

THERAPIES FOR ADVANCED PARKINSON DISEASE

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UAB Department of Neurology
Aug 19, 2023

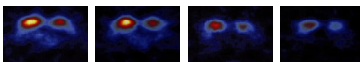
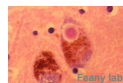
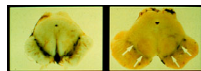
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DISCLOSURES

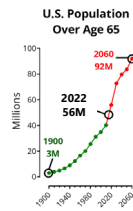
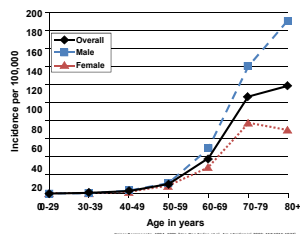
- Dr. Standaert has served as a paid consultant to these companies within the last 12 months:
 - Abbvie Inc.
 - Curium Pharma
 - Appello Pharma
 - F. Hoffman La Roche
 - Coave Therapeutics
 - Blue Rock Therapeutics
 - Sanofi-Aventis Research and Development (DSMB member)
 - Alnylam Pharmaceuticals (DSMB member)
 - Theravance, Inc. (DSMB member)

CLASSICAL FEATURES OF PARKINSON DISEASE

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance



PD IS COMMON. AGE IS THE PRIMARY RISK FACTOR



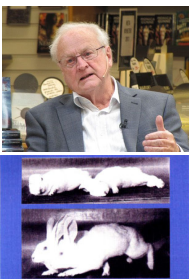
- Parkinson disease today affects about 1M in the US, about 7-10M worldwide.
- The prevalence is increasing rapidly because of aging of the population.

STATES OF PARKINSON DISEASE

At Risk	Prodromal "Pre-PD"	Early PD	Advanced PD
<ul style="list-style-type: none"> ▪ No symptoms ▪ Genetic risk factors 	<ul style="list-style-type: none"> ▪ Hyposmia – loss of the sense of smell ▪ REM Behavior Disorder – "acting out dreams" ▪ Constipation 	<ul style="list-style-type: none"> ▪ Tremor ▪ Bradykinesia ▪ Rigidity ▪ Fatigue 	<ul style="list-style-type: none"> ▪ Impaired balance ▪ Wearing off ▪ Dyskinesia ▪ Memory problems ▪ Hallucinations

DOPAMINE DEFICIENCY AND REPLACEMENT

Arvid Carlsson 1923-2018



Oleh Hornykiewicz 1926-2020



O. Hornykiewicz
Ether Dome, 2004

George Cotzias 1918-1977



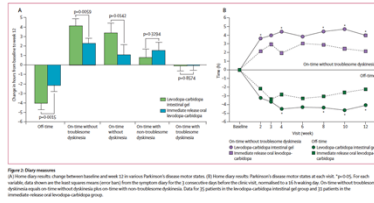
The New England
Journal of Medicine

NEUROLOGY OF PARKINSONISM - GEORGE COTZIAS, MD, L.D. LEWIS, MD, and ROBERT LEWIS, MD
 George Cotzias, MD, and Robert Lewis, MD, in the laboratory of George Cotzias, MD, at the University of Pennsylvania, Philadelphia, PA.

LCIG: RANDOMIZED DOUBLE BLIND

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study
Lancet Neurology, 2014; 13:141-49

- 66 patients studied for 12 weeks in a randomized double blind study
- Off time improved by 4 hours with LCIG, compared to 2 hours improvement with placebo



LCIG: RESPONDER CHARACTERISTICS

Parkinson's Disease

www.nature.com/jparkdis

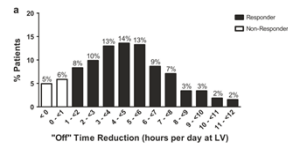
ARTICLE OPEN

Systematic evaluation of levodopa-carbidopa intestinal gel patient-responder characteristics

David G. Standaert¹, James T. Boyd², Peter Dainoff³, William J. Robinson⁴, Jorge Zarrubio⁵ and Kari Chaturvedi⁶
NPJ Parkinsons Dis. 2018 Jan 24;4:4. doi: 10.1038/s41531-017-0040-2

Which patients show the most improvement with LCIG?

- ☒ Age
- ☒ Sex
- ☒ BMI
- ☒ Duration of PD
- ☒ Mini Mental Status score
- ☒ UPDRS Score
- ☒ Hours of OFF time at baseline



LCIG: NON-MOTOR FEATURES

Movement Disorders

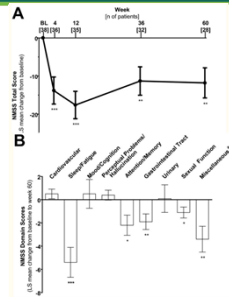
RESEARCH ARTICLE

CLINICAL PRACTICE

Effect of Levodopa-carbidopa Intestinal Gel on Non-motor Symptoms in Patients with Advanced Parkinson's Disease

David G. Standaert¹, James T. Boyd², Peter Dainoff³, William J. Robinson⁴, Jorge Zarrubio⁵ and Kari Chaturvedi⁶
Mov Disord Clin Pract. 2017 Nov-Dec;4(6):828-837. doi: 10.1093/mc3.12526

- 39 patients enrolled in a 60 week open-label study
- Non-motor symptoms improved dramatically with LCIG
- Improvement seen at 12 weeks and lasts at least 60 weeks
- Sleep and fatigue is the domain which is most improved



LCIG: DYSKINESIA

Movement Disorders
CLINICAL PRACTICE

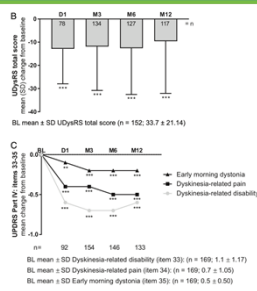
RESEARCH ARTICLE

DUOGLLOBE: One-Year Outcomes in a Real-World Study of Levodopa Carbidopa Intestinal Gel for Parkinson's Disease

David G. Storch, MD, PhD^{1,2}, Jason Altmann, MD³, Maria Anis-Mercier, MD⁴, Paul Bourgeois, MD⁵, Esther Cubo, MD, PhD⁶, Thomas L. Davis, MD⁷, Robert G. Deane, MD⁸, John D. Dugger, MD⁹, Robert G. Deane, MD⁸, Francisco J. Fernandez, MD¹⁰, Martin S. Glick, MD¹¹, John H. Han, MD¹², Laura H. Han, MD¹³, Peter H. Han, MD¹⁴, William J. Hickey, MD¹⁵, and R. Roy Shoulson, MD, PhD¹⁶

MOVEMENT DISORDERS CLINICAL PRACTICE 2021; 17(1): 1001-1016. doi: 10.1002/mds.27338

- A "real world" study, where patients were selected by their treating physicians
- 195 patients, 55 centers in 10 countries
- Off time improved by 4 hours
- Dyskinesia (measured using UDysRS) also improved



LCIG: ADVERSE EVENTS

- Adverse events are most common immediately after tube placement, and decline over time.
- Most adverse events are related to the tube, usually abdominal pain
- After the first two weeks, serious AE's are rare

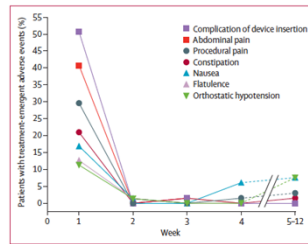


Figure 3: Timing of treatment-emergent adverse events reported by >10% of patients
Lancet Neurology, 2014; 13:141-49

LCIG: LONG TERM OUTCOMES

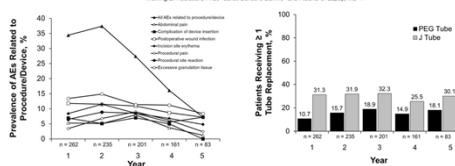
RESEARCH ARTICLE

Long-Term Safety and Efficacy of Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease

Hubert H. Fernandez, MD^{1,2}, James T. Boyd, MD³, Victor S. C. Fung, MD⁴, Mark F. Law, MD⁵, Ramon L. Rodriguez, MD⁶, John T. Stein, MD⁷, David G. Storch, MD, PhD⁸, Cindy Zerkow, MD⁹, Annette D. Vandenberg, MD¹⁰, John Chalmers, PhD¹¹, Susan E. Egan, PhD¹², Martin S. Glick, MD¹³, Cohen H. Han, MD¹⁴, and Albert J. Espay, MD, PhD¹⁵

MOVEMENT DISORDERS CLINICAL PRACTICE 2018; 14(3): 301-310. doi: 10.1002/mds.27338

- 262 patients followed for a mean of 4.1 years
- Adverse events decline over time
- About 10% of patients discontinue each year
- Over 5 years, 30% of patients will require a tube replacement

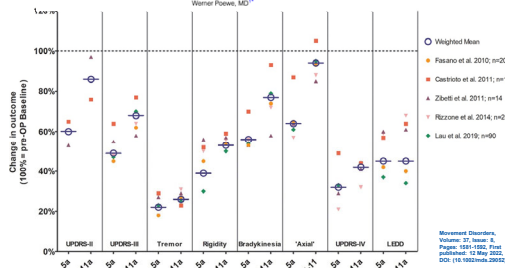


Mov Disord. 2018 Mar 23. doi: 10.1002/mds.27338

- Tremor is the feature which is most improved
- UPDRS IV (measuring off time and dyskinesia) also markedly improved
- LEDD is lower
- “Axial” symptoms are not improved.

How Does Deep Brain Stimulation Change the Course of Parkinson's Disease?

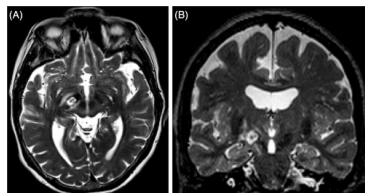
Philipp Mahlknecht, MD, PhD,¹ Thomas Fotynie, MD, PhD,² Patricia Limousin, MD, PhD,² and Werner Poewe, MD^{1*}



FOCUSED ULTRASOUND



<https://www.precisionhealth.com.au>

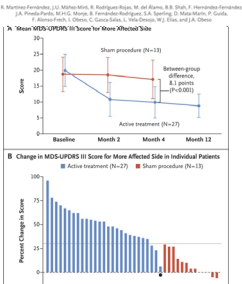


Postoperative imaging following transcranial MRgFUS subthalamotomy. Axial (A) and coronal (B) T2-weighted MRI scans 1 day after right subthalamotomy. Moosa et al., <https://doi.org/10.1002/mds.27779>

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1932 DECEMBER 24, 2020 VOL. 303 NO. 26

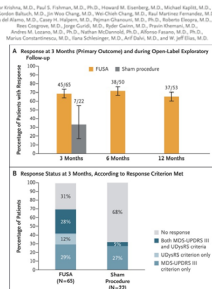
**Randomized Trial of Focused Ultrasound Subthalamotomy
for Parkinson's Disease**



The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1911 FEBRUARY 23, 2023 VOL. 100 NO. 2

**Trial of Globus Pallidus Focused Ultrasound Ablation
in Parkinson's Disease**



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5-2-1 SCREENING CRITERIA

NEURODEGENERATIVE DISEASE MANAGEMENT, VOL. 10, NO. 5 | RESEARCH ARTICLE

Open Access

Application of the '5-2-1' screening criteria in advanced Parkinson's disease: interim analysis of DUOGLOBE

This article is certified by

Jason Aldred¹, Mariela Anco-Herschkovitch, Angelo Antonini, Ovidiu Bărganu, Lars Bergmann, Paul Bourgeois, Esther Cubo, Thomas L. Davis, Robert Jansen, Norbert Kovács, Pavani Kukreja, Karel Orús, Francesco E. Pontieri, Weining Robinson, Mustafa S. Sabbagh, Mihaila Simu, David G. Standevert & R. Ray Chaudhuri

Published Online: 2 Sep 2020 | <https://doi.org/10.2217/nmt.2020-0021>

5-2-1 Criteria

- 5 or more doses of levodopa daily
- 2 or more hours of off time
- 1 or more hours of troublesome dyskinesia

CASE 1

- 58 year old man, onset of PD at age 42
- Currently takes:
 - Carbidopa/levodopa 25/100 every 3 hours (5x/day)
 - Entacapone 200 mg 5x/day
 - Amantidine 100 mg bid
- Main complaint is motor fluctuations
 - 30-60 min "off" at the end of each dose
 - Moderately severe dyskinesias with afternoon doses
- Works as technician in medical laboratory
- MOCA score 27

CASE 2

- 75 year old woman with PD since age 65
- Currently takes:
 - Carbidopa/levodopa 25/100 four times a day, plus 50/200 CR at bedtime
 - Rasagiline 1 mg daily
- Main complaint is early morning slowness and wearing off during the day, about 3 hours total. No dyskinesias,
 - Didn't tolerate trial of ropinirole
 - Entacapone caused severe diarrhea
- Mild memory problems, MOCA of 23.

CASE 3

- 68 year old with PD for 5 years
- Currently on:
 - Carbidopa/levodopa 25/100 3/day
 - Ropinerole ER 12 mg daily
- Main complaint is tremor – right handed, and tremor is most severe on the right.
- Attempts at increasing either carbidopa/levodopa or ropinirole caused fatigue and didn't help the tremor

CASE 4

- 58 year old, onset of parkinsonism at age 55
- Mild rest tremor, but prominent bradykinesia and gait disorder. Frequent falls.
- Moderate orthostatic hypotension with occasional syncope
- Also has history of REM behavior disorder
- Has tried multiple medications, but none seem to help:
 - Carbidopa/levodopa 25/100 tid
 - Rytary
 - Rotigotine transdermal
 - Pramipexole

CASE 5

- 74 year old man with PD since age 65
- Currently on:
 - Carbidopa/levodopa 25/100 2 tabs qid
 - Carbidopa/levodopa ER 50/200 qhs
 - Ropinerole 6 mg daily
 - Use inhaled carbidopa/levodopa (Inbrejia) about between 1 and 3 times daily for "off" episodes
- Has history of bilateral subdural hematomas after falling off a horse 5 years ago
- On Apixiban for atrial fibrillation
- Main complaint is unpredictable off time, totals about 3-5 hours daily
- Also some moderate dyskinesias, especially in the afternoon

UAB DIVISION OF MOVEMENT DISORDERS



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