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REVIEW



Fixed-dose combination therapy for Parkinson's disease with a spotlight on entacapone in the past 20 years: a reduced pill burden and a simplified dosing regime

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ABSTRACT

Introduction: Parkinson's disease (PD) is a progressive, chronic neurodegenerative disorder. The main neuropathological cause of the disease is the death of dopaminergic neurons in the substantia nigra. Unfortunately, there is no curative treatment yet. The gold-standard of the treatment is levodopa (LD). During the course of the disease, motor complications develop, which postulates the addition of entacapone (ENT) to the dopaminergic medication. Previous studies have suggested that patients have a better quality of life when entacapone is added in a combination with LD.

Areas covered: A systematic literature search was performed. Articles were identified through PubMed (MEDLINE), Web of Science, Ovid, and ClinicalTrials.gov databases. The following search terms were used: 'Levodopa' AND 'Carbidopa' OR 'Benserazide' AND 'Entacapone'. The search period was between 2000 and 2020. Twenty randomized and 10 non-randomized clinical trials (12,893 subjects) were included in the qualitative analysis. The systematic review was written in line with the PRISMA guideline.

Expert opinion: ENT administered in combination with LD resulted in a better quality of life compared to separate tablets. Therefore, in PD patients where impaired motor performance develops and the application of entacapone is necessary, it is suggested to be administered in a single tablet form.

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KEYWORDS

Adherence; combination; entacapone; fixed-dose; non-motor symptoms; Parkinson's disease; UPDRS

1. Introduction

Parkinson's disease is the second most common neurodegenerative disorder [1]. The estimated prevalence is around 10–18 per 100 000 [2]. The most important motor symptoms are bradykinesia, tremor, and/or rigidity [2]. The main neuropathological cause of the disease is the death of the dopaminergic neurons in the substantia nigra [3]. Unfortunately, there is no curative treatment yet, however extensive preclinical and clinical studies are ongoing [4]. Today, the focus of treatment is on the compensation of the hypodopaminergic state of the brain with exogenous levodopa (LD) substitution [5]. In general, a significant proportion of levodopa is rapidly metabolized by the peripheral aromatic amino-acid decarboxylase (AADC) [6–8]. To prevent this process, dopa-decarboxylase inhibitors (DDCI) have been introduced in daily clinical practice (benserazide (B) and carbidopa (CD)) [6–8]. However, AADC is not the only enzyme which is involved in this metabolic pathway [6–8]. Catechol-O-methyltransferase (COMT) can also convert LD to 3-O-methyldopa (3-OMD) [6–8]. To block this pathway as well, three widely known COMT inhibitors (entacapone (ENT), tolcapone (TLC), and opicapone (OPC)) have been introduced [6–8]. Although ENT is the most widely used COMT inhibitor, it requires multiple daily doses. In contrast, it is sufficient to administer OPC once a day. The only

central acting COMT inhibitor is TLC; however, due to its hepatotoxic effects, it should be closely monitored [6]. The treatment of patients with Parkinson's disease becomes very complicated as the disease progresses [5]. The 'ON'-time will get shorter and the number of hours with inappropriate movement increases [5]. Fractionation and intensification of the LD treatment gradually become necessary [5]. If end-of-dose motor fluctuations develop, an option is to introduce the COMT-inhibitors in combination with LD/DDCI [5]. In addition to the motor symptoms of the disease, many non-motor symptoms, including Parkinson's dementia are known [9]. Given that the treatment strategy gets more complicated as the disease progresses and, simultaneously, the condition of the patient gradually deteriorates, combination therapies play a major role in achieving optimal compliance and therapeutic response [5]. Furthermore, the cost-effectiveness of combination therapies is not negligible [10].

For the reasons mentioned above, the primary aim of this systematic review is to summarize the efficacy data on entacapone as an adjunct therapy to LD on motor fluctuations (in line with PRISMA criteria [11]). Furthermore, the secondary objective is to compare the pharmacological and quality of life effects of two modes of oral ENT administration (LD/DDCI plus ENT separately versus LD/DDCI/ENT). An additional purpose of our study is to demonstrate the importance of

Article highlights

- Parkinson's disease is the second most common neurodegenerative disorder with an estimated prevalence of around 10-18 persons per 100 000.
- The gold-standard of the treatment is levodopa (LD). However, during the course of the disease, motor complications develop which often leads the prescription of entacapone (ENT) in addition to the dopaminergic medication.
- ENT is a peripherally acting COMT-inhibitor.
- ENT administered in combination (LD/CD/ENT) results in a better quality of life compared to the drugs administered separately (LD/CD + ENT or LD/B + ENT)
- The cost-effectiveness of combination formulations may be an important future aspect for the patient's and health insurance's budget, especially as an increased QoL could increase a patient's number of active years and reduce the need for hospital care.

This box summarizes key points contained in the article.

combination therapies in Parkinson's disease, using the example of LD/CD/ENT.

2. Methods

2.1. Eligibility criteria

English language, available online reviews, editorial articles, and original publications have been included in the systematic literature analysis, as well as clinical trials with accessible results. The search period was between 2000 and 2020 (January). Clinical trials on individuals below the age of 18 are not included in the analysis. The main focus of the literature search was on the effect of ENT on the motor performance of Parkinsonian patients. Due to the lack of LD combination formulation for OPC and TLC, it was not possible to compare these with ENT combinations. For this reason, OPC and TLC were beyond the scope of this article. Furthermore, the studies addressing the impact of ENT on levodopa-induced hyperhomocysteinemia and vitamin B12 deficiency were also excluded.

2.2. Information sources and search strategy

Articles were identified through PubMed (MEDLINE), Web of Science, Ovid, and ClinicalTrials.gov databases. The following search terms were used in all applied online databases: 'Levodopa' AND 'Carbidopa' OR 'Benserazide' AND 'Entacapone'.

2.3. Data items

The following information was searched in the identified publications: (1) type of the trial; (2) participant characteristics (number of included subjects, inclusion, and exclusion criteria); (3) purpose of the study; (4) intervention and groups; (5) duration of the study; (6) clinical assessment scales; (7) outcome measures (primary and secondary); (8) main findings.

3. Results

3.1. Study selection process

Through PubMed (MEDLINE) searches 179 items were identified (Figure 1). Using the Web of Science, Ovid, and ClinicalTrials.gov databases, we identified an additional 497 items. Duplications were removed using Mendeley software (n = 208). After screening the 468 identified findings (titles and abstracts were read), 39 articles were eligible for full-text review. After the detailed evaluation of the above-mentioned texts, 30 studies were included in this systematic analysis.

3.2. Study characteristics

Study type – 20 randomized (double-blind, cross-over (n = 8); double-blind, parallel-group (n = 5); single-blind, cross-over (n = 1); single-blind, parallel-group (n = 1); open-label, cross-over (n = 2); open-label, parallel-group (n = 3)) and 10 non-randomized (open-label) clinical trials were identified (Table 1).

Number and characteristics of participants – 12,893 subjects (male and female patients) were involved in these studies (PD patients = 12,784; healthy subjects = 109). Age range: 30 to 80 years.

Inclusion and exclusion criteria (PD population) – The most widely used inclusion criteria were the following: (1) – idiopathic PD; (2) – Hoehn-Yahr stage 1 to 3; (3) – motor fluctuation information (absent; no or minimal, nondisabling motor fluctuation; 'end-of-dose type'; wearing-off; on-off phenomenon; early end-of-dose wearing-off defined by QUICK questionnaire; mild wearing-off phenomena; without unpredictable fluctuations; wearing-off with or without mild dyskinesia; at least 1 'yes' on the Motor Fluctuation Questionnaire) (4) – LD dose (stable dose; not optimally treated) and formulation information (standard; IR; SR; RR). The main exclusion criteria used in the studies were the following: (1) – secondary or atypical parkinsonism; (2) – severe systemic or psychiatric illness; (3) – previous or current treatment which interferes with the tested drug; (4) – previous treatment with ENT; (5) – motor performance information (unpredictable dyskinesia; unpredictable "OFF" periods; painful dyskinesia; disabling dyskinesia; unpredictable fluctuations; complex motor fluctuations; severe dyskinesia; more than mild dyskinesia).

Duration of the study – the duration of the studies ranged from 2 days to 136 weeks.

Clinical assessment scales – the following tests were generally used in the identified clinical trials: (1) – UPDRS scale; (2) – PDQ-39 and –8; (3) – SF-36; (4) – PSI; (5) – VAS; (6) – Clinical Global Impression (patient and investigator); (7) – Motor fluctuations Questionnaire; (8) – QoL; (9) – ESS; (10) – MMSE; (11) – Schwab and England ADL scores; (12) – BDI; (13) – Wearing Off Card; (14) – Motor performance tests (grip strength, line tracing test, peg insertion test); (15) – pharmacokinetic test; (16) – LD dose equivalent.

3.3. Main findings

3.3.1. Pharmacokinetic data

The majority of the performed pharmacokinetic studies focused on the effect of ENT on LD in different administration

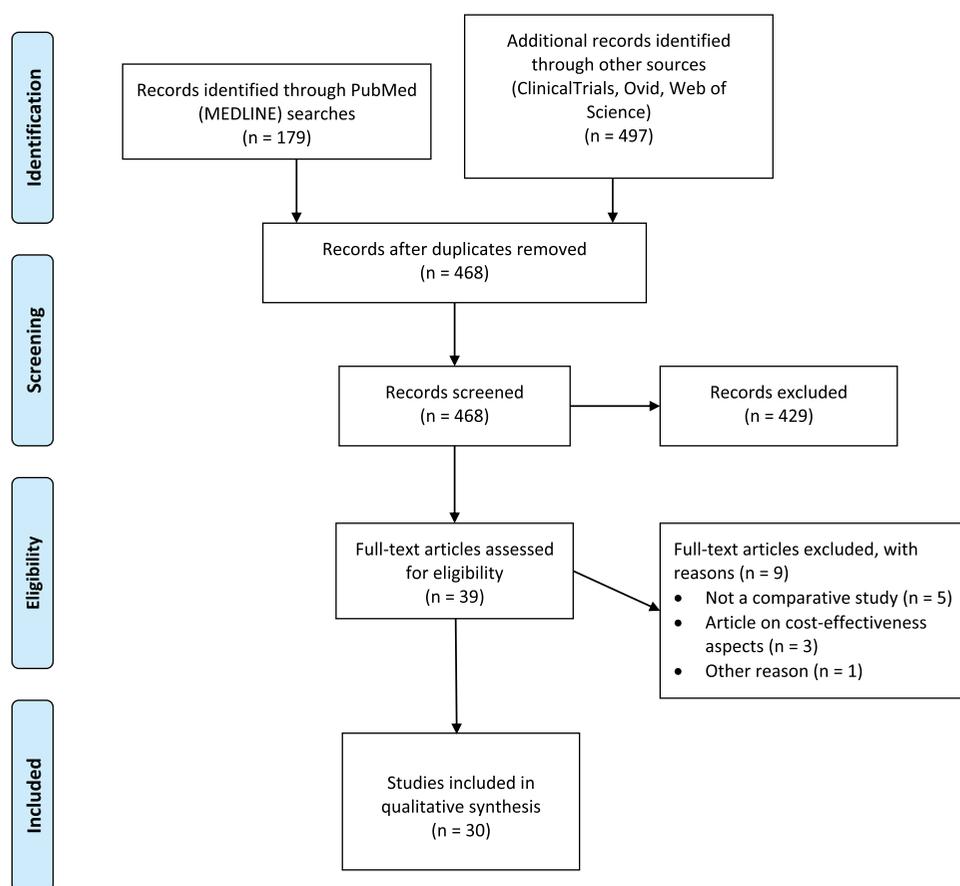


Figure 1. PRISMA flow diagram.

and combination settings. There was no relevant pharmacokinetic difference between LD/CD and LD/B after ENT administration. However, other authors [16] suggested, that LD/B may have more significant AADC inhibitory effects. Addition of ENT to LD/CD or LD/B resulted in increased AUC and decreased 3-OMD levels (regardless of the type of the LD formulation (e.g. RR, CR, IR; separately administered or single tablet form)) [17–24].

3.3.2. Scale-based assessments, motor performance

To estimate the alteration in motor performance, UPDRS scale was the most widely used [26–37 and NCT00391898, NCT00642356]. The overall conclusion of many of the identified studies was that regardless of the administration form of ENT (administered separately or in single tablet form), motor performance improved [20,25–27]. This positive effect is also detectable in different subpopulations (e.g. in early-stage PD patients) [25]. However, in the STRIDE-PD clinical trial, an earlier appearance and increased frequency of dyskinesias were detected in the ENT group [26]. Interestingly, in the SIMCOM study, a pronounced improvement was found in the UPDRS score (the mean UPDRS score (parts III) improved significantly (from 24.0 by 1.9; $p < 0.01$)) with the single tablet LD/CD/ENT group compared to LD/CD plus ENT (separately) group [28]. The repeated administration of ENT containing LD combination resulted in significantly better motor scores (UPDRS) and

performance in comparison to repeated administration of LD/CD alone, meanwhile, there was lesser pronounced fluctuation of movements [23]. In the START-M trial – similarly to the TC-INIT study – a switch from the previous LD medication to LD/CD/ENT resulted in a 29% reduction rate on the UPDRS [29].

3.3.3. Quality of life

The effect of entacapone addition to LD/DDCI and the formulation-related effects (LD/DDCI + ENT vs. LD/CD/ENT) were also examined from the perspective of QoL.

Hauser et al. found over 39 weeks, in early PD populations, that LD/CD/ENT resulted in greater clinical improvement than LD/CD alone [25]. The risk of motor complications was not elevated in the ENT group [25]. ADL (Part II, UPDRS, $p = 0.025$) and Schwab and England scores (by patient: $p = 0.006$, by rater: 0.003) were significantly better in the LD/CD/ENT group [25]. There was a similar tendency with the PDQ-39 and PDQ-8 scores [25]. The p-CGI was significantly better as well in the above-mentioned group (LD/CD group – 34.8% reported that they were ‘much improved’; however, in the LD/CD/ENT group it was 36.7%) [25]. Another study found that in patients without motor complications, separately administering ENT for 21 weeks did not improve the ADL section of UPDRS scale [30]. However, this treatment resulted in a significant improvement in the QoL measures (PDQ-39 ($p < 0.01$), SF-36 (vitality domain – $p = 0.04$; physical component – $p = 0.009$), PSI

Table 1. Identified clinical trials (Abbreviations: 3-OMD – 3-O-methyldopa; AADC – Aromatic L-amino acid decarboxylase; ADL – Activities of daily living scale; AE – adverse event; AUC – Area under the curve; CD – Carbidopa; CGI – Clinical global impression scale; Cmax – Maximum concentration; CR LD – Controlled-release levodopa; CR LD/CD – Controlled-release levodopa/carbidopa; ENT – Entacapone; ESS – Epworth sleepiness scale; IR LD/CD – Immediate-release levodopa/carbidopa; IR LD/DDCI – Immediate-release levodopa/dopa decarboxylase inhibitor; LD – Levodopa; LD/B – Levodopa/benserazide; LD/CD – Levodopa/carbidopa; LD/CD + ENT – Levodopa/carbidopa + entacapone (separately); LD/CD/ENT – Levodopa/carbidopa/entacapone (single pill); LD/DDCI – Levodopa/dopa decarboxylase inhibitor; M/F – Male/female; n.d. – No data; N.S. – Not significant; PD – Parkinson's disease; PDQ-39 – The 39-item Parkinson's disease questionnaire; PDQ-8 – The 8-item Parkinson's disease questionnaire; PLC – Placebo; q.d. – Four times a day; QoL – Quality of life; QUICK – QQ – 19-item questionnaire for identifying wearing-off symptoms; RR LD/CD – Retarded-release levodopa/carbidopa (Nacomp retard); SF-36 – 36-item short form survey; SR LD/CD – Sustained-release levodopa/carbidopa; t.i.d. – three times a day; UPDRS – Unified Parkinson's disease rating scale; VAS – Visual analog scale).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
Piccini et al. [41]	Double-blind, placebo-controlled, single dose, randomized, cross-over trial	14 PD patients (M/F)	Testing the clinical change of ENT addition to standard LD and to CR LD	Group I: 200/50 mg standard LD/CD + 200 mg ENT q.d.; Group II: 200/50 mg standard LD/CD + PLC q.d.; Group III: 200/50 mg CR LD/CD + 200 mg ENT q.d.; Group IV: 200/50 mg CR LD/CD + PLC q.d.	4 days	(nonconsecutive)	Primary: "ON" time duration; Secondary: UPDRS score maximal improvement; latency of motor response; duration and severity of dyskinesias	1 patient – diagnosis modification (MSA)
The duration of "ON"-time prolonged in both groups after ENT administration.			UPDRS maximal improvement was significant in the CR LD/CD + ENT group compared to CR LD/CD + PLC group. The addition of ENT to standard LD/CD reduced the severity, but not the duration of dyskinesias.					
Stocchi et al. [24]	Single-blind, placebo-controlled, randomized, cross-over study	12 PD patients (M/F)	To test the clinical and pharmacokinetic consequences of ENT addition to CR LD administration.	200/50 mg CR LD/CD + 200 mg ENT or PLC	2 days	(nonconsecutive)	Primary: "ON"-time duration; Secondary: latency of motor response	All patients completed the study
ENT	significantly prolonged the "ON"-time (37%). The AUC was significantly increased after ENT			Olanow et al. – US01 Study Team [30]	Double-blind, placebo-controlled, prospective trial	750 PD patients (M/F)	To test the clinical effect of ENT addition to LD in PD patients without motor complications	Group I: LD/CD + ENT (with each dose of LD); Group II: LD/CD + PLC

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
26 weeks	Primary: UPDRS motor subscale changing from baseline to week 26; Secondary: ADL subscale of UPDRS changing from baseline to week 26; total UPDRS score; change in the clinical scales	In the	treatment group: 41 – adverse event, 2 – unsatisfactory therapeutic effect, 55 – discontinued study medication, 49 – other reason	There was no significant difference between the groups in UPDRS (motor, ADL) scale. Entacapone treatment significantly improved the QoL measures (PDQ-39, SF-36, PSI and subject clinical global assessment).				
Myllylä et al. – SIMCOM Study [28]	Open-label, single-group, cross-over, multicenter study	52 PD patients (M/F)	To start LD/CD/ENT in patients, who were previously treated with IR LD/DDCI plus separately administered ENT	Group I: IR LD/DDCI (CD or B) + ENT; Group II: LD/CD/ENT	4 weeks	Primary: preference estimation; LD/CD/ENT dose changing; Secondary: treatment success rate (investigator and patient global impression); UPDRS (“ON”); QoL assessment with VAS; mean daily LD dose and frequency of dosing	In the treatment group: 4 – premature discontinuation, 3 – adverse event, 1 – other reason	69% of the patients preferred (54% N.S.) LD/CD/ENT or considered it as equivalent (15%) to previously applied treatment. 85% of the patients in LD/CD/ENT group found the clinical condition equal or better (evaluated by investigator, 75% if the patients evaluated themselves). UPDRS (part III) score reduced significantly after drug shift. The patients rated LD/CD/ENT easier to handle (84%), remember (67%) and swallow (59%). The treated group found it convenient to use LD/CD/ENT and found the dosage simpler (94%).
Brooks et al. – TC-INIT Study Group [32]	Open, randomized, parallel-group, multinational study	176 PD patients (M/F)	To compare the safety, tolerability and efficacy after switching from IR LD/DDCI to LD/DDCI + ENT (separately) or to LD/CD/ENT	Group I: IR LD/DDCI (CD or B) + ENT; Group II: LD/CD/ENT	6 weeks	Treatment success rate assessed by patient and by investigator (CGI-C); Success rate calculation between the groups; Motor Fluctuation Questionnaire; UPDRS (part III) change; QoL; VAS	5% discontinuation rate (8/177) because of AE (most common AEs: nausea, diarrhea, dyskinesia)	The UPDRS score (I, III and total) significantly improved in both groups at week 6. There was no significant difference between the groups in motor performance. Over 70% of patients in both groups felt their clinical condition improved. Over 80% of patients experienced reduction in fluctuations (87% – combination; 81% – separate ENT). QoL was significantly better in the LD/CD/ENT group.

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
Koller et al. – SELECT-TC Study Group [33]	Open-label, multicenter, single-arm study	169 PD patients (M/F)	To compare the effect of switching from IR LD/DDCI to LD/CD/ENT	Group I: IR LD/DDCI (CD or B); Group II: LD/CD/ENT	4 weeks	UPDRS (I, II, III, IV); “OFF”-time (UPDRS question 39); PDQ-39; Change of total LD dose; investigator and patient global clinical assessment	12/169 –	discontinuation – AE (nausea, “OFF” period worsening; etc.), 2 – other reason
UPDRS (I, II, III, IV), Question 39) and PDQ-39 scores improved	significantly in the LD/CD/ENT group. There was a reduction of “OFF”-time in 31.7% of patients. “OFF”-time increased in 7% of patients. Both investigator- and patient-rated global		improvement increased after LD/CD/ENT (“slightly improved”).					
Paija et al. [18]	Double-blind, randomized, cross-over study	16 males	To evaluate the effect of ENT (200 mg) on CR LD/CD	Group I: 100/25 mg CR LD/LD + 200 mg ENT (q.i.d.); Group II: 100/25 mg CR LD/CD + PLC (q.i.d.)	2 days	n.d.	1/16 – early discontinuation, because of the refusal to allow insertion of intravenous cannula	AUC was increased after ENT administration (39%). ENT reduced daily LD plasma level variation by 25%. ENT decreased 3-OMD formation compared to PLC (50%).
Lyons et al. [27]	Open-label study	62 PD patients (M/F)	To evaluate the effect of conversion from SR LD/CD to LD/CD/ENT in suboptimally treated patients	Group I: SR LD/CD + ENT was converted to LD/CD/ENT. Group II: SR LD/CD was converted to LD/CD/ENT. Group III: SR LD/CD + LD/CD + ENT was converted to LD/CD/ENT. Group IV: SR LD/CD + LD/CD was converted to LD/CD/ENT	1 month	Primary: change in PDQ-39 score at 1 month compared to baseline	13/62 – adverse effect (nausea, vomiting, increased “OFF” time, increased dyskinesia)	LD/CD/ENT was preferred by 42 patients. By the patients who preferred LD/CD/ENT, the UPDRS, PDQ-39, ADL, ESS scores significantly improved.
Müller et al. [20]	Open-label study	22 PD patients (M/F)	To determine the clinical consequence of ENT plasma concentration of LD and 3-OMD.	Day 1: only LD/CD t.i.d.; Day 2: LD/CD/ENT (t.i.d., equal dose)	2 days	Any alteration in motor performance and/or in pharmacokinetic results	N.D.	On day 2, motor performance was significantly better. Higher LD maximum concentration and AUC were detected.
Boiko et al. – START-M trial [29]	Open-label, multicenter study	50 PD patients (M/F)	To evaluate the efficacy of and tolerance to LD/CD/ENT.	The previous medication was switched to LD/CD/ENT (equivalent LD dose)	6 weeks	Any alteration in motor functions	N.D. (10% of the patients reported side effect)	In the LD/CD/ENT group, the UPDRS score reduced by 29%. There was significant reduction in the behavioral and mood domains as well. The activities of daily living improved by 25.1%.

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
Müller et al. [22]	Double-blind, randomized trial	13 PD patients (M/F)	To determine the clinical change from ENT addition to RR LD/CD. Estimate the plasma concentration of LD and 3-OMD.	Group I: day 1: 200 mg RR LD/CD; day 2: 150 mg LD/CD/ENT; Group II: day 1: 150 mg LD/CD/ENT; day 2: 200 mg RR LD/CD	2 days	Any alteration in motor performance and/or in pharmacokinetic results	N.D.	LD/CD/ENT was significantly better than LD/CD in the attention related components.
Müller et al. [23]	Open-label, standardized study	20 PD patients (M/F)	To determine the clinical effect and the alteration in complex motions after ENT addition to LD/CD. To test the effect of repeated drug administration.	Day 1: LD/CD (t.i.d., 50–150 mg); Day 2: LD/CD/ENT (identical dosage)	2 days	Any alteration in the UPDRS (part III)	N.D.	Motor scores and performance were significantly better after ENT addition.
Linazoro et al. – Spanish Stalevo Study Group [12]	Multicentric, prospective, single-blind, randomized and clinically controlled study	39 PD patients (M/F)	To determine the best way to switch from LD/CD to LD/CD/ENT.	Group I: LD/CD with the same dose ± ENT (single tablet); Group II: 15–25% reduction of the LD/CD dose ± ENT (single tablet)	4 weeks	Difference between the basal and the 4 week test results	1 patient discontinued the study, because the exacerbation of dyskinesia (Group 1); 2 patients found the effect unsatisfactory in Group 2.	Both groups showed increased “ON”-time and reduction of daily “OFF”-time. No difference was found during the clinical assessment (e.g. QoL test) between the groups.
Müller et al. [42]	Randomized, double-blind, cross-over clinical trial	12 PD patients (M/F)	To compare the effect on motor performance and grip strength of RR LD/CD compared to LD/CD/ENT.	Group I: day 1: 200 mg RR LD/CD; day 2: 150 mg LD/CD/ENT; Group II: day 1: 150 mg LD/CD/ENT; day 2: 200 mg RR LD/CD	2 days	Difference between the baseline and the outcome measures	N.D.	LD increased the muscle strength. In both groups there was similar antiparkinsonian efficacy.
LeWitt et al. [13]	Randomized, open-label, cross-over study	17 PD patients (M/F)	To compare the pharmacokinetics and clinical efficacy of CR LD/CD with LD/CD/ENT	Group I: LD/CD/ENT (37.5 – 150 – 200 mg), then CR LD/CD (50–200 mg); Group II: CR LD/CD (50–200 mg), then LD/CD/ENT (37.5 – 150 – 200 mg)	2 weeks	Change in the PD symptoms diary or in the UPDRS and global assessment scores	No subjects have discontinued the medication due to adverse events.	The LD AUC was nearly equivalent. In the LD/CD/ENT treatment regimen the hourly LD fluctuation index was higher. “OFF”-time was significantly lower and “ON”-time ‘with non-troublesome dyskinesia’ was more in the LD/CD/ENT group.

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
Hausser et al. – FIRST-STEP Study Group [25]	Randomized, double-blind, multicenter, parallel-group study	423 PD patients (M/F)	To compare the efficacy, safety and tolerability of LD/CD/ENT with LD/CD	Group I: LD/CD t.i.d.; Group II: LD/CD/ENT t.i.d.	39 weeks	Change in the UPDRS, CGI, PDQ-39 scores	14.9% of patients discontinued the study in LD/CD/ENT group (AE, lost to follow-up, etc.) 11.6% of patients discontinued the study in the LD/CD group (AE, etc.)	Over 39 weeks, in early PD, the LD/CD/ENT resulted in greater clinical improvement than LD/CD alone. The risk of motor complications was not elevated in the ENT group. ADL (Part II, UPDRS), Schwab and England scores were significantly better in the LD/CD/ENT group. The p-CGI was significantly better in the above-mentioned group.
Fung et al. – QUEST-AP Study Group [31]	Multicenter, randomized, parallel-group, double-blind study	184 PD patients (M/F)	To investigate the effect of LD/DDCI compared to LD/CD/ENT on quality of life in PD patients	Group I: LD/CD or LD/B 100/25 to 200/50 mg t.i.d.- q.i.d.; Group II: LD/CD/ENT (equally LD dose) t.i.d. – q.i.d.	12 weeks	Primary: change from the baseline in the total PDQ-8 score; Secondary: change from the baseline of the UPDRS scale (4 or 12 weeks after starting the trial). Change in the Wearing Off Card score.	7.6% of the patients discontinued the study (AE)	In the LD/CD/ENT group, the PDQ-8 sum score and in a non-motor domain were significantly improved compared to LD/CD or LD/B groups. The UPDRS II scores improved significantly with ENT addition.
Delea et al. [36]	Retrospective, observational cohort study	8646 patients (M/F)	To compare the treatment adherence of PD patients receiving LD/CD/ENT or two separate tablets (LD/CD + ENT)	Group I: LD/CD/ENT; Group: LD/CD + ENT	365 days	Primary: change in the treatment adherence	N.D.	The use of LD/CD/ENT vs. LD/CD + ENT (separate tablets) resulted better adherence (79% lower mean non-adherence; 86% lower odds of unsatisfactory adherence).
Eggert et al. – SENSE Study Group [34]	Multinational, multicenter, open-label, single-arm study	115 PD patients (M/F)	To study the efficacy, safety and feasibility of switching from LD/CD or from LD/B to LD/CD/ENT	Three strengths of LD/CD/ENT were used according to the previous medication (LD: 50, 100, 150 mg)	6 weeks	Primary: change in the p-CGI-C; Secondary: change in the i-CGI-C and in the UPDRS score and QoL-VAS scales	7% of the patients discontinued the study (3% on LD/B, 13% on LD/CD)	After switching, 77% of patients reported 'improvement'. Significant improvement was in the i-CGI-C, UPDRS and QoL-VAS scales. Patients who were previously treated with LD/B responded well to ENT addition compared to LD/CD group.
Stocchi et al. – STRIDE-PD Study [26]	Prospective, double-blind trial	747 PD patients (M/F)	To test the hypothesis, that ENT addition reduces the risk of the development of motor complications	Group I: start LD substitution with LD/CD; Group II: start LD substitution with LD/CD/ENT (in both groups the drug was administered q.i.d.)	134 weeks	Primary: time to onset of dyskinesia; Secondary: frequency of dyskinesia, change of UPDRS (Parts II and III) score; time and frequency of wearing-off episodes	LD/CD group: 25.8% (96/372) (AE, unsatisfactory therapeutic effect, etc.); LD/CD/ENT group: 29% (108/373) (AE, unsatisfactory therapeutic effect, etc.)	Patients receiving LD/CD/ENT had a shorter time to onset of dyskinesia and increased frequency. There was no significant difference between motor scores and wearing off.

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
NCT00391898	Double-blind, randomized, parallel, multicenter study	95 PD patients (M/F)	To evaluate the efficacy of LD/CD/ENT vs. LD/CD in PD patients with impairment of activities in daily living and early wearing-off with LD	Group I: LD/CD/ENT (100/25/200 or 150/37.5/200 mg); Group II: LD/CD (one and one-half 100/25 mg)	3 months	Primary: change in the UPDRS (Part II) score from baseline to month 3; Secondary: change in the UPDRS (Part I, III and IV), PDQ-39, QQ and Patient- and Investigator Global Evaluation of the Patient scales from baseline to month 3	LD/CD group – 10/49; LD/CD/ENT group – 11/46	In the LD/CD/ENT group there was – 2.5 point decrease in the UPDRS (part II) scale compared to – 0.5 in the LD/CD group. UPDRS (part III): LD/CD/ENT: – 4.0 vs. LD/CD: – 1.42. PDQ-39 scale: LD/CD/ENT: 6.3 vs. LD/CD: 0.8.
NCT00642356	Prospective, randomized, double-blind, double-dummy, active-controlled, multi-center comparison study	14 PD patients (M/F)	To study the effects of LD/CD/ENT vs. IR LD/CD on non-motor symptoms in patients who have idiopathic PD and demonstrate non-motor symptoms of wearing-off	Group I: LD/CD/ENT (100/25/200 mg); Group II: IR LD/CD (100/25 mg)	8 weeks	Primary: change from baseline of QWOQ-9 scale (non-motor section); Secondary: change from baseline of QWOQ-9 scale (motor section)	IR LD/CD group: 3/7; LD/CD/ENT group: 2/7	QWOQ-9 change (non-motor part): LD/CD/ENT: – 0.9 vs. LD/CD: – 0.2. QWOQ-9 change (motor part): LD/CD/ENT: – 1.2 vs. LD/CD: 0.0.
Lew et al. – LCE QoL Study Group [35]	Prospective, randomized, multicenter, open-label study	359 PD patients (M/F)	To compare the effect of immediate versus delayed switch from LD/CD to LD/CD/ENT on motor function and QoL	Group I: switch the LD/CD immediately (IS) to LD/CD/ENT at baseline; Group II: switch the LD/CD to LD/CD/ENT 4 weeks (DEL) after the baseline	16 weeks	Primary: mean change from the baseline at week 4 in the UPDRS III score; Secondary: change in the PDQUALIF and PDQ-39 scores from the baseline to week 4, 8 and endpoint	44/180 patients discontinued in the IS group (AE, lack of efficacy, etc.); 51/179 patients discontinued in the DEL group (AS, lack of efficacy, etc.)	A significant decrease was observed in the IS group at week 4 compared to DEL group. At week 8 the PDQUALIF and PDQ-39 total score was significantly lower in the IS group.
Tolosa et al. – DERBI Study Group [43]	Prospective, multicenter, parallel-group, double-blind, randomized study	95 PD patients (M/F)	To compare the efficacy and safety of LD/CD/ENT versus LD/CD in early PD patients experiencing mild or only minimally disabling wearing-off	Group I: IR LD/CD (100 mg) or LD/CD/ENT; Group II: IR (higher dose) LD/CD or LD/CD/ENT	3 months	Primary: comparing the efficacy of two treatment regime (UPDRS – part II); Secondary: change in the UPDRS (I, III, IV), QUICK and PDQ-39, CGI scores	LD/CD: 10/49 dropout rate (unsatisfactory therapeutic effect, etc.); LD/CD/ENT: 11/46 dropout rate	Treatment with LD/CD/ENT resulted in significant improvement in the UPDRS scale part II. An improvement in the score of UPDRS scale part III and CGI was also observed.
Kuoppamäki et al. [14]	Pooled analysis of three randomized, double-blind, phase III studies	551 PD Patients (M/F)	To compare the treatment effects of ENT in PD patient receiving LD/CD or LD/B	Group I: LD/CD +ENT; Group: LD/B + ENT	6 months	Primary: difference between LD/CD and LD/B groups	4% of the patients discontinued the study in the LD/B group and 1.8% in the LD/CD group	At 6 months ENT improved the mean daily “OFF”- and “ON”- time in both groups. In the part II (just in the LD/B group) and III (in both groups) of UPDRS scale there was a statistically significant improvement. No statistically significant difference was found in the treatment’s effect between the groups.

(Continued)

Table 1. (Continued).

Study [Reference]	Trial type	Participants	Purpose of study	Intervention	Duration	Efficacy outcome	Dropout rate – reason	Main findings
Park et al. [15]	Randomized, multicenter, double-arm, open-label study	107 PD patients (M/F)	To determine the efficacy, safety and tolerability of maintaining or reducing the LD dose when switching to an containing combination	Group I: maintaining the LD dose until ENT addition; Group II: the LD dose was reduced by 15–25% (the applied LD/CD/ENT doses were the followings: 50/12.5/200 mg, 75/25/200 mg, 100/25/200 mg, 125/25/200 mg, 150/37.5/200 mg and 200/37.5/200 mg)	8 weeks	Primary: change in the PGI-C score at the final visit; Secondary: changes in the scales between baseline and final visits	13/107 patients discontinued the trial (Group I: 5; Group II: 8)	The patient's global impression of a change scores was significantly better in Group I. There was no statistically significant change in the UPDRS, duration of "OFF", "ON" and dyskinesia between the groups.

(frequency – $p = 0.007$) and subject clinical global assessment ($p = 0.02$) [30]. The most affected domains of the PDQ-39 scale were mobility ($p = 0.001$) and ADL (< 0.001) [30]. The conversion from SR LD/CD to LD/CD/ENT resulted in a significant improvement in QoL measures after 1 month [27]. The UPDRS (motor score, total score) and the 'mobility', 'ADL', 'emotional', 'cognition' and 'bodily discomfort' domains of PDQ-39 scale improved significantly [27]. These patients also had better scores on the Epworth Sleepiness Scale (ESS) [27]. In the 12 weeks study [31] (184 patients, no or minimal, nondisabling motor fluctuation), the effect of LD/DDCI compared to LD/CD/ENT on the quality of life was investigated. The applied PDQ-8 scale significantly improved in the LD/CD/ENT group ($p = 0.021$) [31]. The most affected parts of the PDQ-8 scale were 'depression' ($p = 0.025$), 'close personal relationship' ($p = 0.037$), 'communication' ($p = 0.007$) and 'social stigma' ($p = 0.033$) [31]. In another comparative study [32], over 70% of the patients in both groups (LD/CD + ENT and LD/CD/ENT) felt that their clinical condition was better after the switch from the previously applied medication (LD/DDCI). Over 80% of patients experienced a reduction of fluctuations (87% – combination; 81% – separate ENT) [32]. In the SELECT-TC study [33], the effect of switching from IR LD/DDCI to LD/CD/ENT on QoL was estimated in a 4 week study of patients with wearing-off. The total score of the PDQ-39 scale improved significantly ($p = < 0.001$). Most of the patients reported a slight improvement on the p-CGI scale (34.9%) [33]. Consistently with these results in a similar study [29], the activities of daily living improved by 25.1% as well. The effect of the switch from different DDCI inhibitors (LD/CD or LD/B) to LD/CD/ENT was tested as well [34]. It was found that after switching 77% of patients reported 'improvement' (p-CGI: LD/CD to LD/CD/ENT: $p = 0.008$; LD/B to LD/CD/ENT: $p = < 0.0001$). There was a significant improvement in the i-CGI-C, UPDRS and QoL-VAS scales as well [34]. Furthermore, it seems that an immediate switch (IS) from LD/CD to LD/CD/ENT, compared to a delayed switch, has more advantages in terms of QoL [35]. At week 8, the PDQUALIF ($p = 0.0133$) and PDQ-39 ($p = 0.0136$) total scores were significantly lower in the IS group [35].

In the SIMCOM study [28], the effect of the switch from separately administered LD/CD + ENT to LD/CD/ENT (single tablet) was tested. 69% of the patients preferred (54%, N.S.) LD/CD/ENT or considered it equivalent (15%) to previously applied treatments (N.S.). Eighty-five percent of the patients in the LD/CD/ENT group found the clinical condition equal or better (evaluated by investigator, 75% if the patients evaluated themselves). The patients rated LD/CD/ENT easier to handle (84%), remember (67%) and swallow (59%) [28]. The treated group found it convenient to use LD/CD/ENT and found the dosage simpler (94%) [28]. In a previously mentioned comparative study (TC-INIT) [32] the QoL was significantly better as well in the LD/CD/ENT group (CGI-C scale: 'very much improved' – LD/CD + ENT (4%) versus LD/CD/ENT (12%) compared to LD/CD + ENT group [32]. Furthermore, an important large retrospective study [36] was performed which tested the therapeutic adherence between the separate (LD/CD + ENT) and single tablet

Table 2. Brief summary of the identified studies (Abbreviations: CGI – Clinical global impression scale; CR LD – Controlled-release levodopa; CR LD/CD – Controlled-release levodopa/carbidopa; ENT – Entacapone; IR LD/CD – Immediate-release levodopa/carbidopa; IR LD/DDCI – Immediate-release levodopa/dopa decarboxylase inhibitor; LD – Levodopa; LD/CD + ENT – Levodopa/carbidopa; LD/CD + ENT – Levodopa/carbidopa + entacapone (separately); LD/CD/ENT – Levodopa/carbidopa/entacapone (single pill); PDQ-39 – The 39-item Parkinson's disease questionnaire; QoL – Quality of life; RR LD/CD – Retarded-release levodopa/carbidopa; SR LD/CD – Sustained-release levodopa/carbidopa; UPDRS – Unified Parkinson's disease rating scale; VAS – Visual analogue scale).

Main comparisons (size of the tablets/lowest dose/)	Conclusions	References
Standard LD/CD versus Standard LD/CD + ENT (7.14 mm x 12.7 mm versus 7.14 mm x 12.7 mm + 17 mm x 8 mm)	ENT addition significantly improves the QoL measures, but does not improve the UPDRS score in PD patients without motor fluctuations. ENT addition to LD/CD prolonged the 'ON' time duration and reduced the severity, but not the duration of dyskinesias.	[30,41]
Standard LD/CD versus LD/CD/ENT (7.14 mm x 12.7 mm versus 6.85 mm x 14.2 mm)	The change from LD/DDCI to LD/CD/ENT resulted in a significant motor improvement in early PD and in patients with wearing off (UPDRS). The QoL measures (PDQ-39, CGI, QoL VAS) were improved in the LD/CD/ENT group after switching. However, patients receiving LD/CD/ENT had a shorter time to onset and increased frequency of dyskinesias.	[20,23,25,26,29,31,33,34]
Standard LD/CD + ENT versus LD/CD/ENT (7.14 mm x 12.7 mm + 17 mm x 8 mm versus 6.85 mm x 14.2 mm)	The UPDRS score reduced significantly after drug switch. The patients rated LD/CD/ENT easier to handle, remember and swallow. The treated group found it convenient to use LD/CD/ENT and found the dosage simpler. The therapeutic adherence and the QoL measures were better in the single tablet groups.	[28,32,36]
CR LD/CD versus CR LD/CD + ENT (7.52 mm x 12.70 mm versus 7.52 mm x 12.70 mm + 17 mm x 8 mm)	ENT addition to CR LD/CD improves the 'ON' time duration (by 37%), but does not increase the severity or duration of dyskinesias.	[18,24,41]
CR LD/CD versus LD/CD/ENT (7.52 mm x 12.70 mm versus 6.85 mm x 14.2 mm)	'OFF'-time was significantly lower in the LD/CD/ENT group. 'ON'-time 'with non-troublesome dyskinesia' was improved as well.	[13]
SR LD/CD versus LD/CD/ENT (7.52 mm x 12.70 mm versus 6.85 mm x 14.2 mm)	In Parkinson patients with minimal disabling motor complications or with suboptimally controlled symptoms, the LD/CD/ENT combination therapy has greater efficacy than the SR LD/CD treatment.	[27,43]
RR LD/CD versus LD/CD/ENT (7 mm x 13 mm versus 6.85 mm x 14.2 mm)	The switch from RR LD/CD to LD/CD/ENT resulted in an improvement in attention-related components and in muscle strength.	[22,42]

(LD/CD/ENT) forms. The use of LD/CD/ENT vs. LD/CD + ENT (separate tablets) resulted in better adherence (79% lower mean non-adherence; 86% lower odds of unsatisfactory adherence) [36]. As a conclusion, some studies suggest that the single tablet form results in a better QoL; however, no strong evidence is available so far.

4. Conclusions

The identified clinical trials provided data on the clinical and pharmacokinetic efficacy of ENT addition. Only a minority of the identified studies ([28,32,36]) compared the administration mode of ENT. The SIMCOM study proved that 69% of the patients preferred (54%, not significant) or considered equivalent (15%) the LD combination in a single tablet [28]. Additionally, they felt their own clinical condition (85%) was significantly improved [28]. As opposed to separate dosing, patients found it easier to swallow (59%), handle (84%) or remember (67%) [28]. In the TC-INIT study, it was demonstrated that the QoL measures were significantly better in the LD/CD/ENT group compared to the LD/CD + ENT group [32]. Furthermore, the only one involved cohort study (which included 8646 patients) found better patient adherence in the LD/CD/ENT combination group [36]. *In conclusion*, in PD patients where impaired motor performance justifies the addition of ENT to the previously applied treatment regimen, administration of the single tablet form is suggested.

5. Expert opinion

Although many factors (e.g. familial, financial, social) influence the adherence of a PD patient to the applied medication, the importance of non-motor symptoms should be emphasized. The prevalence of depression in Parkinson's disease is 30–40% [37] and furthermore, around 30–40% of patients fulfill the diagnostic criteria of cognitive impairment (cumulative prevalence: up to 78%) [38]. These two non-motor symptoms have been demonstrated to have a relation with drug non-adherence in Parkinson's disease, and therefore optimization and simplification (single pills) of dopaminergic therapy is very important to achieve the optimal therapeutic effects [39,40].

This systematic review summarizes the most important comparative studies regarding ENT administered separately and in combination. During these studies, the administered medicines were closely controlled (no medication error remained unexplained), the UPDRS score did not differ significantly between the LD/CD/ENT versus LD/CD + ENT (separately) groups [32]. Nonetheless, the majority of patients strongly preferred the combination products [28,32]. They felt it easier to handle, swallow, and to remember the appropriate dose [28]. The majority of the performed studies showed a reduction of daily levodopa dose, not only in PD patients who previously were not treated with ENT, but also after switching between separately administered ENT to a combination tablet [18,20–34,36,41–43].

From the pharmacokinetic perspective, there is a need for optimal timing of the oral administration of ENT to achieve the highest bioavailability of LD [16]. The possibility of incorrect administration (e.g. less frequent) of ENT is higher with

separate tablets [36]. Furthermore, the widely applied products, which have distinct drug-releasing profiles (e.g. extended-, controlled-release), could make the pharmacokinetics more complex with an additionally increased prevalence of suboptimal LD brain concentration and inappropriate motor symptom control [44]. These facts support the hypothesis that ENT administered in combination yields better bioavailability. ENT addition has a risk of worsening dyskinesia intensity. Dyskinesia was one of the most important factors behind the dropouts (Table 2). The majority of studies showed a discrete reduction in the 'OFF' time; however, we think that 'ON' time is more relevant in judging the efficacy of the ENT treatment.

Examining the cost-effectiveness of combination formulations can be a very important future aspect for the patient's and health insurance's budget. A significantly better quality of life, as documented by clinical studies, is capable of increasing the number of active years and reducing the need for hospital care.

In summary, combination treatments (in particular, ENT combinations in the current work) have been shown to be more effective in terms of quality of life compared to separately administered drugs. During the disease course, cognitive and other non-motor problems, along with motor symptoms, become the leading reasons for non-adherence to medication and not appropriate movement control [36]. The final conclusion of this systematic literature review is that switching to combination ENT treatment in PD patients with end-of-dose wearing-off phenomena is a good option to achieve better QoL. However, patients with motor complications should be reevaluated from time to time regarding instrumental therapies for advanced disease stages [45].

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Declaration of interest

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 - **An excellent consensus paper, which emphasizes the importance of early recognition of patients with advanced stage disease to improve the QoL by applying device-aided therapies.**