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Levodopa/carbidopa intestinal gel can improve both motor and non-motor experiences of daily living in Parkinson's disease: An open-label study

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ABSTRACT

Background: Levodopa/carbidopa intestinal gel therapy (LCIG) can efficiently improve several motor and non-motor symptoms of advanced Parkinson's disease (PD). The recently developed Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) improved the original UPDRS making it a more robust tool to evaluate therapeutic changes. However, previous studies have not used the MDS-UPDRS and the Unified Dyskinesia Rating Scale (UDysRS) to assess the efficacy of LCIG.
Objectives: Our aim was to determine if the MDS-UPDRS and UDysRS could detect improvement in the experiences of daily living following 1-year LCIG treatment.
Methods: In this prospective, multicenter, open-label study, 34 consecutive patients undergoing LCIG treatment were enrolled. Patients were examined twice: prior to LCIG initiation and 12 months later. Impact of PD-related symptoms and dyskinesia was assessed by the MDS-UPDRS and UDysRS.
Results: Non-motor Experiences of Daily Living part of MDS-UPDRS improved from 20 (median, interquartile-range, IQR:14–23) to 16 points (median, IQR:12–20, $p = 0.044$) and the Motor Experiences of Daily Living ameliorated from 24 (median, IQR:20–29) to 18 points (median, IQR:13–25, $p = 0.025$). Health-related quality of life, measured by PDQ-39, also improved from 35.4 (median, IQR:26.9–50.3) to 27.0 (median, IQR:21.3–31.4) points ($p = 0.003$). The total score of UDysRS decreased from 47 (median, IQR:36–54) to 34 (median, IQR:21–45) points ($p = 0.003$).
Conclusions: As far as the authors are aware of, our paper is the first to evaluate the impact of LCIG on dyskinesia by the means of UDysRS. Changes in MDS-UPDRS and UDysRS confirm that LCIG treatment can efficiently improve experiences of daily living in advanced PD.

Abbreviations: AE, Adverse event; DDS, Dopamine dysregulation syndrome; ESS, Epworth Sleepiness Scale; HRQoL, Health-related Quality of Life; HYS, Hoehn-Yahr Stage; ICD, impulse control disorders; IQR, interquartile range; LCIG, levodopa/carbidopa intestinal gel; LED, levodopa-equivalent dosage; MADRS, Montgomery-Asberg Depression Rating Scale; MC, Motor Complications (Part IV of MDS-UPDRS); MDS-UPDRS, The Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; ME, Motor Examination (Part III of MDS-UPDRS); M-EDL, Motor Experiences of Daily Living (Part II of MDS-UPDRS); MoCA, Montreal Cognitive Assessment; nM-EDL, Non-motor Experiences of Daily Living (Part I of MDS-UPDRS); NMSS, Non-motor Symptoms Scale; PD, Parkinson's disease; PDSS-2, Parkinson's Disease Sleep Scale 2nd version; PEG-J, percutaneous endoscopic gastrostomy tube with jejunal extension; PGI-S, Patient's Global Impression -Severity; SD, standard deviation; UDysRS, Unified Dyskinesia Rating Scale.

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1. Introduction

Although in the early stages of Parkinson's disease (PD) most motor and non-motor symptoms can be well controlled by dopaminergic therapy (honey-moon phase), motor complications eventually develop in conjunction with disease progression. Despite optimal pharmacological treatment, the control of motor and non-motor fluctuations is often challenging. In this advanced stage of PD, only functional neuromodulation and pump therapies can provide dramatic and long-lasting improvement in both PD-related symptoms and the health-related quality of life (HRQoL).

Levodopa/carbidopa intestinal gel (LCIG) therapy provides continuous enteral infusion of water-soluble formulation of levodopa into the site of absorption via percutaneous endoscopic gastrostomy tube with jejunal extension (PEG-J). Since the approval of LCIG treatment in the European Union in 2004, extensive amounts of information regarding its efficacy and safety have been collected. However, so far there is only a recent controlled study [1], and the long-term information is still sparse and incomplete [2–4].

Although all available long-term studies clearly demonstrated dramatic improvement in HRQoL, they provided conflicting data on the efficacy of LCIG on the experiences of daily living. Whereas some studies demonstrated that the motor aspects of daily living (Unified Parkinson's Disease Rating Scale Part 2 score, UPDRS-2) improved compared to baseline [4–7], others did not reveal any changes [8,9] at all, or did not analyze and report this information separately [2,10,11]. Meanwhile, some studies demonstrated worsening in UPDRS-2 compared to baseline [12]. We can partly explain these incongruent findings by some methodological issues. All of the previously mentioned studies utilized the UPDRS and consequently the UPDRS-2 to assess changes in the motor experiences of daily living. Recently the Movement Disorders Society Task Force identified several weaknesses of UPDRS on its ability to capture PD-related symptoms and their consequences; and subsequently published a revised and more reliable version called Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [13]. The MDS-UPDRS [13] is a clinimetrically validated scale to assess non-motor aspects of experiences of daily living (Part I, nM-EDL), motor aspects of experiences of daily living (Part II, M-EDL), motor examination (part III, ME) and motor complications (Part IV, MC). Although the MDS-UPDRS was published in 2008, none of the larger studies has utilized it to assess the efficacy of LCIG so far.

Additionally, all major LCIG studies demonstrated a dramatic improvement in fluctuations and dyskinesia by the increase in ON time without dyskinesia and the decrease in OFF time [7,8,11,14,15]. However, they assessed only patient diaries and the motor complication part of UPDRS (UPDRS-4) to detect these changes. Because these instruments are only capable of detecting the temporal characteristics of dyskinesia, they cannot provide information concerning the disability and the direct impact of dyskinesia on daily living. Recently the Unified Dyskinesia Rating Scale (UDysRS) was developed to reliably measure all aspects of dyskinesia [16]. UDysRS has four parts evaluating the presence and impact of ON- and OFF-dyskinesia on patients' experiences of daily living (UDysRS-1 and UDysRS-2, respectively), and the intensity and disability of dyskinesia (UDysRS-3 and UDysRS-4, respectively). Therefore, the UDysRS is suitable for simultaneously detecting the severity of dyskinesia ('Objective' parts, UDysRS-3 and UDysRS-4) and their influence on daily living ('Historical' parts, UDysRS-1 and UDysRS-2). Moreover, a recent study demonstrated that UDysRS has better sensitivity to detect changes in dyskinesia and consequently in therapy response compared to other rating scales [17]. Despite its advantages over UPDRS-4, none of the LCIG-related studies applied the UDysRS for detecting changes in dyskinesia.

The Hungarian DUODOPA Registry (LCIG01), established originally by the University of Pécs independently from the industry, now includes all the Hungarian Movement Disorder Centers performing LCIG treatment (Departments of Neurology at the University of Pécs, Pécs; the Semmelweis University, Budapest; the University of Szeged, Szeged, and the Borsod-Abaúj-Zemplén County Hospital, Miskolc). The aim of this multicenter registry is to evaluate the efficacy and safety profile of LCIG treatment in Hungary simultaneously serving both clinical and research purposes. This registry was approved by the National Ethics Board and the National Institute of Pharmacy (OGYI/47439-6/2013).

Based on the Hungarian DUODOPA Registry, we intended to evaluate how the LCIG can improve dyskinesia and the experiences of daily living in advanced PD following 1-year treatment by the means of MDS-UPDRS and UDysRS.

2. Materials and methods

2.1. Patients

In this prospective, open-label and multicenter study, 34 consecutive patients receiving LCIG treatment and participating in the Hungarian DUODOPA Registry were enrolled. All patients fulfilled the UK Brain Bank criteria for PD. Each subject gave written informed consent in accordance with the ethics approval. Following the Hungarian guidelines for advanced PD, the indication for the LCIG treatment was the severe motor fluctuations despite of optimal oral antiparkinsonian therapy in all cases [18]. Since in Hungary only deep brain stimulation and LCIG are available, we could offer only these two options. The selection of the recommended advanced therapy was based on the results of the preoperative evaluation, the patients' preference and the financial availability. The option of deep brain stimulation was either medically contraindicated ($n = 30$) or refused by the patients ($n = 4$).

2.2. Rating scales utilized in the study

Patients were examined twice: prior to the LCIG treatment initiation (baseline) and 12 months later (follow-up). Severity of PD symptoms was globally assessed by the Hungarian validated version of the MDS-UPDRS [19]. Included in the MC part, MDS-UPDRS has two items evaluating the time spent with dyskinesia (excluding OFF-state dystonia, item 4.1) and time spent in OFF state (item 4.3). Each item can have a value between 0 (none) to 4 (>75% of a waking day). As a part of the MDS-UPDRS, the Hoehn-Yahr Scale was also taken to detect the overall severity of PD.

To assess the severity and impact of dyskinesia, the Hungarian validated version [20] of Unified Dyskinesia Rating Scale (UDysRS) [16] was also taken. Besides, patient diaries were also obtained to calculate the average ON time without dyskinesia, ON time with slight dyskinesia, ON time with severe dyskinesia, OFF time and time spent with daytime sleep based on three consecutive days. Subsequently, 'good time' was also determined as the sum of ON time without dyskinesia and ON time with slight dyskinesia as described elsewhere [21].

We also applied the Patient's Global Impression– Severity scale (PGI-S) to evaluate the overall illness severity on a 7-item Likert-type scale: 1: normal, not at all ill; 2: borderline ill; 3: mildly ill;

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4: moderately ill; 5: markedly ill; 6: severely ill; or 7: extremely ill. Subsequently, the portion of patients reporting severe disease state (i.e., a PGI-S score > 4) was calculated.

To assess non-motor symptoms globally, the Non-Motor Symptoms Scale (NMSS) was also included. This scale is obtained by trained professionals and capable of simultaneously capturing the severity and frequency of nine non-motor domains typical for PD (sleep, cardiovascular, cognitive, mood, hallucinatory, gastrointestinal, urinary and sexual symptoms, and miscellaneous problems).

Presence and severity of sleep disturbances were specifically measured by the Parkinson's Disease Sleep Scale 2nd version (PDSS-2). The threshold indicating clinically relevant sleep problems is 11 points for the Hungarian validated version of PDSS-2 [22]. Meantime, daytime sleepiness was assessed by the Epworth Sleepiness Scale with the cutoff value of 8 points [22].

As part of the neuropsychological domain, depression (Hungarian validated version of Montgomery Depression Scale) and cognitive performance (Hungarian validated versions of Montreal Cognitive Assessment, MoCA [23] and Mini-Mental Status Examination, MMSE [24]) were also examined. HRQoL was measured simultaneously by the Hungarian validated version of PDQ-39 and EQ-5D [21]. Patients were evaluated in ON state while receiving their usual antiparkinsonian and other medications.

Treatment responsiveness was also ascertained by the threshold of minimal clinically important difference (MCID) threshold values. MCID is the smallest change of scores that are clinically meaningful to patients and clinicians. Therefore, any therapeutic changes not exceeding the MCID threshold value may be judged as clinically irrelevant. Based on the established values, improvements higher than 2 points on MADRS [25], 3.44 points on PDSS-2 [26] or 3.25 points on the MDS-UPDRS ME part [27] were considered clinically meaningful.

2.3. Statistical analysis

For statistical analyses the IBM SPSS software package (version 23.0.1, IBM Inc., Armonk, NY, USA) was utilized. Since data from the obtained scales were ordinal and did not follow the normal distribution, non-parametric tests were performed. We calculated medians with interquartile range (IQR: 25th-75th percentile) for the description of the data. Wilcoxon signed rank test was applied for the comparison of baseline and follow-up values. For dichotomous variables, (e.g., presence or absence of sleep-problems, usage of levodopa, etc.) a McNemar test, and for categorical variables Chi-square tests were used. Following the recommendations of Rothman [28], in our open-label study we did not perform post-hoc corrections. To allow better interpretation of the data, we calculated effect-sizes using the following formula suitable for nonparametric groups:

$$\text{Effect} - \text{size} = \frac{Z}{\sqrt{N}}$$

where Z is the Z statistic produced by the Wilcoxon tests and N is the size of the study. These effect-size values can be compared to proposed thresholds of 0.1, 0.3 and 0.5 for small, medium and large magnitudes of change, respectively [29]. Statistical significance level was set at 5%.

3. Results

3.1. Demographic and PD-related clinical data

The study population consisted of 34 PD patients (19 males, mean age: 67 ± 6 years, disease duration: 12 ± 5 years). Nineteen patients had rigid-akinetic and 15 had mixed-type of PD. The disease-specific characteristics of the enrolled patients and their baseline medication are summarized in Table 1.

At follow-up, the average levodopa dosage was 1222.4 ± 667.0 mg. Out of the 34 patients, 3 received 24-h LCIG treatment, while the rest was on 16-h daytime treatment only. Whereas 27 patients were on LCIG monotherapy, 3 patients received water-soluble levodopa formulation in the morning in order to be capable of assembling and initiating the Duodopa® system. The indication for low dosage dopamine-agonist treatment (4–6 mg ropinirole in 2 cases, 1.05 mg pramipexole in 1 case and 4 mg rotigotine in 1 case) was the better control of non-motor symptoms, especially mood- and sleep-related problems. Besides, 5 patients received typically 100–200 mg levodopa/carbidopa/entacapone tablets at bedtime for optimal nighttime control.

3.2. Severity of PD

With the prominent exception of the ME, most parts of the MDS-UPDRS (nM-EDL, M-EDL and MC) demonstrated significant improvement representing large effect-sizes (0.51–0.77). Changes in the ME part were neither clinically meaningful in magnitude nor statistically significant (Table 2). Although the HYS showed some improvement, it did not reach the level of statistical significance ($p = 0.095$). Based on PGI-S, significantly less patients reported severe disease state (a PGI-S score > 4) at follow-up compared to the baseline (11 vs. 20, $p = 0.049$, McNemar test).

Although the severity of dyskinesia demonstrated only tendentious changes (UDysRS Part 3, from 10 to 8 points, medians, $p = 0.063$), it had a medium effect-size (0.47). The disability associated with dyskinesia (Part 4) and the impact of both ON and OFF dyskinesia on daily living (Parts 1&2, respectively) improved significantly to a large extent (effect-size: 0.67–0.69, Table 2). The analysis of the patient diaries revealed that the median OFF time significantly decreased from 5.0 (IQR: 4.0–9.0) to 0.5 h (IQR: 0.0–1.8, $p = 0.001$) while the 'good time' (the sum of ON without dyskinesia and ON with slight, non-disturbing dyskinesia) increased from 8.0 (IQR: 6.0–10.5) to 14.8 h (IQR: 13.0–15.5, $p = 0.001$, effect-size = 0.87, Table 2).

3.3. HRQoL

HRQoL also improved from 35.4 (IQR: 26.9–50.3) to 27.0 (IQR: 21.3–31.4) points ($p = 0.003$, effect-size = 0.75) measured by the PDQ-39 Summary Index. Meanwhile, the EQ-5D index value increased from 0.518 (IQR: 0.393–0.604) to 0.629 (IQR: 0.543–0.691, $p = 0.043$, effect-size = 0.52), also advocating a better HRQoL status.

3.4. Non-motor symptoms

Although only the cardiovascular and mood sections showed significant changes at follow-up (effect-sizes: 0.56–0.60), the total score of NMSS also significantly improved ($p = 0.027$, effect-size: 0.56, Table 2). At baseline, 15 patients reported sleep problems (i.e., a total score of PDSS-2 ≥11 points), but 1 year after the LCIG initiation only 7 did ($p = 0.021$, McNemar test). Simultaneously, the total score of PDSS-2 decreased from 25 (IQR: 19–34) to 20 (IQR: 14–29) points ($P = 0.042$, effect-size = 0.34). Since the magnitude of this improvement exceeded the MCID threshold, the observed change in sleep quality was clinically meaningful.

Before LCIG, 19 patients reported daytime sleepiness (i.e., total score of ESS ≥8 points), which decreased to 12 patients at follow-up ($p = 0.289$, McNemar test). Meanwhile, neither the ESS nor the

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Table 1
Descriptive data of the study population at baseline.

		Mean or count	SD or percentage	Median	Percentile 25	Percentile 75
Age (years)		67	6	69	63	72
Disease duration (years)		12	5	12	9	15
Levodopa treatment (years)		10	6	9	6	12
Duration of fluctuations (years)		4	3	4	2	6
Education (years)		14	3	15	11	16
Sex	Male	19	55.9%			
	Female	15	44.1%			
Disease subtype	Rigid-akinetic	19	55.9%			
	Mixed	15	44.1%			
Handedness	Right	31	91.2%			
	Left	3	8.8%			
Hoehn-Yahr Scale	2	9	26.5%			
	3	18	52.9%			
	4	6	17.6%			
	5	1	2.9%			
Levodopa usage		34	100.0%			
Dopamine agonist usage		21	61.8%			
Monoamine-oxidase inhibitor usage		7	20.6%			
Catechol-*O*-methyl transferase inhibitor usage		26	76.5%			
Anticholinergic drugs usage		0	0.0%			
Levodopa LED (mg)		1000.2	577.6	940.0	700.0	1155.0
Dopamine agonist LED (mg)		256.3	264.3	240.0	0.0	400.0
Total medication LED (mg)		1376.5	604.5	1155.0	910.0	1515.0

Abbreviations: LED = levodopa-equivalent dosage; SD = standard deviation.

MoCA score showed any changes. Based on the MADRS, severity of depression improved from 19 (IQR: 14–23) to 15 (IQR: 12–19) points ($p = 0.047$, effect-size: 0.51), which can also be considered as clinically meaningful by comparing to the respective MCID value.

3.5. Side-effects

The observed LCIG therapy-related side-effects are summarized in Table 3. The majority of adverse events were either implantation- or PEG-J-related and occurred within the first 2 weeks after PEG-J tube implantation. None of the enrolled patients discontinued the treatment.

4. Discussion

The aim of the present study was to measure the effects of LCIG treatment on the patients' experiences of daily living. As far as the authors are aware, this is the first prospective multicenter study utilizing the recent MDS-UPDRS and UDysRS scales to assess longitudinal changes in the disability caused by the non-motor and motor symptoms of PD. Previous LCIG-related studies analyzed only patient diaries and UPDRS-4 to measure changes in dyskinesia, which could give mainly time- and severity-related data, but did not provide information on the topical distribution of dyskinesia and their impact on daily functioning [16,17]. Since the UDysRS has distinct sections, we could independently analyze how the LCIG treatment improved the severity and disability of dyskinesia and their impact on the experiences of daily living [16].

A 1-year LCIG treatment considerably ameliorated both motor- and non-motor symptoms of advanced PD. Based on the analysis of MDS-UPDRS nM-EDL and M-EDL parts, we clearly demonstrated that LCIG improved the impact of PD-related symptoms on the experiences of daily living with large magnitude (effect-size). Seemingly, it may be surprising that the MDS-UPDRS ME did not change significantly from baseline. Since both baseline and follow-up MDS-UPDRS ME examinations were assessed in the ON state at optimal pharmacological therapy, the patients had comparable motor symptoms and consequently similar motor examination scores at these occasions.

As far as the authors are aware of, our paper is the first to evaluate the impact of LCIG on dyskinesia by the means of UDysRS (PubMed search, keywords UDysRS and LCIG, UDysRS and Duodopa, UDysRS and enteral levodopa, accessed on August 31, 2016). The disability associated with dyskinesia (UDysRS-4) and the impact of ON and OFF dyskinesia upon daily living (UDysRS-1 and UDysRS-2, respectively) markedly ameliorated. Although the objective severity of dyskinesia did not improve significantly (UDysRS-3), a p-value of 0.063 and an effect-size of 0.47 may suggest a statistical under-power behind this phenomenon. Meanwhile, the time spent with ON dyskinesia and OFF states (MDS-UPDRS items 4.1 and 4.3) also significantly decreased. Consequently, the 'good time' significantly and meaningfully increased. Probably all of these prominent changes contributed to the improvement in the HRQoL of our patients. Of note, the magnitude of improvement in both PDQ-39 and EQ-5D was in the range of the previously published studies [4,7].

Because many non-motor-symptoms are unrelated to dopamine, it may be a surprising finding that the mood, cardiovascular and sleep problems were also better controlled during LCIG treatment. We can assume that the stable levodopa blood concentration level and the OFF period reduction can yield improvement in various non-motor symptoms by the reduction of non-motor fluctuations. While in some patients the severity of mood problems are completely unrelated to the motor performance, in other subset of patients the severity of depression and/or anxiety worsen to a great extent during OFF periods and becomes mild or negligible during ON periods. In these cases LCIG can improve mood problems by eliminating or reducing the OFF periods. Similarly, LCIG can also improve orthostatic hypotension by eliminating high peak levodopa blood concentration levels). Improvement in sleep quality was also reported by other groups [30].

Similarly to a randomized trial on LCIG, most adverse events (AEs) occurred within the first two weeks after PEG-J tube implantation [1]. Moreover, the majority of these early side-effects were related to the surgical procedure (including pain or local injection site complications) and mild to moderate in severity

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Table 2
Comparison of clinical symptoms and their impact on experiences of daily living and health-related quality of life.

		Baseline					1-year follow-up					Statistics	
		Mean or count	SD	Median	Percentile 25	Percentile 75	Mean or count	SD	Median	Percentile 25	Percentile 75	p-value	Effect size
MDS-UPDRS	MDS-UPDRS nM-EDL	19.7	6.9	20	14	23	16.7	6.9	16	12	20	0.044	0.51
	MDS-UPDRS M-EDL	23.9	6.2	24	20	29	19.4	9.0	18	13	25	0.025	0.57
	MDS-UPDRS ME	42.5	16.0	45	29	57	45.3	16.4	42	35	53	0.354	0.24
	MDS-UPDRS MC	10.4	4.0	11	8	14	7.5	4.0	7	5	10	0.002	0.77
	item 4.1 Dyskinesia time	2.8	1.1	3	1	3	2.1	1.2	2	1	2	0.045*	0.32
	item 4.3 OFF time	1.9	0.9	2	1	3	1.2	0.8	1	1	2	0.002*	0.77
	MDS-UPDRS Total score	96.4	20.6	98	84	111	89.2	27.5	83	68	108	0.049	0.46
UDysRS	UDysRS Part1 ON dyskinesia	20.5	8.6	23	17	26	14.5	9.3	14	10	22	0.008	0.67
	UDysRS Part2 OFF dyskinesia	9.5	4.7	11	6	14	6.3	4.2	6	4	9	0.008	0.67
	UDysRS Part3 Impairment	9.9	5.2	10	8	12	6.9	5.2	8	0	12	0.063	0.47
	UDysRS Part4 Disability	6.0	3.1	6	4	9	3.8	3.0	4	0	6	0.007	0.69
	UDysRS Total Score	45.9	16.7	47	36	54	32.1	17.3	34	21	45	0.003	0.76
HRQoL	Schwab-England Scale	60.0	17.3	60	50	80	67.4	17.3	70	60	80	0.524	0.16
	EQ-5D index value	0.483	0.243	0.518	0.393	0.604	0.561	0.270	0.629	0.543	0.691	0.043	0.52
	EQ-5D Visual Analogue Scale	51.0	18.4	50	40	60	60.8	14.4	60	50	70	0.011	0.64
	PDQ-39 Mobility	55.7	27.5	56.3	33.8	77.5	45.0	25.6	40.0	25.0	67.5	0.027	0.56
	PDQ-39 Activities of Daily Living	47.1	21.3	50.0	29.2	64.6	35.1	24.4	29.2	16.7	41.7	0.003	0.76
	PDQ-39 Emotional well being	42.2	22.6	41.7	22.9	60.4	34.2	20.7	25.0	20.8	45.8	0.038	0.53
	PDQ-39 Stigma	42.6	29.3	40.7	12.5	62.5	24.2	23.2	18.8	6.2	31.2	0.000	0.94
	PDQ-39 Social support	14.8	15.4	8.3	8.3	25.0	10.6	12.4	8.3	0.0	16.7	0.434	0.20
	PDQ-39 Cognition	30.1	18.4	25.0	18.8	43.8	23.1	13.9	18.8	12.5	37.5	0.054	0.49
	PDQ-39 Communication	28.1	20.5	16.7	16.7	37.5	22.5	21.0	16.7	8.3	33.3	0.022	0.58
	PDQ-39 Bodily discomfort	47.4	20.9	41.7	29.2	70.9	42.2	23.3	41.7	25.0	58.3	0.163	0.35
	PDQ-39 Summary index	38.5	14.9	35.4	26.9	50.3	29.6	13.6	27.0	21.3	31.4	0.003	0.75
NMS	Montgomery-Asberg Depression Rating Scale	18.2	7.2	19	14	23	15.4	6.2	15	12	19	0.047	0.51
	PDSS-2	27.2	10.5	25	19	34	23.2	12.0	20	14	29	0.042	0.34
	Epworth Sleepiness Scale	9.1	4.8	8	6	14	8.1	4.6	7	4	11	0.225	0.31
	Lille Apathy Rating Scale	−19.0	10.0	−19	−29	−13	−20.4	7.4	−22	−26	−14	0.807	0.06
	NMSS Cardiovascular dysfunction subscore	5.4	3.2	5	4	8	3.8	5.3	2	0	4	0.018	0.60
	NMSS Sleep problems subscore	19.8	7.5	19	16	24	17.3	9.5	16	12	23	0.117	0.40
	NMSS Mood problems subscore	24.4	17.4	24	10	34	18.3	11.6	16	12	26	0.029	0.56
	NMSS Hallucinations subscore	3.3	5.7	1	0	3	2.1	3.7	0	0	2	0.453	0.19
	NMSS Memory problems subscore	7.3	6.2	6	2	12	6.1	6.5	4	0	10	0.056	0.49
	NMSS Gastrointestinal dysfunction subscore	8.4	7.1	6	4	13	6.5	7.8	4	0	14	0.151	0.36
	NMSS Urinary dysfunction subscore	10.9	6.6	11	8	15	10.7	7.8	8	4	16	0.885	0.04
	NMSS Sexual dysfunction subscore	2.8	4.8	0	0	4	1.5	4.8	0	0	0	0.092	0.43
	NMSS Miscellaneous subscore	6.6	5.7	6	2	10	5.7	6.6	2	0	10	0.446	0.19
	NMSS Total score	88.9	40.3	88	60	106	72.0	32.2	69	49	99	0.027	0.56
Patient diary	ON time without dyskinesia (hours)	4.9	2.8	4.0	3.5	6.0	10.0	4.6	10.8	8.3	13.8	0.011	0.65
	ON time with slight dyskinesia (Hours)	3.6	2.5	3.0	2.0	5.0	4.0	4.4	3.4	0.5	5.3	0.624	0.12
	ON time with severe dyskinesia (hours)	1.8	1.7	2.0	0.0	2.5	0.4	1.6	0.0	0.0	0.0	0.034	0.54
	OFF time (hours)	6.3	3.6	5.0	4.0	9.0	1.0	1.3	0.5	0.0	1.8	0.001	0.87
	Good time (hours)	8.5	3.2	8.0	6.0	10.5	14.0	2.8	14.8	13.0	15.5	0.001	0.87
	Daytime Sleep Time (Hours)	0.7	1.1	0.0	0.0	1.0	0.9	1.0	1.0	0.0	1.5	0.147	0.37
	Nighttime Sleep Time (Hours)	6.6	1.5	6.5	6.0	7.0	7.7	1.7	7.5	6.8	8.8	0.043	0.51
Neurocognitive	Mini-Mental Status Examination	26.7	2.3	27	26	28	26.4	2.0	27	25	27	0.566	0.15
	Montreal Cognitive Assessment	21.4	3.6	22	19	24	21.9	3.4	22	20	25	0.160	0.36

Uncorrected p-values are shown. Wilcoxon's test was applied with the exception of values marked with *, where Chi-square test was used.
Abbreviations: HRQoL = Health-related Quality of Life; MC = Motor Complications (Part IV of MDS-UPDRS); MDS-UPDRS = The Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; ME = Motor Examination (Part III of MDS-UPDRS); M-EDL = Motor Experiences of Daily Living (Part II of MDS-UPDRS); nM-EDL = Non-motor Experiences of Daily Living (Part I of MDS-UPDRS); NMSS= Non-motor Symptoms Scale; PD = Parkinson's disease; PDSS-2 = Parkinson's Disease Sleep Scale 2nd version; SD = standard deviation; UDysRS = Unified Dyskinesia Rating Scale.

(Table 3). The overall number of patients having at least one AE was approximately 88%, which is comparable to other studies having at least 1-year follow-up (77% [2], 92% [3] and 47% [4]). Despite of this high rate of AEs, the occurrence of severe AEs was much lower (20.6%) similarly to other studies (23%–32%) [2–4]. Although similar studies had a discontinuation rate of 4.2%–38.8% [1–4,8], none of our patients were withdrawn from either the study or the treatment due to AEs. In the first year, 4 patients required PEJ tube replacement (Table 3). Despite regular B12 vitamin blood level monitoring, we observed newly developed polyneuropathy in 2 patients (5.9%). Because we did not perform electroneurography, we are unable to exclude the possibility of having subclinical neuropathy at the time of LCIG treatment initiation. Although one may think that LCIG can prevent impulse control disorders (ICD), punding and dopamine dysregulation syndrome (DDS), we observed one elderly male patient with the history of punding and

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Table 3
Adverse effects associated with levodopa/carbidopa intestinal gel therapy.

AE category	Preferred term	Overall complications		Early postoperative complications (≤2weeks)		Late complications (>2weeks)	
		Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
	Patients with at least one AE	30	88.2%	28	82.4%	14	40.2%
	Patients with at least one serious AE	7	20.6%	5	14.7%	6	17.6%
	LCIG discontinuation	0	0.0%	0	0.0%	0	0.0%
Drug-related	Weight decreased	5	14.7%	0	0.0%	5	14.7%
	Hallucination/confusion	4	11.8%	1	2.9%	4	11.8%
	Symptomatic orthostatic hypotension	3	8.8%	1	2.9%	3	8.8%
	Polyneuropathy	2	5.9%	0	0.0%	2	5.9%
	Impulse control disorder	1	2.9%	0	0.0%	1	2.9%
	Dopamine dysregulation syndrome	1	2.9%	0	0.0%	1	2.9%
Surgery-related	Abdominal pain	24	70.6%	24	70.6%	4	11.8%
	Injection site infection (local)	5	14.7%	4	11.8%	1	2.9%
	Postoperative wound infection	3	8.8%	3	8.8%	0	0.0%
	Peritonitis	2	5.9%	2	5.9%	0	0.0%
Stoma-related	Stoma infection (unrelated to surgery)	3	8.8%	0	0.0%	3	8.8%
	Granuloma	8	23.5%	0	0.0%	8	23.5%
	Buried bumper syndrome	0	0.0%	0	0.0%	0	0.0%
Device-related	Intestinal tube occlusion	1	2.9%	0	0.0%	1	2.9%
	Intestinal tube dislocation	3	8.8%	0	0.0%	3	8.8%
	Intestinal tube kinking	1	2.9%	0	0.0%	1	2.9%
	Intestinal tube replacements	4	11.8%	0	0.0%	4	11.8%
	Intestinal perforation	0	0.0%	0	0.0%	0	0.0%
	Pump breakage/malfunction	1	2.9%	0	0.0%	1	2.9%

Side-effects are categorized based on their temporal relation to PEG-J tube implantation either as early (within 2 weeks after implantation) or late (>2 weeks after implantation). Since some patients experienced both early and late complications, the overall number of patients with complications does not necessarily equal with the sum of patients with early and late complications.
Abbreviation: AE = adverse event.

another young male with the history of DDS, whose behavioral problems recurred on LCIG therapy and required psychiatric and psychological treatment. In a recent Australian 1-year single center study, Chang et al. described that four out of their 15 patients (27%) developed ICD (pathological gambling or punding) or DDS despite negative screening at treatment initiation. Two out of these four patients had such prior known alterations before starting the pump treatment, but in the cases of other two individuals these problems developed newly [10].

5. Conclusions

LCIG not only can decrease fluctuations but can also improve the motor and non-motor experiences of daily living. This improvement can be consistently demonstrated by the UDysRS and the MDS-UPDRS. Furthermore, several non-motor symptoms and the HRQoL can also be ameliorated by LCIG therapy. Since our results suggest the MDS-UPDRS and UDysRS can reliably detect the PD-related changes following LCIG, we recommend that these recent scales should be utilized in future LCIG studies.

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Author roles

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

AJ 1, 2, 3
ZA 1B, 2C, 3B
PA 1B, 2C, 3B
JJ 1A, 2C, 3B
MK 1C, 2B, 3B
AM 1C, 2B, 3B
MH 1C, 2B, 3B
DT 1C, 2B, 3B
KK 1C, 2B, 3B
SK 1C, 2B, 3B
A Takáts 1C, 2B, 3B
A Tóth 1C, 2B, 3B
HN 1C, 2B, 3B
PK 1C, 2B, 3B
GD 1C, 2B, 3B
DL 1C, 2B, 3B
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