Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Levodopa/carbidopa/entacapone versus levodopa/dopa-decarboxyiase inhibitor for the treatment of Parkinson's disease: systematic review, meta-analysis, and economic evaluation

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Aims: To review the evidence for efficacy, safety, and cost-effectiveness of levodopa/carbidopa/entacapone (LCE) compared with levodopa/dopa-decarboxyiase inhibitor (DDCI) for Parkinson's disease (PD).

Methods: PubMed, Embase, the Cochrane Library, and Chinese databases WangFang Data, Chinese Sci-tech Journals Database and China National Knowledge Infrastructure, as well as ClinicalTrials.gov, were searched for randomized controlled trials with "levodopa/carbidopa/entacapone" as keywords. The search period was from inception to August 2017. We conducted meta-analyses to synthesize the evidence quantitatively.

Results: A total of 5,693 records were obtained. We included seven randomized controlled trials and one cost-effectiveness study after the screening process. Compared with levodopa–DDCI, LCE improved patient Unified Parkinson's Disease Rating Scale (UPDRS) II score (mean difference [MD] −1.17, 95% CI −1.64 to −0.71), UPDRS III score (MD −1.55, 95% CI −2.29 to −0.81), and Schwab and England daily activity rating (MD 2.05, 95% CI 0.85–3.26). There was no statistically significant difference in the risk of serious adverse events (AEs) or discontinuation due to AEs in patients with LCE, and the risk of total AEs was higher in the LCE group (risk ratio [RR] 1.33, 95% CI 1.05–1.70). The incremental cost-effectiveness ratio of LCE was £3,105 per quality-adjusted life-year (QALY) gained in the UK.

Conclusion: LCE can improve PD patients' motor symptoms and daily living functioning when compared with levodopa/DDCI.

Keywords: Unified Parkinson's Disease Rating Scale, quality of life, wearing off, adverse events, cost-effectiveness, health technology assessment

Introduction

Parkinson's disease (PD) is considered one of the commonest neurodegenerative diseases. Regarding pathophysiology, the primary cause of PD is the degeneration of dopamine-producing neurons in the substantia nigra and the formation of Lewy bodies. PD is usually suspected in patients presenting with bradykinesia, rigidity, tremors, and/or postural instability.[1] Furthermore, the risk of PD increases nearly exponentially with age and peaks after 80 years of age.[2] Globally, the estimation of incidence of PD is 10–18 per 100,000 person-years,[2] which imposes a considerable disease burden on the patient, the family, and society as a whole, due to medication, hospitalization, and productivity loss.

There is currently no definitive cure for PD. Current pharmacological therapy is mainly designed to control the signs and symptoms associated with PD and includes

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dopamine replacement and dopamine agonists.[3,4] Levodopa is the most efficacious treatment of PD, developed in the late 1960s; however, approximately 70% of oral levodopa is metabolized by aromatic amino-acid decarboxylase in the intestinal mucosa and liver.[5] A dopa-decarboxylase inhibitor (DDCI), such as carbidopa or benserazide, is then administered with levodopa to increase drastically the half-life and concentration area under the curve of levodopa. Additionally, another peripheral route of levodopa metabolism is via catechol-*O*-methyltransferase (COMT). Finally, entacapone is a peripheral, reversible COMT inhibitor that increases the half-life of levodopa to make more levodopa sustainable.

A series of clinical trials on PD patients suggested that the addition of entacapone to levodopa/DDCI increased the "on" time (when patients experience benefit from levodopa) and meanwhile reduced the mean daily levodopa dose.[6,7] Moreover, the combination therapy was supposed to be potentially cost-effective compared with levodopa monotherapy.[8] The combination product of levodopa/carbidopa/entacapone (LCE) was approved by the US Food and Drug Administration in 2003 and introduced to the Chinese market in 2013.[5] However, no systematic review on its efficacy and safety has been conducted until now, and due to inconsistent evidence on its efficacy, safety, and economy across end points, it has not been covered by medical insurance in China.[9,10] The objective of this article is to review the evidence for efficacy, safety, and cost-effectiveness of LCE compared with levodopa/DDCI in the treatment of PD patients.

Methods

Search strategy

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and three Chinese databases – WanFang Data, Chinese Science and Technology Journal Database, and China National Knowledge Infrastructure – from inception to August 2017 for studies that compared LCE and levodopa/DDCI in the treatment of PD. The keywords used in the search were "Parkinson's disease" for the disease, and terms including "levodopa" "carbidopa" "entacapone" for the medication. We used the Boolean logic "AND" to combine the two sets of terms. We limited the language of articles to English and Chinese only. The systematic review with meta-analysis was registered on Prospero (CRD 42017077349). We also manually searched the reference list of the included studies and ClinicalTrials.gov as a supplementary source for the literature search. Manufacturers of LCE were consulted for unpublished manuscripts.

Study selection and outcome measures

Two independent investigators (ZMY and TTQ) manually screened the references of all retrieved records for potentially eligible studies, through title and abstract screening in the first stage and full-text screening in the second. In the title- and abstract-screening stage, studies appearing to meet the inclusion criteria, potentially relevant, or with insufficient information to make a clear judgment, judged by either investigator or both, were included the in full-text screening process. We obtained full texts of all these studies. We included studies if they had enrolled adults diagnosed with PD,[11] compared the efficacy and safety of LCE and levodopa/DDCI with more than ten patients included in each arm, compared the same dosage of levodopa/DDCI in two groups with treatment duration longer than 1 week, and had were randomized controlled trials (RCTs). We resolved disagreements through discussion, and if necessary a third party (NL or SDZ) was consulted.

The primary efficacy outcomes focused on changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores; among which the UPDRS I subscale measured mental function, the UPDRS II and UPDRS Schwab and England activities of daily living (ADL) subscale measured daily living function, the UPDRS III subscale measured motor function, and the UPDRS IV subscale measured treatment-related complications. The secondary efficacy outcomes included quality of life (QoL), frequency of wearing-off symptoms, safety, and cost-effectiveness. For PD, disease-specific QoL-measurement instruments included the 39-item Parkinson's Disease Questionnaire (PDQ) 39 and the PDQ8. Wearing-off symptoms may develop further into delayed dose failures or unpredictable fluctuations as the disease progresses.[12] Safety outcomes included the incidence of adverse events (AEs) and discontinuation due to AEs.

Data extraction and quality assessment

Data extraction was performed by two independent investigators (ZMY and TTQ) according to a predesigned data-collection form. Extracted information included authors, publication year, participant characteristics (participation-eligibility criteria, sex, and age), intervention information (dosage and duration), outcome of interest, and dropout rate.

The two investigators independently assessed the methodological quality of included studies. We assessed the risk of bias in the eligible RCTs with the Cochrane risk-of-bias assessment tool.[13] We evaluated the quality of eligible pharmacoeconomic studies with Consolidated Health Economic Evaluation Reporting Standards.[14] In cases of missing data,

we contacted study authors for clarification. All disagreements about data extraction and quality assessment were resolved through discussion among all authors.

Statistical analysis

We compared treatment effects through meta-analysis in an intention-to-treat manner (following the allocation of participants in studies). Only the results of studies evaluating similar interventions in similar participants were pooled. We calculated mean differences (MDs) and their 95% CIs for continuous outcomes and RRs for categorical outcomes. For outcomes related to symptom scores or QoL scores, we combined change values from baseline to the last observation. If SDs of change values were not available, we used the recommended method from the Cochrane handbook to estimate them,[15] and we converted the SD results of UPDRS scores to SE if needed.[16] We calculated RRs and their 95% CIs for all dichotomous data (ie, risk of AEs). We calculated the number needed to harm for potential AEs. We performed meta-analyses with RevMan 5.3 software using a random-effect model. Statistical heterogeneity was assessed with Mantel–Haenszel χ^2 and quantified with I^2. Sensitivity analysis was conducted by excluding studies that used different effect measures from other studies to test the robustness of the results. Finally, publication bias was examined by funnel plot if the number of included studies ≥ 10. $P<0.05$ was considered statistically significant.

Results

Study selection

The initial search identified 5,693 relevant records. Of these, 5,055 of 5,093 were excluded after title/abstract screening, and 38 reports were eligible for full-text review. Additionally, five reports were obtained through the references of eligible studies. After full-text review, we excluded 35 reports: 14 studies because dosages of combined levodopa/DDCI and entacapone were different from LCE, ten studies were not RCTs, three studies used different dosages of levodopa/DDCI in two groups, three studies were duplicate reports of included trials, three studies were abstracts without full-text data, and two studies gave treatment only once. Finally, we included seven RCTs with 2,123 PD patients and one pharmacoeconomic study in this systematic review.[17–24] The literature-search and study-selection process is presented in Figure 1.

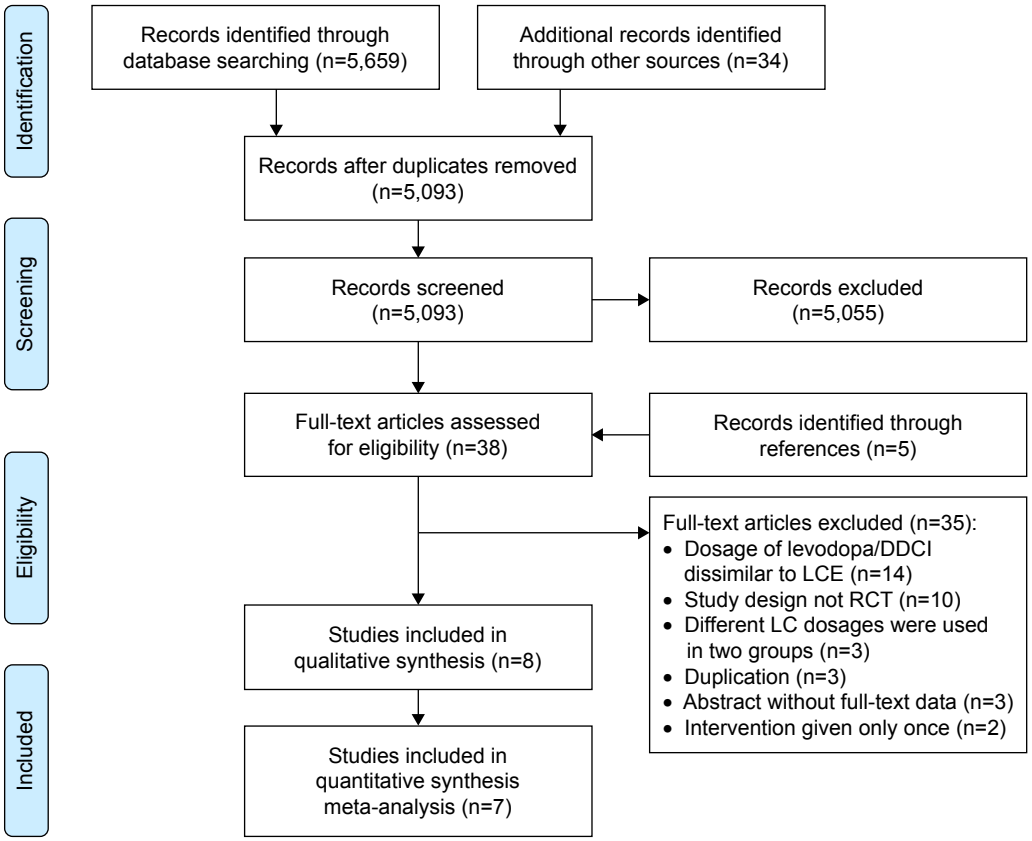

Figure 1 Literature search and study selection.
Abbreviations: DDCI, dopa-decarboxylase inhibitor; LCE, levodopa/carbidopa/entacapone; RCT, randomized controlled trial.

Study characteristics and quality assessment

Of the seven included RCTs, five compared LCE to levodopa/DDCI[17–20,23] and two compared the combined treatment of entacapone plus LC (dosages were similar to LCE) to levodopa/DDCI.[21,22] Treatment duration ranged from 12 weeks to 134 weeks (Table 1). The risk of bias of included studies was generally low, except those by Li et al and Lew et al.[21,23] We classified six RCTs at low risk of bias in the domain of random-number generation.[17–20,22,23] Five RCTs used the double-blind design and adopted the intention-to-treat principle to analyze data (Table 2).[17–20,22]

Efficacy

UPDRS scores

Five studies (1,014 patients) reported the UPDRS I subscale to evaluate mental function. Follow-up ranged from 12 weeks to 39 weeks.[17,18,20–22] Meta-analysis showed that the difference in UPDRS I was not statistically different between LCE and levodopa/DDCI (MD −0.09, 95% CI −0.23 to 0.16, P=0.25; I^2=8%, P-value for heterogeneity test 0.36).

The same five studies (1,014 patients) evaluated ADL with the UPDRS ADL subscale and UPDRS III to evaluate motor function.[17,18,20–22] Meta-analysis showed that LCE had a potential advantage in improving the UPDRS ADL subscale compared to levodopa/DDCI (MD −1.17, 95% CI −1.64 to −0.71, P<0.00001; I^2=21%, P-value for heterogeneity test 0.28) and improving UPDRS III (MD −1.55, 95% CI −2.29 to −0.81, P<0.0001; I^2=12%, P-value for heterogeneity test 0.34). We did not observe a similar trend for UPDRS IV to evaluate treatment-related complications. With the three studies (386 patients) reporting this outcome, the follow-up was 12 weeks.[17,20,21] Meta-analysis showed that there was no difference in UPDRS IV between LCE and levodopa/DDCI (MD −1.49, 95% CI −3.80 to 0.83, P=0.21; I^2=99%, P-value for heterogeneity test <0.00001) (Figure 2). Additionally, two studies (533 patients) evaluated the Schwab and England subscale,[18,21] and meta-analysis showed that LCE improved this subscale when compared to levodopa/DDCI (MD 2.05, 95% CI 0.85–3.26, P=0.0008; I^2=28%, P-value for heterogeneity test 0.24).

QoL

Four studies (1,282 patients)[18–20,23] and two studies (599 patients)[17,18] evaluated QoL with the PDQ39 and PDQ8, respectively. Follow-up ranged from 12 weeks to 208 weeks. Meta-analyses showed that there was no difference in the PDQ39 (MD 0.80, 95% CI −1.88 to 3.48, P=0.56; I^2=68%, P-value for heterogeneity test 0.03) or PDQ8

Table 1 Characteristics of included studies

Study	Inclusion criteria	Participants		Intervention		Duration (weeks)	Efficacy outcome		Dropouts
		LCE	Levodopa/DDCI	LCE	Levodopa/DDCI		Primary	Secondary	LCE/levodopa/DDCI
Li et al[21]	Mild or moderate PD in (modified) Hoehn–Yahr stage 0–3	n=60 A=53.92±5.39 M/F=36/24	n=52 A=50.10±10.33 M/F=31/21	CR LC 25/100 mg, twice daily, interval ≥6 hours, then titrated gradually (total daily dose ≤600 mg) + entacapone 100 mg	CR LC 25/100 mg, twice daily, interval ≥6 hours, then titrated gradually (total daily dose ≤600 mg)	12	Change from baseline in UPDRS I–VI	NR	NR
Parkinson Study Group[22]	Idiopathic PD patients in (modified) Hoehn–Yahr stage 1.5–4; had response to levodopa treatment and motor fluctuations paralleling their levodopa dosing; took a stable regimen of 4–10 daily doses of LC	n=103 A=63.9±8.0 M/F=69/34	n=102 A=62.7±19.7 M/F=64/38	4–10 daily doses of LC + entacapone 200 mg	4–10 daily doses of LC + placebo 200 mg	28	Percentage on time while awake	Percentage on time while awake in the morning, afternoon, and evening; percentage time asleep, total daily levodopa dosage; number of levodopa doses per day and levodopa dose failures; UPDRS total score and mental, motor, and ADL subscale scores; global evaluations	13/10

Fung et al[17]	≥30 years old; idiopathic PD with modified Hoehn–Yahr stage 1.0–2.5; 0–3 hours of nondisabling time off over a consecutive 48-hour period; took 3–4 stable equal doses of LC, with total daily levodopa dose of 300–800 mg/day for at least 1 month before study entry	n=93 A=64.8±10.2 M/F=57/36	n=91 A=62.9±9.45 M/F=50/41	3–4 stable doses of LC + entacapone 200 mg	3–4 stable doses of LC	12	Change from baseline to week 12 in total PDQ8 score	Change from baseline to weeks 4 and 12 in UPDRS I, II, III, and IV subscale scores; UPDRS I–III scores combined; number of wearing-off symptoms and proportion of patients experiencing wearing off	10/9
Hauser et al[18]	30–80 years old; had impairment warranting treatment with levodopa; UPDRS II + III >18; modified Hoehn–Yahr stage 1.0–2.5	n=208 A=65.3±9.26 M/F=144/64	n=215 A=64.5±8.79 M/F=128/87	LCE 100/25/200 mg, three times daily	LC 100/25 mg, three times daily	39	Change from baseline to week 39 in total UPDRS score (II + III)	Change from baseline in individual UPDRS subscale, PDQ39, PDQ8, modified Hoehn–Yahr stage, and Schwab and England ADL score; CGI score; responder rate	56 (total)
Stocchi et al[19]	30–70 years old; required initiation of levodopa therapy; disease duration <5 years; took stable doses of a dopamine agonist or other antiparkinsonian medications (no change in previous 4 weeks), but not amantadine, within preceding 270 days	n=373 A=60.6±8.7 M/F=245/128	n=372 A=59.8±8.2 M/F=222/150	LC 50/12.5 mg twice daily, then titrated to 100/25 or 150/37.5 mg four times daily, at 3.5-hour intervals + entacapone 200 mg	LC 50/12.5 mg twice daily, then titrated to 100/25 or 150/37.5 mg four times daily, at 3.5-hour intervals	134	Time to onset of dyskinesia	Frequency of dyskinesia, change from baseline in total UPDRS (II + III), and time and frequency of wearing-off episodes	108/96
Tolosa et al[20]	30–80 years old; received at least 1 month stable doses of IR/SR LC 100/25 mg or SR LC 200/50 mg (total daily levodopa dose 300–600 mg); experienced wearing off and impaired ADLs; had either absent or mild dyskinesia	n=46 A=66.4±8.2 M/F=21/25	n=49 A=66.5±9.0 M/F=27/22	LCE 100/25/200 mg (1 tablet) or LCE 150/37.5/200 mg (1 tablet)	IR LC 100/25 mg (1 tablet) or IR LC 100/25 mg (1.5 tablets)	36	Mean change from baseline to 3-month visit in UPDRS II score	UPDRS I, III, and IV, PDQ39, and QUICK questionnaires	11/10
Lew et al[23]	30–80 years old; received at least 1 month stable doses of IR LC; Hoehn–Yahr stage ≤2.5	n=180 A=68.7±9.2 M/F=106/74	n=179 A=68.3±10.4 M/F=108/71	IS group: switched to LCE 12.5/50/200 mg, 25/100/200 mg, or 37.5/150/200 mg immediately	Del group: switched to LCE treatment 4 weeks after completion of the baseline visit to simulate a "placebo" control	4	UPDRS III score	PDQUALIF score, PDQ39 score	44/51

Note: Age presented as mean ± SD.

Abbreviations: A, age; ADL, activity of daily living; DDCI, dopa-decarboxylase inhibitor; Del, delayed switch; IS, immediate switch; M, male; F, female; IR, immediate release; LCE, levodopa/carbidopa/entacapone; NR, not reported; PD, Parkinson's disease; SR, slow release; PDQ, Parkinson's Disease Questionnaire; PDQualif, PD quality-of-life instrument; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2 Risk of bias of randomized controlled trials

Study	Random-sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other source of bias
Li et al[21]	Unclear	Unclear	Unclear	Low	Unclear	Low
Parkinson Study Group[22]	Low	Low	Low	Low	Low	Low
Fung et al[17]	Low	Low	Low	Low	Low	Low
Hauser et al[18]	Low	Low	Low	Low	Low	Low
Stocchi et al[19]	Low	Low	Low	Low	Low	Low
Tolosa et al[20]	Low	Low	Low	Low	Low	Unclear
Lew et al[23]	Low	High	High	Low	Unclear	Unclear

(MD −0.70, 95% CI −1.82 to 0.43, P=0.11; I^2=58%, P-value for heterogeneity test 0.12) between LCE and levodopa/DDCI. We observed significant heterogeneity across included studies.

Wearing off

Three studies (1,352 patients) reported wearing-off outcomes. Follow-up ranged from 12 weeks to 208 weeks.[17–19] The incidence of wearing off in the LCE and levodopa/DDCI

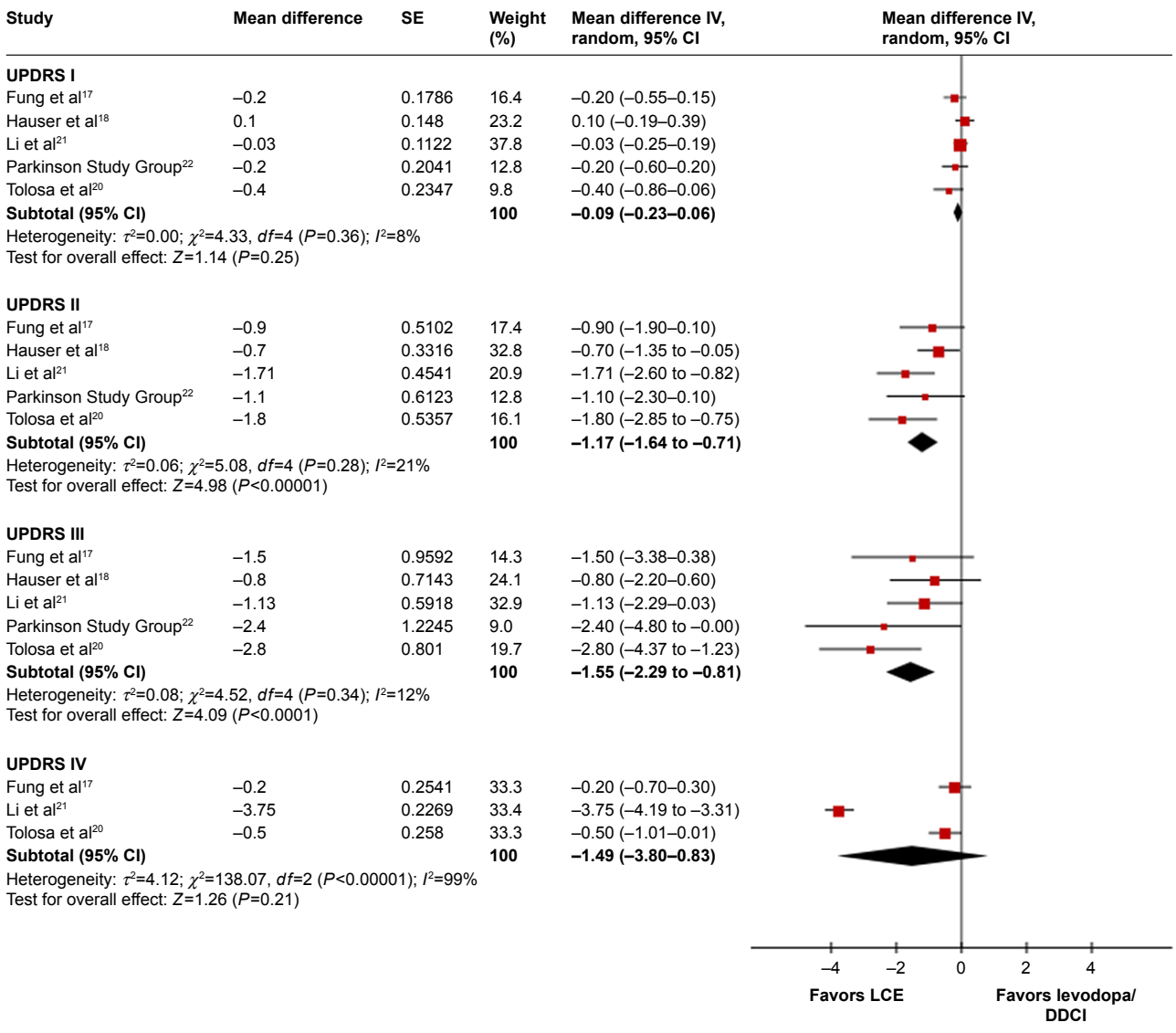

Figure 2 Changes in UPDRS scores from baseline.
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; DDCI, dopa-decarboxylase inhibitor; LCE, levodopa/carbidopa/entacapone.

groups was 37.2% and 42.5%, respectively. Meta-analysis indicated that wearing-off frequency was not statistically different between LCE and levodopa/DDCI (RR 0.89, 95% CI 0.77–1.02, P=0.10; I^2=15%, P-value for heterogeneity test 0.31).

Safety

Serious AEs

Serious AEs occurred in 4.35% and 5.92% patients in the LCE and levodopa/DDCI groups, respectively. The number needed to harm for the LCE group was 64. Meta-analysis based on three studies (700 patients) indicated that there was no significant difference in risk of serious AEs between LCE and levodopa/DDCI (RR 0.75, 95% CI 0.39–1.44, P=0.39; I^2=0, P-value for heterogeneity test 0.70) (Figure 3).[17,18,20]

Discontinuation due to AEs

The risk of discontinuation due to AEs was 8.48% and 6.13% for the LCE and levodopa/DDCI groups, respectively. The number needed to harm for the LCE group was 43. Meta-analysis based on four studies (905 patients) indicated that there was no significant difference in risk of discontinuation due to AEs between LCE and levodopa/DDCI (RR 1.38, 95% CI 0.86–2.21, P=0.18; I^2=0, P-value for heterogeneity test 0.83) (Figure 3).[17,18,20,22]

Total AEs

Risks of total AEs were 78.2% and 63.5% for the LCE and levodopa/DDCI groups, respectively. Meta-analysis based on six studies (2,008 patients) indicated that those on LCE had a higher risk of experiencing AEs compared to levodopa–DDCI (RR 1.33, 95% CI 1.05–1.70, P<0.00001; I^2=97%, P-value for heterogeneity test 0.02) (Figure 3).[17–20,22,23]

Single AEs

The risk of dyskinesia, urine abnormality, dizziness, nausea, constipation, diarrhea, and sleepiness was 14.5%, 34.0%, 13.2%, 24.2%, 11.1%, 14.3%, and 8.45% in the LCE group compared with 7.7%, 2.94%, 9.42%, 13.8%, 7.96%, 6.26%, and 5.56% in the levodopa/DDCI group, respectively. Meta-analyses indicated that LCE had a higher risk of dyskinesia (four studies,[17,19,20,22] 1,228 patients, RR 1.80, 95% CI 1.35–2.42; P<0.0001), urine abnormality (three studies,[17,18,22] 149 patients, RR 9.86, 95% CI 2.95–32.97;

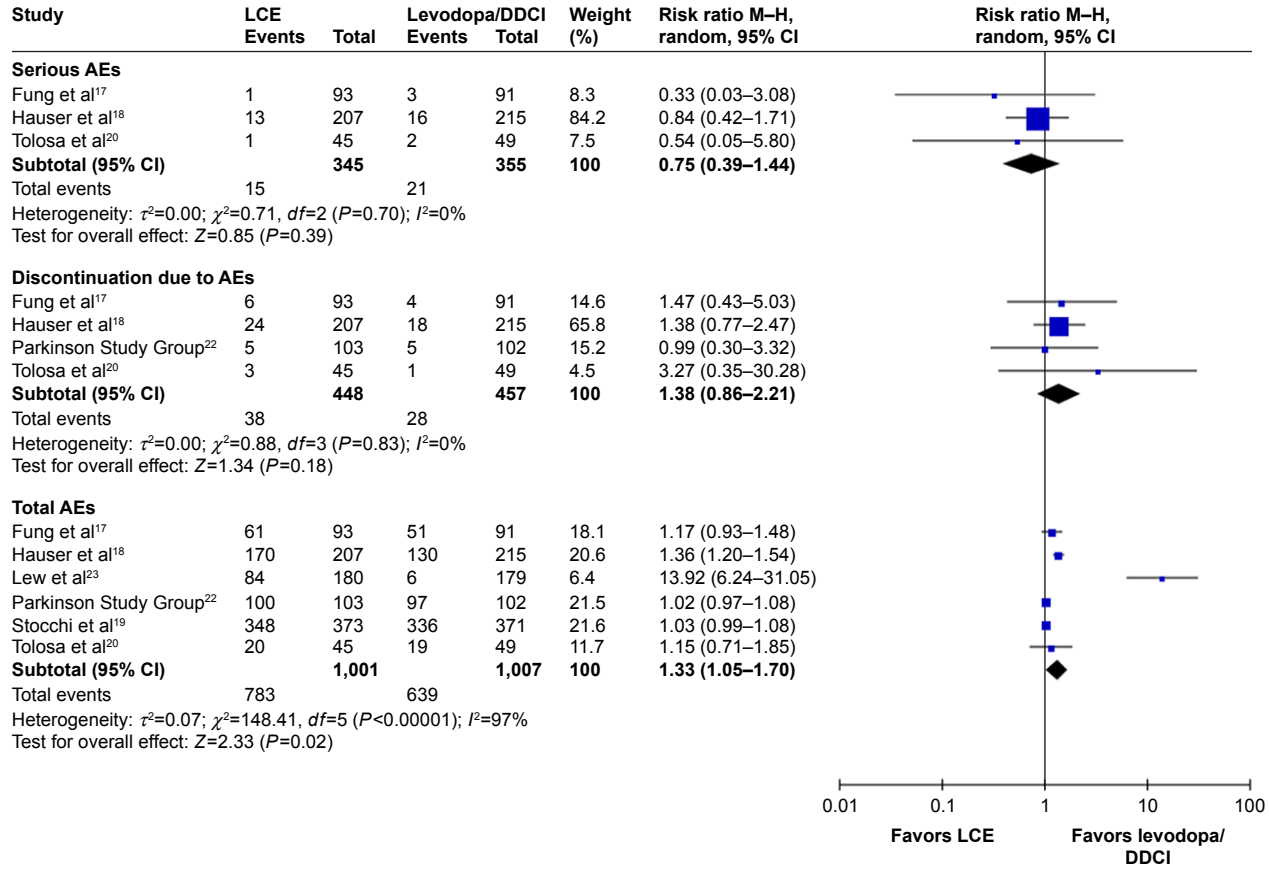

Figure 3 Risk of serious AEs, discontinuation due to AEs, and total AEs.
Abbreviations: AEs, adverse events; LCE, levodopa/carbidopa/entacapone; DDCI, dopa-decarboxylase inhibitor.

P=0.0002), dizziness (five studies,[17–20,22] 1,649 patients, RR 1.38, 95% CI 1.05–1.82; *P*=0.02), nausea (five studies,[17–20,22] 1,649 patients, RR 1.74, 95% CI 1.41–2.13; *P*<0.00001), and diarrhea (three studies,[17,19,20] 105 patients, RR 2.24, 95% CI 1.51–3.32; *P*<0.0001) than levodopa/DDCI. There was no significant difference in the risk of constipation (four studies,[17–19,22] 148 patients, RR 1.38, 95% CI 0.99–1.91; *P*=0.05) or sleepiness (two studies,[19,20] 838 patients, RR 1.34, 95% CI 0.85–2.12; *P*=0.21) between the two groups. Significant heterogeneity was found between studies reporting outcomes of urine abnormality (I^2=68%, *P*-value for heterogeneity test 0.04).

Economy

The only cost–utility analysis using a Markov model found indicated that LCE was beneficial to individual patients and the incremental cost-effectiveness ratio of LCE was £3,105 per quality-adjusted life-year (QALY) gained (<£30,000 per QALY gained, within the range considered to indicate acceptable cost-effectiveness) compared with traditional levodopa/DDCI therapy in the UK over a period of 10 years.[24] What is more, LCE gained an average 1.04 QALYs and reduced direct costs by £10,198 per patient in 10 years from the UK perspective. Sensitivity analyses confirmed the results were robust when different discount rates or a 5-year shorter time horizon was applied.

Sensitivity analysis

Only one study, by the Parkinson Study Group, did not clearly explain that MD was used as an effect measure, although changes in UPDRS scores were reported in tables.[22] Therefore, the sensitivity analysis was performed excluding this study. No significant changes in the results of UPDRS I (MD −0.08, 95% CI −0.25 to 0.10; *P*=0.39), UPDRS II (MD −1.21, 95% CI −1.78 to −0.64; *P*<0.0001), or UPDRS III (MD −1.48, 95% CI −2.31 to −0.64; *P*=0.0006) were indicated, although the heterogeneity among studies was increased in these outcomes. For Stocchi et al, we used scores from ClinicalTrials.gov that were different from the data published in the paper.[19] No significant changes in the results were indicated when the different data were used.

Discussion

The meta-analysis of RCTs indicated that LCE therapy improved UPDRS II, UPDRS III, and Schwab and England ADL scores for PD patients when compared with levodopa/DDCI therapy. However, there was no difference in UPDRS I, UPDRS IV, frequency of wearing off, PDQ39, or PDQ8 scores. LCE therapy increased the risk of total AEs, motor disturbance, nausea, and diarrhea, but did not increase the risk of serious AEs or discontinuation risk when compared with levodopa/DDCI therapy.

Most of these results are in line with clinical observations in the published paper, except for QoL data. The UPDRS offers a comprehensive evaluation of four relevant dimensions in PD: mentation, behavior, and mood (UPDRS I), ADL (UPDRS II), motor examination (UPDRS III), and complications (UPDRS IV).[25] In a pooled analysis of published Phase III studies on 808 PD patients, entacapone showed promising results in UPDRS II (*P*<0.01) and III (*P*<0.01) scores.[26] A meta-analysis of 14 studies also indicated adjuvant treatment with entacapone improved UPDRS ADL and motor scores.[27] Considering the fact that entacapone can increase levodopa sustainability by extending the drug's half-life, it was reasonable to find that LCE improved scores of UPDRS II and UPDRS III in our study, which is also consistent with previous findings. Three published RCTs with a minimum 3-month follow-up suggested that levodopa with entacapone had a slightly beneficial effect on patient QoL, but at a low level.[28] In this meta-analysis, LCE did not show any improvement in PDQ39 or PDQ8 scores. This may be explained by the relatively small samples and short follow-up of included studies. Moreover, nonmotor symptoms can influence QoL even more than motor symptoms, and levodopa influences few nonmotor symptoms. There is a likelihood that patients with relatively earlier and milder diseases experience a higher impact on QoL, and thus heterogeneity in the characteristics of included patients may also have contributed to these nonsignificant results. This study suggested that there was a trend for less wearing off in the LCE group than in LC, although it failed to reach statistical significance. Inconsistently with our study, previous studies assessing wearing-off time demonstrated a substantial reduction in for the LCE group, but not for the LC group.[29,30] In the included studies, we reported no statistical difference in the incidence of wearing-off between LCE and LC. Given the fact that entacapone prolongs the response to levodopa, we cannot exclude the possibility that a difference in effect on duration was not captured by the included studies.

In terms of adverse reactions, LCE was generally well tolerated compared with levodopa/DDCI, with no significant difference in serious AEs or discontinuation due to AEs found between the two groups. Risks of total AEs and single AEs were higher in the LCE group, but all were noted in the package insert and published articles on entacapone.[27] Such adverse reactions to entacapone are supposed to be associated

with enhanced dopamine activity. Urine abnormality was the most commonly reported AE in the LCE group, but this is a benign event related to the color of entacapone metabolites eliminated in the urine. As for economy, only one study with a cost–utility analysis showed that LCE had favorable cost-effectiveness. Therefore, further studies are needed to confirm these observations.

The results are consistent with those of the only found health-technology assessment, by the Canadian Agency for Drugs and Technologies in Health, published in 2008.[31] However, this report included only two RCTs and indicated that LCE showed significant improvement in UPDRS motor scores when compared with levodopa/DDCI in PD patients with mild motor fluctuations, and the statement that LCE would be less costly was not based on economy analysis. LCE compound preparations allow PD patients to use a COMT inhibitor earlier and reduce the dose of levodopa, which can provide a modest clinical benefit over levodopa/DDCI for up to 5 years.[32]

To the best of our knowledge, this study is the first systematic review and meta-analysis to compare LCE with levodopa/DDCI for PD patients. We included high-quality RCTs to ensure the rigor of the systematic review process and the relevance of results in the following aspects. First, compared with the single-study data presented in the guidelines and recommendations,[5,10] this study used systematic literature-search methods in an attempt to include all relevant studies and reduce publication bias. Conducting meta-analysis for data synthesis can give us a quantitative estimation of outcomes of interest, thus providing the best evidence available to make up for the deficiencies of existing guidelines. We further performed pharmacoeconomic evaluations to get a more comprehensive view of LCE, which could not be seen in previous meta-analyses. Although there has been a published meta-analysis on ten drugs for PD, no comparisons on compound formulations, such as LCE or levodopa/DDCI, were made.[33] Second, during the course of the study, the authors of the study continued to check the references of included literature, contact the authors, consult the manufacturers, and search ClinicalTrials.gov for unpublished data. For example, the UPDRS I data after treatment in Fung et al[17] were extracted from ClinicalTrials.gov.[34] Third, the literature included not only took into account the formulation of the LCE compound but also similar dosages of levodopa/carbidopa plus entacapone, taking into account the bioequivalence between drugs demonstrated by a series of pharmacokinetic studies,[35] so this study further expanded research sources and enriched the research data. Fourth, the study comprehensively pooled outcome data and objectively evaluated advantages and disadvantages of LCE, which could provide useful information for decision-making for appropriate LCE target patients.

Our study has some limitations. First, the number of studies included was limited, and thus no further subgroup analysis of early PD patients or PD patients with dyskinesia was done. It is expected that more research will be published in future further to differentiate between the two subpopulations. Second, we were unable to conduct further subgroup analysis for different courses of treatment. Considering the potential of the LCE compound to improve patient adherence and benefit in maintaining function in patients receiving chronic oral levodopa therapy,[36] longer treatment duration may link to better outcomes. However, we lacked the ability to test this hypothesis with available data, due to the relatively short follow-ups in the included studies. Furthermore, only English-language and Chinese-language studies were included. We tried to include important conference abstracts in the databases search, but we failed to find relevant studies. Thirdly, due to the four primary outcomes (UPDRS I–IV) included, the possibility of an increase in false-positive test results could not be ruled out.

In summary, LCE therapy can improve PD patients' symptoms by improving UPDRS II, UPDRS III, and Schwab and England ADL scores for PD patients when compared with levodopa/DDCI therapy. As for safety, LCE therapy was associated with higher risks of total AEs and single AEs, including dyskinesia, urine abnormality, dizziness, nausea, diarrhea, and sleepiness but did not increase the risks of serious AEs or discontinuation from studies.

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Disclosure

The authors report no conflicts of interest in this work.

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