

Long-Term PEG-J Tube Safety in Patients With Advanced Parkinson's Disease

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OBJECTIVES: The objectives of this study were to present procedure- and device-associated adverse events (AEs) identified with long-term drug delivery via percutaneous endoscopic gastrojejunostomy (PEG-J). Levodopa-carbidopa intestinal gel (LCIG, also known in US as carbidopa-levodopa enteral suspension, CLES) is continuously infused directly to the proximal small intestine via PEG-J in patients with advanced Parkinson's disease (PD) to overcome slow and erratic gastric emptying and treat motor fluctuations that are not adequately controlled by oral or other pharmacological therapy.

METHODS: An independent adjudication committee of three experienced (>25 years each) gastroenterologists reviewed gastrointestinal procedure- and device-associated AEs reported for PD patients (total $n = 395$) enrolled in phase 3 LCIG studies. The rate, clinical significance, and causality of the procedure/device events were determined.

RESULTS: The patient median exposure to PEG-J at the data cutoff was 480 days. Procedure- and device-associated serious AEs (SAEs) occurred in 67 (17%) patients. A total of 42% of SAEs occurred during the first 4 weeks following PEG-J placement. SAEs of major clinical significance with the highest procedural incidence were peritonitis (1.5%), pneumonia (1.5%), and abdominal pain (1.3%). The most common non-serious procedure- and device-associated AEs were abdominal pain (31%), post-operative wound infection (20%), and procedural pain (23%). In all, 17 (4.3%) patients discontinued treatment owing to an AE.

CONCLUSIONS: In conclusion, incidences of PEG-J AEs with the LCIG delivery system and PEG-J longevity were compared favorably with ranges described in the PEG/PEG-J literature. A low discontinuation rate in this study suggests acceptable procedural outcomes and AE rates in PD patients treated with this PEG-J drug delivery system.

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INTRODUCTION

The efficacy of oral medications can be affected by gastric emptying and intestinal absorption.^{1,2} Altered gastric emptying can lead to undesirable fluctuations in serum concentrations of oral medications; this is particularly important for illnesses that require a quick drug onset and for diseases that benefit from steady serum concentrations.^{1,2} One such example is that of levodopa, a mainstay of Parkinson's disease (PD) pharmacotherapy. Conventional oral levodopa formulations are absorbed mainly in the proximal small intestine where absorption is heavily influenced by gastric emptying.³ Oral levodopa treatment is associated with motor symptoms ("wearing off", "dyskinesias", and "on-off" fluctuations) in 40% of patients after 4 to 6 years of therapy and almost 90% of patients after 9 years.⁴ These motor symptoms are related to non-physiologic, pulsatile stimulation of striatal dopamine receptors produced by irregular gastric emptying and intestinal absorption, and the short half-life of levodopa.^{5,6}

A new method of drug delivery via the small bowel, continuous infusion of levodopa-carbidopa intestinal gel (LCIG (Duodopa); also known as carbidopa-levodopa enteral suspension in the United States, CLES (Duopa); AbbVie, North Chicago, IL) has been developed. The LCIG system provides continuous levodopa infusion directly into the proximal jejunum via percutaneous endoscopic gastrostomy (PEG) with jejunal extension tube (J-tube; PEG-J) connected to a portable infusion pump. LCIG delivery into the small intestine overcomes slow and erratic gastric emptying, producing more consistent levodopa plasma levels.⁷ Continuous infusion of LCIG reduces motor complications of PD by reducing the time when PD symptoms are not controlled (off time) by as much as 4 h when compared with the baseline, and by 1.9 h when compared with the oral levodopa ($P = 0.0015$), and increasing the time when PD symptoms are controlled (on time without dyskinesias).^{8,9} Treatment with LCIG via PEG-J is associated with improvements in quality of life in patients with

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advanced PD; on the Clinical Global Impression of Improvement scale, 78% of patients reported they were “very much improved” or “much improved” after 54 weeks of LCIG treatment.⁸

There is a paucity of data exploring long-term use and durability of PEG-J. Data available on this topic are often gleaned from studies involving immobile patient populations who are receiving enteral nutrition.^{10–12} The aim of this analysis was to review long-term gastrointestinal (GI) safety of PEG-J in mobile patient populations. An independent committee of expert gastroenterologists reviewed and adjudicated safety data from four separate phase 3 studies of LCIG. Although there have been recent reports from smaller studies on the long-term safety of levodopa infusion,^{13–16} this is the first report of LCIG procedure and device safety data that were collected in rigorous, prospective clinical trials and systematically evaluated by GI experts. Furthermore, this study provides the largest data set of patients receiving levodopa via PEG-J for the longest duration in a mobile patient population.

METHODS

Study design. The phase 3 program for LCIG consists of four prospective, multicenter studies in patients with advanced PD who continued to experience persistent motor fluctuations despite optimized treatment. These studies included: (1) a 12-week, randomized, double-blind, double-dummy, parallel-group study ($n=71$, NCT00357994/NCT00660387)⁹; (2) a 12-month open-label extension of the double-blind study ($n=62$, NCT00360568)¹⁷; (3) a separate 12-month, open-label study ($n=354$, 324 of whom had PEG-J placement, NCT00335153)⁸; and (4) an open-label, continuation-of-treatment study of both 12-month, open-label studies ($n=220$ at time of adjudication, NCT00660673). A total of 90 institutions in 16 countries enrolled patients in the program. Study protocols were approved by each participating institution's respective internal review board or ethics committee, and written informed consent was obtained from each patient before any procedure was performed.

The analyses presented herein include all patients from four phase 3 studies ($n=395$) who underwent a PEG-J placement with a data cutoff date of 4 May 2012. Major inclusion/exclusion criteria have been previously published.^{8,9} Eligible patients had severe motor fluctuations defined as ≥ 3 h of daily “off time” at baseline, and did not have any conditions that would preclude placement of PEG-J tubes. Data were combined to provide a complete overview of adverse events (AEs) related to the GI procedure or device.

LCIG delivery via PEG-J. LCIG is supplied as a homogenous suspension of levodopa (20 mg/ml) and carbidopa monohydrate (5 mg/ml) in an aqueous gel (sodium carboxymethylcellulose), which is administered continuously during the waking day (~16 h per day) through a portable infusion pump device (CADD-Legacy, Smiths Medical, Minneapolis, MN). The medication is delivered directly to the proximal

small intestine (the duodenum and/or jejunum) via PEG-J, which requires a GI procedure.

Insertion of the PEG and J-tubes in patients was performed by qualified, experienced gastroenterologists, surgeons, or interventional radiologists (J-tubes only). A diagram of the LCIG system is provided in Supplementary Figure S1 online. A training video was provided to standardize surgical technique and outline consistent management strategies. A study reference manual,^{18,19} which was provided to each study site, contained comprehensive information to aid investigators with various procedural and patient-care aspects associated with permanent PEG-J placement. Specific information included the components required for the LCIG system insertion procedure and optimal tube placement; instructions on disconnecting and flushing the tubing; procedures for mitigating risk for periprocedure AEs such as bleeding, perforation, peritonitis, and stoma site infection; use of antibiotic prophylaxis; post-operative patient-care guidelines; and an overview of the European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines for PEG care before and after wound healing.²⁰

All patients underwent placement of both a 15 French Freka PEG tube via the pull method and a 9 French Freka J-tube during the same procedure. The instructed technique for placing/positioning the J-tube was to grasp the tube tip with forceps and advance the endoscope into the distal duodenum/proximal jejunum. The scope was slowly withdrawn into the stomach while the forceps were advanced to hold the tip of the J-tube in place. Once the endoscope was in the stomach, the forceps were opened, releasing the J-tube. Oftentimes this technique sequence was repeated to achieve a satisfactory J-tube tip position, preferably distal to the ligament of Treitz. J-tube extension location was confirmed radiographically. In some centers, intra-procedural fluoroscopy was used to monitor and confirm the tube position.

AE collection. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 (developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and were tabulated by MedDRA preferred term. Study neurologists in consultation with study gastroenterologists rated each AE as mild, moderate, or severe and serious or non-serious. A single AE could be coded to > 1 preferred term (e.g., an AE that was coded to the broad “complication of device insertion” could also be coded to additional terms such as “abdominal pain”, “abdominal discomfort”, or “abdominal distension”).

Adjudication. The independent adjudication committee comprised of three board-certified gastroenterologists, each with > 25 years of experience in the placement and management of PEG and J-tubes. The committee included a non-voting executive secretary who was a staff interface to AbbVie and assisted in extracting, tabulating, and analyzing data. Adjudication committee members worked in accordance with the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

Adjudication took place during closed sessions with only committee members present.

A sponsor-created product “MedDRA Query”, reviewed and revised by the adjudication committee, was used to sort out procedure- and device-associated AEs from all AEs in the phase 3 program. All procedure- and device-associated AEs were evaluated by the committee, and only these events are reported herein (full safety profiles of LCIG are published^{8,9,17}). When deemed appropriate, events redundantly coded to > 1 preferred term were consolidated under a single term most descriptive of the event.

GI procedure- and device-associated serious AEs (SAEs) were examined separately from procedure- and device-associated non-serious events, through a comprehensive review of each case report. The committee sought to further clarify the clinical implications by classifying each SAE as clinically significant or not. A “clinically significant SAE” is an event for which intervention had an effect of practical meaning to the patient and health-care provider, requiring further evaluation and treatment. For example, benign pneumoperitoneum that resolved spontaneously was deemed not clinically significant. Clinically significant SAEs were further classified as minor (a clinically significant SAE that was successfully addressed with a brief course of therapy but did not seriously threaten the patient’s baseline health) or major (a clinically significant SAE requiring an alternative therapy and/or intervention that was not part of the patient’s routine management). The incidence of AEs as a proportion of patients across all LCIG studies (termed “patient incidence”, $n = 395$) and AE incidence as a proportion of all the PEG-J procedures performed in the studies (termed “procedural incidence”, $n = 468$) were evaluated.

A literature search of peer-reviewed publications dating back to January 1980 (FDA approval of PEG) until August 2013 was conducted to determine the known rates of AEs associated with PEG or PEG-J. The search was conducted using PubMed and Ovid MEDLINE databases with the keywords: “percutaneous endoscopic gastrostomy”, “percutaneous endoscopic jejunostomy”, “endoscopic complications”, and “enteral feeding”. Case reports and non-English-language publications were excluded, and additional articles were culled as necessary. The literature usually did not distinguish between serious and non-serious or major and minor AEs in terms defined by the committee; thus, the same reported incidences were used for comparison across all categories.

RESULTS

A total of 395 patients who underwent the PEG-J procedure in the four studies were included in this analysis. Mean (s.d.) patient age was 64.3 (8.8) years. Patient demographics were: 58% (231) male, 42% (164) female, 93% (367) white, 6% (24) Asian, 0.8% (3) black, and 0.3% (1) American Indian or Alaska Native. Mean (s.d.) duration of PD was 12.2 (5.5) years. The mean (s.d.) mini-mental state examination, a questionnaire used to measure cognitive impairment (any score < 27 (out of 30) indicates signs of dementia), total score at baseline was 28.6 (1.6). Mean (s.d.) duration of PEG-J exposure in the LCIG phase 3 program as of the data cutoff date was 546 (299) days

Table 1 Patient exposure to PEG-J across the LCIG phase 3 program

Duration interval (days)	PEG-J exposure ($n = 395$), patients, n (%) ^a
1–14	9 (2.3)
15–29	4 (1.0)
30–59	7 (1.8)
60–89	10 (2.5)
90–179	14 (3.5)
180–364	44 (11)
365–729	194 (49)
≥ 730	113 (29)
At least 6 months (≥180 days)	351 (89)
At least 12 months (≥364 days)	307 (78)
At least 18 months (≥540 days)	180 (46)
Mean (s.d.)	546 (299)
Median (min/max)	480 (1/1,276)

LCIG, levodopa-carbidopa intestinal gel; min/max, minimum/maximum; PEG-J, percutaneous endoscopic gastrojejunostomy.

^aExposure is difference between start date (PEG-J placement) and end date (the last dose of study drug or PEG-J removal, whichever is later); 208 patients were available at the time of data cutoff.

(range, 1–1,276 days), and 113 (29%) patients were exposed for ≥ 730 days (208 patients were ongoing in the studies at data cutoff; Table 1).

During the follow-up period, the PEG tube did not need to be replaced in 339 (86%) patients; the PEG tube was replaced one time in 42 (11%) patients and two times or more in 13 (3.3%) patients. The J-tube was not replaced in 223 (56%) patients, but was replaced one time in 80 (20%) patients and two times or more in 91 (23%) patients. At the end of the first year, 91% of patients retained the original PEG tube and 63% retained the original J-tube.

GI procedure- and device-associated AEs were common (Supplementary Table S1), occurred early after the procedure, and usually resolved in the first 4 weeks (Supplementary Figure S2). The most common pre-adjudication AE, “complication of device insertion”, was a term most often additionally double-coded with “abdominal pain”, “abdominal discomfort”, “abdominal distension”, “flatulence”, and “pneumoperitoneum”.

As multiple MedDRA preferred terms (PTs) could be used to characterize a single event, the committee consolidated redundant terms for AEs reported by ≥ 5% of patients. Before adjudication, 158 SAE PTs and 1,078 non-SAE PTs were reported. After removing redundant PTs, there were 105 SAE PTs and 891 non-SAE PTs. Despite adjusting for redundant PTs, adjudication did not significantly alter the temporal profile of the events observed pre-adjudication, with the majority of AEs still occurring and resolving within the first 4 weeks after the procedure (Supplementary Figure S2). In general, rates were comparable across study sites.

The committee determined that 105 SAEs occurred in 67 (17%) patients. Of the adjudicated SAEs, 38% occurred during the first 2 weeks of treatment and 42% in the first 4 weeks. Eight SAEs were determined not clinically significant, 36 SAEs were of minor clinical significance, and 61 SAEs were of major clinical significance (Table 2). SAEs reported by only one patient are listed in the

Table 2 Post-adjudication: incidence of all major and minor SAEs occurring in ≥ 2 patients

Category and preferred term	Patient incidence, <i>n</i> (%) ^a	Procedural incidence, % ^b	Literature range, % ^{ref(s)}
Major SAEs	61 (15.4)	13.0	
Peritonitis	7 (1.8)	1.5	0.5–1.3 ²⁷
Pneumonia ^c	7 (1.8)	1.5	0.3–3.0 ^{12,24,27,28,31–40}
Abdominal pain ^d	6 (1.5)	1.3	4.0–13 ¹⁰
Pneumoperitoneum ^e	4 (1.0)	0.9	0.5–1.3 ^{12,24,27,28,31–40}
Post-operative wound infection	3 (0.8)	0.6	5.4–30 ^{10,11,26,41–44}
Acute abdomen	2 (0.5)	0.4	NR
Gastrointestinal hemorrhage	2 (0.5)	0.4	0–2.5 ^{12,24,27,28,31–34,36–40,45,46}
Ileus paralytic	2 (0.5)	0.4	1–2 ^{12,24,27,28,31–38,40}
Intestinal ischemia	2 (0.5)	0.4	NR
Intestinal perforation	2 (0.5)	0.4	0.5 ²⁶
Sepsis	2 (0.5)	0.4	NR
Minor SAEs	36 (9.1)	7.7	
Abdominal pain	7 (1.8)	1.5	4.0–13 ¹⁰
Pneumoperitoneum	7 (1.8)	1.5	0.5–1.3
Post-operative wound infection	3 (0.8)	0.6	5.4–30 ¹⁰
Parkinson's disease ^f	3 (0.8)	0.6	NR

NR, no reported rate; SAE, serious adverse event.

^aPatient incidence is relative to all patients who received a PEG-J (*n* = 395).

^bProcedural incidence is relative to all the PEG-J procedures performed (*n* = 468).

^cRange is for aspiration pneumonia.

^dAbdominal pain requiring hospitalization without other diagnosis.

^ePneumoperitoneum with concomitant abdominal pain with or without signs of infection.

^fParkinson's disease refers to the re-emergence of Parkinson's symptoms, often due to interruption of drug delivery.

Table 3 Post-adjudication: incidence of non-serious AEs occurring in $\geq 5\%$ of patients

Preferred term	Severity events, <i>n</i> ^a			Patient incidence, <i>n</i> (%) ^b	Procedural incidence, % ^c	Literature range, %
	Mild	Moderate	Severe			
Abdominal pain	63	78	20	123 (31)	26	4.0–13 ¹⁰
Procedural pain	54	48	4	91 (23)	19	NR
Post-operative wound infection	83	37	0	79 (20)	17	5.4–30 ^{10,11}
Excessive granulation tissue	81	17	0	71 (18)	15	27 ⁴⁷
Incision site erythema	67	9	0	63 (16)	13	NR
Procedural site reaction	45	14	0	40 (10)	8.5	NR
Post-procedural discharge ^d	35	9	1	40 (10)	8.5	17 ²⁶

AE, Adverse event; NR, no reported rate; PEG-J, percutaneous endoscopic gastrojejunostomy.

^aSeverity as reported by the study investigator.

^bPatient incidence (%) is relative to all patients who received a PEG-J (*n* = 395).

^cProcedural incidence (%) is relative to all the PEG-J procedures performed (*n* = 468).

^dDischarge from around tube at incision site.

Supplementary Data. Overall procedural incidence of major and minor SAEs was 13% and 7.7%, respectively. Peritonitis and pneumonia were the most commonly reported major clinically significant SAEs, followed by abdominal pain. Procedural incidence of all device-related pneumonic events was 1.9% (7 SAEs of pneumonia of major clinical significance plus 1 minor SAE of pneumonia and 1 major SAE of aspiration pneumonia). Abdominal pain and pneumoperitoneum were the most commonly reported minor clinically significant SAEs. In all, 15 (3.8%) patients underwent 16 surgeries (excluding endoscopy procedures) following reports of an SAE, 10 of these SAEs were adjudicated as related to the device insertion.

Originally, 12 cases of peritonitis were reported across all studies by the study investigators: 11 classified as SAEs and one classified as a non-SAE. The committee determined that four of the cases were not peritonitis and eight were possibly or definitely peritonitis (one of which was the non-serious case). All cases with one exception occurred within 6 days of PEG placement. Five of the eight cases of peritonitis resolved without surgery (i.e., three patients underwent laparotomy) and no deaths resulted from peritonitis.

The majority of the AEs reported (89%) were non-serious and were mild or moderate in intensity (Table 3). Two hundred ninety-five (33%) of the non-SAEs occurred within the first 4 weeks of the PEG-J placement. The most commonly

reported non-SAEs were abdominal pain, procedural pain, and post-operative wound infection. The distinction between abdominal pain and procedural pain was made at the discretion of the study investigator.

The adjudication committee determined that 17 (4.3%) patients discontinued treatment owing to a procedure- or device-related AE compared with 18 (4.6%) pre-adjudication. Seven discontinuations occurred within the first 14 days after the PEG-J procedure, two occurred between days 14 to 60, two occurred between days 90 to 150, and six occurred after 1 year (two of which occurred after 2 years). The AEs that most frequently led to discontinuation were abdominal pain (four patients) and peritonitis (two patients). Of the 18 deaths reported in the phase 3 program, which included 590.2 patient years of PEG-J exposure, the committee concluded that 1 (0.2%) fatality was probably associated with the device insertion owing to the temporal association with the PEG-J placement procedure. Post procedure, the patient developed staphylococcal epidermis sepsis and died of problems related to pneumonia, renal failure, and rhabdomyolysis. There were no intra- or peri-procedural difficulties, and the patient was not observed to have aspirated during the procedure.

DISCUSSION

Intrajejunal infusion of LCIG via PEG-J for long-term treatment of advanced PD patients improves motor fluctuations and quality of life.^{7-9,13,16,17} The low discontinuation rate due to AEs of patients treated with LCIG via PEG-J suggests a favorable benefit-risk profile for this PD treatment.^{8,9,13,16,17} This analysis presents the first methodical adjudication of safety data related to the GI procedure and device in PD patients treated with this PEG-J drug delivery system. This study includes the largest group of patients using enteral tubes with the longest duration of follow-up reported in the GI literature to date, representing 590.2 total patient years of PEG-J exposure. Overall, treatment with LCIG via PEG-J produced an expected GI-related safety profile with most events occurring immediately following the procedure and usually resolving within the first 4 weeks after placement of PEG-J tubing.

PEG/PEG-J is typically performed in patients with stroke, amyotrophic lateral sclerosis, or other illnesses that lead to severe malnutrition. This is a population of patients who frequently have major limitations in mobility and activity. Conversely, PEG-J is used in the LCIG system to deliver long-term treatment to a mobile population. There is a paucity of information on the (1) incidence of long-term AEs and device durability of the PEG/PEG-J procedure, and (2) safety of PEG-J in the advanced PD population.²¹ Longevity of the PEG-J device in the advanced PD population included in this analysis was favorable considering the published short-term data. Average longevity for a J-tube is 3–6 months for immobile patient populations receiving enteral nutrition,^{22,23} whereas 62.9% of patients in the phase 3 program retained their original J-tube for at least 1 year. Despite the length of exposure of these patients to the PEG-J tubes, the committee found the rates of both SAEs and non-SAEs to be mainly lower than or consistent with ranges quoted in the

literature (Tables 2 and 3). Procedure-related mortality for PEG is reported to be 0–2%,²¹ which is consistent with the 0.2% mortality associated with the PEG-J procedure in this study.

Pneumoperitoneum is an expected occurrence with the PEG or PEG-J procedure but is not necessarily clinically significant and usually goes undetected. Although reporting of pneumoperitoneum rates in the literature are low (0.5–1.3%), actual occurrence is reported to be up to 56%,²⁴ and, realistically, some degree of pneumoperitoneum likely occurs in every case. Seven cases of pneumoperitoneum SAEs reported in the phase 3 program were of minor clinical significance (1.5%), whereas four cases were classified as major due to concomitant abdominal pain (0.9%). “In-and-out” movement of the PEG tube (during wound care or when checking the tightness of the bolster) within 72 h of placement, before the stomach wall adheres to the peritoneal cavity, should be avoided as it may contribute to pneumoperitoneum rates as well as leakage and peritonitis as was reported in the study. The size of gastrostomy incisions, repeated attempts to place J-tubes in optimally distal positions, J-tube advancement techniques, tube site cleaning techniques, or prolonged/excessive intra-procedural air insufflation may also have contributed to pneumoperitoneum and peritonitis rates. Use of CO₂ insufflation instead of air may lessen the impact of pneumoperitoneum, particularly if the endoscopic procedure is prolonged.

Procedural and abdominal pain are AEs not commonly noted in the GI literature because these events are expected as a consequence of the endoscopic procedure, which requires percutaneous abdominal wall puncture for PEG-J placement. Reporting in this data set may be reflective of the controlled, clinical trial reporting of AEs or of this special ambulatory population, not seen in AE reporting by the typical patient with PEG or PEG-J placement. In one study, rates of abdominal pain were 13% at 2 weeks post procedure and 4% at 8 weeks.¹⁰ Abdominal pain of major clinical significance (requiring hospitalization) was comparatively low in the phase 3 program at 1.5%. Abdominal pain owing to wound infection or site reaction can occur at any time, whereas pain due to granulation tissue usually occurs later.²⁵

Common AEs of PEG-J (e.g., post-procedural discharge and post-operative wound infection) were lower or similar to AE rates reported in the literature. Despite the long exposure of these patients to the PEG-J, post-operative wound infection rate (major SAE = 0.6%, minor SAE = 0.6%, non-serious = 20%) was low compared with most reports in the literature, which were between 5 and 30%.^{10,11} Post-operative discharge (10%) was below the literature-reported rate of 17%.²⁶

Procedural incidence of peritonitis (1.5%) was slightly higher than ranges in the literature (0.5–1.3%).²⁷ Peritonitis immediately after the procedure usually indicates damage to the viscus or leakage of gastric contents into the peritoneum. Peritonitis observed in this analysis, diagnosed clinically and not based on the presence of abnormal bacterial cultures, may be due to early post-operative “in-and-out” movement of the PEG-J tube as described above. Taping of PEG and J-tubes flush to the abdominal wall immediately

after placement may increase lateral tension on the tubes, increasing the risks of peritonitis, pneumoperitoneum, and leakage.²⁸ The PEG-J procedure requires more than a PEG procedure, increasing the risk of peritonitis. Finally, peritonitis may be increased in this population due to the mobility of the patients, resulting in accidental pulling/removal of the tube.

As the advanced PD population commonly experiences dysphagia and is predisposed to aspiration and pneumonic events,^{29,30} the committee reviewed these events carefully and concluded that incidence of pneumonia related to the GI procedure or device (1.9%) was well within the acceptable range for this high-risk population, based on reported rates in the literature (0.3–3.0%).^{11,12,25,28,29,31–39}

All events reported in the LCIG phase 3 program could be subject to the reporting bias of participation in a clinical study, whereby all symptoms may be evaluated beyond the normal scope of practice. This study limitation is countered by the study's large patient database as well as the long PEG-J exposure duration and follow-up. An additional strength of this study is the independent adjudication of the safety data by expert gastroenterologists.

The authors developed recommendations regarding the procedure and follow-up care to potentially reduce incidence of peritonitis and post-procedure surgical intervention. The following are a few highlighted recommendations for long-term use of PEG-J; a full list of recommendations can be found in the Supplementary Data. Patients should see a GI expert routinely to be monitored for AEs from long-term use of PEG-J. In particular, care and maintenance of the tubing is important, and patients should be educated on these requirements. Prophylactic antibiotics were used in 75% of the study population, supporting the low infection rate and suggesting that it may be possible to obtain an even lower infection rate with uniform prophylactic antibiotic use. Infections should be treated aggressively; tubing should be removed if infection is resistant. The external bolster should allow 1 cm of in-and-out movement in the tube, which may reduce ulceration, buried bumper, local ischemia, and wound infection. To prevent peritonitis and pneumoperitoneum, it is recommended that the tube be dressed to prevent accidental traction, and the pump should be secured in a binder or harness during the day, with the tube being secured with a bulkier dressing at night.

Overall, the LCIG delivery system was compared favorably with the existing technology and clinical use of PEG and PEG-J. Only one death was temporally associated with the device placement procedure, and the low discontinuation rate suggests acceptable procedural outcomes and AE rates. The adjudication committee determined that there were no series of events or sentinel event(s) that should limit use of the device in the advanced PD patient population. Future studies are necessary to gather more long-term data on the safety and efficacy of drug delivery via PEG-J. The LCIG treatment system for advanced PD is a unique system requiring both movement disorders specialists and GI proceduralists to work closely to provide effective, well-tolerated treatment over a long period.

CONFLICT OF INTEREST

Guarantor of the article: Michael Epstein, MD.

Specific author contributions: Design and execution of the adjudication: Michael Epstein, David A. Johnson, and Robert Hawes; performance of literature review: Michael Epstein, David A. Johnson, Robert Hawes, and Arvydas D. Vanagunas; organization and analysis of adjudication data: E. Roderich Gossen; original research project conception, organization and execution: Weining Z. Robieson, Krai Chatamra, Jordan Dubow, and Janet Benesh; design and execution of statistical analysis: Weining Z. Robieson, Susan Eaton, Krai Chatamra, Jordan Dubow, and Janet Benesh; organization, review, and analysis of the adjudication data: Susan Eaton. All the authors reviewed and critiqued the statistical analysis and the manuscript throughout the editorial process. All the authors approved of the final manuscript draft submitted for publication.

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currently employed by ZS pharma. Susan Eaton is a former employee of AbbVie and holds stock and/or stock options. Jordan Dubow was an employee of AbbVie with stock/stock options at the time of the study and is currently employed with stock options by Marathon Pharmaceuticals. Krai Chatamra is an employee of AbbVie and holds stock and/or stock options. Janet Benesh is an employee of AbbVie and holds stock and/or stock options.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Altered gastric emptying can lead to undesired fluctuations in serum concentrations of oral medications.
- ✓ Continuous daytime levodopa delivery for Parkinson's disease (PD) treatment can stabilize drug levels.
- ✓ Levodopa-carbidopa intestinal gel administered via percutaneous endoscopic gastrojejunostomy (PEG-J) improves motor complications in patients with advanced Parkinson's disease.
- ✓ PEG-J-related adverse events and limited tube durability are common in immobile patients.
- ✓ There is a paucity of data exploring long-term use and durability of PEG-J.

WHAT IS NEW HERE

- ✓ Largest enteral tube data set reported in the literature with the longest follow-up.
- ✓ PEG-J adverse events in ambulatory patients are consistent with adverse events in immobile patients.
- ✓ Durability of PEG-J in the advanced PD population was favorable considering short-term data in literature.
- ✓ Practical recommendations for PEG-J post-operative care are provided.
- ✓ A unique treatment system requiring both movement disorder specialists and gastroenterologists to work closely together.

1. Prescott LF. Gastric emptying and drug absorption. *Br J Clin Pharmacol* 1974; **1**: 189–190.
2. Horowitz M, Su YC, Rayner CK et al. Gastroparesis: prevalence, clinical significance and treatment. *Can J Gastroenterol* 2001; **15**: 805–813.
3. Rivera-Calimlim L, Dujovne CA, Morgan JP et al. Absorption and metabolism of L-dopa by the human stomach. *Eur J Clin Invest* 1971; **1**: 313–320.
4. Ahlskog JE, Muentner MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001; **16**: 448–458.
5. van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. *CNS Drugs* 2003; **17**: 475–489.
6. Stocchi F. The hypothesis of the genesis of motor complications and continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Parkinsonism Relat Disord* 2009; **15**: S9–S15.
7. Nyholm D, Odin P, Johansson A et al. Pharmacokinetics of levodopa, carbidopa, and 3-O-methyldopa following 16-hour jejunal infusion of levodopa-carbidopa intestinal gel in advanced Parkinson's disease patients. *AAPS J* 2013; **15**: 316–323.

8. Fernandez HH, Standaert DG, Hauser RA et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: Final 12-month, open-label results. *Mov Disord* 2015; **30**: 500–509.
9. Olanow CW, Kieburtz K, Odin P et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol* 2014; **13**: 141–149.
10. Blomberg J, Lagergren J, Martin L et al. Complications after percutaneous endoscopic gastrostomy in a prospective study. *Scand J Gastroenterol* 2012; **47**: 737–742.
11. Sheehan JJ, Hill AD, Fanning NP et al. Percutaneous endoscopic gastrostomy: 5 years of clinical experience on 238 patients. *Ir Med J* 2003; **96**: 265–267.
12. Rabeneck L, Wray NP, Petersen NJ. Long-term outcomes of patients receiving percutaneous endoscopic gastrostomy tubes. *J Gen Intern Med* 1996; **11**: 287–293.
13. Antonini A, Odin P, Opiano L et al. Effect and safety of duodenal levodopa infusion in advanced Parkinson's disease: a retrospective multicenter outcome assessment in patient routine care. *J Neural Transm* 2013; **120**: 1553–1558.
14. Pickut BA, van der Linden C, Dethy S et al. Intestinal levodopa infusion: the Belgian experience. *Neural Sci* 2014; **35**: 861–866.
15. Zibetti M, Merola A, Artusi CA et al. Levodopa/carbidopa intestinal gel infusion in advanced Parkinson's disease: a 7-year experience. *Eur J Neurol* 2014; **21**: 312–318.
16. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. *Eur J Neurol* 2012; **19**: 1079–1085.
17. Slevin JT, Fernandez HH, Zadikoff C et al. Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. *J Parkinsons Dis* 2015; **5**: 165–174.
18. Abbott Study Reference Manual (Protocol No. S187.3.001 and S187.3.002). Abbott Products, Inc., Chicago, IL, 2008.
19. Abbott Study Reference Manual (Protocol No. S187.3.004). Abbott Products, Inc., Chicago, IL 2010.
20. Loser C, Aschl G, Hebuterne X et al. ESPEN guidelines on artificial enteral nutrition—percutaneous endoscopic gastrostomy (PEG). *Clin Nutr* 2005; **24**: 848–861.
21. Itkin M, DeLegge MH, Fang JC et al. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). *Gastroenterology* 2011; **141**: 742–765.
22. DeLegge MH, Patrick P, Gibbs R. Percutaneous endoscopic gastrojejunostomy with a tapered tip, nonweighted jejunal feeding tube: improved placement success. *Am J Gastroenterol* 1996; **91**: 1130–1134.
23. Gore DC, DeLegge M, Gervin A et al. Surgically placed gastro-jejunostomy tubes have fewer complications compared to feeding jejunostomy tubes. *J Am Coll Nutr* 1996; **15**: 144–146.
24. Wojtowycz MM, Arata JA Jr., Micklos TJ et al. CT findings after uncomplicated percutaneous gastrostomy. *Am J Roentgenol* 1988; **151**: 307–309.
25. Fang JC. Minimizing endoscopic complications in enteral access. *Gastrointest Endosc Clin N Am* 2007; **17**: 179–196.
26. Venu RP, Brown RD, Pastika BJ et al. The buried bumper syndrome: a simple management approach in two patients. *Gastrointest Endosc* 2002; **56**: 582–584.
27. Lynch CR, Fang JC. Prevention and management of complications of percutaneous endoscopic gastrostomy (PEG) tubes. *Pract Gastroenterol* 2004; **Series #22**: 66–76.
28. McClave SA, Chang WK. Complications of enteral access. *Gastrointest Endosc* 2003; **58**: 739–751.
29. Beyer MK, Herlofson K, Arsland D et al. Causes of death in a community-based study of Parkinson's disease. *Acta Neuro Scand* 2001; **103**: 7–11.
30. Di Rocco A, Molinari SP, Kollmeier B et al. Parkinson's disease: progression and mortality in the L-DOPA era. *Adv Neurol* 1996; **69**: 3–11.
31. Foutch PG. Complications of percutaneous endoscopic gastrostomy and jejunostomy: recognition, prevention, and treatment. *Gastrointest Endosc Clin N Am* 1992: 231–248.
32. Grant MD, Rudberg MA, Brody JA. Gastrostomy placement and mortality among hospitalized Medicare beneficiaries. *JAMA* 1998; **279**: 1973–1976.
33. Larson DE, Burton DD, Schroeder KW et al. Percutaneous endoscopic gastrostomy. Indications, success, complications, and mortality in 314 consecutive patients. *Gastroenterology* 1987; **93**: 48–52.
34. Moller P, Lindberg CG, Zilling T. Gastrostomy by various techniques: evaluation of indications, outcome, and complications. *Scand J Gastroenterol* 1999; **34**: 1050–1054.
35. Neeff M, Crowder VL, Mclvor NP et al. Comparison of the use of endoscopic and radiologic gastrostomy in a single head and neck cancer unit. *ANZ J Surg* 2003; **73**: 590–593.
36. Safadi BY, Marks JM, Ponsky JL. Percutaneous endoscopic gastrostomy. *Gastrointest Endosc Clin N Am* 1998; **8**: 551–568.
37. Schapiro GD, Edmundowicz SA. Complications of percutaneous endoscopic gastrostomy. *Gastrointest Endosc Clin N Am* 1996; **6**: 409–422.
38. Westaby D, Young A, O'Toole P et al. The provision of a percutaneously placed enteral tube feeding service. *Gut* 2010; **59**: 1592–1605.
39. Souba WW. Nutritional support. *N Engl J Med* 1997; **336**: 41–48.

40. Gauderer MW. Percutaneous endoscopic gastrostomy-20 years later: a historical perspective. *J Pediatr Surg* 2001; **36**: 217–219.
41. Gossner L, Keymling J, Hahn EG *et al.* Antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): a prospective randomized clinical trial. *Endoscopy* 1999; **31**: 119–124.
42. Jain NK, Larson DE, Schroeder KW *et al.* Antibiotic prophylaxis for percutaneous endoscopic gastrostomy. A prospective, randomized, double-blind clinical trial. *Ann Intern Med* 1987; **107**: 824–828.
43. Lee JH, Kim JJ, Kim YH *et al.* Increased risk of peristomal wound infection after percutaneous endoscopic gastrostomy in patients with diabetes mellitus. *Dig Liver Dis* 2002; **34**: 857–861.
44. Preclik G, Grune S, Leser HG *et al.* Prospective, randomised, double blind trial of prophylaxis with single dose of co-amoxiclav before percutaneous endoscopic gastrostomy. *BMJ* 1999; **319**: 881–884.
45. Obeso JA, Olanow CW, Nutt JG. Levodopa motor complications in Parkinson's disease. *Trends Neurosci* 2000; **23**: S2–S7.
46. Luman W, Kwek KR, Loi KL *et al.* Percutaneous endoscopic gastrostomy—indications and outcome of our experience at the Singapore General Hospital. *Singapore Med J* 2001; **42**: 460–465.
47. Kurien M, White S, Simpson G *et al.* Managing patients with gastrostomy tubes in the community: can a dedicated enteral feed dietetic service reduce hospital readmissions? *Eur J Clin Nutr* 2012; **66**: 757–760.



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