

Implementing Levodopa-Carbidopa Intestinal Gel for Parkinson Disease: Insights from US Practitioners

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Abstract: **Background:** Levodopa-carbidopa intestinal gel (LCIG, designated in the United States as carbidopa-levodopa enteral suspension, CLES) was approved in the United States in 2015 for the treatment of refractory motor fluctuations in individuals with Parkinson disease (PD). Many neurologists in the United States have not had personal experience with implementation and management of the unique delivery system for this treatment.

Methods and Findings: This educational review was developed to provide practitioners with an understanding of LCIG use from the clinician's point of view. Practical recommendations for the use of LCIG from the early planning stages through long-term patient management were compiled from the published literature, regulatory guidance, and clinical experience. Among the topics reviewed were: assembling a multidisciplinary treatment team, identifying treatment candidates, patient/care partner education, procedural considerations, post-procedural care, LCIG initiation and titration, troubleshooting issues, and ongoing monitoring. For most of these steps, a considerable amount of individualization is possible, which allows clinicians to tailor protocols based on the needs of their teams, the healthcare system, and the patient and care partner. Although clinical practices are heterogeneous, themes of early planning, ongoing education, and a team-based approach to management are universal.

Conclusions: By using established protocols and insights gleaned from experienced practitioners, clinicians who are unfamiliar with LCIG can more feasibly incorporate this treatment option into their armamentarium for treating PD motor fluctuations.

Introduction

Management of motor fluctuations in Parkinson disease (PD) has benefitted from an increasing number of treatment options. Although available in many parts of the world for more than 10 years, intrajejunal delivery of levodopa-carbidopa intestinal gel (LCIG; designated in the United States as carbidopa-levodopa enteral suspension; DuopaTM) was only recently approved in the United States (January 2015), and is, therefore, relatively

unfamiliar to most US-based neurologists. LCIG is a carboxymethylcellulose aqueous gel formulation that is administered via a portable pump through a percutaneous jejunostomy tube, which allows medication delivery directly to the site of absorption in the upper intestine. The ability to circumvent the stomach in the delivery process avoids the fluctuations in drug delivery that result from variability in gastric emptying; these fluctuations are often profound in patients with PD.¹ Results from controlled clinical trials and observational studies have demonstrated that LCIG

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treatment is effective in improving motor function, non-motor symptoms, daily activities, and health-related quality of life in patients with advanced PD whose motor symptoms are not adequately managed with optimized oral medical therapy.¹⁻⁵

Using our collective experience, we have compiled insights on the use of LCIG with an emphasis on practical guidance for incorporating LCIG into routine practice. Not discussed here are data on the general efficacy and safety/tolerability of LCIG; these aspects of LCIG therapy have been previously described.⁶⁻⁹ However, our exploration does include discussions of clinical evidence and practical experience for patient subgroups that lie outside the bounds of existing regulatory approvals and clinical trial experience. Our goal is to assist clinicians in moving through the process of treatment, from the initial stages of assembling a multidisciplinary team through long-term monitoring of a patient receiving LCIG.

Assembling a Multidisciplinary Team

The involvement of multiple specialties and practitioners (e.g., general neurologists, movement disorder specialists, specialty nurses, allied health professionals, neuropsychologists, social workers) is common in the management of patients with advanced PD.^{10,11} In the case of LCIG, the intrajejunal delivery system requires that the patient management team be expanded to include proceduralists (gastroenterologist, surgeon, or interventional radiologist), whose role is to assess the patient's eligibility for placement of a percutaneous jejunostomy tube, perform the tube placement procedure, make recommendations for acute aftercare, and manage procedure and/or tube-related adverse events.

The exact composition of the multidisciplinary team will vary based on the individual practice, the clinical practice setting, and the healthcare system. Although connections among multidisciplinary team members may have already been established, early clarification of team member roles and responsibilities is beneficial to workflow. For example, determining a priori the touch points for proceduralist involvement maximizes efficiency and allows scheduling sufficient lead time for preprocedural evaluation. The multidisciplinary team lead should also contact those responsible for formulary and medical equipment decisions to ensure availability and access to LCIG and delivery system-specific procedural supplies.

Recruitment of proceduralist team members can be challenging. Personal contact with the movement disorder specialist or neurologist is important at this stage to foster relationship building and advocate LCIG as a treatment option for advanced PD with other specialists. It is wise, when possible, to engage more than one proceduralist to ensure the necessary coverage for tube-related issues.

For more detailed guidance on the role and structure of the multidisciplinary team, see the comprehensive review published by Pedersen et al., 2017.¹²

Patient Selection

The evaluation process for LCIG treatment candidacy is an extension of that used for determining a patient's suitability for other treatment options for motor fluctuations. Recommended elements are listed in Table 1. The individual tests undertaken will vary by clinician/center practice, and the level of additional investigation necessary is dictated by the patient's history and provenance (i.e., new referral vs. long-term patient). Local practice also informs whether the decision on LCIG candidacy is made by the movement disorder specialist or by a multidisciplinary team. Centers with an established committee that determines patient suitability for deep brain stimulation (DBS) may choose to model the same type of structure to evaluate a patient's LCIG candidacy.

Along with clinical assessments, patient education, with clearly articulated goals and expectations of therapy, is key to informed treatment decisions. A care partner, when available, should be involved throughout the evaluation process, and his or her ability to contribute necessary support should be assessed early. Important aspects of care partner support include his or her ability to assist with tubing/stoma care and pump setup and to provide a reliable collateral source of information regarding motor status and side effects, especially during the LCIG titration process. In the absence of a care partner or other support system, the patient must have sufficient motor skills and cognitive status to manage the delivery system independently and provide reliable, accurate self-report regarding symptoms. This aspect of treatment is especially important for patients in the assisted-living setting, where the patient may be required to initiate the pump and handle tube flushing after daily use.

Inclusion/Exclusion Criteria

LCIG is indicated for the treatment of motor fluctuations in patients with advanced PD.¹³ Patients with a strong probability of a beneficial response to LCIG are those who are similar to those included in large clinical trials of LCIG. In particular, qualifying patients demonstrate a robust response to levodopa and have 3 or more hours of daily "off" time, despite optimized medical therapy.^{1,2} These patients have been shown to experience reductions from baseline in "off" time and increased "on" time without troublesome dyskinesias compared with patients taking standard oral levodopa-carbidopa therapy.²

Among patients who qualify for LCIG therapy, there do not appear to be demographic characteristics that portend a favorable or unfavorable response. Using data from a 54-week, open-label study, investigators found a comparable likelihood of response to LCIG regardless of age, disease duration, gender, or body mass index.¹⁴

Patients with advanced PD in real-world practice often differ from those in clinical trials. Emerging clinical evidence and experience suggest that patients beyond the specific phenotype included in the clinical trials may also benefit from LCIG (Table 2). One example would be patients in whom dyskinesia, rather than "off" time, is the major troublesome symptom. In US LCIG

TABLE 1 Elements of Screening for LCIG Suitability**Verify PD diagnosis**

- Presence of core features (bradykinesia plus rigidity, rest tremor, or postural instability)
- Presence of supportive features (unilateral onset/asymmetry, choreiform dyskinesias)
- Absence of atypical features (early severe autonomic involvement, early cognitive impairment, supranuclear gaze palsy, neuroleptic exposure, upper motor neuron signs)

Characterize “off”/“on” duration and severity

- Suggested quantitative assessment tools^a
 - Motor diaries
 - UPDRS Part IV (motor complications)
 - “Off” and “on” state Hoehn and Yahr staging
 - “Off” and “on” state UPDRS Part III (motor examination)
 - “Off” and “on” state UPDRS Part II (activities of daily living, by history)
 - AIMS or MDS-UDYSRS in ON state (to benchmark dyskinesia severity)

Appraise levodopa responsiveness

- Historical data
- Difference in Part III (motor examination) UPDRS score in “off” vs. “on” states^b
- Difference between Hoehn and Yahr stage in “off” vs. “on” states^a
- Consider trial of nasojugal LCIG (if there is a question about the responsiveness of particular symptoms)

Evaluate severity of non-motor comorbidities (cognitive, mood, neuropsychiatric)

- Suggested quantitative assessment tools^a
 - Non-motor Symptoms Scale (NMSS)
 - Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE)
 - Beck Depression Inventory (BDI) or Geriatric Depression Scale (GDS)
 - Neuropsychiatric Inventory (NPI)

Assess support status^c

- Zarit Caregiver Burden Inventory
- General medical fluency and capabilities of caregiver

Calibrate expectations of patients and caregivers

- What are their goals? What will be considered success? If the patient’s definition of success is clearly out of the scope of feasibility for LCIG, discuss further
- Encourage caregivers to be present for “off”/“on” testing and ensure that they understand their expected supporting role

Patient education resources

- Provide written materials in addition to discussions
- Peer education (formal [e.g., through AbbVie-sponsored Peer Mentor program] or informal [e.g., within your own patient cohort, if available])
- Consider trial of wearing pump accessory at home (without tube)

Abbreviations: LCIG, levodopa-carbidopa intestinal gel; UPDRS, Unified Parkinson Disease Rating Scale or MDS-UPDRS (Movement Disorder Society-sponsored revision of the UPDRS).

^aAlthough not routinely used in the clinical setting, use of these tools at baseline screening and early titration of therapy is suggested to facilitate longitudinal monitoring of treatment response.

^bFormal carbidopa/levodopa challenge after overnight withdrawal may be performed, particularly if there is a question about the levodopa responsiveness of particular-target symptoms. Documentation of “off” and “on” motor severity occurring spontaneously during clinic visits may suffice for patients who are not able to tolerate intentional medication withdrawal.

^cThe care partner, or (in the absence of a support system) the patient, needs sufficient visual acuity and manual dexterity to manipulate pump, tubing, etc. (for patients, this should be assessed in the “off” and “on” with troublesome dyskinesia state, where applicable), and should be sufficiently cognitively intact to interpret pump alarms and provide reliable collateral source- or self-report regarding symptom response.

registration trials, patients were selected based on the duration of “off” time rather than the presence or extent of dyskinesia; the resulting patient population had a very low baseline level of troublesome dyskinesia.² Post hoc analysis of the subset of patients who had one hour or more of troublesome dyskinesia at baseline showed a decrease in “on” time with troublesome dyskinesia, although the difference between LCIG ($n = 11$) and oral therapy ($n = 12$) was not statistically significant.¹⁵ Observational studies have further suggested an antidyskinetic effect of LCIG treatment.^{3–5} Likewise, a recent open-label pilot study in patients with at least 3 hours of daily “on” time with troublesome dyskinesias at baseline ($N = 9$) reported a mean 47% decrease in “on” time with troublesome dyskinesias.¹⁶ Notably, levodopa equivalent daily dose *increased* by an average of 35% from pre-procedure to the 6-month follow-up visit, yet troublesome dyskinesias

decreased. Together, these data suggest that patients with a considerable dyskinesia burden may warrant consideration for LCIG treatment. Further evaluation inadequately powered, blinded clinical trials may provide more definitive support for these findings.

Another group of patients who may benefit from LCIG treatment is those with levodopa-responsive motor fluctuations in the setting of clinically significant cognitive impairment. Cognitive impairment is a common finding among patients with advanced PD, with 75% or more of patients with a disease duration > 10 years developing dementia.¹⁷ Mild cognitive impairment is also frequently observed in conjunction with PD, affecting approximately one-quarter of all patients.¹⁷ DBS, particularly of the subthalamic nucleus, is not recommended for patients with significant cognitive impairment due to the potential risk of

TABLE 2 Identifying Candidates for LCIG Therapy**Characteristics of individuals for whom LCIG benefit is well established^a**

- Levodopa-responsive PD^b with motor fluctuations and/or dyskinesias
- “Off” periods that are not adequately controlled with optimized medical therapy
- Adequate trials of oral/transdermal therapies
- Daily “off” duration of at least 3 hours

Individuals who may benefit from LCIG^c

- Patients in whom troublesome dyskinesias rather than “off” time are the major source of disability
- Patients with an “off” duration of less than 3 hours, but still disabling
- Patients receiving DBS who experience refractory fluctuations, despite programming optimization for more than 1 year
- Patients with a history of cognitive impairment and/or neuropsychiatric complications of dopaminergic therapy (mild cognitive impairment, non-disabling impulse control symptoms, or mild hallucinations)

Patient groups with uncertain benefit from LCIG treatment^c

- Patients with levodopa “unresponsive” freezing of gait^d
- Patients with a history of severe neuropsychiatric complications of dopaminergic therapy (e.g., disabling impulse control disorders or psychosis) worsened by peak levodopa

Relative contraindications to LCIG treatment

- Neurological factors
 - Insufficient duration or severity of “off” time
 - Lack of meaningful response to levodopa, or levodopa-responsive symptoms are not the major source of disability
 - Cognitive or psychiatric problems that would make therapy difficult (e.g., active severe psychosis, major impulse control disorder)
 - Secondary parkinsonism
 - Treatment-refractory tremor
- Environmental/social factors
 - Inability to independently manage the pump and tube/stoma care OR inadequate care partner or other social support
 - Barriers to access (nursing home resident; high out-of-pocket costs)
- Other factors
 - Labeled contraindication to LCIG therapy
 - Contraindication for PEG-J tube placement^d

Abbreviations: DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; PD, Parkinson disease; PEG-J, percutaneous endoscopic gastrojejunostomy.

^aCharacteristics of patients enrolled in pivotal clinical trials.

^bAs determined by the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria for PD.

^cLimited evidence of benefit for these groups is available from case reports/observational studies, but not evaluated in controlled clinical trials.

^dAbsolute contraindications to PEG-J tube placement include known or suspected intestinal obstruction, serious coagulation disorder, sepsis, and active peritonitis. Relative contraindications include ascites and infiltrative disease of the gastric/intestinal and abdominal walls.

worsening existing deficits.¹⁸ LCIG, in contrast, has been used in many patients with cognitive impairment without adverse sequelae.^{3,19} A recent consensus statement derived from an international survey of more than 100 experts in the field supports LCIG as a treatment option in carefully selected patients with cognitive impairment or dementia.¹⁸ An important caveat is that the presence of cognitive impairment increases the need for care partner assistance. Individuals with dementia are at increased risk of pulling out percutaneous tubing due to confusion;²⁰ these risks can sometimes be mitigated with customized garments that limit the patient's access to the hardware.

Other groups for whom LCIG data are limited include patients with levodopa “unresponsive” freezing of gait (FOG), patients receiving DBS who experience refractory fluctuations despite programming optimization, and patients with a history of neuropsychiatric complications with dopaminergic therapy. Chang et al.²¹ reported improvements in 360 degree turn time, fall frequency, and FOG questionnaire score after six months of 24-hour LCIG treatment in a small cohort of patients (N = 5) with disabling FOG considered unresponsive to levodopa (defined as FOG that persisted during levodopa challenge in otherwise “on” periods). Notably, four of these five patients were initially

levodopa responsive during 16-hour LCIG infusion but developed levodopa unresponsive FOG before the start of the study.

There is little information in the published literature regarding LCIG use in patients with DBS implanted long term who experience refractory motor fluctuations, although some authors have reported successful outcomes with this approach. Case reports suggest that progressive worsening of “off” time that cannot be addressed with DBS programming adjustments (e.g., due to side effects of stimulation) or further augmentation of oral therapy can be improved by more than 50%, and in some cases as much as 80% to 90%, with LCIG.^{22–24} Hence, LCIG may be considered on a case-by-case basis for individuals in whom benefit for motor fluctuations remains suboptimal with DBS despite optimization of programming and oral therapy.

Regarding use of LCIG in patients with significant neuropsychiatric symptoms, available safety data suggest that LCIG, compared with other device-aided therapies, may be better tolerated in patients with a history of psychosis.¹⁰ One possible mechanism is avoidance of delirium noted at peak levodopa concentration and the worsening of anxiety disorders in “off” states in patients with cognitive impairment or severe behavior comorbidities who experience significant motor fluctuations.

Implementation of LCIG specifically to improve neuropsychiatric complications of dopaminergic therapy has not been studied.

Circumstances warranting careful consideration include cases in which the patient may soon enter a skilled nursing facility, due to differences in Medicare reimbursement for LCIG in institutional settings (hospital inpatient or skilled nursing facility). Patients in whom enteral nutrition is under consideration for severe dysphagia also require special consideration, particularly concerning the risk of tube displacement and selection of tubing gauge (see Supporting Table 1). Table 2 outlines additional clinical and social factors that are relative contraindications to LCIG treatment.

Discussing LCIG With Patients

Patient education regarding device-aided therapies, including LCIG, should ideally occur early in the course of motor fluctuations to build familiarity with available treatment options. This familiarity enables more prompt implementation of device-aided therapy when indicated as the disease progresses.¹¹ The early introduction also allows patients to consider LCIG as one of several treatment options rather than a last-resort option. In general, expert opinion is moving toward earlier implementation of device-aided treatments such as LCIG.¹¹ The advantage of this approach is that change can be effected at a time when there is a greater likelihood for a response to dopaminergic therapy, rather than waiting until later stages of the disease when non-dopaminergic symptoms play a greater role. Moreover, it is a more effective strategy to attempt to maintain rather than restore mobility. For patients who are already experiencing motor fluctuations refractory to oral therapy, LCIG can be raised as an option during the discussion of other advanced therapies, such as DBS.

Patients can receive education about LCIG at routine visits through one-on-one discussion and by receiving and reading supporting educational materials. Community education events in conjunction with local support/advocacy groups have also been effective in reaching a larger audience. Peer mentoring, wherein a patient receiving LCIG discusses the experience with an individual or small group considering LCIG, can also be highly beneficial.

Education should include several key messages: (1) LCIG is levodopa, but in a form that is delivered continuously through a pump to the site of levodopa absorption in the jejunum. (2) The tube is part of the treatment. The tube bypasses a slow or inconsistent gastric emptying, thus achieving stable levodopa levels in the bloodstream. (3) The treatment is reversible. Removal of the percutaneous tubing results in closure and healing of the stoma. If after a 6-month period or other set time point there is not improvement, LCIG may be discontinued and other therapeutic options pursued.

As a patient's disease progresses, more detailed information about LCIG can be provided, including specifics of the tube

placement procedure and its possible risks. Setting realistic expectations is key.

Initiating LCIG Treatment

Levodopa Response

Levodopa responsiveness is an important predictor of success. In general, this can be tested with standard oral medications. Measurements of baseline Unified Parkinson's Disease Rating Scale "on" and "off" scores may be helpful in this process but are not required. There is no specific cutoff or minimum change; this remains a matter of clinical judgment. A key difference in the US clinical trials of LCIG compared with previous studies was that a test of LCIG via temporary nasojejunal tube before percutaneous tube placement was not required.^{2,25} In US practice, patients proceed to percutaneous endoscopic gastrojejunostomy (PEG-J) placement without the nasojejunal tube step and LCIG is initiated on an outpatient basis, thereby minimizing or eliminating the need for hospitalization.

Tube Insertion

Changes in oral PD medications are not necessary before the gastrojejunostomy procedure. Every attempt should be made to ensure that the fewest possible doses of levodopa are missed on the day of the procedure. Although the patient will be prohibited from oral intake of food or fluids four to six hours before the procedure, with proceduralist approval, scheduled levodopa doses should be taken with small sips of water as close to the usual schedule as possible. Post-procedure, oral levodopa administration should be resumed promptly and continued until LCIG titration is begun.

Prophylactic antibiotic administration perioperatively is strongly recommended.²⁶ The preferred agent is typically a second-generation cephalosporin; however, if the patient has a penicillin allergy, vancomycin may be used. Prophylactic antibiotic use is not necessary in cases of tube replacement. We recommend that the neurologist alert the proceduralist to avoid dopamine antagonist antiemetics and antipsychotics perioperatively.

As with any gastrointestinal endoscopic procedure, risk of bleeding associated with antithrombotic therapy use should be taken into consideration. The decision to maintain or discontinue antithrombotic therapy should weigh thrombotic risk against risk of bleeding. Recent guidelines from the American Society for Gastrointestinal Endoscopy recommend continuation of low-dose aspirin or non-steroidal anti-inflammatory drugs in the perioperative period and discontinuation of thienopyridines for five to seven days, or switching to aspirin monotherapy before the procedure.²⁷ In patients requiring dual antiplatelet therapy, thienopyridine treatment may be stopped five to seven days before the procedure (or three to five days for ticagrelor) while aspirin treatment is maintained; however, the procedure should be deferred in patients who have undergone intracoronary stent placement or who have had a recent acute coronary syndrome and have not

completed the minimum duration of antithrombotic therapy. For patients receiving warfarin, transition to low-molecular-weight heparin as a bridging agent, with discontinuation shortly before the procedure and resumption after, has been used safely.²⁸

Using data from phase 3 clinical trials of LCIG, a panel of gastroenterologists has compiled best-practice recommendations for performing PEG-J placement and for post-placement care (see Epstein et al. 2016).²⁶ Our additional suggestions are presented in Supporting Table 1.

LCIG Initiation and Titration

There is no set interval for initiating LCIG after the percutaneous tube has been placed. Some practices will start titration the day after the procedure, whereas others will wait a minimum of one to two weeks to allow the stoma to heal and for pain and discomfort to ease.²⁹ Shorter intervals between PEG-J placement and LCIG initiation may be preferred for patients who must travel a considerable distance to the clinic. Scheduling and titration duration is also highly practice-specific. The patient may be evaluated for up to eight hours on the first day of titration (although a titration period of two to four hours is used by some practices), during which time he or she will be monitored frequently by a nurse practitioner or medical assistant (approximately every 15 to 30 minutes), with intermittent examinations by the movement disorder specialist/neurologist. The second day of titration is usually shorter, and the need for subsequent titration days will depend on the patient's response to therapy and physician's standard practice. Starting on day two, most specialists will ask the patient to present to the office in the "on" state with the pump running to allow for fine tuning adjustments.

The starting dose of LCIG is based on the patient's daytime oral levodopa dose (assuming that oral levodopa will continue to be administered at bedtime) combined with the approximate equivalent dose of other antiparkinson medications if they will be replaced by LCIG. If the patient's antiparkinson medications had been converted to levodopa equivalents pre-procedurally, then the starting dose of LCIG is based solely on the patient's daytime oral levodopa dose. Non-levodopa PD medications may be discontinued at the time of titration, continued during LCIG treatment, or phased out after the initial LCIG titration period at the clinician's discretion. It is important, particularly with dopamine agonists, to wean patients off medication slowly to prevent withdrawal reactions. The presence of certain symptoms may drive the decision to maintain concomitant therapy. For example, dopamine agonists may be maintained for a patient who experiences restless legs.

A conversion chart for levodopa dose equivalency of PD medications has been published by Tomlinson et al.³⁰ Not included in Tomlinson's review, however, is a discussion of carbidopa/levodopa extended-release capsules (Rytary). Based on a recommended dose conversion from immediate-release levodopa to extended-release capsules of approximately 2-fold,³¹ an estimated equivalent levodopa dose can be calculated by multiplying the milligrams of levodopa in Rytary form (i.e., 95 mg for a 23.75/

95-mg capsule) by the number of capsules per day, and dividing the result by 1.75 (if the patient has predominantly "off" time) or 2 (if the patient has troublesome peak dose side effects on oral therapy).

On the first day of titration, the patient should come to the clinic without having taken his or her usual morning dose of levodopa (i.e., in the "off" state). The morning LCIG bolus dose is administered in clinic and the initial continuous dose is begun. The morning LCIG bolus volume is calculated by multiplying the usual morning levodopa dose by 0.8 (to decrease hyperkinesia) and dividing the result by 20 mg/mL (the concentration of LCIG). For a patient whose pre-LCIG morning levodopa dose was 150 mg, the LCIG morning dose calculation would be: $(150 \text{ mg} \times 0.8) \div 20 \text{ mg/mL} = 6 \text{ mL}$. After priming the system by adding 3 mL to fill the standard tubing (or determining the fill volume using a graduated syringe for non-standard tubing), the LCIG morning dose volume is administered over 10 to 30 minutes.

The initial continuous LCIG dose infusion rate is calculated by subtracting the morning levodopa dose from the total daytime levodopa equivalent and dividing the resulting difference by 20 mg/mL (each LCIG cassette holds 100 mL of a 20-mg/mL suspension, for a total available dose of 2000 mg). The resulting volume is then divided by the infusion time (typically 16 hours; although other intervals are possible). For a patient with a pre-LCIG levodopa morning dose of 150 mg and a total daytime levodopa equivalent of 1500 mg, the infusion rate would be calculated as: $((1500 \text{ mg} - 150 \text{ mg}) \div 20 \text{ mg/mL}) \div 16 \text{ hr} = 4.2 \text{ mL/hr}$. Although LCIG is not indicated for continuous 24-hour use, treatment of nocturnal akinesia with 24-hour infusion has been reported.³²

The LCIG delivery system allows patients to administer extra doses of LCIG as needed; any such administration during the titration period that occurs outside the clinic should be noted by the patient and used to inform subsequent dose adjustment. Patients should also note any need to pause the pump due to excessive dyskinesias. Excessive dyskinesias typically subside within 10 to 15 minutes of pausing the pump infusion. Continued excessive dyskinesia beyond 15 minutes after stopping levodopa infusion suggests either an excessively high continuous rate or possibly diphasic dyskinesia (which would suggest the need for a paradoxically higher continuous rate).

On subsequent titration days, the patient or caregiver will initiate treatment with the morning bolus dose before the patient comes to the clinic for further dose adjustment and monitoring. Determining when the patient has reached the proper titration point is a matter of clinical judgment. One strategy that has been effective is to identify the most affected motor abnormality that will respond to levodopa (e.g., tremor, gait) and titrate to that symptom. Patient perceptions of "off" time, "on" time, and improvements thereof should be weighed in titration decisions. Over the short term, "properly titrated" could be defined as the best "on" state without requiring extra LCIG dosing for at least 90 minutes. Completion of the titration stage should also require that the patient understand how to use the pump and how/when to make changes to LCIG delivery.

TABLE 3 Best Practices for Gastroduodenojejunal Catheter Care and Maintenance

<p>Stoma care</p> <p><i>Initial placement (~1 to 2 weeks)</i></p> <ul style="list-style-type: none"> • Remove dressing before cleaning stoma site • Wash area with mild soap and water • Dry well • Avoid alcohol- or polyvidone/iodine-containing products • Avoid in and out movement of PEG tube in stoma for 72 to 96 hours • For interventional radiology-inserted gastro-jejunal tube, sutures will dissolve in 1-2 weeks with button falling off. No bumper is used for this and only the tube is present <p><i>Once the stoma has healed</i></p> <ul style="list-style-type: none"> • Mobilize PEG tube frequently by moving it 2 to 3 cm in and out in the stoma (to prevent PEG bumper from becoming embedded) • Do not rotate the tubing • Patients can shower or swim after disconnecting the pump, making sure to dry the stomal area after the activity <p>PEG-J maintenance</p> <ul style="list-style-type: none"> • Gentle flush of the J tube (intestinal port) and PEG tube (gastric port) with 5 to 20 mL of room-temperature water daily at bedtime* • Gently moving the PEG tube back and forth a few centimeters periodically will prevent the internal PEG bumper from becoming embedded • 5 to 20 mL of water, carbonated beverage, or cranberry juice may be used to flush the tube if it is clogging • Do not rotate the J extension, as it may cause kinking or knotting
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Abbreviations: PEG, percutaneous endoscopic gastrostomy; PEG-J, percutaneous endoscopic gastrojejunostomy.

*Patients/care partners should be trained on the flushing technique.

The patient management team has options in terms of determining the extent to which a patient can adjust his or her morning dose and continuous dose rate through “lock level” settings on the pump. In lock level two, the healthcare team will be the only individuals capable of changing the dose settings. In lock level one, the patient or care partner is able to adjust the settings within a range specified by the provider. Lock level one is the most useful setting to maximize benefit without frequent clinic visits (e.g., for patients who must travel a considerable distance to the clinic), but it is only feasible if the patient and/or care partner has sufficient health literacy and intellectual capacity to make changes to the pump programming.

Patients who have DBS or may have levodopa-induced neuropsychiatric side effects warrant special consideration. For patients with DBS in globus pallidus (GPi), LCIG may be initiated at the calculated dose with any increase in dyskinesia addressed by increasing GPi stimulation. For patients with subthalamic nucleus DBS, the stimulation may be adjusted gradually with the calculated levodopa dose. LCIG titration in these patients may also be considered with the DBS device off. For patients with neuropsychiatric complications of levodopa, careful monitoring, especially with report of nocturnal symptoms from care partners, is crucial to improving quality of life with LCIG treatment.

Monitoring and Maintenance

Once reasonably stable titration is achieved, the timing and frequency of follow-ups are determined at the discretion of the neurological team. One scenario used in practice is to schedule a patient visit with the movement disorder specialist or nurse practitioner within four to six weeks of titration completion to ensure adequate dosing, and every three to six months thereafter for routine care. More frequent visits may be needed as symptoms

present. At each visit, the tube site should be examined. Efficacy measures may include the Parkinson’s Disease Questionnaire (PDQ-39) and patient estimates of hours per day of best “on” time, “off” time, and time with troublesome dyskinesias.

Routine monitoring of vitamin and homocysteine levels is recommended, given the association between levodopa treatment, vitamin B6 deficiencies, homocysteine elevation, and peripheral neuropathy.^{33,34} Cases of symptomatic and subclinical peripheral neuropathy (more frequently the latter) have been observed among patients treated with LCIG.^{34,35} Clinicians should be mindful of peripheral neuropathy symptoms (e.g., paresthesia, pain, gait abnormalities) when evaluating patients receiving LCIG and should monitor them as they would individuals receiving oral levodopa treatment. We suggest measuring B6 and B12 vitamin levels before the start of treatment. For patients with balance or gait complaints, performing baseline lower-extremity electromyography to compare with future studies may be useful. Vitamin supplementation may be performed prophylactically or if evidence of deficits is detected. Weight loss of unknown etiology has been reported with LCIG treatment,¹ although the consensus from our clinical experience is that major weight loss is not a frequent occurrence.

Changes or abnormalities in the appearance of the stoma site are a common cause of patient concern that result in emergent physician consultation. It is important for the treatment team to recognize when these issues merit intervention, and if they do, determine the immediacy of the action required (e.g., granulation at the stoma site is often misdiagnosed as infection). Peristomal infections typically occur early, within two to four weeks after percutaneous tube placement. It is rare to have a peristomal skin infection occur more than one month after the procedure. A small amount of seepage, crusting, redness, or modest pain at the stoma site is very common and is not indicative of an infection. A diagnosis of stomal infection requires clear erythema of more than 1 cm induration and pain at the site. Diagnosis can be expedited by having the patient send a digital image of the stoma site.

TABLE 4 Troubleshooting and Managing Stoma Site or Delivery System Issues

Finding	Possible Cause	Management/Treatment
Mild stoma leakage	This may occur, particularly if the PEG-J is used for feeding	<ul style="list-style-type: none"> • None indicated
Clear, demarcated erythema and pain at stoma site	Stoma infection; these will typically occur early after placement and are rare after 3 to 4 weeks	<ul style="list-style-type: none"> • Circling erythematous area to assess spreading is important to determine if there is active infection or cellulitis • Infection should be treated with antibiotics; topical antibiotics are generally not helpful • If the infection does not respond to treatment, the PEG-J tube will need to be removed
Discolored discharge, granulation tissue, or “proud flesh” develops without pain at the stoma site	This finding does not necessarily indicate infection	<ul style="list-style-type: none"> • Granulation tissue can be treated topically with silver nitrate
Pump alarm with a “High Pressure” message OR Sudden lack of therapeutic effect with LCIG without pump alarm OR Vague abdominal pain	PEG-J tube is knotted, kinked, obstructed, or has migrated	<ul style="list-style-type: none"> • J tube occlusion may be relieved with gentle water, Coca-Cola®, or cranberry juice flushing • If no external cause of blockage is observed, check the position of the tube with a plain abdominal film • Water soluble contrast through the J tube may be helpful • Abdominal CT scan may be performed, although routine X-rays are often sufficient • If the tube is kinked or has migrated, repositioning may be possible; if it is knotted, replacement is needed
Pump alarm OR LCIG infusion stops controlling symptoms in a previously stable patient	Tube has been pulled or connections have come loose	<ul style="list-style-type: none"> • If there is question about connectors coming apart or tubing that has pulled back, sending a cell phone picture to the patient management team is very helpful • The patient should resume oral PD medications • Replacement should be done expeditiously, but it is not an emergency

Abbreviations: CT, computed tomography; LCIG, levodopa-carbidopa intestinal gel; PD, Parkinson disease; PEG-J, percutaneous endoscopic gastrojejunostomy.

Establishing workflows with the proceduralist regarding the preferred method of communication for possible infection issues is advised.

In their quest to prevent infection, many patients and care partners overtreat the stoma site with topical creams and ointments. Best practices for stoma care are presented in Table 3. It is important to keep the area dry. A dressing can be used during the day (which absorbs seepage and limits rubbing and skin irritation from the PEG-J tube), but the stoma should be open to air at night. After the stoma has healed (typically in three to five days), the PEG tube should be mobilized frequently by moving it 2 to 3 cm in and out of the stoma (to prevent buried bumper syndrome, wherein the internal PEG bumper retracts into the stomach wall), but the tubing should not be rotated, as this increases the risk for displacement of the J tube.

Maintenance requirements for the PEG-J tube are generally minimal (Table 3). The need for PEG-J tube replacement is highly individualized. Some patients develop issues after three to four months, whereas others can go years with the original tubing.³⁶ Among 395 patients enrolled in four LCIG phase 3 clinical

trials, 9% required replacement of the PEG tube and 37% required replacement of the J tube during the first year of treatment.²⁶ Most clinicians opt to not routinely replace the PEG or J tubes; they only perform replacement if there is breakage, leakage, occlusion that cannot be opened with gentle flushing, or displacement of the tubing from the small bowel. PEG and J tubes may be replaced separately or at the same time (with minimal additional expense). Repositioning of the tube rather than replacement may be possible if the displacement is not substantial.

Guidance on troubleshooting and managing the stoma site and delivery system issues is presented in Table 4. The movement disorder specialist/neurologist or other member of the multidisciplinary team can address minor issues such as separation of the connectors from the LCIG pump to the J extension, whereas more complex issues such as tube migration require the assistance of the proceduralist. Patients are often unclear regarding whom they should contact when issues arise. It is important that contacts be determined a priori by the treatment team and clearly communicated to the patient. A point person from the neurology team who coordinates care with other team members

TABLE 5 Clinical Pearls**Assembling a multidisciplinary team**

- LCIG management requires a team-based approach that spans various medical disciplines
- Early establishment of roles and responsibilities facilitates work flow

Patient selection

- Patient selection for LCIG follows a similar process to that of other device-aided therapies, with the addition of consideration for gastrointestinal procedure suitability and an assessment of care partner support
- For a clinician or program that is new to LCIG treatment, we recommend starting with patients who fit the profile of the registration trial. Experience and accumulating clinical data may reveal additional LCIG candidate patient populations
- Patient education regarding LCIG should be implemented early in the disease process, with more detailed discussions as the patient's disease progresses

Initiating LCIG treatment

- Initiating LCIG treatment can be individualized to fit the needs of the practice
- The duration of the LCIG titration process varies among patients and practices, but generally ranges from 1 to 5 days

Monitoring and maintenance

- Vitamin supplementation may be administered prophylactically (e.g., with folic acid, vitamin B6, and vitamin B12 daily) or if deficiencies are detected
- Familiarity with common stoma site observations and delivery system issues can streamline diagnostic determination and the appropriate patient management solution
- Patients should be provided with guidance regarding whom to contact in the event of a possible complication or delivery system issue, and how to manage symptoms with oral levodopa pending correction of the problem

Abbreviations: LCIG, levodopa-carbidopa intestinal gel.

as needed gives the patient a single contact point and ensures consistency in the management approach. Patients should also be advised of when to contact DuoConnect (the manufacturer-sponsored support program for patients and providers) vs. the healthcare team.

Patients should be provided with explicit instructions regarding management in the event of tube issues or pump failure, and when this does occur, they should always have a supply of immediate-release carbidopa/levodopa on hand. The prescription should be checked periodically to be certain the medications have not expired. Patients should have written instructions regarding the number of tablets to take and the frequency to achieve a dose comparable to that of the LCIG infusion. Patients should be aware that LCIG treatment can be resumed after the system has been restored to functionality; however, hospitals unfamiliar with LCIG therapy may not be able to support use of the therapy during hospitalization (including rehabilitation). In the event of J tube obstruction, the gastric port of the PEG-J can be used for LCIG infusion (in lieu of reverting to oral therapy) as a temporary measure until the J extension can be replaced.

Conclusions

The introduction of LCIG in the US gives patients with advanced PD another option when conventional therapy is no longer sufficiently effective. The guidance provided herein and summarized in Table 5 provides a starting point for US clinicians to gain familiarity with LCIG therapy. Exploring additional resources related to clinical data, technical specifications, and patient management are recommended to augment this overarching review. By building on the existing framework and tailoring protocols to their practice needs, clinicians who have not previously utilized LCIG can incorporate this option into their treatment armamentarium for advanced PD.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Conception, B. Outline Development and Review, C. Identification of Cited Research/Literature; D. Writing of the First Draft, E. Review and Critique.

M.B.: 3A, 3B, 3C, 3E

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A.V.: 3A, 3B, 3E

K.K.: 3E

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H.F.: 3E

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References

1. 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(4):500-509.
2. 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(2):141-149.
3. Antonini A, Yegin A, Preda C, et al. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. *Parkinsonism Relat Disord* 2015;21(3):231-235.
4. Lopiano L, Modugno N, Marano P, et al. Motor outcomes in patients with advanced Parkinson's disease treated with levodopa/carbidopa intestinal gel in Italy: an interim analysis from the GREENFIELD observational study. *Neurol Sci* 2016;37(11):1785-1792.
5. Valldeoriola F, Grandas F, Santos-Garcia D, et al. Long-term effectiveness of levodopa-carbidopa intestinal gel in 177 Spanish patients with advanced Parkinson's disease. *Neurodegener Dis Manag* 2016;6(4):289-298.
6. Abbruzzese G, Barone P, Bonuccelli U, Lopiano L, Antonini A. Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection. *Funct Neurol* 2012; 27(3):147-154.
7. Seeberger LC, Hauser RA. Carbidopa levodopa enteral suspension. *Expert Opin Pharmacother* 2015;16(18):2807-2817.
8. Wirdefeldt K, Odin P, Nyholm D. Levodopa-Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. *CNS Drugs* 2016;30(5):381-404.
9. Virhammar J, Nyholm D. Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: clinical evidence and experience. *Ther Adv Neurol Disord* 2017;10(3):171-187.
10. Volkmann J, Albanese A, Antonini A, et al. Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: an evidence-based review. *J Neurol* 2013;260(11):2701-2714.
11. Kruger R, Hilker R, Winkler C, et al. Advanced stages of PD: interventional therapies and related patient-centered care. *J Neural Transm (Vienna)* 2016;123(1):31-43.
12. Pedersen SW, Suedmeyer M, Liu LW, et al. The role and structure of the multidisciplinary team in the management of advanced Parkinson's disease with a focus on the use of levodopa-carbidopa intestinal gel. *J Multidiscip Healthc* 2017;10:13-27.
13. *Duopa (carbidopa and levodopa) enteral suspension*. North Chicago, IL: AbbVie Inc.; 2016.
14. Standaert D, Odin P, Robieson WZ, Zamudio J, Chatamra K. Baseline characteristics associated with therapeutic response to levodopa-carbidopa intestinal gel treatment for advanced Parkinson disease. 20th International Congress of Parkinson's Disease and Movement Disorders. Berlin, Germany; 2016.
15. Antonini A, Fung VS, Boyd JT, et al. Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. *Mov Disord* 2016;31(4):530-537.
16. Timpka J, Fox T, Fox K, et al. Improvement of dyskinesias with l-dopa infusion in advanced Parkinson's disease. *Acta Neurol Scand* 2016;133(6): 451-458.

17. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. *Front Neurol* 2012;3:88.
18. Odin P, Ray Chaudhuri K, Slevin JT, et al. Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program. *Parkinsonism Relat Disord* 2015;21(10):1133–1144.
19. Devos D, French DSG. Patient profile, indications, efficacy and safety of duodenal levodopa infusion in advanced Parkinson's disease. *Mov Disord* 2009;24(7):993–1000.
20. 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(2):742–765.
21. Chang FC, Tsui DS, Mahant N, et al. 24 h Levodopa-carbidopa intestinal gel may reduce falls and "unresponsive" freezing of gait in Parkinson's disease. *Parkinsonism Relat Disord* 2015;21(3):317–320.
22. Burack MA, Santiago A, Biglan K, Barbano R. Levodopa-carbidopa intestinal gel therapy (LCIG) choices and clinical outcomes in DBS-eligible versus palliative stage PD patients. Parkinson Study Group Annual Meeting. Portland, Oregon; 2016.
23. Klostermann F, Jugel C, Marzinzik F. Jejunal levodopa infusion in long-term DBS patients with Parkinson's disease. *Mov Disord* 2011;26(12):2298–2299.
24. Eggert K, Schrader C, Hahn M, et al. Continuous jejunal levodopa infusion in patients with advanced parkinson disease: practical aspects and outcome of motor and non-motor complications. *Clin Neuropharmacol* 2008;31(3):151–166.
25. Standaert DG, Rodriguez RL, Slevin JT, et al. Effect of Levodopa-carbidopa Intestinal Gel on Non-motor Symptoms in Patients with Advanced Parkinson's Disease. *Mov Disord Clin Pract* 2017;4(6):829–837.
26. Epstein M, Johnson DA, Hawes R, et al. Long-term PEG-J tube safety in patients with advanced Parkinson's disease. *Clin Transl Gastroenterol* 2016;7:e159.
27. ASGE Standards of Practice Committee, Acosta RD, Abraham NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016;83(1):3–16.
28. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood* 2011; 117(19):5044–5049.
29. Fasano A, Liu LW, Poon YY, Lang AE. Initiating intrajejunal infusion of levodopa/carbidopa intestinal gel: an outpatient model. *Mov Disord* 2015;30(4):598–599.
30. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25(15):2649–2653.
31. Hauser RA. How to dose carbidopa and levodopa extended-release capsules (Rytary). *Clin Med J* 2015;1(2):34–37.
32. Ricciardi L, Bove F, Espay KJ, et al. 24-Hour infusion of levodopa/carbidopa intestinal gel for nocturnal akinesia in advanced Parkinson's disease. *Mov Disord* 2016;31(4):597–598.
33. Ceravolo R, Cossu G, Bandettini di Poggio M, et al. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. *Mov Disord* 2013;28(10):1391–1397.
34. Uncini A, Eleopra R, Onofri M. Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management. *J Neurol Neurosurg Psychiatry* 2015;86(5): 490–495.
35. Merola A, Romagnolo A, Zibetti M, Bernardini A, Cocito D, Lopiano L. Peripheral neuropathy associated with levodopa-carbidopa intestinal infusion: a long-term prospective assessment. *Eur J Neurol* 2016;23(3): 501–509.
36. Lang AE, Rodriguez RL, Boyd JT, et al. Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials. *Mov Disord* 2016; 31(4):538–546.

Supporting Information

Supporting information may be found in the online version of this article.

Supporting Table 1. Percutaneous Endoscopic Gastrojejunostomy (PEG-J) Procedural Recommendations