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Review article

Can suitable candidates for levodopa/carbidopa intestinal gel therapy be identified using current evidence?

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ABSTRACT

Advanced Parkinson's disease (APD) is characterized by increased functional disability, caused by motor complications, the presence of axial symptoms, and emergent disease- and drug-related non-motor symptoms. One of the advanced therapies available is intrajejunal infusion of levodopa/carbidopa intestinal gel (LCIG); however, patient selection for this treatment is sometimes difficult, particularly because of overlapping indications with other alternatives.

In recent years, strong evidence has supported the use of LCIG in treating motor fluctuations associated with APD, and several clinical studies provide emerging evidence for additional benefits of LCIG treatment in certain patients. This article provides an overview of the published literature on the benefits, limitations, and drawbacks of LCIG in relation to PD symptoms, the psychosocial impact of the disease, and the quality of life of patients, with the aim of determining candidates for whom treatment with LCIG would be beneficial. According to current evidence, patients with APD (defined as inability to achieve optimal control of the disease with conventional oral treatment), a relatively well-preserved cognitive-behavioral status, and good family/caregiver would count as suitable candidates for LCIG treatment. Contraindications in the opinion of the authors are severe dementia and active psychosis.

1. Introduction

The aim of currently available conventional drug treatments of Parkinson's disease (PD; levodopa, dopamine agonists [DAs], and enzyme inhibitors) is to enhance dopaminergic transmission [1]. These treatments greatly improve symptoms of PD in the early and middle stages of the disease [2–6]. Due to the progressive nature of PD, however, the benefits are gradually reduced as the symptoms worsen [7,8]. The concept of advanced PD (APD) is broad, but it is generally associated with motor complications (fluctuations and dyskinesia that cannot be adequately controlled by standard medications), increased functional disability, the stage of the disease [9], by the presence of axial symptoms (gait and balance impairment), and by emergent disease- and drug-related non-motor symptoms (NMS; mainly neuropsychiatric complications, including cognitive impairment) [10,11],

Abbreviations: APD, Advanced Parkinson's disease; DBS, Deep brain stimulation; ICD, Impulse control disorders; LCIG, Levodopa-carbidopa intestinal gel; NMS, Non-motor symptoms; NMSS, Non-motor symptoms scale; PD, Parkinson's disease; PDSS, Parkinson's disease sleep scale; PEG, Percutaneous endoscopic gastrostomy; QoL, Quality of life

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Table 1
Summary of improvement in OFF time, ON time and dyskinesia with LCIG as reported in the literature.

Study	Change in OFF time	Change in ON time without dyskinesia	Change in ON time with dyskinesia
Antonini et al. 2007 [44] 9 patients Observational prospective	At 12 months, 9.5-fold reduction. (mean reduction from 284 to 30 min; $p < 0.01$)		Reduced by nearly 4-fold at 6 and 12 months (mean reduction from 156 to 40 min; $p < 0.01$)
Antonini et al. 2008 [45] 22 patients Observational prospective	UPDRS IV item 39 Baseline: 2.6 ± 1.2 After 1 year 1.28 ± 0.5 After 2 years: 1.48 ± 0.8 ($p < 0.05$)	No changes in dyskinesia duration	No changes in dyskinesia duration
Eggert et al. 2008 [46] 13 patients Observational prospective	Percentage of time Baseline: 50 ± 14% After 6 months: 11 ± 7% ($p < 0.01$)		Percentage of time Baseline: 17 ± 15% After 6 months: 5 ± 6% ($p < 0.01$)
Santos-García, 2010 [48] 9 patients Observational retrospective	90.9% improvement	Daily ON time showed 66.6% improvement	
Puente et al. 2010 [49] 9 patients Observational retrospective	Reduced from 9.4 ± 2.1 h to 3.1 ± 2.7 h ($p < 0.05$)	Daily ON time increased from 6.1 ± 1.9 to 12.0 ± 3.4 h ($p < 0.05$)	
Fasano et al. 2012 [52] 14 patients Observational retrospective	UPDRS IV item 39 unchanged (−7.6%) Off duration reduced by 48.6% ($p = 0.00001$)		Reduced by 38.5% ($p = 0.001$)
Antonini et al. 2013 [59] 73 patients Observational prospective	UPDRS IV item 39. OFF time duration Baseline 1.59 ± 0.96 Month 6: 0.85 ± 0.63 ($p < 0.05$) Month 12: 1.06 ± 0.73 ($p < 0.05$)		UPDRS IV item 32. Dyskinesia duration Baseline: 1.72 ± 0.98 Month 6: 1.15 ± 0.87 ($p < 0.05$) Month 12: 1.45 ± 0.83 ($p < 0.05$)
Foltynie et al. 2013 [23] 12 patients Observational prospective	Percentage of time Baseline: 29.4 ± 13.2% Follow-up 16.7 ± 22.2% ($p = 0.06$)		Percentage of time Baseline: 16.6 ± 18.6% Follow-up 8.2 ± 10.3% ($p = 0.22$)
Caceres Redondo et al. 2014 [62] 29 patients Observational retrospective	UPDRS IV item 39. OFF time duration Baseline: 58.1 ± 11.5 Follow-up: 24.6 ± 7.2 ($p < 0.05$)		UPDRS IV item 32. Dyskinesia duration Baseline: 60.6 ± 37.8 Follow-up: 48.8 ± 28.7 ($p < 0.05$).
Olanow et al. 2014 [37] 35 patient allocated to LCIG Prospective, double-blind trial	Decreased by 4.04 ± 0.65 h	Increased by 4.11 ± 0.75 h	Decreased by 1.8 ± 1.3
Slevin et al. 2015 [38] Open-label extension of ref. [37] LCIG-naive: 29 patients LCIG continuing: 33 patients	LCIG-naïve: Decreased 2.34 ± 2.78 h ($p < 0.001$) LCIG-continuing: Sustained reduction 0.42 ± 2.67 h ($p = 0.377$)	LCIG-naïve: Increased 2.19 ± 3.70 h ($p = 0.005$) LCIG-continuing: Increased 1.00 ± 2.58 h ($p = 0.036$)	
Pickut et al. 2014 [22] 37 patients Observational prospective	UPDRS IV item 39 89.5% of patients experienced improvement		UPDRS IV item 32. Dyskinesia duration 60–70% of patients experienced improvement
Sensi et al. 2014 [35] 28 patients Observational prospective	UPDRS IV item 39. OFF time duration Baseline: 2.3 ± 0.9 24 months: 48% improvement ($p < 0.00001$)		UPDRS IV item 32. Dyskinesia duration Baseline: 2.2 ± 1.1 Significant improvement after 24 months
Zibetti et al. 2014 [66] 59 patients Observational retrospective	UPDRS IV item 39. OFF time duration Baseline: 1.8 ± 0.7 Follow-up: 0.9 ± 0.5 Duration reduced by 49%($p < 0.001$)		UPDRS IV item 32. Dyskinesia duration Baseline: 1.7 ± 0.9 Follow-up: 1.2 ± 0.0.7 Duration reduced by 30% ($p = 0.002$)
Antonini et al. 2015 [70] 56 patients with data for this analysis Observational prospective	Baseline: 7.1 ± 3.5 h 12 months reduced by 4.7 ± 3.4 ($p < 0.0001$)		Baseline: 5.2 ± 4.5 h 12 months reduced by 1.7 ± 5.0 ($p = 0.023$)
Buongiorno et al. 2015 [74] 72 patients Observational prospective	Baseline: 6.8 ± 2.8 h (45% of day) Last visit: 3.0 ± 3.5 h (20% of day)		Patients with < 50% at baseline: increased from 18% to 35% at last visit Patients with > 50% at baseline: no change
Calandrella et al. 2015 [81] 35 patients	UPDRS IV item 39. OFF time duration Baseline: 2.4 ± 0.6 Follow-up 1.1 ± 0.6 ($p < 0.001$)		Dyskinesia score (UPDRS IV items 32–33) Baseline: 2.2 ± 0.7 Follow-up 1.5 ± 0.7 ($p < 0.001$)

(continued on next page)

Table 1 *(continued)*

Study	Change in OFF time	Change in ON time without dyskinesia	Change in ON time with dyskinesia
Observational prospective			
Fernandez et al. 2015 [41] 324 patients Observational prospective	Baseline: 6.75 ± 2.35 h 12 months: 2.32 ± 2.05 h (65.6% reduction $p = 0.001$)	Baseline: 17.4 ± 6.6 h 12 months: + 4.8 ± 3.4 h (62.9% increase; $p < 0.001$)	Baseline: 1.61 ± 2.03 h 12 months: 1.24 ± 2.10 h (22.5% increase; $p < 0.023$)
Chang et al. 2016 [80] 15 patients Observational prospective	Reduced from 6.3 ± 2 to 1.9 ± 2 h	Increased from 4.5 ± 3 to 7.5 ± 5 h	
Băjenaru et al. 2016 [73] 113 patients Observational retrospective	Reduced 1.36 h (from 7.5 h to 6.14 h) ($p < 0.0001$)		Reduced by 29.4%
Valldeoriola et al. 2016 [65] 117 patients Observational retrospective	Baseline 47.6% LCIG reduced to 16.2%	Baseline 21.6% LCIG: increased to 55.6%	
Timpka et al. 2016 [72] 9 patients Observational prospective		112% increase after 6 months ($p < 0.01$)	47% decrease after 6 months ($p < 0.05$)
Lopiano et al. 2016 [75] 145 patients (Interim results) Observational prospective	UPDRS IV item 39. OFF time duration Decreased from 2.1 ± 0.8 to 0.9 ± 0.7 (57% reduction $p < 0.0001$)		Reduced 28%

with onset generally several years after diagnosis [12]. Together, these aspects of the disease, heterogeneous and requiring an individualized approach, lead to progressive disability and impaired quality of life (QoL) for patient and caregivers [13–16].

In individuals with APD clinicians may consider the use of non-conventional device-aided alternatives such as deep brain stimulation (DBS), apomorphine continuous subcutaneous infusion, or intrajejunal infusion of levodopa/carbidopa intestinal gel (LCIG) [11,17–19]. Determining which patients will most likely benefit from these device-aided therapies can be challenging, particularly because of overlapping indications. In any event, the invasive nature [20,21] and cost [20–23] of these therapies make it imperative to assess patient's suitability on a case-by-case basis [18,19,24].

Pulsatile dopaminergic stimulation with oral levodopa is considered to play a role in the development of late complications in PD [25,26]. Non-oral administration of levodopa was developed with the aim of providing more continuous dopaminergic delivery and overcoming the inherent variability in absorption related to gastric emptying [18,27]. LCIG requires the placement of a gastroduodenal tube to elicit continuous infusion and absorption of the drug bypassing the stomach [1], so that relatively stable plasma levels of levodopa are achieved [28]. In this regard, pharmacokinetic studies have established that the degree of fluctuation of levodopa and carbidopa plasma concentrations (($C_{max} - C_{min}$)/average concentration) is very low within hours 2 to 16 in a 16-h long infusion of LCIG (0.52 and 0.96 respectively) [29]. Intra-subject coefficients of variation of these drugs were also very low in this analysis (13% and 19%, respectively). Additionally, two studies have reported reduced variability of levodopa levels compared to oral tablets. Kurth et al. found a reduction from 38 ± 11% with tablets to 17 ± 9% with infusion) [30], and Nyholm et al. reported a reduction from 34% intraindividual coefficient of variation with oral tablets to 14% ($p < 0.01$) with infusion in a series of 16 patients [31]. This was also observed in a mixed-effects model characterizing population pharmacokinetics, based on results of phase I and phase III trials, that showed similar bioavailability with half the intra-subject variability, and faster absorption compared to oral tablets [32]. Such “continuous dopaminergic delivery” [33] improves motor and potentially some non-motor fluctuations, and dyskinesias. These symptoms are common in patients undergoing long-term treatment with oral levodopa, particularly in those with the onset of motor symptoms before the age of 60 [2]. Although clinical trials have demonstrated the efficacy and safety of DBS, apomorphine, and LCIG, the choice of suitable candidates depends on multiple clinical and patient-related variables [11,21,24,34–41].

No randomized controlled trials have directly compared these three treatments [18,19,42], and in patients with APD, selection of the most appropriate therapy is often challenging. In recent years, strong evidence has supported the use of LCIG in treating motor fluctuations associated with APD, and several clinical studies provide emerging evidence for additional benefits of LCIG treatment in certain patients. The aim of this review is to define the benefits and drawbacks of treatment with LCIG that may help identify the profile of suitable candidates.

2. Motor complications: fluctuations and dyskinesias

The progression of PD and the chronic use of oral levodopa are associated with narrowing of the therapeutic window, leading to motor complications (fluctuations, dyskinesia). A typical fluctuation is the end-of-dose or wearing-off phenomenon; however, more complex and unpredictable patterns often follow. Dyskinesias include peak-dose and biphasic dyskinesias during ON time, as well as dystonia during OFF time. As these complications may result in severe disability, reduction of OFF time, dyskinesia, and other motor symptoms are of the utmost importance. The vast majority of patients with PD eligible for device-aided treatment are currently treated with levodopa with or without DAs, along with other antiparkinsonian drugs. The lack of success in controlling motor symptoms and/or the presence of adverse effects due to high doses or combinations of oral medications define the eligibility for patients included in studies of LCIG.

2.1. Motor fluctuations

The continuous absorption of levodopa/carbidopa achieved with LCIG has been shown to extend ON time maintaining relatively stable plasma drug levels with less extreme peaks and troughs [29]. Most

studies have reported positive outcomes in motor complications [22,23,31,35,37–41,43–75], with reduced duration of OFF time and increased ON time without disabling dyskinesia (Table 1). Two recent prospective clinical trials, a double-blind, double-dummy study [37] and an open-label baseline-controlled study [41], reported a reduction in OFF time of approximately 4 h per day from the baseline (12 weeks [37] and 12 months [41], respectively). The first of these studies, a phase III trial published by Olanow et al., reported a significantly greater reduction in OFF time with LCIG (4.04 h) compared with the reduction in the control group treated with oral levodopa (2.14 h) [37]. Although this study had a short follow-up period, the improvement was maintained in patients who continued from the double blind study into the 52-week open-label extension study [38]. Additionally, LCIG-naïve patients starting treatment in this extension study experienced a reduction in OFF time similar to that reported by the LCIG arm in the double-blind trial. In the Fernandez et al. phase III open-label, baseline-controlled study [41], a similar 4-h reduction in OFF time in a cohort of 354 patients was reported, representing a significant 65.6% improvement in this outcome over a 12-month follow-up period (with 272/354 patients completing the study).

Studies consistently report a significant reduction in OFF time, leaving little doubt regarding the beneficial effects of LCIG in patients with this complication over long periods of time [22,35,39,41,44,46–48,52,59,61,66,68,70,73–81]. Furthermore, some studies suggest that LCIG may improve other OFF time-related PD symptoms, such as dystonic pain [46,82–84] and selected patients with morning akinesia and OFF-related dystonia have also been successfully treated with 24-h infusions [46,85]. Significant improvements have also been reported in motor fluctuations, including wearing-off, delayed ON, no-ON, unpredictable OFF periods, and morning akinesia [74,75].

Preliminary evidence suggested that the magnitude of improvement varied with disease duration: in a retrospective national cohort, patients with disease duration of ≥ 10 years showed significantly less improvement in OFF time (28.9% reduction) compared to patients with PD duration of < 10 years (38% reduction) [86]. However, the recently reported analysis from the 2-year data of the GLORIA registry suggested that age (dichotomized into < or ≥ 65 years) or disease duration (dichotomized into < or ≥ 10 years) did not impact outcomes in quality of life and daily life activities [87], and OFF time reduction was very stable over the two years. Also, in a post-hoc analysis of baseline characteristics related to the therapeutic response to LCIG performed in the open-label phase-III study by Fernandez et al. [41], age and disease duration did not play a role in OFF time improvement [88]. At any rate, several studies have shown that, in the absence of severe adverse events, control of motor fluctuations continues for several years in most patients [53,66,83].

2.2. Dyskinesias

With regard to improvement in dyskinesia, trials report increases in ON time with no disabling dyskinesia similar to the reduction in OFF time (4 h/day) [37,38,41,89]. General improvement is consistent in retrospective and prospective studies with follow-up periods of up to 2 years, and significant reductions in ON time with troublesome dyskinesia have also been reported [46,48,52,59,61,69,70,72,73,75,79,90]. However, this improvement seems to be heterogeneous. Some studies describe a significant improvement in nearly all patients [47,69], while others report a worsening of disease in some patients [74,91]. A recent study of 72 patients found that in individuals with dyskinesia for < 50% of the day before LCIG, overall time with dyskinesia significantly increased after 3 months of treatment. In patients with > 50% of time with dyskinesia before LCIG, periods of troublesome dyskinesia were significantly reduced, while the percentage of time with dyskinesia remained the same [74]. These variations might be partly explained by a narrow therapeutic window and difficulty in achieving an accurate dose adjustment. Also, many patients are titrated against OFF time, and accept an increase in mild dyskinesia that does not interfere with daily activities. These results suggest that dyskinesia is an indication for LCIG. Preliminary results suggest that disease duration before LCIG may have no impact on dyskinesia outcomes [86], and long-term improvement has been reported [43].

2.3. Other motor symptoms

Levodopa/carbidopa intestinal gel has also been shown to systematically improve efficacy parameters, such as the Unified Parkinson's Disease Rating Scale (mostly evaluated in ON). General improvement with LCIG treatment compared with conventional treatment or baseline disease activity has been reported [37,38,49,55,92]. This improvement affects activities of daily living [41,44,49,55,62,70,89], motor symptoms [37,49,56,70,82], and motor complications [35,37,38,49,52,55,56,58,59,62,66]. Improvements in the subscales of activities of daily living and motor complications are consistent with a longer duration of dyskinesia-free ON time (allowing for independence in daily activities) and the reduction of OFF time with LCIG. It is interesting to note, however, that several studies found no improvement with LCIG in the motor symptoms subscale [35,44,52,62], usually measured during OFF time, and a long-term study (up to 2 years follow-up) even reported worsened symptoms [58]. This underlines the benefit of continuous infusion of levodopa in order to maintain ON time. Additionally, in 2 short series, treatment with LCIG has been shown to improve freezing of gait (measured by the specific questionnaire) in up to 45% of patients with severe disability due to this complication [68,69]. This improvement was also accompanied by a reduction in falls in one of these studies [68], and similar results had been previously reported [35]. Motor outcomes in some retrospective and prospective studies have suggested that starting treatment earlier in younger patients and in those with shorter disease duration might improve overall outcomes in patients treated with LCIG [23,47,86] but, as previously noted, there is conflicting evidence, since the 2-year analysis from the GLORIA registry and the 1-year post-hoc analysis of the open-label phase-III trial have not found differential outcomes related to age or disease duration [87,88]. Some authors have suggested that a long life expectancy might also be taken into account [90].

2.4. Non-motor complications

Patients with APD may present with cognitive impairment, depression, anxiety, apathy, sleep disorders [93,94], pain, and sensory and autonomic impairment (such as orthostatic hypotension, genitourinary problems, and constipation). Unfortunately, treatment of these symptoms is often suboptimal [94,95]. Psychiatric disorders secondary to dopaminergic treatment are also common, particularly impulse control disorders (ICDs), such as pathological gambling or shopping, and psychotic symptoms [90]. These NMS are relevant in APD, since they intensify as the disease progresses, and may become incapacitating in advanced stages of the disease [96].

Several open-label studies have evaluated the effect of LCIG treatment on NMS using validated tools, most often the Non-Motor Symptoms Scale (NMSS). A recent non-randomized open-label trial reported by Dubow et al. showed a 38.3% improvement in the NMSS compared to baseline after a mean of 18 ± 106 days of treatment [67], which is similar to the − 41.0% relative change observed in the EuroInf study [60] after 6 months of treatment with LCIG. However, Fasano et al. [52] reported a significant 14% improvement in the NMSS after a follow-up of 24 ± 14.4 months. These results are generally consistent with several other studies [56,62,70,97], and the final results of the GLORIA registry, with a significant and persistent reduction in NMSS score from baseline through month 24 [98]. However, reductions in the NMSS did not always reach statistical significance [35]. Regarding

studies that did not specifically use this scale, a general improvement of 81.8% in NMS was reported in a retrospective study [48], as well as in more specific NMS (pain, dysphagia, and dysarthria) [47].

2.5. Neuropsychiatric disorders

Improvement of several neuropsychiatric disorders after medium to long-term treatment (> 2 years) with LCIG has been reported. PD-related symptoms such as depression [52,83], anxiety, and apathy have been shown to improve significantly [61,78,83]. This could be correlated with better control of motor symptoms, as anxiety (general disorder, social phobia, or panic attacks) may be associated with OFF periods (as non-motor fluctuations), and depression can be influenced by the severity of symptoms [99].

Most studies have excluded patients with severe psychiatric disorders; however, some patients with psychosis (particularly drug-induced) [4,46,78,90], and hallucinations [47,61,83,97,100] have been successfully treated, and either improved or did not worsen [46,101–103]. Therefore, patients with psychiatric disorders should be assessed on a case-by-case basis to determine if therapy with LCIG is warranted [11], and treatment should be exercised with caution. Some of these symptoms (e.g., ICDs) often result from or are aggravated (e.g., psychosis) by other antiparkinsonian drugs; therefore, discontinuation of the previous medication (tapering according to label) when initiating LCIG therapy may be beneficial [52]. Dopamine dysregulation syndrome occurred in 3 of 6 patients in a short series [91], and evaluation of personality traits (i.e., personality that could be predictive of a dopamine dysregulation syndrome) has been proposed. The recent *E*-DUO study in Spain, a retrospective analysis of 185 patients from 2006 to 2011, provided favorable preliminary evidence of LCIG therapy on hallucinations in 46.6% of patients and ICDs in 39.4% of patients [61]. Also, infusion therapies (apomorphine and LCIG) may present low risk of development of ICDs, and preexisting ones were found to improve in a small prospective study [103].

Recent studies on the use of LCIG suggest that patients with mild to moderate dementia (if they have a caregiver) [35,47,78,82,97], including moderate memory complaints, impaired attention and disorientation, reduced verbal fluency, and organizational abilities [56,78,84,97], may be candidates for treatment with LCIG. Some authors, however, exclude patients with dementia, or only include patients with less severe cases of dementia [22,40,52,62]. In LCIG studies, no worsening of Mini-Mental State Examination scores were noted during follow-up [22,52]. Treatment with LCIG does not significantly influence the clinical course of cognitive deterioration, and worsening of dementia has been reported in the long-term [35,62]. Gastrostomy and infusion systems are delicate enough; thus, poor medical conditions or dramatic worsening may contraindicate treatment with LCIG or advise discontinuation. Therefore, mental performance should be carefully assessed and taken into account when considering treatment with LCIG and, in the authors' opinion, the use of LCIG in patients with severe dementia is currently not recommended.

2.6. Sleep disorders

In patients with APD and sleep disorders, Fasano et al. [52] observed significant improvement (14%) in the Parkinson's Disease Sleep Scale (PDSS) after a follow-up of 24 ± 14.4 months. Similarly, prospective studies have reported a significant reduction in sleep disorders [46,56,63,97]. Treatment with LCIG seems to improve disturbed/fragmented sleep [46,82–84], and 24-h infusion has been used with success in selected patients with sleep disturbances [46]. Favorable results for LCIG therapy have been reported in detailed sleep-related NMS: in one report [61], sleep disturbances (insomnia, daytime sleepiness/fatigue, dystonia) improved in > 50% of patients, and a decrease in insomnia was also reported after 3 months of treatment with LCIG, which was related to an improvement in nocturnal akinesia [68]. Also, the 24-month results of the GLORIA registry showed improvement in each of the 9 NMSS domain scores and, particularly, the significant reduction observed in sleep/fatigue (24-month value: -5.3 ± 11.1; $p < 0.001$) was maintained throughout the study [98].

2.7. Dysautonomic symptoms

The efficacy of treatment with LCIG on cardiovascular symptoms, urinary and sexual dysfunction, gastrointestinal symptoms (including dysphagia and constipation), and excessive sweating, among others, has been varied. In some studies, significant improvements have been reported in cardiovascular symptoms [61,97], gastrointestinal symptoms [97], and in urinary dysfunction [56,97]. Improvements in pain, dysphagia, and dysarthria were also noted in one study [47]. However, in a recent retrospective multicenter *E*-DUO study exploring the effects of LCIG on individual symptoms [61], most patients did not experience changes in urinary symptoms and sexual difficulties; some patients reported worsening of these symptoms. Constipation also remained similar in half of the sample. Outcomes in drooling and swallowing problems were mixed, as similar percentages of patients reported improvement, no changes, or worsening of these symptoms. In contrast, falls and dizziness improved in approximately half of the cohort [61].

In conclusion, although control of NMS is not included among the main indications of LCIG, evidence suggests that patients experiencing some of the wide range of NMS in advanced stage PD may experience benefit from LCIG treatment, and should not be automatically excluded from offering treatment with LCIG, with the exception of patients with severe dementia. Psychiatric disorders such as depression, ICDs, or hallucinations are not an absolute contraindication for treatment with LCIG. Several studies have excluded these patients, so data on the treatment of such patients is limited and patients should be assessed on a case-by-case basis for the suitability of LCIG treatment.

3. Contraindications and exclusion criteria

Labelled contraindications include intolerance to levodopa/carbidopa, narrow-angle glaucoma, severe heart failure, severe arrhythmia, acute stroke, conditions in which adrenergic drugs are contraindicated, and concomitant use of MAO inhibitors. Logically, any condition that contraindicates surgery or gastrostomy makes the patient unsuitable for this therapy. Generally, advanced age is not an issue, and among cognitive symptoms, in our opinion only severe dementia would exclude LCIG therapy. In any event, a caregiver capable of handling the device should be present, and this should be considered as favoring the decision to start treatment [52], especially in the light of studies showing the need for a nurse or caregiver to set up the device in the morning and at other times during the day [47,66].

4. Safety considerations: why and when to discontinue LCIG (Table 2)

LCIG is a costly treatment and insertion of the device requires a brief hospital stay, surgery, and close clinical monitoring during the initial months of therapy [22,23]. Therefore, the likelihood of discontinuation is an important factor to be considered when selecting patients. According to a Swedish study, the mean treatment duration with LCIG is approximately 8 years, and in most cases, LCIG therapy is continued until the death of the patient (for other causes) [53]. LCIG may be considered a lifelong treatment. According to previous evidence, discontinuation (even when due to death) generally occurred in patients of a more advanced age [47,81]. Clinical observations suggested that patient age at the time of implant could be related to the risk of discontinuation [81], and in light of this information, earlier initiation of LCIG therapy has been proposed [47,90]. In a study specifically addressing the risk of discontinuation, the probability of discontinuation was not associated with a particular set of baseline clinical and

Table 2
Summary of most relevant safety issues with levodopa-carbidopa intestinal gel in the literature.

Issue	Reported in studies
Device and gastrostomy-related	
Technical problems with PEG-tube (dislocation, occlusion, disconnection, accidental removal, etc.)	[22,23,31,35,37,41,46,52,58,59,62,66,70,73,74,81,85,92,111]
Technical problems with device (malfunction, breakage or unsatisfactory pump control)	[22,31,35,46,70,74]
Local problems related with tube insertion (stoma infection, granuloma)	[35,37,58,59,62,66,70,74,81,92,111]
Intestinal perforations due to PEG-tube	[22,58,66,74,81]
Non-local infections related to tube insertion (e.g. Peritonitis)	[35,41,59,66,81,111]
Medication-related	
Sleep disturbances	[39,41,74]
Hallucinations, psychosis	[35,45,58,59,62,70,74,111]
Confusion	[22,39,52]
Neuropathy/polyneuropathy	[35,41,52,59,62,66,70,74,81,85]
Weight loss	[35,41,46,52,59,66,70,74,111]
Mood disturbances	[35,59]
Other problems less-frequently reported	
Constipation, abdominal pain, gastric ulcer, bezoar, procedural pain, depression.	

demographic characteristics, apart from patient age and longer OFF time and longer ON time with dyskinesia at baseline [104]. However, the recently published integrated safety analyses from 4 prospective clinical trials [105] (963 patient-years of exposure) demonstrated that age at initiation was not related to discontinuations. Also, patient with a longer duration presented slightly lower discontinuation rates.

The safety profile of LCIG is similar to that of oral levodopa [83], and discontinuation due to lack of efficacy, levodopa-induced adverse events, or symptoms related to disease progression are to be expected. The procedure involves percutaneous endoscopic gastrostomy (PEG) and the permanent insertion of an intrajejunal tube. Granuloma and complications related to the device are the most frequently observed adverse events with LCIG therapy, may occur in up to 69% of cases in the literature [47,106], and considered very frequent ($\geq 1/10$) according to label. However, procedure-related problems (duodenal ulcer, stoma infection, granuloma, abdominal pain, broken connectors, migration of the internal line, or kinks) [35,47,48,57,61,83] generally do not lead to discontinuation when appropriately managed [44,47,67,70], and are often resolved with conservative treatment (in the case of infections) or tube replacement [35,47,48,57]. The most important reasons for discontinuation are severe cases of peritonitis or infection [35,47,53,59,82], and prophylactic antibiotics after PEG are recommended to prevent peristomal infections [107,108].

The set of disease- or treatment-related adverse events potentially leading to discontinuation mainly include neuropsychiatric disorders, but only a few severe cases of dementia and hallucinations have led to discontinuation [44,47]. Peripheral polyneuropathy has been described in patients on long-term treatment with high doses of oral levodopa [109,110]. The causes for this remain unclear but, in our opinion, the clinical situation of acute inflammatory demyelinating polyneuropathy (AIDP) might be considered a relative contraindication for continuation of LCIG. A recent study by Merola, 2016 et al. [111] has suggested the contribution of homocysteine-mediated neurotoxicity. According to their results regarding the development of subacute or chronic polyneuropathy in a small cohort of patients treated with LCIG, the authors considered serial clinical-electrophysiological evaluations mandatory in patients treated with LCIG. Many, though not all, of these patients improved with vitamin B12 supplements [35,57,70,92,110], and by adjusting the infusion rate [57]; thus, discontinuation can be avoided except in the most severe cases [110].

Finally, some causes of discontinuation related to disease progression, such as repeated problems with the infusion system, have been associated to the development of significant cognitive decline and dementia [44,53,58,61]. This supports the recommendation by some authors that LCIG therapy should be initiated early in APD to achieve the maximum benefit [47]. Indeed, it was suggested that t relatively large number of discontinuations in studies reflects the current trend to use LCIG in patients with end-stage APD [59].

Importantly, no irreversible sequelae have been reported in patients who discontinued long-term LCIG therapy [83]. Thus, this should not be a concern if a moderate probability of discontinuation is taken into account when considering LCIG therapy for a particular candidate.

5. Assisting the patient: caregiver, multidisciplinary team and social aspects

Neurodegenerative disorders place a considerable burden on the individuals involved in caring for patients [16]. Psychological stress associated with caring for a patient has gained consideration in recent years, as the role of the main caregiver, usually a family member, is crucial in this context [16,112–114]. The progressive nature of PD, the clinical characteristics of the disease (e.g., severity and the level of disability at a certain point), its unpredictability, and drug adverse events are among the most influential factors [112–114].

In the case of treatment with LCIG, the presence of a caregiver capable of handling the equipment and monitoring complications is beneficial, and management and maintenance of the pump and daily care of the stoma require some basic training [82]. A recent report has indicated that morning set-up of the pump could be performed by the patient alone in only 6% of cases, while self-administration of extra doses was possible in 32% [47]. However, 50% of patients in this cohort were mentally impaired, and these findings probably reflect the limitation of using LCIG therapy in patients with dementia. Additionally, complications related to gastrostomy and the tubes call for monitoring by a caregiver. In some studies, the unavailability of a suitable caregiver is an exclusion criterion in patients with dementia or mild cognitive impairment [35,52,97], while inability of the caregiver to handle the pump has led to exclusion in others [97]. Therefore, the caregiver should be capable of handling the equipment, and trained to do so. If no suitable caregiver is available (e.g., the caregiver is elderly and disabled), the availability of local/community help, such as PD nurses and trained volunteers, should be explored before considering LCIG therapy.

Several studies have reported improved patient independence following LCIG therapy. Patients reported significantly less need for help from a caregiver [66,82] (i.e., improved autonomy [over 90%]) [47] and reported fewer difficulties handling their daily chores [40]. This would suggest that the treatment of patients with APD with LCIG lightens the burden placed on caregivers. Despite its limitations and complications, there is no evidence that LGIC therapy worsens patient QoL or increases caregiver burden. Contrary to this, improvements in caregiver burden [37,38,115], levels of stress, and QoL (not significant) [35,52,62] have been reported.

Table 3
Summary of LCIG use according to clinical demographic characteristics.

1) Most suitable LCIG patient profile

- Levodopa-responsive advanced PD
- Motor fluctuations (ON-OFF phenomena) and/or dyskinesias despite receiving optimal oral treatment (> 1–2 h with disabling OFF time)
- Duration of the disease < 10 years

2) Patients in whom LCIG could be of benefit. Relative contraindications that need to be assessed (reduced chance of success)

- Duration of disease > 10 years
- Mild cognitive impairment
- Freezing in ON
- Mild hallucinations
- Other NMS

3) Absolute contraindications

- Severe dementia
- Active psychosis
- Labelled contraindications:
  - Intolerance to levodopa/carbidopa
  - Narrow-angle glaucoma
  - Severe heart failure
  - Severe arrhythmia
  - Acute stroke
  - Conditions in which adrenergic drugs are contraindicated
  - Concomitant use of MAO inhibitors

LCIG, levodopa/carbidopa intestinal gel; NMS, non-motor symptoms; PD, Parkinson's disease; MAO, monoamine oxidase.

6. Improvements in QoL

Considering its benefits in treating several motor symptoms and NMS, it is not surprising that LCIG therapy in patients with APD has been widely shown to be associated with improved QoL, both in clinical trials and other studies [23,35,38,39,41,45,49,57,66,70,97]. Sustained improvements in QoL measured by validated tools have been reported in studies with follow-up periods of up to 2 years [38,40,41,45,52,59]. Most of these studies based their assessment on the Parkinson's Disease Questionnaire-39. Generally, significant improvements were noted both overall and in particular domains in periods ranging from 6 to 24 months [38,41,44,45,48,49,55,57]. In 2 studies, however, the observed improvements were not statistically significant at all time points [40,55]. Domains that have been observed to improve include satisfaction with mobility [23,40,41,44,57,62], overall functioning, ability to carry out daily chores [23,40,41,44,57], sense of stigma [23,41,44], and cognition [23,41,49]. After a mean follow-up of 36 months, a study reported overall improvement in patients as measured using the Parkinson's Disease Questionnaire-39, except for “cognition” [58]. Consistent with these findings, studies that assessed patients using the Parkinson's Disease Questionnaire-8 reported similar results [35,56,59,70,97] after 6 months of treatment. These findings correlate with improvements in motor symptoms and NMS [35,97]. In studies in which patient QoL was assessed, the majority of patients reported improvements, with > 90% of cases in one multicenter study [47] and 100% in another reporting improved QoL [66]. Improvements in quality of life, as measured by PDQ-8, and activities of daily living have been reported as independent of the patient's age (< or ≥ 65 years) or disease duration (< 10 or ≥ 10 years) at baseline [87].

7. Discussion and conclusions

Despite several suggested approaches in the literature, there are no definitive criteria for selection of patients with APD as suitable candidates for each of the currently available device-aided treatment alternatives. While clinical indications may overlap in some patients, exclusion criteria differ for each technique. Overall, the decision depends on many factors, including the characteristics of the patient, family support, and the preferences of both the patient and their caregivers. It is our opinion that some basic characteristics, however, are applicable to candidates for all 3 treatment alternatives (LCIG, DBS, and continuous subcutaneous infusion of apomorphine): > 1–2 h of disabling OFF time [19] and good ON time quality, with mild to moderate dyskinesia, largely refractory to conventional oral treatment, and mild or no cognitive impairment. Indeed, signs that optimized conventional therapies are no longer providing symptom control should be identified before considering advanced therapies [11,18].

Clinical observations by Calandrella et al. suggested that patient age > 70 years at implant was associated with discontinuation of LCIG therapy [81]. However, more recent evidence from the integrated safety analyses from 4 prospective clinical trials [105] indicated there was no impact of age on discontinuations and, regarding disease duration. Therefore, this treatment can also be considered in the geriatric population, particularly since other treatment alternatives are inapplicable. Similarly, there are no limits regarding disease duration at the initiation of LCIG therapy. Most of the studies reviewed in this paper enrolled patients with a long duration of disease (> 10 years). In a national retrospective study, disease duration > 10 years was associated with a poorer outcome in terms of motor disability compared with patients with a shorter disease duration, although this does not seem to affect motor complications such as dyskinesia [86]. Considering the deterioration in cognition with disease progression, some authors have proposed that implementing LCIG early may be associated with greater LCIG clinical benefit [23,35,47]. This hypothesis was not confirmed by results of a recent post-hoc analysis of the patients enrolled in the open-label phase-3 study and in the GLORIA registry although this may be related to the small sample size in most subgroups [87,88]. The suitable candidate for LCIG would be a relatively young patient suboptimally controlled with conventional therapy and with a good cognitive status whose QoL would be significantly improved with the control of APD symptoms [23]. However, older patients even with impaired gait, freezing episodes, and mild cognitive impairment may also find benefit with LCIG therapy (see Table 3 for a summary of indications and contraindications). Treatment with LCIG provides increased overall QoL in patients with APD and potentially relieves some caregiver burden. Improvements in mobility and activities of daily living are particularly significant. Some dopamine-responsive NMS seem to improve with LCIG treatment, and patients with severe sleep disorders despite oral treatment, including nocturnal dystonic pain and akinesia, might benefit from 24-h treatment with LCIG [56,82,116] Several studies suggest that certain patients with a wide spectrum of motor complications may also benefit from treatment with LCIG, as some complications improve with therapy (e.g., freezing, tremor, falls, dysphagia [35,47,61,106]) and the motor subscale in the Unified Parkinson's Disease Rating Scale has been consistently shown to improve [38,52,66]. Regarding the risk of discontinuation, some aspects related to the lack of efficacy or neuropsychiatric disorders may be minimized with careful selection of candidates.

In conclusion, any patient with APD (i.e., in whom optimal control with conventional oral treatment cannot be achieved) with a relatively preserved cognitive–behavioral status and good family/caregiver support, who is not likely to be particularly susceptible to safety concerns that commonly lead to premature discontinuation, would be a candidate for treatment with LCIG.

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