RESEARCH ARTICLE

Concomitant Medication Usage with Levodopa-Carbidopa Intestinal Gel: Results from the COSMOS Study

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ABSTRACT: Background: Levodopa-carbidopa intestinal gel (LCIG) is administered directly to the small intestine of patients with advanced Parkinson's disease (APD) to help maintain stable plasma levodopa levels.
Objective: The objective of this study was to investigate the effect of LCIG in reducing polypharmacy for the treatment of APD.
Methods: The COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel (COSMOS) is a large, real-world, multinational observational study investigating comedication use with LCIG. All enrolled patients had used LCIG for ≥12 months and data were collected cross-sectionally (study visit) and retrospectively. The primary endpoint was the percentage of patients using LCIG as monotherapy (without add-on PD medications) at initiation and at 3, 6, 9, and 12 months thereafter.
Results: Overall, 409 patients were enrolled from 14 countries and were treated with LCIG for a mean of 35.8 ± 23.2 months. A total of 15.2% of patients initiated LCIG as monotherapy and 31.7% were receiving monotherapy at 12 months after initiation. The mean duration

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of LCIG monotherapy was 39.3 ± 25.6 months. Use of add-on medications decreased over time with all LCIG regimens. From LCIG initiation to the patient visit, mean off time decreased by 3.8, 4.6, and 3.9 hours/day for LCIG monotherapy, LCIG daytime monotherapy, and LCIG polytherapy groups, respectively, while duration of dyskinesia decreased by 1.7, 2.0, and 1.9 hours/day, respectively. Adverse events likely related to study treatment occurred in 112 patients (27.4%) during LCIG treatment.

Conclusions: LCIG is an effective long-term monotherapy option with a positive risk–benefit profile and contributes to reduced polypharmacy for patients with APD.

Key Words: levodopa-carbidopa intestinal gel; monotherapy; Parkinson's disease; drug polytherapy; observational studies

Despite proven efficacy and widespread use of levodopa for the treatment of Parkinson's disease (PD), the chemical properties of orally administered levodopa include a short plasma half-life that leads to intermittent receptor stimulation and subsequent fluctuations in symptom control.[1] As PD progresses, the therapeutic window of levodopa treatment narrows and patients experience intermittent motor and nonmotor symptoms that require addition of drugs such as dopamine agonists, catechol-*O*-methyl-transferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, or amantadine.[2] Poor treatment adherence is common among patients with PD, possibly because of side effects and/or drug–drug interactions from comedications to help manage PD, other comorbidities, or aspects of PD disease progression such as cognitive decline and dysphagia.[3-5] Therefore, the complex oral drug regimens that are often used and frequently result in inadequate symptom control can be particularly burdensome to patients with advancing PD, creating a paradoxical need to simplify drug regimen while the disease progresses.[6,7]

Levodopa-carbidopa intestinal gel (LCIG) allows individualized doses of levodopa to be infused continuously into the small intestine to maintain physiological dopamine levels.[8] Evidence to date suggests LCIG is clinically superior to oral polypharmacy in patients with advanced PD (APD),[9,10] and leads to clinically significant improvements in dyskinesias, motor and nonmotor fluctuations, and health-related quality of life (HRQoL) compared with immediate-release levodopa.[1,8,10-14] Such evidence suggests LCIG has the potential to be administered as monotherapy, thereby reducing pill burden, drug–drug interactions, side effects, and poor treatment adherence. However, pivotal trials investigating LCIG required patients to take LCIG monotherapy, which can affect real-world outcomes.[10,11]

The effect of LCIG on reducing medication burden has not been thoroughly investigated. In many studies, LCIG titration and oral drug management is left to the judgment of neurologists, which contribute to a lack of standardization and reproducibility.[10,11] Results from 1 phase 3 study demonstrated LCIG treatment reduced the percentage of patients using COMT inhibitors, dopamine agonists (DA), MAO-B inhibitors, and amantadine over 12 months compared with baseline usage; however, in that study, patients were required to stop all treatments other than LCIG for the first 4 weeks of the trial.[11] Data from the Global LOng-term Registry on efficacy and safety of LCIG In patients with APD in routine care (GLORIA) demonstrated decreased use of COMT inhibitors, DAs, MAO-B inhibitors, and amantadine over 2 years of LCIG treatment compared with use before LCIG initiation. Results showed 37% of patients were taking LCIG monotherapy at 24 months, whereas 57% who initiated LCIG as monotherapy were taking LCIG monotherapy at 24 months, and 23% of patients used LCIG monotherapy exclusively over the entire 24-month period.[15,16]

Other device-aided therapies (DATs) include continuous subcutaneous apomorphine infusion (CSAI) therapy and deep brain stimulation (DBS), which have shown promise as therapeutic options.[17,18] However, despite their effectiveness, results on their efficacy and safety as monotherapies are limited.[17-20]

The COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel (COSMOS) is a large, multinational study, and the first dedicated to investigating comedication use with LCIG and the potential usability of LCIG as a monotherapy by generating relevant data from routine clinical practice. Here, we report medication usage patterns over 12 months in patients with APD who were treated with LCIG and compare attributes of LCIG therapy such as use of concomitant medications versus monotherapy, duration of LCIG monotherapy, and patient- and physician-based predictors for achieving long-term LCIG monotherapy.

Methods

Study Design and Setting

COSMOS (Clinicaltrials.gov identifier: NCT03362879) was a multinational, retrospective, and cross-sectional,

post-marketing observational study of patients with APD who were treated with LCIG in routine clinical care. Data were collected retrospectively from patient medical records covering a period of at least 12 months since LCIG initiation and cross-sectionally during a clinic visit.

Participants

Patients were eligible for inclusion if they were diagnosed with APD and received ongoing LCIG treatment for ≥12 months and for ≥80% of days in the year preceding the study. Patients who had used LCIG therapy as part of a previous or concurrent interventional trial or were unable to complete study questionnaires were excluded. Written informed consent was obtained by each patient or legal authorized representative before any data collection.

Variables and Data Sources

All clinical data obtained at the patient visit or from medical records were entered into a web-based electronic data capture system for analysis.

Patient Demographics and Disease Characteristics

During the study visit, the physician collected current patient demographic information and sociodemographic information both current to the visit and from before initiation of LCIG. These data included patient PD status based on Unified Parkinson's Disease Rating Scale (UPDRS) categories I–V, and Mini-Mental State Examination (MMSE) scores. Patients or caregivers were asked to state their overall preference for LCIG as a monotherapy compared with LCIG with add-on PD medication. Medical history was recorded based on available information in patient medical records and included PD phenotype, disease and symptom chronology, time spent in the "off" state and the "on" state with troublesome/nontroublesome dyskinesia, presence of motor and nonmotor PD symptoms, UPDRS scores, modified Hoehn and Yahr stage (UPDRS part V) ratings, and comorbidities related to PD as judged by the physician at the time the record was taken. Information on PD-related treatment (medication or DATs) from just before LCIG initiation was also collected.

Treatments

Patients were stratified by LCIG treatment regimen into 3 groups based on their treatment regimen at 12 months of therapy; (1) "LCIG monotherapy," defined as use of LCIG only with no add-on PD medications; (2) "LCIG daytime monotherapy," defined as LCIG with add-on PD medications used in the evening after the daily LCIG infusion hours are completed; and (3) "LCIG polytherapy," defined as LCIG with add-on medications at any time, including during LCIG infusion hours.

Primary Endpoint

The primary endpoint was the percentage of patients receiving LCIG monotherapy immediately after LCIG initiation (after permanent system placement) and at 3, 6, 9, and 12 months after LCIG initiation.

Secondary Analyses

Secondary objectives included describing LCIG treatment settings, analyzing patterns of add-on medication use during LCIG treatment, assessing clinical outcomes between treatment groups, and examining predictors of LCIG monotherapy regimen versus LCIG with add-on medication. Clinical characteristics such as duration of dyskinesia and off time from the day before the study visit, and UPDRS, nonmotor symptom scale (NMSS), PDSS-2, and 8-item PD Questionnaire (PDQ-8) scores at the patient visit were also analyzed.

Safety

Data from safety assessments previously collected from healthcare professionals for other purposes were used to document adverse events (AEs) that had a reasonable possibility of being causally related to the treatment drug or device.

Statistical Methods

Sample size was determined based on predefined precision of the estimators, expressed as the maximum length of the corresponding two-sided 95% confidence intervals (CIs). A sample of least 385 evaluable patients was considered necessary to achieve a precision of ±5% (ie, CIs ≤10%) and considering an underlying percentage of 50% (ie, the percentage that leads to the largest sample size).

Data collected from patient medical records and the single-study visit are presented using descriptive statistics. All results are expressed as mean ± SD unless otherwise stated. Two-sided 95% CIs were calculated for primary and secondary endpoints defined by proportions. Logistic regression was applied to investigate the impact of potential prognostic factors for LCIG monotherapy, including demographic variables, baseline disease characteristics at LCIG initiation, and physician and study site characteristics. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

TABLE 1. Demographics and baseline characteristics

	LCIG monotherapy[a] N = 120		LCIG daytime monotherapy[a] N = 94		LCIG polytherapy[a] N = 164		Total population N = 409	
Description	n	%	n	%	n	%	n	%
Sex								
Female	45	37.5	28	29.8	60	36.6	142	34.7
Male	75	62.5	66	70.2	104	63.4	267	65.3
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
Age, at LCIG initiation, y	118	66.4 ± 8.2	94	67.8 ± 7.4	164	65.9 ± 7.8	389	66.5 ± 7.8
Duration of "off" period,[b] h	89	5.7 ± 3.3	66	6.7 ± 4.4	110	6.1 ± 3.3	277	6.1 ± 3.6
Duration of dyskinesia,[b] h	85	3.3 ± 2.9	59	4.6 ± 3.5	110	3.8 ± 3.4	268	3.7 ± 3.4
Time from PD diagnosis to[c]:								
LCIG initiation, y	118	12.0 ± 5.1	94	12.7 ± 4.8	164	13.5 ± 5.8[d]	390	12.8 ± 5.4
Motor fluctuation onset, y	119	7.3 ± 3.4	92	7.1 ± 3.6	156	7.5 ± 4.1	396	7.3 ± 3.7
Morning akinesia, y	68	7.6 ± 3.9	62	7.2 ± 4.0	124	8.0 ± 4.1	268	7.7 ± 4.1
Wearing off, y	105	7.5 ± 3.5	87	7.2 ± 3.6	150	7.8 ± 4.3	364	7.5 ± 4.0
Dyskinesia, y	89	8.1 ± 3.5	82	8.0 ± 3.9	135	9.0 ± 4.6	326	8.4 ± 4.2
MMSE total score	74	27.4 ± 3.1	46	26.6 ± 2.7	80	28.0 ± 2.7	222	27.5 ± 2.8
UPDRS total score	35	58.2 ± 22.9	33	55.5 ± 26.6	45	60.8 ± 24.7	118	57.7 ± 24.5
Part I	34	4.5 ± 2.5	31	4.1 ± 2.9	44	4.6 ± 2.5	112	4.4 ± 2.6
Part II	43	17.0 ± 8.3	36	15.4 ± 6.9	51	17.5 ± 8.1	135	16.6 ± 7.8
Part III	54	26.8 ± 12.5	48	28.3 ± 12.9	82	33.9 ± 17.8[e]	190	30.1 ± 15.3
Part IV	43	8.2 ± 5.1	37	8.5 ± 4.6	62	9.9 ± 6.0	147	8.8 ± 5.4
PD medication before LCIG initiation, n (%)								
Any medication	100	83.3	79	84.0	141	86.0	329	80.4
Levodopa[f]	91	75.8	78	83.0	132	80.5	309	75.6
DA	40	33.3	41	43.6	55	33.5	139	34.0
MAO-B inhibitors	27	22.5	22	23.4	25	15.2	74	18.1
COMT inhibitors	13	10.8	17	18.1	25	15.2	56	13.7
NMDA antagonists	13	10.8	19	20.2	16	9.8	51	12.5
APO injection	0	0	0	0	7	4.3	7	1.7
APO CI	1	0.8	1	1.1	1	0.6	3	0.7
Anticholinergics	1	0.8	2	2.1	6	3.7	9	2.2
Other	0	0	0	0	6	3.7	6	1.5
Symptoms at LCIG initiation, n (%)								
Hallucination	1	0.8	2	2.1	4	2.4	7	1.7
Sleep disorders	29	24.2	22	23.4	38	23.2	91	22.2
Any impulsive-compulsive disorder	21	18.9	18	20.5	31	20.9	71	18.9
Previous deep brain stimulation	2	1.7	1	1.1	7	4.3	11	2.7

[a]Patients were grouped by their treatment regimen at 12 months, including 31 patients with inconclusive/missing treatment regimen data.
[b]Hours during the day before the clinical visit as reported by the patient.
[c]Restricted to patients with these conditions.
[d]$P < 0.05$ vs. LCIG monotherapy.
[e]$P < 0.05$ vs. before LCIG initiation.
[f]Levodopa use included levodopa/carbidopa, levodopa/carbidopa/entacapone, and/or levodopa/benserazide.
Abbreviations: APO, apomorphine; CI, continuous infusion; COMT, catechol-*O*-methyl transferase; DA, dopamine agonist; LCIG, levodopa-carbidopa intestinal gel; MAO-B, monoamine oxidase-B; MMSE, Mini-Mental State Examination; NMDA, *N*-methyl-*D*-aspartate; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Results

Participants

A total of 409 patients from 49 sites in 14 countries were included in the analysis. These sites treat a mean of 730.3 ± 768.8 patients with PD/APD annually; the average frequency of routine visits for patients with APD who were receiving DAT was 4.3 visits per year. A total of 74 neurologists participated in the study and 71.4% of the 56 physicians who stated a preference "preferred LCIG as monotherapy versus polytherapy."

Most patients were male (65.3%) with a mean age of 66.5 ± 7.8 years, UPDRS total score of 57.7 ± 24.5, and MMSE score of 27.5 ± 2.8 before LCIG initiation (Table 1). Baseline characteristics were generally well matched between treatment groups (Table 1; Supplementary Table S1), although the UPDRS Part III score and time between PD diagnosis and LCIG initiation were significantly increased in the LCIG polytherapy group compared with the LCIG monotherapy group (Table 1). The primary reasons for LCIG initiation were disabling motor fluctuations (n = 375; 91.7%) and decreased quality of life (n = 231; 56.5%) (Supplementary Table S2). At the patient visit, the mean duration of LCIG therapy among patients was 35.8 ± 23.2 months (Supplementary Table S3).

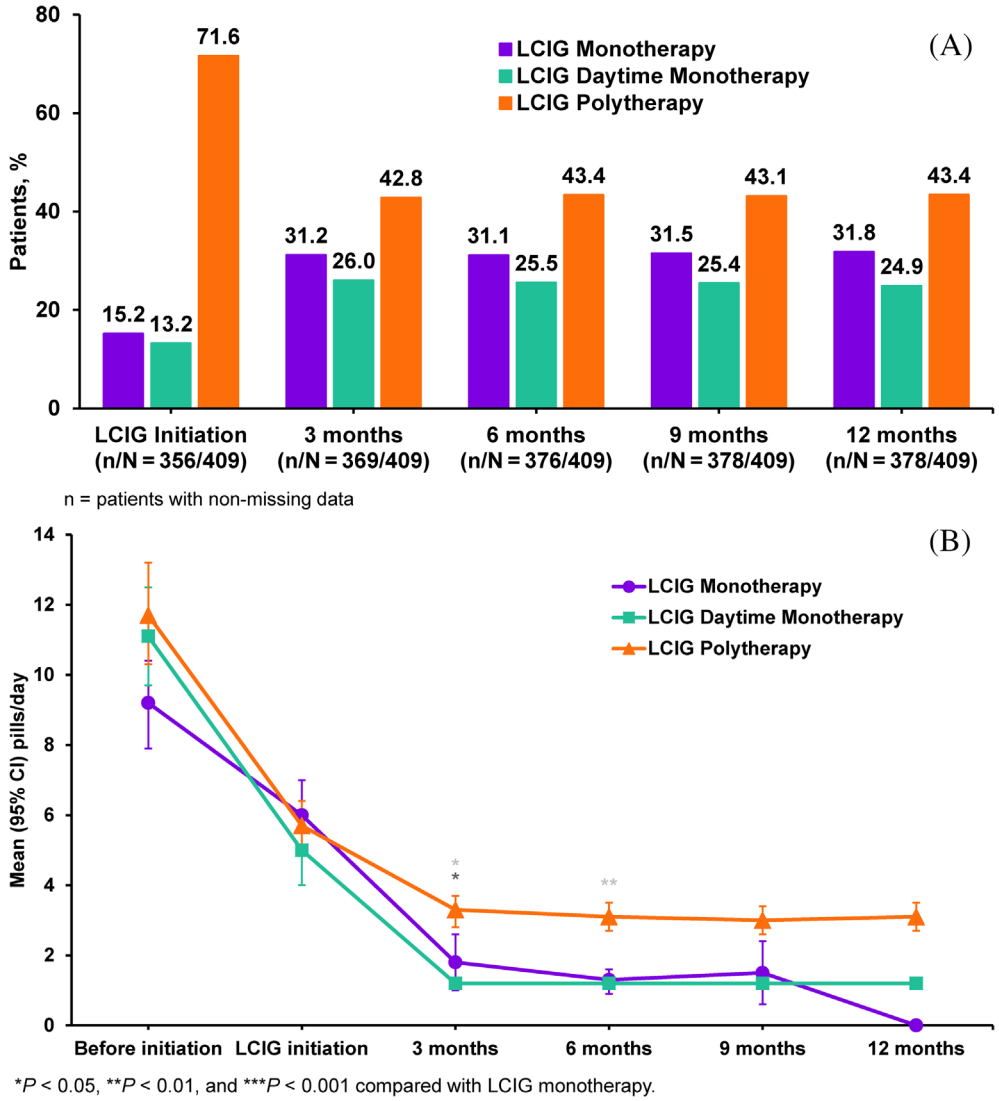

FIG. 1. Percentages of patients taking levodopa-carbidopa intestinal gel (LCIG) monotherapy at indicated time points (**A**). Number of pills per day of add-on Parkinson's disease medication by treatment group over time (**B**).

Study patients were receiving LCIG monotherapy (n = 120), LCIG daytime monotherapy (n = 94), or LCIG polytherapy (n = 164) 12 months after LCIG initiation. Patients in the LCIG monotherapy group were receiving monotherapy for a mean of 30.7 ± 20.4 months and were receiving any LCIG regimen for 39.3 ± 25.6 months, which was significantly longer than the duration of any LCIG regimen for patients in the LCIG daytime monotherapy group (31.8 ± 22.3 months; $P < 0.05$), but not in the LCIG polytherapy group (35.7 ± 21.9 months; $P = 0.428$). LCIG titration was achieved most rapidly for patients in the LCIG monotherapy group (6.0 ± 3.4 days), which was significantly decreased compared with LCIG daytime monotherapy patients (8.8 ± 6.2 days; $P < 0.001$; Supplementary Table S3).

Primary Endpoint

The percentage of patients treated with LCIG monotherapy increased from 15.2% (n = 54/356) at LCIG initiation to 31.7% (n = 120/378) at 12 months, whereas 13.2% (n = 47/356) of patients initiated treatment with LCIG daytime monotherapy, which increased to 24.9% (n = 94/378) at 12 months (Fig. 1A). Therefore combined, the LCIG monotherapy group and LCIG daytime monotherapy group comprised 28.4% of patients at baseline and 56.6% of patients at month 12. LCIG polytherapy was most common, with 71.6% of patients (n = 255/356) initiating LCIG therapy with this regimen; however, usage decreased notably by month 3 to 42.8% of patients (n = 158/369), then remained stable until month 12 (43.4% [n = 164/378]; Fig. 1A).

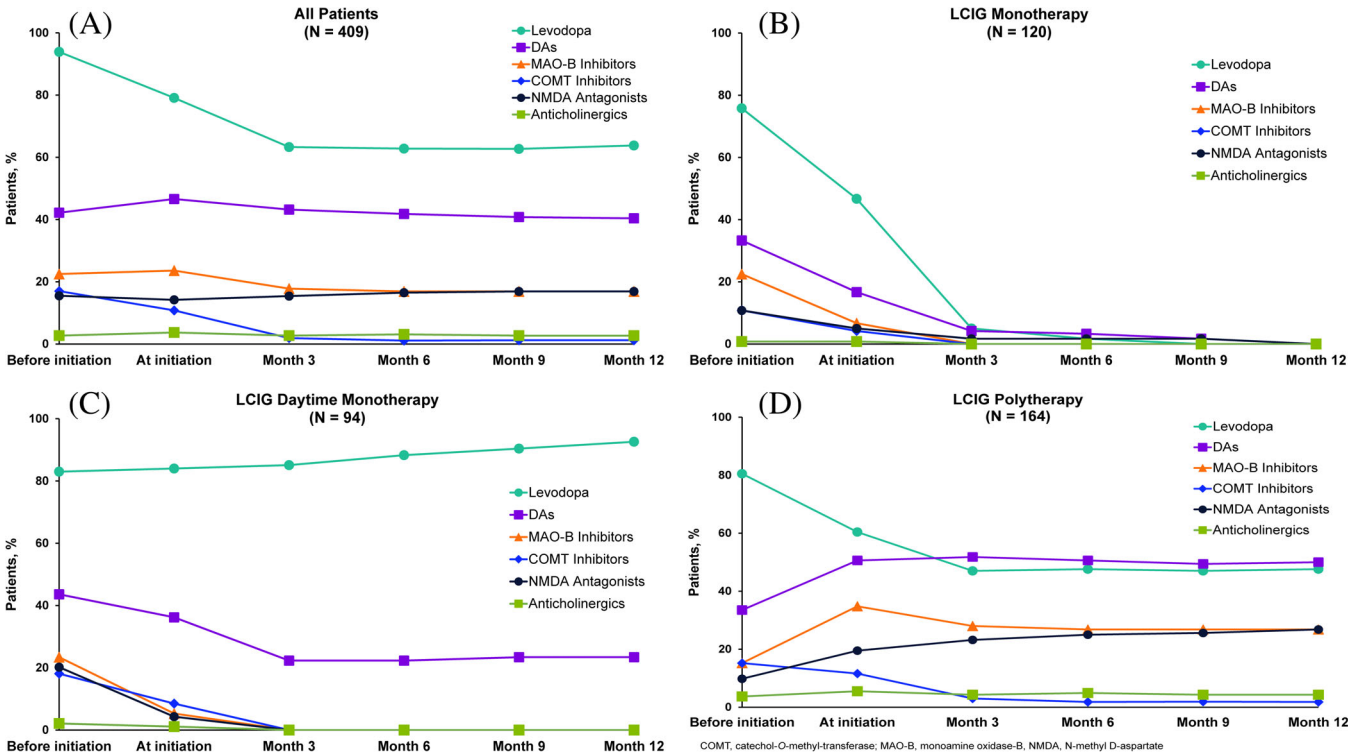

FIG. 2. Percentages of patients with reported Parkinson's disease medication usage before initiation of levodopa-carbidopa intestinal gel (LCIG) and as add-on therapy over time by class. All patients (**A**), LCIG monotherapy (**B**), LCIG daytime monotherapy (**C**), and LCIG polytherapy (**D**). "Levodopa" indicates oral formulations. COMT, catechol-O-methyl-transferase; MAO-B, monoamine oxidase-B, NMDA, N-methyl D-aspartate.

Secondary Analyses

Add-on PD Medication Use by Class

The percentages of patients using add-on PD medication by class and the LCIG treatment regimen are presented in Figure 2 and Supplementary Table S4. The numbers of patients using DA, COMT inhibitor, and MAO-B inhibitors decreased over time in both the LCIG monotherapy and LCIG daytime monotherapy groups, whereas only COMT inhibitors decreased among patients in the LCIG polytherapy group. As expected, LCIG initiation was the most common reason for discontinuation of add-on medications (73.3% of patients; not shown). Most patients in the LCIG monotherapy group (93.8%) and LCIG daytime monotherapy group (73.8%) discontinued DA, MAO-B, and COMT inhibitor use within 3 months of LCIG initiation. No percentage increases in DA, MAO-B, and COMT inhibitor use were observed in any treatment group after 3 months of LCIG therapy (Fig. 2). Before LCIG initiation, the mean numbers of pills per day of all add-on medications were 9.2 ± 6.6 for LCIG monotherapy, 11.1 ± 6.7 for LCIG daytime monotherapy, and 11.7 ± 9.2 for LCIG polytherapy groups. At month 12, the corresponding values were 0, 1.2 ± 0.4, and 3.1 ± 2.6 pills per day, respectively, with a statistically significant difference from baseline in all groups (Fig. 1B).

Overall Medication Needs

At LCIG initiation, the levodopa equivalent daily dose (LEDD) for the LCIG daytime monotherapy group (2583.0 ± 922.6) and LCIG polytherapy group (2630.8 ± 1099.4) was significantly higher than the LEDD in the LCIG monotherapy group (2266.6 ± 929.7; $P < 0.05$; Supplementary Fig. S1A). Similar results occurred at 12 months when the LEDD of the LCIG daytime monotherapy and LCIG polytherapy groups were 2227.4 ± 614.5 and 2331.0 ± 879.7, respectively, versus 1834.6 ± 793.1 for LCIG monotherapy group (both $P < 0.0001$). The LEDD for add-on PD medications decreased from initiation to month 12 overall; however, the LEDD remained significantly increased for the LCIG daytime monotherapy and LCIG polytherapy groups compared with the LCIG monotherapy group at all time points after LCIG initiation (Supplementary Fig. S1B).

For all patients, the daily LCIG dose was similar at 12 months versus at initiation (1384 ± 520 mg/day and 1312 ± 498 mg/day, respectively). Yet, patients in the LCIG daytime monotherapy group had higher daily doses of LCIG than did patients in the LCIG monotherapy group at initiation (1388 ± 444 mg/day vs. 1242 ± 506 mg/day; $P < 0.01$) and at 12 months (1458 ± 414 mg/day vs. 1326 ± 568 mg/day; $P < 0.01$) (Supplementary Fig. S1C).

TABLE 2. Unified Parkinson's Disease Rating Scale, Non-Motor Symptoms Scale, Parkinson's Disease Sleep Scale 2, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale, and 8-item Parkinson's Disease Questionnaire scores at the patient visit

	LCIG monotherapy N = 120		LCIG daytime monotherapy N = 94		LCIG polytherapy N = 164		Total population N = 409	
Mean ± SD	n	Result	n	Result	n	Result	n	Result
UPDRS total score	120	54.8 ± 24.5[a]	94	54.8 ± 20.3	164	57.2 ± 23.0	408	56.2 ± 23.6
Part I	120	3.6 ± 2.9	94	3.4 ± 2.6	164	3.6 ± 2.4[a]	409	3.5 ± 2.6
Part II	120	16.8 ± 8.3	94	17.3 ± 7.4	164	17.6 ± 7.9	409	17.4 ± 8.0
Part III	120	29.2 ± 13.6	94	28.2 ± 12.2	164	30.1 ± 13.6	408	29.7 ± 13.7
Part IV	120	5.2 ± 3.6[b]	94	5.9 ± 3.1[b,d]	164	5.9 ± 3.5[c]	409	5.6 ± 3.4[c]
Dyskinesias and dystonia, score	120	2.5 ± 2.4	94	2.9 ± 2.0	164	2.8 ± 2.3	409	2.7 ± 2.3
Motor fluctuations, score	120	1.8 ± 1.5	94	2.0 ± 1.3	164	2.3 ± 1.4[d]	409	2.0 ± 1.5
Other complications, score	120	0.9 ± 0.9	94	1.0 ± 0.9	164	0.8 ± 0.9	409	0.8 ± 0.9
Dyskinesias duration during the day, h	120	1.6 ± 2.6	93	2.5 ± 2.8[d]	163	1.8 ± 2.4[d]	404	1.8 ± 2.5
Change from pre-LCIG initiation	85	−1.7 ± 2.9	59	−2.0 ± 4.4	110	−1.9 ± 3.8	267	−1.8 ± 3.6
"Off" time during waking day, h	120	2.1 ± 3.6	92	1.9 ± 2.2	162	2.3 ± 3.1[a]	403	2.1 ± 3.1
Change from pre-LCIG initiation	89	−3.8 ± 4.4	64	−4.6 ± 4.3	110	−3.9 ± 4.2	275	−4.0 ± 4.3
Duration of dyskinesias or "off" state[e] during waking day, h	120	3.6 ± 5.0	92	4.4 ± 4.1[d]	162	4.1 ± 4.7	402	4.0 ± 4.6
Change from pre-LCIG initiation	83	−5.8 ± 4.9	56	−6.6 ± 6.1	105	−6.0 ± 6.4	255	−6.0 ± 5.7
NMSS total score	120	58.2 ± 45.4	94	60.8 ± 38.1	160	57.5 ± 41.4	404	57.6 ± 42.2
Cardiovascular including falls	120	2.2 ± 3.4	94	1.7 ± 3.4	164	1.9 ± 3.1	409	1.9 ± 3.2
Sleep/fatigue	120	9.7 ± 8.7	94	9.4 ± 8.3	164	9.6 ± 8.2	409	9.5 ± 8.4
Mood/cognition	120	11.8 ± 14.7	94	11.5 ± 14.9	164	9.1 ± 11.0	409	10.5 ± 13.3
Perceptual problems/hallucinations	120	2.2 ± 4.0	94	1.4 ± 3.1	164	1.9 ± 4.0	409	1.8 ± 3.7
Attention/memory	120	6.8 ± 8.7	94	6.5 ± 7.2	164	6.9 ± 8.5	409	6.6 ± 8.2
Gastrointestinal tract	120	5.0 ± 6.1	94	5.7 ± 7.0	164	6.1 ± 7.4	409	5.6 ± 6.8
Urinary	120	9.0 ± 8.9	94	11.3 ± 9.2	164	10.7 ± 10.0	409	10.3 ± 9.4
Sexual function	120	4.5 ± 7.3	94	4.5 ± 6.6	160	3.2 ± 5.8	404	3.7 ± 6.4
Miscellaneous	120	7.1 ± 8.5	94	8.8 ± 7.9[d]	164	8.4 ± 9.3	409	8.0 ± 8.7
QUIP-RS total score	112	12.6 ± 13.9	91	11.4 ± 11.8	154	11.2 ± 14.5	387	11.5 ± 13.4
Gambling	117	0.7 ± 1.9	94	0.6 ± 1.7	163	0.8 ± 2.2	404	0.7 ± 1.9
Sex	116	1.8 ± 2.9	93	1.9 ± 3.2	160	1.9 ± 2.8	400	1.8 ± 2.9
Buying	117	1.6 ± 2.7	94	1.8 ± 2.9	162	1.5 ± 2.6	404	1.6 ± 2.7
Eating	117	2.3 ± 3.2	94	2.1 ± 2.8	160	2.0 ± 3.2	402	2.1 ± 3.1
Hobbyism/punding	116	4.9 ± 6.2	93	3.9 ± 4.5	158	3.8 ± 5.2	398	4.1 ± 5.3
Medication use	116	2.4 ± 3.4	92	1.3 ± 2.2	161	1.8 ± 3.5[d]	400	1.8 ± 3.1
Total ICD score	114	5.9 ± 7.3	93	6.4 ± 7.3	158	6.0 ± 8.6	395	6.0 ± 7.8
PDSS-2 total score	112	19.6 ± 11.0	90	19.5 ± 10.6	152	21.6 ± 10.8	383	20.6 ± 10.8
PDQ-8 summary index scores	119	41.5 ± 17.7	93	36.5 ± 18.1	161	40.2 ± 18.3	404	40.3 ± 18.2

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] $P < 0.0001$ vs. baseline.
[d] $P < 0.05$ vs. LCIG monotherapy.
[e] Change of the duration of dyskinesias or "off" state duration should be considered additional "on time."
Abbreviations: ICD, impulsive-compulsive disorder; LCIG, levodopa-carbidopa intestinal gel; NMSS, Non-Motor Symptoms Scale; PD, Parkinson's disease; PDSS-2, PD Sleep Scale 2; PDQ-8, 8-item PD Questionnaire; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale; UPDRS, Unified PD Rating Scale.

Motor and Nonmotor Symptoms

In all groups, off time and dyskinesia duration were reduced at the patient visit compared with LCIG initiation, with no significant differences between groups (Table 2). The mean number of motor symptoms decreased from 6.6 ± 2.1 at LCIG initiation to 5.8 ± 2.4 at the patient visit for all patients ($P < 0.0001$). The proportion of patients who experienced rigidity, tremor, dystonia/cramps, gait impairment, balance problems, hypophonia, dysphagia, nocturnal/morning akinesia, and freezing of gait showed significant decline at the patient visit compared with LCIG initiation in all treatment groups ($P < 0.0001$). Motor symptoms were similarly reduced from the initiation of LCIG to the patient visit in all treatment groups, although patients in the LCIG monotherapy group showed significantly greater reductions in nocturnal/morning akinesia versus those in the LCIG daytime monotherapy group (20.8% reduction vs. 11.7% reduction; $P = 0.0099$) and freezing of gait versus those in the LCIG polytherapy group (14.2% reduction vs. 0% reduction; $P = 0.0036$;

Supplementary Fig. S2). The percentage of patients who experienced nonmotor symptoms of anxiety, pain, depression, and constipation decreased significantly from the initiation of LCIG to the patient visit, whereas the percentages of patients who experienced cognitive impairment, apathy, fatigue, urinary symptoms, and orthostatic hypotension increased significantly over that time (all $P < 0.001$; Supplementary Fig. S2). The total NMSS score, or any domain scores, were not significantly different between treatment groups, and no significant differences between treatment groups were observed in UPDRS total score, PDSS-2 total score, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale total score, and PDQ-8 summary index scores (Table 2).

Predictors of Combined LCIG Monotherapy

Significant predictors of LCIG monotherapy use at 12 months after initiation were treatment with DA before LCIG initiation versus no prior DA treatment (odds ratio [OR], 1.743 [95% CI, 1.094, 2.777]; $P = 0.0194$), patient visits to their physician ≥3 versus <3 times/year while receiving DAT (OR, 2.297 [95% CI, 1.178, 4.478]; $P = 0.0146$), and approximate number of patients with APD treated with LCIG annually by the physician (OR, 1.019 [95% CI, 1.000, 1.038]; $P = 0.0489$; Supplementary Table S5). Other variables that predicted use of LCIG monotherapy were lower number of motor symptoms (OR, 0.828 [95% CI, 0.714, 0.960]; $P = 0.0125$), and lower gross national income of the treatment site location (OR, 0.976 [95% CI, 0.958, 0.994]; $P = 0.0101$).

Safety

A total of 274 AEs likely related to study treatment occurred in 112 patients (27.4%) from LCIG initiation to the patient visit. The most common AEs reported were stoma site infection (n = 11; 2.7%), dyskinesia (n = 9; 2.2%), and device malfunction (n = 8; 2.0%). Neuropathies occurred in 6 patients (1.5%): polyneuropathy in 4 patients (1.0%), and 1 patient (0.2%) each was reported with demyelinating polyneuropathy and peripheral neuropathy. A decrease in vitamin B6 was reported for 1 patient (0.2%) and decreased weight for 5 patients (1.2%).

Discussion

In this observational study, the percentages of patients with APD treated with LCIG monotherapy (either with no add-on medications or with add-on medications outside LCIG infusion hours) increased between treatment initiation and month 3 and remained relatively stable through month 12. LCIG with add-on medications (LCIG polytherapy) was the most frequently used treatment regimen, although the frequency of prescribing add-on medications decreased considerably between LCIG initiation and month 3, after which usage remained stable. Titration of LCIG was achieved most rapidly in the LCIG monotherapy group, potentially because most were able to discontinue DA, MAO-B, and COMT inhibitor therapy quickly (within 3 months of LCIG therapy, without increase after 3 months of LCIG therapy), possibly because part of the titration was performed during the naso-jejunal test phase. Moreover, during the 12-month observation period, COMT inhibitor use decreased within all LCIG treatment groups. All groups demonstrated a significant improvement in off time and dyskinesia, and we did not observe any clinically significant differences between groups in symptomatic outcomes, as rates of off time and dyskinesia decreased by month 12 compared with LCIG initiation in all treatment groups. Use of LCIG monotherapy was predicted by previous DA usage, more frequent physician visits (≥3 times in a year), and number of motor symptoms, suggesting advancing disease may predict use of LCIG monotherapy; this supports the notion that DAs are less tolerated in patients who need more frequent evaluations. Most physicians preferred to prescribe LCIG monotherapy to simplify the medication regimen after a DAT was implemented and to reduce the pill burden.

This primary analysis of the COSMOS study represents the first investigation dedicated to add-on PD medication use and monotherapy before and during LCIG therapy. Our findings are supported by results of a post hoc analysis from the multinational GLORIA registry study that monitored LCIG therapy over 24 months in patients with APD. In that study, between 36% and 40% of patients were treated with LCIG monotherapy at all time points, and at the end of 24 months, 23% of patients (n = 59) had used LCIG monotherapy exclusively over the full observation period.[16] In the GLORIA study, the proportion of patients who used oral levodopa, DAs, COMT inhibitors, MAO-B inhibitors, and the *N*-methyl-*D*-aspartate receptor antagonist amantadine decreased during LCIG therapy compared with baseline.[15] Other results that support our findings include those from a 12-month, phase 3, single-arm trial, where percentages of patients using add-on DA decreased from 55.4%–12.7%, COMT inhibitors from 28.2%–3.7%, MAO-B inhibitors from 12.7%–1.5%, and amantadine from 29.9%–9.6%; whereas the 26.6% of patients who were taking monotherapy at baseline increased to 76.5%, this increased use included those patients who received LCIG with or without oral supplementation.[11] However, it is notable that patients enrolled in that study were required to stop all non-LCIG PD medications for the first 4 weeks of LCIG treatment, which does not occur in clinical practice, suggesting rates of add-on medication use in the COSMOS and GLORIA studies more closely

represent real-world clinical treatment than medication dosing in a phase 3 clinical trial. Both the COSMOS and GLORIA studies presented favorable data on symptomatic outcomes, supporting the feasibility of using long-term LCIG monotherapy in selected patients.[16]

Poor treatment adherence is a pervasive issue among patients treated for PD, for whom up to 67% take <80% of their prescribed medications.[7] Lack of medication adherence often increases over time for several likely reasons. First, patients with PD are susceptible to high pill burden. In addition to standard dopaminergic medications that may be needed up to 10 times per day, more than half of patients have multiple prescriptions for nonmotor symptoms and comorbidities.[7] Unfortunately, neurodegenerative processes that create the need for higher quantities and more frequent medications underlie progressive cognitive deficits that render the patient less capable of managing increasingly complex regimens. Further, patients with advancing PD can experience problems such as difficulty swallowing and irregular gastric emptying that negatively affect the ingestion and absorption of oral medications.[5,21] Poor treatment adherence in PD may negatively impact patients both in terms of motor and nonmotor complications, and in HRQoL.[22] Overall, in patients with PD, the fewer medications prescribed, the better the treatment adherence.[23]

A few studies have been performed to investigate the need for add-on medications with DATs. Results from investigations of CSAI revealed that, although use of this treatment approach could significantly reduce the need for oral levodopa, most patients continue to require oral levodopa to achieve a full clinical effect.[24,25] Similar findings were observed in studies on DBS, which can significantly reduce oral anti-PD medications for improving motor function, yet evidence is lacking to support DBS as long-term monotherapy.[26,27] In our study, even though nearly one-third of patients were taking LCIG monotherapy at 12 months of LCIG treatment, no clinically significant differences in symptomatic outcomes (off time and dyskinesia) were apparent between groups receiving LCIG monotherapy and groups that used LCIG and add-on medications. These data suggest LCIG monotherapy was as effective as LCIG plus add-on medication in controlling symptoms, which could not be explained by any remarkable differences in demographic or PD history between groups. Therefore, when possible, LCIG monotherapy is a valid solution for many patients with APD to achieve similar symptom control as when using add-on medications, while reducing PD-related pill burden.

A major strength of this study was use of real-world, multinational, large-cohort clinical data on LCIG monotherapy and add-on PD medication use. The study was limited by partially retrospective data collection and purely observational data, which resulted in missing data for some analyses. Further, patients were grouped by their status at month 12, so lack of randomization precluded meaningful comparisons between groups. Choice of medication regimen may have correlated with disease severity, although no major differences in disease characteristics between groups were apparent. We noted in our study that patients with more severe disease tended to remain on polytherapy. Further detailed analysis may be required to clarify this observation. Finally, our study only included patients treated with ongoing LCIG and able to sustain LCIG treatment for at least 12 months; therefore, results are not representative of all patients who initiate LCIG. This requirement, in addition to limiting AEs to those related to LCIG treatment, likely contributed to the low frequency of AEs in this study versus the rates of AEs in phase 3 studies.[28]

Conclusion

The data from this observational, real-world study in patients with APD provided evidence that LCIG monotherapy is a feasible and effective long-term treatment option for symptoms of APD. Patients who reduced their pill intake by receiving LCIG as monotherapy experienced similar clinical benefits as patients who continued to take add-on medications. Yet patients with preserved combination therapy also experienced considerable reductions in comedication use. The safety results were consistent with the known profile of LCIG. These results reveal LCIG monotherapy is an effective means to manage symptoms while reducing pill burden. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.