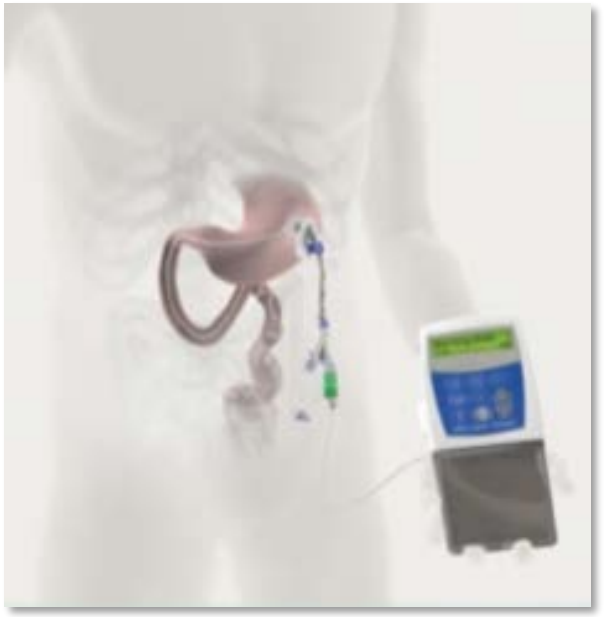
Deep Brain Stimulation (DBS)



Continuous Subcutaneous Apomorphine Infusion (CSAI)



Levodopa-Carbidopa Intestinal Gel (LCIG)



GLORIA: Efficacy of LCIG in APD

Parkinsonism and Related Disorders xxx (2017) 1–8

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

Levodopa-carbidopa intestinal gel in advanced Parkinson's: Final results of the GLORIA registry

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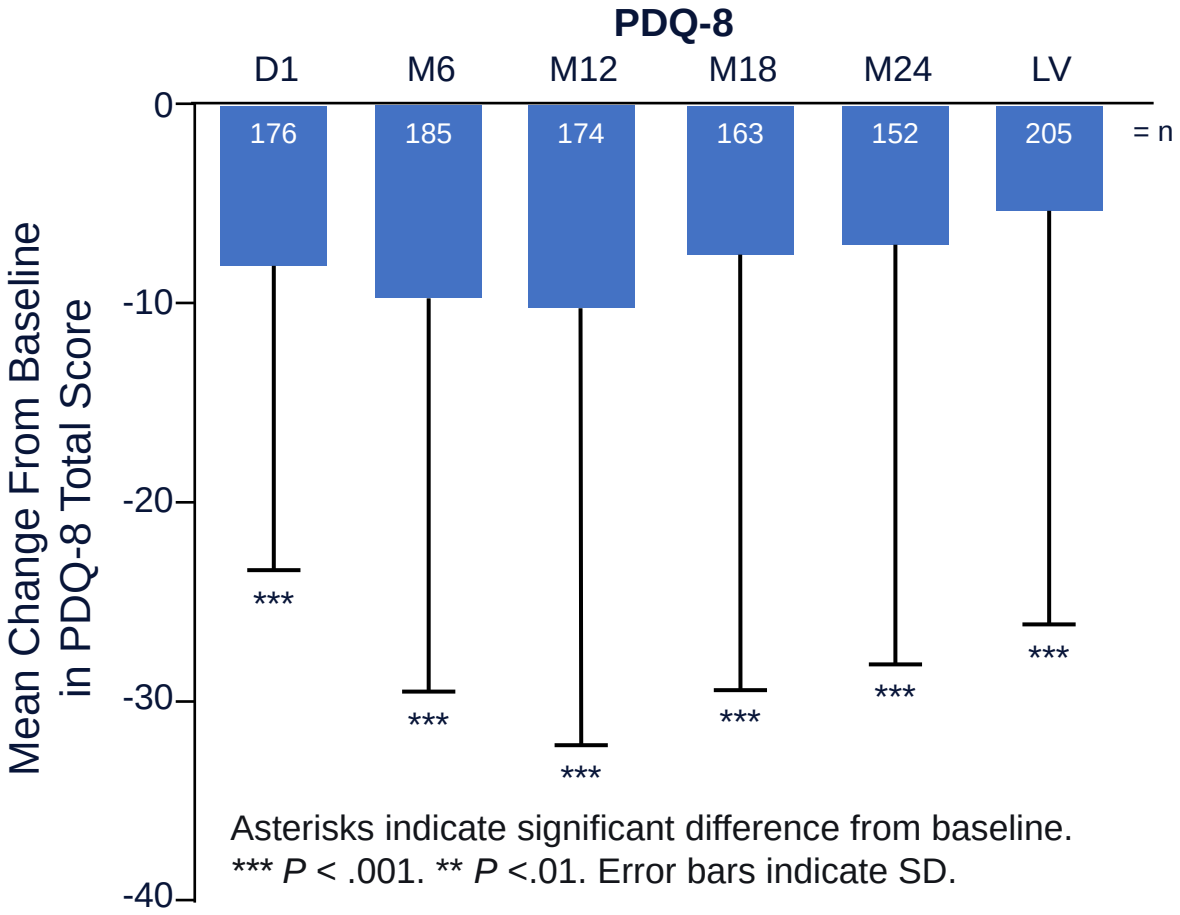


D1, discharge from hospital after PEG-J placement; LV, last visit reported by patient; M, month.

Antonini A, Poewe W, Chaudhuri KR, Jech R, Pickut B, Pirtošek Z, Szasz J, Valldeoriola F, Winkler C, Bergmann L, Yegin A, Onuk K, Barch D, Odin P; GLORIA study co-investigators. (2017) Parkinsonism Relat Disord, 13-20.

GLORIA: Safety of LCIG in APD

Safety (N = 356)	n (%)
≥ 1 ADR	194 (55)
≥ 1 GI-related ADR	139 (39)
≥ 1 serious ADR	109 (31)
≥ 1 severe ADR	55 (15)
Deaths	29 (8.1)
Unrelated to treatment	23 (6.5)
Possibly related to treatment	5 (1.4)
Probably related to treatment	1 (0.3)

Safety events were consistent with the established safety profile of LCIG

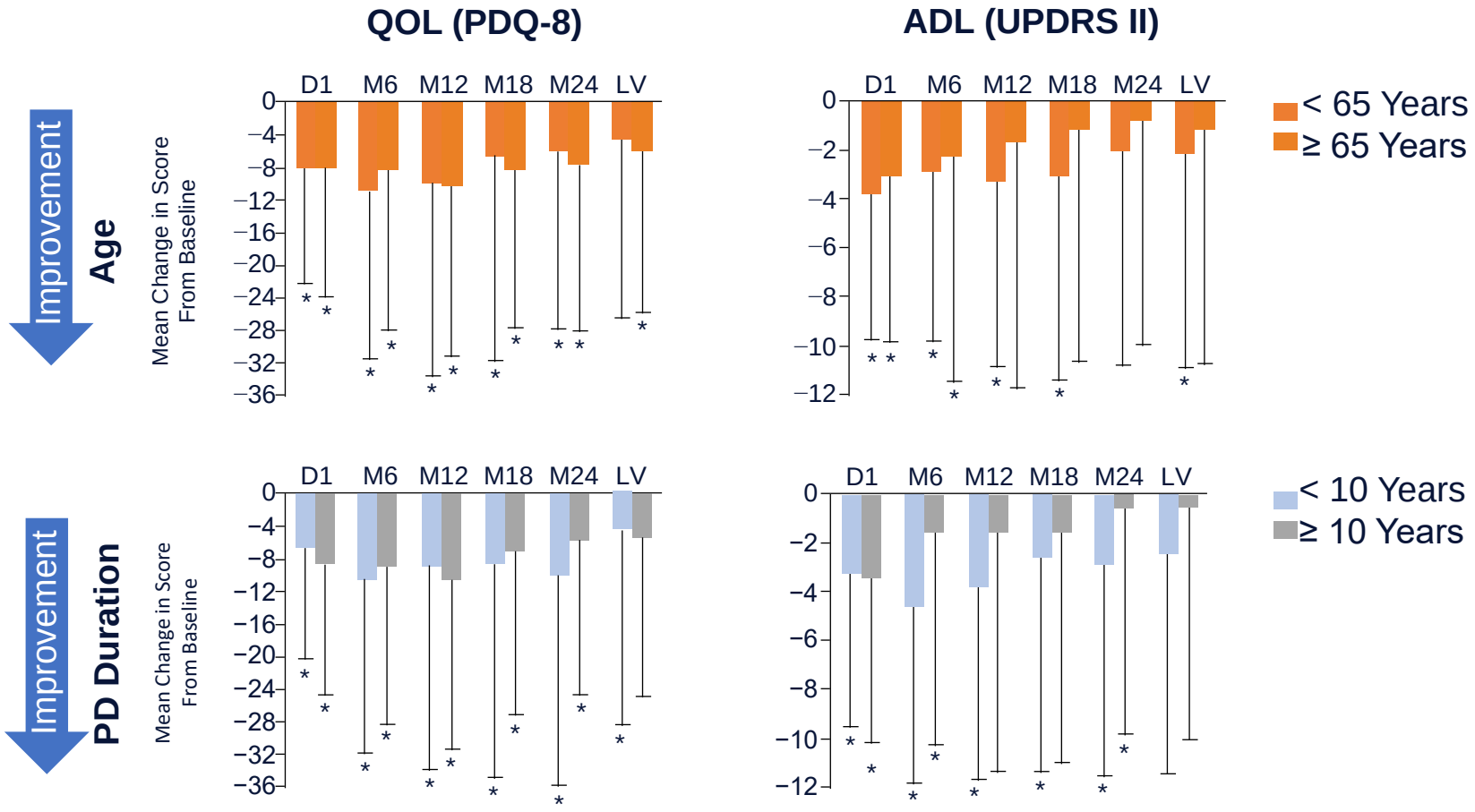
ADRs Occurring in ≥ 3% of Patients	n (%)
Weight decreased	24 (6.7)
Device-related infection	21 (5.9)
Device dislocation	17 (4.8)
Device issue	17 (4.8)
Polyneuropathy	16 (4.5)
Device lead issue	14 (3.9)
Medical device complication	13 (3.7)
Abdominal pain	13 (3.7)
Hallucination	12 (3.4)

Serious ADRs Occurring in ≥ 1% of Patients	n (%)
Device dislocation	8 (2.2)
Device issue	7 (2.0)
PD	7 (2.0)
Parkinsonism	7 (2.0)
Medical device complication	6 (1.7)
Device malfunction	5 (1.4)
Device occlusion	5 (1.4)
Abdominal pain	4 (1.1)
Hallucination	4 (1.1)
Pneumonia	4 (1.1)
Polyneuropathy	4 (1.1)

ADR, adverse drug reaction; GI, gastrointestinal.

Antonini A, Poewe W, Chaudhuri KR, Jech R, Pickut B, Pirtošek Z, Szasz J, Valldeoriola F, Winkler C, Bergmann L, Yegin A, Onuk K, Barch D, Odin P; GLORIA study co-investigators. (2017) Parkinsonism Relat Disord, 13-20.

GLORIA: Post Hoc Analysis of the Influence of Age and Disease Duration on QOL and ADL



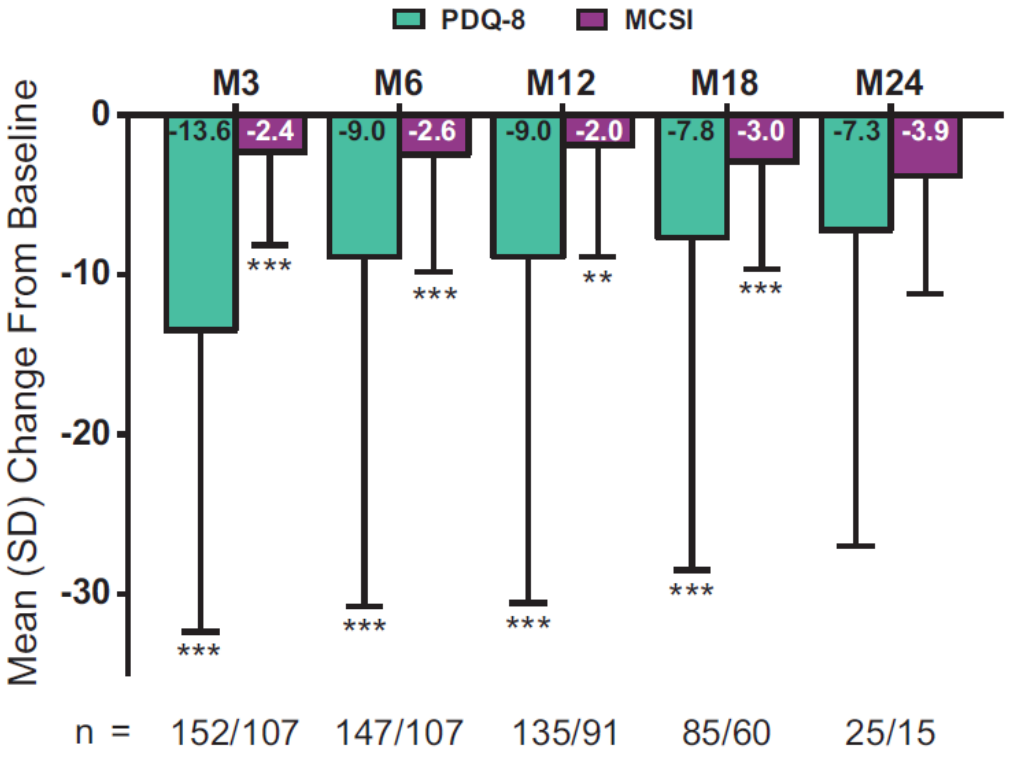
- Use of LCIG led to consistent and sustained improvements in **QOL**, irrespective of baseline patient age and disease duration
- Improvements in **ADL** were greater and more sustained in patients treated with LCIG *earlier in life* and *after shorter disease duration*

Error bars indicate SD. P values from a paired t test indicate statistical significance compared with baseline at P < .05 (*).
D1, discharge from hospital post–PEG-J placement.

Antonini A, Robieson WZ, Bergmann L, Yegin A, Poewe W. (2018) Neurodegener Dis Manag, 161-170.

DUOGLOBE Study of LCIG: Significant Improvements in Patient QOL through 12 Months and in Caregiver Burden through 6 Months

Figure 5. Treatment With LCIG Significantly Improved Patient QoL and Caregiver Burden Through Month 18



BL (n = 171): Mean (SD) PDQ-8 Summary Index: 45.1 (18.10)

BL (n = 128): Mean (SD) MCS I Total Score: 11.1 (6.41)

Interim data from DUOGLOBE, the first multinational observational routine care study of LCIG with a 3-year follow-up

* p<0.001.

ıa-carbidopa intestinal gel; M, month; MCSI, Modified Caregiver Strain Index; PDQ-8, 8-item PD Questionnaire; QOL, quality of life.

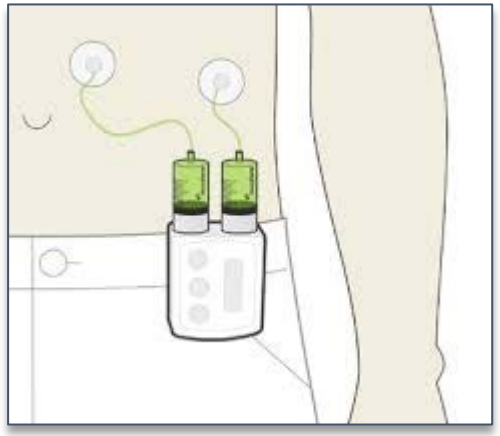
al. (2019) 23rd International Congress of Parkinson's Disease and Movement Disorders. Nice, France. Abstract LBA-20.

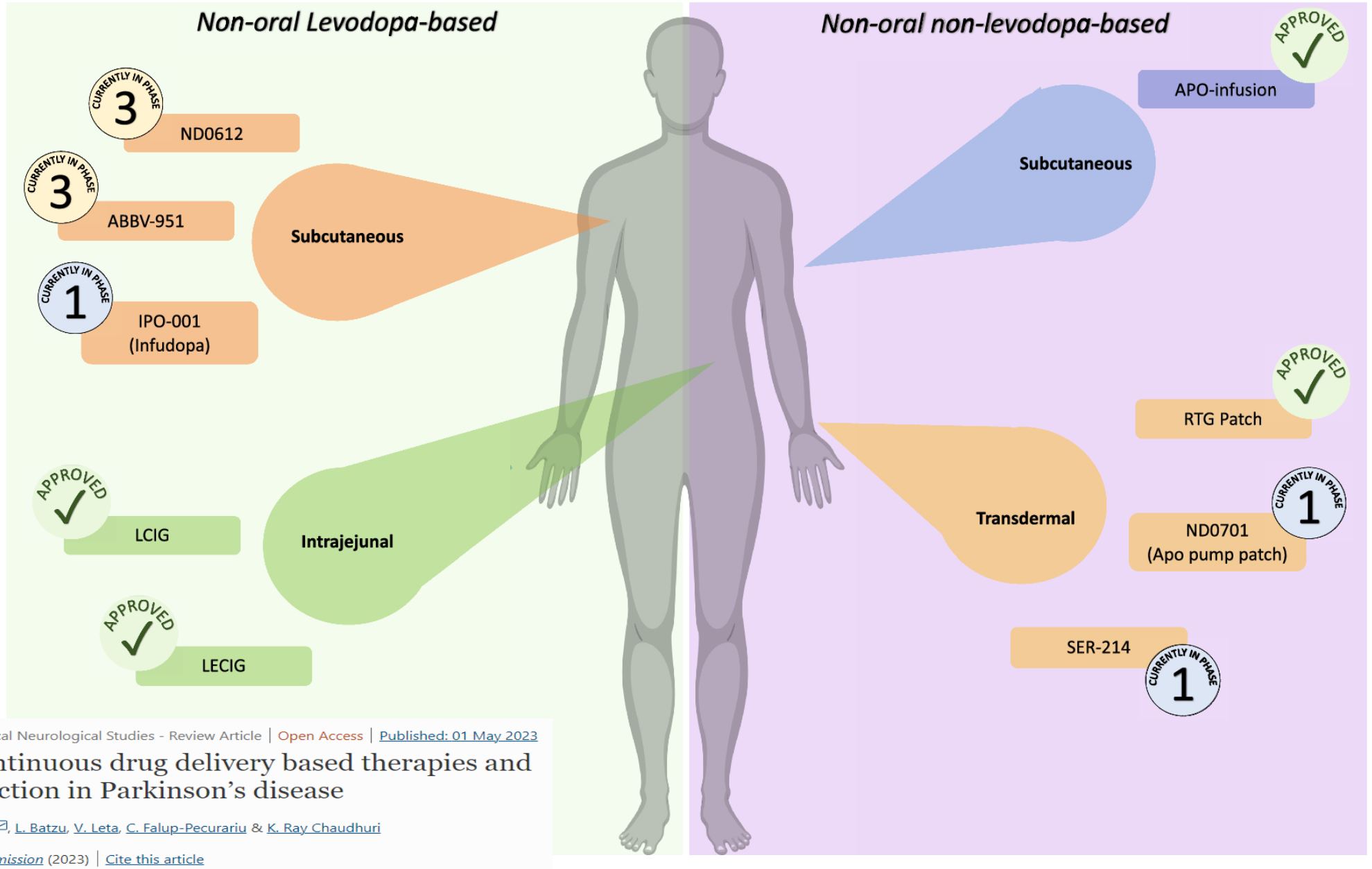
New formulations and delivery systems

Sublingual apomorphine

Levodopa-carbidopa-entacapone intestinal infusion

- **Levodopa-carbidopa subcutaneous infusion**





Neurology and Preclinical Neurological Studies - Review Article | Open Access | Published: 01 May 2023

Non-oral continuous drug delivery based therapies and sleep dysfunction in Parkinson's disease

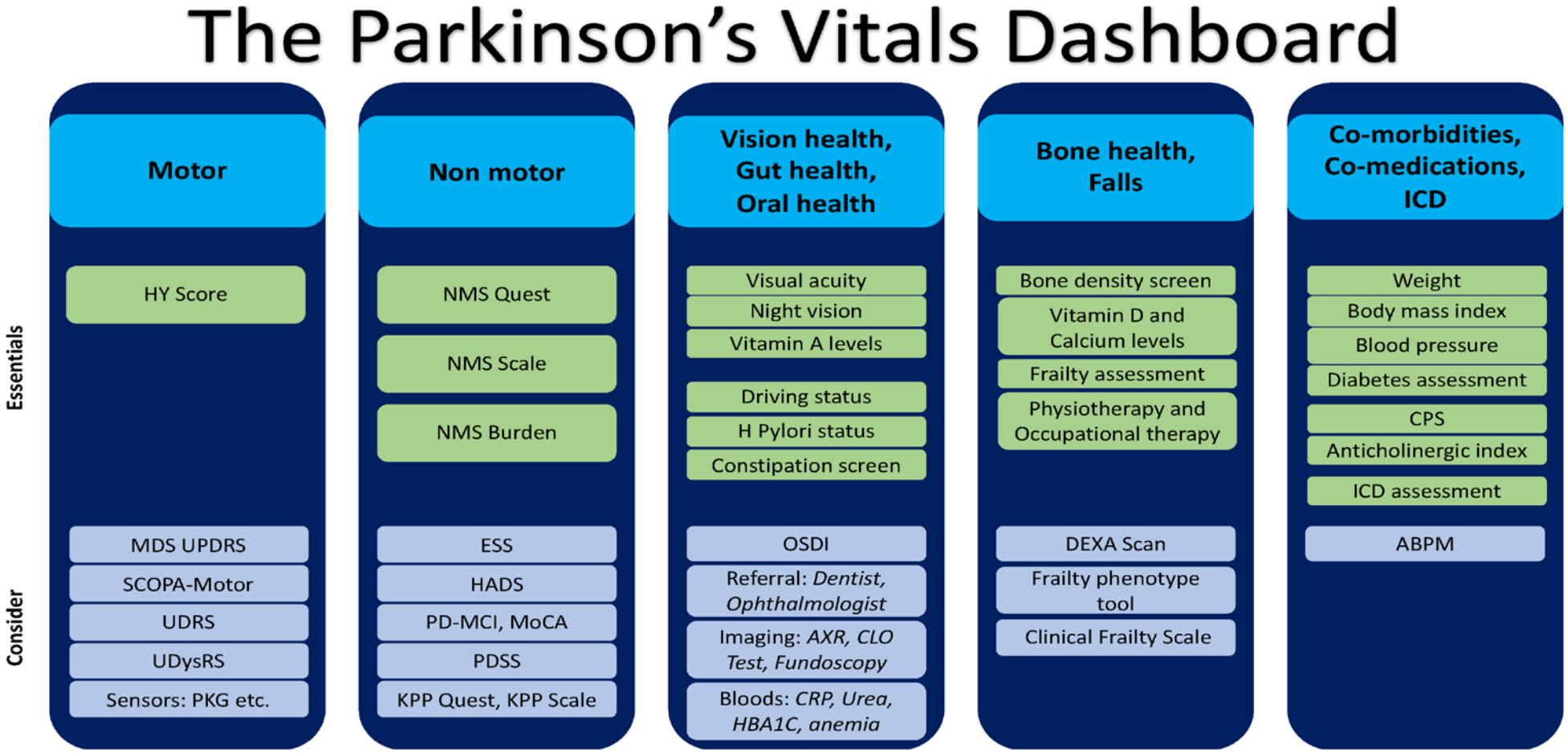
P. Tall, M. A. Qamar, L. Batzu, V. Leta, C. Falup-Pecurariu & K. Ray Chaudhuri

Journal of Neural Transmission (2023) | Cite this article

Open Access Editorial

The Dashboard Vitals of Parkinson's: Not to Be Missed Yet an Unmet Need

by Kallol Ray Chaudhuri [1,2,*], Nataliya Titova [3,4], Mubasher A. Qamar [1,2], Iulia Murășan [5] and Cristian Falup-Pecurariu [5,6]



Benefits of Support Groups

- Finding commonality among members
- Being educated and finding information
- Help adjusting to a diagnosis
- Learning practical techniques
- Feeling understood
- Reducing stigma
- Finding socialization and friendships

PARKINSON'S MENTAL HEALTH SUPPORT HUB

Parkinson's Support Group

Caregivers and family members are welcome!

Summary

- Deterioration in quality of life is a key aspect of concern for patients and carers with advanced PD

- A continually growing body of evidence has provided insights to support the use of device-aided therapies in a variety of patients with advanced PD and the fact that such interventions improve quality of life parameters even in advanced disease

- However, multiple considerations regarding the benefit-to-risk ratio of each therapy will help decide the final choice of therapeutic decision-making process and personalising treatment

ACKNOWLEDGEMENTS

King's Parkinson's Centre of Excellence Research Team

This is a Zambon UK promotional session. Prescribing Information and details on reporting adverse events can be displayed upon request, and will be shown at the end of the presentation GB_XAD_679 May 2023

Prof K Ray Chaudhuri, Director

- Dr L Batzu, Clinical PhD Fellow
- Dr M Qamar, Clinical Research Fellow
- Dr K Rukavina, Clinical PhD Fellow
- Dr A Podlewska, Clinical PhD Fellow
- Dr S Rota, Clinical PhD Fellow
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- Ms S Jones, Pharmacology PhD Fellow

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- Dr N Dimitrov, Consultant (UHL)
- Dr P Reddy, Consultant (KCH)

Statistical and Data Support

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- Dr Carmen Rodriguez Blazquez (Madrid)

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EUROPAR

KING'S College LONDON

Non-Motor Parkinson's Disease Study Group MDS NM-PD-SG

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Xadago Prescribing Information

Xadago 50 and 100 mg film-coated tablets. Consult Summary of Product Characteristics before prescribing. Legal Category: POM **Marketing Authorisation number and basic NHS cost:** PLGB 31654/0012 and PLGB 31654/0011 £69 for 30 tablets. **Presentation**: Each film-coated tablet contains safinamide methansulfonate equivalent to 50 or 100mg safinamide. **Uses**: Xadago is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients. **Dosage and administration**: Treatment with safinamide should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need. If a dose is missed the next dose should be taken at the usual time the next day. Method of administration: Xadago is for oral administration. It should be taken with water. It may be taken with or without food. **Special populations:** Paediatric population: The safety and efficacy of safinamide in children and adolescents under 18 years of age have not been established. Elderly: No change in dose is required for elderly patients. Experience of use of safinamide in patients over 75 years of age is limited. Hepatic impairment: Caution should be exercised when initiating treatment with safinamide in patients with moderate hepatic impairment. The lower dose of 50 mg/day is recommended for patients with moderate hepatic impairment. It is contraindicated in severe hepatic impairment. Renal impairment: No change in dose is required for patients with renal impairment.
Women of childbearing potential: Safinamide should not be given to women of childbearing potential unless adequate contraception is practiced. Pregnancy: There are no or limited amount of data from the use of safinamide in pregnant women. Xadago should not be given during pregnancy. Breast-feeding: Available pharmacodynamic/ toxicological data in animals have shown excretion of safinamide in milk. A risk for the breast-fed child cannot be excluded. Xadago should not be used during breast-feeding. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Concomitant treatment with other monoamine oxidase (MAO) inhibitors or with pethidine.

GB_XAD_433.3 September 2022

Xadago should not be used in patients with severe hepatic impairment nor in patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy.
Warnings and Precautions: Xadago may be used with selective serotonin re-uptake inhibitors (SSRIs) at the lowest effective dose, with caution for serotoninergic symptoms. The concomitant use of Xadago and fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary these medicinal products should be used at low doses. A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with Xadago. At least 7 days must elapse between discontinuation of Xadago and initiation of treatment with MAO inhibitors or pethidine. When safinamide is co-administered with products that are BCRP substrates, please refer to the SmPC for that particular medicinal product. Impulse control disorders can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Patients and carers should be made aware of the behavioural symptoms of ICDs that were observed in patients treated with MAO-inhibitors, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying. Safinamide used as an adjunct to levodopa may potentiate the side effects of levodopa, and pre-existing dyskinesia may be exacerbated, requiring a decrease of levodopa. Somnolence and dizziness may occur during safinamide treatment, therefore patients should be cautioned about using hazardous machines, including motor vehicles, until they are reasonably certain that safinamide does not affect them adversely. **Interactions:** Safinamide must not be administered along with other MAO inhibitors (including moclobemide) as there may be a risk of non-selective MAO inhibition that may lead to a hypertensive crisis. Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors. Concomitant administration of dextromethorphan or sympathomimetics such as ephedrine or pseudoephedrine, requires caution. Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary. Safinamide may transiently inhibit BCRP, a weak interaction was observed with rosuvastatin. It is recommended to monitor patients when safinamide is taken with medicinal products that are BCRP substrates (e.g., rosuvastatin, pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide) and to refer to their SmPCs to determine if a dose adjustment is needed.
Side Effects: Consult the summary of product characteristics for other side effects. Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis, neuroleptic malignant syndrome, serotonin syndrome, and hypotension. Other serious adverse reactions include bronchopneumonia, pyoderma, basal cell carcinoma, leukopenia, cachexia, hyperkalaemia, delirium, suicidal ideation, Parkinson's disease, syncope, cataract, glaucoma, diabetic retinopathy, eye haemorrhage, papilloedema, arrhythmia, myocardial infarction, hypertensive crisis, peptic ulcer, upper gastrointestinal haemorrhage, hyperbilirubinaemia, ankylosing spondylitis, prolonged QT on ECG, and fat embolism. Common undesirable effects include insomnia, dyskinesia, somnolence, dizziness, headache, Parkinson's Disease, cataract, orthostatic hypotension, nausea and fall.

Further information is available from: Zambon UK Limited, Ground Floor, Suite F, Breakspear Park, Breakspear Way, Hemel Hempstead HP2 4TZ, United Kingdom
Email: infoUK@zambongroup.com
Tel: +44 (0)800 0288 942

Prescribing Information drawn up: July 2022

Adverse reactions should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse reactions should also be reported to Zambon UK Limited. At drugsafetyUK@ZambonGroup.com or telephone: +44 (0) 800 0288 942

GB_XAD_679 May 2023

Zambon 1906

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