Day 2: Thursday, May 7

Overview and Updates on Levodopa Infusion Therapy Based on the Real-World Experience

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International Parkinson and Movement Disorder Society
Asian & Oceanian Section

COI Disclosure

Presenter's name: Noriko Nishikawa
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As a company or other entity with a COI relationship that should be disclosed in connection with the presentation

(1) Advisor: Abbvie GK

(2) Shareholding/profit: None

(3) Patent royalties: None

(4) Lecture fees

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ONO PHARMACEUTICAL CO., LTD., Abbvie GK

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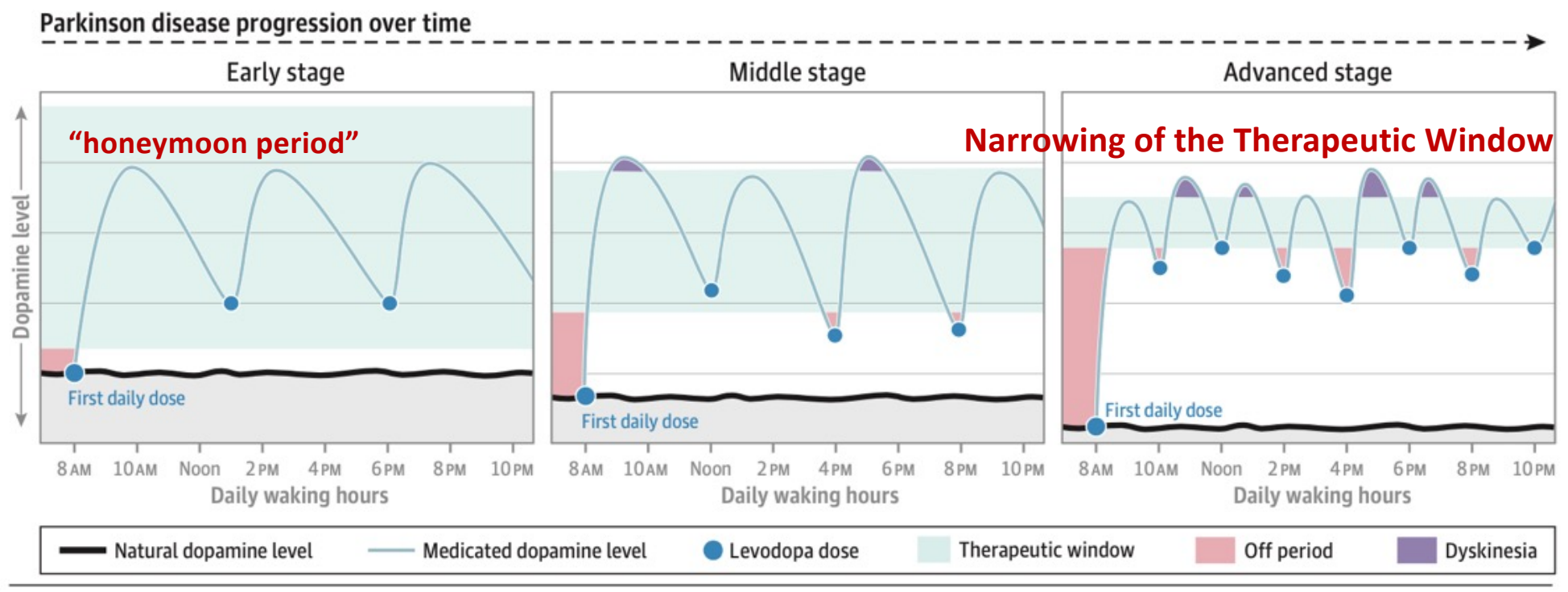
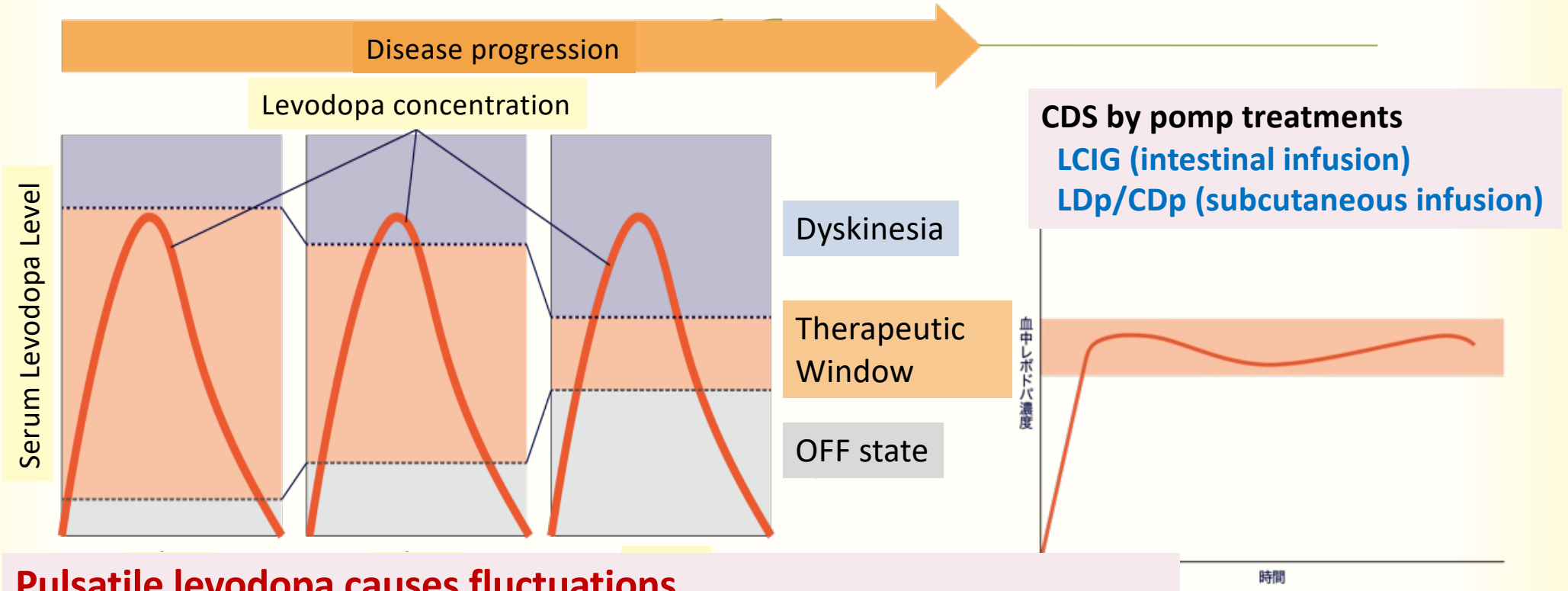
Progression of Parkinson's Disease and Narrowing of the Therapeutic Window



The therapeutic window narrows as Parkinson's disease progresses
Motor fluctuations and dyskinesia become more frequent
Continuous dopaminergic stimulation becomes necessary

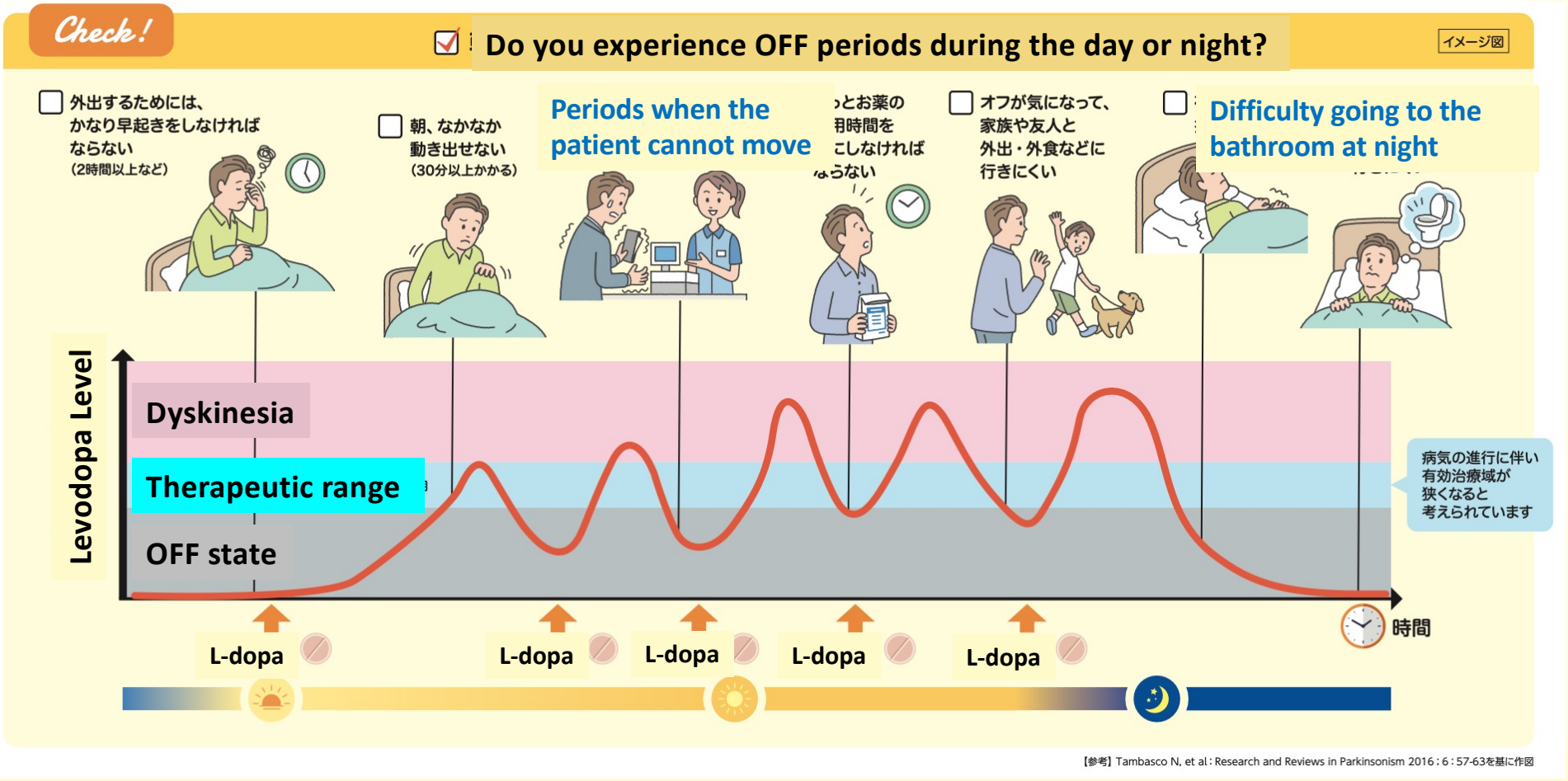
MA. 2020;323(6):545–560

Continuous Dopaminergic Stimulation (CDS)



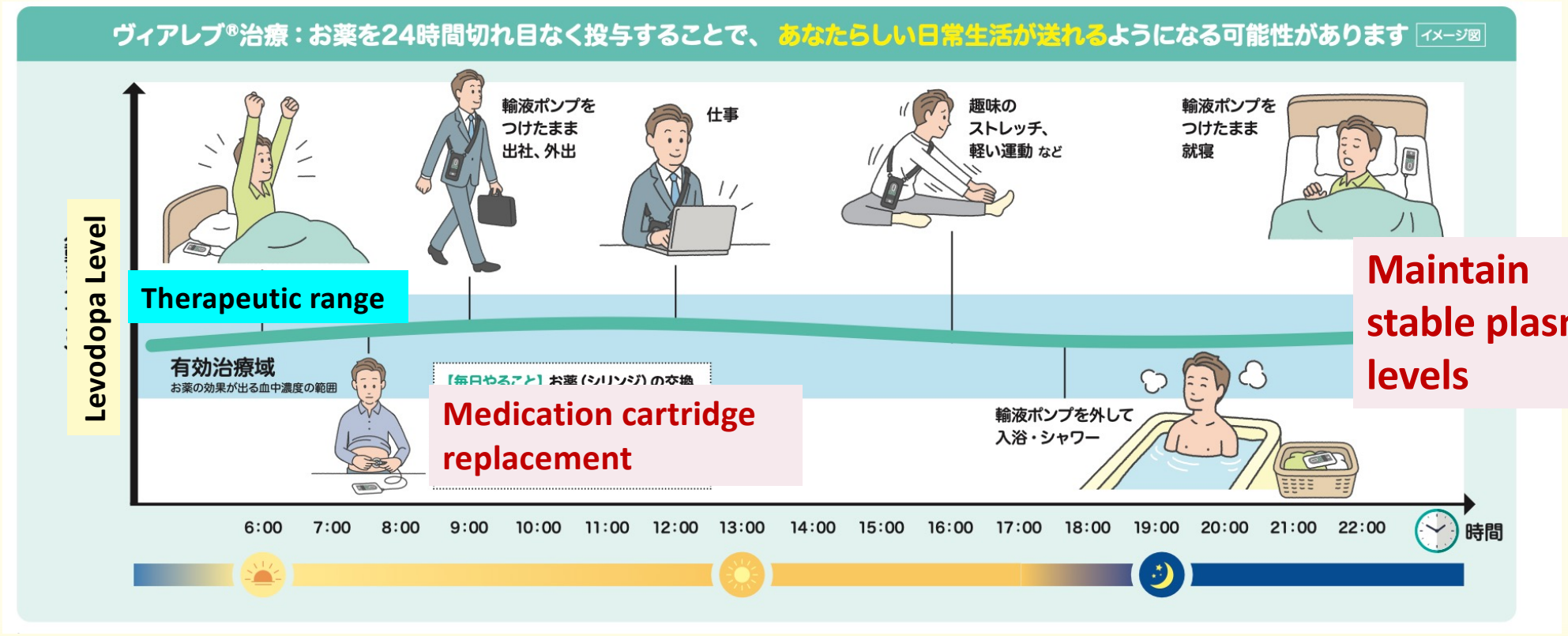
Pulsatile levodopa causes fluctuations
Continuous drug delivery stabilizes dopamine levels
This concept is called Continuous Dopaminergic Stimulation (CDS)

Degree of difficulty in daily life due to symptom fluctuations



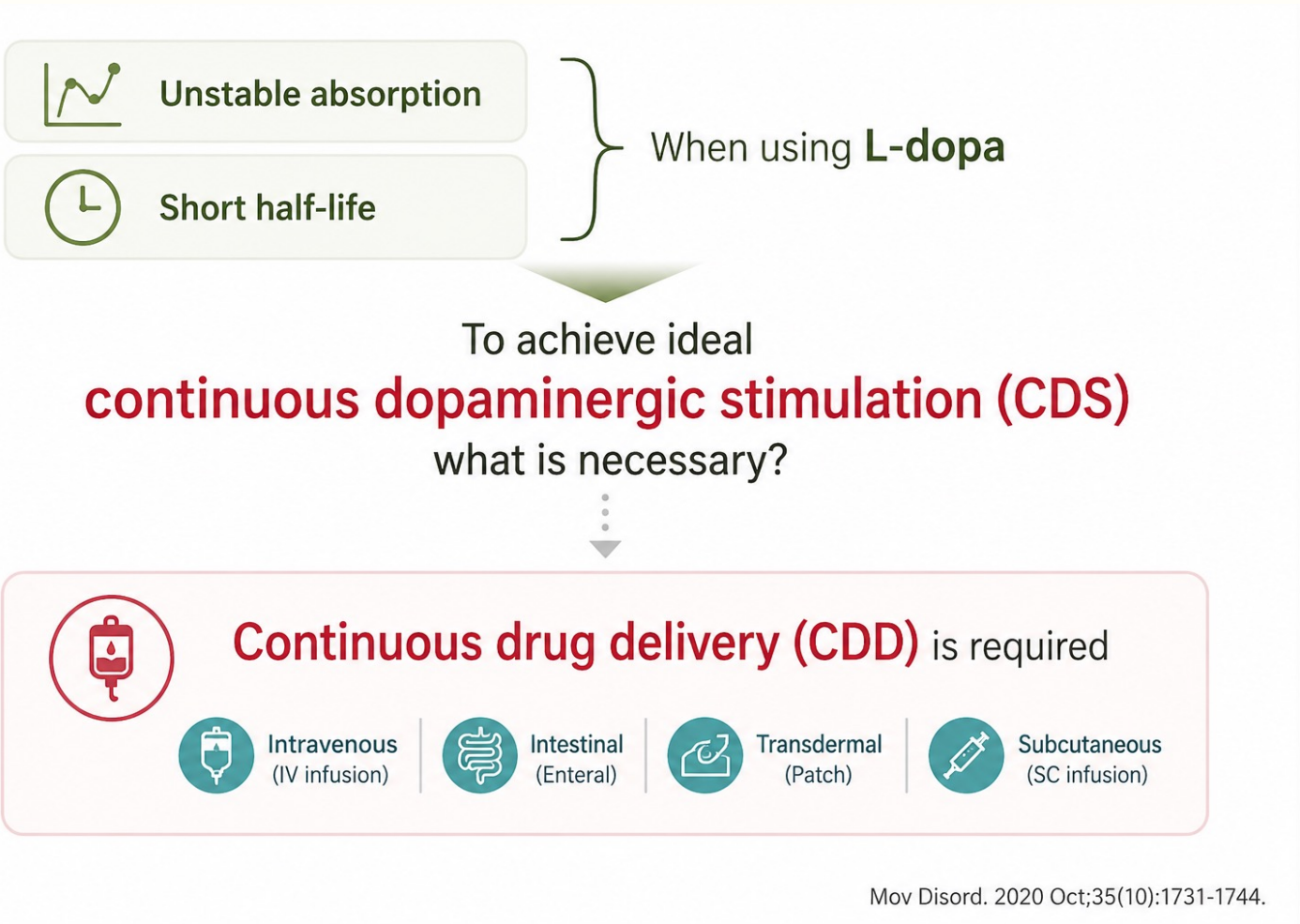
【参考】Tambasco N, et al : Research and Reviews in Parkinsonism 2016 ; 6 : 57-63を基に作図

Treatment Goal: Reduce off-state difficulties



アッヴィ資料

Why Continuous Drug Delivery is Needed

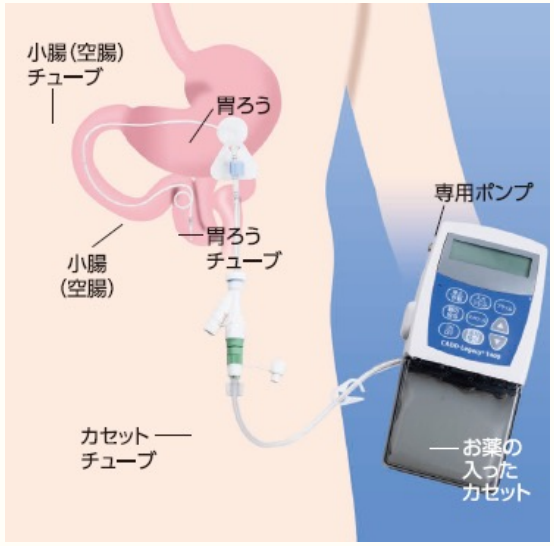


Mov Disord. 2020 Oct;35(10):1731-1744.

Two Levodopa Infusion Therapies

LCIG

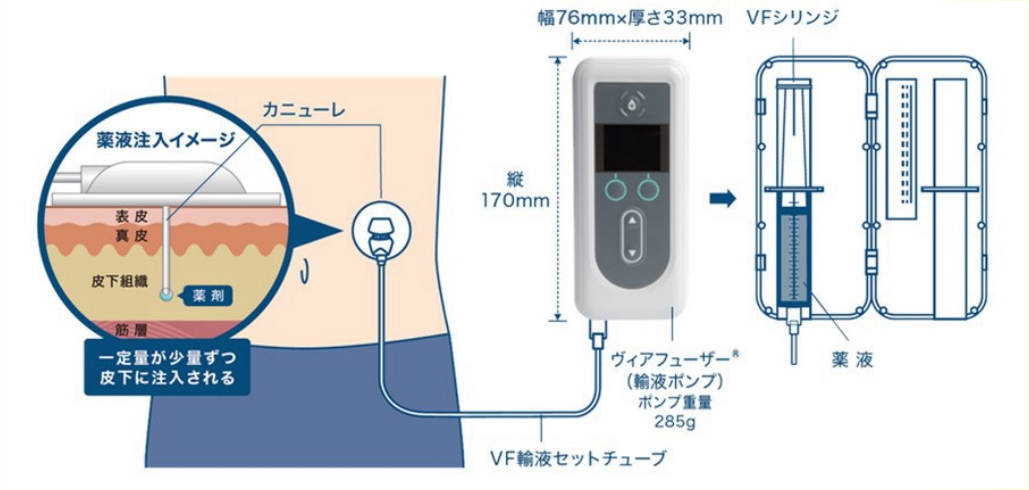
(Levodopa-Carbidopa Intestinal Gel)



Intestinal infusion

LDp/CDp

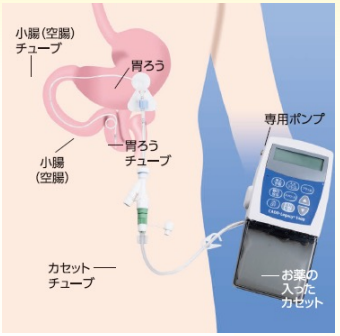
(Foslevodopa/Foscarbidopa, subcutaneous infusion)

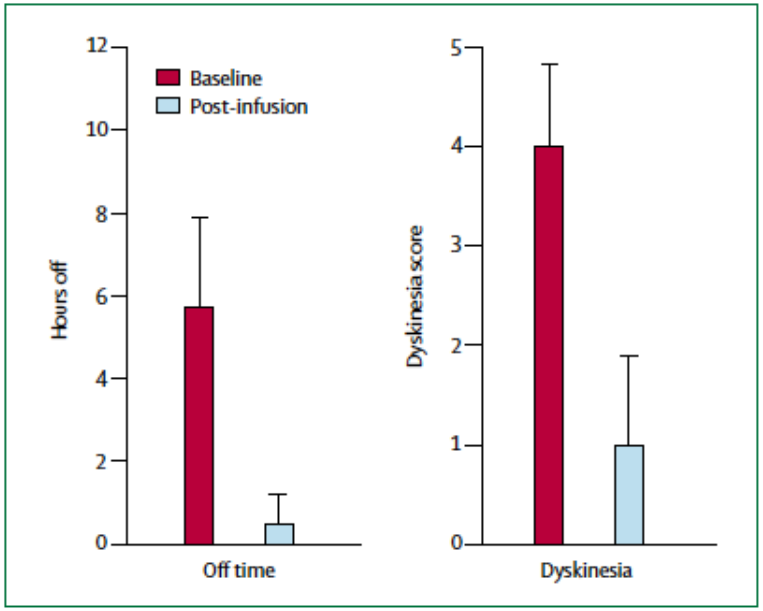


Subcutaneous infusion

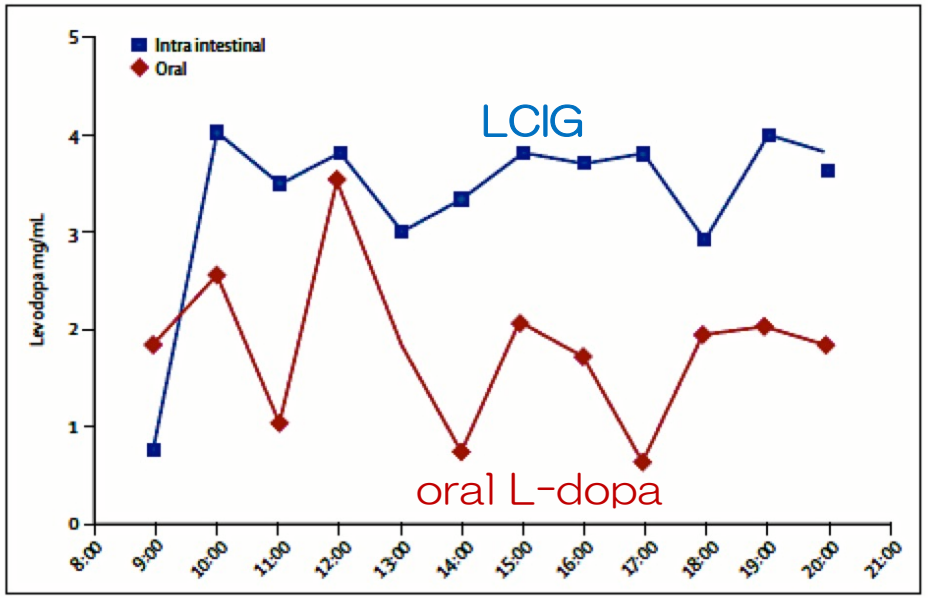
LCIG Overview

LCIG (Levodopa/carbidopa intestinal gel)





Reduced OFF time and dyskinesia



More stable plasma levodopa concentrations

(Stocchi, et al. Arch Neurol 2005;62:905-10)

LCIG Efficacy from real-world experience:

- Consistently reduces OFF time by approximately 2-4 hours daily
- Increases ON time without troublesome dyskinesia
- Improves activities of daily living, quality of life, and reduces caregiver burden
- Long-term effectiveness sustained up to 7-8 years
- The GREENFIELD observational study (145 patients, mean 2.8 years follow-up) showed 55% reduction in motor fluctuations (UPDRS-IV item 39) and significant reductions in dyskinesia duration (-28%), disability (-40%), and painful dyskinesia (-50%)
- The COSMOS study demonstrated sustained benefits across all treatment duration groups (1-2 years to >5 years), with similar LCIG doses and add-on medication requirements over time

The Lancet. Neurology. 2014. Olanow CW, Kieburtz K, Odin P, et al.
Journal of Neurology. 2019. Lopiano L, Modugno N, Marano P, et al.
Journal of Neurology. 2023. Fasano A, García-Ramos R, Gurevich T, et al.

LCIG Safety profile:

- Overall discontinuation rate approximately 34% (10% annual rate) in long-term studies
- Device-related complications occur in 16-27% of patients, including tube displacement, occlusion, and infection
- Systemic adverse events consistent with standard levodopa therapy

Journal of Neurology. 2019. Lopiano L, Modugno N, Marano P, et al.
Movement Disorders : Official Journal of the Movement Disorder Society. 2018. Fernandez HH, Boyd JT, Fung VSC, et al.

LCIG vs DBS: Clinical Comparison

Item	LCIG	DBS
Age limitation	Efficacy confirmed even ≥80 years	≥75 years: relatively contraindicated
Cognitive impairment	Usable in mild impairment	Contraindicated
Dyskinesia	Limited improvement	Marked improvement (−66–69%)
Tremor	Limited effect	Effective even if drug-resistant
Gait / balance	No effect	Risk of worsening
Speech disturbance	No effect	Common adverse effect
Impulse control disorder	No effect	May improve with DA reduction
Non-motor symptoms	Improves sleepiness, autonomic	Improves fluctuations
Complication rate	0.68/year	0.13/year
Reversibility	Easily stopped	Removal possible but invasive
Cost	Highest lifetime cost	Lower than LCIG

(Merola A, et al. PRD 2016;29:104-108, Front. Neurol. 10:934.)

Complex Dyskinesia in LCIG Therapy

Parkinsonism and Related Disorders 69 (2019) 140–146

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Complex dyskinesias in Parkinson patients on levodopa/carbidopa intestinal gel

Massimo Marano[a], Taline Naranian[b], Lazzaro di Biase[a], Alessandro Di Santo[a], Yu-Yan Poon[b], Roberta Arca[c], Giovanni Cossu[d], Pietro Marano[e], Vincenzo Di Lazzaro[a], Alfonso Fasano[b,f,g,h,*]

Conventional dyskinesia

A: Peak-dose dyskinesia (typically in the morning)

B: Peak-dose dyskinesia + biphasic dyskinesia
(at LCIG initiation and discontinuation)

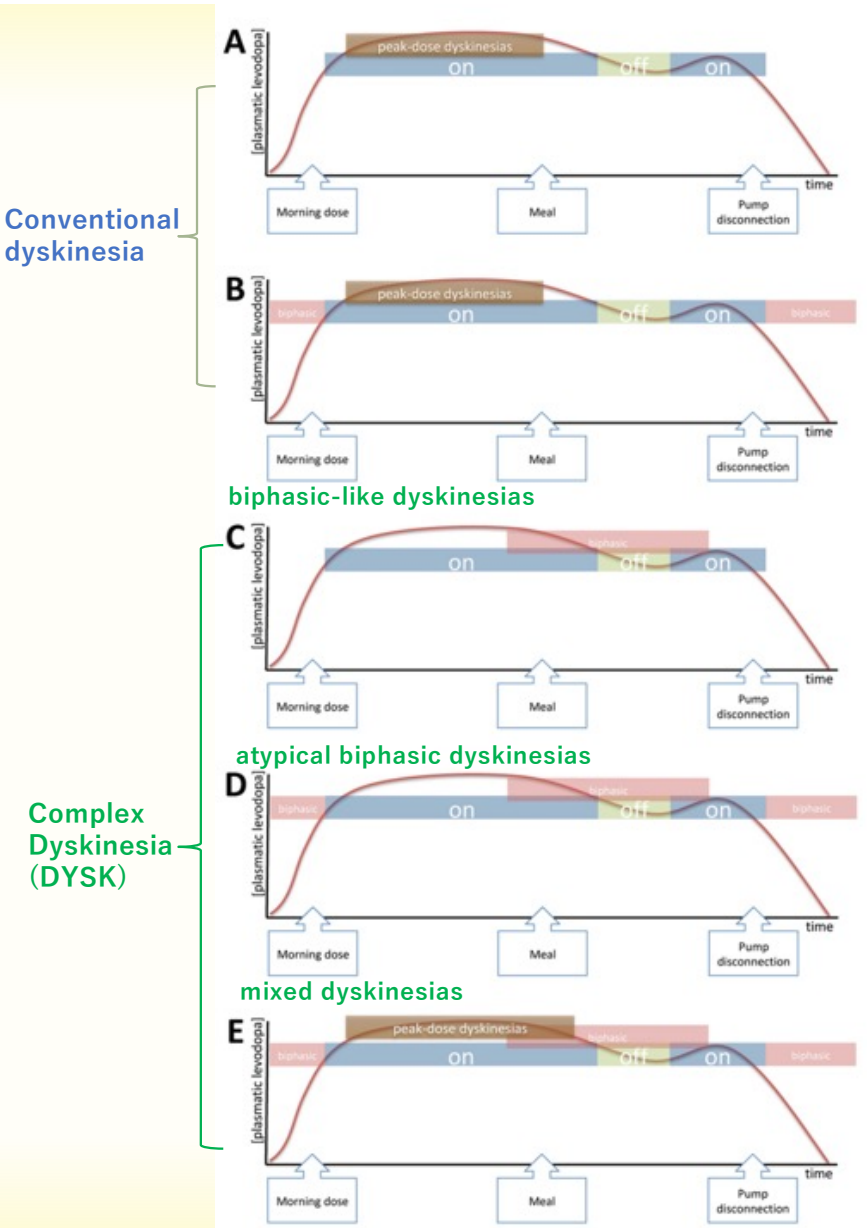
Complex Dyskinesia (DYSK)

C: biphasic-like dyskinesia(prolonged, plateau-like pattern)

D: atypical biphasic dyskinesia(C + biphasic at start/end)

E: mixed dyskinesias(D + peak-dose dyskinesia)

- DYSK observed in **30/208 patients (14.4%)**
- DYSK is a **risk factor for treatment discontinuation**
- **24-hour LCIG showed only transient benefit** (n=2)
- Pre-existing biphasic dyskinesia → **risk factor for DYSK after LCIG**



24-Hour LCIG May Reduce Troublesome Dyskinesia

NPJ Parkinsons Dis. 2018 Nov 20;4:34.

ARTICLE OPEN

24-hour levodopa-carbidopa intestinal gel may reduce troublesome dyskinesia in advanced Parkinson's disease

Belinda Cruse[1], Hugo Morales-Briceño[1,2], Florence C F Chang[1,2], Neil Mahant[1], Ainhi D Ha[1], Samuel D Kim[1], Nigel Wolfe[1], Vu Kwan[3], David S Tsui[1], Jane M Griffith[1], Donna Galea[1] and Victor S C Fung[1,2]

- Among 74 LCIG-treated patients,
- **12 patients with troublesome dyskinesia** were switched to 24-h LCIG
- **75% (9/12) showed improvement** in dyskinesia
- In 5 patients, dyskinesia improved **despite an increase in LEDD**

  → suggests a mechanism beyond simple levodopa exposure

JMD
https://doi.org/10.14802/jmd.22021 / J Mov Disord 2022 Jul 26 [Epub ahead of print]
pISSN 2005-940X / eISSN 2093-4939

LETTER TO THE EDITOR

Continuous 24-h Levodopa-Carbidopa Intestinal Gel Infusion After a Levodopa Holiday Suppressed Refractory Dyskinesia Despite Increasing Levodopa Dose

Journal of Movement Disorders 2022;15(3):290-292.

24-Hour LCIG: Who Benefits and What to Consider

CNS Drugs (2021) 35:137–149

24-Hour Levodopa-Carbidopa Intestinal Gel: Clinical Experience and Practical Recommendations

Sandeep Thakkar[1] · Victor S. C. Fung[2] · Aristide Merola[3] · Meredith Rollins[4] · Michael J. Soileau[4] · Norbert Kovács[5,6]

Potential Benefits (Selected Patients)

- Severe nocturnal akinesia
- Improved sleep quality
- Early morning OFF
- Freezing of gait (FOG)
- Troublesome dyskinesia

Clinical Considerations

Limited evidence (small, open-label studies)

Requires dose adjustment (especially night-time rate)

Careful monitoring is essential

Monitoring Points

Autonomic dysfunction

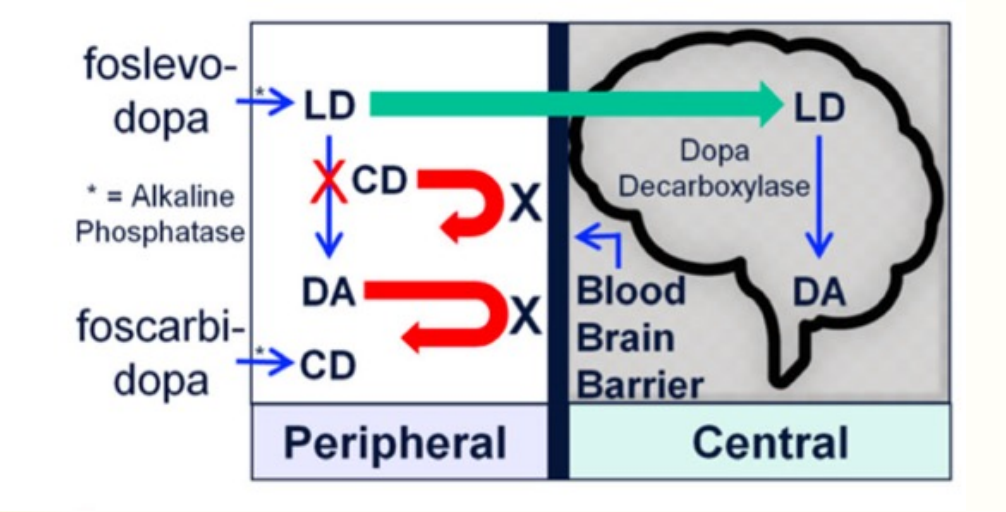
Weight loss

Vitamin B6/B12/folate ↓, homocysteine ↑

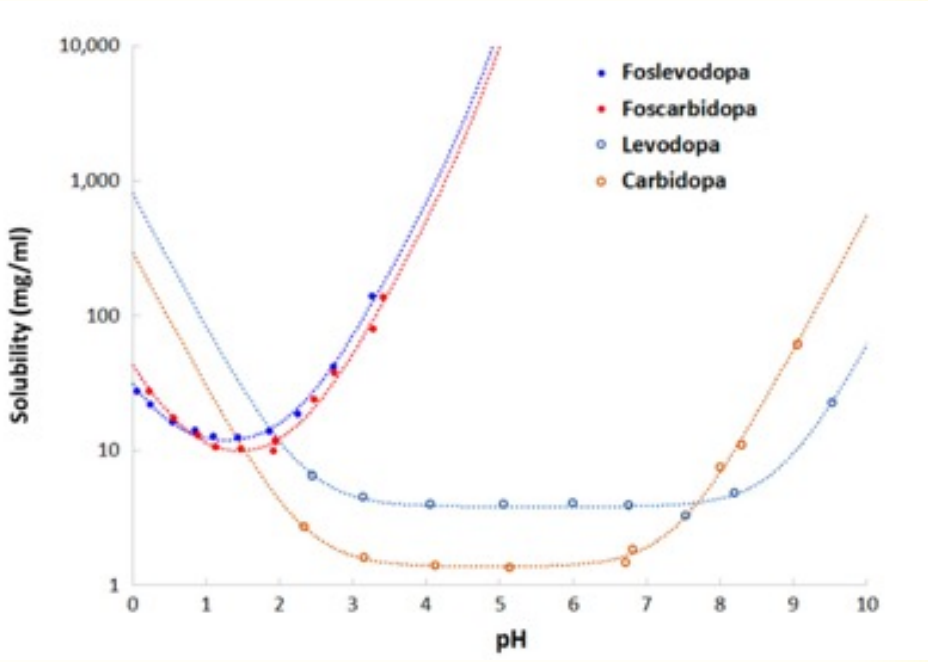
Sleep pattern changes

Hallucinations / delusions

Foslevodopa/foscarbidopa (LDp/CDp)



Per 10 mL vial:
Foslevodopa / Foscarbidopa
2400 mg / 120 mg (20:1)
⇒ levodopa / carbidopa (4:1)
Equivalent to 1700 mg of levodopa



Increased solubility at physiological pH through prodrug modification

ANN NEUROL 2021;90:52–61

Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study

M15-741試験

Global Phase 3 Study
52-week open-label trial
Long-term safety and efficacy of LDp/CDp therapy

Table 1 Baseline demographics and clinical characteristics (safety analysis set)

Characteristic	Total N = 244
Age, years	63.9 (9.2)
< 65, *n* (%)	119 (48.8)
≥ 65, *n* (%)	125 (51.2)
Sex, *n* (%)	
Female	98 (40.2)
Male	146 (59.8)
Race, *n* (%)	
White	207 (84.8)
Black or African American	1 (0.4)
Asian	34 (13.9)
American Indian or Alaska Native	1 (0.4)
Multiple	1 (0.4)
BMI, kg/m^2	25.0 (4.8)[a]
MMSE total score	28.7 (1.7)[b]
PD duration since diagnosis, years	10.7 (5.2)
< 10, *n* (%)	131 (53.7)
≥ 10, *n* (%)	113 (46.3)
Duration of motor fluctuations, years	6.6 (4.7)[c]
Total daily levodopa equivalent dose[d], mg	1064.9 (584.8)[a]

Table 1 continued

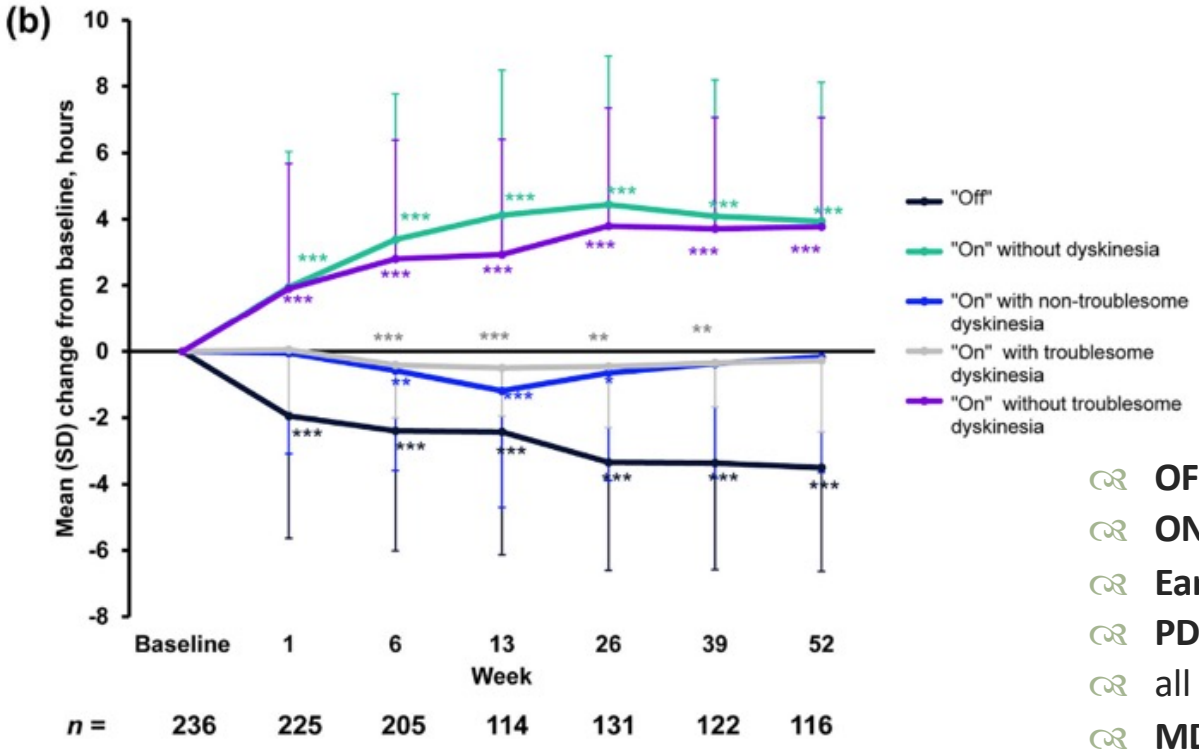
Characteristic	Total N = 244
Daily "On" time without troublesome dyskinesia[e], h	9.1 (2.5)[f]
MDS-UPDRS total score[g,h]	50.4 (18.9)
Part I	11.1 (6.4)
Part II	15.8 (7.4)
Part III	23.5 (11.5)
Part IV	9.5 (3.2)
Hoehn and Yahr	2.2 (0.7)
PDSS-2 total score	20.4 (9.6)[c]
PDQ-39 summary index	34.5 (15.0)[c]
EQ-5D-5L summary index[i]	0.644 (0.1745)[j]
EQ-5D-5L VAS	57.0 (22.2)[j]

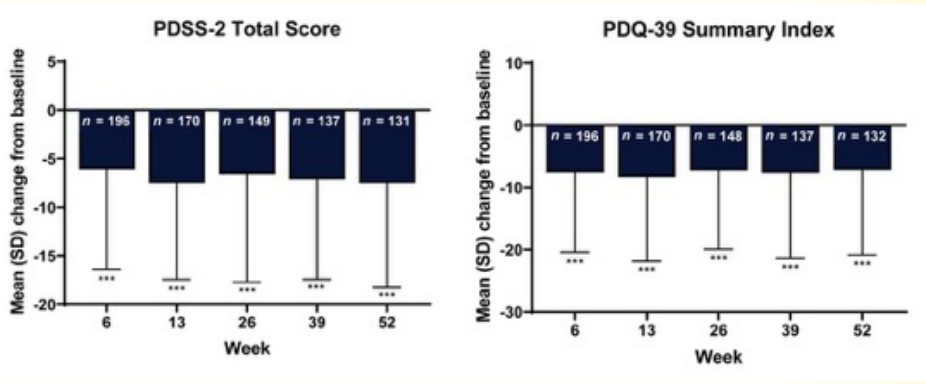
Study Design

Phase 3, single-arm, open-label, 52 weeks
N = 244 patients (60 sites in 13 countries)
Levodopa-responsive PD patients
with ≥2.5 hours of OFF time during the day
Dose individualized
(levodopa equivalent: ~700–4250 mg/day)
Primary endpoint: Safety
Secondary endpoints: Motor symptoms, sleep, QOL, etc.

Neurol Ther. 2023 Dec;12(6):1937-1958.

Efficacy Outcomes





- **OFF time:** −3.5 hours/day (−59%)
- **ON time (without dyskinesia):** +3.9 hours/day (+58%)
- **Early morning akinesia:** reduced from 77.7% to 27.8%
- **PDSS-2 (sleep), PDQ-39 (QOL), EQ-5D-5L (HRQOL):**
- all significantly improved ($p < 0.001$)
- **MDS-UPDRS Part II–IV:** significantly improved
- **MDS-UPDRS Part III:** no significant change

Neurol Ther. 2023 Dec;12(6):1937-1958.

Neurol Ther. 2023 Dec;12(6):1937-1958.

Safety and Tolerability

- **Adverse events (AEs):** 94.3%
  - Most were **injection-site reactions** (e.g., erythema 52%, nodules 29%)
- **Serious AEs (SAEs):** 25.8%
  - Mainly **injection-site infections** (cellulitis, abscess)
- **Discontinuation rate:** 26.2%
  - Most common reasons: **hallucinations and skin reactions**
- Overall, tolerability is **comparable to other subcutaneous infusion therapies**,and most adverse events are **manageable**
- Discontinuations occurred mainly **early in treatment**

  (primarily within the first 10 weeks)

24-hour subcutaneous LDp/CDp therapy provides continuous dopaminergic stimulation (CDS) without the need for surgical intervention, and is a useful option for advanced PD

Table 3 Overview of treatment-emergent adverse events (safety analysis set)

Adverse events, *n* (%)	Total *N* = 244
AEs	230 (94.3)
AEs considered associated with study drug	224 (91.8)
Severe AEs[a]	63 (25.8)
SAEs[a]	63 (25.8)
AEs leading to discontinuation of study drug	64 (26.2)
Deaths[b,c]	3 (1.2)
AEs occurring in > 10% of patients	
Infusion site erythema	127 (52.0)
Infusion site nodule	70 (28.7)
Infusion site cellulitis	56 (23.0)
Infusion site edema	47 (19.3)
Hallucination	42 (17.2)
Fall	41 (16.8)
Infusion site pain	38 (15.6)
Infusion site reaction	30 (12.3)
Anxiety	29 (11.9)
Infusion site abscess	27 (11.1)
Dizziness	25 (10.2)
SAEs occurring in > 2 patients	
Infusion site cellulitis	10 (4.1)
Infusion site abscess	8 (3.3)
Hallucination	7 (2.9)
Parkinson's disease	6 (2.5)
Psychotic disorder	6 (2.5)
Urinary tract infection	4 (1.6)
Sepsis	3 (1.2)

Post Hoc Analysis of a Randomized Trial

Neurol Ther
https://doi.org/10.1007/s40120-025-00856-1

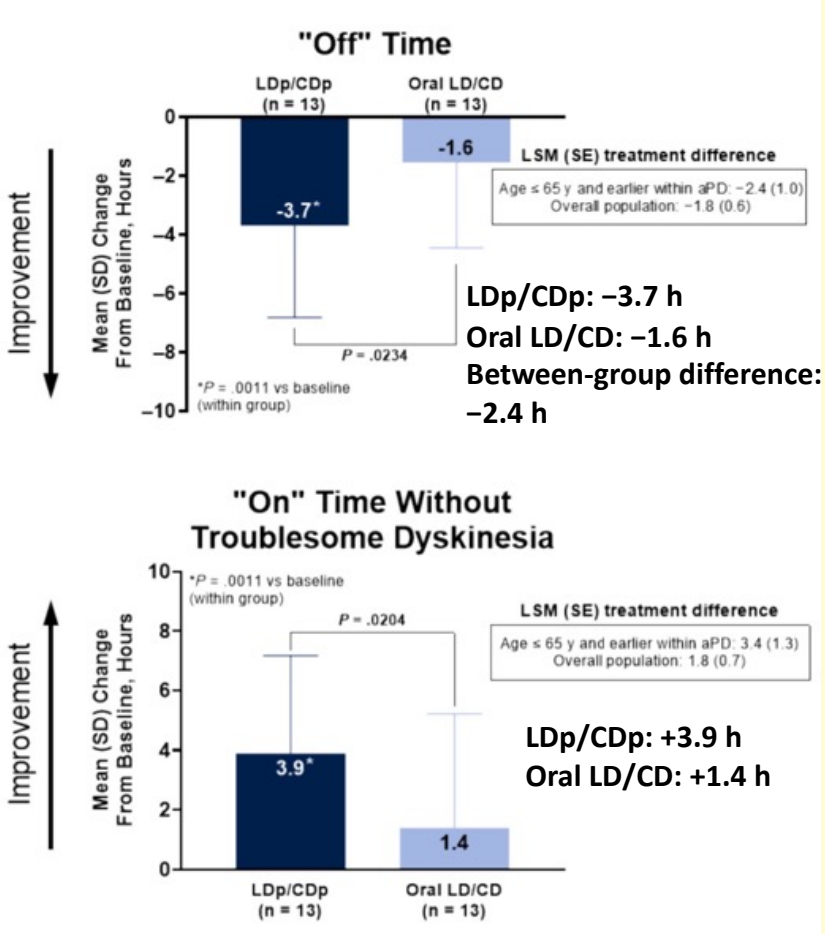
ORIGINAL RESEARCH

Foslevodopa/Foscarbidopa in Younger Patients Earlier Within Advanced Parkinson's Disease: Post Hoc Analysis of a Randomized Trial

Angelo Antonini · Bruno Bergmans · Drew S. Kern · Florin Gandor · Noriko Nishikawa · David G. Standaert · Bjoern Fritz · Resmi Gupta · Toshiki Nozaki · Megha B. Shah · Lars Bergmann · Thomas Kimber

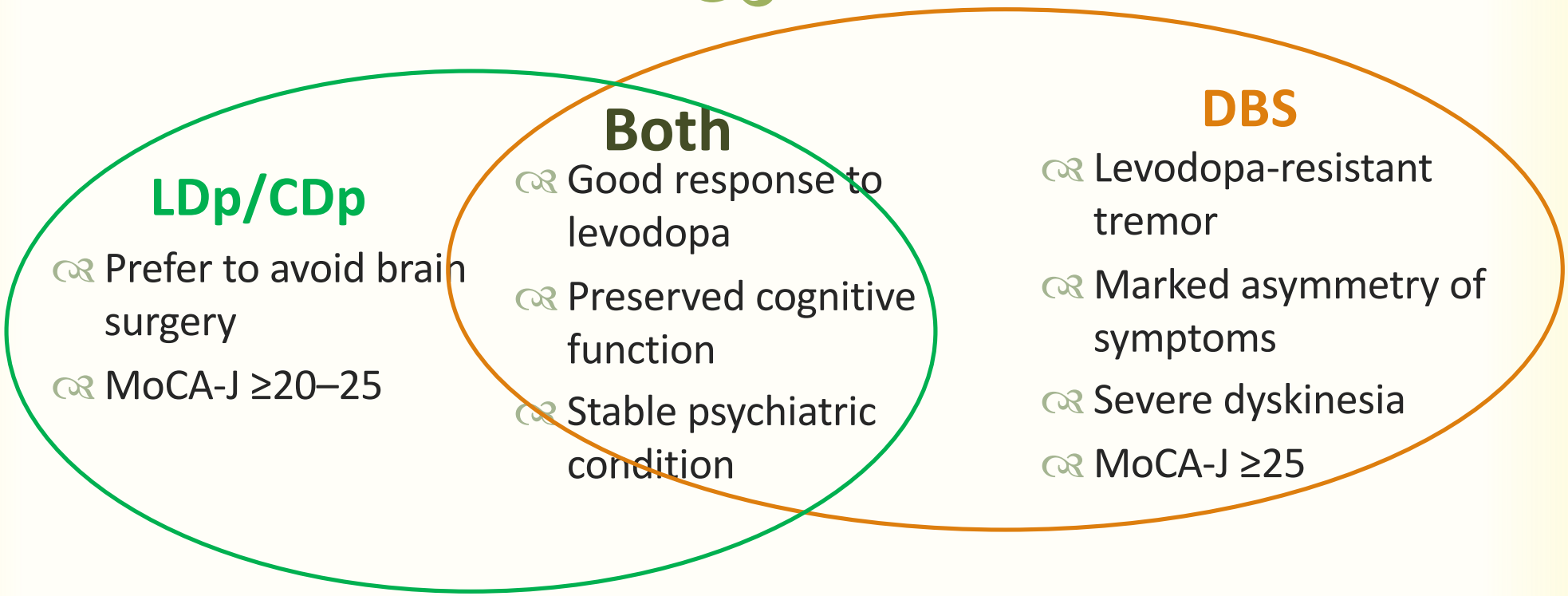
- Post hoc analysis of a randomized controlled trial (NCT04380142)
- **Study population (subgroup definition): early advanced PD**
  - Age ≤65 years
  - Hoehn & Yahr ≤2 (ON state)
  - ≤5 years since onset of motor fluctuations
  - N = 26 (LDp/CDp: 13, oral LD/CD: 13)
- In younger patients with early advanced PD, the treatment effect of LDp/CDp tended to be greater than in the overall population

Primary Outcomes (Week 12)



Neurol Ther. 2025 Dec 1. doi: 10.1007/s40120-025-00856-1. Online ahead of print.

Suitable Patient Profiles Are Similar



(authorised by the speaker)

LCIG vs LDp/CDp

Key Differences in Clinical Practice

	LCIG	LDp/CDp
Route	Intestinal (PEG-J)	Subcutaneous
Infusion time	~16 hours/day	24 hours/day
Formulation	Levodopa : Carbidopa = 4:1	Foslevodopa/Foscarbidopa → Levodopa
Advantages	Established therapy	No surgery required
Main AEs	Tube-related complications	Skin reactions
Other concerns	Device management	Psychiatric symptoms

Select based on patient profile and preferences

Pharmacokinetic comparison in healthy subjects

Foslevodopa/foscarbidopa subcutaneous infusion maintains equivalent levodopa exposure to levodopa-carbidopa intestinal gel delivered to the jejunum

Matthew Rosebraugh [a,*], Sven Stodtmann [b], Wei Liu [a], Maurizio F. Facheris [c]

Study Design (M17-220 Study)
25 healthy subjects

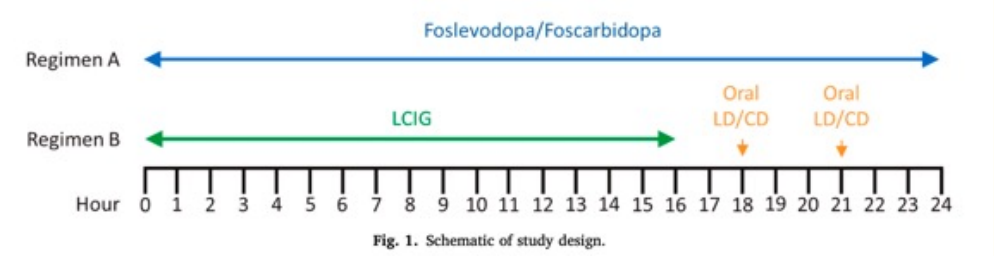
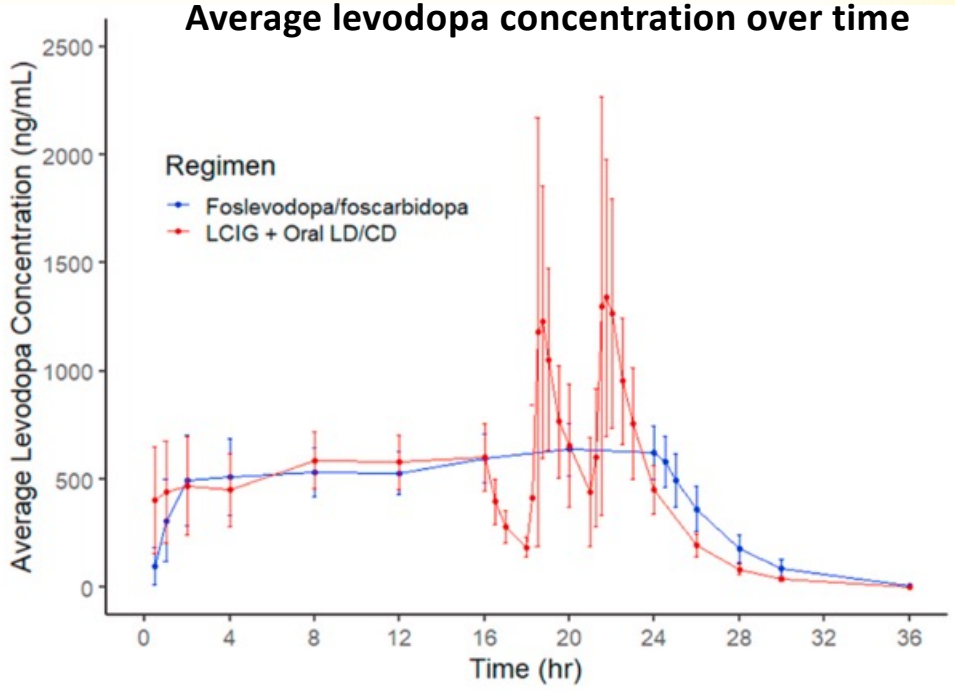


Fig. 1. Schematic of study design.

Average levodopa concentration over time



Regimen A: Foslevodopa/Foscarbidopa
Loading dose: 80/4 mg
Followed by continuous infusion over 24 hours: 700/35 mg

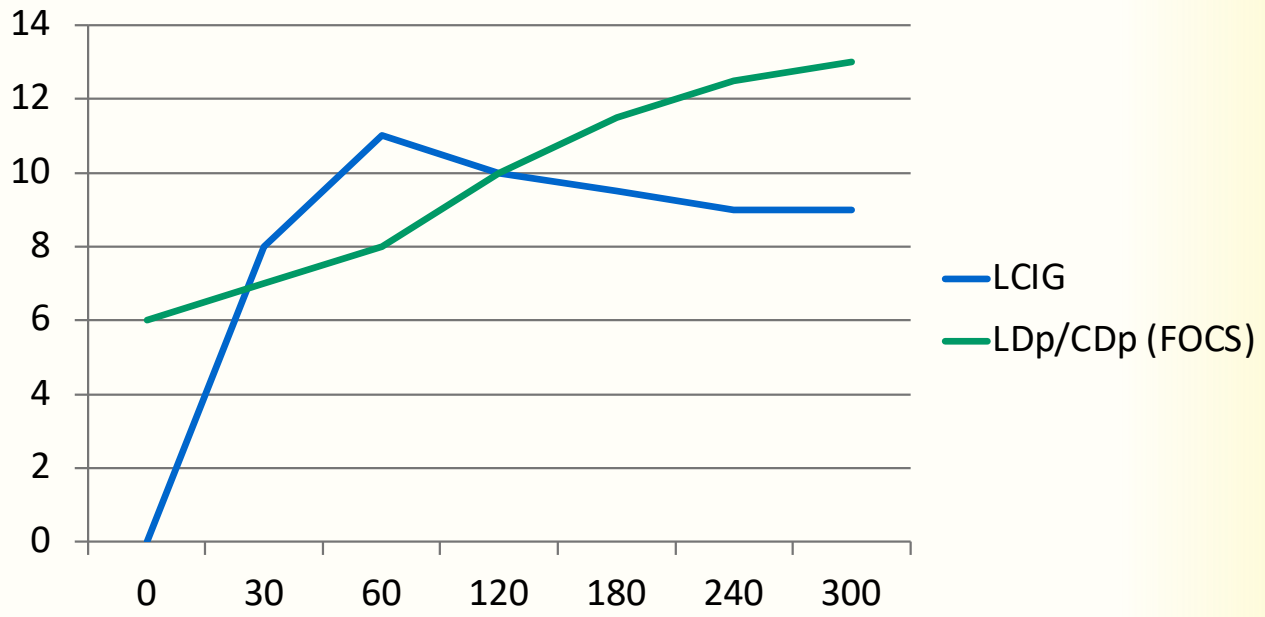
Regimen B: LCIG + Oral LD/CD
Loading dose: 50/12.5 mg (2.5 mL)
Continuous LCIG infusion for 16 hours: 350/87.5 mg (1.1 mL/h)
Oral levodopa/carbidopa: 100/25 mg × 2 doses

Parkinsonism and Related Disorders 97 (2022) 68–72

Distinct Pharmacokinetic Profiles: LCIG vs LDp/CDp

LCIG
- Rapid rise (morning bolus)
- Fast ON (~45 min)
- Clear OFF→ON transition
- Lower steady-state
- Interrupted overnight

LDp/CDp (FOCS)
- Gradual increase
- Slower ON during initiation
- Modifiable with loading strategies
- Higher steady-state
- Continuous 24-hour delivery



Same ON threshold (~10 nmol/mL)
— different pathways to reach and maintain it

Parkinsonism Relat Disord. 2026 Mar:144:108197.

How to Choose Between LCIG and LDp/CDp

LCIG may be preferred when:

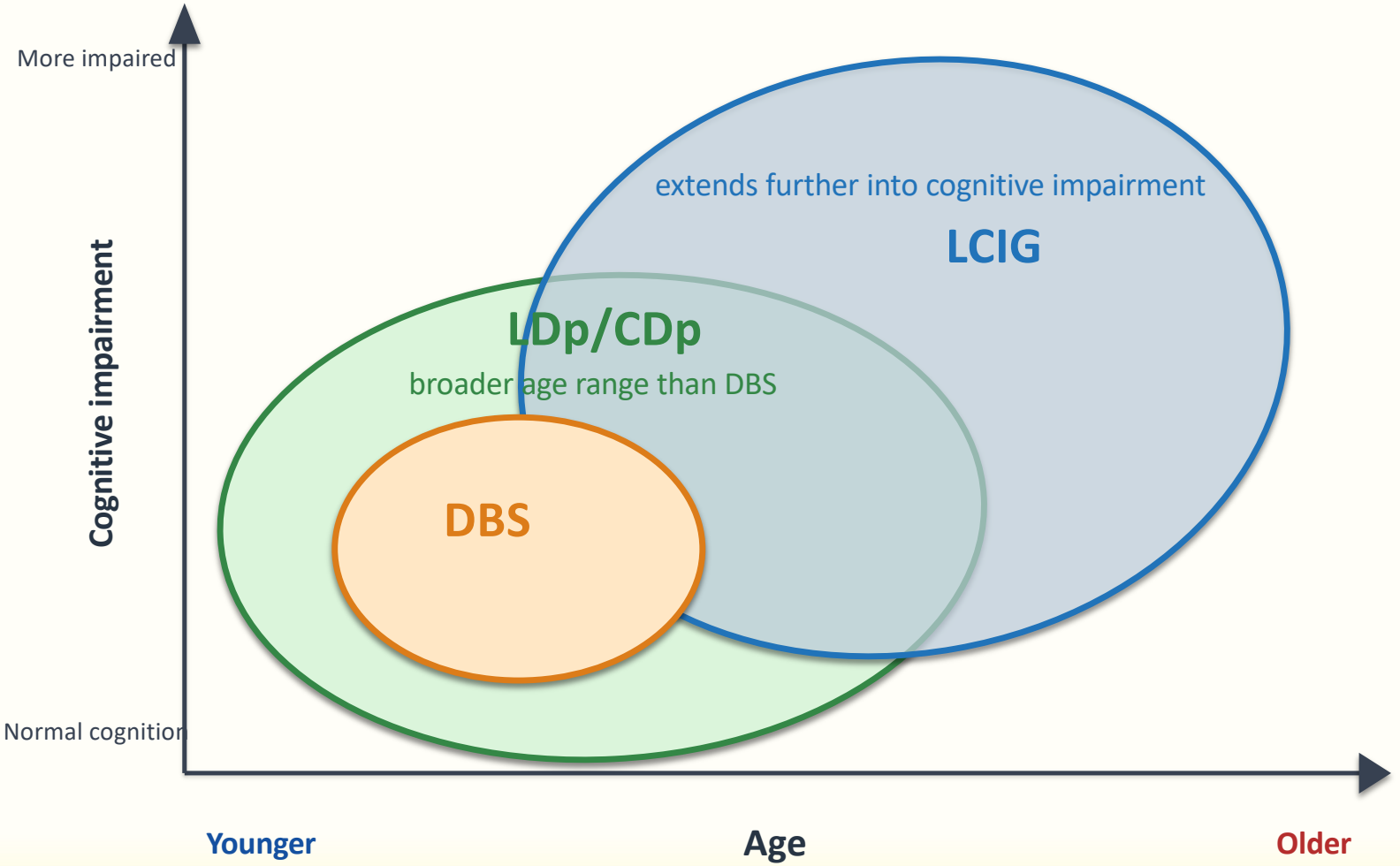
- Rapid and clear ON response
- Clear OFF→ON contrast
- Avoid 24-hour stimulation
- Concern for nighttime neuropsychiatric symptoms
- Acceptable PEG-J procedure

LDp/CDp may be preferred when:

- Need 24-hour symptom control
- Avoid surgical procedures
- Stable levodopa levels
- Troublesome early-morning OFF
- Acceptable skin/psychiatric AEs

(authorised by the speaker)

Clinical Positioning of Device-Aided Therapies

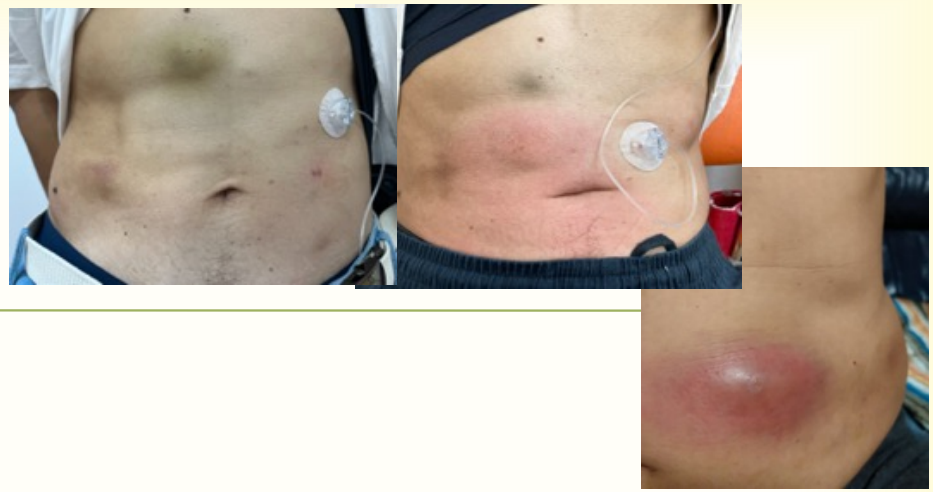


(authorised by the speaker)

CLINICAL PRACTICE

Considerations for Initiation and Maintenance of Foslevodopa/Foscarbidopa for Advanced Parkinson's Disease

K. Ray Chaudhuri, MD, DSc,[1,2,3,*] Bruno Bergmans, MD, PhD,[4,5] Eric Freire-Alvarez, MD,[6,7] Lucie Hopes, MD,[8] Drew S. Kern, MD, MS,[9] Robert S. Kirsner, MD, PhD,[10] Giulia Lazzeri, MD,[11] Pedro Mendes-Bastos, MD,[12] Noriko Nishikawa, MD, PhD,[13] Per Odin, MD, PhD,[14] Karolina Poplawska-Domaszewicz, MD, PhD,[1,2,15] Rajesh Pahwa, MD,[16] Yuval Ramot, MD, MSc,[17,18] Klaus Seppi, MD,[19] Tobias Warnecke, MD,[20] Robert Wiggins, MD,[21] Megha B. Shah, PharmD,[22] Pavnit Kukreja, PharmD,[22] Bjoern Fritz, PhD, MBA,[22] Koray Onuk, MD,[22] and Stuart H. Isaacson, MD[23,24]



Basic Principles for Preventing Injection-Site Reactions

- **Careful Selection of Injection Sites**
  - First choice: periumbilical abdominal area (adequate subcutaneous fat)
  - Alternatives: flanks, thighs, upper arms, scapular region
  - Avoid: scars, stretch marks, bony prominences, damaged skin
- **Regular Rotation of Injection Sites**
  - Standard: every 72 hours
  - If reactions occur: every 24–48 hours
- **Appropriate Cannula Selection**
  - 9 mm is generally recommended
  - 6 mm for patients with low BMI or limited subcutaneous fat
  - 9 mm may provide better stability in physically active patients
- **Aseptic Technique and Skin Care**
  - Clean with mild (low-irritation) soap up to 3 times daily
  - (especially in case of erythema)
  - Use fragrance-free moisturizers
  - Alcohol-free barrier films can be used
- **Cannula Handling**
  - Insert at 90° with skin stretched
  - Leave cannula in place for ~1 hour after use

Mov Disord Clin Pract. 2026 Jan 16.

Practical Management to Reduce Injection-Site Reactions

① Prevention of Drug Pooling

- **Causes**
  - Improper insertion
  - Insufficient cannula length
  - High infusion volume
- **Prevention**
  - Use a 9-mm cannula
  - Apply the device firmly and perpendicular to the skin during insertion
  - Frequent site rotation
  - Gentle massage (avoid erythematous areas)

② Prevention of Dermatitis and Infection

- **Inflammatory reactions**
  - Often improve with site rotation
  - Mild cases: moisturizers ± low-potency topical steroids
- **Prevention of cellulitis**
  - Strict aseptic technique
  - If spreading erythema, pain, or warmth occurs → early antibiotic treatment

③ Patient Education is Essential

- Awareness of early signs
- Prompt reporting of skin changes
- Close follow-up during the first 4–6 weeks

Mov Disord Clin Pract. 2026 Jan 16.

LETTER: NEW OBSERVATION

Skin Inflammatory Reactions in Patients with Continuous Subcutaneous Injection of Foslevodopa-Foscarbidopa Hydrate: Histopathology

Histopathological Findings

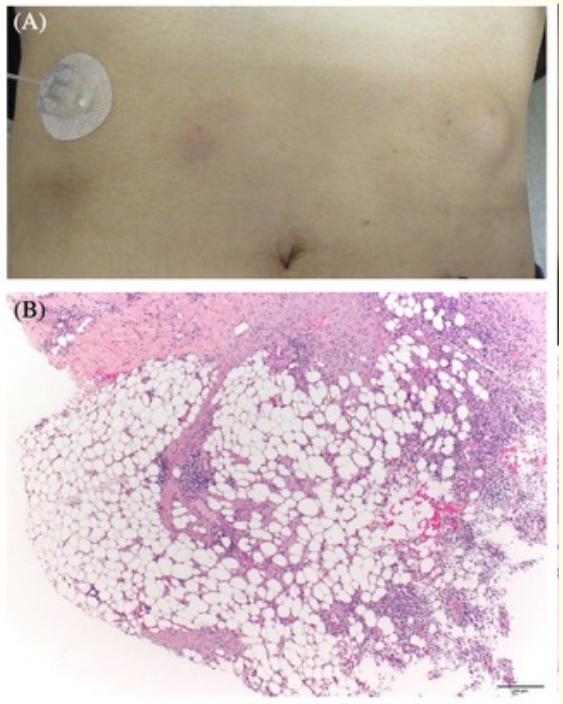
- No abnormalities in the epidermis
- Lymphocyte-predominant inflammatory cell infiltration
- in the subcutaneous septa
- Diagnosis: **panniculitis**

Proposed Mechanism

- Reactive inflammation due to
- high-concentration drug exposure in subcutaneous fat

Interpretation

- More consistent with **reactive inflammatory panniculitis (drug-induced)** rather than an infectious process



Mov Disord. 2025 Feb;40(2):378-379.

Take-home message

- Continuous dopaminergic stimulation is essential in advanced PD
- LCIG and LDp/CDp provide different approaches to achieve this
- LDp/CDp enables less invasive and potentially earlier intervention
- Treatment should be individualized based on patient profile and preferences

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