

Research Report

Effects of Levodopa-Carbidopa Intestinal Gel on Dyskinesia and Non-Motor Symptoms Including Sleep: Results from a Meta-Analysis with 24-Month Follow-Up

K. Ray Chaudhuri^{a,*}, Angelo Antonini^b, Rajesh Pahwa^c, Per Odin^d, Nataliya Titova^{e,f}, Sandeep Thakkar^g, Sonya J. Snedecor^h, Saket Hegdeⁱ, Ali Alobaidi^{j,k}, Juan Carlos Parraj^l, Cindy Zadikoff^j, Lars Bergmann^j and David G. Standaert^l

^a*Parkinson Foundation Centre of Excellence, King's College Hospital and Kings College, London, UK*

^b*Parkinson and Movement Disorders Unit, Study Center for Neurodegeneration CESNE,*

Department of Neuroscience, University of Padova, Padova, Italy

^c*University of Kansas Medical Center, Kansas City, KS, USA*

^d*University of Lund, Lund, Sweden*

^e*N.I. Pirogov Russian National Research Medical University, Moscow, Russia*

^f*Federal State Budgetary Institution «Federal center of brain research and neurotechnologies» of the Federal Medical Biological Agency, Moscow, Russia*

^g*Hoag Hospital Newport Beach, Newport Beach, CA, USA*

^h*OPEN Health, Bethesda, MD, USA*

ⁱ*OPEN Health, New York, NY, USA*

^j*AbbVie Inc., North Chicago, IL, USA*

^k*University of Illinois at Chicago, Chicago, IL, USA*

^l*University of Alabama at Birmingham, Birmingham, AL, USA*

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Abstract.

Background: In advanced Parkinson's disease (PD), dyskinesias and non-motor symptoms such as sleep dysfunction can significantly impair quality of life, and high-quality management is an unmet need.

Objective: To analyze changes in dyskinesia and non-motor symptoms (including sleep) among studies with levodopa-carbidopa intestinal gel (LCIG) in patients with advanced PD.

Methods: A comprehensive literature review identified relevant studies examining LCIG efficacy. Outcomes of interest were dyskinesia (UDysRS, UPDRS IV item 32), overall non-motor symptoms (NMSS), mentation/behavior/mood (UPDRS I), and sleep/daytime sleepiness (PDSS-2, ESS). The pooled mean (95% confidence interval) change from baseline per outcome was estimated for each 3-month interval with sufficient data (i.e., reported by ≥ 3 studies) up to 24 months using a random-effects model.

*Correspondence to: K. Ray Chaudhuri, MBBS, MD, FRCP (Lond), FRCP (Edin), DSc, FEAN, Department of Basic and Clinical Neuroscience, The Maurice Wohl Clinical Neuro-

science Institute, King's College London, Cutcombe Road, London SE5 9RT, UK. Tel.: +44 0 7958249738; E-mail: ray.chaudhuri@kcl.ac.uk.

Results: Seventeen open-label studies evaluating 1,243 patients with advanced PD were included. All outcomes of interest with sufficient data for meta-analysis showed statistically significant improvement within 6 months of starting LCIG. There were statistically significant improvements in dyskinesia duration as measured by UPDRS IV item 32 at 6 months (−1.10 [−1.69, −0.51] h/day) and 12 months (−1.35 [−2.07, −0.62] h/day). There were statistically and clinically significant improvements in non-motor symptoms as measured by NMSS scores at 3 months (−28.71 [−40.26, −17.15] points). Significant reduction of NMSS burden was maintained through 24 months (−17.61 [−21.52, −13.70] points). UPDRS I scores significantly improved at 3 months (−0.39 [−0.55, −0.22] points). Clinically significant improvements in PDSS-2 and ESS scores were observed at 6 and 12 months in individual studies.

Conclusion: Patients with advanced PD receiving LCIG showed significant sustained improvements in the burden of dyskinesia and non-motor symptoms up to 24 months after initiation.

Keywords: Parkinson's disease, carbidopa/levodopa, quality of life, motor symptoms, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive disorder primarily associated with the degeneration of brain dopamine neurons and depletion of striatal dopamine [1–3]. The gold standard treatment for PD is levodopa, which is converted to dopamine in the brain [4]. Administration of levodopa orally can lead to motor fluctuations due to its short half-life and delayed or variable gastric emptying [5]. In addition, intermittent or pulsatile dopamine receptor stimulation can lead to postsynaptic plasticity and further drive fluctuations and worsen the motor and non-motor symptoms of PD [2, 5, 6]. Continuous levodopa infusion can be provided in an effort to sustain plasma levels of levodopa, leading to improvement in both motor complications and the shortening response observed with oral levodopa as PD progresses [2, 7–9].

Levodopa-carbidopa intestinal gel (LCIG) is a stable gel suspension suitable for continuous delivery through percutaneous gastrojejunostomy via a portable pump [10]. By continuously delivering medication directly to the jejunum, LCIG can avoid blocks to oral absorption of dopaminergic drugs via delayed gastric emptying and other factors [11], and generate sustained dopamine release and receptor stimulation within a therapeutic window [4–6, 12].

Although motor symptoms traditionally define PD, patients with PD can experience both motor and non-motor symptoms. The development of dyskinesia, a motor symptom, is common in patients with advanced PD [2, 7]. While mild dyskinesia may minimally impact patients, moderate to severe dyskinesia can be disabling and associated with functional impairment, patient discomfort, and social limitations/stigma, as well as reduced quality of life and increased healthcare costs [13–16]. Non-motor symptoms include anxiety, mood disorders,

fatigue, cognitive decline and dementia, autonomic dysfunction, and sleep-wake cycle regulation disorders and are an important feature of advanced PD and a chief therapeutic challenge [2, 17]. Approximately 28% of patients with PD rated fluctuations in non-motor symptoms as more disabling than fluctuations in motor symptoms [18]. The burden of non-motor symptoms is a key determinant of quality of life, overall disability progression, and nursing home placement in patients with PD [2, 19, 20]. In particular, sleep and mood are significant predictors of patients reporting poor quality of life [21].

Results from a previously conducted meta-analysis showed improvement in “off” time, activities of daily living, and quality of life for patients with advanced PD treated with LCIG persisting up to 24 months [22]. LCIG has been shown to be safe and effective in clinical trials and real-world evidence studies in reducing dyskinesias in patients with advanced PD [6, 23–26], and a range of open-label and global registry studies have shown consistent and robust improvement in a range of non-motor symptoms, including sleep quality improvement [25, 27–30]. However, the length of follow-up, inclusion criteria, study design, and outcome measures varied among these studies [31]. In addition, there is no previous meta-analysis on non-motor symptoms, sleep, and dyskinesia in advanced PD. Thus, the objective of the present analysis was to pool the available data to assess the impact of LCIG on dyskinesia and non-motor symptoms (such as sleep and mood/behavior) in patients with advanced PD.

MATERIALS AND METHODS

Study identification

We conducted a literature review to identify interventional, prospective observational, or retro-

spective studies published in the Embase and Medline databases through October 6, 2020. Studies of interest were single-arm or comparative evaluations of patients with advanced PD who were initiating LCIG treatment; studies had to report at least 1 outcome of interest and have a follow-up time of at least 3 months. Studies of patients with early PD, case reports, conference abstracts without a full-text publication, and trials or observational studies that did not examine the outcomes of interest were excluded. Following the literature search, 2 reviewers independently screened each title and abstract to identify relevant articles and reviewed the full-text articles for final study inclusion. Disagreements were resolved by discussion and consensus.

Outcome measures

Outcomes of interest for measuring dyskinesia were the Unified Dyskinesia Rating Scale (UDysRS) and items 32 (modified from percent improvement to hours per day) or items 32–34 (score) of the Unified Parkinson's Disease Rating Scale (UPDRS) Part IV (UPDRS IV), depending on the study. Outcomes for measuring non-motor symptoms included the Non-Motor Symptoms Scale for Parkinson's Disease (NMSS), Part I of the UPDRS (UPDRS I) for measuring mood/behavior, the Parkinson's Disease Sleep Scale-2 (PDSS-2) for sleep, and the Epworth Sleepiness Scale Questionnaire (ESS) for daytime sleepiness.

Statistical analysis

Data for each outcome were grouped into 3-month intervals (e.g., 1–3 months ["3 months"], 4–6 months ["6 months"], 7–9 months ["9 months"]) up to 24 months. For each outcome of interest, the pooled mean change from baseline (CFB) with 95% CI was estimated for each time interval with sufficient data for meta-analysis (i.e., outcome reported by ≥ 3 available studies). Data were pooled using random-effects methods to generate overall estimates for each outcome and time point (See the Interactive Appendix in the Supplementary Material for fixed-effects results). Heterogeneity among the studies was assessed for each outcome and time point reported by 3 or more studies using the I^2 and Q statistics.

Outcomes in which the confidence intervals for mean change from baseline do not include zero are statistically significant. Mean changes from baseline that exceed the minimum clinically important differ-

ences (NMSS: -13.91 points [32]; PDSS-2: -3.44 points [33]) are considered clinically significant.

Evaluation of the associations between study outcomes and factors such as mean duration of PD, mean age at study entry, Hoehn and Yahr On or Hoehn and Yahr Off score showed no impact of differences among the studies; thus, no statistical adjustment for these factors was considered. Further, no formal risk of bias assessment was performed since the conduct of the studies is unlikely to affect the reported outcomes, which are measured with standard instruments and no association between baseline patient characteristics and outcomes were observed. Analyses were conducted using Microsoft Excel software.

RESULTS

Study selection and characteristics

A total of 17 studies evaluating a total of 1243 patients with advanced PD were included in the analysis (Fig. 1). No studies were excluded during the similarity assessment. At baseline, mean patient age in the individual studies ranged from 57.8 to 70.6 years and mean PD duration ranged from 10.0 to 16.1 years (Table 1).

Outcomes

All outcomes of interest with sufficient data for meta-analysis showed statistically significant improvement within 6 months of starting LCIG treatment (Table 2). Meta-analysis was possible for UPDRS IV modified item 32 (hours per day) outcome scores at 4 time points, NMSS scores at 5 time points, and UPDRS I scores at 2 time points. Even for time points where meta-analysis was not possible, the majority of results from individual studies showed improvement in the evaluated outcomes.

The results of our meta-analysis showed statistically significant improvements in dyskinesia duration as measured by UPDRS IV item 32 starting at 6 months (mean [95% CI] CFB, -1.10 [$-1.69, -0.51$] h/day) that was sustained through 24 months (-0.76 [$-1.31, -0.22$] h/day). Change from baseline in UDysRS and UPDRS IV items 32–34 scores were not meta-analyzed, as there were no 3-month intervals in which 3 or more studies reported these outcomes. However, among the individual studies, improvements in UDysRS and UPDRS IV items 32–34 scores were observed at 3 months, 6 months, and 12 months.

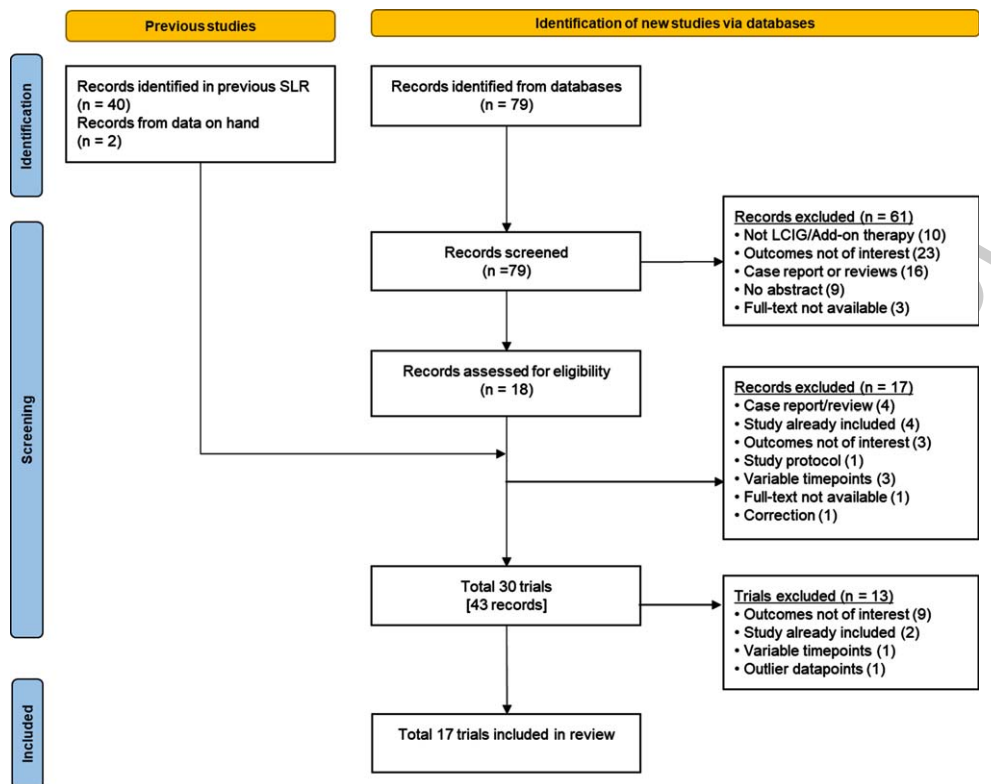


Fig. 1. Study selection flow diagram. LCIG, Levodopa-carbidopa intestinal gel; SLR, systematic literature review.

Non-motor symptoms as measured on the NMSS scale showed statistically and clinically significant improvement starting at 3 months (mean [95% CI] CFB, -28.71 [-40.26 , -17.15] points) that was sustained through 24 months (-17.61 [-21.52 , -13.70] points) (Fig. 2).

Mentation, behavior, and mood as measured by UPDRS I scores was significantly improved at 3 months (mean [95% CI] CFB, -0.39 [-0.55 , -0.22] points). No statistically significant CFB in UPDRS I scores was observed at 12 months (0.11 [-0.20 , 0.42] points). There were insufficient data for meta-analysis for the 4 to 6 month, 16 to 18 month, and 22 to 24 month intervals, but among the individual studies, improvements were observed at 6 months and 24 months, with no improvement observed at 18 months.

Sleep outcomes as measured by PDSS-2 and ESS scores were not meta-analyzed, as there were no 3-month intervals in which 3 or more studies reported these outcomes. However, among the individual studies, clinically significant improvements in PDSS-2 scores were observed at 3 months [28], 6 months [28], 12 months [26, 28], 18 months [28], and 24 months [28]. For ESS scores, improvements were observed at

3 months [28], 6 months [28, 34], 12 months [26, 28], 18 months [28], and 24 months [28], with clinically significant improvement at 6 months and 12 months.

Forest plots showing input data from individual studies along with the meta-analysis outcomes are presented in the interactive Appendix.

DISCUSSION

Our analysis including data from 17 clinical and observational studies provides one of the most comprehensive assessments to date of the impact of LCIG therapy on non-motor symptom and dyskinesia outcomes among patients with advanced PD. Results of the meta-analysis suggest that the effects of LCIG on non-motor symptoms and dyskinesia are evident as early as 1 to 3 months and 4 to 6 months following treatment initiation, respectively, and both are sustained over a period of 24 months. The improvement in non-motor symptoms from baseline was statistically significant and greater than the reported minimum clinically important difference for NMSS scores (-13.91) across 24 months

Table 1
Summary of included studies

Author, Year	Data Source(s) ^a	Study Characteristics			Patient Baseline Characteristics, Mean (SD)				Patient Scores at Baseline, Mean (SD)						
		Study Design	Follow-up, mo ^b	ITT, N	Age, y	PD Duration, y	Daily L-dopa Dose, mg	Hoehn and Yahr Score	UPDRS IV Item 32, h/d	UPDRS IV Items 32–34	UDysRS	NMSS	UPDRS I	PDSS-2	ESS
DUOGLOBE 2020	Publication, CSR [28, 61]	Global, multicountry, single-arm, post-marketing observational analysis	36	164	70.2 (8.17)	11.2 (4.72)	1432 (101.82)	On: 3 (0.83) Off: 3.6 (0.8)	4.1 (3.7)	NA	33.7 (21.14)	88.2 (51.09)	NA	26.6 (11.65)	9.8 (5.26)
Alvarez 2020	Publication, CSR [62, 63]	Open-label, randomized, multicenter interventional study	3	25	69.3 (7.0)	12.7 (4.2)	1211.5 (374.89)	NA	NA	NA	53.2 (12.24)	NA	NA	NA	NA
Antonini 2017	Publication, CSR [27, 64]	Observational non-interventional	24	Retro-spective: 140 Prospective: 189	67.4 (8.1)	12.6 (6.6)	854.8 (513.3)	On: 2.9 (0.8) Off: 4.1 (0.8)	4.1 (3.7)	NA	NA	76.2 (47.9)	NA	NA	NA
Caceres-Redondo 2014	Publication [65]	Observational	24	16	66.5 (9.3)	15.1 (5.4)	1473.0 (449.0)	On: 2.4 (0.5) Off: 3.7 (0.8)	NA	NA	NA	17.3 (4.7)	NA	NA	NA
De Fabregues 2017	Publication [34]	Long-term, open-label, prospective, observational	12	37	68.2 (6.8)	13.5 (5.6)	NA	On: 2.5 Off: 3.8	NA	NA	NA	NA	3.2 (2.4)	NA	5.6 (3.6)
Fasano 2012	Publication [54]	Phase III, open-label	24.9 (14.4)	14	67.1 (11.5)	12.9 (4.8)	929.1 (682.2)	NA	NA	NA	NA	126 (56.18)	8.71 (3.15)	39.08 (8.58)	NA
Fernandez 2015	Publication, CSR, trial registry [66–68]	Phase III, open-label	12	354	64.1 (9.1)	12.5 (5.5)	1082.9 (582.1)	NA	NA	3.7 (2.4)	NA	NA	2.2 (1.9)	NA	NA
Honig 2009	Publication [25]	Prospective open-label observational	6	22	58.6 (9.1)	15.3 (5.9)	NA	Off: 3.8	NA	NA	NA	89.9 (56.5)	NA	NA	NA
Juhasz 2017	Publication [26]	Prospective, multicenter, open-label cohort study	12	34	67.0 (6.0)	12.0 (5.0)	1000.2 (577.6)	3.0	NA	NA	45.9 (16.7)	88.9 (40.3)	NA	27.2 (10.5)	9.1 (4.8)

(Continued)

Table 1
(Continued)

Author, Year	Data Source(s) ^a	Study Characteristics			Patient Baseline Characteristics, Mean (SD)				Patient Scores at Baseline, Mean (SD)						
		Study Design	Follow-up, mo ^b	ITT, N	Age, y	PD Duration, y	Daily L-dopa Dose, mg	Hoehn and Yahr Score	UPDRS IV Item 32, h/d	UPDRS IV Items 32–34	UDysRS	NMSS	UPDRS I	PDSS-2	ESS
Kruger 2017	Publication, CSR [69, 70]	Phase III single-arm, open-label, baseline-controlled, multicenter study	12	64	70.4 (7.8)	13.9 (5.4)	NA	NA	NA	NA	NA	95.5 (54.5)	NA	NA	NA
Martinez-Martin 2015	Publication [30]	Prospective, multicenter, open-label cohort study	6	44	62.7 (9.1)	16.1 (6.7)	1815.4 (771.5)	4 ^c	NA	NA	NA	90.95 (45)	NA	NA	NA
Olanow 2014	Publication, CSR, 2 trial registries [10, 71–73]	Phase III, double-blind RCT	3	37	63.7 (9.5)	10.0 (4.6)	1005.4 (373.6)	On: 2.3 (0.6)	NA	2.4 (1.6)	NA	NA	1.8 (1.7)	NA	NA
Palhagen 2016	Publication, CSR, trial registry [74–76]	Prospective, open-label, long-term study	36	27	64.6 (6.4)	10.7	NA	On: 2.0 (0.9) Off: 3.6 (1.1)	NA	NA	NA	NA	2.9 (1.9)	NA	NA
Reddy 2012	Publication [77]	Single-center, real-life setting, matched based on PCT funding restrictions	6	17	57.82 (7.71)	16.12 (5.84)	1996 (675)	On: 3.5	NA	NA	NA	113.88 (49.26)	NA	NA	NA
Sensi 2014	Publication [78]	Prospective open-label cohort study	24	17	67.6 (6.1)	15.5 (4.0)	1158.9 (334.5)	On: 3.2 (0.7)	NA	NA	NA	51.8 (37.3)	NA	NA	NA
Slevin 2015	Publication, trial registry [79, 80]	Phase III, open-label, multicenter	12	29	64.8 (6.6)	11.4 (5.7)	NA	NA	NA	NA	NA	NA	1.2 (1.0)	NA	NA
Standaert 2017	Publication, CSR, trial registry [6, 81, 82]	Phase IIIb open-label	12	38	64.3 (10.2)	11.5 (5.3)	NA	NA	NA	NA	NA	48.3 (35.6)	1.6 (1.6)	NA	NA

CSR, clinical study report; ESS, Epworth Sleepiness Scale; ITT, intent to treat; L-dopa, levodopa; N, number; NA, not available; NMSS, Non-Motor Symptoms Scale for Parkinson's Disease; PCT, primary care trust; PD, Parkinson's disease; PDSS-2, Parkinson's Disease Sleep Scale-2; RCT, randomized controlled trial; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale. ^aThe individual record(s) used per study are cited in this column. ^bValues in this table express the follow-up period defined in study publication(s). If a study did not report a prespecified follow-up period, but did report mean (SD) follow-up time, the mean (SD) follow-up time reported is presented in this table. ^cMedian score, not mean.

Table 2
Impact of LCIG on dyskinesia, non-motor symptoms, and sleep outcomes in patients with advanced PD

Symptom Domain	Outcome Measure	MCID	Score Range	Change from Baseline at Time Interval ^a				
				1 to 3 Months	4 to 6 Months	10 to 12 Months	16 to 18 Months	22 to 24 Months
Dyskinesia	UPDRS IV, item 32 (h/day)	NA	0 (best) to 24 (worst)	<i>n</i> = 99	<i>n</i> = 422	<i>n</i> = 363	<i>n</i> = 140, <i>n</i> = 189	<i>n</i> = 140, <i>n</i> = 189
	UPDRS IV, items 32–34 (score)	NA	0 (best) to 12 (worst)	-0.7 (4.77) ^{[28].c} <i>n</i> = 34, <i>n</i> = 275	-1.10 (-1.69, -0.51) <i>n</i> = 267	-1.35 (-2.07, -0.62) <i>n</i> = 250	-0.77 (-1.31, -0.22)	-0.76 (-1.31, -0.22)
	UDysRS score	NA	0 (best) to 104 (worst)	-0.2 (1.9) ^{[10].c} -1.4 (0.2) ^{[68].b} <i>n</i> = 24, <i>n</i> = 91	-1.2 (0.2) ^{[68].b} <i>n</i> = 83	-1.2 (0.2) ^{[68].b} <i>n</i> = 34, <i>n</i> = 26	No data	No data
Non-motor symptoms	NMSS score	-13.91 ^[32]	0 (best) to 243 (worst)	-17.4 (2.79) ^{[63].b} -11.9 (18.92) ^{[28].c} <i>n</i> = 174	-12.5 (19.91) ^{[28].c} <i>n</i> = 561	-13.8 (NR) ^[26] -9.9 (22.73) ^{[28].c} <i>n</i> = 459	-9.00 (21.69) ^{[28].c} <i>n</i> = 178, <i>n</i> = 189	-8.1 (22.57) ^{[28].c} <i>n</i> = 376
	Mood/Behavior	NA	0 (best) to 16 (worst)	-28.71 (-40.26, -17.15) <i>n</i> = 407	-27.81 (-35.73, -19.89) <i>n</i> = 267, <i>n</i> = 27	-20.97 (-25.85, -16.09) <i>n</i> = 339	-18.84 (-22.56, -15.12) <i>n</i> = 27	-17.61 (-21.52, -13.70) <i>n</i> = 14, <i>n</i> = 27
Sleep	PDSS-2 score	-3.44 ^[33]	0 (best) to 60 (worst)	-0.39 (-0.55, -0.22) <i>n</i> = 106	-0.2 (0.1) ^{[68].b} (1.7) ^{[76].c} <i>n</i> = 99	-0.1 <i>n</i> = 34, <i>n</i> = 37	1.1 (3.1) ^{[76].c} <i>n</i> = 178, <i>n</i> = 189	-1.92 (NR) ^[54] (3.0) ^{[76].c} <i>n</i> = 14
	ESS score	NA	0 (best) to 24 (worst)	-7.2 (13.35) ^{[28].c} <i>n</i> = 107	-8.1 (13.09) ^{[28].c} <i>n</i> = 37, <i>n</i> = 100	-4.0 (NR) ^[26] -6.6 (12.19) ^{[28].c} <i>n</i> = 34, <i>n</i> = 36	-5.9 (12.34) ^{[28].c} <i>n</i> = 178, <i>n</i> = 189	-5.62 (NR) ^[54] (13.15) ^{[28].c} <i>n</i> = 14
				-1.5 (5.12) ^{[28].c}	-2.8 (NR) ^[34] -1.2 (5.66) ^{[28].c}	-1.0 (NR) ^[26] (5.73) ^{[28].c} -1.0	-1.10 (6.08) ^{[28].c}	-1.40 (6.11) ^{[28].c}

ESS, Epworth Sleepiness Scale; LCIG, Levodopa-carbidopa intestinal gel; MCID, minimum clinically important difference; NA, not available; NMSS, Non-Motor Symptoms Scale; NR, not reported; PD, Parkinson's disease; PDSS-2, Parkinson's Disease Sleep Scale-2; UDysRS, Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale. ^a**Bold** values in these columns indicate meta-analysis outcomes, which are reported as mean (95% CI) change from baseline and were estimated using random effects analysis. When fewer than 3 studies were available, meta-analysis was not performed. Insufficient data for meta-analysis were available for any outcome for the 7–9 month, 13–15 month, and 19–21 month time intervals. ^bResults shown in table are mean (SE) values as reported in individual source publications. See citations in cells for specific source publication(s) referenced. Further information on values from individual source studies is presented in the Interactive Appendix. ^cResults shown are mean (SD) values as reported in individual source publications.

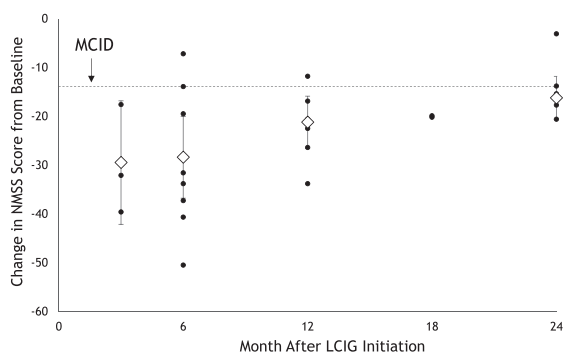


Fig. 2. Impact of LCIG on Non-Motor Symptoms Up to 24 Months After Initiation^a. LCIG, levodopa-carbidopa intestinal gel; MCID, minimum clinically important difference; NMSS, Non-Motor Symptoms Scale. ^aBlack circles represent reported mean change from baseline. Diamonds represent pooled mean change from baseline with 95% CIs estimated using random effects meta-analysis.

[32]. Mood and behavior was significantly improved at 3 months. In most outcomes, the available data showed a pattern of initial improvement followed by a gradual worsening. This pattern was also observed in quality of life and activities of daily living outcomes [22], which could be attributed to disease progression. However, most measures still remain improved or significantly improved over baseline at 24 months.

Although multiple treatments address dyskinesia in advanced PD, there is an unmet need for therapies to address the substantial burden of non-motor symptoms [2, 19, 20]. The results of our meta-analysis provide an important summary of the published evidence on the effect of LCIG on non-motor symptoms in advanced PD. Our analysis included 12 studies reporting NMSS scores in patients with PD. The statistically significant and clinically meaningful improvement in NMSS scores observed with LCIG in our analysis are consistent with the robust non-motor symptom effects observed in a systematic literature review of multiple large multicentre and observational studies, specifically in the sleep, mood, and fatigue domains [31]. Some recent studies such as INSIGHTS are not included in our analysis due to the study identification cut-off date. However, the changes from baseline to 6 months reported in this trial for NMSS and PDSS-2 were consistent with our estimates [35].

The results of our meta-analysis suggest the use of LCIG for sleep and other key non-motor symptoms of PD. While pathophysiology for improvements in NMS is not fully understood, several domains of

NMS may be partly driven by dopamine control [36]. These domains include depression, sleep dysfunction such as insomnia, restless legs syndrome, nocturia, pain, sexual dysfunction, apathy, and anhedonia [25, 36, 37]. The link between sleep dysfunction and dopamine pathophysiology can also be supported by reduced binding of 11 C-raclopride in the hypothalamus among PD patients, which is a key sleep and autonomic regulatory center [38]. Switching to LCIG would allow reduction in other anti-parkinsonian medications and potentially achieving monotherapy during the day [39]. As result, reduction in other dopaminergic medications may lead to improvements in other NMS such as insomnia, sedation and urinary urgency [25]. Improvements in motor symptoms at nights (as measured by PDSS-2) may also be correlated with reduction in daytime sleepiness (as measured by ESS). Lastly, LCIG treatment can be maintained during night when medically justified. This can lead to improvements in dopamine-driven NMS including sleep [25, 40]. Therefore, improvement in dopamine-driven NMS symptoms is likely to be associated with continuous and stable delivery of levodopa with LCIG compared to orals.

In observational studies, improvement in non-motor symptoms and dyskinesias was associated with improved quality of life in patients with advanced PD receiving LCIG treatment as well as their caregivers [19, 41]. In a cross-sectional epidemiologic study conducted in Italy, caregiver burden also tended to be lower when patients were treated with LCIG compared with continuous subcutaneous apomorphine infusion or continuation of standard of care [42]. Our previous meta-analysis showed that improvement in activities of daily living (ADLs) and quality of life for patients with advanced PD receiving LCIG persisted up to 24 months [22].

Results from this meta analysis show statistically and clinically significant improvements in non-motor symptoms and statistically significant reduction in dyskinesia duration, which contribute to LCIG's overall impact in improving patients' quality of life and ability to perform ADLs. Few studies assessed dyskinesia disability (UPDRS IV item 33, UDysRS), leading to limited evidence and inability to evaluate these outcomes in meta-analysis. PD is associated with substantial economic burden to patients, caregivers, payers, and society [43–46]; improvements in patient quality of life could in turn reduce caregiver burden and improve caregiver quality of life [47]. Informal care costs are a large component of total costs [44, 46, 48], so potential reductions in care-

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333 giver burden and use of informal care could impact
334 the total economic toll of PD.

335 However, while LCIG has been shown to improve
336 dyskinesia, it is worth noting that breakthrough
337 dyskinesia has been described in the long-term,
338 although this occurs only in a minority of patients
339 [49]. Few patients may experience exacerbation of
340 levodopa-induced dyskinesia (LID) after LCIG initiation,
341 [49–53] which can present in different forms
342 including “peak of dose”, “on” period, or diphasic
343 dyskinesia. Monitoring of patient symptoms and tailoring
344 LCIG dose are warranted to insure optimal
345 outcomes during LCIG initiation.

346 Although there were insufficient data to meta-
347 analyze sleep outcomes in our analysis, clinically
348 significant improvements with LCIG were observed
349 in at least 1 study at 3, 6, 12, 18, and 24 months
350 for PDSS-2 scores [26, 28, 54], and at 6 months and
351 12 months for ESS scores [26, 28, 34]. Improve-
352 ments in sleep outcomes could also affect patients’
353 and caregivers’ daily lives, as patient sleep quality is
354 significantly correlated with caregiver burden, quality
355 of life, and sleep quality [47].

356 To our knowledge, there has been only one other
357 meta-analysis to date evaluating LCIG in patients
358 with advanced PD that included any of the outcomes
359 used in our analysis. Liu et al. found significant
360 improvement for subthalamic nucleus deep-brain
361 stimulation versus LCIG for dyskinesia/motor fluctuation,
362 measured using overall UPDRS IV scores [55]. These results
363 are consistent with those of our meta-analysis, which
364 evaluated UPDRS IV items 32 and 32–34 and UDysRS
365 total score change. However, this study focused on
366 the efficacy of LCIG in improving outcomes versus
367 baseline. The comparative efficacy of LCIG versus
368 other treatment options for advanced PD was not
369 assessed in this study.

370 Our meta-analysis presents a robust evaluation of
371 the impact of LCIG on key PD-related outcomes
372 over 24 months, overcoming the challenge of sample
373 size in individual studies. However, as in all meta-
374 analyses, our evaluation pools data from multiple
375 studies with different study characteristics. We have
376 closely examined the patient populations and outcome
377 definitions to evaluate the impact these factors may
378 have on LCIG treatment outcomes and to create a
379 collection of studies with sufficient similarity to be
380 suitable for meta-analytic combination. No studies
381 were excluded during the similarity assessment.

382 A tailored, multidisciplinary approach to treatment
383 decisions is recommended in advanced PD [4, 56–58],
384 and the modern approach concentrates

385 on personalized precise delivery of care using the
386 circle of personalized medicine [59]. The choice of
387 personalized therapy in PD is driven by motor and
388 non-motor symptoms, comorbidities, age, caregiver
389 support, and patient/caregiver preferences [60].
390 Improvements in patients daily functions and quality
391 of life are a key component of treatment decision
392 making [56], so the significant improvement in dyskinesia
393 and non-motor symptoms with LCIG in this meta-analysis
394 and the potential impact on patient and caregiver
395 quality of life could influence healthcare providers’
396 treatment choices.

397 *Conclusions*

398 In this large-scale meta-analysis involving 1243
399 unique patients with advanced PD treated with LCIG,
400 we found significant improvement in dyskinesia
401 duration from 6 through 24 months and in non-motor
402 symptoms from 3 through 24 months after treatment
403 initiation. Improvement in NMSS scores was both
404 statistically significant and clinically meaningful.
405 Improvement in UPDRS IV and NMSS was rapid,
406 appearing within the first 6 months, and remained
407 consistent for up to 24 months. LCIG provided
408 improvement in dyskinesia and NMSS including
409 sleep and mood scores. The data available on other
410 sleep endpoints were insufficient for meta-analysis,
411 and additional studies are needed to evaluate the
412 impacts of LCIG on sleep parameters in patients
413 with PD.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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REFERENCES

- [1] Antonini A, Moro E, Godeiro C, Reichmann H (2018) Medical and surgical management of advanced Parkinson's disease. *Mov Disord* **33**, 900-908.
- [2] Coelho M, Ferreira JJ (2017) The natural history of Parkinson's disease. In *Movement Disorders Curricula*, Falup-Pecurariu C, Ferreira J, Martinez-Martin P, Chaudhuri KR, eds. Springer Vienna, Vienna, pp. 129-137.
- [3] Mamelak M (2018) Parkinson's disease, the dopaminergic neuron and gamma-hydroxybutyrate. *Neurol Ther* **7**, 5-11.
- [4] Virhammar J, Nyholm D (2017) Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: Clinical evidence and experience. *Ther Adv Neurol Disord* **10**, 171-187.
- [5] Thakkar S, Fung VSC, Merola A, Rollins M, Soileau MJ, Kovács N (2021) 24-hour levodopa-carbidopa intestinal gel: Clinical experience and practical recommendations. *CNS Drugs* **35**, 137-149.
- [6] Standaert DG, Rodriguez RL, Slevin JT, Lobatz M, Eaton S, Chatamra K, Facheris MF, Hall C, Sail K, Jalundhwal YJ, Benesh J (2017) Effect of levodopa-carbidopa intestinal gel on non-motor symptoms in patients with advanced Parkinson's disease. *Mov Disord Clin Pract* **4**, 829-837.
- [7] Ahlskog JE, Muenter MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* **16**, 448-458.
- [8] Nyholm D, Odin P, Johansson A, Chatamra K, Locke C, Dutta S, Othman AA (2013) Pharmacokinetics of levodopa, carbidopa, and 3-O-methyldopa following 16-hour jejunal infusion of levodopa-carbidopa intestinal gel in advanced Parkinson's disease patients. *AAPS J* **15**, 316-323.
- [9] Chaudhuri KR, Rizos A, Sethi KD (2013) Motor and non-motor complications in Parkinson's disease: An argument for continuous drug delivery? *J Neural Transm (Vienna)* **120**, 1305-1320.
- [10] Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, Vanaganas A, Othman AA, Widnell KL, Robieson WZ, Pritchett Y, Chatamra K, Benesh J, Lenz RA, Antonini A (2014) Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled,

- 540 double-blind, double-dummy study. *Lancet Neurol* **13**, 141-149.
- 541
- 542 [11] Chaudhuri KR, Qamar MA, Rajah T, Loehrer P, Sauerbier A, Odin P, Jenner P (2016) Non-oral dopaminergic therapies for Parkinson's disease: Current treatments and the future. *NPJ Parkinsons Dis* **2**, 16023.
- 543
- 544 [12] Amjad F, Bhatti D, Davis TL, Oguh O, Pahwa R, Kukreja P, Zamudio J, Metman LV (2019) Current practices for outpatient initiation of levodopa-carbidopa intestinal gel for management of advanced Parkinson's disease in the United States. *Adv Ther* **36**, 2233-2246.
- 545
- 546 [13] Encarnacion EV, Hauser RA (2008) Levodopa-induced dyskinesias in Parkinson's disease: Etiology, impact on quality of life, and treatments. *Eur Neurol* **60**, 57-66.
- 547
- 548 [14] Hechtner MC, Vogt T, Zöllner Y, Schröder S, Sauer JB, Binder H, Singer S, Mikolajczyk R (2014) Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. *Parkinsonism Relat Disord* **20**, 969-974.
- 549
- 550 [15] Manson A, Stirpe P, Schrag A (2012) Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. *J Parkinsons Dis* **2**, 189-198.
- 551
- 552 [16] Thanvi B, Lo N, Robinson T (2007) Levodopa-induced dyskinesia in Parkinson's disease: Clinical features, pathogenesis, prevention and treatment. *Postgrad Med J* **83**, 384-388.
- 553
- 554 [17] Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner E-M, Poewe W, Rascol O, Goetz CG, Sampaio C (2011) The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disorder* **26**(Suppl 3), S42-S80.
- 555
- 556 [18] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Chérif AA (2002) Nonmotor fluctuations in Parkinson's disease. *Neurology* **59**, 408.
- 557
- 558 [19] Chaudhuri KR, Antonini A, Robieson WZ, Sanchez-Solano O, Bergmann L, Poewe W, GLORIA study co-investigators (2019) Burden of non-motor symptoms in Parkinson's disease patients predicts improvement in quality of life during treatment with levodopa-carbidopa intestinal gel. *Eur J Neurol* **26**, 581-e543.
- 559
- 560 [20] Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D, Sampaio C, The collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee (2019) Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Mov Disord* **34**, 180-198.
- 561
- 562 [21] Prakash KM, Nadkarni NV, Lye WK, Yong MH, Tan EK (2016) The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: A longitudinal study. *Eur J Neurol* **23**, 854-860.
- 563
- 564 [22] Standaert DG, Patel V, Snedecor SJ, Thakkar S, Jalundhwal YJ, Kukreja P, Kratochvil D, Bao Y, Pahwa R (2021) Impact of carbidopa-levodopa enteral suspension on quality of life and activities of daily living in patients with advanced Parkinson's disease: Results from a pooled meta-analysis. *Parkinsonism Relat Disord* **86**, 52-57.
- 565
- 566 [23] Antonini A, Yegin A, Preda C, Bergmann L, Poewe W (2015) Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. *Parkinsonism Relat Disord* **21**, 231-235.
- 567
- 568 [24] Antonini A, Fung VSC, Boyd JT, Slevin JT, Hall C, Chatamra K, Eaton S, Benesh JA (2016) Effect of levodopa-carbidopa intestinal gel on dyskinesias in advanced Parkinson's disease patients. *Mov Disord* **31**, 530-537.
- 569
- 570 [25] Honig H, Antonini A, Martinez-Martin P, Forgacs I, Faye GC, Fox T, Fox K, Mancini F, Canesi M, Odin P, Chaudhuri KR (2009) Intrajunctional levodopa infusion in Parkinson's disease: A pilot multicenter study of effects on nonmotor symptoms and quality of life. *Mov Disord* **24**, 1468-1474.
- 571
- 572 [26] Juhasz A, Aschermann Z, Acs P, Janszky J, Kovacs M, Makkos A, Harmat M, Tenyi D, Karadi K, Komoly S, Takats A, Toth A, Nagy H, Klivenyi P, Dibo G, Dezsi L, Zadori D, Annus A, Vecsei L, Varannai L, Kovacs N (2017) Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: An open-label study. *Parkinsonism Relat Disord* **37**, 79-86.
- 573
- 574 [27] Antonini A, Poewe W, Chaudhuri KR, Jech R, Pickut B, Pirtošek Z, Szasz J, Valdeoriola F, Winkler C, Bergmann L, Yegin A, Onuk K, Barch D, Odin P (2017) Levodopa-carbidopa intestinal gel in advanced Parkinson's: Final results of the GLORIA registry. *Parkinsonism Relat Disord* **45**, 13-20.
- 575
- 576 [28] Aldred J, Anca-Herschkovitsch M, Antonini A, Bajenaru O, Bergmann L, Bourgeois P, Cubo E, Davis TL, Ianssek R, Kovács N, Kukreja P, Onuk K, Pontieri FE, Robieson W, Siddiqui MS, Simu M, Standaert DG, Chaudhuri KR (2020) Application of the '5-2-1' screening criteria in advanced Parkinson's disease: Interim analysis of DUOGLOBE. *Neurodegener Dis Manag* **10**, 309-323.
- 577
- 578 [29] 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, on behalf of EUROPAR the International Parkinson Movement Disorders Society Non-Motor Parkinson's Disease Study Group (2019) EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Mov Disord* **34**, 353-365.
- 579
- 580 [30] 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, Samuel M, Wenzel K, Tomantschger V, Storch A, Reichmann H, Pirtosek Z, Trost M, Svenningsson P, Palhagen S, Volkman J, Chaudhuri KR (2015) EuroInf: A multicenter comparative observational study of apomorphine and levodopa infusion in Parkinson's disease. *Mov Disord* **30**, 510-516.
- 581
- 582 [31] Wirdefeldt K, Odin P, Nyholm D (2016) Levodopa-carbidopa intestinal gel in patients with Parkinson's disease: A systematic review. *CNS Drugs* **30**, 381-404.
- 583
- 584 [32] Martinez-Martin P, Rodriguez-Blazquez C, Abe K, Bhat-tacharyya KB, Bloem BR, Carod-Artal FJ, Prakash R, Esselink RAJ, Falup-Pecurariu C, Gallardo M, Mir P, Naidu Y, Nicoletti A, Sethi K, Tsuboi Y, van Hilten JJ, Visser M, Zappia M, Chaudhuri KR (2009) International study on the psychometric attributes of the Non-Motor Symptoms Scale in Parkinson disease. *Neurology* **73**, 1584.
- 585
- 586 [33] Horváth K, Aschermann Z, Ács P, Deli G, Janszky J, Komoly S, Karádi K, Kovács M, Makkos A, Faludi B, Kovács N (2015) Minimal clinically important difference
- 587
- 588
- 589
- 590
- 591
- 592
- 593
- 594
- 595
- 596
- 597
- 598
- 599
- 600
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- 657
- 658
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- 661
- 662
- 663
- 664
- 665
- 666
- 667
- 668
- 669

- on Parkinson's Disease Sleep Scale 2nd Version. *Parkinsons Dis* **2015**, 970534.
- [34] De Fabregues O, Dot J, Abu-Suboh M, Hernández-Vara J, Ferré A, Romero O, Ibarria M, Seoane JL, Ragner N, Puiggros C, Gómez MR, Quintana M, Armengol JR, Alvarez-Sabín J (2017) Long-term safety and effectiveness of levodopa-carbidopa intestinal gel infusion. *Brain Behav* **7**, e00758.
- [35] AbbVie Inc., A Study to Examine the Effect of Levodopa-Carbidopa Intestinal Gel (LCIG) Therapy Relative to That of Optimized Medical Treatment (OMT) on Non-motor Symptoms (NMS) Associated With Advanced Parkinson's Disease (PD) (NCT02549092), 2021. <https://clinicaltrials.gov/ct2/show/results/NCT02549092>.
- [36] Chaudhuri KR, Healy DG, Schapira AHV (2006) Non-motor symptoms of Parkinson's disease: Diagnosis and management. *Lancet Neurol* **5**, 235-245.
- [37] Dhawan V, Healy DG, Pal S, Chaudhuri KR (2006) Sleep-related problems of Parkinson's disease. *Age Ageing* **35**, 220-228.
- [38] Politis M, Piccini P, Pavese N, Koh S-B, Brooks DJ (2008) Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: An in vivo 11C-raclopride PET study. *Exp Neurol* **214**, 112-116.
- [39] Soileau MJ, Pagan F, Fasano A, Rodriguez-Cruz R, Wang L, Kandukuri PL, Yan CH, Alobaidi A, Bao Y, Kukreja P, Oh M, Siddiqui MS (2022) Comparative effectiveness of carbidopa-levodopa enteral suspension and deep brain stimulation on Parkinson's disease-related pill burden reduction in advanced Parkinson's disease: A retrospective real-world cohort study. *Neurol Ther* **11**, 851-861.
- [40] Nyholm D, Jansson R, Willows T, Remahl IN (2005) Long-term 24-hour duodenal infusion of levodopa: Outcome and dose requirements. *Neurology* **65**, 1506-1507.
- [41] Ciurleo R, Corallo F, Bonanno L, Lo Buono V, Di Lorenzo G, Versaci R, Allone C, Palmeri R, Bramanti P, Marino S (2018) Assessment of Duodopa® effects on quality of life of patients with advanced Parkinson's disease and their caregivers. *J Neurol* **265**, 2005-2014.
- [42] Tessitore A, Marano P, Modugno N, Pontieri FE, Tambasco N, Canesi M, Latorre A, Lopiano L, Sensi M, Quatrala R, Solla P, Defazio G, Melzi G, Costanzo AM, Gualberti G, di Luzio P, Paparati U, Antonini A (2018) Caregiver burden and its related factors in advanced Parkinson's disease: Data from the PREDICT study. *J Neurol* **265**, 1124-1137.
- [43] Gomez-Inhieto E, Acaiturri-Ayesta MT, Ustarroz-Aguirre I, Camahualí D, Urtaran-Laresgoiti M, Basabe-Aldecoa M, Nuño-Solinís R, Urizar E (2020) Direct cost of Parkinson's disease: A real-world data study of second-line therapies. *Parkinsons Dis* **2020**, 9106026.
- [44] Gumber A, Ramaswamy B, Thongchundee O (2019) Effects of Parkinson's on employment, cost of care, and quality of life of people with condition and family caregivers in the UK: A systematic literature review. *Patient Relat Outcome Meas* **10**, 321-333.
- [45] Martinez-Martin P, Macaulay D, Jalundhwala YJ, Mu F, Ohashi E, Marshall T, Sail K (2019) The long-term direct and indirect economic burden among Parkinson's disease caregivers in the United States. *Mov Disord* **34**, 236-245.
- [46] Yang W, Hamilton JL, Kopil C, Beck JC, Tanner CM, Albin RL, Ray Dorsey E, Dahodwala N, Cintina I, Hogan P, Thompson T (2020) Current and projected future economic burden of Parkinson's disease in the U.S. *NPJ Parkinsons Dis* **6**, 15-15.
- [47] Bartolomei L, Pastore A, Meligrana L, Sanson E, Bonetto N, Minicuci GM, Marsala SZ, Mesiano T, Bragagnolo L, Antonini A (2018) Relevance of sleep quality on caregiver burden in Parkinson's disease. *Neurol Sci* **39**, 835-839.
- [48] Whetten-Goldstein K, Sloan F, Kulas E, Cutson T, Schenkman M (1997) The burden of Parkinson's disease on society, family, and the individual. *J Am Geriatr Soc* **45**, 844-849.
- [49] Marano M, Naranian T, di Biase L, Di Santo A, Poon Y-Y, Arca R, Cossu G, Marano P, Di Lazzaro V, Fasano A (2019) Complex dyskinesias in Parkinson patients on levodopa/carbidopa intestinal gel. *Parkinsonism Relat Disord* **69**, 140-146.
- [50] Buongiorno M, Antonelli F, Cámara A, Puente V, de Fabregues-Nebot O, Hernandez-Vara J, Calopa M, Pascual-Sedano B, Campolongo A, Valdeoriola F, Tolosa E, Kulisevsky J, Martí MJ (2015) Long-term response to continuous duodenal infusion of levodopa/carbidopa gel in patients with advanced Parkinson disease: The Barcelona registry. *Parkinsonism Relat Disord* **21**, 871-876.
- [51] Catalán M-J, Escibano PM, Alonso-Frech F (2017) Dyskinesias in levodopa-carbidopa intestinal gel infusion era: New challenges, new features. *Mov Disord* **32**, 624-625.
- [52] Fabbri M, Zibetti M, Calandra-Buonaura G, Contin M, Sambati L, Mohamed S, Romagnolo A, Berchiolla P, Imbalzano G, Giannini G, Rizzone MG, Artusi CA, Cortelli P, Lopiano L (2020) Levodopa/carbidopa intestinal gel long-term outcome in Parkinson's disease: Focus on dyskinesia. *Mov Disord Clin Pract* **7**, 930-939.
- [53] Meloni M, Solla P, Mascia MM, Marrosu F, Cannas A (2017) Diphasic dyskinesias during levodopa-carbidopa intestinal gel (LCIG) infusion in Parkinson's disease. *Parkinsonism Relat Disord* **37**, 92-96.
- [54] Fasano A, Ricciardi L, Lena F, Bentivoglio AR, Modugno N (2012) Intrajejunal levodopa infusion in advanced Parkinson's disease: Long-term effects on motor and non-motor symptoms and impact on patient's and caregiver's quality of life. *Eur Rev Med Pharmacol Sci* **16**, 79-89.
- [55] Liu XD, Bao Y, Liu GJ (2019) Comparison between levodopa-carbidopa intestinal gel infusion and subthalamic nucleus deep-brain stimulation for advanced Parkinson's Disease: A systematic review and meta-analysis. *Front Neurol* **10**, 934.
- [56] Volkmann J, Albanese A, Antonini A, Chaudhuri KR, Clarke CE, de Bie RMA, Deuschl G, Eggert K, Houeto J-L, Kulisevsky J, Nyholm D, Odin P, Østergaard K, Poewe W, Pollak P, Rabey JM, Rascol O, Ruzicka E, Samuel M, Speelman H, Sydow O, Valdeoriola F, van der Linden C, Oertel W (2013) Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: An evidence-based review. *J Neurol* **260**, 2701-2714.
- [57] Burack M, Aldred J, Zadikoff C, Vanaganas A, Klos K, Bilir B, Fernandez HH, Standaert DG (2018) Implementing levodopa-carbidopa intestinal gel for Parkinson disease: Insights from US practitioners. *Mov Disord Clin Pract* **5**, 383-393.
- [58] Weernink MGM, van Til JA, van Vugt JPP, Movig KLL, Groothuis-Oudshoorn CGM, Ijzerman MJ (2016) Involving patients in weighting benefits and harms of treatment in Parkinson's disease. *PLoS One* **11**, e0160771.
- [59] Titova N, Chaudhuri KR (2017) Personalized medicine in Parkinson's disease: Time to be precise. *Mov Disord* **32**, 1147-1154.

- [60] Odin P, Ray Chaudhuri K, Slevin JT, Volkmann J, Dietrichs E, Martinez-Martin P, Krauss JK, Henriksen T, Katzenschlager R, Antonini A, Rascol O, Poewe W (2015) Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program. *Parkinsonism Relat Disord* **21**, 1133-1144.
- [61] AbbVie Inc. Data on File. Clinical Study Report: DUOGLOBE.
- [62] AbbVie Inc. Data on File. Clinical Study Report: DYSCOVER.
- [63] Alvarez EF, Spanaki C, Pekkonen E, Manzanares L, Liu Y, Sánchez-Soliño O, Barbato L (2020) Effect of levodopa-carbidopa intestinal gel versus optimized medical treatment on dyskinesia in advanced Parkinson's disease patients: Final results of the randomized 12-week DYSCOVER study [abstract]. *Mov Disord* **35**, Abstr. No. 867.
- [64] AbbVie Inc. Data on File. Clinical Study Report: GLORIA.
- [65] Cáceres-Redondo MT, Carrillo F, Lama MJ, Huertas-Fernández I, Vargas-González L, Carballo M, Mir P (2014) Long-term levodopa/carbidopa intestinal gel in advanced Parkinson's disease. *J Neurol* **261**, 561-569.
- [66] AbbVie Inc., Levodopa-Carbidopa Intestinal Gel Open-Label Study in Advanced Parkinson's Disease (NCT00335153), 2015. <https://clinicaltrials.gov/ct2/show/NCT00335153>.
- [67] Abbot Laboratories, Data on File. Clinical Study Report: An Open-Label, 12-Month Safety and Efficacy Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Subjects with Advanced Parkinson's Disease and Severe Motor Fluctuations Despite Optimized Treatment with Available Parkinson's Disease Medications. (2012).
- [68] Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VS, Klostermann F, Lew MF, Odin P, Steiger M, Yakupov EZ, Chouinard S, Suchowersky O, Dubow J, Hall CM, Chatamra K, Robieson WZ, Benesh JA, Espay AJ (2015) Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: Final 12-month, open-label results. *Mov Disord* **30**, 500-509.
- [69] AbbVie Inc. Data on File. Clinical study report: MONOTREAT.
- [70] Krüger R, Lingor P, Doskas T, Henselmans JML, Danielsen EH, de Fabregues O, Stefani A, Sensken SC, Parra JC, Onuk K, Yegin A, Antonini A (2017) An observational study of the effect of levodopa-carbidopa intestinal gel on activities of daily living and quality of life in advanced Parkinson's disease patients. *Adv Ther* **34**, 1741-1752.
- [71] Abbott Laboratories, Data on File. Clinical Study Report: A Randomized, Double-Blind, Double-Dummy, Efficacy, Safety, and Tolerability Study of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects Receiving Optimized Treatments with Parkinson Medicinal Products Who Continue to Experience Persistent Motor Fluctuations. (2012).
- [72] AbbVie Inc., Study of Efficacy, Safety and Tolerability of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects (NCT00660387), 2015. <https://clinicaltrials.gov/ct2/show/NCT00660387>.
- [73] AbbVie Inc., Study of Efficacy, Safety and Tolerability of Levodopa-Carbidopa Intestinal Gel in Levodopa-Responsive Parkinson's Subjects (NCT00357994), 2015. <https://clinicaltrials.gov/ct2/show/NCT00357994>.
- [74] Abbott Products AG, Data on File. Clinical Study Report: A Long-term Health Economics Study of Intraduodenal Levodopa (Duodopa®) in Routine Care for Subjects with Advanced Idiopathic Parkinson's Disease with Severe motor Fluctuations and Hyper-/dyskinesia DAPHNE (Duodopa in Advanced Parkinson's: Health outcomes & Net Economic impact), (2012).
- [75] Solvay Pharmaceuticals GmbH, Clinical Trial Results: A long-term health economics study of intraduodenal levodopa (Duodopa®) in routine care for patients with advanced idiopathic Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia. (EudraCT 2005-002654-21). 2016. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-002654-21/results>.
- [76] Pålhagen SE, Sydow O, Johansson A, Nyholm D, Holmberg B, Widner H, Dizdar N, Linder J, Hauge T, Jansson R, Bergmann L, Kjellander S, Marshall TS (2016) Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: An open-label prospective observational study of effectiveness, tolerability and healthcare costs. *Parkinsonism Relat Disord* **29**, 17-23.
- [77] Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, Odin P, Antonini A, Chaudhuri KR (2012) Intra-jejunal levodopa versus conventional therapy in Parkinson disease: Motor and nonmotor effects. *Clin Neuropharmacol* **35**, 205-207.
- [78] Sensi M, Preda F, Trevisani L, Contini E, Gragnaniello D, Capone JG, Sette E, Golfre-Andreas N, Tugnoli V, Tola MR, Quatralè R (2014) Emerging issues on selection criteria of levodopa carbidopa infusion therapy: Considerations on outcome of 28 consecutive patients. *J Neural Transm (Vienna)* **121**, 633-642.
- [79] AbbVie Inc., Safety/Efficacy Study of Levodopa-Carbidopa Intestinal Gel in Parkinson's Subjects (NCT00360568), 2015. <https://clinicaltrials.gov/ct2/show/NCT00360568>.
- [80] Slevin JT, Fernandez HH, Zadikoff C, Hall C, Eaton S, Dubow J, Chatamra K, Benesh J (2015) Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: An open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. *J Parkinsons Dis* **5**, 165-174.
- [81] AbbVie Inc., Data on File. Clinical Study Report: M12-920.
- [82] AbbVie Inc., A Study to Assess the Safety and Efficacy of Levodopa-carbidopa Intestinal Gel (LCIG) for the Treatment of Non-motor Symptoms in Patients With Advanced Parkinson's Disease (NCT01736176), 2017. <https://clinicaltrials.gov/ct2/show/NCT01736176>.