REVIEW

The Advantages of Levodopa-Carbidopa Intestinal Gel for Patients with Advanced Parkinson's Disease: A Systematic Review

Xing-Ru Zhang[1,*]
Zhi-Yu Jiang[2,*]
Zeng-Rui Zhang[3]
Hui-Jun Chen[1]
Ke Wu[4]
Jin-Cai He[1]
Cheng-Long Xie[1]

[1]The Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, People's Republic of China; [2]The Department of General Surgery, The Sir Run Run Shaw Hospital, Medical College of Zhejiang University, Hangzhou 310000, People's Republic of China; [3]Department of Neurology, Huzhou Central Hospital, Huzhou 313000, People's Republic of China; [4]Zhejiang Provincial Key Laboratory of Aging and Neurological Disorder Research, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, People's Republic of China

*These authors contributed equally to this work

Background: Levodopa-carbidopa intestinal gel (LCIG) is a new type of administration that results in steadier levodopa plasma concentrations in advanced Parkinson's disease (PD) patients and effectively reduces poor mobility and dyskinesia.

Methods: Electronic databases were searched up to January 1, 2018. The inclusion criteria for this review were as follows: LCIG vs oral medication in advanced PD patients.

Results: Five trials, with a total of 198 patients, met all the inclusion criteria. The quality score of these studies ranged from 3 to 5. Two clinical trials showed that compared with oral medication, LCIG had a better treatment effect on on-time with troublesome dyskinesia (TSD) ($p = 0.02$) and on-time without TSD ($p < 0.00001$) in advanced PD patients. In addition, four of the 5 studies showed that the LCIG may have better efficacy than oral medication for improving the scores of the UPDRS, and two studies found that LCIG demonstrated better efficacy for improving the PDQ-39 scores. The video recording results indicated a potential decline in both dyskinesia and the "off" state in LCIG-treated patients. The incidence of adverse events was not significantly different between the LCIG and oral medication groups.

Conclusion: Compared with oral treatment, LCIG exerts its effectiveness, mostly by reducing the time of on-time with TSD, increasing the time of on-time without TSD and scores of UPDRS and PDQ-39. It is suggesting that LCIG was likely to be a new type of administration used in clinical applications. However, due to methodological flaws, these findings should be viewed with caution, and more RCTs are needed in the field to complement our findings.

Keywords: Levodopa-carbidopa intestinal gel, Parkinson's disease, oral medication, clinical trials, systematic review

Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative and disabling disorder characterized by effects on dopaminergic neurotransmission and movement disorders.[1] Using dopamine replacement agents can alleviate motor symptoms effectively, and the administration of levodopa is the standard therapy for the treatment of PD.[2] PD symptoms are often well controlled with oral levodopa at an early disease stage. With PD progression, a number of patients report disabling motor complications, including daily motor fluctuations and dyskinesia, and these complications are closely associated with chronic levodopa treatment.[3] Moreover, unstable levodopa plasma concentrations resulting from factors such as pulsatile

Correspondence: Cheng-Long Xie; Jin-Cai He
Tel/Fax +86 577 88 83 2693
Email cl_xie1987@sohu.com; hjc@wmu.edu.cn

delivery of oral levodopa, labile gastric emptying, and narrowing therapeutic windows, may contribute to these complications.[4]

Levodopa-carbidopa intestinal gel (LCIG) is a newly device-aided therapy that in Japan is named ABT-SLV187, and in the United States is referred to as carbidopa-levodopa enteral suspension (CLES).[5] With a portable pump that is connected to a PEG-J, a percutaneous endoscopic gastrostomy with a thinner inner J-tube, LCIG is continuously administered to the upper intestine.[6] According to pharmacokinetic studies, direct intestinal levodopa administration can effectively lead to steady state concentrations of levodopa in plasma. LCIG may also reduce poor mobility and dyskinesia.[7] However, adverse events associated with the pump or the tube are common.[8]

To date, a detailed comparison between the treatment of advanced PD patients with LCIG and oral medication has not been performed. Furthermore, it is unclear whether LCIG is a more suitable treatment for avoiding motor symptoms and dyskinesia in patients with advanced PD. Therefore, the objective of this review was to systematically evaluate the efficacy and advantages of LCIG, by comparing the two therapeutic methods (LCIG vs oral medication). Thus, we hope to describe the therapeutic potential of LCIG in advanced PD patients.

Methods
Search Strategy

A comprehensive literature search was performed to identify related publications evaluating LCIG vs oral medication in the treatment of patients with advanced Parkinson's disease from the following databases: PubMed, Google Scholar and the Cochrane Library, up to January 1, 2018. An experienced reviewer (ZYJ) independently filtered the titles, abstracts and references based on the eligibility criteria. The following search strategy was used for each database:

1. Levodopa-carbidopa intestinal gel
2. Levodopa-carbidopa intestinal infusion
3. LCIG
4. or/1–3
5. Oral treatment
6. Oral medication
7. or/5–6
8. Parkinson disease
9. Parkinson's disease
10. PD
11. or/8–10
12. 4 and 7 and 11

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) clinical trials comparing LCIG with oral medication to treat advanced PD; (2) participants (aged ≥30 years) with advanced PD who signed an informed consent form; (3) trials depicting advanced PD patients; (4) studies describing advanced PD patients with certain degrees of responses such as motor fluctuations, dyskinesia, painful dystonia, or bradykinesia despite optimal pharmacological treatment; and (5) studies that were published in English.

The exclusion criteria were as follows: (1) case reports, abstracts, reviews, editorials, letters comments or end game; (2) nonhuman subjects; and (3) no tests evaluating the efficacy of treatment of LCIG vs oral medication.

Outcome measurements The primary outcome was the UPDRS scores. The secondary outcomes were the results of the video recording, PDQ-39 scores, time of the on-time with troublesome dyskinesia (TSD) and the on-time without TSD.

Data Extraction and Quality Assessment

The detailed information from each trial was carefully extracted by two authors and was recorded as follows: (1) name of the first author, year of publication and follow-up time; (2) study design, study population and treatment types; (3) individual data obtained from each treatment group, including sample size, sex, mean age, race and duration of PD; and (3) treatment regimen, baseline indexes, outcome measures and adverse events. Based on our previous study, we used a six–item modified scale[9] to assess the risk of bias of the incorporated clinical trials. If the outcome data of the meta-analysis were only expressed graphically or missing, we attempted to contact the authors for further information. When no response was received, we used digital ruler software to measure the data from the graphs. We made an attempt to extract data of the mean value and standard deviation for each comparison from every study.

Statistical Analysis

All statistical analyses were performed with Cochrane's Review Manager version 5.3. We considered all the frequencies of adverse events as dichotomous data, and expressed the 95% confidence intervals (CIs). Moreover, we considered the outcomes of on-time with TSD and

on-time without TSD as continuous data. The weighted mean difference (WMD) was applied as a standard statistic to measure the absolute difference between the mean values in the two groups. The mean effect was shown as the WMD with its 95% CI.[10] We used a fixed effects model, and the statistical heterogeneity among studies was assessed using the Q statistic and the I^2 index. I^2 values <50% indicate an acceptable degree of heterogeneity among studies.[11] A probability value of P<0.05 was considered significant. Ethical approval was not required for this type of literature research.

Results
Results of the Search
Our initial search of three databases identified 1352 publications. After removing duplicates, a total of 1052 references remained. After screening the titles and abstracts, we removed 454 references for at least one of the following reasons: (1) case reports, abstracts, reviews, editorials, letters comments or end games; (2) basic experiment trials; and (3) other disease. Finally, after screening the full texts

of 153 remaining studies, which explored the efficacy of LCIG vs oral medication, 5 studies were identified for the final analysis[12–16] (Figure 1).

Study Characteristics
In this review, five clinical trials (2 crossover trials, 3 RCTs), with a total of 198 advanced PD patients who met the inclusion criteria, were included in the analysis. Of the patients in the crossover trials, 18 were randomized to begin with oral tablets, followed with crossing over to LCIG, and 18 were randomized to begin therapy in the opposite order. Of the patients in the RCTs, 93 were randomized to the LCIG group, and 69 were randomized to the oral medication group. The sample size included in this review ranged from 12 to 71. The follow-up duration ranged from 7 to 54 weeks. Moreover, in this review, the baseline indexes of H&Y (Hoehn & Yahr stage) were recorded in 2 trials, UPDRS (Unified Parkinson's Disease Rating Scale) in 4 trials, PDQ-39 (39-item Parkinson's Disease Questionnaire) in 2 trials, "off" time in 2 trials, on-time with troublesome dyskinesia (TSD) in 2 trials, and on-time without TSD in 2 trials. Regarding outcome measures, UPDRS was recorded in 4 trials; video recording was shown
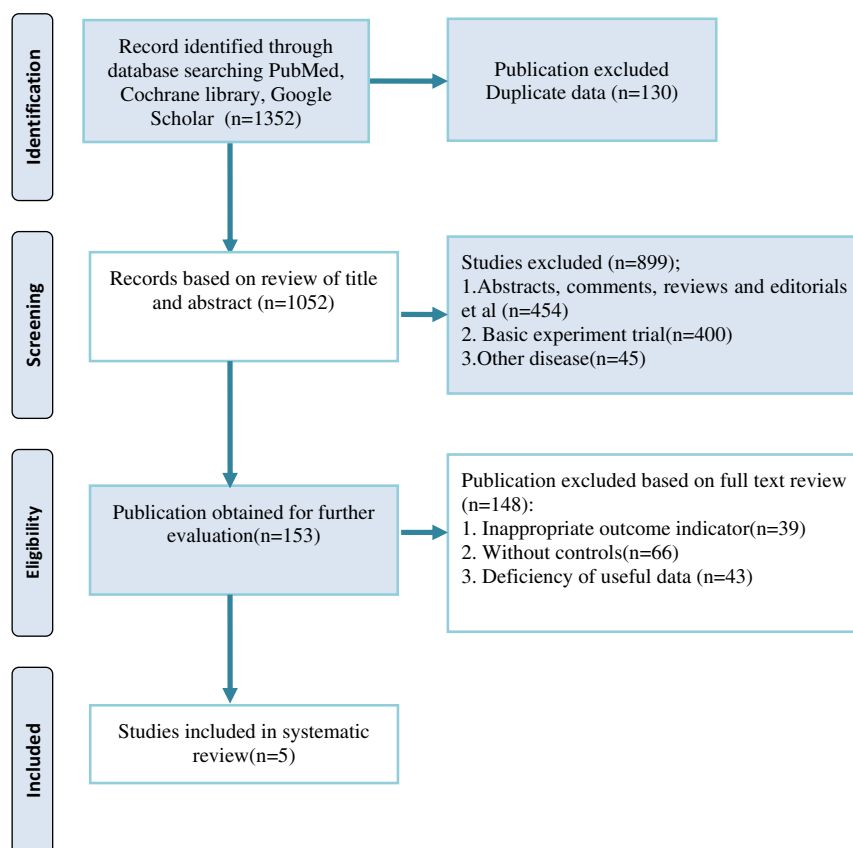

Figure 1 Algorithm of study selection and inclusion in the review.

in 2 trials, PDQ-39 was observed in 2 trials, on-time with TSD and on-time without TSD were reported in 2 trials. The basic characteristics collected from five studies are shown in Tables 1 and 2.

Effectiveness

Outcome Measures of UPDRS

The UPDRS is currently the gold standard for the assessment of disease state in Parkinson's disease, and it includes a comprehensive assessment of motor symptoms and reliable clinimetric properties.[17] In Nyholm et al, the total score of the UPDRS sections I, II and IV was 34.9±7.6 at baseline. At the end of the trial, there was no significant change in the score between the treatment groups, but in section IV, LCIG-treated patients had fewer complications.[12] In Nyholm et al, the baseline score of the UPDRS sections I, II, III and IV are shown in Table 2. At the end of the trial, the LCIG-treated patients reported lower median total scores of the UPDRS than the oral medication group ($p<0.05$), especially in all sections of the UPDRS in the LCIG group.[13] In Olanow et al,

the UPDRS sections I, II and III scores at the beginning of the trial are shown in Table 2. After the short-term endpoint of the study, LCIG-treated patients showed significant improvement in the UPDRS section II score and quality of life measures compared with the oral medication group. However, no significant difference was found between the treatment groups ($p=0.502$) in the UPDRS section III.[14] In Antonini et al, the score of the UPDRS section IV dyskinesia questions (#32-34) at baseline is reported in Table 2. Finally, there was no significant difference between the treatment groups in the UPDRS section IV dyskinesia questions (#32-34) ($p>0.05$). However, the oral-treated patients showed significant worsening, while LCIG-treated patients showed no change from baseline to the end of the study.[16]

Outcome Measures of Video Recording

The video recording comprised four different examinations, such as rising from a chair, walking, alternating hand movements, and "piano playing".[12] In Nyholm et al, the video recording showed a significant decline in

Table 1 Basic Characteristics of the Included Studies

Author (Years)	Design	Time	Study Population	Treatment	No. of Patient	Sex (M/F)	Mean Age (Years)	PD Duration	Race
Nyholm 2003[12]	Randomized crossover trial	7 weeks	Idiopathic PD and Diurnal motor fluctuations	Oral SRT/ Intestinal gel Intestinal gel/Oral SRT	6 6	6/0 4/2	59.8±10.9 62.5±12.0	12.2±4.8 20.5±8.4	– –
Nyholm 2005[13]	Randomized crossover trial	28 weeks	Motor fluctuations and dyskinesia	Conventional/ Intestinal gel Intestinal gel/ Conventional	12 12	9/3 9/3	68(51–79)* 64(50–75)*	– –	– –
Olanow 2014[14]	Randomized, double-blind, double-dummy, double-titration trial	12 weeks	Advanced PD with motor complications	Intestinal gel Immediate-release oral	37 34	24/13 22/12	63.7±9.5 65.1±6.8	10.0±4.6 11.8±5.6	W:35 W:31
Othman 2014[15]	Double-blind, double-dummy study	12 weeks	Advanced PD	Intestinal gel Oral treatment	45 23	28/17 14/9	64.3±9.6 64.7±6.9	–	W:44 O:1 A:-; W:21 O:- A:2
Antonini 2016[16]	Randomized, double-blind study	54 weeks	Advanced PD	Intestinal gel Oral treatment	11 12	7/4 6/6	66.0±10.2 65.8±6.6	11.6±5.5 13.4±6.4	W:10 O:1 A:- W:11 O:- A:1

Note: *Median (Range).
Abbreviations: M, male; F, female; SRT, sustained-release tablets; Conventional, conventional oral and subcutaneous pharmacotherapy; Intestinal gel, intraduodenal levodopa/carbidopa gel infusion; PD, Parkinson's disease; W, White; O, other; A, Asian.

Table 2 Main Outcome Measures of Included Studies Baseline Indexs Outcome Measures

Author (Years)	Treatment Regimen	Baseline Indexes	Outcome Measures
Nyholm 2003[12]	(1) Sinemet CR tablets (carbidopa/levodopa 50/200mg) or to start nasoduodenal infusion of levodopa (46–116mg/h, 6AM to 10PM) during week 1 to 3; (2) After week 3, patients were crossed over to infusion and Sinemet CR tablets for the next 3 weeks;	(1) H&Y: 4±0.6; (2) UPDRS I+II+IV: 34.9±7.6; (3) UPDRS q32, proportion dyskinesias,%: -; (4) UPDRS q39, Proportion OFF,%: -;	(1) Average intraindividual CV for the plasma concentrations of levodopa afrer oral medication was 34% and decreased significantly (CV, 14%)during continuous infusion; (2) Video evaluations showed a significantly increased number of observations in the near-normal state during infusion and a significant decrease in both the OFF state and dyskinesia;MT showed no significant difference between treatments in the two groups; (3)The total score of UPDRS I+II+IV did not change much during this short-term study;
Nyholm 2005[13]	(1) G1: conventional oral, crossing over to daytime continuous intraduodenal levodopa/carbidopa gel infusion; (2) G2: with the treatments in opposite order;	(1) UPDRS I: G1: 3.5(0–7)*; G2: 3.0(0–9)*; (2) UPDRS II: G1: 16.0(11–27)*; G2: 17.5(9–26)*; (3) UPDRS III: G1: 36.5(14–53)*; G2: 25.5(12–61)*; (4) UPDRS IV: G1: 9.5(3–12)*; G2: 10.0(6–12)*; (5) UPDRS Sum: G1: 66.5(37–82)*; G2: 59.0(36–92)*; (6) H&Y: Best: G1: 3(2–4)*; G2: 2(2–4)*; Worst: G1: 4(3–5)*; G2: 4(2–5)*;	(1) Video scoring: moderate to severe "off" state (−2 to −3) was markedly reduced in all patients during treatment with infusion; moderate to severe dyskinesia (+2 to +3) was uncommon in both treatment arms; (2) Median total UPDRS score at the end of each treatment arm was 53 with Conventional and 35 with Infusion; Infusion provided lower median scores in all parts of the UPDRS; Parts I, II, and IV shows a significant improvement, whereas improvement in prats III was not significant; (3) Median PDQ-39 summary index was 35 (range 16 to 55) with Conventional and 25(range 10 to 42) with Infusion; (4) Median total score of the generic QoL instrument 15D was increased from 0.72 (range 0.58 to 0.88) to 0.78 (range 0.64 to 0.95) with Infusion, meaning higher QoL with Infusion; Among the DQs, dyskinesia was reported to be unchanged;
Olanow 2014[14]	(1) G1: over-encapsulated immediate-release oral levodopa-carbidopa(25 mg carbidopa, 100mg levodopa) plus placebo intestinal gel infusion; (2) G2: levodopa-carbidopa intestinal gel infusion (20mg/mL levodopa, 5mg/mL carbidopa)plus over-encapsulated oral placebo;	(1) UPDRS I: G1: 1.8±1.8; G2: 1.8±1.7; (2) UPDRS II: G1: 11.8±7.0; G2: 11.6±6.9; (3) UPDRS III: G1: 22.5±11.7; G2: 18.1±9.9; (4) UPDRS Sum: G1: 35.8±18.9; G2: 31.5±15.6; (5) PDQ-39: G1: 38.6±17.9; G2: 35.1±18.0; (6) Off-time: G1:7.0±2.1; G2:6.3±1.7; (7) On-time without dyskinesia: G1:5.6±3.2; G2: 6.3±2.7; (8) On-time with non-troublesome dyskinesia: G1: 2.2±2.2; G2: 2.4±1.8; (9) On-time without troublesome dyskinesia: G1: 7.8±2.5; G2: 8.7±2.0; (10) On-time with troublesome dyskinesia: G1: 1.2±1.7; G2: 1.0±1.6;	(1) Efficacy analyses done in hierarchical order showed significant improvements in the levodopa-carbidopa intestinal-gel group for off-time, on-time without troublesome dyskinesia, PDQ-39 summary index, CGI–I score, and UPDRS part II score; (2) For the primary outcome analysis, treatment with levodopa-carbidopa intestinal gel provided a greater reduction (improvement) in off-time between baseline and final visit than did immediate-release oral levodopa-carbidopa; (3) Intestinal gel treatment was also associated with a significantly greater improvement than immediate-release oral treatment in on-time without troublesome dyskinesia, and in on-time without dyskinesia; (4) Benefits of levodopa-carbidopa intestinal gel compared with standard immediate-release oral levodopa-carbidopa were shown by significant improvement in the activities of daily living subscale of the UPDRS (part II) and measures of quality of life; (5) No significant difference between treatment groups was detected for UPDRS part III (motor subscale);

(Continued)

Table 2 (Continued).

Author (Years)	Treatment Regimen	Baseline Indexes	Outcome Measures
Othman 2014[15]	(1) LCIG infusion (1117±474 mg/d) plus placebo capsules; (2) Over-encapsulated immediate release levodopa/carbidopa 100/25mg (LC-oral) (1351±618 mg/d) plus placebo gel infusion;	(1) Weight: G1: 64.3±9.6; G2: 64.7 ±6.9; (2) BMI: G1: 24±4.58; G2: 26.1±7.14;	(1) The final model was a two compartment model with a transit compartment for absorption, first order elimination, bioavailability for LCIG (97%; confidence interval = 95% to 98%) relative to LC-oral, different first order transit absorption rate constants (LCIG = $9.2h^{-1}$vs. LC-oral = $2.4h^{-1}$;corresponding mean absorption time of 7 min for LCIG vs 25min for LC-oral); (2) Different residual (intra-subject) variability for LCIG (15% proportional error, $0.3\mu g\ mL^{-1}$ additive error) vs LC-oral (29% proportional error, $0.59\mu g\ mL^{-1}$ additive error); Estimated oral clearance and steady-state volume of distribution for levodopa were $24.8\ l\ h^{-1}$ and 131 l, respectively;
Antonini 2016[16]	(1) LCIG cohort received placebo tablets identical in size and color to LC-IR; (2) LC-IR cohort received placebo gel;	(1) MMSE: G1: 28.5±1.3; G2: 29.2±0.9; (2) On-time with troublesome dyskinesia: G1: 3.1±1.6; G2: 3.0±1.7; (3) On-time without troublesome dyskinesia: G1: 7.4±2.1; G2: 6.7±2.5; (4) Off-time: G1: 5.5±1.3; G2: 6.4±1.7; (5) UPDRS Part IV dyskinesia questions (#32-34): G1: 3.5±1.6; G2: 3.1±1.6; (6) PDQ-39: G1: 39.4±19.9; G2: 45.2 ±13.4; (7) CGI-S: G1: 4.5±0.5; G2: 5.1±0.7;	(1) Off-time was significantly reduced for these patients in each treatment group when compared with baseline, and there was no significant difference between treatment groups; LCIG-treated patients had a significant mean decrease from baseline to final visit in hours of "on" time with troublesome dyskinesia; (2) LCIG-treated patients showed a trend of improvement in on-time without troublesome dyskinesia and on time with troublesome dyskinesia from baseline; however, these improvements were not significant when compared with LC-IR-treated patients; LCIG-treated patients showed no change on the UPDRS Part IV dyskinesia questions (nos. 32–34), whereas LC-IR patients showed a significant worsening, though there was no significant difference between treatment groups;

Note: *Median (Range).
Abbreviations: G1, group 1; G2, group 2; Sinemet CR, controlled-release carbidopa/levodopa 50/200 mg; LC-IR, Immediate release oral levodopa-carbidopa; LCIG, Levodopa-carbidopa intestinal gel; BMI, body mass index; CV, Coefficient of variation; H&Y, Hoehn & Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale; QoL, Quality of Life; PDQ-39, 39-item Parkinson's Disease Questionnaire; DQs, Daily questions; CGI-I, Clinical Global Impression-Improvement; MMSE, Mini-mental state Examination; CGI-S, Clininal Global Impression-Severity.

both dyskinesia and the off-state during infusion. The mean-variance scores were 2.0 for oral treatment and 1.1 for LCIG.[12] In Nyholm et al, the video evaluations showed a marked reduction in moderate to severe "off" state in LCIG-treated patients. The "no" or "mild symptoms" categories of the five UPDRS items were all significantly increased in both treatment arms. Regarding the video evaluation of dyskinesia, there were no significant differences between the treatment groups.[13]

Outcome Measures of PDQ-39
PDQ-39 is a questionnaire that reflects the quality of life of PD patients and has been proven to have test-retest reliability and satisfactory internal validity.[18] In Nyholm et al, the summary index of the median PDQ-39 was 25 (range 10 to 42) with

infusion and 35 (range 16 to 55) with oral medication, which is consistent with a higher of quality of life with infusion ($p<0.01$).[13] In Olanow et al, compared to the baseline, the summary index of PDQ-39 was −10.9±3.3 with infusion and −3.9±3.2 with oral medication ($p=0.0155$).[14]

Outcome Measures of on-Time with TSD
For the 5 studies evaluating the time of on-time with TSD, 1 study provided clear data,[14] and 1 study provided graphical data.[16] In Olanow et al, the time of on-time with TSD was 1.0±1.6 h per day in LCIG-treated patients and 1.2±1.7 h per day in the oral medication group at baseline. After the short-term study, the time of on-time with TSD was −0.11 ±0.52 h per day with infusion and −0.03±0.52 h per day with oral ($p=0.8574$).[14] In Antonini et al, compared to the

baseline, the hours of on-time with TSD had a significant mean decrease in the LCIG-treated patients ($p<0.05$).[16] A meta-analysis of 2 studies revealed that the LCIG group showed a significantly decreased time of on-time with TSD (n = 94, WMD = −0.30, 95% CI: −0.54 to −0.06, p = 0.02; heterogeneity: Chi^2 = 1.07, p = 0.30, I^2 = 6%, Figure 2A).

Outcome Measures of on-Time Without TSD

Of the 5 studies evaluating the time of on-time without TSD, 1 study provided clear data,[14] and 1 study provided graphical data.[16] In Olanow et al, the time of on-time without TSD was 8.7±2.0 h per day in LCIG-treated patients and 7.8±2.5 h per day in the oral medication group at baseline. After week 12, the time of on-time without TSD was 4.11±0.75 h per day with infusion and 2.24±0.76 h per day with oral medication (p=0.0059).[14] In Antonini et al, a significant improvement was shown in both groups. Beginning as early as week 2, the hours of on-time without TSD improved from baseline to every time point in the LCIG-treated patients, but when compared with the oral-treated patients, these improvements were not significant (p=0.491).[16] A meta-analysis of 2 studies showed that the LCIG group significantly improved the time of on-time without TSD compared with the oral-treated group (n = 94, WMD = 2.77, 95% CI: 2.42 to 3.12, $p<$ 0.00001; heterogeneity: Chi^2 = 0.00, p = 0.96, I^2 = 0%, Figure 2B).

Risk of Bias

Table 3 shows the risk of bias of the included trials. The total score of the six–item modified scale is 6 points. The risk of bias of the included trials ranged from 3 to 5 points.

Table 3 Risk of Bias of Included Studies

Study	Nyholm 2003[12]	Nyholm 2005[13]	Olanow 2014[14]	Othman 2014[15]	Antonini 2016[16]
A	🟠	🟠	🟠	🟠	🟠
B	🟠	🟠	🟠	🟠	🟠
C			🟠	🟠	🟠
D					
E	🔵	🔵	🔵	🔵	🔵
F				🔵	🔵
Total	3	3	5	5	5

Notes: A: Peer reviewed publication; B: Random allocation to group; C: Blinded assessment of outcome; D: A sample size calculation; E: Compliance with animal welfare regulations; F: A statement of a potential conflict of interest.

Two trials received 3 points (40%), and three trials received 5 points (60%).

Adverse Events

In the three trials, the incidence of adverse events (AEs) was not significantly different between the LCIG and oral medication groups. There were a variety of AEs that involved the digestive, nervous, and psychiatric systems. Among these, the most common AEs included abdominal pain (33.3% in the levodopa-carbidopa intestinal gel group vs 20.9% in the oral medication group, p = 0.07), procedural pain (22.2% vs 26.9%, p = 0.60), constipation (15.3% vs 22.4%, p = 0.37), nausea (22.2% vs 11.9%, p = 0.23), dyskinesia/hyperkinesia (15.3% vs 19.4%, p = 0.49), wound infection (8.3 vs 17.9, p = 0.11), insomnia (9.7% vs 16.4%, p = 0.44), depression (12.5% vs 10.4%,
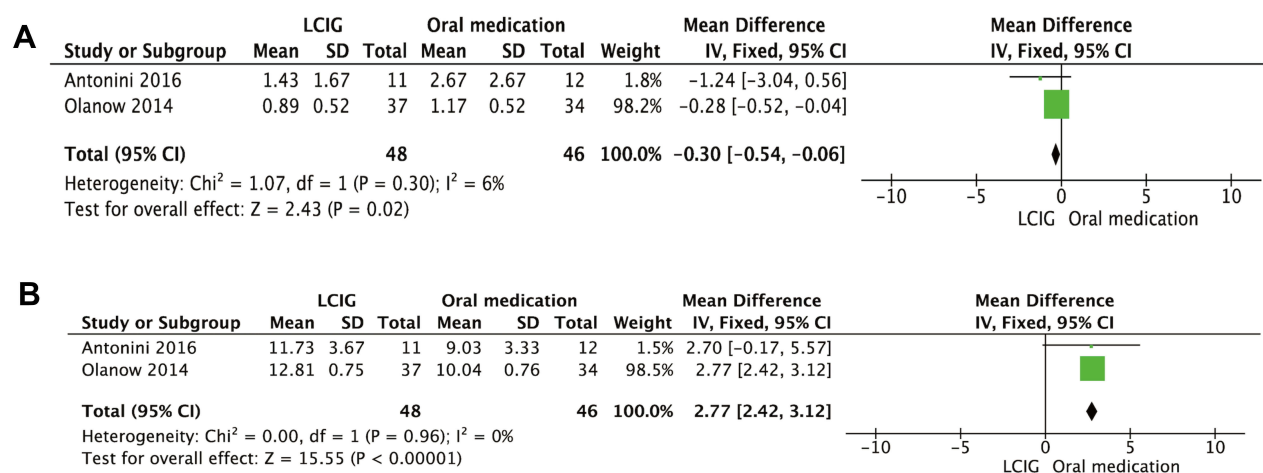

Figure 2 (**A**) The forest plot: effects of LCIG for decreasing the on-time with TSD compared with oral medication group. (**B**) The forest plot: effects of LCIG for increasing the on-time without TSD compared with oral medication group.

Table 4 Summary of Most Common Adverse Events

Adverse Events	Total N=139	Oral Treatment N=67	Intestinal Gel N=72	p-value	95% CI
Most Common AEs, n(%)					
Abdominal pain	38(27.3)	14(20.9)	24(33.3)	0.07	1.63(0.97, 2.74)
Procedural pain	34(24.5)	18(26.9)	16(22.2)	0.60	0.87(0.51, 1.47)
Constipation	26(18.7)	15(22.4)	11(15.3)	0.37	0.70(0.32, 1.54)
Nausea	24(17.3)	8(11.9)	16(22.2)	0.23	2.06(0.64, 6.64)
Dyskinesia/hyperkinesia	24(17.3)	13(19.4)	11(15.3)	0.49	0.77(0.37, 1.61)
Wound infection	18(12.9)	12(17.9)	6(8.3)	0.11	0.49(0.20, 1.19)
Insomnia	18(12.9)	11(16.4)	7(9.7)	0.44	0.67(0.25, 1.82)
Depression	16(11.5)	7(10.4)	9(12.5)	0.75	1.23(0.35, 4.34)
Orthostatic hypotension	13(9.4)	8(11.9)	5(6.9)	0.28	0.57(0.21, 1.59)
Incision site erythema	13(9.4)	5(7.5)	8(11.1)	0.44	1.51(0.53, 4.30)
Falling	13(9.4)	7(10.4)	6(8.3)	0.83	0.86(0.21, 3.48)
Flatulence	10(7.2)	4(6.0)	6(8.3)	0.59	1.38(0.43, 4.47)
Anxiety	9(6.5)	4(6.0)	5(6.9)	0.82	1.15(0.33, 4.00)
Somnolence	7(5.0)	4(6.0)	3(4.2)	0.55	0.66(0.17, 2.60)
Post-procedure discharge	7(5.0)	3(4.5)	4(5.6)	0.78	1.23(0.30, 5.08)
Headache	6(4.3)	2(3.0)	4(5.6)	0.49	1.75(0.36, 8.61)
Pneumoperitoneum	5(3.6)	1(1.5)	4(5.6)	0.23	3.68(0.43, 31.28)
Agitation	4(2.9)	2(3.0)	2(2.8)	0.89	0.88(0.13, 5.68)
Dystonia	3(2.2)	3(4.5)	-	0.16	0.13(0.01, 2.30)
Diarrhea	3(2.2)	1(1.5)	2(2.8)	0.64	1.75(0.17, 17.95)
Palpitation	3(2.2)	3(4.5)	-	0.16	0.13(0.01, 2.30)
Urinary tract infection	1(0.7)	1(1.5)	-	0.52	0.36(0.02, 8.04)

Abbreviation: AE, adverse event.

$p = 0.75$). No deaths were reported in either treatment groups in any of the trials. The more details are shown in Table 4.

Discussion
Summary of the Main Result
Five clinical trials, with a total of 198 advanced PD patients, were included in the analysis. The quality score of these studies ranged from 3 to 5. First, our results showed that LCIG had a greater treatment effect on on-time with TSD ($p = 0.02$) and on-time without TSD ($p < 0.00001$) than oral medication did. In addition, compared with oral medication, four of the 5 studies showed that the LCIG may have a better effect on improving the scores of the UPDRS, and two studies suggested that LCIG improved PDQ-39 scores. The results of video recording indicated a potential decline in both dyskinesia and the "off" state in LCIG-treated patients. Second, three trials analyzed the incidence of AEs, and no deaths were found. There was no significant difference between the LCIG and oral medication groups; the most common AEs included abdominal pain, procedural pain, constipation and nausea.

Interpretation of the Results
Dyskinesia is usually referred to as levodopa-induced dyskinesia (LID) and often occurs as a motor complication in patients with advanced PD. Chronic levodopa treatment is a major contributor to the development of dyskinesia, especially in a dose-dependent fashion. However, chronic levodopa treatment is insufficient to generate dyskinesia.[16] Several conditions such as presynaptic nigrostriatal degeneration, correspondingly preserved postsynaptic nigrostriatal system and a short half-life (pulsatile delivery) are required to generate dyskinesia. In most atypical parkinsonism, levodopa hardly induces LID, such as a postsynaptic system disease and progressive supranuclear palsy.[19] When levodopa is administered orally, there is a dose-dependent increase in peak-dose dyskinesia,[20] except when it is delivered continuously, such as when LCIG is administered. Furthermore, LCIG, which involves a higher dose than that used orally, still typically reduces pre-existent LID. Indeed, this result may be due to the ability of LCIG to effectively maintain steady state levodopa plasma concentrations.[7] Our review consistently found that LCIG demonstrated a better treatment effect compared with oral

administration on the time of the on-time with TSD and on-time without TSD in advanced PD patients. Nevertheless, the sample size of these trials was limited, and the trials had different designs. Therefore, we were not able to perform a systematic analysis to confirm whether LCIG treatment had a greater therapeutic effect on the scores of the UPDRS and PDQ-39 when compared with oral treatment. Thus, the results of this review require additional multicenter RCTs to evaluate the whole potential of LCIG in the treatment of advanced PD patients.

In our review, four studies used UPDRS to evaluate the disease state of PD patients. UPDRS has been in development since 1987 and is widely used in the assessment of PD patients.[17] The advantages of UPDRS include its almost comprehensive coverage of PD motor symptoms and its effectiveness and reliability. However, it also has some shortcomings, including some ambiguity in the text content, insufficient indication of the scorer, some defects in the metrics, and problems in the screening of some important non-motor symptoms in PD patients.[21] In 2001, the Movement Disorder Society (MDS) revised UPDRS and produced a new version, called MDS-sponsored UPDRS revision (MDS-UPDRS).[22] Compared to the original UPDRS 55 options, MDS-UPDRS has 65 rating options. The evaluation of MDS-UPDRS is more comprehensive than UPDRS, especially the evaluation of several important non-motor symptoms of PD. According to the original UPDRS, there are still 5 grades for each question: (0) normal, (1) slight, (2) mild, (3) moderate, (4) severe, but MDS-UPDRS is more focused on the degree of impairment and disabilities in slight and mild patients. Another important point is that MDS-UPDRS provides detailed guidance for evaluators, and MDS-UPDRS requires patients and caregivers to participate in the assessment of some non-motor and motor symptoms in daily life.[23] Therefore, in some future studies, we should try to use the MDS-UPDRS scale to make our results more reliable.

Limitation

Some limitations of this review are summarized as follows. First, reversely small sample size was included from five clinical trials. In addition, fragmentary data from a few trials may contribute to the unclear risk of bias. Second, 52 weeks was the longest duration of treatment in the five included trials. Therefore, a key challenge was that the benefits over time and the cost-effectiveness of LCIG cannot be evaluated at present.

The Implication for Further Studies

The findings from this review revealed a better treatment effect on the hours of on-time with TSD or on-time without TSD in LCIG-treated patients. However, because of the limited number of included trials, we are not certain whether LCIG treatment has a notable treatment effect on the UPDRS, PDQ-39 scores and the results from video recordings. Therefore, more multicenter RCTs in the future are indispensable, especially with longer follow-up times. AEs such as abdominal pain and procedural pain were more likely to occur with greater frequency with PEG-J tubes, because the PEG could move back and forth, gliding along the PEG tube. During the first days postprocedure when the stoma is maturing, the movement of the PEG may predispose the patients to develop peritonitis. Moreover, with the leaking gastric fluids, the skin around the peristomal area may become irritated.[6,8,24] Therefore, we should explore advanced technology to solve these issues. In summary, no deaths occurred in either treatment group. Finally, patients with dementia were excluded from some trials, because patients could participate only if the MMSE was 28 to 29.[24] Therefore, we require more rigorous RCTs to assess whether LCIG is suitable for patients with mild to severe dementia.

Conclusions

In general, compared with oral treatment, LCIG exerts its effectiveness, mostly by reducing the time of on-time with TSD, increasing the time of on-time without TSD and scores of UPDRS and PDQ-39. It is suggesting that LCIG was likely to be a new type of administration used in clinical applications. However, due to methodological flaws, these findings should be viewed with caution, and more RCTs are needed in the field to complement our findings.

Author Contributions

Z-RZ, Z-YJ, K-W, H-JC, X-RZ, J-CH and C-LX substantially contributed to conception and design, acquisition of data, or analysis and interpretation of data. All authors drafted the article or revised it critically for important intellectual content, approved final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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