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SYSTEMATIC REVIEW

Levodopa–Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review

Karin Wirdefeldt[1,2] · Per Odin[3,4] · Dag Nyholm[5]

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Abstract

Background Levodopa–carbidopa intestinal gel (LCIG) is available in several countries for the treatment of advanced levodopa-responsive Parkinson's disease (PD) with severe motor fluctuations and dyskinesia when other treatments have not given satisfactory results.

Objective Our objective was to summarize the present evidence base for LCIG therapy through a systematic review of the literature.

Methods Studies were identified from the PubMed and EMBASE databases up to 12 March 2016 using the following search terms: Parkinson disease, duodopa, levodopa/carbidopa intestinal gel, levodopa–carbidopa intestinal gel, LCIG, l-dopa infusion, levodopa infusion, duodenal l-dopa infusion, and duodenal levodopa infusion. Data extraction focused on whether LCIG therapy improves motor and non-motor outcomes as well as quality of life in PD patients compared with conventional therapy, apomorphine infusion, or deep brain stimulation. Randomized controlled trials (RCTs) and observational studies, with or without a control group, that included more than ten patients were included. The search was limited to peer-reviewed articles published in full in the English language and involving humans.

Results Infusion of LCIG reduced "off" time, increased "on" time without increasing troublesome dyskinesias, and improved quality of life in three RCTs (one double-blind). Open-label follow-ups confirm these findings. The data evaluating long-term efficacy and safety are still limited.

Conclusions The quality of evidence that LCIG is effective in reducing fluctuating motor symptoms and improving quality of life is moderate. Quality of evidence for reduction of non-motor symptoms is very low. Safety issues mainly relate to the intestinal infusion system. LCIG might be a useful treatment option in PD patients with severe motor fluctuations.

Key Points

Levodopa–carbidopa intestinal gel is effective in reducing 'off' time without increasing troublesome dyskinesia according to three randomized controlled trials (RCTs). Health-related quality of life was improved in two RCTs.

Safety issues are common and mainly relate to the intestinal infusion system.

Evidence is still limited, as only one double-blind RCT has been reported.

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✉ Dag Nyholm
dag.nyholm@neuro.uu.se

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden

[2] Department of Clinical Neuroscience, Karolinska Institutet, Solna, Sweden

[3] Department of Neurology, Skåne University Hospital, Lund, Sweden

[4] Klinikum-Bremerhaven, Bremerhaven, Germany

[5] Department of Neuroscience, Neurology, Uppsala University, Uppsala, Sweden

1 Introduction

Levodopa, in combination with a peripheral decarboxylase inhibitor, is remarkably effective against many motor and non-motor symptoms in idiopathic Parkinson's disease (PD). Its efficacy, tolerability, and low cost make levodopa the drug of choice in all stages of PD, although combination therapy, primarily with dopamine agonists and inhibitors of cathecol-*O*-methyltransferase (COMT) or monoamine oxidase-B (MAO-B), is often useful [1]. Although levodopa is still highly effective after 5–10 years of therapy, response fluctuations, typically with wearing-off of the levodopa effect and development of dyskinesias, become increasingly difficult to manage. The patients fluctuate between the "off" state, characterized by motor and non-motor PD symptoms, and the "on" state, where symptoms are relieved but is often associated with dyskinesias. A common therapeutic strategy to adapt to the narrowing therapeutic window is to fractionate levodopa dosage into smaller and more frequent doses. This is effective to a certain extent, but some patients eventually cannot be managed with conventional dopaminergic therapy. This group of patients may be considered for device-aided therapies such as deep brain stimulation (DBS) or infusion of apomorphine or levodopa/carbidopa [2].

The present review focuses on infusion of levodopa/carbidopa intestinal gel (LCIG). Historically, intravenous [3] and intraduodenal [4] infusions of water solutions of levodopa were successful in ameliorating motor fluctuations and paved the way for the development of the highly concentrated LCIG [5]. The strategy to fractionate levodopa dosage is utilized because the pump administers small doses of levodopa/carbidopa roughly once every minute to the small intestine. This mode of administration thus bypasses gastric emptying, which is responsible for irregular absorption of levodopa. Infusion of LCIG provides stable levodopa concentrations in plasma throughout the day, which is why LCIG theoretically should be superior to orally administered levodopa [6–8].

LCIG was developed in Sweden in the 1990s and approved in the EU in 2004 and in the USA in 2015. It is marketed as Duodopa®/Duopa® by AbbVie, MI, USA, and is presently available in more than 40 countries worldwide. The indication is treatment of advanced levodopa-responsive PD with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. LCIG is administered via percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J).

The rationale for the present review was to summarize the current evidence base for LCIG therapy through a systematic review of the literature. Specifically, we wanted to address whether LCIG therapy improves motor and non-motor outcomes as well as quality of life in patients with PD compared with conventional therapy, apomorphine infusion, or DBS.

2 Methods

2.1 Eligibility Criteria

Studies eligible to be included were randomized controlled trials (RCTs) and cohort studies, with or without a control group, comparing LCIG therapy versus conventional therapy, apomorphine infusion, or DBS; or, for studies without a control group, comparing LCIG therapy with baseline. Only studies with more than ten patients with PD were included. Further, we only included peer-reviewed articles published in full in the English language and involving only humans. We applied no publication date restriction.

2.2 Search Strategy and Eligibility Assessment

Studies were identified from the PubMed and EMBASE databases by KW; the last search was performed on 12 March 2016. We used the following search terms: Parkinson disease, duodopa, levodopa/carbidopa intestinal gel, levodopa–carbidopa intestinal gel, LCIG, l-dopa infusion, levodopa infusion, duodenal l-dopa infusion, duodenal levodopa infusion. Details are given in the electronic supplementary material (ESM).

One author (KW) screened the identified studies for eligibility, first by title and abstract, then by reading the full text. In addition, the reference lists of included studies were screened, and we also considered studies referred to us by experts.

2.3 Data Extraction

One author (KW) extracted the following data from the included studies: study design, characteristics of patient and comparison group, and intervention. The following outcome measures were extracted: off time (or on time without dyskinesia), on time with dyskinesia, Unified Parkinson's Disease Rating Scale (UPDRS) II–IV, the 39- or 8-question version of the Parkinson's Disease Questionnaire (PDQ), or Non-Motor Symptom Scale (NMSS). Risk of bias was extracted for RCTs but not for cohort studies because of their obvious lower evidence level. Instead, we narratively describe risk of bias associated with cohort studies. Adverse effects were recorded for all studies. The other two authors checked the extracted data, and any disagreements were resolved by discussion. We did not register a review protocol.

As only three RCTs were identified and studies were heterogeneous, we did not perform a meta-analysis. Likewise, we did not draw a funnel plot to evaluate potential publication bias.

3 Results

3.1 Study Selection

In total, 353 studies were identified via the database search (200 studies in EMBASE, nine studies in PubMed, and 144 studies in both PubMed and EMBASE). One additional study was referred to us by an expert. After reviewing the title and abstract, 298 studies were found to be ineligible. The full text of the remaining 56 studies were reviewed, and a further 31 studies were excluded. Thus, 25 studies were included in the review: 25 evaluated motor symptoms, eight evaluated non-motor symptoms, and 17 evaluated quality of life (Fig. 1). The characteristics of included studies are described in Table 1.

3.2 Efficacy on Motor Symptoms and Dyskinesias

Only three RCTs reporting motor outcome were identified (Table 2). However, several observational studies provide valuable data in the absence of large long-term RCTs.

The first RCT of LCIG included 12 patients and reported a significantly increased number of observations in the near-normal state (including mild off state and mild dyskinesia) during LCIG infusion compared with controlled-release levodopa monotherapy [6]. The estimated mean difference was 19 % (95 % confidence interval [CI] 12–26). A significant decrease in both off state and dyskinesia was demonstrated. UPDRS parts I and II were unchanged, but part IV was significantly reduced with LCIG.

A Swedish multicenter RCT demonstrated significant reduction of observations in moderate to severe off state with LCIG compared with individually selected conventional therapies in 21 patients [9]. There was no difference in occurrence of dyskinesias. UPDRS parts II and IV were significantly improved with LCIG, whereas part III in the on state was unchanged.

The double-blind double-dummy 12-week RCT allocated 37 patients to LCIG and 34 to immediate-release oral levodopa/carbidopa. The number of hours in patient-rated off state was significantly lower with LCIG than with immediate-release levodopa [10]. The difference was −1.91 h (95 % CI −3.05, −0.76]. On time without troublesome dyskinesia was significantly increased with LCIG, whereas time with troublesome dyskinesia was unchanged, at a low level. UPDRS part II was significantly improved with LCIG, whereas part III in the on state was unchanged.

The risks of bias for the RCTs in terms of, for example, blinding and dropout rate are presented in Table 3.

The open-label studies confirm the efficacy in reducing off time and increasing on time without troublesome dyskinesia (Table 2). This improvement in stability was maintained in several studies of at least 12 months. Several risks of bias, often inherent to the open-label study design, need to be considered. The lack of blinding means a bias in outcome assessment is likely. Most open-label studies had no control group, several were retrospective or did not recruit patients in a consecutive manner (recruitment of patients was also often incompletely described). Further, several open-label studies either had a high dropout rate (sometimes because of adverse events or lack of efficacy) or did not report dropout rate. These types of bias would lead to overestimation of an intervention effect.

3.3 Non-Motor Symptoms

Several open-label non-controlled studies have evaluated the effects of LCIG on non-motor symptoms using validated instruments, mostly the NMSS (Table 4). The NMSS consists of nine domains, and sub-scores were reported in all studies. Six studies reported significant improvement in NMSS total score. The largest study [11] reported significant improvements in sub-scores for the sleep/fatigue, gastrointestinal, and urinary domains at 12 months. A study that compared LCIG versus apomorphine subcutaneous infusion reported significant improvement in NMSS total score with both LCIG and apomorphine [12]. LCIG showed a better effect on the subscales sleep/fatigue, gastrointestinal symptoms, urinary symptoms, and sexual functioning, whereas apomorphine showed a better effect on the subscale mood/apathy [12]. No RCTs with non-motor symptoms as a primary outcome have been reported.

Improvement of sleep has, apart from the NMSS, also been documented with the Parkinson's Disease Sleep Scale (PDSS), version 1 and 2, in open-label studies [13, 14].

3.4 Health-Related Quality of Life

The double-blind double-dummy RCT reported improved health-related quality of life, with a difference between LCIG and immediate-release levodopa of −7.0 (95 % CI −12.6, −1.4) for the PDQ39 summary score at 12 weeks of follow-up [10]. Another RCT also reported improved quality of life (median PDQ39 summary score 25 after 3 weeks LCIG treatment vs. 35 after 3 weeks of conventional treatment) [9]. In total, 12 of the 15 open-label studies that assessed health-related quality of life reported statistically significant improvement with LCIG, mostly of similar magnitude as found in the RCTs (Table 5); however, as noted above, several risks of bias are inherent in

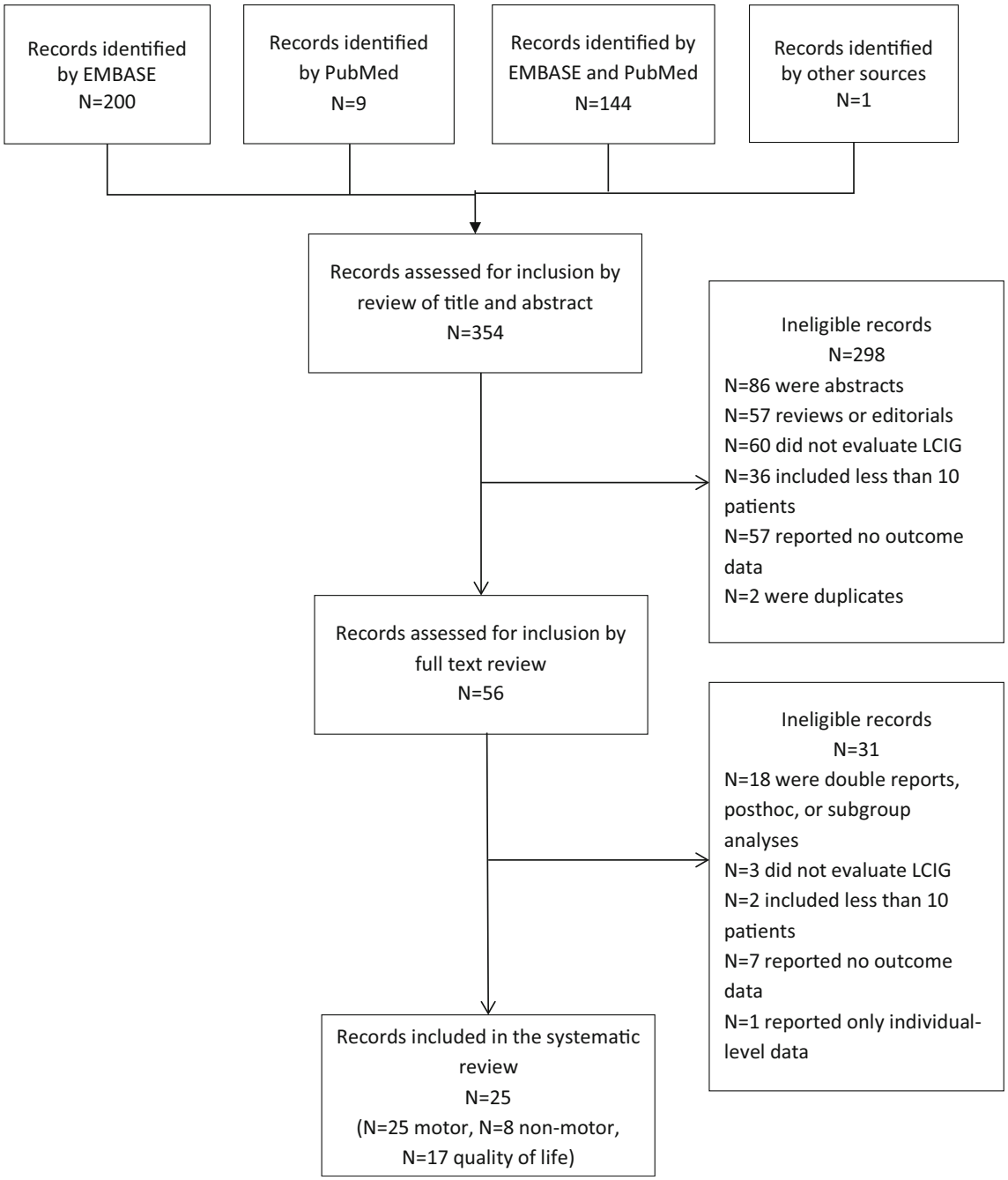

Fig. 1 PRISMA flow diagram

open-label studies, and the dropout rate was often high or not reported. The remaining three open-label studies showed no change in health-related quality of life or did not test for statistical significance (Table 5).

3.5 Safety

Safety results from the included studies are summarized in Table 6. As the methodology for safety monitoring varies considerably between studies, a statistical analysis covering all studies is not meaningful. The 25 studies included in the review comprise in total 1244 patients treated with LCIG, with a mean follow-up period of 15.5 months. Adverse events related to the device or procedure were most common. The most common adverse events (with at least ten reports) related to device or procedure were dislocation of tube (160 reports); complication of device insertion (147 reports); abdominal pain (133 reports);

Table 1 Characteristics of studies included in the systematic review

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Nyholm et al. [6]	Ran, co (Sweden)	Pts with motor fluctuations despite optimized oral tx recruited via pt organization Group 1: 6 pts (all M): LD-CD, CR + IR/LCIG Group 2: 6 pts (4 M, 2 F): LCIG/LD-CD, CR + IR 4 pts withdrew early due to difficulties in converting from previous medication to LD-CD only	Group 1: 48–76 Group 2: 39–70	Group 1: Age of onset, range 35–59 Group 2: Age of onset, range 31–50	3 + 3 wk	X	X	X		X		
Nyholm et al. [9]	Ran, co (Sweden)	Pts with motor fluctuations and dyskinesia in spite of individually optimized tx Group 1: 12 pts (9 M, 3 F): conventional tx/LCIG Group 2: 12 pts (9 M, 3 F): LCIG/conventional tx 1 pt was not ran	Group 1: Median 68, range 51–79 Group 2: Median 64, range 50–75	Group 1: Age of onset, median 56, range 38–67 Group 2: Age of onset, median 50, range 37–63	3 + 3 wk	X	X	X	X	X	X	
Antonini et al. [42]	Open, mc, pro (Italy, 3 centers)	Motor fluctuations and dyskinesia that could not be controlled with LD and dopamine agonist oral tx; 22 pts (13 M, 9 F)	NR	NR	2 y			X	X	X	X	

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Eggert et al. [43]	Open, mc, pro (Germany, 3 centers)	Advanced PD with disabling motor fluctuations and dyskinesia despite individually optimized oral tx or DBS 13 pts (7 M, 6 F) (2 pts had STN DBS)	Median 65, range 44–71	Age of onset, median 51, range 27–57	6 (–12) mo	X	X					
Honig et al. [14]	Open, mc (UK, Germany, Italy, 5 centers)	Advanced PD with motor fluctuations with daily symptomatic "off" and "on" periods with troublesome dyskinesias, refractory to manipulations of oral medications, rotigotine skin patch, and/or APO infusion At least 30 % improvement of UPDRSIII with LD; 22 pts (16 M, 6 F)	58.6 ± 9.1	15.3 ± 5.9	6 mo				X	X	X	X
Merola et al. [44]	Open, sc, ret (Italy)	Group 1: 20 (13 M, 7 F) of first 26 consecutive pts who underwent PEG for LCIG infusion 2005–2009; 6 pts excluded due to lack of follow-up (whereof one removed the PEG after 2 mo due to poor compliance) Group 2: 20 (16 M, 4 F) of 166 PD pts who underwent STN DBS 1998–2009	Group 1: 69 ± 5.9 Group 2: 66.6 ± 2.5	Group 1: Age of onset, mean ± SD 13.9 ± 4.5 Group 2: Age of onset, mean ± SD 16.4 ± 4.3	Group 1: mean ± SD 14.7 ± 7.6 mo Group 2: 14.8 ± 3.3 mo			X	X	X		

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Fasano et al. [13]	Open, two-center, ret (Italy, 2 centers)	Consecutive pts with severe motor fluctuations refractory to manipulations of oral medications, rotigotine patch and/or APO infusion, good l-dopa responsiveness, who underwent LCIG 2008–2011; 14 pts (10 M, 4 F)	67.1 ± 11.5	Age of onset, mean ± SD 55 ± 10.4	Mean ± SD 24.9 ± 14.4 mo			X	X	X	X	X
Pålhagen et al. [38]	Open, mc (Sweden, Norway, 7 centers)	Pts with advanced motor symptoms with fluctuations despite optimized conventional oral medication who had received long-term LD therapy, consecutively recruited 37 pts (16 M, 11 F), whereof 27 pts with follow-up data 10 pts withdrew (1 withdrew consent early, 5 due to lack of efficacy, 2 withdrew consent after LCIG start, 2 due to AE)	64.6 ± 6.4	Age of onset, mean ± SD 52 ± 5.8	12 mo			X	X	X	X	

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Reddy et al. [39]	Open, sc (UK)	Pts referred to King's College Hospital for LCIG therapy 2009–2011 who were clinically eligible for LCIG Group 1: 17 pts (11 M, 6 F) eligible for LCIG Group 2: 9 pts (7 M, 2 F) who were denied funding for LCIG: conventional tx	Group 1: 57.8 ± 7.7 Group 2: 62.0 ± 6.1	Group 1: 16.1 ± 5.8 Group 2: 13.2 ± 4.2	6 mo				X	X	X	X
Antonini et al. [45]	Open, mc, ret (Italy, Germany, Sweden, Austria, Belgium, Switzerland, 7 centers)	Pts treated with LCIG until March 2010 98 pts for safety analysis, whereof 73 pts with follow-up data; 23 pts withdrew (5 due to AE, 7 due to procedure- and device-related events, 3 due to lack of compliance, 8 due to lack of efficacy); 2 pts lost to follow-up	65.3 ± 10.4	14.9 ± 6.6	Mean ± SD 608 ± 292 days			X	X		X	
Foltynie et al. [46]	Open, sc (UK)	12 pts with advanced PD with motor fluctuations and dyskinesias despite optimal oral tx and SC apomorphine, who had been considered for DBS surgery (2 pts had undergone DBS previously)	66 (SD NS)	Age of onset, mean 42.8	12 mo	X	X				X	

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Zibetti et al. [47]	Open, sc, pro (Italy)	25 pts (16 M, 9 F) who started LCIG between 2005 and 2009, whereof 17 pts reached follow-up; 5 pts discontinued LCIG, 3 pts died unrelated to LCIG	69.9 ± 5.8	12.1 ± 4.1	Mean ± SD 36.2 ± 11.5 mo	X[b]		X	X	X[b]	X	
Caceres-Redondo et al. [22]	Open, sc (Spain)	29 pts (12 M, 17 F) who started LCIG between 2007 and 2013, whereof 16 pts reached follow-up; 7 pts discontinued LCIG before 24 mo; 6 pts did not reach follow up at 24 mo	66.5 ± 9.3	15.1 ± 5.4	Mean 32.2 mo	X		X	X	X	X	X
Olanow et al. [10]	Ran, mc, pro, PC, db, dd (Germany, NZ, USA, 26 centers)	Pts with advanced PD with off periods at least 3 h/day despite optimized medical therapy (LD-CD, dopamine agonist, plus COMT inhibitor or MAOB inhibitor) Group 1: 37 pts (24 M, 13 F): LCIG + LD-CD IR PL Group 2: 34 pts (22 M, 12 F): LD-CD IR + LCIG PL All pts received PEG	Group 1: 63.7 ± 9.5 Group 2: 65.1 ± 6.8	Group 1: 10.0 ± 4.6 Group 2: 11.8 ± 5.6	12 wk	X	X	X	X		X	

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Pickut et al. [20]	Open, mc (Belgium, 27 centers)	100 pts who underwent naso-intestinal evaluation for LCIG; 13 pts excluded due to ongoing reimbursement process when study ended, 20 pts excluded due to reimbursement criteria not met. Of 67 pts who started LCIG, 37 had follow-up data	67 pts: 67.4 ± 9.3	NR	Mean ± SD 336 ± 162 days	X		X	X	X		
Sensi et al. [23]	Open, sc (Italy)	28 consecutive pts (16 M, 12 F) with LCIG between January 2008 and March 2013, whereof 7 pts had LCIG since APO pump or DBS STN failed; 6 pts discontinued LCIG; 5 pts did not reach follow-up at 24 mo	67.6 ± 6.1	15.5 ± 4.0	Mean ± SD 32.4 ± 9.4 mo	X			X	X	X	X
Zibetti et al. [48]	Open, sc, ret (Italy)	59 consecutive pts (40 M, 19 F) with LCIG between 2005 and 2012; 25 pts included in Zibetti 2013; of 59 pts, 7 died unrelated to LCIG, 11 discontinued LCIG prior to cutoff date, 2 were lost to follow-up	69.3 ± 5.9	13.0 ± 3.8	Mean ± SD 25.8 ± 19.5 mo	X				X		

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Antonini et al. [11]	Open, mc, routine care (Australia, Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Spain, Switzerland, UK, 75 centres)	172 pts (76 M, 96 F) with advanced PD and motor complications eligible for LCIG tx according to European Commission SPC and to national reimbursement criteria; of 172 pts, 13 withdrew from naso-jejunal test period or long-term LCIG, 11 lacked follow-up data 148 pts had at least one follow-up visit	66.5 ± 9.3	12.6 ± 6.6	12 mo	X	X	X	X		X	X
Bohlega et al. [49]	Open, sc, pro (Saudi Arabia)	20 consecutive pts (7 M, 13 F) with advanced PD with motor fluctuations and non-motor symptoms between 2008 and 2014; of 20 pts, 2 withdrew during naso-jejunal test period	52.8 ± 12.1[c]	11.4 ± 4.2	Mean ± SD 48.5 ± 23.2 mo	X			X		X	X
Buongiorno et al. [50]	Open, mc, pro (Spain, 5 centers)	72 pts (41 M, 31 F) with motor fluctuations not satisfactory controlled by standard tx between 2008 and 2012; of 72 pts, 28 discontinued (11 due to AEs, 13 due to lack of efficacy, 4 due to no acceptance of device)	68.4 ± 7.3	13.1 ± 5.1	Mean 22 ± 14 mo	X		X	X			

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Calandrella et al. [51]	Open, sc, ret (Italy)	35 pts (15 M, 20 F) who started LCIG between 2007 and 2013; of 35 pts, 21 had follow-up data	64.8 ± 13.5	12.3 ± 3.9	Mean ± SD 32.3 ± 24.7 mo	X			X			
Fernandez et al. [52]	Open, mc, pro (16 countries worldwide, 86 centers)	354 pts (202 M, 152 F) with ≥3 h of daily off time despite optimized tx with available medications; of 354 pts, 30 withdrew from naso-jejunal test period (12 withdrew consent, 7 due to protocol violation, 5 due to AE, 5 due to lack of efficacy, 1 due to administrative reason) and 52 withdrew from long-term LCIG (22 due to AE, 13 due to administrative reason, 13 withdrew consent, 2 due to lack of efficacy, 2 due to protocol violation); 272 pts completed the study	64.1 ± 9.1	12.5 ± 5.5	54 wk	X	X	X	X	X	X	
Gmitterová et al. [53]	Open, sc (Slovakia)	21 pts (11 M, 10 F) with motor fluctuations inadequately responding to oral PD medication with LCIG tx between 2009 and 2014	69, range 59–74	16, range 6–25	6–8 months	X	X		X			

Table 1 continued

Study	Study design (country)	Pt/control—population	Age[a]	Disease duration[a]	Follow-up duration	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV	PDQ39 or PDQ8	NMSS
Martinez-Martin et al. [12]	Open, mc, pro (Spain, UK, Austria, Italy, Sweden, Denmark, Germany, Slovenia, 13 centers)	Pts recruited among pts selected to receive LCIG or SC APO infusion as part of routine clinical care based on discussion regarding suitability for advanced tx, including DBS and informed choice of pts Group 1: 44 pts (56.8 % M): LCIG Group 2: 43 pts (48.8 % M): SC APO infusion Withdrawal rate NR	Group 1: 62.7 ± 9.1 Group 2: 62.3 ± 10.6	Group 1: 16.1 ± 6.7 Group 2: 14 ± 4.5	6 mo				X	X	X	X
Chang et al. [54]	Open, sc, pro (Australia)	First consecutive 15 pts (10 M, 5 F) with LD-responsive advanced PD with motor fluctuations despite optimal pharmacological tx	62 ± 4.7	14	12 mo	X			X		X	

AE adverse event, *APO* apomorphine, *CO* controlled, *COMT* cathecol-O-methyltransferase, *CR* controlled-release, *db* double-blind, *dd* double-dummy, *DBS* deep brain stimulation, *F* female, *IR* immediate release, *LCIG* levodopa/carbidopa intestinal gel, *LD* levodopa, *LD-CD* levodopa-carbidopa, *M* male, *MAOB* monoamine oxidase-B, *mc* multicenter, *mo* month, *NMSS* Non-Motor Symptom Scale, *NR* not reported, *NS* not stated, *PC* placebo-controlled, *PD* Parkinson's disease, *PDQ* Parkinson's Disease Questionnaire, *PEG* percutaneous endoscopic gastrostomy, *PL* placebo, *pt(s)* patient(s), *pro* prospective, *ran* randomized, *ret* retrospective, *sc* single-center, *SC* subcutaneous, *SD* standard deviation, *SPC* summary of product characteristics, *STN* subthalamic nucleus, *tx* treatment, *UPDRS* Unified Parkinson's Disease Rating Scale, *wk* week, *X* indicates data reported, *y* year

[a] Mean years ± standard deviation, unless otherwise stated

[b] Due to overlap with Zibetti 2014, effect measure not considered

[c] Calculated

Table 2 Efficacy of levodopa–carbidopa intestinal gel on motor symptoms

Study	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV
Nyholm et al. [6]	Oral tx 25 % of observations LCIG 12 % of observations	Oral tx 14 % of observations LCIG 8 % of observations	No significant difference in on state		Oral tx median 7.5 LCIG median 4.5 ($p < 0.01$)
Nyholm et al. [9]	Conventional tx, % of ratings, mean ± SD 19.2 ± 17.9 LCIG 1.8 ± 5.0 ($p < 0.01$) ITT population ($N = 21$)	Conventional tx, % of ratings, mean ± SD 6.3 ± 14.6 LCIG 7.5 ± 17.3 ($p = 1$) ITT population ($N = 21$)	Conventional tx, median, range 14 (6–25) LCIG 11 (6–20) ($p < 0.01$) PP population ($N = 18$)	Conventional tx, median, range 22.5 (0–46) LCIG 14.5 (5–36) ($p = 0.06$) PP population ($N = 18$)	Conventional tx, median, range 8.5 (3–13) LCIG 7 (2–13) ($p = 0.02$) PP population ($N = 18$)
Antonini et al. [42]			BL 12.8 ± 2.9 12 mo 9.1 ± 3.1 ($p < 0.01$) 24 mo 9.4 ± 3.9 ($p < 0.01$)	BL 24.6 ± 5.2 12 mo 23.8 ± 4.3 24 mo 24.8 ± 6	BL 8.4 ± 0.8 12 mo 6.4 ± 0.5 ($p < 0.05$) 24 mo 6.6 ± 0.9 ($p < 0.05$)
Eggert et al. [43]	BL 50 ± 14 % 6 mo 11 ± 7 % ($p < 0.01$)	BL 17 ± 15 % 6 mo 5 ± 6 % ($p < 0.01$)			
Honig et al. [14]				BL 19.1 ± 14.0 6 mo 11.6 ± 7.2 ($p < 0.01$)	BL 10.5 ± 2.9 6 mo 4.5 ± 2.2 ($p < 0.001$)
Merola et al. [44]			BL 25.9 ± 8.6 14 mo 18.3 ± 7.6 ($p < 0.001$)	BL 45.7 ± 14.8 14 mo 29.1 ± 15.9 ($p < 0.001$)	BL 8.6 ± 4.2 14 mo 5.6 ± 3.4 ($p < 0.05$)
Fasano et al. [13]			Unchanged	−7.6 % from BL (NS)	−29.3 % from BL ($p = 0.00003$)
Pålhagen et al. [38]			BL 15.4 ± 5.7 0 mo 12.3 ± 5.1 ($p = 0.005$) 12 mo 12.2 ± 6.8 ($p = 0.005$)	BL 24.4 ± 11.0 0 mo 22.0 ± 9.7 ($p = 0.057$) 12 mo 21.5 ± 13.2 ($p = 0.205$)	BL 9.4 ± 2.6 0 mo 6.5 ± 2.7 ($p < 0.001$) 12 mo 5.7 ± 3.4 ($p < 0.001$)
Reddy et al. [39]				82.35 % improvement from BL ($p = 0.006$)	88.24 % improvement from BL ($p = 0.0004$)
Antonini et al. [45]			BL 14.79 ± 8.88 End of follow-up 13.25 ± 8.46 (NS)	BL 25.34 ± 13.55 End of follow-up 24.45 ± 13.03 (NS)	Items 32, 33, 39 significant improvements
Foltynie et al. [46]	Percentage BL 29.4 ± 13.2 Follow-up 16.7 ± 22.2 ($p = 0.06$)	Percentage BL 16.6 ± 18.6 Follow-up 8.2 ± 10.3 ($p = 0.22$)			
Zibetti et al. [47]	[a]		BL 16.1 ± 7.2 3 y 20.9 ± 7.5 ($p < 0.05$)	BL 23.2 ± 9.2 3 y 32.2 ± 12.6 ($p < 0.001$)	[a]
Caceres-Redondo et al. [22]	Off duration (UPDRS item 39) BL 58.1 ± 11.5 32.2 mo 24.6 ± 7.2 ($p < 0.05$)		BL 14.5 ± 5.3 32.2 mo 16.5 ± 5.0 (NS)	BL 27.2 ± 8.1 32.2 mo 29.5 ± 6.4 (NS)	BL 8.7 ± 2.3 32.2 mo 6.7 ± 2.8 ($p < 0.05$)

Table 2 continued

Study	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV
Olanow et al. [10]	BL LCIG group, h/d 6.3 ± 1.7 BL oral group 7.0 ± 2.1 12 w LCIG −4.04 ± 0.65 12 w oral −2.14 ± 0.66 ($p = 0.0015$ for difference between groups)	BL LCIG group, h/d 1.0 ± 1.6 BL oral group 1.2 ± 1.7 12 w LCIG −0.11 ± 0.52 12 w oral −0.03 ± 0.52 ($p = 0.8574$ for difference between groups)	BL LCIG group 11.6 ± 6.9 BL oral group 11.8 ± 7.0 12 w LCIG −1.8 ± 1.3 12 w oral 1.3 ± 1.3 ($p = 0.0086$ for difference between groups)	BL LCIG group 18.1 ± 9.9 BL oral group 22.5 ± 11.7 12 w LCIG −1.5 ± 2.4 12 w oral −2.9 ± 2.4 ($p = 0.5020$ for difference between groups)	
Pickut et al. [20]	Off duration (UPDRS item 39) 89.5 % improvement		Unchanged	−6.8 (95 % CI −13.9, 0.23) from BL	−6.3 (95 % CI −8.1, −4.5) from BL
Sensi et al. [23]	Off duration (UPDRS item 39) BL 2.3 ± 0.9 24 mo 1.0 ± 0.6 ($p < 0.00001$)			BL 35.5 ± 11.5 24 mo 34.7 ± 12.4	BL 8.4 ± 2.5 24 mo 4.4 ± 1.9 ($p < 0.00001$)
Zibetti et al. [48]	Off duration (UPDRS item 39) BL 1.8 ± 0.7 26 mo 0.9 ± 0.5 ($p < 0.001$)				BL 8.5 ± 3.1 26 mo 5.7 ± 2.4 ($p < 0.001$)
Antonini et al. [11]	BL, h/d 7.1 ± 3.5 12 mo ($n = 46$) −4.7 ± 3.4 ($p < 0.0001$)	BL, h/d 5.2 ± 4.5 12 mo ($n = 47$) −1.7 ± 5.0 ($p = 0.0228$)	BL 16.2 ± 10.7 12 mo ($n = 56$) −3.1 ± 8.7 ($p = 0.0107$)	BL 26.5 ± 12.3 12 mo ($n = 74$) −3.3 ± 11.0 ($p = 0.0128$)	
Bohlega et al. [49]	BL, h/d 5.2 6 mo 1.4 ($p < 0.001$)			BL in off 55.8 ± 11.7 6 mo in on 19.6 ± 8.4	
Buongiorno et al. [50]	BL, h/d 6.8 ± 2.8 Last visit 3.0 ± 3.5		BL 13.6 Last visit 14.3	BL 21.9 Last visit 22.3	Item 33 similar at BL and last visit
Calandrella et al. [51]	Off duration (UPDRS item 39) BL 2.4 ± 0.6 Follow-up 1.1 ± 0.6 ($p < 0.001$)	Dyskinesia score (UPDRS items 32 + 33) BL 2.2 ± 0.7 Follow-up 1.5 ± 0.7 ($p < 0.001$)		BL 36.5 ± 2.4 Follow-up 28.5 ± 5.0 ($p < 0.001$)	
Fernandez et al. [52]	BL, h/d 6.75 ± 2.35 12 mo 2.32 ± 2.05 ($p = 0.001$)	BL, h/d 1.61 ± 2.03 12 mo 1.24 ± 2.10 (**p** = 0.023)	BL 17.4 ± 6.6 12 mo −4.4 ± 6.6 ($p < 0.001$ according to figure)	BL 28.8 ± 13.7 12 mo improvement ($p < 0.001$ according to figure)	Dyskinesia items only BL 3.7 ± 2.4 12 mo improvement ($p < 0.001$ according to figure)
Gmitterová et al. [53]	BL, h/d 5.8 ± 1.6 6–8 mo 2.7 ± 1.1 ($p < 0.0001$)	BL, h/d 3.3 ± 1.4 6–8 mo 2.1 ± 1.2 ($p = 0.007$)		BL 32 ± 4.8 6–8 mo 30 ± 8.3 ($p < 0.001$)	
Martinez-Martin et al. [12]				BL 27.29 ± 12.28 6 mo 15.07 ± 10.37 ($p < 0.0001$) No difference between LCIG/APO groups at 6 mo ($p = 0.88$)	BL 9.93 ± 3.29 6 mo 4.36 ± 3.07 ($p < 0.0001$) No difference between LCIG/APO groups at 6 mo ($p = 0.15$)

Table 2 continued

Study	Off time	On time with dyskinesia	UPDRS II	UPDRS III	UPDRS IV
Chang et al. [54]	BL, h/d 6.3 ± 2 6 mo 1.9 ± 2 12 mo 1.8 ± 2			6 mo improvement 31 ± 36 % 12 mo improvement 37 ± 11 %	

APO apomorphine, *BL* baseline, *CI* confidence interval, *h/d* hours per day, *ITT* intention to treat, *LCIG* levodopa–carbidopa intestinal gel, *NS* not statistically significant, *PP* per protocol, *SD* standard deviation, *tx* treatment, *UPDRS* Unified Parkinson's Disease Rating Scale, *y* year

[a] Due to overlap with Zibetti 2014, effect measure not considered

Table 3 Risk of bias for randomized controlled trials

Study	Appropriate randomization procedure	Blinding	Proportion of pts lost to follow-up	Stopping of trial early due to benefit	Intention-to-treat principle
Nyholm et al. [6]	Randomization procedure not described	No blinding	4 of 16 pts withdrew early due to difficulties converting from previous medication to LD-CD only	No	Followed
Nyholm et al. [9]	Yes	Assessors of motor outcomes blinded but collectors of other data, study participants, and study investigators not blinded	1 of 25 pts was not randomized 6 of 24 randomized pts withdrew (1 did not enter the cross-over part due to relapse of inguinal hernia, 2 did not tolerate the nasoduodenal tube or pump on first day of infusion, 2 due to confusion, 1 was satisfied with infusion and did not want to return to conventional therapy)	1 of 25 pts	Off time and on time with dyskinesia analyzed according to ITT; UPDRS II-IV and PDQ39 according to per protocol
Olanow et al. [10]	Yes	Study participants and investigators blinded	26 of 97 pts were not randomized (20 due to protocol violation, 5 withdrew consent, 1 due to AE) 5 of 71 randomized pts discontinued intervention, 2 in LCIG group (1 due to AE, 1 due to protocol disorder), and 3 in LD-CD IR group (2 due to AE, 1 due to lack of efficacy)	No	Followed

AE adverse event, *IR* immediate release, *ITT* intention to treat, *LD-CD* levodopa–carbidopa, *PDQ* Parkinson's Disease Questionnaire, *pt(s)* patient(s), *UPDRS* Unified Parkinson's disease rating scale

irritation, granulation, or erythema at stoma (118 reports); infection at stoma (117 reports); occlusion, kinking, or obstruction of tube (117 reports); procedural pain (78 reports); constipation (58 reports); PEG internal retention failure (24 reports); peritonitis (20 reports); pneumoperitoneum (24 reports); problems leading to replacement of PEG (13 reports); accidental removal of tube (12 reports); and pump malfunction (27 reports). The most common adverse events (with at least ten reports) related to the LCIG infusion were nausea (65 reports), falls (54 reports), sleep disturbance (52 reports), neuropathy (45 reports), weight loss (31 reports), hallucinations (28 reports), troublesome dyskinesia (17 reports), and mood disturbance (10 reports).

4 Discussion

All studies that evaluated motor outcome consistently reported that LCIG infusion increases on time without troublesome dyskinesia because off time is reduced. Severe troublesome dyskinesias were unchanged or reduced (Table 2). The quality of evidence is moderate, following the 12-week double-blind RCT [10]. One 3-week RCT

Table 4 Efficacy of levodopa–carbidopa intestinal gel on non-motor symptoms

Study	Length of follow-up	NMSST, BL	NMSST, follow-up	NMSST, % improvement
Honig et al. [14]	6 mo	89.9 ± 56.5	39.4 ± 33.9	56*
Reddy et al. [39]	6 mo	113.9 ± 49.3		40*
Fasano et al. [13]	25 mo			14#
Sensi et al. [23]	24 mo	51.8 ± 37.3	38.0 ± 24.7	27#
Caceres-Redondo et al. [22]	24 mo			17*
Antonini et al. [11]	12 mo	75.3 ± 42.2	22.2 ± 50.6 reduction	29*
Bohlega et al. [49]	6 mo	237.1 ± 45.5	81.6 ± 25.7	65*
Martinez-Martin et al. [12]	6 mo	90.95 ± 45.00	53.66 ± 38.67	51*

BL baseline, *NMSST* Non-Motor Symptom Scale total score

* Significant ($p < 0.05$)

\# Not significant

used blinded video evaluations [9], but the remaining studies were open-label, thus prone to bias. Non-motor symptoms were improved according to the NMSS in six of eight open-label studies. The strength of evidence is poor because NMSS was not included in any of the RCTs. Most studies that assessed quality of life reported improvement on the PDQ39 or PDQ8 following LCIG treatment, but the evidence level is considered moderate, as there were only two RCTs [9, 10]. Safety issues mainly relate to the intestinal infusion system, where mild complications are common and the risk of life-threatening complications is not negligible. Information on long-term safety is still limited to a few studies.

The reduction in off time is often reported to be more prominent than the reduction in dyskinesia, partly because patients were usually more off than dyskinetic at baseline. However, this difference is also likely because patients usually prefer mild dyskinesias over mild parkinsonism. The stability of the levodopa exposure during LCIG therapy may allow for a slight increase of the total daily levodopa dose without causing peak-dose dyskinesias or other side effects related to high doses. An increased dose clearly avoids off episodes efficiently, but some patients are then constantly in a mild dyskinetic state.

Measuring on/off time in fluctuating PD is a challenge. The most common strategy is to use patient at-home diaries that are completed every 30 min. The frequency of data entry is important, considering the minute-to-minute changes in fluctuating PD. However, the method requires proper education of patients, and compliance with the frequent diary entries is a major problem [15]. A few studies have used electronic diaries with time-stamped data entry, which may combine subjective information with objective tests. Such smartphone applications or sensor systems will likely become more common, and hopefully more accurate, than paper diaries in the near future [16]. Video recordings for blinded assessments of motor function are more useful than diaries, but are more expensive and time consuming. Deriving on/off time from UPDRS items captured at hospital visits is convenient, but recall bias is an obvious problem.

The UPDRS is widely used in evaluations of LCIG. The different parts are differently reported. Part IV, which includes off time and dyskinesia time and severity, was most commonly reported to be improved by LCIG, and activities of daily living, reported in part II, were also reported to be improved. However, part III, the motor examination, was mostly unchanged. In a levodopa-responsive PD patient, levodopa is expected to give major symptom relief in part III, no matter how the drug is administered. Thus, LCIG is not expected to have a greater maximal effect on PD symptoms than oral levodopa. Nevertheless, the motor examination might be more likely to be performed in a good on state with LCIG than with oral therapy, because of the stability of motor performance.

The results of open-label, non-controlled studies indicate that there might be improvements concerning several non-motor symptoms with LCIG, but these results must be interpreted with care. No RCTs with non-motor symptoms as outcome have been reported, but one is presently running. Among the non-motor scale subscores, the most consistent results were seen concerning the sleep/fatigue and gastrointestinal subscores, improving in five of the seven studies presenting NMSS subscores. Thus, sleep may improve even though patients receive LCIG only during daytime; it might further improve with 24-h LCIG therapy [17], but this remains to be shown. LCIG improved impulse control disorders (ICDs) and, in some patients, dopamine dysregulation syndrome (DDS) in three case series [13, 18, 19]. Although the evidence level is poor, this is of interest, as these side effects are common. Cognitive function was stable after starting LCIG in some studies [13, 20], or even improved in single patients [21], but long-term LCIG does not seem to change the clinical course of

Table 5 Efficacy of levodopa–carbidopa intestinal gel on health-related quality of life

Study	PDQ39[a]	PDQ8[a]	Comment
Nyholm et al. [9]	Conventional treatment (median, range) 35 (16–55) LCIG (median, range) 25 (10–42) ($p < 0.01$)		Based on per protocol population (18 of 24 patients)
Antonini et al. [42]	BL 59.5 ± 14.4 12 mo 46.4 ± 14.5 ($p < 0.01$) 24 mo 49.2 ± 10.3 ($p < 0.01$)		
Honig et al. [14]		BL 44.2 ± 18.4 6 mo 20.7 ± 12.0 ($p < 0.001$))	
Fasano et al. [13]		BL 18.1 ± 6.6 Follow-up 16.7 ± 6.0 ($p = 0.29$)	
Pålhagen et al. [38]	BL, mean 33.6 0 mo 27.1($p = 0.001$) 12 mo 28.8 ($p = 0.126$)		
Reddy et al. [39]		Significant improvement ($p = 0.017$)	
Antonini et al. [45]		BL 53.3 ± 21.7 Follow-up 47.0 ± 15.2 ($p = 0.0158$)	Based on 20 of 98 patients
Foltynie et al. [46]	BL 49.7 ± 10.4 3 mo 35.8 ± 13.3 ($p = 0.02$) Latest follow-up (mean 20.2 mo) 38.7 ± 11.2 ($p = 0.02$)		
Zibetti et al. [47]	BL 59.2 ± 18.7 Follow-up 43.1 ± 13.9 ($p < 0.01$)		
Caceres Redondo et al. [22]	BL 84.2 ± 18.7 32.2 mo 74.3 ± 21.3 ($p < 0.01$)		
Olanow et al. [10]	Difference in least square means between BL and 12 w LCIG −10.9 ± 3.3 LD-CD IR −3.9 ± 3.2 ($p = 0.0155$)		
Sensi et al. [23]		BL 46.3 ± 13.7 24 mo 29.9 ± 17.0 ($p = 0.006$)	
Antonini et al. [11]		Difference in means between BL and 12 mo −8.6 ± 22.6 ($p = 0.01$)	
Bohlega et al. [49]		BL 23.2 ± 4.4 6 mo 8.0 ± 3.5 ($p < 0.001$)	
Fernandez et al. [52]	Difference in means between BL and 12 mo −6.9 ± 14.1 ($p < 0.001$)		
Martinez-Martin et al. [12]	LCIG BL 48.58 ± 14.62 6 mo 31.96 ± 14.89 ($p < 0.0001$) Apomorphine BL 49.85 ± 16.59 6 mo 35.03 ± 18.00 ($p < 0.0001$) Difference in means between LCIG and apomorphine at 6 mo non-significant ($p = 0.66$)		
Chang et al. [54]	BL 38.3 ± 14 6 mo 22.8 ± 17 12 mo 24.5 ± 16		

BL baseline, *IR* immediate-release, *LCIG* levodopa-carbidopa intestinal gel, *LD-CD* levodopa–carbidopa, *PDQ* Parkinson's Disease Questionnaire, *SD* standard deviation

[a] Mean ± SD unless otherwise stated

Table 6 Safety of levodopa–carbidopa intestinal gel

Study	AEs
Nyholm et al. [6]	2 pts had dislocation of PEG-tube or technical problems with pump
Nyholm et al. [9]	17 pts had AE with LCIG treatment (16 under conventional therapy)
	3 pts had SAE: 1 regarded as related to LCIG (sleep disturbance and confusion)
	6 pts withdrew from study (1 inguinal hernia, 2 did not tolerate LCIG infusion or pump, 2 confusion, 1 did not agree to switch to control group)
Antonini et al. [42]	AEs not leading to dropout not reported
	5 pts withdrew: 2 poor compliance, 3 AE (1 dislocation of tube, 1 psychosis, 1 severe polyneuropathy)
Eggert et al. [43]	6 pts had occlusion of the tube, 3 dislocation of the tube from jejunum to stomach, 4 disconnection of the tube, 3 infection of the stoma, 2 backache due to the pump weight, 1 pump interfered with daily living
	4 pts withdrew: 3 PEG or infusion device problems, 1 difficulties handling the pump
Honig et al. [14]	AEs not reported
Merola et al. [44]	Significantly higher rate of complications in LCIG group: 11 accidental removal of PEG tube, 2 dislocation of intestinal tube, 1 tube jejunal incarceration, 1 tube occlusion, 1 buried bumper syndrome, 3 infection, 1 psychosis, 3 weight loss, 1 intestinal occlusion
Fasano et al. [13]	1 axonal neuropathy, 3 tube dislocation or occlusion, 1 severe constipation, 2 transient confusion, 1 PEG infection, 1 weight loss
Pålhagen et al. [38]	43 pts had SAE: 27 were regarded as related to LCIG; of these 5 related to gastrostomy, 7 to technical aspects of the treatment; 2 pts withdrew because of AEs
Reddy et al. [39]	AEs not reported
	2 pts died of unrelated causes after 2 years' LCIG treatment
Antonini et al. [45]	76 procedure and device-related AE (of these, 7 terminated prematurely): 5 buried bumper syndrome; 3 caro luxuriance around PEG; 1 coloenteric fistula; 4 dislocation of jejunal tube; 1 erysipelas around PEG; 6 granulation at PEG puncture; 2 infect of stoma; 9 PEG problems, repositioning, replacemement; 4 postop peritonitis; 4 tube damage/disconnection; 22 tube dislocation; 15 tube occlusion
	8 adverse drug reactions (5 of these terminated prematurely): 3 polyneuropathy, 2 weight loss, 1 hypersexuality, 1 overall skin reaction, 1 mood disturbance, 1 hallucination, 1 psychosis, 1 other
Foltynie et al. [46]	3 of 11 pts receiving PEG were not treated >3 months (2 AE related to PEG; 1 died [unrelated reasons]). 4 of remaining 8 pts had recurrent mild problems with PEG
Zibetti et al. [47]	25 had AEs; 34 dislocation of intestinal tube, 12 PEG internal retention failure, 24 intestinal tube kinking or obstruction, 6 PEG pulled out accidently, 1 duodenal perforation, 1 phlegmon, 1 localized peritonitis, 1 intestinal volvulus, 12 peristomal infection, 1 severe psychosis
Caceres-Redondo et al. [22]	29 pts had AEs; 4 neuropathy, 1 psychosis, 5 granuloma, 2 pneumoperitoneum, 10 peristomal infection, 2 phlegmon, 8 intestinal tube dislocated with migration into the stomach, 1 intestinal tube kinking or obstruction
Olanow et al. [10]	35 of 37 pts in the LCIG-treated group reported AEs (all 34 pts in the control group reported AEs). Most AEs related to the PEG procedure or the pump were mild to moderate and occurred during the first week after the PEG procedure. 63 pts (89 %) had AEs related to PEG and pump (dislocation of tubing, complications to gastrojejunostomy and stoma, pump dysfunction, pneumoperitoneum). 1 pt in the LCIG and 3 pts in the control group had symptoms of polyneuropathy
Pickut et al. [20]	5 pts had SAE: 1 abdominal pain leading to LCIG discontinuation; 1 fever after jejunal tube placement; 1 loss of consciousness, probably blood-pressure related; 1 confusion due to device occlusion; 1 liver injury due to accidental perforation by the tube
	11 pts had LCIG device malfunctions: 4 device leakage, 2 device breakage, 1 device dislocation, 2 device failure, 2 drug-delivery system malfunction
Sensi et al. [23]	20 pts had AEs estimated as related to levodopa: 9 polyneuropathy (4 of which were present already at BL; 1 developed a severe, subacute sensorimotor polyneuropathy), 3 weight loss, 2 mood disturbance, 3 hallucinations, 3 agitation (1 of which was present already at BL)
	4 pts had AE estimated as related to procedure: 1 duodenal ulceration, 2 peritonitis, 1 peristomal infections
	16 pts had AEs estimated as related to device: 1 PEG pulled out accidently, 4 dislocation/replacement of jejunal tube, 2 tube occlusion, 4 granulation at PEG puncture, 5 pump failure
Zibetti et al. [48]	83 AEs related to infusion devices: 36 intestinal tube dislocation, 28 intestinal tube occlusion or kinking, 12 PEG internal retention failure, 5 accidental external PEG damage, 15 possibly related to LCIG infusion, 1 severe psychosis, 10 important weight loss, 4 neuropathy, 25 gastrostomy related, 14 peristomal infection, 1 phlegmon, 1 localized peritonitis, 1 pneumo-peritoneum, 2 intestinal volvulus, 2 buried bumper syndrome, 1 gastric ulcer caused by the tube, 1 jejurnal perforation

Table 6 continued

Study	AEs
Antonini et al. [11]	75 (47.2 %) of pts in the safety analysis population had at least one AE during the 12 months: 37 (23.3 %) had SAEs. AEs occurring in at least 1.5 %: weight decrease (5.6 %), device dislocation (3.8 %), abdominal pain (3.1 %), polyneuropathy (3.1 %), granuloma (2.5 %), injection site infection (2.5 %), postoperative wound infection (2.5 %), device complication (1.9 %), gastrointestinal stoma complication (1.9 %), hallucination (1.9 %). Most frequent SAEs: device dislocation (4 pts), postoperative wound infection (2), on-off phenomenon (2), hallucination (2 s). 8 pts died during the study, none determined as related to LCIG. 24 pts (14.4 %) discontinued LCIG prematurely; the reason for discontinuation was AEs in 15 pts (8.7 %)
Bohlega et al. [49]	AE related to hardware (20): 2 stoma infection, 1 skin rash, 10 tube dislocation, 2 tube knotting, 3 pump malfunction, 2 pump breakage. 2 pts dropped out (1 spine fracture, 1 uncontrollable dyskinesia)
Buongiorno et al. [50]	Drug-related AEs: 1 acatisia, 13 hallucination/confusion, 3 anorexia, 1 anxiety, 13 troublesome dyskinesia, 2 polyneuropathy, 5 weight loss, 2 punding, 3 excessive daytime sleepiness, 3 symptomatic orthostatic hypotension. Device-related AEs: 13 intestinal tube kinking, 5 bezoar, 13 tube and connection issue, 3 intestinal tube dislocation, 2 intestinal tube occlusion, 2 intestinal impaction, 1 intestinal perforation. PEG-related AEs: 2 abdominal cellulite, 5 wound infection, 9 pneumoperitoneum, 12 pump breakage/malfunction
Calandrella et al. [51]	Surgery-related AEs: 2 cardia bleeding, 2 PEG breakage, 1 duodenal perforation, 1 abdominal distention, 1 atrial fibrillation, 1 aspiration pulmonitis, 1 stoma ulcer. Device-related AEs: 5 stoma infection, 3 intestinal tube kinking, 1 duodenal phytobezoar, 3 intestinal tube dislocation, 1 peritonitis. Infusion-related AEs: 3 worsening of dyskinesias, 4 peripheral neuropathy. AEs unrelated to procedure: 1 accidental trauma, 1 hepatocarcinoma, 1 acute marrow aplasia, 1 suicide (depression). 10 pts discontinued LCIG due to AE (4 stoma infection, 3 worsening of dyskinesias, 1 duodenal perforation, 1 peritonitis, 1 duodenal phytobezoar)
Fernandez et al. [52]	166 (46.9 %) had AEs during the NJ period; most common: insomnia (7.9 %), complication of device insertion (7.3 %), oropharyngeal pain (6.5 %) 298 (92.0 %) had AEs during the post-PEG-J period; most common complication of device insertion (34.9 %), abdominal pain (31.2 %), procedural pain (20.7 %) 105 (32.4 %) had SAEs; most common: complication of device insertion (6.5 %), abdominal pain (3.1 %), peritonitis and polyneuropathy (each 2.8 %) Procedure- or device-related AEs reported for 68.5 % of pts, most common: complication of device insertion (33.6 %), abdominal pain (26.5 %), procedural pain (20.4 %), excessive granulation tissue (15.4 %), postoperative wound infection (15.1 %), incision-site erythema (12.7 %), procedural-site reaction (9.3 %), postprocedural discharge (7.7 %), incision-site pain (6.2 %), and pneumoperitoneum (5.9 %). Aspiration-related AEs (14.8 % of pts) were primarily dyspnea (4.0 %), pneumonia (3.1 %), gastroesophageal reflux disease (2.2 %), pyrexia (2.2 %), dysphagia (1.9 %), and atelectasis (1.5 %). Polyneuropathy occurred in 3.1 %. Weight loss-related AEs in 15.4 %. 7.6 % had an AE leading to withdrawal. 8 deaths (2.3 %) were reported; none considered treatment related
Gmitterová et al. [53]	AEs and dropouts not reported
Martinez-Martin et al. [12]	AEs reported: 8 irritation at stoma, 7 swollen abdomen, 9 dislocation of tubing, 1 peritonitis
Chang et al. [54]	4 pts developed impulse control disorder or dopamine dysregulation syndrome. Other AEs: 2 stoma infection, 6 local tube problems, 7 sensorimotor peripheral neuropathy secondary to B_{12} or B_6 deficiency

AE adverse event, *BL* baseline, *LCIG* levodopa–carbidopa intestinal gel, *NJ* naso-jejunal, *PEG* percutaneous endoscopic gastrostomy, *PEG-J* PEG with a jejunal extension tube, *pt(s)* patient(s), *SAE* serious adverse event

cognitive deterioration, and worsening of dementia has been reported [22, 23]. Again, no RCTs are available, and it is likely that not all non-motor symptoms are levodopa responsive.

In sum, open-label results indicate a possibility of improvement of several non-motor symptoms with LCIG infusion, but RCTs are highly warranted, not least since these effects might be highly relevant for choice of therapy for individual patients. The mechanisms behind these improvements probably vary for different non-motor symptoms, and might involve fluctuations in non-motor symptoms that are related to fluctuations in motor symptoms [24], and alleviation of side effects of earlier pharmacological treatments when moving to levodopa monotherapy. Improvements in non-motor symptoms have also been seen with subcutaneous apomorphine infusion [12] and DBS [25].

Only two RCTs [9, 10] assessed health-related quality of life, but both showed improvement with LCIG treatment. The minimally important difference, or smallest change that is subjectively meaningful to patients, has been estimated at 1.6 (with a standard deviation of 8.9) based on a study that compared the change in PDQ39 summary scores associated with patients reporting from "about the same" to "a little worse" [26]. The magnitude of the improvement reported in the two RCTs (10 points [9] and 7 points [10] on the PDQ39 summary score) is thus most probably clinically relevant. The RCTs are limited by short follow-

up, but several open studies with longer follow-up have reported an improvement of similar magnitude, albeit with the important limitations of open studies.

The safety data from the included studies are summarized in Table 6. The methodology for safety reporting varies between the studies, and it is difficult to get an overall quantitative overview of the safety situation from these publications. However, the results do seem compatible with those in a recent publication summarizing the safety results of four prospective studies (one double-blind, three open-label) involving 412 patients [27] and the interim 1-year results of the first 172 included patients in an open-label registry study [11]. In Lang et al. [27], mean treatment duration with LCIG was 911 days (range 1–1980 days) with 963 patient-years of LCIG exposure in total. Procedure/device adverse events occurred in 300 patients (76 %). The most common events were complications of device insertion (41 % of the patients) and abdominal pain (36 %). Serious adverse events occurred in 68 (17 %) patients, and the most common were complications of device insertion (8 %) and abdominal pain (4 %). Most procedure/device-related adverse events occurred within the first 2 weeks of treatment and resolved thereafter. Adverse events unrelated to procedure or device occurred in 379 patients (92 %), the most common being insomnia (23 %) and falls (23 %). Serious adverse events unrelated to procedure or device occurred in 171 patients (42 %), the most common being pneumonia (5 %) and PD symptoms (2 %). Adverse events led to discontinuation of LCIG treatment in 72 patients (17 %), and the most common reasons were complications of device insertion (2.4 %), death (1.2 %), abdominal pain (1.0 %), pneumonia (1.0 %), myocardial infarction (0.7 %), and fall (0.7 %). In total, 34 patients died during follow-up, two of these deaths were considered "possibly related" to the treatment: one had a cardiac arrest, the other intestinal dilatation. There were two suicides during the study, both in patients with a history of depression. During the PEG-J exposure period (median 986 days), 102 patients (26 %) had at least one PEG tube replacement and 222 (56 %) had at least one J-tube replacement. At the end of the second year, 82 % retained the original PEG tube and 49 % retained the original J-tube. Polyneuropathy was reported in 24 patients (5.8 %). Weight decrease was reported in 59 patients (14 %).

Most of the safety data still come from open-label studies; this could be regarded as a drawback; however, the majority of safety data for new therapies are derived from open-label studies (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). The Lang et al. [27] data have the advantage of being from the largest prospective safety evaluation thus far. However, the data also have the limitations connected to most clinical studies, with risk of selection bias with patient inclusion, as well as the consequences of a more rigorous follow-up, which could not only reduce the risk for adverse events but also lead to more frequent reports of adverse events than in routine practice. Safety data from observational studies, like that by Antonini et al. [11] (see Table 6), might be closer to what is seen in routine care. Continued monitoring of safety issues related to LCIG is warranted.

Procedure/device-related adverse events are common. The safety of the PEG-J has been in focus in the safety evaluations. These procedures can cause life-threatening complications, which, although rare, include intestinal perforation, peritonitis, and intestinal hemorrhage. Most of these severe adverse events occur during the first 2–4 weeks of treatment. Overall, the safety of the PEG-J procedure has been regarded as consistent with the recognized complications of this procedure in non-PD patient populations [28]. It is likely that a high degree of expertise and experience, particularly among the gastroenterological personnel, is an important step towards minimizing these complications.

In terms of the side effects not related to procedure or device, the safety profile of LCIG seems to be comparable to that of oral formulations of levodopa–carbidopa. Neuropathy has been considered a possible complication of LCIG treatment. The etiology of this remains unclear, as does the degree to which this side effect is specific for LCIG, related to L-dopa therapy in general, or related to the disease. It has been suggested that vitamin B_{12} and/or folic acid deficiency might be implicated and that these should be monitored and/or supplemented during LCIG treatment [29, 30]. The treating physician should be aware of these risks and handle the situation accordingly.

The rate of discontinuation of therapy because of side effects seems to be slightly higher than would be expected with oral dopaminergic treatments [31]. Regarding exposure duration, the rates support an overall tolerability of LCIG. The number of deaths reported would be expected given the mortality rates, including suicides, in a PD population of this type [32].

Evidence of efficacy for LCIG is increasing but is still limited. The three RCTs [6, 9, 10] were up to 12 weeks in duration and comprised a total of 107 patients. The short duration and small number of patients are clear limitations. Further, only one of them was double blind and placebo controlled [10]. Such a design is certainly the most relevant, but difficult to perform in a treatment that is administered with a pump for intestinal delivery when standard treatment is oral tablets. The three RCTs all assessed motor outcomes, but only two of them assessed quality of life,

and none assessed non-motor outcomes. The limited number of studies implies that retrieval of identified research for review is likely complete. Clinical experience is reported in larger populations, for up to 16 years of LCIG treatment [33], and results similar to those from the RCTs were found in studies from several countries, worldwide, but certainly with a considerably lower evidence level. There is a potential risk of selection bias in studies where data from early withdrawals are lacking. As there were only three RCTs, we were unable to assess potential publication bias with a funnel plot. Studies from different countries ensure that different populations of patients are reported, but there is some publication bias in terms of follow-up reports from some groups. Although such studies were excluded from our review, we still cannot exclude that the same patients were included in more than one study, as this might not always be reported. Likewise, we cannot exclude selective reporting within studies, as this was difficult to assess because most studies lacked published protocols. Uncertainty regarding PD diagnosis because of a lack of objective diagnostic tools is not expected to be a problem in a population of advanced fluctuating PD patients, but the specificity of clinical PD diagnosis compared with neuropathological diagnosis post mortem is far from 100 % [34, 35].

Appropriate patient selection is important when choosing between advanced therapies. Young age and absence of psychiatric/behavioral symptoms are considered valid predictors for a good outcome with LCIG [23], but these are also valid predictors for apomorphine infusion and DBS, so a tailored approach is required for each patient [2]. In fact, the double-blind RCT by Olanow et al. [10] showed that dose titration of immediate-release oral levodopa reduced off time from baseline by about 2 h, highlighting the importance of careful follow-up and dose titration of conventional treatment. Assessing patients' expectations before initiating advanced therapy may be useful because expectations are often unrealistically high [36]. Thus far, no randomized comparative data between DBS and pump treatments are available. Such studies would be of value to analyze and compare the motor and non-motor effects of the individual therapies, as well as quality of life and safety. Until comparative studies are available, patient selection for advanced therapy relies on clinical experience and consensus statements [37].

Several studies were performed to provide data to medical authorities to justify reimbursement of LCIG, which is substantially more expensive than oral levodopa preparations [20, 38, 39]. The magnitude of improvement might be considered cost effective in properly selected patients, but the high cost does limit the number of patients who are eligible for LCIG, depending on cost-effectiveness thresholds [40, 41].

5 Conclusions

The quality of evidence that LCIG is effective in reducing fluctuating motor symptoms and improving quality of life is moderate. The quality of evidence for reduction of non-motor symptoms is very low. Maintained long-term efficacy on motor fluctuations is reported in several open-label studies of at least 1 year, but the quality of evidence is low. Adverse effects are common and mainly relate to the intestinal infusion system. Future, well-designed studies are needed to confirm efficacy on motor fluctuations and quality of life and to specifically address efficacy on non-motor symptoms and long-term safety.

Compliance with Ethical Standards

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