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REVIEW

The Long-Term Impact of Levodopa/Carbidopa Intestinal Gel on 'Off'-time in Patients with Advanced Parkinson's Disease: A Systematic Review

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ABSTRACT

Introduction: Levodopa/carbidopa intestinal gel (LCIG; carbidopa/levodopa enteral suspension) has been widely used and studied for the treatment of motor fluctuations in levodopa-responsive patients with advanced Parkinson's disease (PD) when other treatments have not given satisfactory results. Reduction in 'off'-time is a common primary endpoint in studies of LCIG, and it is important to assess the durability of this response. This systematic literature review was conducted to qualitatively summarise the data on the long-term effects of LCIG therapy on 'off'-time.

Methods: Studies were identified by searching PubMed, EMBASE and Ovid on 30 September 2019. Studies were included if they reported on patients with PD, had a sample size of ≥ 10, LCIG

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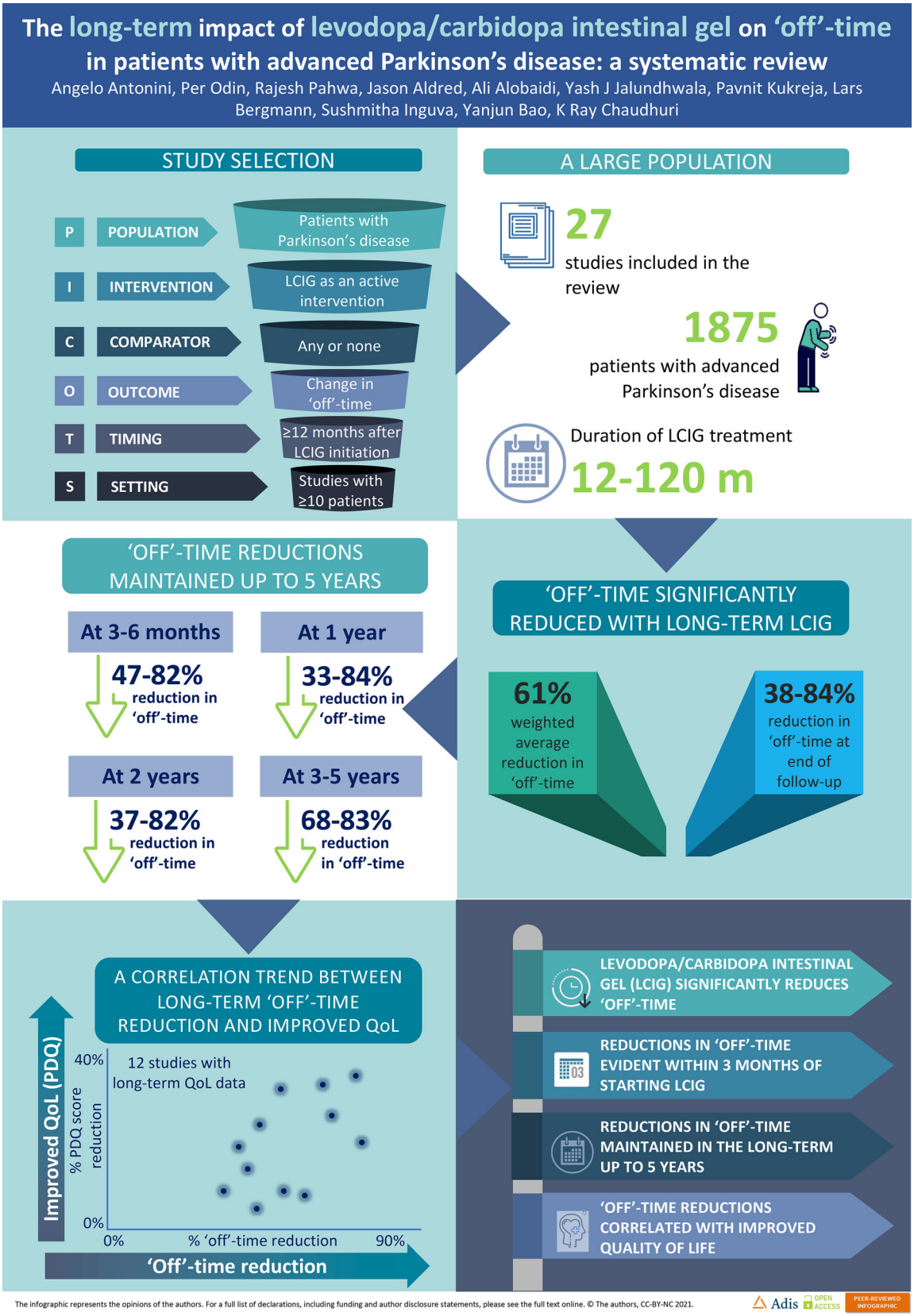
was an active intervention and 'off'-time was reported for $\geq$ 12 months after initiation of LCIG treatment. Randomised clinical trials, retrospective and prospective observational studies, and other interventional studies were included for selection. Data were collected on: 'off'-time (at pre-specified time periods and the end of follow-up), study characteristics, Unified Parkinson's Disease Rating Scale (UPDRS) II, III and IV total scores, dyskinesia duration, quality of life scores, non-motor symptoms and safety outcomes.

Results: Twenty-seven studies were included in this review. The improvement in 'off'-time observed shortly after initiating LCIG was maintained and was statistically significant at the end of follow-up in 24 of 27 studies. 'Off'-time was reduced from baseline to end of follow-up by 38–84% and was accompanied by a clinically meaningful improvement in quality of life. Stratified analysis of 'off'-time demonstrated mean relative reductions of 47–82% at 3–6 months and up to 83% reduction at 3–5 years of follow-up. Most studies reported significant improvements in activities of daily living and motor complications. Most frequent adverse events were related to the procedure or the device.

Conclusion: In one of the largest qualitative syntheses of published LCIG studies, LCIG treatment was observed to provide a durable effect in reducing 'off'-time.

Infographic:


The long-term impact of levodopa/carbidopa intestinal gel on 'off'-time in patients with advanced Parkinson's disease: a systematic review
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STUDY SELECTION
P POPULATION Patients with Parkinson's disease
I INTERVENTION LCIG as an active intervention
C COMPARATOR Any or none
O OUTCOME Change in 'off'-time
T TIMING ≥12 months after LCIG initiation
S SETTING Studies with ≥10 patients
A LARGE POPULATION
27 studies included in the review
1875 patients with advanced Parkinson's disease
Duration of LCIG treatment
12-120 m
'OFF'-TIME REDUCTIONS MAINTAINED UP TO 5 YEARS
At 3-6 months
47-82% reduction in 'off'-time
At 1 year
33-84% reduction in 'off'-time
At 2 years
37-82% reduction in 'off'-time
At 3-5 years
68-83% reduction in 'off'-time
'OFF'-TIME SIGNIFICANTLY REDUCED WITH LONG-TERM LCIG
61% weighted average reduction in 'off'-time
38-84% reduction in 'off'-time at end of follow-up
A CORRELATION TREND BETWEEN LONG-TERM 'OFF'-TIME REDUCTION AND IMPROVED QoL
Improved QoL (PDQ)
% PDQ score reduction
40%
0%
12 studies with long-term QoL data
0%
% 'off'-time reduction
90%
'Off'-time reduction
LEVODOPA/CARBIDOPA INTESTINAL GEL (LCIG) SIGNIFICANTLY REDUCES 'OFF'-TIME
REDUCTIONS IN 'OFF'-TIME EVIDENT WITHIN 3 MONTHS OF STARTING LCIG
REDUCTIONS IN 'OFF'-TIME MAINTAINED IN THE LONG-TERM UP TO 5 YEARS
'OFF'-TIME REDUCTIONS CORRELATED WITH IMPROVED QUALITY OF LIFE
The infographic represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC 2021.
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PLAIN LANGUAGE SUMMARY

By synthesising publications from scientific journals, this article shows that levodopa/carbidopa intestinal gel (LCIG; also known as carbidopa/levodopa enteral suspension or the tradenames Duodopa® and Duopa®) may have benefits for patients with advanced Parkinson's disease that last for 12 months or more. Pills taken by mouth for Parkinson's disease often do not work as well after a few years. This means the symptoms of Parkinson's disease, such as shaking or slow movements, etc., re-emerge despite medication (known as 'off'-time). To reduce the amount of 'off'-time, people with advancing Parkinson's disease may switch from pills to other types of treatments, for example, those that use devices to deliver the drug into the body, such as LCIG. LCIG has been available for many years and is known to help patients by reducing 'off'-time. Despite this, less is known about how long the benefits of LCIG last. By summarising all information available on the long-term use of LCIG, this report shows that when patients have been taking LCIG for at least 12 months, they have 2–4 h less 'off'-time each day than they did before starting the LCIG treatment. This effect is maintained for 3–-5 years after starting LCIG treatment. There were no unexpected side effects with long-term use of LCIG. The time not spent in 'off' may allow people with advanced Parkinson's to increase their independence in daily activities.

Keywords: Advanced Parkinson's disease; LCIG; Long-term; 'Off'-time

Key Summary Points

This systematic review of the literature, which includes 27 studies, is the most comprehensive qualitative synthesis of data on the long-term (≥ 12 months follow-up from treatment initiation) impact of levodopa/carbidopa intestinal gel on 'off'-time in patients with advanced Parkinson's disease

Of the 27 studies, 14 (52%) were multicentre studies and 10 (37%) had a sample size of ≥ 50 patients. Study follow-ups ranged from 12–120 months with 15 (56%) studies having follow-ups ≥ 24 months

Treatment of advanced Parkinson's disease with levodopa/carbidopa intestinal gel was observed to be consistently effective in significantly reducing 'off'-time within 3 months, and this improvement is maintained in the long-term, even after 24 months

The improvement in 'off'-time may be associated with clinically meaningful improvement in health-related quality of life in the long term

Safety issues with levodopa/carbidopa intestinal gel are most frequently related to the procedure or the device, and the emergence of unexpected adverse events in the long-term is not frequent

Dose optimisation of levodopa/carbidopa intestinal gel allows personalisation of treatment that should further enhance the maintenance of long-term efficacy

DIGITAL FEATURES

This article is published with digital features, including a summary slide, plain language summary, infographic and video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13056008.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that in the long-term presents with motor and non-motor fluctuations in many patients [1, 2]. As symptoms

worsen with disease progression, daily activities and quality of life (QoL) are negatively affected [3]. Most patients progress to a disease state often referred to as 'advanced PD'. While there is no consensus for the definition of advanced PD, it is generally characterised by motor (and non-motor) symptoms that respond poorly to optimised oral medication, longer 'off'-time per day, shorter 'on'-time per day and dyskinesia [4–11], which in turn may result in limited mobility and risk of falls. In addition, many people with advanced PD have cognitive and psychotic problems [9].

Levodopa combined with peripheral decarboxylase inhibitor remains the most effective symptomatic therapy for PD [12], but one defining aspect of advanced PD is the inability to provide sustained benefit with oral levodopa. As PD advances, presynaptic storage of levodopa/-dopamine in striatal dopaminergic neurons, which buffers synaptic transmission against the fluctuations in plasma levodopa levels, is lost and response to levodopa more closely follows plasma concentrations [13]. Due to the short half-life of levodopa and erratic absorption caused by unpredictable gastric emptying, fractionated and intermittent oral dosing of levodopa results in fluctuating plasma levels as well as motor fluctuations and complications, limiting its benefit for patients with advanced PD [9, 14–16].

Levodopa/carbidopa intestinal gel (LCIG; Duodopa®, carbidopa/levodopa enteral suspension; Duopa®, AbbVie Inc., North Chicago, IL, USA) is a stable gel suspension suitable for continuous delivery to the proximal jejunum through percutaneous endoscopic gastrostomy and a jejunal extension tube (PEG-J) via a portable pump [17]. Continuous infusion of LCIG bypasses the stomach and hence removes the influence of gastric emptying on plasma levels of levodopa [18], stabilises plasma levodopa concentrations and avoids the peaks and troughs that lead to motor fluctuations and dyskinesia [16]. Many studies have demonstrated that LCIG can significantly reduce 'off'-time, increase 'on'-time (without troublesome dyskinesia) and improve activities of daily living (ADL) and QoL in patients with advanced PD [19–22]. The length of follow-up in published studies varies from 3 months to > 5 years. The flexible and personalised dosing that LCIG offers, including adjustable flow rate, ability to administer bolus doses and benefits of using as monotherapy or with other anti-PD medications [17, 23], means that good long-term efficacy is achievable.

LCIG was first approved in 2004 (in the EU) and there is, therefore, long-term experience with this treatment. As PD is a progressive disease, it is important to ascertain how long the benefits of LCIG are sustained. Furthermore, a systematic review of LCIG was published in 2016 to assess outcomes compared with conventional therapy, apomorphine infusion and deep-brain stimulation [24], but this did not provide detailed information on the long-term outcomes with LCIG therapy. The results of several studies and registries of LCIG therapy have been reported since 2016; therefore, a review of the data on LICG therapy is overdue. This systematic literature review summarises data on the long-term (≥ 12 months) efficacy of LCIG in PD, with a focus on 'off'-time.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Sources

Searches were conducted on PubMed, EMBASE and Ovid on 30 September 2019.

Search Strategy

Search strategy was limited to studies involving humans and published in English language. An example of the full search strategy is given here: ((“Parkinson Disease”[Majr]) OR (parkinson's disease[tiab] OR parkinsons disease[tiab] OR parkinson disease[tiab] OR parkinsons[tiab] OR parkinson's disease[ot] OR parkinsons disease[ot]

OR parkinson disease[ot] OR parkinsons[ot])) AND (duopa[tiab] OR carbidopa and levodopa enteral suspension[tiab] OR CLES[tiab] OR duodopa[tiab] OR levodopa/carbidopa intestinal gel[tiab] OR levodopa-carbidopa intestinal gel[tiab] OR LCIG[tiab] OR L-dopa-infusion[tiab] OR levodopa infusion[tiab] OR duodenal levodopa infusion[tiab] OR duodenal l-dopa infusion[tiab] OR duopa[ot] OR carbidopa and levodopa enteral suspension[ot] OR CLES[ot] OR duodopa[ot] OR levodopa/carbidopa intestinal gel[ot] OR levodopa-carbidopa intestinal gel[ot] OR LCIG[ot] OR L-dopa-infusion[ot] OR levodopa infusion[ot] OR duodenal levodopa infusion[ot] OR duodenal l-dopa infusion[ot]). Searches were made for major article topic terms ('Majr'), free text terms in title or abstract ('tiab') and other terms ('ot'). Any important papers known by the authors that were not identified with this search strategy were included in the search results ('hand search').

Eligibility Criteria

The following criteria (PICOS) were used for inclusion of studies: patients with PD, sample size of $\geq$ 10 and LCIG as an active intervention irrespective of the inclusion of a comparator arm. The main outcome measure assessed was 'off'-time if reported for at least 12 months after initiation of LCIG treatment. Randomised clinical trials (RCTs), retrospective and prospective observational studies and other interventional studies were included for selection, if published between 1 January 2000 and 30 September 2019.

Screening, Selection and Data Extraction

Identified publications were initially screened by title to remove duplicates and papers of a type not meeting with the PICOS eligibility criteria. Screening and data extraction were conducted independently by two reviewers (A. Alobaidi and S. Inguva). Results were matched between reviewers and discordance was resolved by consensus through a third reviewer (referring to the original publication if necessary).

Data on 'off'-time at all reported timepoints were collected from each selected publication. Other available information that was extracted from the selected publications, where reported and at all reported timepoints, was: study characteristics (study design and setting, treatment regimen, length of follow-up, sample size, the number of patients receiving each regimen and key inclusion/exclusion criteria), change from baseline in motor symptoms (Unified Parkinson's Disease Rating Scale [UPDRS] III total score), change from baseline in motor complications (UPDRS IV total score), change from baseline in dyskinesia duration, change from baseline in motor experiences of daily living (UPDRS II total score), change from baseline in QoL scores, change from baseline in non-motor symptoms (NMS) and safety outcomes.

These data were extracted independently by both reviewers from selected publications using a standardised Microsoft Excel-based form. Extracted data were verified in the drafting of this manuscript by a third reviewer. As identified studies were not RCTs, the domains to address in a risk of bias assessment, according to the Cochrane Collaboration [26], were absent in most studies. Therefore, we did not draw a funnel plot or conduct a formal assessment of the risk of bias of included publications.

RESULTS

Search Results and Study Selection

The literature search identified 344 records, and 27 studies fulfilled the eligibility criteria and are included in this review (Fig. 1) [19, 20, 27–51]. The characteristics of the 27 studies are summarised in the Supplementary Table 1. Fourteen of the 27 studies (52%) were multicentre studies and ten of 27 (37%) had a sample size of $\geq$ 50 patients. Data were not extracted on co-medication/LCIG monotherapy use, LCIG dose, or previous therapies. None of the identified studies was a RCT (one study was an open-label extension of a pivotal RCT [41] and one was an open-label study that included patients from the aforementioned open-label extension study and a separate open-label study [48]); therefore, no assessment of risk bias was made.

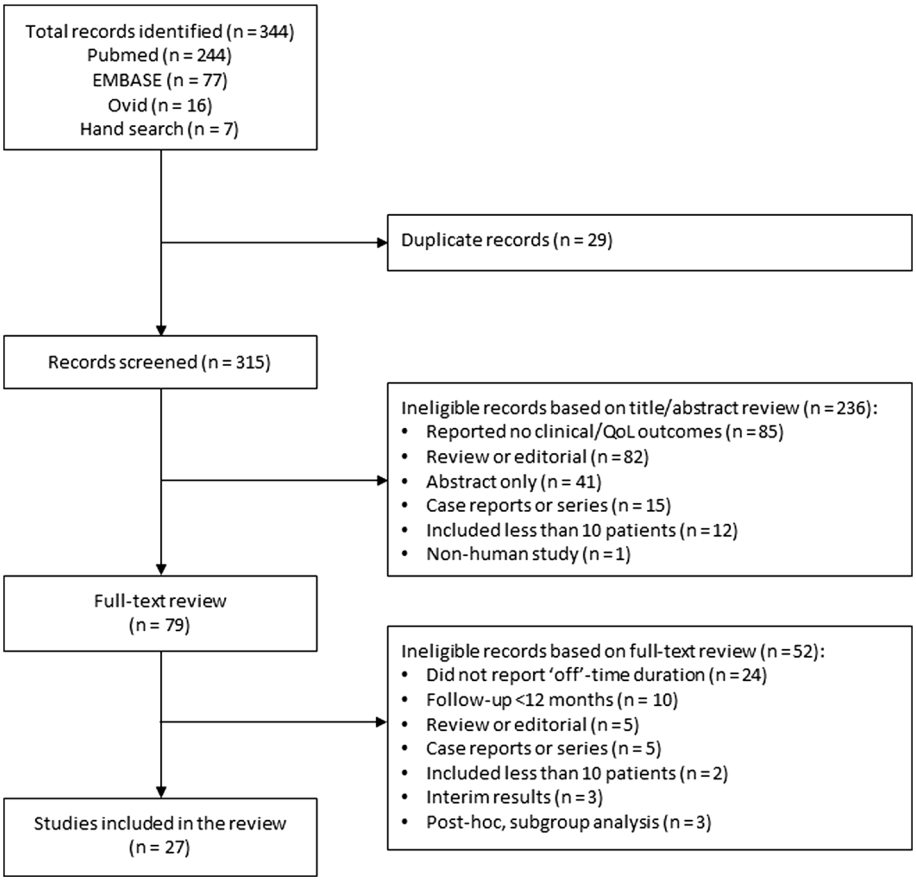

Fig. 1 PRISMA flow chart showing identification and selection of studies

Long-Term 'Off'-time

Attrition rate in the studies varied by the length of follow-up, with follow-ups ranging from 12–120 months (Table 1).

The effect of LCIG therapy on 'off'-time was evaluated using UPDRS IV item 39 (n = 15, but with 1 study using Movement Disorder Society (MDS)-UPDRS item 4.3 to also assess h/waking day), PD patient diary (n = 9), healthcare professional assessment (n = 3) and MDS-UPDRS item 4.3 (n = 2; used in addition to UPDRS IV item 39) (Table 1). Mean baseline 'off'-time ranged from 1.1 to 7.6 h/waking day when assessed by the healthcare provider and 4.7–8.0 h/waking day when assessed by patient diary, and mean baseline UPDRS IV item 39 scores ranged from 1.6 to 2.9 (Table 1).

Mean 'off'-time was significantly reduced by the end of follow-up (i.e., at least 12 months after starting LCIG therapy) in 24 of the 27 studies, with reductions from baseline in 'off'-time of 38–84% (weighted average 61.0%; Table 1; Fig. 2). Reductions in 'off'-time at the end of follow-up were consistent across studies irrespective of the method used for measuring 'off'-time. When UPDRS IV item 39 was used, the percentage of the waking day spent in 'off'-time was reduced from baseline by 36–68% (Table 1; Fig. 2). In studies using patient diaries or healthcare provider assessment to determine the hours of the waking day spent in 'off'-time, the reduction from baseline was 43–84 and 56–71%, respectively (Table 1; Fig. 2).

All 16 studies with a mean follow-up of at least 24 months had statistically significant 'off'-time reductions at the end of this longer follow-up, ranging from 38–83% reduction from baseline (Table 1). In nine studies reporting change in 'off'-time 3–6 months after

Table 1 Population characteristics and effect of LCIG therapy on 'off'-time in the studies included in this review

Study	N[a]	Age (years)[b]	Disease duration (years)[b]	Mean follow-up (months)	Baseline 'off'-time[c]	Reduction from baseline in 'off'-time at end of follow-up (%)	Reduction from baseline in 'off'-time at specific timepoints (%)			
							3–6 months	1 year	2 years	3–5 years
'Off'-time assessed by UPDRS IV item 39 (score)										
Lopiano et al. 2019 [51]	145	70.4 (7.7)	14.6 (6.5)	36[d]	2.0	50*	nr	55*	nr	nr
Fabbri et al. 2019 [49]	44	67.4 (5.8)	14.0 (5.8)	52[d]	2.0	60*	nr	nr	nr	nr
Zibetti et al. 2018 [27]	32	67.5 (6.9)	14.0 (4.2)	31[d]	2.1	62*	nr	nr	nr	nr
Antonini et al. 2017 [19]	375	66.4 (8.8)	12.7 (6.3)	24	6.0[i]	65*	70*	68*	68*	nr
Merola et al. 2016 [28][e]	20	64.6 (7.0)	13.8 (2.6)	62[d]	1.7	55*	nr	nr	nr	nr
Calandrella et al. 2015 [29]	35	64.8 (13.5)	12.3 (3.9)	32[d]	2.4	54*	nr	nr	nr	nr
Caceres-Redondo et al. 2014 [30]	29	66.5 (9.3)	15.1 (5.4)	24	2.9[f]	58*	nr	nr	nr	nr
Zibetti et al. 2014 [31]	59	69.3 (5.9)	13.0 (3.8)	26[d]	1.8	49*	nr	nr	nr	nr
Sensi et al. 2014 [32]	28	67.6 (6.1)	15.5 (4.0)	24	2.3	57*	48*	nr	57*	nr
Antonini et al. 2013 [33]	98	65.3 (10.4)	14.9 (6.6)	24	1.6	38*	47*	33*	37	nr
Zibetti et al. 2013 [34]	25	69.9 (5.8)	12.1 (4.1)	36[d]	1.6	50*	nr	nr	nr	nr

Table 1 continued

Study	N[a]	Age (years)[b]	Disease duration (years)[b]	Mean follow-up (months)	Baseline 'off'-time[c]	Reduction from baseline in 'off'-time at end of follow-up (%)	Reduction from baseline in 'off'-time at specific timepoints (%)			
							3–6 months	1 year	2 years	3–5 years
Fasano et al. 2012 [47]	14	67.1 (11.5)	12.9 (4.8)	25[d]	nr	49*	nr	nr	nr	nr
Merola et al. 2011 [35][e]	20	69 (5.9)	13.9 (4.5)	15[d]	1.6	68*	nr	nr	nr	nr
Antonini et al. 2010 [36]	19	nr	nr	14[d]	1.6	68*	52	36	52	68*
Antonini et al. 2008 [37]	22	nr	nr	24	2.6	46*	nr	54*	46*	nr
'Off'-time assessed by patient diary (h/day)										
Fernandez et al. 2018 [48][g]	86	65.1 (8.3)	10.5 (4.5)	49[d]	6.0 [h]	67*	nr	nr	nr	nr
Standaert et al. 2017 [50]	38	64.3 (10.2)	11.5 (5.3)	14	6.6	74*	61*	nr	nr	nr
De Fabregues et al. 2017 [38]	37	68.2 (6.8)	13.5 (5.6)	120	6.0	83*	82*	nr	82*	83*
Juhasz et al. 2017 [39][j]	34	67 (6)	12 (5)	12	6.3	84*	nr	84*	nr	nr
Chang et al. 2016 [40]	15	62 (4.7)	14	12	6.3	71	70	71	nr	nr
Slevin et al. 2015 [41][k]	62	64.8 (6.6)	11.4 (5.7)	13	5.1	46*	nr	46*	nr	nr
Fernandez et al. 2015 [20]	354	64.1 (9.1)	12.5 (5.5)	14	6.8	66*	64*	66*	nr	nr
Foltynie et al. 2013 [42]	12	66[f]	23.2[f]	12	4.7 [l]	43	nr	43	nr	nr

Table 1 continued

Study	N[a]	Age (years)[b]	Disease duration (years)[b]	Mean follow-up (months)	Baseline 'off'-time[c]	Reduction from baseline in 'off'-time at end of follow-up (%)	Reduction from baseline in 'off'-time at specific timepoints (%)			
							3–6 months	1 year	2 years	3–5 years
Eggert et al. 2008 [43]	13	65 (44–71)[m]	17 (10–26)[m]	12	8.0[f]	70	78*	70	nr	nr
'Off'-time assessed by healthcare provider (h/day)										
Valldeoriola et al. 2016 [44]	177	70.6 (8.4)	14.3 (6.9)	35	7.6[l]	66*	nr	nr	nr	nr
Buongiorno et al. 2015 [45]	72	68.4 (7.3)	13.1 (5.1)	22[d]	6.8	56*	nr	nr	nr	nr
Lundqvist et al. 2014 [46]	10	64 (58–70)[m]	10 (2)	12	1.1[l]	71*	nr	71*	nr	nr

nr not reported. *LCIG* levodopa/carbidopa intestinal gel

*Statistically significant ($p < 0.05$)

[a] Number of patients receiving LCIG

[b] Reported as mean (SD)

[c] UPDRS IV item 39 score, or h/day. UPDRS IV item 39 score (What proportion of the waking day is the patient 'off' on average?): 0 = none, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%

[d] Reported as mean follow-up duration as intended follow-up is not reported

[e] Results are presented for LCIG arm only

[f] Calculated value

[g] Reported for the efficacy population ($n = 86$)

[h] 'Off'-time before LCIG initiation, and therefore, the baseline value recorded in Fernandez et al. 2015[20] and Slevin et al. 2015[41]

[i] UPDRS IV item 39 score was modified using MDS-UPDRS item 4.3 to calculate 'off'-time duration in h/day

[j] Also reported 'off'-time using MDS-UPDRS item 4.3

[k] Results presented for LCIG-naïve arm

[l] Calculated values using 16 h waking day

[m] Median (range)

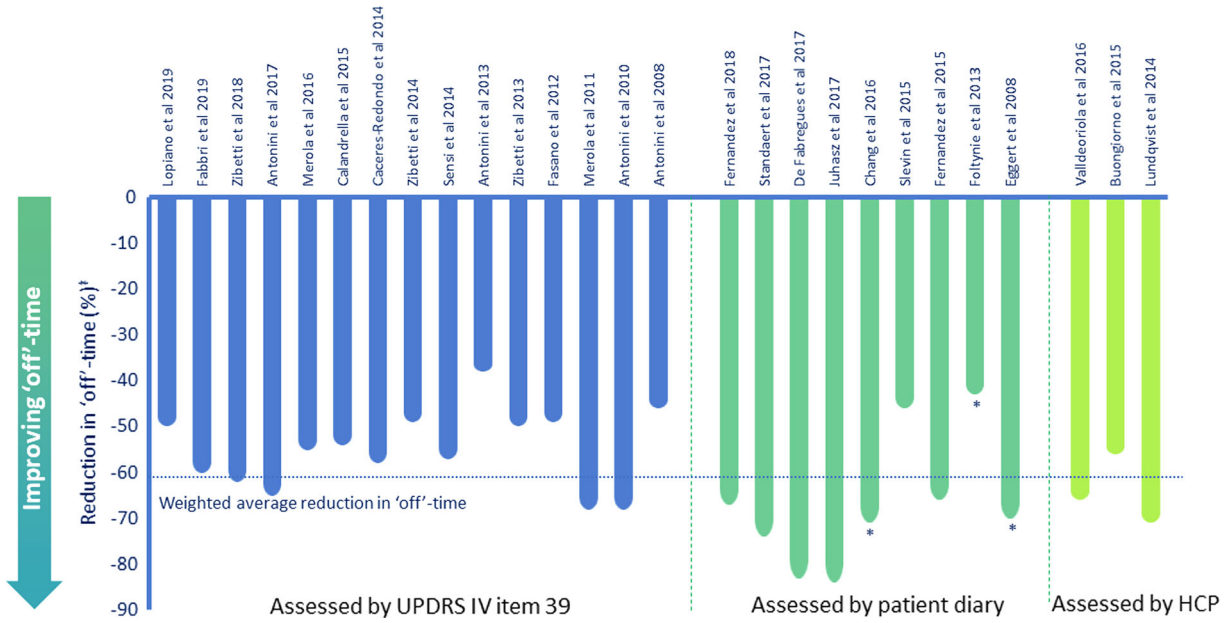

Fig. 2 Percentage reduction in 'off'-time from baseline to last follow-up in the studies included in this review. *Denotes non-significant change from baseline, all other changes are statistically significant. ‡'Off'-time improvement at end of follow-up of each individual study (minimum 12 months; range 12–120 months). Horizontal dotted line represents the weighted average reduction in 'off'-time across all studies. *HCP* healthcare professional. *UPDRS* Unified Parkinson's Disease Rating Scale

initiating LCIG therapy, reductions from baseline ranged from 47 to 82%; in two studies reporting change in 'off'-time at 3–5 years of follow-up, reductions from baseline were 68 and 83% (Table 1).

Other Motor Symptoms

Motor symptoms assessed by UPDRS III total score (includes ratings for tremor, bradykinesia, rigidity and balance) were measured inconsistently in the 'on' or 'off' state. In the 20 studies reporting UPDRS III total score changes, statistically significant improvements were observed in seven studies at follow-ups ranging from 3 to 32 months (three of these seven studies showed improvement in UPDRS III scores at follow-ups of $\geq$ 24 months; Table 2).

ADL assessed by UPDRS II total score were reported in 18 studies (Table 2). These scores were statistically significantly improved with LCIG therapy in nine studies (follow-up: 12–-36 months), significantly worsened in three studies, and there was no statistically significant change in six studies (Table 2).

Motor complications assessed by UPDRS IV total score were reported in 14 studies and significantly improved in 13 studies (follow-up: 12–52 months; Table 3). One of the 14 studies did not report on the significance of change from baseline in UPDRS IV total score as it was a comparator trial [28]. Change in dyskinesia duration was reported in 26 studies, but the method of measuring dyskinesia varied considerably between studies (Table 3). In the 12 studies reporting UPDRS IV item 32 score (dyskinesia duration—in some studies this was modified to h/day), nine studies reported statistically significant improvements at follow-ups ranging from 6 to 36 months, and no study showed an increase in dyskinesia duration (Table 3).

Table 2 Effect of LCIG therapy on other motor symptoms (UPDRS II and III total scores) in the studies included in this review

Study	UPDRS II total score[a, b]		UPDRS III total score[a, b]	
	Baseline	Follow-up[c]	Baseline	Follow-up[c]
Lopiano et al. 2019 [51]	'Off': 29.2 (9.6) 'On': 18.2 (9.4)	'Off': 25.5 (8.8)* 'On': 16.2 (8.5)*	nr	nr
Fabbri et al. 2019 [49]	17.1 (7.2)	29.5 (9.6)*	31.0 (12.4)	49.2 (15.0)*
Zibetti et al. 2018 [27]	'On': 13.3 (6.0)	'On': 12.9 (6.9)	'On': 23.5 (9.9)	'On': 22.8 (13.4)
Fernandez et al. 2018 [48]		3.1 (7.8)[d,e]*		4.6 (14.7)[d,e]*
Standaert et al. 2017 [50]	'On': 16.7 (6.5)	− 4.8 (0.7)[e]* (1 wk) − 5.5 (0.9)[e]* (12 wk) − 4.2 (0.9)[e]* (36 wk) − 4.7 (0.9)[e]* (60 wk)	'On': 25.0 (13.2)	− 3.5 (1.2)[e]* (1 wk) − 5.6 (1.2)[e]* (12 wk) − 2.6 (1.5)[e] (36 wk) − 3.6 (1.5)[e]* (60 wk)
Antonini et al. 2017 [19]	'On': 16.5 (9.8)	− 2.0 (9.1)[e]* (18 mo)	'On': 24.6 (12.0)	− 1.9 (11.8)[e]*
De Fabregues et al. 2017 [38]	nr	nr	'Off': 40.9 (13.2) 'On': 22.2 (8.4)	'Off': 39.0 (12.0)* (3 mo) 'On': 21.1 (8.8) (3 mo)
Juhasz et al. 2017 [39]	23.9 (6.2)	19.4 (9.0)*	42.5 (16.0)	45.3 (16.4)
Merola et al. 2016 [28][f]	7.8 (3.5)	13.5 (9.8)	'Off': 41.3 (9.0) 'On': 19.9 (11.4)	'Off': 53.8 (13.0) 'On': 23.9 (10.1)
Chang et al. 2016 [40]	nr	nr		'On': 31 (36)%[e] (6 mo) 'On': 37 (11)%[e] (12 mo)
Valldeoriola et al. 2016 [44]		'Off': -2.3 (23.2)[e] 'On': 3.1 (19.0)[e]	nr	nr
Calandrella et al. 2015 [29]	nr	nr	'On': 36.5 (2.4)	'On': 28.5 (5.0)*
Slevin et al. 2015 [41][g]		'On': − 1.0 (7.0)[e]		− 0.5 (10.4)[e]
Fernandez et al. 2015 [20]		'On': − 4.4 (6.5)[e]*	28.8 (13.7)	Sig. improvement (12 mo)
Buongiorno et al. 2015 [45]	'On': 13.6	'On': 14.3	'On': 21.9	'On': 22.3

Table 2 continued

Study	UPDRS II total score[a, b]		UPDRS III total score[a, b]	
	Baseline	Follow-up[c]	Baseline	Follow-up[c]
Caceres-Redondo et al. 2014 [30]	'Off': 27.2 (8.5) 'On': 14.5 (5.3)	'Off': 23.8 (5.9)* 'On': 16.5 (5.0)	'Off': 48.0 (8.9) 'On': 27.2 (8.1)	'Off':45.5 (8.9) 'On': 29.5 (6.4)
Zibetti et al. 2014 [31]	nr	nr	nr	nr
Sensi et al. 2014 [32]	nr	nr	'On': 35.5 (11.5)	'On': 33.4 (10.8) (6 mo) 'On': 34.7 (12.4) (24 mo)
Lundqvist et al. 2014 [46]	nr	nr	nr	nr
Antonini et al. 2013 [33]	'On': 14.8 (8.9)	'On': 10.6 (7.2)* (6 mo) 'On': 11.8 (8.2)* (12 mo) 'On': 14.0 (7.5) (24 mo) 'On': 13.2 (8.5) (last f-u)	'On': 25.3 (13.6)	'On': 22.6 (12.9)* (6 mo) 'On': 23.3 (12.5) (12 mo) 'On': 27.1 (13.4) (24 mo) 'On': 24.5 (13.0) (last f-u)
Zibetti et al. 2013 [34]	'Off': 23.2 (8.5) 'On': 16.1 (7.2)	'Off': 25.3 (7.3) 'On': 20.9 (7.5)*	'Off': 43.1 (13.7) 'On': 23.2 (9.2)	'Off': 48.4 (12.4)* 'On': 32.2 (12.6)*
Foltynie et al. 2013 [42]	nr	nr	nr	nr
Fasano et al. 2012 [47]		No significant change		No significant change
Merola et al. 2011 [35][f]	'Off': 25.9 (8.6)	'Off': 18.3 (7.6)*	'Off': 45.7 (14.8)	'Off': 29.1 (15.9)*
Antonini et al. 2010 [36]	nr	nr	nr	nr
Antonini et al. 2008 [37][h]	12.8 (2.9)	9.4 (3.9)*	'On': 24.6 (5.2)	'On': 24.8 (6.0)
Eggert et al. 2008 [43]	nr	nr	nr	nr

nr not reported. *BL* baseline. *LCIG* levodopa/carbidopa intestinal gel. *mo* months. *wk* weeks. *UPDRS* Unified Parkinson's Disease Rating Scale

*Statistically significant ($p < 0.05$) change from baseline

[a] Reported as mean (SD)

[b] Measured in 'on' or 'off' state as indicated. If not defined, the state was not reported

[c] End of follow-up unless otherwise stated

[d] Using the baseline value recorded in Fernandez et al. 2015 [20] and Slevin et al. 2015[41]

[e] Change from baseline

[f] Results are presented for LCIG arm only

[g] Results presented for LCIG-naïve arm

[h] p value versus conventional treatment arm

Table 3 Effect of LCIG therapy on other motor symptoms (dyskinesia and other measures) in the studies included in this review

Study	UPDRS IV total score[a]		Dyskinesia[a]		Other changes[a]	
	Baseline	Follow-up[b]	Baseline	Follow-up[b]	Baseline	Follow-up[b]
Lopiano et al. 2019 [51]	8.2 (3.3)	4.9 (3.1)*	1.8 (1.0) UPDRS IV item 32 1.5 (1.1) UPDRS IV item 33 0.8 (1.0) UPDRS IV item 34	1.3 (1.0)* UPDRS IV item 32 0.9 (1.0)* UPDRS IV item 33 0.4 (0.7)* UPDRS IV item 34	'Off': 4.0 (0.8) UPDRS-V 'On': 3.1 (0.8) UPDRS-V	'Off': 3.7 (0.8)* UPDRS-V 'On': 2.8 (0.8)* UPDRS-V
Fabbri et al. 2019 [49]	9.5 (3.1)	6.1 (2.4)*	1.7 (1.0) UPDRS IV item 32	1.7 (0.8) UPDRS IV item 32	3.0 (0.9) H&Y 63 (13) S&E	3.3 (1.2)* H&Y 56 (19)* S&E
Zibetti et al. 2018 [27]	9.2 (2.5)	6.1 (2.5)*	1.8 (1.0)	1.4 (0.9)*	2.4 (0.9) H&Y 77.8 (15.2) S&E	2.8 (0.9)* H&Y 66.3 (19.1)* S&E
Fernandez et al. 2018 [48]	nr	nr		Unchanged[c,d]	nr	nr
Standaert et al. 2017 [50]	8.7 (3.0)	− 2.7 (0.5)[d*] (1 wk) − 3.5 (0.4)[d*] (12 wk) − 3.5 (0.4)[d*] (36 wk) − 2.9 (0.6)[d*] (60 wk)	3.0 (2.1) UPDRS IV item 32, 33, 34	− 1.1 (0.4)[d*] (1 wk) − 1.1 (0.3)[d*] (12 wk) − 1.1 (0.3)[d*] (36 wk) − 0.6 (0.6)[d] (60 wk) UPDRS IV item 32, 33, 34	nr	nr
Antonini et al. 2017 [19]	nr	nr	4.3 (3.8) Modified UPDRS IV item 32	− 1.1 (4.7)[d*] Modified UPDRS IV item 32	nr	nr

Table 3 continued

Study	UPDRS IV total score[a]		Dyskinesia[a]		Other changes[a]	
	Baseline	Follow-up[b]	Baseline	Follow-up[b]	Baseline	Follow-up[b]
De Fabregues et al. 2017 [38]	nr	nr		Reduced in 16.1%	50 S&E	80* (3 mo) S&E
						'Off' Improved in 45.9%* H&Y
						'On' Improved in 27%* H&Y
Juhasz et al. 2017 [39]	10.4 (4.0)	7.5 (4.0)*	2.8 (1.1)	2.1 (1.2)*	45.9 (16.7) UPDyRS	32.1 (17.3)* UPDyRS
			MDS-UPDRS item 4.1	MDS-UPDRS item 4.1		
			4.9 (2.8)	10.0 (4.6)*	60.0 (17.3) S&E	67.4 (17.3) S&E
			PD diary ('on'-time without dyskinesia)	PD diary ('on'-time without dyskinesia)		
			3.6 (2.5)	4.0 (4.4)		
			PD diary ('on'-time with slight dyskinesia)	PD diary ('on'-time with slight dyskinesia)		
			1.8 (1.7)	0.4 (1.6		
			PD diary ('on'-time with severe dyskinesia)	PD diary ('on'-time with severe dyskinesia)		
Merola et al. 2016 [28][c]	8.3 (2.6)	6.2 (2.1)		− 9.0%[d] Duration	2.4 (0.7) H&Y	3.0 (0.9) H&Y
				− 18.0%[d] Severity	84.5 (12.1) S&E	78.8 (17.5) S&E
Chang et al. 2016 [40]	nr	nr	nr	nr	nr	nr

Table 3 continued

Study	UPDRS IV total score[a]		Dyskinesia[a]		Other changes[a]	
	Baseline	Follow-up[b]	Baseline	Follow-up[b]	Baseline	Follow-up[b]
Valldeoriola et al. 2016 [44]	nr	nr	21.6 (16.5) 'On'-time without disabling dyskinesia 11.3 (13.0) 'On'-time with disabling dyskinesia	55.6 (25.7)* 'On'-time without disabling dyskinesia 10.9 (16.6) 'On'-time with disabling dyskinesia		88.6% improvement CGI-C 86.8% improvement PGI-C
Calandrella et al. 2015 [29]	nr	nr	2.2 (0.7) UPDRS IV item 32 + 33	1.5 (0.7)* UPDRS IV item 32 + 33		No change H&Y
Slevin et al. 2015 [41][f]		− 1.4 (3.0)[d]*		2.2 (3.7)[d]* 'On'-time with troubling dyskinesia		2.3 (1.6)[d]* CGI-I
Fernandez et al. 2015 [20]	nr	nr		4.8 (3.4)[d]* 'On'-time without dyskinesia − 0.4 (2.8)[d]* 'On'-time with dyskinesia	nr	nr
Buongiorno et al. 2015 [45]	nr	nr	1.4 (1.3) UPDRS IV item 33 30% %age of day with dyskinesia	1.2 (1.2) UPDRS IV item 33 40%* %age of day with dyskinesia	nr	70% subjective improvement CGI
Caceres-Redondo et al. 2014 [30]	8.7 (2.3)	6.7 (2.8)*	60.3 (37.8) UPDRS IV item 32	48.8 (28.7)* UPDRS IV item 32	'Off': 3.7 (0.8) H&Y 'On': 2.4 (0.5) H&Y	'Off': 3.5 (1.1) H&Y 'On': 2.7 (0.7) H&Y

Table 3 continued

Study	UPDRS IV total score[a]		Dyskinesia[a]		Other changes[a]	
	Baseline	Follow-up[b]	Baseline	Follow-up[b]	Baseline	Follow-up[b]
Zibetti et al. 2014 [31]	8.5 (3.1)	5.7 (2.4)*	1.7 (0.9) UPDRS IV item 32	1.2 (0.7)* UPDRS IV item 32	nr	nr
Sensi et al. 2014 [32]	8.4 (2.5)	5.6 (2.7)* (6 mo) 4.4 (1.9)* (24 mo)	2.2 (1.0) UPDRS IV item 32	1.8 (1.0) (6 mo) 1.2 (1.0)* (24 mo) UPDRS IV item 32	3.2 (0.7) H&Y	3.1 (0.8) (6 mo) H&Y 3.0 (0.8) (24 mo) H&Y
Lundqvist et al. 2014 [46]	nr	nr	10.0 (9.2)%	2.0 (2.8)%*	2–3 H&Y range 75% S&E 48.9 (10.0) Total UPDRS	1.5–3 H&Y range 79% S&E 30.2 (5.2)* Total UPDRS
Antonini et al. 2013 [33]	nr	nr	1.7 (1.0) UPDRS IV item 32	1.2 (0.9)* (6 mo) 1.5 (0.8) (12 mo) 1.4 (0.8) (24 mo) 1.3 (0.9)* (last f-u)	nr	nr
Zibetti et al. 2013 [34]	8.4 (3.2)	5.6 (2.8)*	1.9 (1.0) UPDRS IV item 32	1.1 (1.0)* UPDRS IV item 32	nr	nr
Foltynie et al. 2013 [42]	nr	nr	16.6 (18.6)%	8.2 (10.3)%	nr	nr
Fasano et al. 2012 [47]		29.3%[d]*		38.5% [d]* UPDRS IV item 32	2.7 (1.8) ADL score 2.9 (2.5) IADL score	3.6 (3.5) ADL score 4.0 (2.6) IADL score

Table 3 continued

Study	UPDRS IV total score[a]		Dyskinesia[a]		Other changes[a]	
	Baseline	Follow-up[b]	Baseline	Follow-up[b]	Baseline	Follow-up[b]
Merola et al. 2011 [35][c]	8.6 (4.2)	5.6 (3.4)*		No change UPDRS IV item 32	nr	nr
Antonini et al. 2010 [36]	nr	nr	2.5 (0.6) UPDRS IV item 32	1.3 (0.9) (1–20 wk) 1.4 (0.6) (21–50 wk) 1.5 (0.6) (51–100 wk) 1.0 (0.0)* (101–200 wk) UPDRS IV item 32	nr	nr
Antonini et al. 2008 [37][g]	8.4 (0.8)	6.6 (0.9)*		No change UPDRS IV item 32	nr	nr
Eggert et al. 2008 [43]	nr	nr	17 (15)%	5 (6)%*	nr	nr

UPDRS IV item 32 (What proportion of the waking day are dyskinesia present?): 0 = none, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%. UPDRS IV item 33 (How disabling are the dyskinesia?): 0 = not disabling, 1 = mildly disabling, 2 = moderately disabling, 3 = severely disabling, 4 = completely disabled. UPDRS IV item 34 (How painful are the dyskinesia?): 0 = no painful dyskinesia, 1 = slight, 2 = moderate, 3 = severe, 4 = marked. MDS-UPDRS item 4.1 (Time spent with dyskinesia): 0 = none, 1 = $\leq$ 25%, 2 = 26–50%, 3 = 51–75%, 4 = $>$ 75%

nr not reported. *H&Y* Hoehn & Yahr. *LCIG* levodopa/carbidopa intestinal gel. *mo* months. *S&E* Schwab & England. *wk* weeks. *UPDRS* Unified Parkinson's Disease Rating Scale

*Statistically significant ($p < 0.05$) change from baseline

[a] Reported as mean (SD)

[b] End of follow-up unless otherwise stated

[c] Using the baseline value recorded in Fernandez et al. 2015[20] and Slevin et al. 2015[41]

[d] Change from baseline

[e] Results are presented for LCIG arm only

[f] Results presented for LCIG-naïve arm

[g] *p* value versus conventional treatment arm

Table 4 Effect of LCIG therapy on non-motor symptoms in the studies included in this review (n = 14)

Study	NMSS total or sub-domain scores[a]		MMSE total score[a]		UPDRS I total score and other NMS measures[a]	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Lopiano et al. 2019 [51]	nr	nr	nr	nr	'Off' 6.8 (4.8) 'On' 4.3 (3.1) UPDRS I 25 (10.4) PDSS-2 10.4 (16.6) QUIP 40.2 (12.4) RSS-2	'Off' 6.0 (3.7)* 'On' 3.8 (2.8)* UPDRS I 22.7 (10.1)* PDSS-2 7.1 (10.1)* QUIP 38.3 (13) RSS-2
Fabbri et al. 2019 [49]	nr	nr	27.2 (2.4)	24.1 (4.0)*	14.5 (7.8) BDI	18.5 (9.5)* BDI
Standaert et al. 2017 [50]	48.3 (35.6) Total score	− 17.6 (3.6)[b]* (12 wk) Total score − 11.8 (4.0)[b]* (60 wk) Total score 5/9 sub-domains (attention/memory, sleep/fatigue, gastrointestinal, sexual function and miscellaneous) significantly improved	nr	nr	1.6 (1.6) UPDRS I	− 0.6 (0.2)* (1 wk) UPDRS I − 0.3 (0.3) (12 wk) UPDRS I − 0.3 (0.3) (36 wk) UPDRS I − 0.1 (0.3) (60 wk) UPDRS I
Antonini et al. 2017 [19]	69.2 (42.1) Total score	− 14.4 (44.8)[b]* Total score 5/9 sub-domains (mood/cognition, sleep/fatigue, gastrointestinal, cardiovascular function and miscellaneous) significantly improved	nr	nr	nr	nr

Table 4 continued

Study	NMSS total or sub-domain scores[a]		MMSE total score[a]		UPDRS I total score and other NMS measures[a]	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
De Fabregues et al. 2017 [38]	nr	nr	Median 28	Median 29 (3 mo)	3.2 (2.4) UPDRS I	2.5 (1.7)* (3 mo) UPDRS I
Juhasz et al. 2017 [39]	88.9 (40.3) Total score	32.2 (69.0)* Total score 2/9 sub-domains (mood problems and cardiovascular function) significantly improved	nr	nr	27.2 (10.5) PDSS 9.1 (4.8) ESS − 19.0 (10.0) LARS 18.2 (7.2) MADRS 19.7 (6.9) MDS-UPDRS nM-EDL	23.2 (12.0)* PDSS 4.6 (7.0) ESS − 20.4 (7.4) LARS 15.4 (6.2)* MADRS 16.7 (6.9)* MDS-UPDRS nM-EDL
Valldeoriola et al. 2016 [44]		Proportion of patients with sub-domain improvements: Dizziness 59.7% Daytime fatigue 57.5% Mood 56.0% Falling asleep in the day 52.6% Insomnia 52.3% Sadness 50.9%	nr	nr	nr	nr
Merola et al. 2016 [28]	nr	nr	29.3 (0.7)	26.6 (4.3)	2.1 (1.9) UPDRS I	3.4 (3.7) UPDRS I
Slevin et al. 2015 [41][c]	nr	nr	nr	nr		0.7 (1.7)[b]

Table 4 continued

Study	NMSS total or sub-domain scores[a]		MMSE total score[a]		UPDRS I total score and other NMS measures[a]	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Caceres-Redondo et al. 2014 [30]	17.3 (4.7) Total score	14.2 (4.3)* Total score 2/9 sub-domains (sleep/fatigue and gastrointestinal) significantly improved	24.7 (3.5)	22.0 (4.9)*	124.9 (17.8) DRS	115.3 (23.6)* DRS No change in NPI-Q
Sensi et al. 2014 [32]	51.8 (37.3) Total score	44.6 (25.6) (6 mo) Total score 38.0 (24.7) (24 mo) Total score	25.0 (2.7)	24.4 (2.8) (6 mo) 23.2 (4.1)* (24 mo)	nr	nr
Zibetti et al. 2013 [34]	nr	nr	24.7 (2.7)	15.6 (3.7)*	nr	nr
Fasano et al. 2012 [47]	126.0 (56.2) Total score	108.3 (49.4) Total score	22.2 (5.6)	22.4 (6.0)	8.7 (3.2) UPDRS I 39.1 (8.6) PDSS 0.6 (0.5) QUIP 41.2 (30.7) NPI 11.9 (3.8) FAB 33.9 (8.0) RSS	6.8 (2.9)* UPDRS I 33.5 (9.2)* PDSS 0.3 (0.5)* QUIP 27.4 (23.0)* NPI 11.8 (3.9) FAB 29.5 (8.0) RSS

Table 4 continued

Study	NMSS total or sub-domain scores[a]		MMSE total score[a]		UPDRS I total score and other NMS measures[a]	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Merola et al. 2011 [35]	nr	nr	nr	nr	3.9 (2.3) UPDRS I	4.3 (2.2) UPDRS I

BDI Beck depression inventory. *DRS* Mattis dementia rating scale. *FAB* frontal assessment battery. *LARS* Lille apathy rating scale. *MADRS* Montgomery-Asberg depression rating scale. *MMSE* mini-mental state examination. *mo* months. *nM-EDL* non-motor aspects of experiences of daily living. *NMS* non-motor symptom. *NMSS* non-motor symptom scale. *NPI-Q* neuropsychiatric inventory brief questionnaire. *nr* not reported. *PDSS* Parkinson's disease sleep scale. *QUIP* questionnaire for impulsive-compulsive disorders. *RSS* relative stress scale. *UPDRS* Unified Parkinson's Disease Rating Scale

*Statistically significant ($p < 0.05$) change from baseline

[a] Reported as mean (SD) unless otherwise stated. If no p-value is shown, the change from baseline is not significant

[b] Change from baseline

[c] Results presented for LCIG-naïve arm

Non-Motor Symptoms and Quality of Life

NMS endpoints were reported in 14 of the selected studies (Table 4). A wide variety of assessment tools were used, making general conclusions difficult. The most frequently used scales were the non-motor symptom scale (NMSS), the mini-mental state examination (MMSE) and part I of the UPDRS (mentation, behaviour and mood).

Of six studies reporting NMSS total score, four showed statistically significant improvements at follow-up with LCIG (Table 4). Improvements in the NMSS sub-scale scores were also observed but with no clear trend across studies. The MMSE scores significantly worsened in four studies (at follow-ups of 24–-52 months), and three studies reported no statistically significant change (Table 4). UPDRS I total score improved in four studies with follow-ups of 3 weeks to 36 months and there was no statistically significant change in two studies (Table 4).

Health-related QoL (HRQoL) outcomes were reported in 17 studies (Table 5). Most studies reporting HRQoL used the Parkinson's Disease Questionnaire (PDQ)-39 and 8 of 11 studies reported statistically significant improvements in PDQ-39 scores from baseline 12–36 months after starting LCIG therapy (Table 5). Of the studies reporting PDQ-39 or PDQ-8, 12 studies reported the change from baseline at end of follow-up, and while there may be too few data points to conclude on correlations, there appears to be a trend for a greater improvement in HRQoL in studies reporting a greater reduction in long-term 'off'-time (Fig. 3).

Safety and Tolerability

The frequency of LCIG-related adverse events (AEs) varied widely in the selected studies because of the way in which data were collected or reported (Table 6). In many studies, the most frequent AEs were related to the PEG procedure or the device, such as wound/stoma infection, abdominal/procedural pain or problems with the tubing such as dislocation (Table 6). AEs that were considered levodopa-related included weight loss, hallucinations and neuropathy (Table 6). However, discontinuation rates due to AEs were lower than the rates of AE occurrence.

Table 5 Effect of LCIG therapy on quality of life outcomes in the studies included in this review (n = 17)

Study	PDQ-39 or PDQ-8 scores[a]		Other QoL scales[a]	
	Baseline	Follow-up	Baseline	Follow-up
Fernandez et al. 2018 [48]		0.5 (16.6)[b] PDQ-39	nr	nr
Standaert et al. 2017 [50]	34.7 (13.0) PDQ-39	− 4.8 (1.8)[b*] (1 wk) PDQ-39 − 11.2 (2.8)[b*] (12 wk) PDQ-39 − 9.1 (2.2)[b*] (30 wk) PDQ-39 − 10.2 (2.6)[b*] (60 wk) PDQ-39	nr	nr
Antonini et al. 2017 [19]	46.8 (18.6) PDQ-8	− 5.3 (20.7)[b*] PDQ-8	0.4 (0.3) EQ-5D	0.06 (0.34)[b*] EQ-5D
De Fabregues et al. 2017 [38][c]	56.9 (11.4) PDQ-39	41.9 (21.5) (1 wk) PDQ-39 35.7 (18.6) (3 mo) PDQ-39 35.5 (19.1)* (6 mo) PDQ-39 35.5 (18.8)* (1 yr) PDQ-39	9.3 (1.7) EQ-5D: BL 1 year 7.5 (1.9) (p = 0.042)	7.9 (2.6)* (1 wk) EQ-5D 7.5 (2.1)* (3 mo) EQ-5D 8.2 (2.5) (6 mo) EQ-5D 7.5 (1.9)* (1 yr) EQ-5D
Juhasz et al. 2017 [39]	38.5 (14.9) PDQ-39	29.6 (13.6)* PDQ-39	0.5 (0.2) EQ-5D index	0.6 (0.3)* EQ-5D index
Chang et al. 2016 [40]	38.3 (14.0) PDQ-39	22.8 (17.0) (6 mo) PDQ-39 24.5 (16.0) (1 yr) PDQ-39	nr	nr
Slevin et al. 2015 [41][d]		− 3.5 (13.4)[b] PDQ-39		− 0.006 (0.220)[b] EQ-5D summary index
Fernandez et al. 2015 [20]		− 6.9 (14.1)[b*] PDQ-39		− 0.064 (0.203)[b*] EQ-5D summary index
Caceres-Redondo et al. 2014 [30]	84.2 (18.7) PDQ-39	74.3 (21.3)* PDQ-39	nr	nr

Table 5 continued

Study	PDQ-39 or PDQ-8 scores[a]		Other QoL scales[a]	
	Baseline	Follow-up	Baseline	Follow-up
Zibetti et al. 2014 [31]	nr	nr		Great improvement 44% Moderate improvement 48% Unspecified 5-point scale
Sensi et al. 2014 [32]	46.3 (13.7) PDQ-8	29.9 (17.0)* PDQ-8	87.8 (19.5) SQLC	94.4 (20.3) SQLC
Lundqvist et al. 2014 [46]	nr	nr	0.6 (0.1) 15D	0.7 (0.1) (3 mo) 15D 0.7 (0.1) (6 mo) 15D 0.7 (0.1) (9 mo) 15D 0.7 (0.1) (12 mo) 15D 0.7 (0.1) (last f-u) 15D
Antonini et al. 2013 [33]	53.3 (21.7) PDQ-8	47.0 (15.2)* PDQ-8	nr	nr
Zibetti et al. 2013 [34]	59.2 (18.7) PDQ-39	43.1 (13.9)* PDQ-39	nr	nr
Foltynie et al. 2013 [42]	49.7 (10.4) PDQ-39	38.7 (11.2)* PDQ-39	nr	nr
Fasano et al. 2012 [47]	18.1 (6.6) PDQ-8	16.7 (6.0) PDQ-8	nr	nr
Antonini et al. 2008 [37]	59.5 (14.4) PDQ-39	46.4 (14.5)* (12 mo) PDQ-39 49.2 (10.3)* (24 mo) PDQ-39	nr	nr

EQ-5D EuroQol-5 dimensions. *nr* not reported. *PDQ* Parkinson's disease questionnaire. *SQLC* scale of quality of life of care partners. *QoL* quality of life

*Statistically significant ($p < 0.05$)

[a] Reported as mean (SD) unless otherwise stated

[b] Change from baseline

[c] In a substudy of 9 patients

[d] Results presented for LCIG-naïve arm

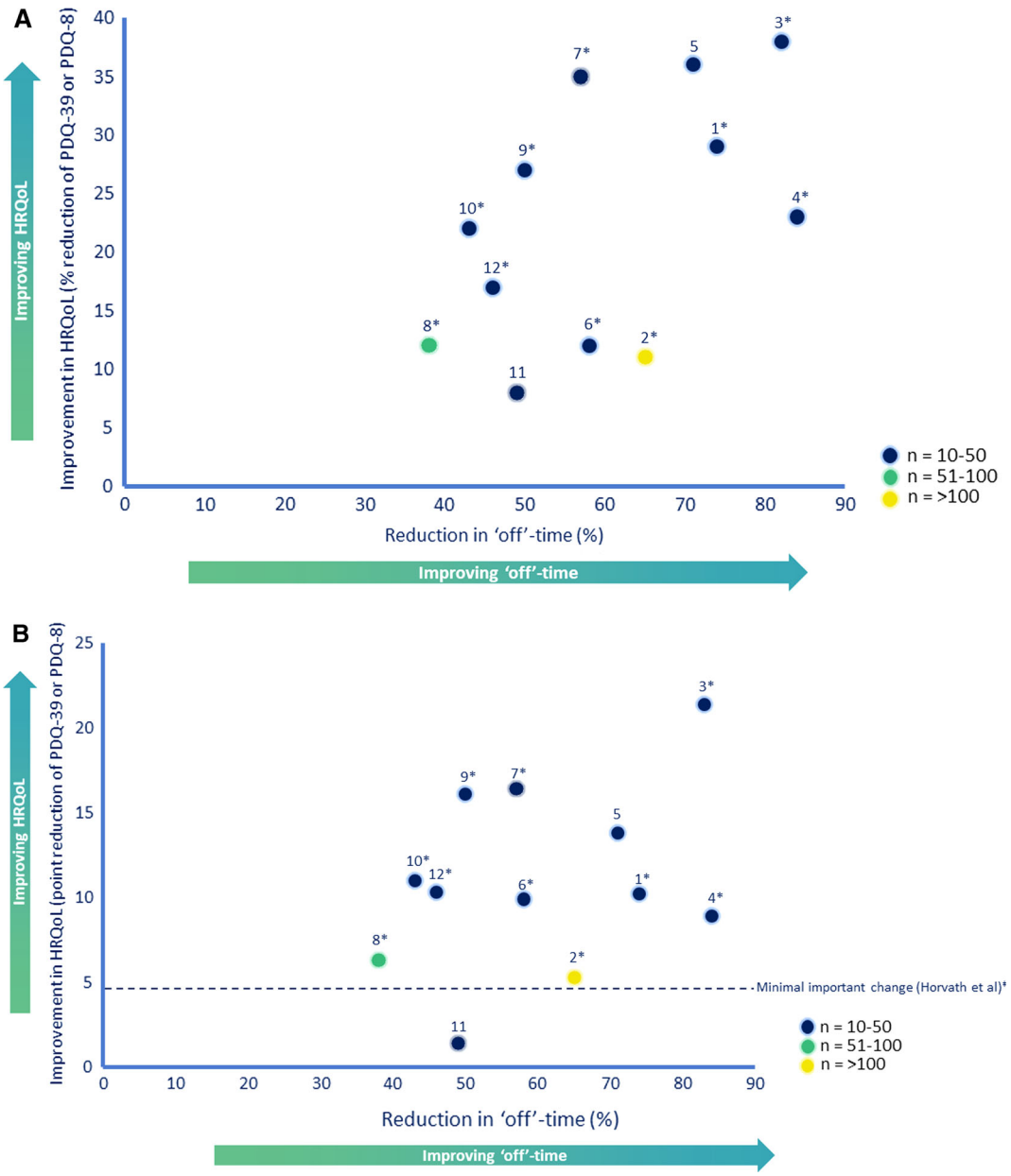

Fig. 3 Percentage reduction in 'off'-time from baseline plotted against the improvement in health-related quality of life (HRQoL according to PDQ-39 or PDQ-8) in the studies reporting both endpoints at end of follow-up. **a** Change in HRQoL as percentage change from baseline; **b** change in HRQoL as actual change in PDQ score from baseline. *Denotes statistically significant change from baseline in HRQoL ($p < 0.05$). ‡Horvath et al. [66]. *HRQoL* health-related quality of life. 1. Standaert et al. 2017 [50]. 2. Antonini et al. 2017 [19]. 3. De Fabregues et al. 2017 [38]. 4. Juhasz et al. 2017 [39]. 5. Chang et al. 2016 [40]. 6. Caceres-Redondo et al. 2014 [30]. 7. Sensi et al. 2014 [32]. 8. Antonini et al. 2013 [33]. 9. Zibetti et al. 2013 [34]. 10. Foltynie et al. 2013 [42]. 11. Fasano et al. 2012 [47]. 12. Antonini et al. 2008 [37]

Table 6 Overall frequency of adverse events in the studies included in this review

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Lopiano et al. 2019 [51]	nr	SAEs in ≥ 1% of patients (not related): Pneumonia 2.8%; femur fracture 2.1%; cardiac failure 2.1%; cardiac arrest 1.4%; peripheral neuropathy 1.4%; worsening of PD 1.4%; peritonitis 1.4%; death 1.4%; fasciitis 1.4% SAEs in ≥ 1% of patients (related to PEG/J or device): Wrong technique in drug usage process 1.4% AEs leading to discontinuation in ≥ 1% of patients: Device occlusion/complication 1.4%; abnormal weight loss/hypoglycaemia 1.4%; fasciitis 1.4%; peripheral sensory neuropathy 1.4%
Fabbri et al. 2019 [49]	nr	nr
Zibetti et al. 2018 [27]	nr	nr
Fernandez et al. 2018 [48]	≥ 15% of patients:[b] Postoperative wound infection 23%; vitamin B6 decreased 22%; fall 21%; urinary tract infection 19%; blood homocysteine increased 18%; excessive granulation tissue 16%; incision-site erythema 15%	SAEs in ≥ 3% of patients:[b] Pneumonia 6%; complication of device insertion 5%; fall 5%; pneumonia aspiration 3%; post-operative wound infection 3%; weight decreased 3% AEs leading to discontinuation in ≥ 2% of patients: Complication of device insertion 2%; death of unknown cause 2%; pneumonia 2%

Table 6 continued

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Standaert et al. 2017 [50]	≥ 15% of patients:[b]	SAEs in ≥ 3% of patients:[b]
	Procedural pain 33%; stoma site infection 28%; stoma site pain 23%; anxiety 21%; stoma site erythema 21%; fall 18%; weight decreased 18%; urinary tract infection 15%	Acute respiratory failure 3%; anxiety 3%; atrial fibrillation 3%; aspiration pneumonia 3%; basal cell carcinoma 3%; congestive cardiac failure 3%; internal hernia 3%; major depression 3%; osteoarthritis 3%; peritonitis 3%; radiculopathy 3%; respiratory distress 3%; sedation 3%; suicidal ideation 3%
		AEs leading to discontinuation in ≥ 2% of patients:
		Stoma site pain or infection 5%; cognitive disorder 3%; pneumonia 3%; congestive cardiac failure, acute respiratory failure and aspiration pneumonia following spinal surgery 3%
Antonini et al. 2017 [19]	≥ 4% of patients:[c]	SAEs in ≥ 1% of patients:[c]
	Weight decrease 6.7%; device related infection 5.9%; device dislocation 4.8%; device issue 4.8%; polyneuropathy 4.5%	Device dislocation 2.2%; device issue 2.0%; Parkinson's disease 2.0%; parkinsonism 2.0%; device complication 1.7%; device malfunction 1.4%; device occlusion 1.4%; abdominal pain 1.1%; hallucination 1.1%; pneumonia 1.1%; polyneuropathy 1.1%
		Most common AE leading to discontinuation:
		Device dislocation 0.6%
De Fabregues et al. 2017 [38][c]	≥ 30% of patients:[c]	SAEs in ≥ 3% of patients:[c]
	Pharmacological:	PEG removal 10.8%; stoma infection 8.1%; PEG hooked related to infusion device 8.1%; dyskinesia 8.1%; weight loss 8.1%; freezing in 'on' 5.4%
	Leg pain 40.5%; polyneuropathy 35.1%; psychosis/ hallucinations 35.1%; vitamin B6 deficit 32.4%	
	PEG procedures gastrostomy:	AEs leading to discontinuation in ≥ 2% of patients:
	Granuloma 37.8%; abdominal pain/nausea/vomiting 32.4%; stoma dermatitis 32.4%	Intolerance to the administration system 5.4%; serious stoma infection 2.7%; worsening of dyskinesia 2.7%
	Infusion device:	
	PEG replacement 91.2%; transitory or permanent obstruction of intestinal tube 35.1%	

Table 6 continued

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Juhasz et al. 2017 [39]	≥ 5% of patients:[c] Drug related: Weight decreased 14.7%; hallucination/confusion 11.8%; symptomatic orthostatic hypotension 8.8%; polyneuropathy 5.9% Surgery related: Abdominal pain 70.6%; injection site reaction 14.7%; wound infection 8.8%; peritonitis 5.9% Stoma related: Granuloma infection 23.5%; stoma infection 8.8% Device related: Tube replacement 11.8%; dislocation 8.8%	nr
Merola et al. 2016 [28]	≥ 5% of patients:[c] Infection 20%; weight loss 10%; serous bloody PEG discharge 5%; buried bumper syndrome 5%	nr
Chang et al. 2016 [40]	≥ 10% of patients:[c] Sensorimotor peripheral neuropathy secondary to B12 or B6 deficiency 47%; local tube problems 40%; impulse control disorder or dopamine dysregulation syndrome 27%; stoma infection 13%	nr
Valldeoriola et al. 2016 [44]	≥ 10% of patients:[c] Tube related events 37.3%; local inflammation 23.7%; transient infection 18.1%; pump failure 17.5%; dyskinesia worsening 14.1%; weight loss/anorexia 11.9%; granuloma 11.3%; psychiatric disorder 11.3%	SAEs in ≥ 3% of patients:[c] Local inflammation 5.1%; tube related events 4.5%; peptic ulcer 3.4%; psychiatric disorders 3.4%; peritonitis 3.4% AEs leading to discontinuation: Related to PEG tube 5.1%
Calandrella et al. 2015 [29]	≥ 5% of patients:[c] Surgery-related: Cardia bleeding 5.7%; PEG breakage 5.7% Device-related: Stoma infection 14.3%; intestinal tube kinking 8.6%; intestinal tube dislocation 8.6% Infusion-related: Peripheral neuropathy 11.4%; worsening of dyskinesias 8.6%	AEs leading to discontinuation in ≥ 2% of patients: Stoma infection 11.4%; worsening of dyskinesias 8.6%; duodenal perforation 2.9%; peritonitis 2.9%; duodenal phytobezoar 2.9%

Table 6 continued

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Slevin et al. 2015 [41][c]	≥ 20% of patients:[c] Pump 55%; J tube 50%; stoma site 44%; PEG 36%; incision site erythema 29%; fall 21%; decreased vitamin B6 21%	SAEs in ≥ 3% of patients:[c] Complication of device insertion 5%; abdominal pain 3%; asthenia 3%; pneumonia 3% AEs leading to discontinuation: Bipolar disorder 1.6%; renal mass 1.6%; intestinal perforation 1.6%
Fernandez et al. 2015 [20]	≥ 20% of patients:[b] Complication of device insertion 34.9%; abdominal pain 31.2%; procedural pain 20.7%	SAEs in ≥ 2% of patients:[b] Complication of device insertion 6.5%; abdominal pain 3.1%; peritonitis 2.8%; polyneuropathy 2.8%; Parkinson's disease 2.5%; pneumoperitoneum 2.5% AEs leading to discontinuation in ≥ 1% of patients: Complication of device insertion 1.7%
Buongiorno et al. 2015 [45]	≥ 5% of patients:[c] Drug-related: Hallucination/confusion 18.1%; troublesome dyskinesia 18.1%; weight loss 6.9% Device-related: Intestinal tube kinking 18.1%; tube and connection issue 18.1%; bezoar 6.9% PEG-related: Pump breakage/malfunction 16.7%; pneumoperitoneum 12.5%; wound infection 6.9%	nr
Caceres-Redondo et al. 2014 [30]	≥ 10% of patients:[c] Drug-related: Peripheral neuropathy 13.8% Device-related: Intestinal tube dislocation 27.6% Gastrostomy-related: Peristomal infection 34.5%; granuloma 17.2%	nr

Table 6 continued

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Zibetti et al. 2014 [31]	≥ 5% of patients:[c] Related to LCIG: Weight loss 16.9%; polyneuropathy 6.8% Infusion device related: Tube dislocation 49.2%; occlusion or kinking 27.1%; PEG retention failure 10.2% PEG damage 6.8% Gastrostomy-related: Peristomal infections 23.7%	AEs leading to discontinuation in ≥ 1% of patients: Device problems 12%
Sensi et al. 2014 [32]	≥ 5% of patients:[c] Related to levodopa: Polyneuropathy 32.1%; weight loss 10.7%; hallucinations 10.7%; agitation 10.7%; mood disturbance 7.1% Related to procedure: Peritonitis 7.1% Related to device: Pump failure 17.9%; dislocation/replacement of jejunal tube 14.3%; granulation at PEG puncture 14.3%; tube occlusion 7.1%	nr
Lundqvist et al. 2014 [46]	≥ 10% of patients:[c] Technical/surgery related: Tube dislocations/leakage 60%; local pain around stoma/local chemical peritonitis not requiring treatment 30%; tube occlusions 20%; stoma infections/secretion from stoma 20% Medication related: Hallucinations 40%; minor depression 30%; diarrhoea 10%; leg cramps 10%; increased dyskinesia 10%	SAEs:[b] Paranoid psychotic reaction; atrial flutter; knotted intestinal tube
Antonini et al. 2013 [33]	≥ 5% of patients:[c] Device-related: Tube dislocation 22.4%; tube occlusion 15.3%; PEG problems, repositioning, replacement 9.2%; granulation at PEG puncture 6.1%; buried bumper syndrome 5.1%	AEs leading to discontinuation in ≥ 1% of patients: PEG problems 2.0%; stoma infection 2.0%; polyneuropathy 2.0%

Table 6 continued

Study	Most frequent AEs[a]	SAEs and AEs leading to discontinuation
Zibetti et al. 2013 [34]	≥ 2 events:[d] Device-related: Dislocation of intestinal tube 34; intestinal tube kinking or obstruction 24; PEG internal retention failure 12; PEG pulled out accidently 6 Gastrostomy-related: Peristomal infection 12; intestinal volvulus 2	nr
Foltynie et al. 2013 [42]	nr	AEs leading to discontinuation: PEG problems 18.2%
Fasano et al. 2012 [47]	≥ 5% of patients:[c] Device- or drug-related: Inner tube dislocation 14.3%; transient confusion 14.3%; axonal neuropathy 7.1%; occlusion 7.1%; severe constipation 7.1%; PEG infection 7.1%; weight loss 7.1%	
Merola et al. 2011 [35]	≥ 10% of patients:[c] Accidental removal of PEG tube 55%; infection 15%; weight loss 15%; dislocation of intestinal tube 10%	nr
Antonini et al. 2010 [36]	Device-related:[c] Tube occlusion 21.1%; tube dislocation 10.5%	nr
Antonini et al. 2008 [37][d]	nr	AEs leading to discontinuation: Dislocation of tube 4.5%; psychosis 4.5%; severe polyneuropathy 4.5%
Eggert et al. 2008 [43]	≥ 10% of patients:[c] Occlusion of the tube 46.2%; disconnection of the tube 30.8%; dislocation of the tube from jejunum to stomach 23.1%; infection of the stoma 23.1%; backache due to the pump weight 15.4%	AEs leading to discontinuation: PEG or infusion device problems 23.1%; difficulties handling the pump 7.7%

AE adverse event. *SAE* serious adverse event. *LCIG* levodopa/carbidopa intestinal gel. *NR* not reported. *PEG* percutaneous endoscopic gastrostomy

[a] Threshold for 'most frequent' varied between studies

[b] Relatedness to LCIG not stated

[c] Possible/probable relationship to LCIG or device

[d] Number of events in 25 patients, possible/probable relationship to LCIG or device

DISCUSSION

To our knowledge, this is the largest qualitative synthesis of published studies evaluating the long-term efficacy of LCIG on 'off'-time in advanced PD. Most studies showed significant reduction in 'off'-time by end of follow-up (38–84%), with the longest follow-up being 120 months. As PD progresses, people with PD spend a greater proportion of the waking day in the 'off' state, which limits mobility and impacts on QoL. The reduction in 'off'-time is, therefore, a key aim of PD management. Key clinical trials of LCIG have demonstrated significant reductions of 'off'-time for 12 weeks after treatment initiation [21]. However, since PD is a progressive disease, it is important to assess the long-term impact of LCIG on 'off'-time, and often such evidence stems from studies that are not RCTs.

The results of this literature review suggest that LCIG extends the benefit of levodopa (in terms of reduced 'off'-time) for at least 2–5 years. This supports the suggestion that the long-term efficacy of LCIG is similar to efficacy at 3 months that was demonstrated in a pivotal RCT [21]. Treatment patterns were not reported consistently in the selected studies; therefore, it is not possible to determine the impact of treatment changes on the sustained effects of LCIG on 'off'-time. The flexibility of dosing provided by LCIG (the ability to adjust the flow rate of the pump and give one-off bolus doses, as well as the possibility to use it as monotherapy or in combination with other anti-PD medications) aids long-term optimisation of outcomes. Data from phase 3 trials suggest that dose optimisation is achieved within 7 days of initiating LCIG and doses remain relatively stable for > 12 months [52]. However, treatment patterns in routine practice are likely to vary between countries and centres. Several publications have provided detailed guidance on patient selection, dose conversion factors, and dose titration and adjustment [53–55], and with this guidance and experience, longer-term LCIG dose adjustment is relatively straightforward [56, 57]. The individualisation of LCIG treatment regimens over time may be an important factor for maintaining the long-term reductions in 'off'-time presented in this review.

The studies reviewed here show that after 1 year or more, the reductions of 'off'-time that occur after starting LCIG therapy remain, i.e., the proportion of the waking day spent in 'off' is reduced compared with baseline by > 2 h, and in many cases > 4 h. These improvements were accompanied by more time spent in the 'on' state, and in most studies there was also a reduction in the duration of dyskinesia. Such changes in 'on/off'-time are likely to have an impact on the patients' ADL and QoL (and that of the care partner). In some of the studies, UPDRS II total scores (ADL) and HRQoL scales did show improvement (that potentially correlates with reduction in 'off'-time), but assessing these endpoints was not the primary goal of this review.

The most frequently used measure of 'off'-time in these studies was UPDRS IV item 39. While capturing 'off'-time at hospital visits with UPDRS items is convenient, especially in the clinical trial setting, this method suffers from recall bias. Most of the remaining studies in this review assessed 'off'-time using patient diaries ($n = 9$), which requires good education of patients and care partners, and compliance with frequent diary entries may be a limitation to their accuracy. Thus, the methodologies used in different studies may have influenced the extent of 'off'-time reduction reported. However, several factors may have influenced the magnitude of 'off'-time reduction across studies, such as the baseline 'off'-time.

Since long-term 'off'-time was the primary outcome measure used to select studies for this review, information on other motor symptoms, NMS and HRQoL was reported less consistently. Motor complications (dyskinesia) and ADL were mostly unchanged or improved in these studies, while some aspect of NMS and HRQoL improved in many studies. It should be stressed that since these endpoints were not part of the PICOS selection criteria, the findings presented here do not represent a comprehensive picture of the effects of LCIG treatment on these endpoints. Dedicated systematic reviews or meta-analyses would be needed to draw firm

conclusions on the long-term effect of LCIG on other motor symptoms, dyskinesia, NMS and HRQoL.

The AE profiles reported in these studies were consistent with the known safety profile of LCIG. The methodological variability in AE reporting makes it difficult to provide a quantitative overview of AE frequency. The most frequent AEs were generally device- and PEG procedure-related including wound/stoma infection, abdominal/procedural pain, erythema and tube dislocation. Generally, discontinuations due to device-related issues or infection occurred in < 5% of patients, and while serious AEs (SAEs) relating to the procedure are known to occur [58], these were of a low frequency in most studies included here. The reason for a higher incidence of device-related SAEs in some studies [29, 38] is not known, but in general an experienced multidisciplinary team is needed to reduce the risk of PEG-related complications. In the pivotal RCT of LCIG, common AEs occurred most frequently in the first 1–2 weeks after initiating LCIG therapy and subsequently declined to considerably lower frequencies [21]. While most studies included in this review reported overall AE frequency and did not specify the timing of AEs, it is likely that the most frequent AEs related to the procedure occurred mostly in the first week [59]. However, other AEs including device-related AEs may have occurred consistently throughout the follow-ups of these studies. Peripheral neuropathy has become recognised as an AE of levodopa-based therapies, and group B vitamin deficiency is thought to play a role [60–62]. In recent years, therefore, vitamin B supplementation has been used to manage and/or prevent this complication [63, 64], and it would be useful analyse the effect of increased awareness and improved management of neuropathy on its incidence in patients receiving LCIG. In this analysis, neuropathy was reported in studies from 2008 [37] to 2019 [51] (Table 6), but because AEs were not the primary outcome used for selection of articles in this review, we cannot draw firm conclusions. A recent review of levodopa-induced neuropathy did not assess the impact of the introduction of vitamin B supplementation on the incidence of neuropathy [65].

Studies were mostly retrospective and observational in nature. While this limits the strength of the evidence, long-term RCTs may be impractical with device-aided therapies for advanced PD. Future evaluations of the heterogeneity between studies are warranted to conduct a pooled analysis of long-term 'off'-time reduction with LCIG treatment in advanced PD patients. However, this qualitative review provides valuable confirmation that long-term 'off'-time reduction with LCIG treatment is relatively consistent in studies using different measures of 'off'-time, in different geographical locations, in the controlled trial setting versus routine practice settings and over the last 12 years.

In conclusion, this large qualitative synthesis of 27 published studies shows that continuous dopaminergic stimulation provided by LCIG reduces 'off'-time and improves other motor complications that were not well controlled on oral levodopa, and these improvements are sustained for > 12 months. People with advanced PD that is not well controlled by oral treatment may gain long-lasting improvements in many aspects of their lives with LCIG therapy via reduced 'off'-time.

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