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Treatment of End-of-Dose Wearing-Off in Parkinson's Disease: Stalevo® (Levodopa/Carbidopa/Entacapone) and Levodopa/DDCI Given in Combination with Comtess®/Comtan® (Entacapone) Provide Equivalent Improvements in Symptom Control Superior to That of Traditional Levodopa/DDCI Treatment

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Key Words
Parkinson's disease · Stalevo® · Levodopa · Dopa-decarboxylase inhibitor · Catechol-O-methyltransferase inhibition · Wearing-off

Abstract
The aim of this study was to evaluate the efficacy of the new optimised levodopa, Stalevo® (levodopa, carbidopa and entacapone) in patients with Parkinson's disease experiencing end-of-dose wearing-off. Treatment with Stalevo was compared to treatment with traditional immediate-release levodopa and dopa-decarboxylase inhibitor (DDCI) formulations along with adjunct entacapone (Comtess®/Comtan®). A European, open, parallel-group, active treatment-controlled phase IIIb study evaluating 176 patients randomised to switch from their current regimen of levodopa/DDCI to either an equivalent dose of Stalevo or levodopa/DDCI plus entacapone. After 6 weeks, treatments were assessed using the Clinical Global Impression of Change, the Unified Parkinson's Disease Rating Scale and a Motor Fluctuations Questionnaire. Over 70% of patients in both the Stalevo and adjunct entacapone arms felt that they were clinically improved and over 80% experienced a reduction in fluctuations. Although there was no significant difference between Stalevo and levodopa/DDCI plus entacapone with regard to motor improvement and side effects, 81% of patients stated that they preferred treatment with Stalevo compared with taking two separate tablets (i.e. levodopa/DDCI and entacapone). Stalevo was well tolerated and safe when substituted for levodopa DDCI preparations.

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Principle Investigators and Study Coordinators of theTC-INIT Study Group are listed in the appendix.

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Introduction

Levodopa remains the most effective therapy for the treatment of Parkinson's disease (PD) [1]. Due to its superiority over other therapies, virtually all PD patients will be treated with levodopa at some point during the progression of their disease [2].

Long-term levodopa therapy is associated with the development of motor complications, the first of which to occur is the 'wearing-off' effect which can emerge within 1 to 3 years of initiating treatment [3]. Wearing-off, characterised by the re-emergence or worsening of parkinsonian symptoms before the next scheduled dose of levodopa takes effect [4] may be accompanied by peak dose or biphasic dyskinesias, which have been shown to affect up to 45% of PD patients within 5 years of initiating traditional levodopa therapy [4, 5]. When treating wearing-off an important goal is therefore to prolong the duration of the symptomatic efficacy of each dose without increasing the peak plasma concentrations above the threshold for inducing dyskinesias.

A number of levodopa modification strategies have been considered in order to optimize its administration. These have included increasing the levodopa frequency and dose and changing the formulation of levodopa, for example, to controlled release (CR). These methods can reduce fluctuations for some patients, but often lead to intermittent re-emergence of symptoms due to the pulsatile nature of the levodopa delivery. Continually increasing the size of individual levodopa doses usually leads to increased severity of dyskinesias. CR levodopa preparations often have unpredictable bioavailability and trials have shown conflicting results; some reporting a significant clinical benefit over standard preparations, others reporting erratic absorption and no additional therapeutic benefit [6–8].

Although the mechanism(s) underlying wearing-off are not fully understood, one of the major contributors is caused by the limited pharmacokinetic profile of levodopa/dopa-decarboxylase inhibitor (DDCI) preparations, specifically its short elimination half-life (1–1.5 h). A recent strategy to overcome this limitation is to shift levodopa pharmacokinetics by inhibiting the second major pathway involved in peripheral levodopa metabolism. This has been achieved by combining levodopa with a peripherally-acting catechol-O-methyltransferase inhibitor such as entacapone [9–12].

Entacapone has a similar pharmacokinetic profile to levodopa and can, therefore, be co-administered with each levodopa dose. This method of administration increases the plasma half-life of levodopa (with DDCI) by 85% and the plasma levodopa area under the curve by 35–40% [10, 11]. The efficacy, safety and tolerability of entacapone (in combination with traditional levodopa/DDCI) has been proven in several phase III clinical trials [13–18]. These trials have shown that entacapone extends the 'on' time up to 1.7 h a day, reduces 'off' time (by 1.1–1.6 h a day) and significantly improves motor function and activities of daily living [13–17].

Stalevo® contains the traditional regimen of levodopa and carbidopa in combination with entacapone in one formulation. Here, we report on data obtained during the first randomised, parallel-group, multinational European clinical trial investigating the use of Stalevo for the treatment of PD. Specifically, we evaluate and compare the efficacy and safety of administering entacapone with levodopa/carbidopa in the form of Stalevo or as separate adjunct entacapone tablets co-administered with the traditional immediate release levodopa/DDCI treatment in PD patients experiencing end-of-dose wearing-off.

Materials and Methods

Male and female patients with a mean age of 65.6 ± 8.3 years (± SD), and a previous diagnosis of idiopathic PD (6.2 ± 3.7 years) were included in the study. Patients were required to have been experiencing end-of-dose wearing-off for at least 1 year prior to study entry and to have answered at least one 'yes' in the 7-point Motor Fluctuation Questionnaire (see below). All patients were required to have Hoehn and Yahr staging one to three. Prior to randomisation, the majority of patients (71.0%) had received additional antiparkinsonian medications such as dopamine agonists and selegiline (selegiline was allowed if its daily dose did not exceed 10 mg). Eligible patients had been treated with three to six daily doses of standard-release levodopa/DDCI for a mean of 5.5 ± 3.6 years and were receiving a stable, unchanged dose of immediate-release levodopa/DDCI and other antiparkinsonian medication for at least 6 weeks prior to study entry. One daily dose of CR levodopa/DDCI was allowed. Patient characteristics were comparable at baseline (table 1).

One hundred and seventy-seven patients were entered into the intent-to-treat population; 83 and 94 of these patients were randomised to Stalevo and levodopa/DDCI+entacapone (L+E) treatment, respectively. Seven percent (12/177) of patients discontinued the study following randomisation; 8 patients discontinued due to adverse events (AEs), 2 patients due to violation of the protocol, 1 patient due to withdrawal of consent and 1 due to loss of follow-up. A total of 77/83 (93%) and 88/94 (94%) patients successfully completed treatment with Stalevo and L+E, respectively. However, 1 patient treated with Stalevo had no post-baseline efficacy data and was subsequently excluded from the ITT population. All patients gave their informed consent using the informed consent form before recruitment.

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Table 1. Characteristics of patients with PD

	L+E group (n = 94)	Stalevo group (n = 82)
Male/female, %	54/46	60/40
Age, years	64.9 ± 8.1	66.4 ± 8.6
Age at onset of PD, years	59.2 ± 8.3	60.1 ± 9.6
Duration of PD, years	5.9 ± 3.4	6.5 ± 4.0
Duration of levodopa treatment, years	4.9 ± 2.9	6.0 ± 4.2
Duration of wearing-off symptoms	1.0 ± 1.1	1.2 ± 1.5
Daily levodopa dose, mg	472 ± 199	493 ± 218
Number of daily levodopa doses	4.1 ± 0.9	4.2 ± 1.1
Carbidopa/benserazide/both, %	46/48/6	36/55/9

Characteristics of the ITT population were assessed following randomisation and were comparable between treatment groups at baseline (n = 176).

Values are expressed as mean ± SD, unless otherwise stated.

This was a multicentre, multinational (36 centres within the UK, France, Germany, Sweden, Denmark and Ireland), open, parallel-group, randomised and active treatment-controlled phase IIIb study performed in compliance with the principles of the Declaration of Helsinki of the World Medical Assembly and Good Clinical Practice (ICH/135/95). The study protocol and any relevant amendments were reviewed and approved by the local Ethics Committees.

The study comprised a 2-week run-in period, a 6-week treatment period and a 2-week follow-up period (a total of 10 weeks). A baseline visit took place following the 2-week run-in period with study visits at weeks 1, 2, 4 and 6. One telephone contact was conducted on day 3. At the end of the treatment period (week 6), a 2-week follow-up period was carried out (week 8). This paper includes mainly the data obtained at week 6 of the study.

Patients received either entacapone (Comtess®/Comtan® 200 mg) taken separately with each dose of their levodopa/DDCI (L+E group), or Stalevo tablets containing a corresponding amount of levodopa, as used during the 2-week run-in period, for 6 weeks. Stalevo was administered in tablet form in formulations of 50/12.5/200 mg, 100/25/200 mg or 150/37.5/200 mg with respect to levodopa/DDCI/entacapone.

The daily dose of levodopa could be altered to prevent dopaminergic side effects, or to increase efficacy, at any time up to and including week 4 of the study. Up to three levodopa boosters per week were allowed on the condition that entacapone was not co-administered.

The primary efficacy variable was defined as treatment success rate assessed by the patient, at week 6 of the study, evaluated by the 7-point Clinical Global Impression of Change (CGI-C). The results from the CGI-C were transformed into binary responses yielding the outcome 'improvement' (if the CGI-C was 'improved', 'much improved' or 'very much improved') or 'no improvement' (if the CGI-C was 'no difference', 'a little worse', 'much worse' or 'very much worse'). Success rates (classed as 'improvement') were compared between both treatment groups.

Treatment success rate was assessed by the investigator (CGI-C), a Motor Fluctuation Questionnaire (patients answered 'yes' if motor symptoms re-appeared before the next dose of levodopa; symptoms included: tremor in the hand, slowing of hand movement, smaller handwriting, slowed or increased effort at arising from sitting position, smaller steps/increased slowness in walking, decreased volume or clarity of the voice and increased generalised stiffness of the muscles), change in the Unified Parkinson's Disease Rating Scale (UPDRS part III) when the patient was 'on', the total levodopa dose and dose frequency at week 6 of treatment compared with baseline.

Two health economic assessments were included in the study. At week 6, treatment preference for Stalevo compared to levodopa/DDCI with adjunct entacapone was assessed using a specially designed, self-administered health economic questionnaire. In addition, at study completion, patients who had been randomised to Stalevo for the 6-week study treatment period, and then changed to the separate levodopa/DDCI and entacapone tablets for a further 2-week follow-up period, rated their quality of life (QOL) on both treatments with a Visual Analogue Scale (VAS). On the 100-mm VAS scale, score 0 (zero) indicated 'worst imaginable QOL', whereas the score 100 indicated 'best imaginable QOL'. All centres, except those in Germany, participated in the follow-up health economic study.

AEs were evaluated by patients and investigators and classified according to the System Organ Classes and Preferred Terms using the WHO coding system.

Statistical Analysis

To achieve statistical significance compared with baseline, with a 95% confidence interval, ≥100 patients were required in each treatment group. An ITT and a per protocol population were used for efficacy assessment. The ITT population consisted of all patients taking part in the randomised trial who had post-baseline characteristics data analysed.

Analysis of efficacy variables for treatment success (CGI-C), UPDRS and daily levodopa dose, included an investigation into the effect of both the study centre and country.

Results

At week 6, patients in both treatment groups were in better clinical condition compared with baseline, according to both the patient and investigator, as evaluated using the CGI-C (fig. 1). Specifically, 73% (60/82) of the patients treated with Stalevo and 76% (71/94) of the patients in the L+E group indicated they were in better clinical condition; 79% of patients in both the Stalevo-treated group (65/82) and L+E groups (74/94) were in better clinical condition according to the investigator especially with respect to end-of-dose wearing-off. The improvement in CGI-C was independent of the DDCI used, either carbidopa or benserazide.

All patients experienced motor fluctuations at baseline. Items assessed were hand tremor, slowing of hand

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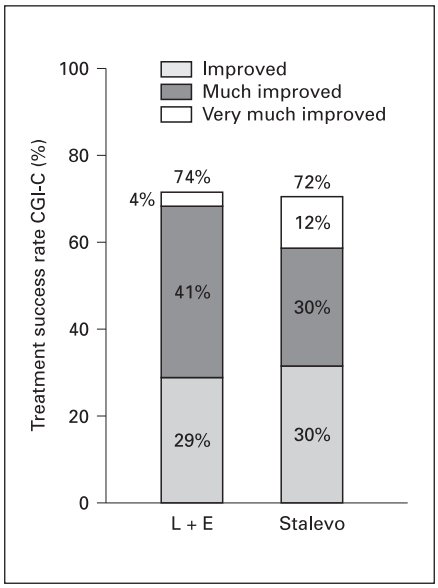

Fig. 1. Equivalent treatment success rate (assessed by clinical condition) between Stalevo and L+E groups. Percentages were calculated from the ITT population. Patients discontinuing the study (due to lack of efficacy or an AE related to study treatment) have missing values and were categorised as having 'no improvement'. Values missing due to reasons other than those described had improvement categorised according to the improvement observed following 2 weeks of treatment.

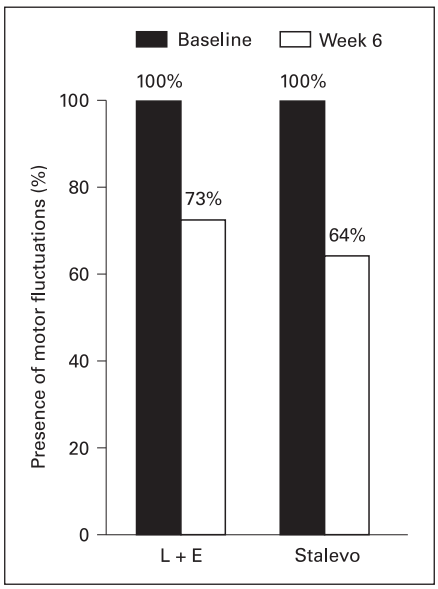

Fig. 2. Equivalent improvements in the control of motor fluctuations between Stalevo and L+E groups (n = 176).

Table 2. Adverse events

	L+E group (n = 94)	Stalevo group (n = 83)	Total population (n = 177)
Nausea	8 (9)	12 (14)	20 (11)
Diarrhoea	7 (7)	6 (7)	13 (7)
Dyskinesia	3 (3)	6 (7)	9 (5)
Urine abnormal	4 (4)	4 (5)	8 (5)
Dizziness	3 (3)	3 (4)	6 (3)
Influenza-like symptoms	0	6 (7)	6 (3)
Back pain	4 (4)	1 (1)	5 (3)
Insomnia	2 (2)	3 (4)	5 (3)
Discontinuation due to AEs	3 (3)	4 (5)	7 (4)

Figures in parentheses indicate percentages.

movement, micrographia, difficulty in rising from seated position, problems with walking, clarity of voice and stiffness of muscles. At week 6, motor fluctuations were reduced compared to baseline, falling from 100% of cases to 64% of Stalevo- and 73% of L+E-treated patients (fig. 2). Altogether, 87% of the Stalevo- and 81% of the L+E-treated patients reported 'improved' responses on a Motor Fluctuation Questionnaire.

The mean levodopa dose and the number of daily levodopa doses did not change significantly in either treatment group compared with baseline.

At week 6 UPDRS scores (part III) were significantly improved from baseline in both the Stalevo- and L+E-treated patients ($p < 001$ and $p = 0.0016$, respectively).

Of the patients who were asked to complete the health economic questionnaire, 93% (113/121, Germany excluded) responded. Of the respondents, 51 (45%) had been treated with Stalevo during the 6-week study treatment period, while 62 (55%) had been treated with L+E administered as separate tablets. A total of 81% (92/113) patients stated that they preferred treatment with Stalevo compared with taking two separate tablets (i.e. levodopa/DDCI and entacapone).

Patients rated their QOL as significantly better on Stalevo than on the separate levodopa/DDCI and entacapone tablets. The mean difference in VAS scores was 9.8 mm (SD $\pm$ 20.9) in favour of Stalevo ($p < 0.001$, paired t test, n = 64).

AEs were reported by 55% of the total population and resulted in 5% (8/177) of patients discontinuing treatment by the end of treatment at week 6 (table 2). The most common AEs (>3% incidence in the total population)

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were nausea, diarrhoea, dyskinesia, abnormal urine, dizziness, influenza-like symptoms, back pain and insomnia. Seventy-five percent of all AEs were classed as 'mild', 24% as 'moderate' with only 1% as 'severe' (including: panic attack-like symptoms, a broken left femoral neck, bilateral inguinal hernia, overdose, syncope and prostate hyperplasia). No deaths were recorded during treatment. There was no significant difference in AEs between treatment groups.

In summary, there was no significant difference between Stalevo and levodopa/DDCI plus entacapone with regard to motor improvement and side effects.

Discussion

Previous studies have focused on the use of traditional levodopa/DDCI with concomitant entacapone versus placebo. These studies have shown that completing levodopa therapy with adjunct entacapone consistently increases daily 'on' time (and correspondingly decreases 'off' time), and results in significantly increased motor function while 'on' [13–17]. This current investigation is the first to compare the efficacy of switching to Stalevo versus initiation of separate entacapone with traditional levodopa/DDCI in those patients experiencing end-of-dose wearing-off.

This study has shown that Stalevo provides equivalent benefits to those obtained with separately administered levodopa/DDCI and entacapone tablets, when outcome is rated with the Clinical Global Improvement Scale and a Motor Fluctuation Questionnaire. There were no significant differences in ADL or the severity of parkinsonian symptoms (assessed using the UPDRS part II) when switching from traditional levodopa to Stalevo or initiating separate entacapone. The reported favourable tolerability profile of Stalevo is in line with the findings of the recently published SELECT-TC open-label trial which evaluated the tolerability of switching from levodopa/carbidopa to treatment with Stalevo.

AEs were recorded throughout this study; dopaminergic AEs, including nausea, dyskinesia and dizziness are not uncommon in PD patients when dopaminergic therapy is increased. A majority (75%) of the reported AEs were classified as mild, and there was no significant difference between Stalevo-treated and L+E-treated groups.

As this was an open-label study, the comparison of efficacy and tolerability of Stalevo and adjunct entacapone must be viewed with caution. However, since patients in both treatment arms were aware they were receiving additional active medication, any placebo effects should be equivalent.

In line with previous open-label entacapone trials, 72–74% of patients were clinically improved with initiation of catechol-O-methyltransferase inhibition [19]. Moreover, although the magnitude of UPDRS (part III) changes were higher than that observed in previous double blind trials [13, 14, 16, 17], they were similar to those observed in previous open-label entacapone trials [19].

Patients in this trial confirmed the view that Stalevo is more convenient to take than separate adjunct entacapone. Further, the available dose combinations of Stalevo provide a regimen that can be titrated in respect to levodopa (in 50-mg steps), without the need to split tablets. Stalevo resulted in a better QOL for patients than adjunct entacapone, and most patients at the end of the trial indeed stated that they preferred treatment with Stalevo.

In conclusion, this study found that Stalevo is well tolerated by patients diagnosed with idiopathic PD experiencing wearing-off. Stalevo provides similar clinical improvements to those obtained with separate levodopa/DDCI and entacapone. Furthermore, when switching from traditional preparations, dosing adjustments were rarely needed.

Appendix

The principle investigators (and study co-ordinators) of the TC-INIT trial are as follows:

The principle co-ordinating investigator was Prof. Brooks.

The UK study group: Prof. Brooks (Dr. Burn, Dr. Gregory, Dr. Grosset, Dr. Steiger, Dr. Castleton, Dr. Spokes, Dr. Majeed, Dr. Murphy, Dr. Sweeny).

The German study group: Prof. Oertel (Dr. Arnold, Prof. Glass, Dr. Ulm (retired December 2002), Prof. Trenkwalder (from January 2003), Dr. Baas, Dr. Fornadi, Dr. Storch, Dr. Kupsch, Dr. Egry, Dr. Fischer, Dr. Simonow).

The French study group: Prof. Agid (Prof. Azulay, Dr. Viallet, Prof. Durif, Prof. Cesaro, Dr. Remy, Prof. Destee, Dr. Robin, Prof. Tison, Dr. Soisson).

The Swedish study group: Dr. Widner (Dr. Kaugesaar, Dr. Tedroff, Dr. Lindh).

The Danish study group: Dr. Østergaard (Dr. Werdelin, Dr. Magnussen).

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