On Demand Therapie der Parkinson-Krankheit

Tobias Warnecke

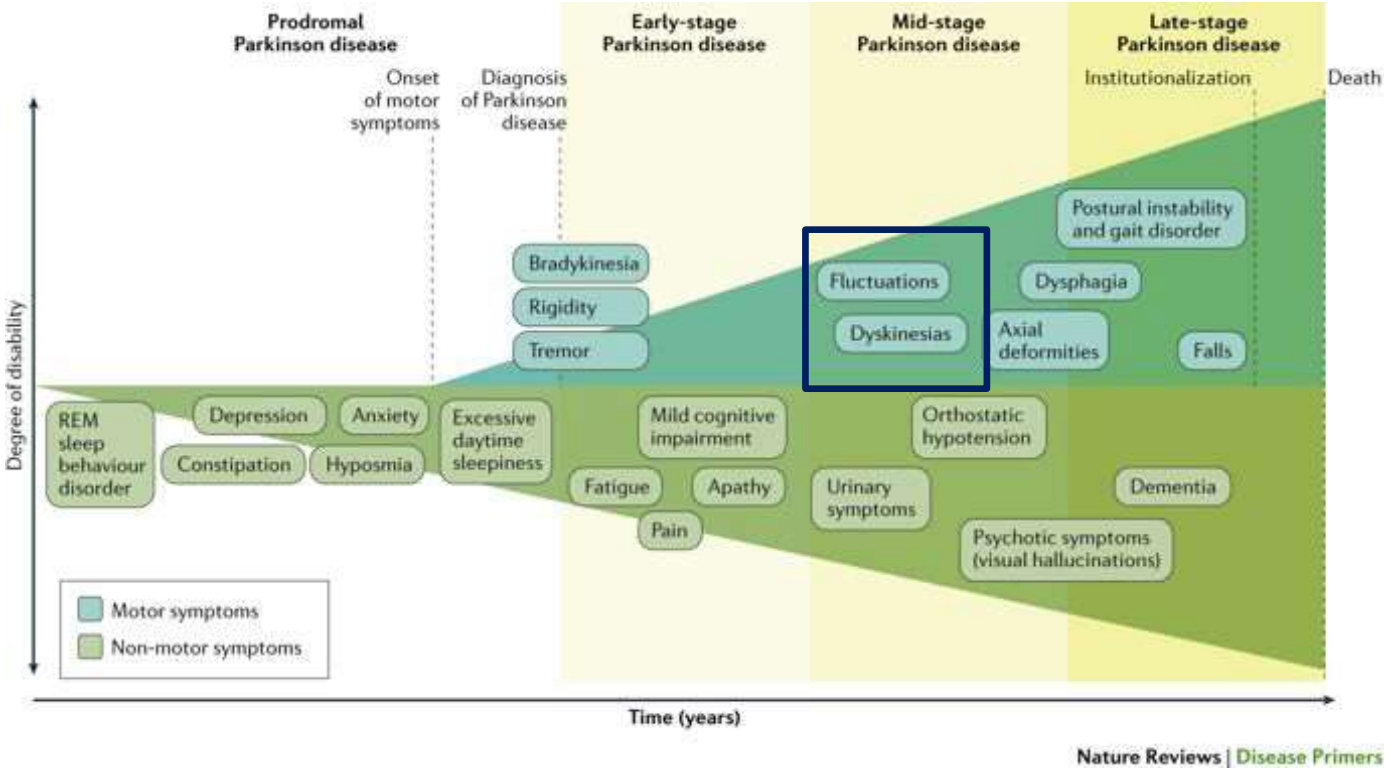
Parkinsonnetze
Münsterland+ und Osnabrück+

PARKINSONNETZ OSNABRÜCK+

PARKINSONZENTRUM Münster-Osnabrück

International Parkinson and Movement Disorder Society

Krankheitsstadien und assoziierte Symptome



Poewe et al. Nat Rev. 2017.

Motorische Komplikationen: Phänomenologie

REVIEW

Clinical Spectrum of Levodopa-Induced Complications

Camila Catherine Aquino, MD, MSc and Susan H. Fox, MRCP (UK), PhD*

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ABSTRACT: The first years of Parkinson disease (PD) treatment are marked by good and sustained responses to dopaminergic therapy. With disease progression and longer exposure to levodopa (L-dopa), patients develop a range of L-dopa–induced complications that include motor and non-motor symptoms. Motor complications include motor fluctuations, characterized by periods of reduced benefit from the medication, and L-dopa–induced dyskinesia, characterized by emergence of hyperkinetic involuntary movements. Dyskinesia can occur at peak effect of L-dopa, at the beginning and end of dose, or between doses. These motor complications are often associated with fluctuations in non-motor symptoms, particularly fluctuations in neuropsychiatric, autonomic, and sensory symptoms. Recognizing such complications and understanding their relationship with the timing of L-dopa doses is essential for adequate diagnosis and management. © 2014 International Parkinson and Movement Disorder Society

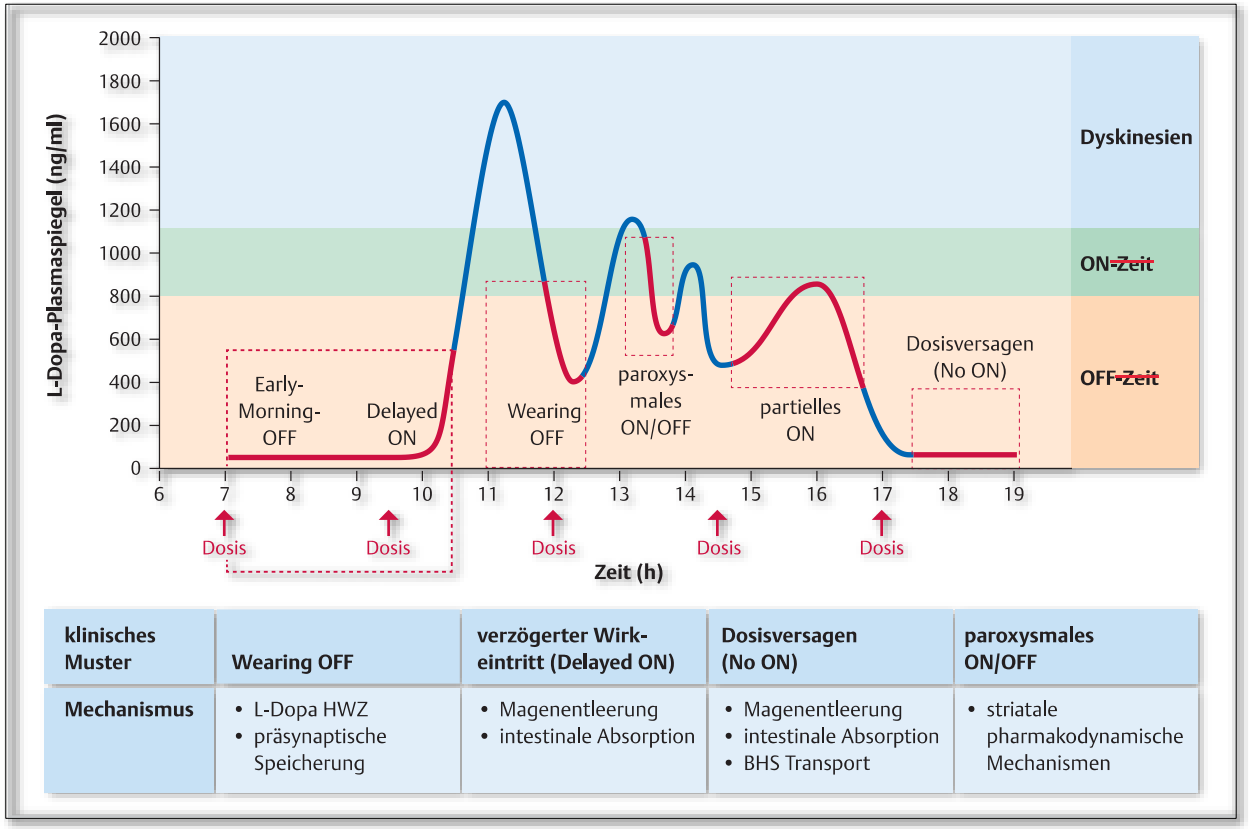
Key Words: wearing-off; dyskinesia; dystonia; non-motor fluctuations; phenomenology

Motorische Komplikationen: Phänomenologie

TABLE 1. Definitions of L-dopa–Induced Motor Fluctuations

Motor Fluctuations	Definitions
Predictable wearing-off	Gradual expected re-emergence of parkinsonian symptoms at the end of an L-dopa dose
Unpredictable, sudden offs	Acute episodes of akinesia that are unrelated to the timing of L-dopa dose
Dose failure, delayed or partial on response	A dose of L-dopa failing to provide the expected benefit in a patient known to be responsive to L-dopa. The benefit can be delayed by minutes or hours or may be absent.
Beginning of dose worsening	Worsening of symptoms, especially tremor, in the first few minutes after a dose of L-dopa, before the onset of benefit
End of dose rebound	PD symptoms that are more severe than in the untreated baseline state and emerge at the end of a dose of L-dopa
On-off fluctuations /"yo-yoing"	Predictable or unpredictable rapid changes or cycling between being "on" and mobile with dyskinesia, to being "off" and immobile over course of dose of L-dopa or over a day

Motorische Komplikationen: Phänomenologie



klinisches Muster	Wearing OFF	verzögerter Wirk-eintritt (Delayed ON)	Dosisversagen (No ON)	paroxysmales ON/OFF
Mechanismus	• L-Dopa HWZ • präsynaptische Speicherung	• Magenentleerung • intestinale Absorption	• Magenentleerung • intestinale Absorption • BHS Transport	• striatale pharmakodynamische Mechanismen

Aus Poewe et al., In: Deuschl, Oertel, Poewe : Parkinson-Syndrome und andere Bewegungsstörungen, Thieme, 2. Auflage, 2020

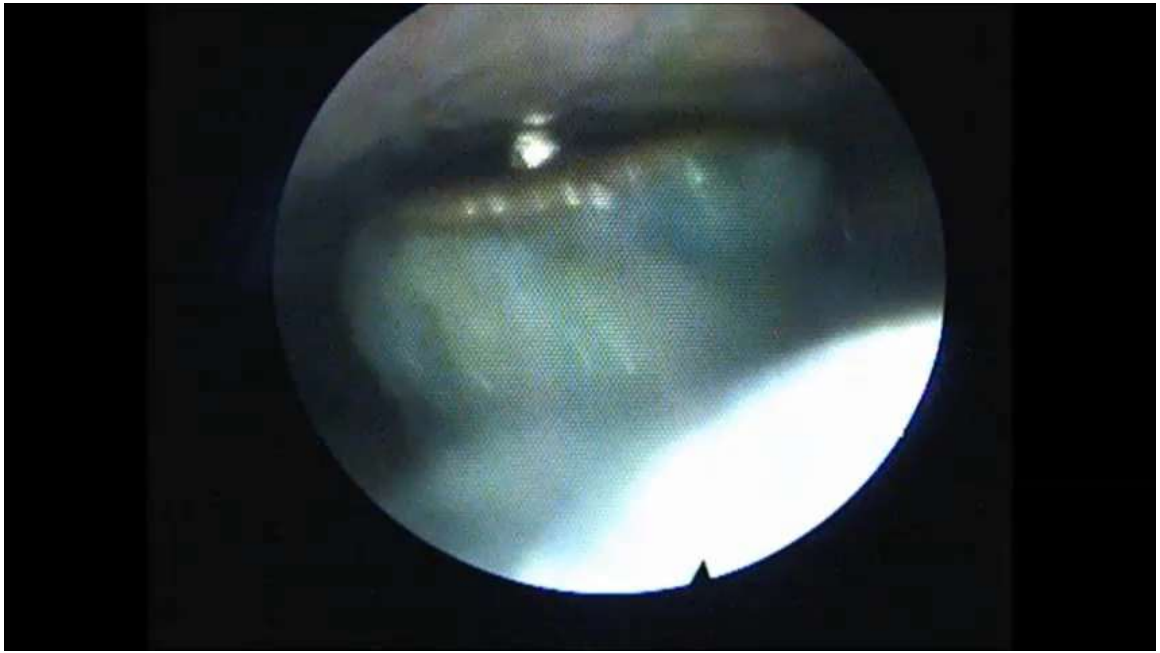
Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Impact of Residual Drug in the Pharynx on the Delayed-On Phenomenon in Parkinson's Disease Patients

*Jiro Fukae, MD, PhD,[1,2] Shinsuke Fujioka, MD, PhD,[1] George Umemoto, DDS, PhD,[3] Hajime Arahata, MD, PhD,[4] Shosaburo Yanamoto, MD,[1] Takayasu Mishima, MD, PhD,[1] and Yoshio Tsuboi, MD, PhD[1]**

ABSTRACT: Background and Objective: The delayed-on phenomenon (DOP) related to levodopa treatment frequently disturbs quality of life in advanced-stage Parkinson's disease (PD) patients. The objective of this study was to explore the impact of swallowing dysfunction on the development of DOP.
Methods: Swallowing function was investigated by endoscopic evaluation in 11 PD patients with the DOP and 9 PD patients without the DOP during the *on* phase. Residual drug in the pharynx after taking the drug in tablet, capsule, and powder forms was also observed.
Results: Residual drug was seen in the pharynx in six cases (30.0%). Pooling of saliva, delayed swallowing reflex, and residual drug were more frequent in the DOP group than in the group without the DOP ($P < 0.05$). The odds ratios for residual drug in the pharynx, pooling of saliva, and delayed swallowing reflex for the DOP were 42.7 (95% confidence interval, 1.89–962.9), 14.0 (95% confidence interval, 1.25–156.6), and 15.8 (95% confidence interval, 1.75–141.4), respectively.
Conclusions: These results suggest that swallowing dysfunction leading to residual antiparkinsonian drug in the pharynx has substantial impacts on the DOP in PD patients.



npj | parkinson's disease

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ARTICLE OPEN

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Dysphagia for medication in Parkinson's disease

Bendix Labeit[1,2✉], Elijahu Berkovich[3], Inga Claus[1], Malte Roderigo[1], Anna-Lena Schwake[1], Dvora Izgelov[3], Dorit Mimrod[3], Sigrid Ahring[1], Stephan Oelenberg[1], Paul Muhle[1,2], Verena Zentsch[1], Fiona Wenninger[1], Sonja Suntrup-Krueger[1,2], Rainer Dziewas[4] and Tobias Warnecke[4]

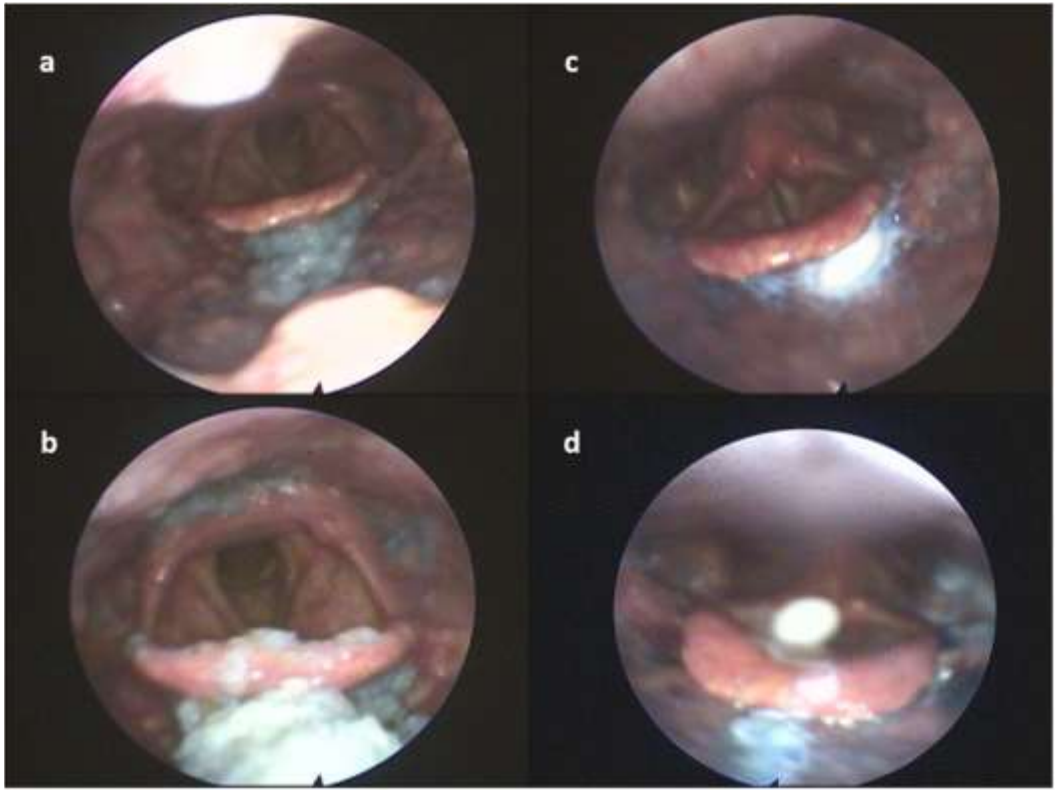
Dysphagia is common in Parkinson's disease (PD) and is assumed to complicate medication intake. This study comprehensively investigates dysphagia for medication and its association with motor complications in PD. Based on a retrospective analysis, a two-dimensional and graduated classification of dysphagia for medication was introduced differentiating swallowing efficiency and swallowing safety. In a subsequent prospective study, sixty-six PD patients underwent flexible endoscopic evaluation of swallowing, which included the swallowing of 2 tablets and capsules of different sizes. Dysphagia for medication was present in nearly 70% of PD patients and predicted motor complications according to the MDS-UPDRS-part-IV in a linear regression model. Capsules tended to be swallowed more efficiently compared to tablets, irrespective of size. A score of ≥1 on the swallow-related-MDS-UPDRS-items can be considered an optimal cut-off to predict dysphagia for medication. Swallowing impairment for oral medication may predispose to motor complications.

npj Parkinson's Disease (2022)8:156; https://doi.org/10.1038/s41531-022-00421-9

Medikationsdysphagie

Ordinale Skala	Schluckeffizienz	Schlucksicherheit
0: keine Beeinträchtigung	Das Medikament wird beim ersten Schluckversuch vollständig geschluckt, ohne sich aufzulösen.	Das Medikament wird geschluckt, ohne dass die Gefahr von Penetrationen oder der Aspiration besteht.
1: leichte Beeinträchtigung	Das Medikament wird beim ersten Versuch nicht geschluckt, lässt sich aber bei weiteren Versuchen leicht schlucken, ohne sich aufzulösen.	Das Medikament oder Wasser gelangt vorzeitig (vor auslösen des Schluckreflex) in den Rachen oder verbleibt nach dem ersten Schluckversuch prolongiert im Rachen, ohne dass es zu einer Penetration oder Aspiration kommt.
2: mäßige Beeinträchtigung	Das Medikament steckt vorübergehend im Oropharynx fest und kann nur durch intensive Schluckversuche (≥5 Versuche oder zusätzliches Wassertrinken) gelöst werden und/oder es kommt zu minimalen Auflösungserscheinungen (Medikamentenbelag auf der Schleimhaut).	Das Medikament oder das Wasser dringt in den Larynxeingang ein, wird aber durch Schutzreflexe wirksam entfernt.
3: schwere Beeinträchtigung	Das Medikament kann nicht vollständig geschluckt werden und löst sich teilweise auf.	Das Medikament oder Wasser dringt in den Larynxeingang ein und wird trotz Schutzreflexen nicht entfernt.
4: sehr schwere Beeinträchtigung	Das Medikament kann nicht geschluckt werden und/oder löst sich vollständig auf.	Das Medikament oder Wasser dringt in den Larynxeingang ein, ohne dass es zu Schutzreflexen kommt, oder es kommt zu Aspirationsereignissen.

Medication dysphagia



Warnecke et al. npj Parkinson's Disease 2022

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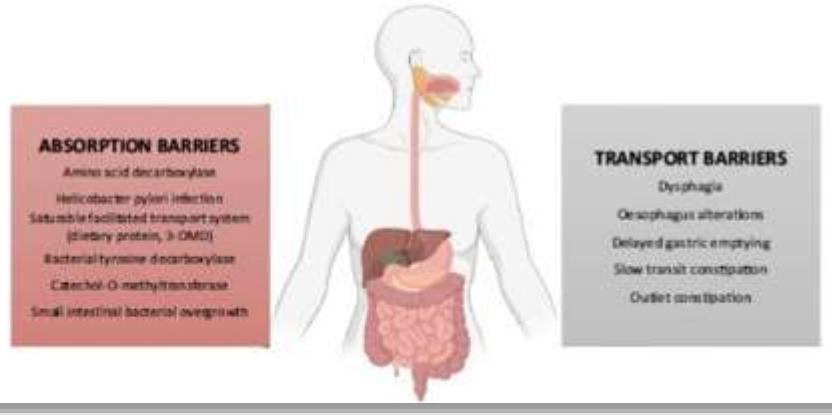
REVIEW ARTICLE

european journal of neurology

FIGURE 2 Barriers to levodopa transport and absorption in the gastrointestinal tract. The figure shows barriers to levodopa pharmacokinetics categorised as absorption barriers (factors which affect levodopa absorption in the small intestine primarily) and transport barriers (factors which affect levodopa transport through the gastrointestinal tract primarily). Of note, transport barriers can ultimately alter levodopa absorption. 3-OMD, 3-O-methyldopa.

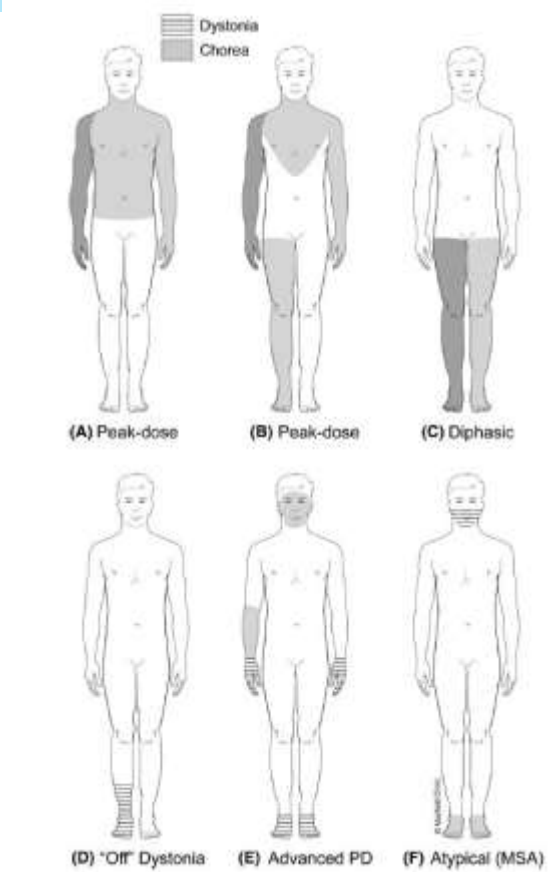


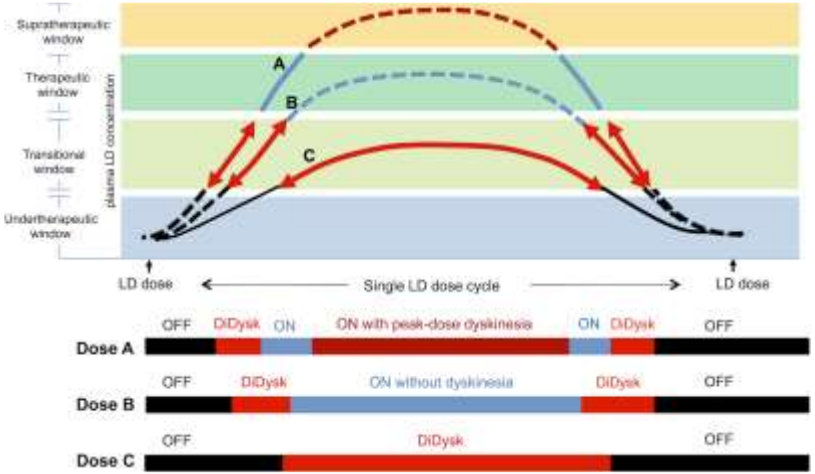
Motorische Komplikationen: Phänomenologie

TABLE 2. Phenomenology of L-dopa–Induced Dyskinesia

Dyskinesia	Phenomenology
Peak dose/square wave	
Chorea/dystonia/ballism	Occurs in the 'on' state, 1-2 h after a dose of L-dopa. Manifest as a mixture of choreic movements of the neck, limbs, trunk, and face, with dystonic posturing of limbs and neck. In more severe cases, ballistic movements can occur.
Ocular dyskinesia	May accompany peak-dose dyskinesia. Two patterns have been described: upward gaze deviation—oculogyric crisis, and slow "to-and-fro" movements.
Myoclonus	Less frequent; usually emerges within 10 to 20 minutes of an L-dopa dose and tends to disappear in the "fully on" state. Myoclonus, when seen, is usually in patients with dementia.
Respiratory	Irregular rate and depth of breathing because of involvement of respiratory muscles in peak-dose dyskinesia
Wearing-off/Off-period	
Dystonia	Usually affects the legs and feet (ankle inversion and extension or flexion of toes). Can be painful and disabling; more frequent in the morning, before first L-dopa dose. Blepharospasm, jaw opening, neck and hand posturing also can occur.
Diphasic dyskinesia	Occurs at the beginning- and end-of-dose. Predominantly dystonia that affects the legs, with slow stereotypical alternating movements, sometimes with ballistic kicking. High stepping during walk can result in "funny gaits."

Dyskinesien





Espay et al. Ann Neurol 2018

Häufigkeit verschiedener motorischer Komplikationen

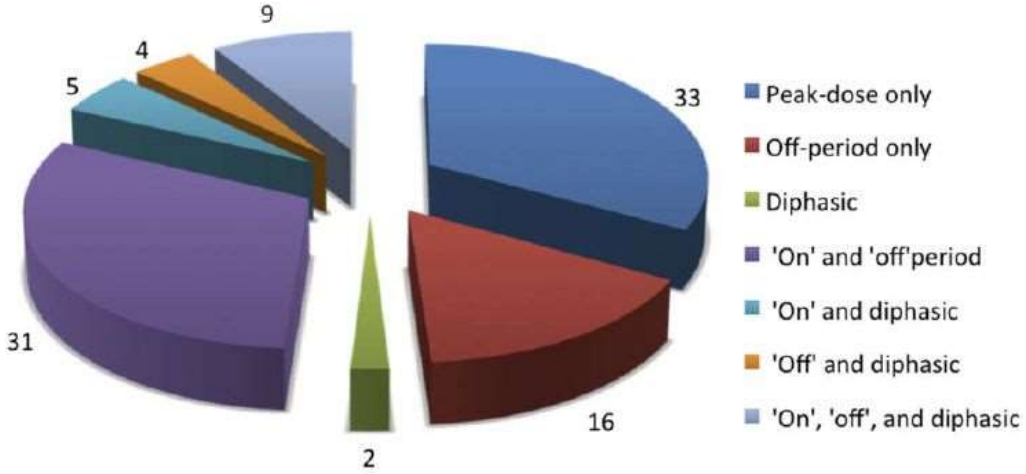


FIG. 1. Estimated frequency (%) of different types of levodopa-induced dyskinesia (modified from Luquin et al[61]).

Neurol Ther (2023) 12:391–424
https://doi.org/10.1007/s40120-022-00435-8

REVIEW

Off-time Treatment Options for Parkinson's Disease

Margherita Fabbri · Raquel Barbosa · Olivier Rascol

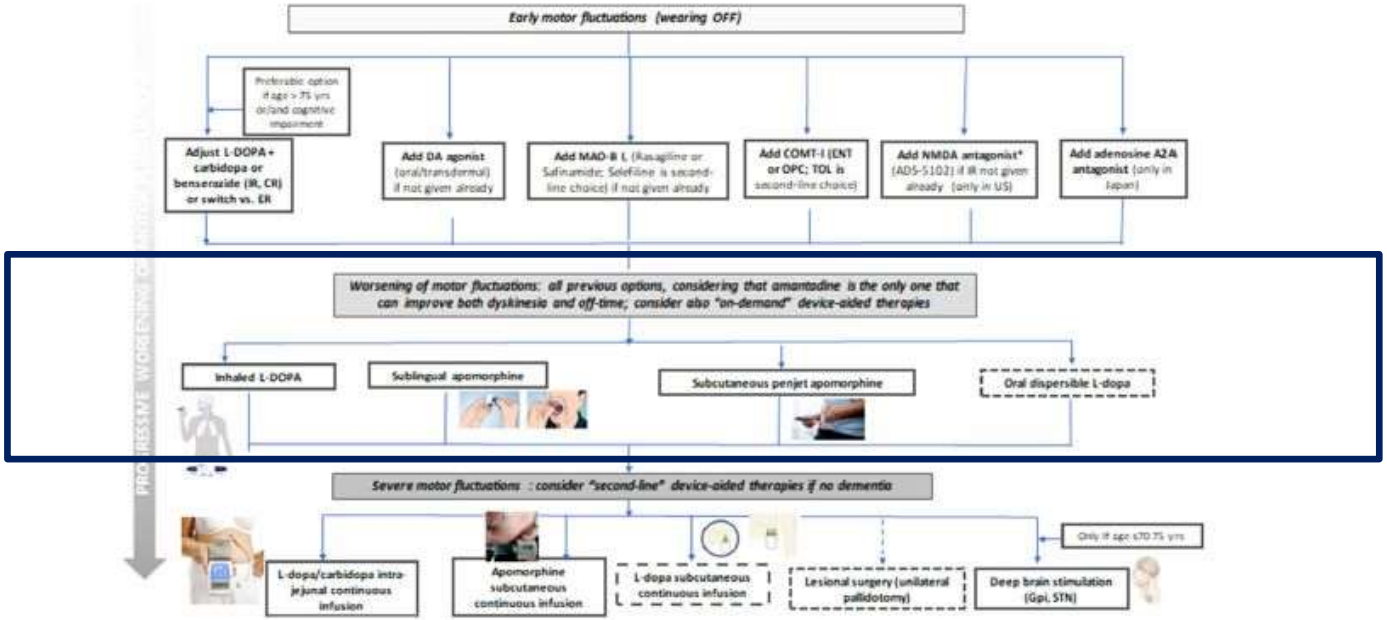


Fig. 2 Algorithm for treatment options for the management of MF, from the early advanced stage to the appearance of troublesome MF in the severe advanced stage. *Dotted lines* indicate treatments with lower levels of evidence (to be considered with limitations, i.e. radiofrequency pallidotomy) or with few data available and still not marketed (CLSI)

REVIEW

On-Demand Therapy for OFF Episodes in Parkinson's Disease

C. Warren Olanow, MD, FRCPC, FRCP(hon),[1,2*] Werner Poewe, MD,[3] Olivier Rascol, MD,[4] and Fabrizio Stocchi, MD[5]

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[2]*Clintrex Research Corporation, Sarasota, Florida, USA*
[3]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*
[4]*Department of Clinical Pharmacology and Neuroscience, Clinical Investigation Center CIC1436, Parkinson Expert Center, NS-Park/F-CRIN, NeuroToul COEN Center; Toulouse University Hospital, INSERM and University of Toulouse 3, Toulouse, France*
[5]*University and Institute for Research and Medical Care, IRCCS San Raffaele Pisana, Rome, Italy*

Olanow et al. Mov Disord. 2021

TABLE 1 *Approved on-demand therapies for OFF episodes*

Drug name	Primary end point mean change in UPDRS part III score in pivotal study (active drug vs placebo)	Additional results of clinical trials	Comments
Apomorphine hydrochloride injection (APOKYN, Apo-Go, Dacepton)	Mean change vs. placebo in UPDRS III 20 minutes postdose (−23.9 vs −0.1; $P < 0.001$) Mean dose of active drug, 5.4 mg	• Rapid time to ON response (10–22 minutes) • Conversion rate from OFF to ON (95%)	• Need for multiple medically supervised visits to titrate to optimal effect • Requires device assembly prior to use • Requires injection • Premedication for nausea and vomiting typically required • Cutaneous lesions and dopaminergic adverse events
Apomorphine sublingual film (KYNMOBI)	Mean change vs. placebo in MDS-UPDRS III 30 minutes postdose (−11.1 vs −3.5; $P < 0.0001$) Mean dose of active drug, 19.6 mg	• Rapid time to ON (<30 minutes) • High response rate on home diary (79%) • ON response maintained through 90 minutes in 47% of patients	• No need for multiple supervised in clinic visits to titrate to optimal effect — can be done at home • Premedication for nausea not required for all patients • Does not require application device • No need for injection • Swallowing can decrease absorption • High rate of oropharyngeal adverse reactions and dropout
Levodopa inhalation powder (INBRIJA)	Mean change vs. placebo in UPDRS III 30 minutes postdose: (−9.8 vs −5.9; $P = 0.009$) Dose of active drug, 84 mg	• ON response achieved by most patients (10–30 minutes) • ON response maintained through 60 minutes in 58% of patients • Patients note functional improvement	• No titration required • No antinausea medication required • No need for injection • Requires device assembly • Levodopa dose limited to 84 mg • Does not include decarboxylase inhibitor • Adverse events include cough, upper respiratory tract infection, and sputum discoloration

Olanow et al. Mov Disord. 2021

Sublinguales Apomorphin

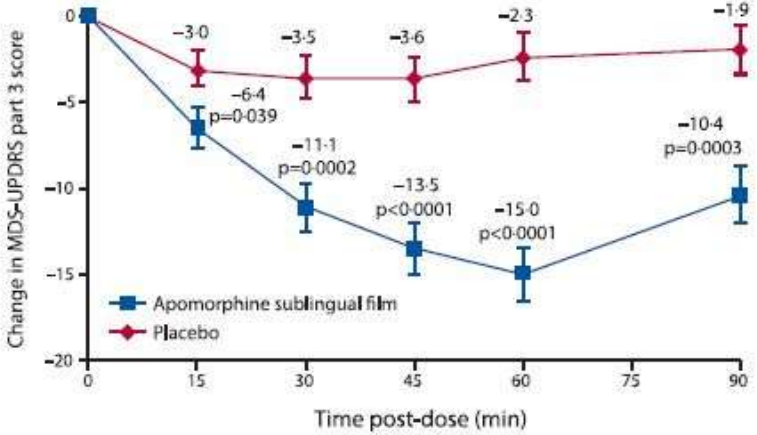


FIG. 2. Comparison of APL versus placebo with respect to change in UPDRS-III at various times postadministration of therapy.[64] Note that there were significant benefits with APL versus placebo at all times recorded and that benefit lasted for 90 minutes. [Color figure can be viewed at wileyonlinelibrary.com]

Olanow et al. Mov Disord. 2021

Sublinguales Apomorphin

- Wird für 3 Minuten unter die Zunge gelegt und setzt dort Apomorphin frei
- Wirkung wird nicht von gestörter gastrointestinaler Motilität oder Nahrung gestört
- Bei fast 80% der Patient wird Off-Phase innerhalb von 30 Minuten durchbrochen, Wirkung hält 90 Minuten an
- Oropharyngeale Nebenwirkungen allerdings bei einem Drittel der Patienten: Lippenulzerationen, Gingivaödeme sowie Schwellungen an Lippen, Schleimhaut oder Rachen

Höfs und Falkenburger. Psychopharmakotherapie 2022

Inhalatives Levodopa

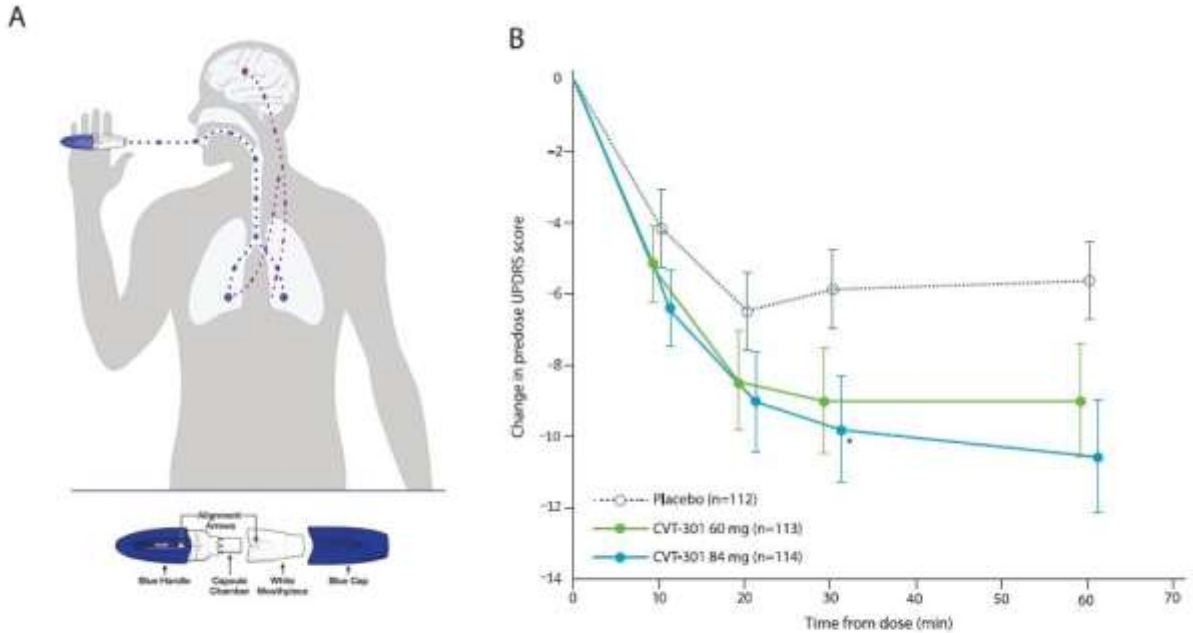


FIG. 3. (**A**) Schematic representation of the inhaler device and the capsule.[70] (**B**) UPDRS-III (motor) scores at various times following administration of 2 doses of inhaled levodopa versus placebo in the phase 3 pivotal trial.[72] [Color figure can be viewed at wileyonlinelibrary.com]

Olanow et al. Mov Disord. 2021

Inhalatives Levodopa

- Direkte Aufnahme von Levodopa über die Lunge durch Inhalieren möglich
- Behandlung Parkinson-assoziierter „Off-Phasen“
- Kombination nur mit Levodopa in Tablettenform (+ Decarboxylasehemmer) möglich
- Bis zu 5 Anwendungen pro Tag (jeweils 2 Kapseln)
- Husten als Nebenwirkung möglich

LeWitt et al., Lancet Neurol 2019

Orale Einnahme von Levodopa / Benserazid und **Veränderung der motorischen Funktionen** im zeitlichen Verlauf am Beispiel eines Patienten [1,*]

Verabreichung von Arzneimitteln durch Inhalation

Potenzielle Vorteile des pulmonalen Weges:

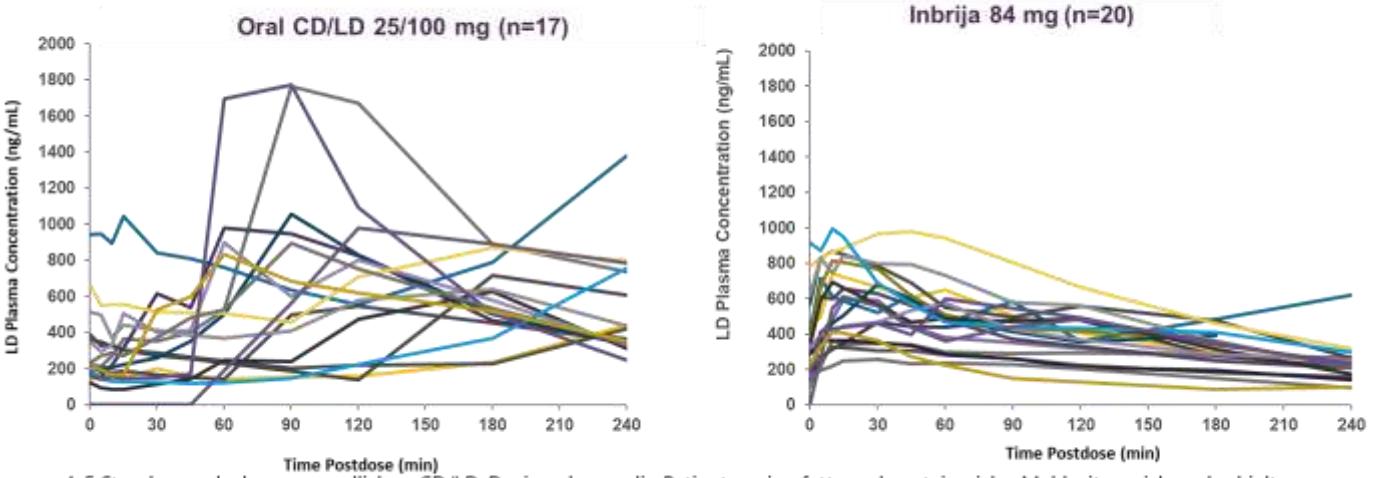
- Bessere Bioverfügbarkeit durch pulmonale Absorption
- Schneller Wirkeintritt
- Vermeidung des First-Pass-Effekt
- Andere pharmakokinetische Aspekte

Herausforderung: Zeitpunkt

Paradigmenwechsel: Therapie der akuten OFF-Phasen mit einer oralen Therapie als Rescue Medikation, gegenüber dem Verhindern einer OFF-Phase durch Inhalationstherapie, schon bei den ersten Anzeichen einer OFF-Phase (→ Überbrückung der OFF-Phase)

Ye et al., Int J Pharmaceut 2022; 614 121457

Postprandial geringere Varianz von Levodopa im Plasma mit inhalativem Levodopa



- 4-5 Stunden nach der morgendlichen CD/LD-Dosis nahmen die Patienten eine fett- und proteinreiche Mahlzeit zu sich und erhielten anschließend die Studienmedikation CVT-301
- CVT-301 84 mg wurde zusammen mit 25 mg oralem Carbidopa verabreicht, um einen echten PK-Vergleich von Levodopa zu ermöglichen.

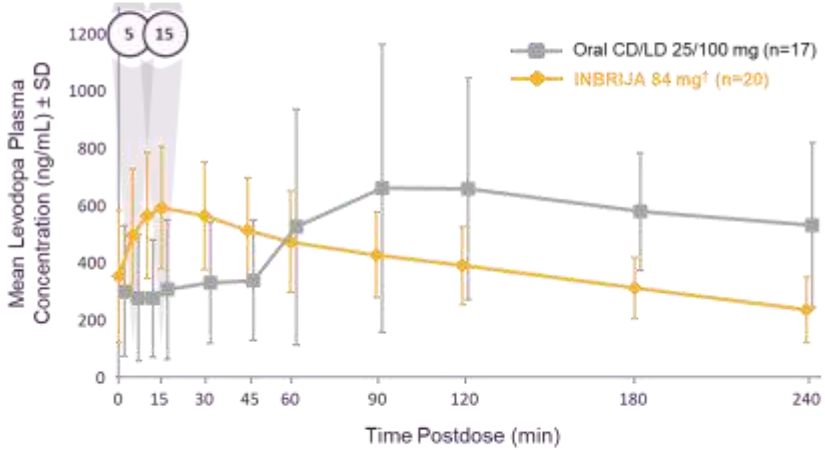
Safirstein BE et al. *Clin Ther.* 2020 Jun;42(6):1034-1046 Pharmakokinetische Studie CVT-301-012 – keine klinischen Schlussfolgerungen möglich

INBRIJA Reaches Mean Peak Plasma Concentrations Faster Than Oral Carbidopa/Levodopa in Fed State

Single-Dose PK Study in PD Patients Following a High-fat, High-protein Meal*

5 MIN — **Rapid Increase** in mean plasma levels within 5 minutes

15 MIN — Median T_{max} as compared to 120 minutes for oral CD/LD



*4-5 hours after morning CD/LD, patients ate meal then received study drug.
†INBRIJA 84 mg coadministered with 25 mg oral carbidopa for true PK comparison of levodopa.

1. Safirstein BE, et al. Poster #167 presented at MDS-PAS; February 14-16, 2020; Miami, FL.

Diskussion!

In den USA ist Inbrija die bevorzugte PD-On-Demand-Behandlung

- US Ärzte berichteten, dass sie sich mit INBRIJA im Allgemeinen wohler fühlten als mit ODTs auf Apomorphinbasis
- ~10.000 Patienten haben seit der Markteinführung 2018 eine Therapie mir INBRIJA erhalten
- Patienten profitieren von Inbrija i.d.R. über einen langen Zeitraum, wenn sie zu Beginn mit der Handhabung des Inhalators und der Atemtechnik gut klarkommen. Einweisung, Motivation und Begleitung ist daher sehr wichtig.
- Für US-Ärzte steht der ideale Inbrija Patient aktiv im Leben, hat eine gute Motorik und kann spontane OFF-Phasen erkennen und bei ersten Anzeichen dagegen inhalieren
- Ein typischer Patient nutzt Inbrija ca. 2 mal am Tag
- Ca 20% der Inbrija einsetzenden US-Ärzte geben die On-Demand Therapien an alle CD/LD Patienten, als ständiger Therapiebegleiter im Falle eines unvorhergesehenen OFF´s

- Meist werden Wirkstoffffluktuationen in erster Linie über eine Anpassung der Basis-Medikation adressiert. Ein frühes Erkennen der OFF-Phasen und eine on-Demand Therapiestrategie ist ein relativ neuer Ansatz.
- 50-70% der US Patienten unter einer CD/LD Therapie haben OFF-Phasen, 33% davon haben über den Tag variable OFF-Phasenmuster

ODT = On Demand Therapie