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# Adverse effects of levodopa/carbidopa intrajejunal gel treatment: A single-center long-term follow-up study

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**Objectives:** Levodopa/carbidopa intrajejunal gel (LCIG) is an effective therapeutic strategy to overcome levodopa-induced motor complications in advanced Parkinson's disease (PD). However, it requires invasive percutaneous endoscopic gastrojejunostomy (PEG-J) and may be associated with serious adverse effects (AE). In this study, we aimed to evaluate long-term AEs related to LCIG treatment in a large homogenous cohort of advanced PD patients.

**Methods:** One hundred three consecutive PD patients were regularly monitored for LCIG-related, PEG-J-related, and device-related AEs up to 14 years. Incidence of AEs was studied in time applying a time-to-event analysis and Cox proportional hazard model with age, disease duration, gender, and recurrent AE as covariates. Health-related quality of life (HRQoL) was estimated at each visit and compared to HRQoL before the LCIG treatment.

**Results:** Among 296 AEs noted, 48.8% were LCIG-related, 32.4% PEG-J-related, and 19.6% device-related. While most of the studied AEs steadily accumulated throughout the follow-up period, 24.3% of the patients (95% CI 10.1%–36.3%) experienced PEG-J-related AE already within the first days after the PEG-J insertion. Cox model revealed that older patients had higher probability of psychosis, PEG-J- and device-related AEs ($p < .05$, $p < .05$, and $p = .02$) and suggested increased recurrence risk in those with early PEG-J and device-related AEs. Despite relatively high incidence of AEs, HRQoL significantly increased in the follow-up period ($p < .0001$).

**Conclusion:** AEs related to LCIG treatment are common. Therefore, careful patient selection and monitoring throughout the treatment is recommended, especially in those with early side effects. Nevertheless, LCIG significantly improves HRQoL in advanced PD patients on a long term.

**KEYWORDS**
advanced Parkinson's disease, levodopa-carbidopa intestinal gel, percutaneous endoscopic gastrojejunostomy, adverse effects, health-related quality of life

## 1 | INTRODUCTION

More than 60 years after first animal studies and 50 years of its clinical use in Parkinson's disease (PD) patients, levodopa remains the most effective treatment for motor symptoms in PD.[1] While efficient for rigidity, bradykinesia and very often for tremor too, motor complications in form of fluctuations and dyskinesia appear with chronic intermittent levodopa therapy after a median honeymoon period of 5 years.[2] Both, motor fluctuations (ie wearing off, on–off phenomena, off-resistant periods) and levodopa-induced dyskinesia are related to PD progression as well as pharmacokinetic and pharmacodynamic characteristics of levodopa[3] and significantly deteriorate patients' health-related quality of life (HRQoL).[4]

To overcome these issues, constant striatal stimulation is needed in advanced PD and may nowadays be achieved by device-aided treatments: chronic infusion of dopamine agonist apomorphine administration by subcutaneous pump,[5] deep brain stimulation of subthalamic (STN) or internal globus palidus (GPi) nuclei[6] or continuous intrajejunal levodopa/carbidopa (LCIG) or levodopa/carbidopa/entacapone gel administration.[7–9] Each device-aided treatment has its (dis)advantages, and careful personalized selection should be made to balance benefits and potential risks and reach best outcome in individual PD patients.

Several studies have shown that LCIG is an efficient treatment of advanced PD with comparable efficiency to intermittent oral levodopa with significantly decreased off time and dyskinesia.[10–12] Moreover, LCIG also improves quality of life, sleep, and several other non-motor symptom.[10,11] However, while being an efficient therapeutic strategy for overcoming motor fluctuation, LCIG requires a percutaneous endoscopic transgastric jejunostomy (PEG-J) and is associated with several adverse effects (AE) experienced by majority (78%–95%) of patients.[12–15] Indeed, close monitoring of patients that undergo this treatment is needed. AEs have been extensively studied in double-blinded and open-label safety studies[12–14,16] early after LCIG initiation and are usually divided on those related to LCIG, PEG-J, or the device. However, little data are available on long-term AEs of LCIG treatment.

In the present study, we evaluated LCIG-related AEs in a large homogenous cohort of 103 consecutive advanced PD patients who were followed up to 14 years after LCIG introduction. A special attention was paid on the temporal evolution of various AEs. AEs were divided to LCIG, PEG-J, or the device-related ones. Beside AEs, we evaluated patients' HRQoL and compared patients' HRQoL just before LCIG treatment initiation and at their last clinical visit.

## 2 | METHODS

### 2.1 | Subjects

We assessed 103 consecutive advanced PD patients with mean age of 71.0 ± 7.3 years and PD duration 15.0 ± 6.1 years (Table 1). They started LCIG treatment at UMC Ljubljana between June 2007 and September 2020 and were followed until September 2021. The diagnosis of PD was made by an experienced movement disorder specialists following UK Brain Bank criteria.[17] Indications for LCIG introduction were levodopa-induced motor complications with fluctuations and/or dyskinesia despite optimal oral dopaminergic therapy. Severe cognitive decline, acute psychosis, lack of patient's caregiver, and unresponsiveness to levodopa were exclusion criteria for LCIG initiation.[18]

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

### 2.2 | Levodopa/carbidopa intrajejunal gel (LCIG) initiation

For the LCIG introduction, patients were hospitalized and LCIG administered for 2 days via nasojejunal tube. In case of the beneficial effect and patients' satisfaction, PEG-J was inserted and continuous LCIG therapy continued. In all cases, the procedure was performed by two gastroenterologists experienced in gastroscopic procedures. Patients were mildly premedicated with benzodiazepine (midazolam 3 mg i.v.), and intravenous antibiotic prophylaxis (cefazolin 2 g i.v) was applied one hour before the procedure. The procedure was performed in local anesthesia by the standard endoscopic "pull" approach (procedure is described in detail in reference [19]). Latex or polyurethane (since 2015) PEG-J system with internal fixation plate (AbbVie Inc.) was used. Patients were normally discharged within 7–10 days after PEG-J placement, when an optimal dosage was adjusted and patients and caregivers learned to safely operate the device.

### 2.3 | Follow-up visits

Patients were routinely followed up by movement disorder specialist in the outpatient clinic 1 month after the PEG-J insertion and then every 6 months, or more regularly if needed. In the meantime, they were able to consult PD nurse and/or movement disorder specialist regarding any problems potentially associated with LCIG therapy.

Neurological and general examination was performed at every visit as well as monitoring for potential AEs. From 2014, serum levels of vitamin B12, homocysteine, and folate were routinely determined once a year as well as nerve conduction studies (NCS) for polyneuropathy

**TABLE 1** Patients' characteristics

| Number of patients | 103 |
|---|---|
| Gender (men/women) | 61/42 |
| Age at treatment onset (years; mean ± SD) | 71.0 ± 7.3 |
| Disease duration at treatment onset (years; mean ± SD) | 15.0 ± 6.1 |
| Duration of treatment (years; mean ± SD) | 4.7 ± 3.4 |

*Note*: Mean value and standard deviation are presented.

screening. Earlier, patients had serum vitamins levels checked or NCS performed in case of clinical suspicion of polyneuropathy. Vitamin B was not routinely supplemented in these patients; however, in case of low vitamin B12 levels or high homocysteine, vitamin B12 substitution was introduced. Patients assessed their HRQoL before LVIG introduction and at every follow-up visit by visual analog scale (VAS) ranging from 0 (worst imaginable quality of life) to 10 (best quality of life).

The PEG-J system was routinely replaced every 2 years since 2014. Earlier, it was replaced only when needed.

LCIG treatment was discontinued in case of severe adverse effects, in case of switch to another device-aided treatment,[20] lack of caregiver, unrelated severe diseases that interfered with treatment also in case of reduced effectiveness of LCIG in very advanced disease stage. The decision to discontinue treatment was made by a multidisciplinary team and in agreement with patient and/or caregiver after a detailed in hospital evaluation of the patient and taking into consideration the efficiency of LCIG on multiple aspects of advanced PD with an emphasis on patient's and caregiver's quality of life.

### 2.4 | Monitored adverse effects

AE related to LCIG treatment were divided into three categories: (1) AE related to LCIG infusion: severe dyskinesia, polyneuropathy due vitamin B12 deficiency (defined as positive NCS result consistent with polyneuropathy and concomitantly reduced vitamin B12/elevated homocysteine levels in absence of other common causes of polyneuropathy such as diabetes), psychosis, weight loss, dopamine dysregulation syndrome, syncope, and frequent falls; (2) PEG-J/procedure-related AE: local skin/subcutaneous infections, pneumoperitoneum (defined as a significant presence of air in the peritoneal cavity observed on abdominal X-ray/CT ordered, which was not performed routinely but only in case of moderate or severe abdominal pain or discomfort), gastric ulcer due to inner tube gastric mucosa irritation, ileus, abscess, gastrocutaneous fistula, peritonitis, or buried bumper syndrome (BBS); and (3) device-related AE: dislocation, accidental removal, disconnection or knotting of the intestinal tube or PEG-J tube,[21] and malfunction or breakage of the device system.

Data on weight loss of over 5 kg were obtained based on patients' weighing at follow-up visit or patients' and caregivers' reports.

### 2.5 | Statistical analysis

The data on AEs were analyzed by standard descriptive statistical methods and time-to-event analysis. For each category of treatment-related AE, Kaplan–Meier curve was plotted, and Cox proportional hazards regression analysis was performed using gender, disease duration, and age at therapy initiation as a covariate. After the first AE in each category, the subject was omitted from further analysis in this category. However, multiple complications within the same category were noted and included in the Cox proportional hazards regression analysis as a covariate together with demographic and clinical data as explained above. Patients who discontinued LCIG treatment (for reasons unrelated to corresponding AE) and those who moved to other medical centers were censored from the day of last visit/report.

The change in HRQoL was studied in patients on LCIG treatment by comparison of VAS score reported before LCIG treatment initiation and at the last visit in 2021. VAS scores were compared by the paired *t* test.

All statistical analyses were performed using JMP software version 14 (SAS Institute Inc.) and GraphPad Prism version 8 (GraphPad Software). *p*-values below .05 (two-tailed) were considered significant.

## 3 | RESULTS

Out of 103 patients treated with LCIG, 44 (42.7%) discontinued therapy by the end of the follow-up period. All the patients were willing to proceed to PEG-J insertion after 2 days of LCIG therapy via nasojejunal tube. Of these, 22 (21.4%) died for reasons unrelated to LCIG treatment. The deceased patients were treated with LCIG for an average of 7.9 ± 3.8 years (mean ± SD). None of them died in the first 30 days after LCIG initiation. The remaining patients who discontinued treatment for other reasons were receiving therapy for an average of 3.6 ± 3.2 years. The reasons for discontinuation were psychosis (in 5/22, 22.7%), switch to DBS (in 5/22, 22.7%), reemergence of PD symptoms/ineffectiveness of LCIG (in 4/22, 18.2%), other severe diseases (in 2/22, 9.0%), severe device-related (in 3/22, 13.6%) or PEG-J-related AE (in 1/22, 4.5%), lack of caregiver (in 1/22, 4.5%), or severe polyneuropathy B12 (in 1/22, 4.5%).

The median follow-up time was 4.0 years (range 10 days–14.3 years, 25% percentile 2.3 years and 75% percentile 6.4 years). The follow-up time frequency distribution is presented in Figure S1.

Among 103 patients, there were a total of 296 AEs noted. Seventy-three patients (70.9%) reported more than one AE. Among 65 patients receiving LCIG for more than 3 years, only seven did not report any AEs. Among 29 patients treated for more than 6 years, there was only one such patient. On average, each patient experienced 2.9 ± 2.0 AEs. The most common were LCIG-related AE ($n = 142$, 48.0%), followed by PEG-J-related AE ($n = 96$, 32.4%) and device-related AE ($n = 58$, 19.6%).

### 3.1 | Levodopa/carbidopa intrajejunal gel-related adverse effects

In the LCIG-related AE group, the most common complaint was disabling dyskinesia, followed by psychosis, weight loss, syncope, polyneuropathy, and other rarer AEs (Table 2).

As observed from the Kaplan–Meier curves (Figure 1), disabling dyskinesia occurred in all patients by 11.1 years of LCIG treatment (considering censoring). The median time of disabling dyskinesia was 9.6 years (95% confidence interval [CI] 8.5–11.2 years,

Figure 1A). Cox proportional hazards regression models did not reveal significant effect of disease duration, age, or gender on dyskinesia (Table 3).

The probability of psychosis gradually progressed in a linear-like way with a median time of 11.9 years (95% CI lower value 7.7 years, upper not available; Figure 1B). As above, disease duration and gender did not affect this AE; however, age did. Older patients had higher probability for psychosis ($p = .03$) (Table 3).

Weight loss (>5 kg) was rare in the first year (4%) and steadily increased thereafter with the median time of reported weight loss at 9.6 years (95% CI 7.4–11.4) (Figure 1C). Disease duration, age, or gender did not have a significant effect on weight loss (Table 3).

Polyneuropathy related to B12 deficiency was rare in the first 3.5 years (6.2%, 95% CI 0.1%–32.0%). After that period, we noticed gradual constant increase. Median time of polyneuropathy occurrence was noted in 12.0 years (95% CI lower value 9.0, upper not available) (Figure 1D). While age and gender did not influence the occurrence of B12 deficiency-related polyneuropathy, there was a marginally significant effect of disease duration found. Namely, patients who started LCIG therapy earlier in their disease course were more likely to develop polyneuropathy B12 ($p < .05$) (Table 3).

### 3.2 | Percutaneous endoscopic gastrojejunostomy/procedure-related adverse effects

In the PEG-J/procedure-related AE group, the most common complication was local skin/subcutaneous infection followed by hypergranulation tissue. Less common AEs were abscess, peritonitis, pneumoperitoneum, gastrocutaneous fistula, decubitus ulcer, and ileus. One patient suffered from BBS. Recurrent PEG-J-related AEs were noted in 15 patients (14.6%). Surgical treatment of these adverse effects was required in four cases: in one case due to an abscess, in two cases due to peritonitis with ileus and in one due to buried bumper syndrome.

PEG-J/procedure-related AEs were frequent in the first 5 days after procedure while patients were still hospitalized. During this period, 24.3% (95% CI 10.1%–36.3%) of patients suffered PEG-J-related AE. After the initial increase in PEG-J-related AE, incidence gradually progressed with a plateau indicated between 6th and 9th year. Median time of PEG-J-related AE was 3.4 years (95% CI 2.1–5.6) (Figure 1E).

The Cox proportional hazards regression model revealed marginally higher risk of PEG-J-related AE in older patients ($p < .05$) (Table 3). Moreover, the occurrence of multiple PEG-J-related AEs

**TABLE 2** Incidence of adverse effects (AEs)

| | | No of patients (%) | No of events |
|---|---|---|---|
| LCIG-related | Severe dyskinesia | 33 (32.0%) | 42 |
| | Psychosis | 28 (27.2%) | 31 |
| | Weight loss | 28 (27.2%) | 28 |
| | Polyneuropathy B12 | 13 (12.6%) | 13 |
| | Syncope | 17 (16.5%) | 18 |
| | Dopamine dysregulation syndrome | 6 (5.8%) | 6 |
| | Orthostatic hypotension | 1 (1.0%) | 1 |
| | Severe and frequent falls | 3 (2.9%) | 3 |
| PEG-J/procedure related | Local infection | 51 (49.5%) | 63 |
| | Hypergranulation tissue | 13 (12.6%) | 14 |
| | Abscess | 6 (5.8%) | 6 |
| | Peritonitis | 4 (3.9%) | 4 |
| | Pneumoperitoneum | 2 (1.9%) | 2 |
| | Gastro-cutaneous fistula | 2 (1.9%) | 2 |
| | Decubitus ulcer | 2 (1.9%) | 2 |
| | Ileus | 2 (1.9%) | 2 |
| | Buried bumper syndrome | 1 (1.0%) | 1 |
| Device-related | Device failure | 21 (20.4%) | 23 |
| | PEG-J extraction | 13 (12.6%) | 14 |
| | Inner tube dislocation | 10 (9.7%) | 10 |
| | Inner tube knotting | 8 (7.8%) | 8 |
| | Connector breakage | 3 (2.9%) | 3 |

*Note*: Number (N) of patients experiencing an individual AE is given in the left column and the number of total events in the right (some events repeated in individual patients).

Abbreviations: LCIG, levodopa/carbidopa intestinal gel; PEG-J, percutaneous endoscopic transgastric jejunostomy; Polyneuropathy B12, polyneuropathy due vitamin B12 deficiency.

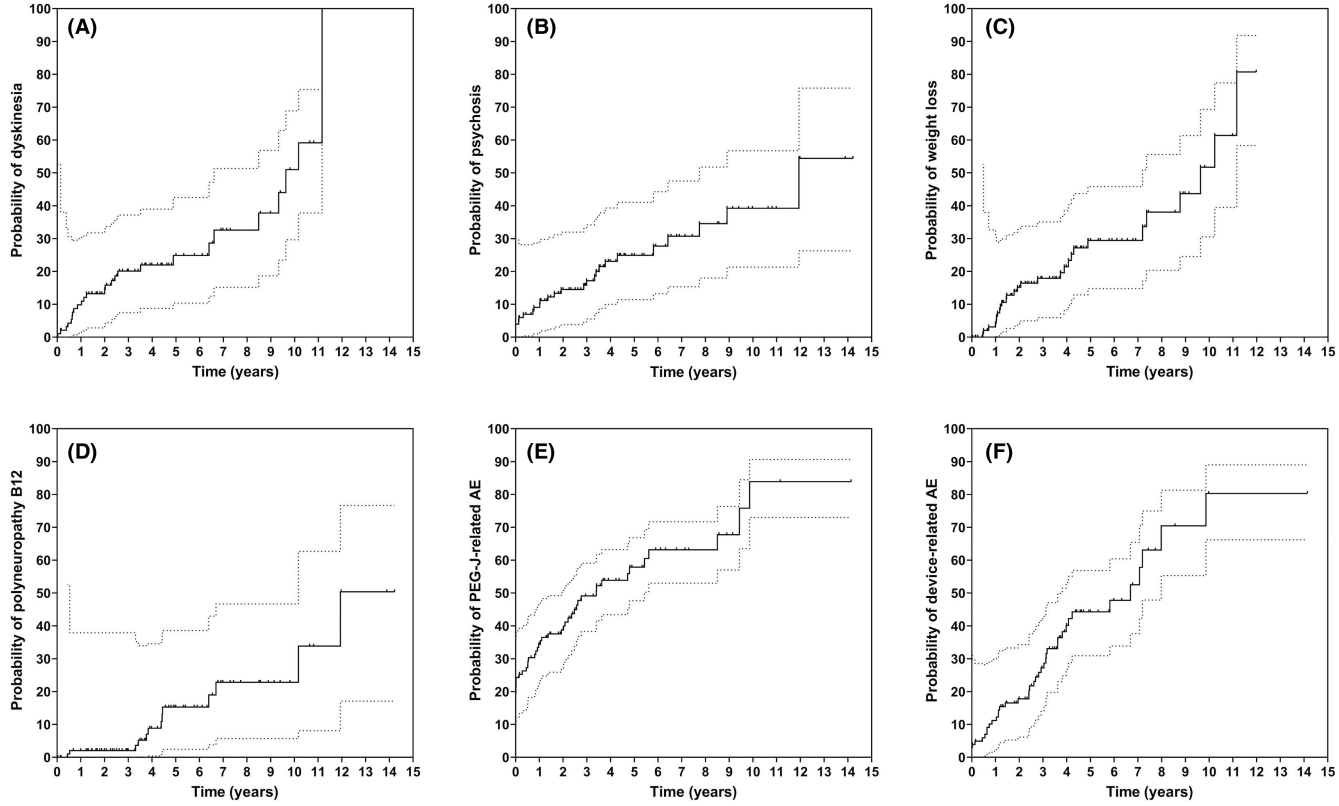


**FIGURE 1** Kaplan–Meier curves estimating time to adverse effects (AE). (A) dyskinesia, (B) psychosis, (C) weight loss, (D) polyneuropathy associated with vitamin B12 deficiency, (E) PEG-J-related AEs, (F) device-related AEs. Censored data are marked with ticks. 95% confidence intervals are indicated by dashed lines.

in a single patient was shown to be a highly significant covariate indicating an early complication in those who are prone to repeated events. Gender and disease duration were not found to significantly affect this AE's occurrence (Table 3).

### 3.3 | Device-related adverse effects

The most frequent complication in this AE group was device failure, followed by accidental PEG-J extraction, inner tube dislocation, inner tube knotting, and connector breakage. PEG-J system was replaced in all the extraction/knotting cases.

The probability of device-related AE progressed steadily throughout the monitoring with median time of 5.8 years (95% CI 3.6–7.2) (Figure 1F). As in PEG-J-related adverse effects, age and repeated events were found significant covariates for device-related AE (Table 3).

### 3.4 | Health-related quality of life

In patients treated with LCIG up to the end of the follow-up period ($n = 59$, treatment duration $5.3 \pm 3.2$ years), the initial pre-LCIG result was $2.9 \pm 1.7$ and increased to $7.6 \pm 1.9$ by the last visit ($p < .0001$, paired $t$ test).

## 4 | DISCUSSION

Substantial benefit of LCIG treatment in advanced PD has been shown in many previous studies.[10–12] However, given the specific characteristics of this approach (high daily levodopa dose, invasive intervention, and device dependence), various AEs may develop. Indeed, while prior studies mostly focused on early AEs up to 1–5 years after LCIG initiation,[14,16,22] the present analysis is, at our best knowledge, among the biggest single-center long-term follow-up studies investigating a follow-up period of LCIG treatment up to 14 years. Despite the high AE rate and the noteworthy proportion of patients who discontinued LCIG treatment, overall HRQoL was significantly improved in patients receiving LCIG therapy. This is all the more compelling as the second HRQoL assessment was made on average over 5 years after LCIG initiation when significant PD worsening could be expected given its progressive natural course.[23]

The incidence of selected AEs in this real-world long-term longitudinal observational study is largely comparable to prior results of randomized prospective double-blinded and open-label safety studies.[12–16] Indeed, as in previous research, the vast majority of patients experienced AEs, 70.9% of our patients even multiple AEs. Several AEs were more frequent in our cohort than shown before, which is most likely due to long follow-up period up to 14 years. Indeed, Kaplan–Meier curves (Figure 1) showed a gradual increase in the

TABLE 3 Hazard ratios with 95% confidence intervals and *p*-values in the Cox proportional hazards regression models for dyskinesia, psychosis, weight loss polyneuropathy caused by vitamin B12 deficiency (polyneuropathy B12), PEG-related complications and device-related complications as dependent variables and age, gender, disease duration, and repeated event as independent. Six independent models are presented

| Variable | Dyskinesia | Psychosis | Weight loss | Polyneuropathy B12 | PEG-related AE | Device-related AE |
|---|---|---|---|---|---|---|
| Age (years) | 1.00, $p = .90$ (0.95–1.06) | **1.06, $p = .03$ (1.00–1.13)** | 1.03, $p = .21$ (0.98–1.09) | 1.04, $p = .37$ (0.96–1.13) | **1.04, $p < .05$ (1.00–1.08)** | **1.06, $p = .02$ (1.01–1.12)** |
| Gender | | | | | | |
| Female | Reference | Reference | Reference | Reference | Reference | Reference |
| Male | 0.69, $p = .39$ (0.30–1.61) | 0.81, $p = .60$ (0.37–1.79) | 1.08, $p = .83$ (0.50–2.39) | 1.50, $p = .48$ (0.48–5.09) | 0.91 $p = .73$ (0.53–1.58) | 0.84, $p = .60$ (0.44–1.62) |
| Disease duration (months) | 1.05, $p = .10$ (0.99–1.12) | 0.96, $p = .22$ (0.89–1.02) | 0.95, $p = .14$ (0.89–1.02) | **0.89, $p < .05$ (0.78–1.00)** | 1.00, $p = .91$ (0.96–1.04) | 0.99, $p = .61$ (0.93–1.04) |
| Repeated event | | | | | **3.6, $p = .0003$ (1.9–6.8)** | **4.3, $p = .0006$ (1.9–9.7)** |

Abbreviations: Polyneuropathy B12, polyneuropathy due to vitamin B12 deficiency; AE, adverse effect.
Bold indicates significant of *p*-values.

likelihood of all the studied categories of AEs throughout the studied period.

High incidence of disturbing dyskinesia that according to the Kaplan–Meier curve evolved in virtually all cases (taken the broad 95% CI in consideration) is somewhat expected considering pathophysiology of progressive presynaptic dopaminergic dysfunction, decreased levodopa buffering capacity,[24] postsynaptic dopaminergic receptor alterations and changes in striatal plasticity.[25] Indeed, even with continuous levodopa administration, it may be difficult to reach the narrow therapeutic window between the "off" state and dyskinesia in very advanced disease.[4] Several situations impacting pharmacokinetics and pharmacodynamics of levodopa, such as systemic infections, may worsen the condition.[26] Prior studies have shown incidence of AEs being 4.3% in the first month[13] and 14% in 3 months[12] in comparison with only 1.0% and 3.1% in our cohort. However, only troublesome dyskinesia requiring LCID dose modification was considered in our study. While none of the demographic parameters significantly affected the occurrence of dyskinesia, a trend was noticed for the disease duration.

Psychosis together with hallucinations was frequently observed as well. Just after treatment initiation, about 7% experienced it. Careful observation in this period is needed to promptly recognize it and modify the LCIG dose. Significantly higher probability of psychosis was seen in older patients indicating that the older the patient, the more careful the LCIG titration should be in order to avoid this AE. On the contrary, weight loss was rare in the first year, but increased in the second and third year up to 17% which is comparable with 14%–30% reported in prior multicentric studies (mean time in those studies was 4.1–6.1 years).[15,16,27] However, our results should be considered with caution as caregivers/patients provided same of the data. Interestingly, gender, disease duration, and age did not affect weight loss.

The B12 deficiency-related polyneuropathy has been found a significant and potentially serious AE of LCIG treatment in many studies.[14,16,28] Accordingly, we found a marked increase in an incidence of this AE after the third year of treatment. A short disease duration at the beginning of LCIG treatment was shown to be a predisposition for B12-related polyneuropathy. This surprising finding may be explained by hypothesis that patients who require early LCIG treatment have more severe disease and therefore may require higher doses of LCIG resulting in more pronounced vitamin B12 deficiency.[28,29] Furthermore, higher alpha-synuclein load may be present in the peripheral nervous system in those cases, which may have further deleterious effect on the peripheral nervous system.[29]

Many prior studies addressed high frequency of device and PEG-J-related AEs.[12–16] These AEs were previously reported to be most frequent in the first 2 years after the procedure (35% of patients each year) and declined to 20% in the fifth year of treatment.[16]

PEG-J/procedure-related AEs were found to be the major challenge in the first days after procedure as almost a quarter of patients in our cohort experienced such an event, most commonly as a local skin/subcutaneous infection. Similar rates of equivalent

AEs were found in prior research.[12,14] After the initial period, PEG-J-related AEs were increasing steadily. In addition, further analysis using the multivariate Cox model showed that AE recurrence was a significant covariate of PEG-J-related AEs. Although this covariate may violate the assumption of independence to some degree, it may be interpreted that patients with the recurrence of PEG-J-related AE experience the first one earlier compared to those with a single event (Figure S2). Indirectly, this finding suggests that patients with early PEG-J-related AE are prone to multiple PEG-J-related AE, and they need a special attention. We hypothesize that the "proneness to multiple PEG-J-related AE" may be associated with factors such as caregiver's support, cognitive status, and skin/PEG management standards. However, further studies would be required to address this question. That said, another significant covariate was age ($p < .05$). The hazard rate increased by 4% with increasing age for each year. Patients that were older at the time of LCIG initiation were therefore more likely to suffer from PEG-J-related AE, which may be again related to factors discussed above.

Mild to moderate short-lasting pain was commonly observed in the skin and stomach early after PEG-J procedure as virtually all participants reported it. However, due to longitudinal design of the study, this short-lasting local pain was not measured and analyzed in this study.

Lastly, we studied AEs related to device. Pump failure was rather commonly reported (23 events in 103 patients) comparable to previous data (18%).[12] Together with the inner tube dislocation and PEG-J extraction, these AEs resulted in abrupt termination of LCIG delivery. Despite a simple and efficient measure of transient oral levodopa therapy following LCIG discontinuation, it may present a considerable stress for patients and/or caregivers based on our clinical experience and their reports. Probability of the device-related AE steadily grew over time. Again, more device-related AEs were found in older patients, and patients with early event were suggested to be at higher risk for a subsequent one.

Among limitations of this study, it is worth mentioning potential data loss during the long follow-up period, although we thoroughly searched our patients' records. Majority of our patients received additional oral antiparkinsonian therapy and the possible effect of these medications was not analyzed in this study. Furthermore, patients and caregivers may have not reported minor transient AEs. Another limitation was the subjectivity of HRQoL assessment.

In conclusion, despite being highly efficient in terms of symptom and motor complications reduction as well as HRQoL improvement, LCIG therapy is associated with high incidence of AEs. Careful patient selection and monitoring throughout the treatment is recommended, especially in older patients and those with early side effects.

## AUTHOR CONTRIBUTIONS

T.R. involved in research project conception, organization, and execution; statistical analysis design and execution, manuscript preparation. M.P. involved in research project conception, data collection, manuscript review, and critique. N.Z.K., M.G., R.R., L.O., and Z.P. involved in patient recruitment, data collection, manuscript review, and critique. M.T. involved in research project conception, organization, and execution; statistical analysis review and critique; manuscript review and critique.

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## CONFLICT OF INTEREST

M.T. has received personal compensation as a consultant or speaker from AbbVie, Stada, and Brittania. N. Z. K. and Z. P. received personal compensation as a speaker from AbbVie and Stada. L. O. and R. R. received personal compensation as a speaker from AbbVie. Other authors declare no conflicts of interest.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13675.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

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