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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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

András Salamon, Dénes Zádor, László Szpisjak, Péter Klivényi and László Vécsei

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.

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-methylldopa (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...
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
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 less pronounced fluctuation of movements [23]. In the START-M trial – similarly to the TCINIT 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/DDC and the formulation-related effects (LD/DDC + 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>
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<tr>
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<tr>
<td>Piccini et al. [41]</td>
<td>Double-blind, placebo-controlled, single dose, randomized, cross-over trial</td>
<td>14 PD patients (M/F)</td>
<td>Testing the clinical change of ENT addition to standard LD and CR LD</td>
<td>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.</td>
<td>4 days</td>
<td>(nonconsecutive)</td>
<td>1 patient – diagnosis modification (MSA)</td>
<td></td>
</tr>
<tr>
<td>Stocchi et al. [24]</td>
<td>Single-blind, placebo-controlled, randomized, cross-over trial</td>
<td>12 PD patients (M/F)</td>
<td>To test the clinical and pharmacokinetic consequences of ENT addition to CR LD</td>
<td>200/50 mg CR LD/CD + 200 mg ENT or PLC</td>
<td>2 days</td>
<td>(nonconsecutive)</td>
<td>All patients completed the study</td>
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</table>

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.

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

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Table 1. (Continued).

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<th>Study [Reference]</th>
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<td>26 weeks</td>
<td>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</td>
<td>In the treatment group: 41 – adverse event, 2 – unsatisfactory therapeutic effect, 55 – discontinued study medication, 49 – other reason</td>
<td>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).</td>
<td>4 weeks</td>
<td>Primary: preference estimation; second: treatment success rate (investigator and patient global impression); UPDRS (&quot;ON&quot;); QoL assessment with VAS; mean daily LD dose and frequency of dosing</td>
<td>In the treatment group: 4 – premature discontinuation, 3 – adverse event, 1 – other reason</td>
<td>69% of the patients preferred (54%, N.S.) LD/CD/ENT or considered it as equivalent (15%) to previously applied treatment. 83% 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%).</td>
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<tr>
<td>Myllylä et al. – SIMCOM Study [28]</td>
<td>Open-label, single-group, cross-over, multinational study</td>
<td>52 PD patients (M/F)</td>
<td>To start LD/CD/ENT in patients, who were previously treated with IR LD/DDCI plus separately administered ENT</td>
<td>Group I: IR LD/DDCI (CD or B) + ENT; Group II: LD/CD/ENT</td>
<td>4 weeks</td>
<td>Primary: preference estimation; second: treatment success rate (investigator and patient global impression); UPDRS (&quot;ON&quot;); QoL assessment with VAS; mean daily LD dose and frequency of dosing</td>
<td>69% of the patients preferred (54%, N.S.) LD/CD/ENT or considered it as equivalent (15%) to previously applied treatment. 83% 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%).</td>
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<tr>
<td>Brooks et al. – TC-NIT Study Group [32]</td>
<td>Open, randomized, parallel-group, multinational study</td>
<td>176 PD patients (M/F)</td>
<td>To compare the safety, tolerability and efficacy after switching from IR LD/DDCI to LD/DDCI + ENT (separately) or to LD/CD/ENT</td>
<td>Group I: IR LD/DDCI (CD or B) + ENT; Group II: LD/CD/ENT</td>
<td>6 weeks</td>
<td>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</td>
<td>5% discontinuation rate (8/177) because of AE (most common AEs: nausea, diarrhea, dyskinesia)</td>
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The UPDRS score (II, 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.
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<tr>
<td>Koller et al. – SELECT-TC Study Group [33]</td>
<td>Open-label, multicenter, single-arm study</td>
<td>169 PD patients (M/F)</td>
<td>To compare the effect of switching from IR LD/DDCI to LD/CD/ENT</td>
<td>Group I: IR LD/DDCI (CD or B); Group II: LD/CD/ENT</td>
<td>4 weeks</td>
<td>UPDRS (II, III, III); “OFF”-time (UPDRS question 39); PDQ-39; change of total LD dose; investigator and patient global clinical assessment</td>
<td>12/169 – discontinuation – AE (nausea, “OFF” period worsening; etc.), 2 – other reason</td>
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<td>UPDRS II, III, II + III; Question 39 and PDQ-39 scores improved</td>
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<tr>
<td>Païja et al. [18]</td>
<td>Double-blind, randomized, cross-over study</td>
<td>16 males</td>
<td>To evaluate the effect of ENT (200 mg) on CR LD/CD</td>
<td>Group I: 100/25 mg CR LD/CD + 200 mg ENT (q.i.d.); Group II: 100/25 mg CR LD/CD + PLC (q.i.d.)</td>
<td>2 days</td>
<td>n.d.</td>
<td>1/16 – early discontinuation, because of the refusal to allow insertion of intravenous cannula</td>
<td>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%).</td>
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<tr>
<td>Lyons et al. [27]</td>
<td>Open-label study</td>
<td>62 PD patients (M/F)</td>
<td>To evaluate the effect of conversion from SR LD/CD to LD/CD/ENT in suboptimally treated patients</td>
<td>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 + ENT was converted to LD/CD/ENT. Group IV: SR LD/CD + PLC was converted to LD/CD/ENT</td>
<td>1 month</td>
<td>Primary: change in PDQ-39 score at 1 month compared to baseline</td>
<td>13/62 – adverse effect (nausea, vomiting, increased “OFF”-time, increased dyskinesia)</td>
<td>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.</td>
</tr>
<tr>
<td>Müller et al. [20]</td>
<td>Open-label study</td>
<td>22 PD patients (M/F)</td>
<td>To determine the clinical consequence of ENT addition. Estimate the plasma concentration of LD and 3-OMD.</td>
<td>Day 1: only LD/CD t.i.d.; Day 2: LD/CD/ENT t.i.d., equal dose</td>
<td>2 days</td>
<td>Any alteration in motor performance and/or in pharmacokinetic results</td>
<td>N.D.</td>
<td>On day 2, motor performance was significantly better. Higher LD maximum concentration and AUC were detected.</td>
</tr>
<tr>
<td>Boiko et al. – START-M trial [29]</td>
<td>Open-label, multicenter study</td>
<td>50 PD patients (M/F)</td>
<td>To evaluate the efficacy of and tolerance to LD/CD/ENT</td>
<td>The previous medication was switched to LD/CD/ENT (equivalent LD dose)</td>
<td>6 weeks</td>
<td>Any alteration in motor functions</td>
<td>N.D. (10% of the patients reported side effects)</td>
<td>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%.</td>
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<tr>
<td>Müller et al. [22]</td>
<td>Double-blind, randomized trial</td>
<td>13 PD patients (M/F)</td>
<td>To determine the clinical change from ENT addition to RR LD/CD. Estimate the plasma concentration of LD and 3-OMD.</td>
<td>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</td>
<td>2 days</td>
<td>Any alteration in motor performance and/or in pharmacokinetic results</td>
<td>N.D.</td>
<td>LD/CD/ENT was significantly better than LD/CD in the attention related components.</td>
</tr>
<tr>
<td>Müller et al. [23]</td>
<td>Open-label, standardized study</td>
<td>20 PD patients (M/F)</td>
<td>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.</td>
<td>Day 1: LD/CD (t.i.d., 50–150 mg); Day 2: LD/CD/ENT (identical dosage)</td>
<td>2 days</td>
<td>Any alteration in the UPDRS (part III)</td>
<td>N.D.</td>
<td>Motor scores and performance were significantly better after ENT addition.</td>
</tr>
<tr>
<td>Linazasoro et al. – Spanish Stalevo Study Group [12]</td>
<td>Multicentric, prospective, single-blind, randomized and clinically controlled study</td>
<td>39 PD patients (M/F)</td>
<td>To determine the best way to switch from LD/CD to LD/CD/ENT.</td>
<td>Group I: LD/CD with the same dose ± ENT (single tablet); Group II: 15–25% reduction of the LD/CD dose ± ENT (single tablet)</td>
<td>4 weeks</td>
<td>Difference between the basal and 4 week test results</td>
<td>1 patient discontinued the study, because the exacerbation of dyskinesia (Group 1); 2 patients found the effect unsatisfactory in Group 2.</td>
<td>Both groups showed increased &quot;ON&quot;-time and reduction of daily &quot;OFF&quot;-time. No difference was found during the clinical assessment (e.g. QoL test) between the groups.</td>
</tr>
<tr>
<td>Müller et al. [42]</td>
<td>Randomized, double-blind, cross-over clinical trial</td>
<td>12 PD patients (M/F)</td>
<td>To compare the effect on motor performance and grip strength of RR LD/CD compared to LD/CD/ENT.</td>
<td>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</td>
<td>2 days</td>
<td>Difference between the baseline and the outcome measures</td>
<td>N.D.</td>
<td>LD increased the muscle strength. In both groups there was similar antiparkinsonian efficacy.</td>
</tr>
<tr>
<td>LeWitt et al. [13]</td>
<td>Randomized, open-label, cross-over study</td>
<td>17 PD patients (M/F)</td>
<td>To compare the pharmacokinetics and clinical efficacy of CR LD/CD with LD/CD/ENT</td>
<td>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)</td>
<td>2 weeks</td>
<td>Change in the PD symptoms diary or in the UPDRS and global assessment scores</td>
<td>No subjects have discontinued the medication due to adverse events.</td>
<td>The LD AUC was nearly equivalent. In the LD/CD/ENT treatment regimen the hourly LD fluctuation index was higher. &quot;OFF&quot;-time was significantly lower and &quot;ON&quot;-time ‘with non-troublesome dyskinesia’ was more in the LD/CD/ENT group.</td>
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<tr>
<td>Hauser et al. – FIRST-STEP Study Group [25]</td>
<td>Randomized, double-blind, multicenter, parallel-group study</td>
<td>423 PD patients (M/F)</td>
<td>To compare the efficacy, safety and tolerability of LD/CD/ENT with LD/CD</td>
<td>Group I: LD/CD t.i.d.; Group II: LD/CD/ENT t.i.d.</td>
<td>39 weeks</td>
<td>Change in the UPDRS, CGL PDQ-39 scores</td>
<td>14.9% of patients discontinued the study in LD/CD/ENT group (AE, lost to follow-up, etc.)</td>
<td>Over 29 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.</td>
</tr>
<tr>
<td>Fung et al. – QUEST-AP Study Group [31]</td>
<td>Multicenter, randomized, parallel-group, double-blind study</td>
<td>184 PD patients (M/F)</td>
<td>To investigate the effect of LD/DDCI compared to LD/CD/ENT on quality of life in PD patients</td>
<td>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.</td>
<td>12 weeks</td>
<td>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.</td>
<td>N.D.</td>
<td>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).</td>
</tr>
<tr>
<td>Delea et al. [36]</td>
<td>Retrospective, observational cohort study</td>
<td>8646 patients (M/F)</td>
<td>To compare the treatment adherence of PD patients receiving LD/CD/ENT or two separate tablets (LD/CD + ENT)</td>
<td>Group I: LD/CD/ENT; Group: LD/CD + ENT</td>
<td>365 days</td>
<td>Primary: change in the treatment adherence</td>
<td>N.D.</td>
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<tr>
<td>Eggert et al. – SENSE Study Group [34]</td>
<td>Multinational, multicenter, open-label, single-arm study</td>
<td>115 PD patients (M/F)</td>
<td>To study the efficacy, safety and feasibility of switching from LD/CD or from LD/B to LD/CD/ENT</td>
<td>Three strengths of LD/CD/ENT were used according to the previous medication (LD: 50, 100, 150 mg)</td>
<td>6 weeks</td>
<td>Primary: change in the p-CGI-C; Secondary: change in the i-CGI-C and in the UPDRS score and QoL-VAS scales</td>
<td>7% of the patients discontinued the study (3% on LD/B, 13% on LD/CD)</td>
<td>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.</td>
</tr>
<tr>
<td>Stocchi et al. – STRIDE-PD Study [26]</td>
<td>Prospective, double-blind trial</td>
<td>747 PD patients (M/F)</td>
<td>To test the hypothesis that ENT addition reduces the risk of the development of motor complications</td>
<td>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.)</td>
<td>134 weeks</td>
<td>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</td>
<td>LD/CD group: 25.8% (96/372) (AE, unsatisfactory therapeutic effect, etc.); LD/CD/ENT group: 29% (108/373) (AE, unsatisfactory therapeutic effect, etc.)</td>
<td>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.</td>
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Table 1. (Continued).

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Trial type</th>
<th>Participants</th>
<th>Purpose of study</th>
<th>Intervention</th>
<th>Duration</th>
<th>Efficacy outcome</th>
<th>Dropout rate – reason</th>
<th>Main findings</th>
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<tr>
<td>NCT00391898</td>
<td>Double-blind, randomized, parallel, multicenter study</td>
<td>95 PD patients (M/F)</td>
<td>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</td>
<td>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)</td>
<td>3 months</td>
<td>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, QoL and Patient- and Investigator Global Evaluation of the Patient scales from baseline to month 3</td>
<td>LD/CD/ENT group – 10/49; LD/CD/ENT group – 11/46</td>
<td>In the LD/CD/ENT group there was a 25 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. QWOO-9 change (non-motor part): LD/CD/ENT: -0.9 vs. LD/CD: -0.2. QWOO-9 change (motor part): LD/CD/ENT: 1.2 vs. LD/CD: 0.0.</td>
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<tr>
<td>NCT0062356</td>
<td>Prospective, randomized, double-blind, double-dummy, active-controlled, multi-center comparison study</td>
<td>14 PD patients (M/F)</td>
<td>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</td>
<td>Group I: LD/CD/ENT (100/25/200 mg); Group II: IR LD/CD (100/25 mg)</td>
<td>8 weeks</td>
<td>Primary: change from baseline of QWOO-Q scale (non-motor section); Secondary: change from baseline of QWOO-Q scale (motor section)</td>
<td>IR LD/CD group: 3/7; LD/CD/ENT group: 2/7</td>
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<tr>
<td>Lew et al. – LCQoL Study Group [35]</td>
<td>Prospective, randomized, multi-center, open-label study</td>
<td>359 PD patients (M/F)</td>
<td>To compare the effect of immediate versus delayed switch from LD/CD to LD/CD/ENT on motor function and QoL</td>
<td>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</td>
<td>16 weeks</td>
<td>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</td>
<td>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.)</td>
<td>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.</td>
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<tr>
<td>Tolosa et al. – DERBI Study Group [43]</td>
<td>Prospective, multicenter, parallel-platform, double-blind, randomized study</td>
<td>95 PD patients (M/F)</td>
<td>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</td>
<td>Group I: IR LD/CD (100 mg) or LD/CD/ENT; Group II: IR (higher dose) LD/CD or LD/CD/ENT</td>
<td>3 months</td>
<td>Primary: comparing the efficacy of two treatment regime (UPDRS – part II); Secondary: change in the UPDRS (I, III, IV), QUICK and PDQ-39, CIGI scores</td>
<td>LD/CD: 10/49 dropout rate (unsatisfactory therapeutic effect, etc.); LD/CD/ENT: 11/46 dropout rate of the patients discontinued the study in the LD/CD group and 1.8% in the LD/CD group</td>
<td>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 CIGI was also observed. 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) UPDRS scale there was a statistically significant improvement. No statistically significant difference was found in the treatment’s effect between the groups.</td>
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<tr>
<td>Kuoppamäki et al. [14]</td>
<td>Pooled analysis of three randomized, double-blind, phase III studies</td>
<td>551 PD Patients (M/F)</td>
<td>To compare the treatment effects of ENT in PD patient receiving LD/CD or LD/B</td>
<td>Group I: LD/CD + ENT; Group: LD/B + ENT</td>
<td>6 months</td>
<td>Primary: difference between LD/CD and LD/B groups</td>
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The most affected domains of the PDQ-39 scale were mobility (p = 0.001) and ADL (< 0.001) [30]. The conversion from SR LD/DDC to LD/DDC/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/DDC compared to LD/DDC/ENT on the quality of life was investigated. The applied PDQ-8 scale significantly improved in the LD/DDC/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/DDC and LD/DDC/ENT) felt that their clinical condition was better after the switch from the previously applied medication (LD/DDC). 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/DDC to LD/DDC/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/DDC or LD/DDC/ENT) to LD/DDC/ENT was tested as well [34]. It was found that after switching 77% of patients reported ‘improvement’ (p-CGI: LD/DDC to LD/DDC/ENT: p = 0.008; LD/DDC/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/DDC to LD/DDC/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/DDC to LD/DDC/ENT (single tablet) was tested. 69% of the patients preferred (54%, N.S.) LD/DDC/ENT or considered it equivalent (15%) to previously applied treatments (N.S.). Eighty-five percent of the patients in the LD/DDC/ENT group found the clinical condition equal or better (evaluated by investigator, 75% if the patients evaluated themselves). The patients rated LD/DDC/ENT easier to handle (84%), remember (67%) and swallow (59%) [28]. The treated group found it convenient to use LD/DDC/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/DDC/ENT group (CGI-C scale: ‘very much improved’ – LD/DDC + ENT (4%) versus LD/DDC/ENT (12%) compared to LD/DDC + ENT group [32]. Furthermore, an important large retrospective study [36] was performed which tested the therapeutic adherence between the separate (LD/DDC + ENT) and single tablet

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<th>Main comparisons (size of the tablets/lowest dose)</th>
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<tr>
<td>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)</td>
<td>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.</td>
<td>[30,41]</td>
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<tr>
<td>Standard LD/CD versus LD/CD/ENT (7.14 mm x 12.7 mm versus 6.85 mm x 14.2 mm)</td>
<td>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.</td>
<td>[20,23,25,26,29,31,33,34]</td>
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<tr>
<td>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)</td>
<td>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.</td>
<td>[28,32,36]</td>
</tr>
<tr>
<td>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)</td>
<td>ENT addition to CR LD/CD improves the ‘ON’ time duration (by 37%), but does not increase the severity or duration of dyskinesias.</td>
<td>[18,24,41]</td>
</tr>
<tr>
<td>CR LD/CD versus LD/CD/ENT (7.52 mm x 12.70 mm versus 6.85 mm x 14.2 mm)</td>
<td>‘OFF’-time was significantly lower in the LD/CD/ENT group. ‘ON’-time with non-troublesome dyskinesia’ was improved as well.</td>
<td>[13]</td>
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<tr>
<td>SR LD/CD versus LD/CD/ENT (7.52 mm x 12.70 mm versus 6.85 mm x 14.2 mm)</td>
<td>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.</td>
<td>[27,43]</td>
</tr>
<tr>
<td>RR LD/CD versus LD/CD/ENT (7 mm x 13 mm versus 6.85 mm x 14.2 mm)</td>
<td>The switch from RR LD/CD to LD/CD/ENT resulted in an improvement in attention-related components and in muscle strength.</td>
<td>[22,42]</td>
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(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].

Funding

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

• An excellent summary of important aspects of Parkinson's disease (symptoms, pathology, epidemiology, genetics, treatment)


• Neuropathology of Parkinson's disease. The author focuses on the most important neuropathological features of PD based upon personal experience as well. The article also includes cell biological and animal experimental data.


• Algorithm for the treatment of Parkinson’s disease. The authors propose an alternative for optimal treatment of Parkinsonian patients.


• An excellent summary paper detailing the non-motor symptoms of Parkinson's disease.


• A manuscript detailing the rules for writing a PRISMA review


• From a clinical perspective, the aim of this important study was to determine the best way to switch from LD/CD to LD/CD/ENT. The reduction of the LD dose after switching did not result in the deterioration of motor performance.


• A great study, which tries to determine the efficacy, safety and tolerability of the maintenance or reduction of the LD dose during a switch to an ENT containing combination.


• An excellent paper about the different pharmacokinetic profiles of LD after LD/CD and LD/B administration in healthy subjects.


• The purpose of this study was to evaluate the effect of ENT (200 mg) in addition to standard LD/CD. They found that ENT increased AUC and decreased 3-OMD formation compared to PLC.


• To evaluate the effect of ENT (200 mg) in addition to CR LD/CD. AUC increased, the 3-OMD level and daily LD plasma level decreased after ENT administration.


• The purpose of this study was to compare plasma LD concentrations after repeated LD/CD and LD/CD/ENT doses.


• Clinical and pharmacokinetic change assessment after ENT addition to RR LD/CD. In the LD/CD/ENT group members performed significantly better in the attention-related tasks.


• A well-written paper, which concluded that over 39 weeks, in early PD patients, the LD/CD/ENT combination could result in a greater clinical improvement, without the augmentation of motor complication development.


• This trial tested the hypothesis that ENT addition could reduce the risk of developing motor complications. Contrarily, they found that the LD/CD/ENT combination resulted in a shorter time to the onset of dyskinesia and increased the frequency.

• Conversion from SR LD/CD to LD/CD/ENT. For the majority of patients, quality of life and motor performance improved after shifting.


• The purpose of this study was to start LD/CD/ENT in patients who were previously treated with IR LD/DDCI plus separately administered ENT. 69% of the patients preferred (54%, N.S.) LD/CD/ENT or considered it as equivalent (15%) to previously applied treatment (N.S.).


• The clinical effect of ENT addition to LD in PD patients without motor complications was tested. They found that ENT addition significantly improved the QoL measures, however, the UPDRS score remained relatively unchanged.


• Comparison of LD/DDCI with LD/CD/ENT on quality of life in PD patients. There was a significant improvement in the PDQ-8 sum score and in a non-motor domain in the LD/CD/ENT group.


• Switching from IR LD/DDCI to LD/DDCI + ENT (separately) to LD/CD/ENT. There was no significant difference between the groups in the motor performance. However, the majority of patients preferred the LD/CD/ENT single tablet form.


• Retrospective, observational cohort study which collected data on the adherence of PD patients receiving LD/CD/DDCI or two separate tablets (LD/CD + ENT). The single tablet form led to better therapeutic adherence.


• A great article which focuses on the important aspects of dementia related to Parkinson’s disease.


• The purpose of this study was to test the clinical consequence of ENT addition to standard LD versus CR LD. UPDRS improvement was higher in the CR LD/CD + ENT group compared to CR LD/DDC + PLC group.


• LD/CD/ENT versus LD/CD in early PD patients experiencing mild or only minimally disabling wearing-off. Treatment with LD/CD/ENT resulted in significant improvement in the UPDRS scale part II.


• 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.