Evidence for the Use of Levodopa–Carbidopa–Entacapone (STALEVO) to Improve Motor Fluctuations in Parkinson's Disease

a report by
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Levodopa is the logical treatment in Parkinson's disease (PD) as it replaces dopamine that is lost due to the neurodegenerative nature of the disease. It could be considered a natural agonist and remains the most effective dopaminergic replacement therapy. However, in many patients the efficacy of long-term conventional levodopa therapy is hampered by its association with the progressive development of motor fluctuations.[1] Initially, PD symptoms reoccur after prolonged levodopa intake due to progressive shortening of the drug effect duration (the so-called 'wearing-off' phenomenon), resulting in the reappearance of disabling PD symptoms, as well as dyskinesia. Motor fluctuations can become more difficult to manage with late (delayed-'on' phenomenon) or even the absence (no-'on' phenomenon) of beneficial effects of levodopa intake. Problematic motor fluctuations can also result from a rapid and sudden reoccurrence of PD symptoms during a successful 'on' that is induced by a single dose of levodopa ('on–off' phenomenon).

The classic consensus is that about 50% of patients develop motor fluctuations after five years of levodopa treatment.[2] However, recent studies have suggested that the frequency is even higher. In the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study, 20% of the patients developed motor fluctuations after six months of conventional levodopa treatment and 50% suffered from complications after 18 months.[3] Due to the disability caused by the reappearance of motor PD symptoms, motor fluctuations create a real burden for patients and have a negative impact on their quality of life;[4] accordingly, there is a real need for physicians to take on the challenge of correcting motor fluctuations for the benefit of their patients. Moreover, evidence also suggests that a non-optimised dopamine replacement strategy, reflected by the presence of motor fluctuations, could be responsible for a deleterious brain plasticity that, with time, could reinforce the fluctuations and contribute to the development of dyskinesia, another complication induced by conventional levodopa therapy.[5]

For decades, levodopa has been co-administered with a dopa decarboxylase inhibitor (DDCI) – carbidopa or benserazide – which prevents levodopa from being metabolised into dopamine before entering the brain. Peripheral dopamine does not cross the blood–brain barrier and, moreover, is responsible for side effects such as hypotension and nausea. More recently, the fixed combination levodopa–carbidopa–entacapone (STALEVO), a new formulation that combines levodopa, carbidopa and entacapone, an inhibitor of catechol-O-methyl transferase (COMT), has been approved for the treatment of adult patients with PD and end-of-dose motor fluctuations not stabilised on levodopa/DDCI treatment. The enzyme COMT catabolises peripheral levodopa to 3-O-methyldopa (3-OMD) (see *Figure 1A*); thus, the addition of entacapone to the formulation increases the availability of levodopa in the plasma (see *Figure 1B*).

Levodopa–Carbidopa–Entacapone Is an Effective and Well-tolerated Treatment to Reduce Motor Fluctuations

STALEVO has been shown to increase the bioavailability of levodopa by 35–40% in plasma and prolongs its elimination half-life from 1.3 to 2.4 hours. The addition of entacapone to each dose of levodopa–carbidopa given three to five times a day leads to a less pulsatile profile of plasma levodopa levels by avoiding deep troughs (see *Figure 1B*).[6] Four six-month prospective, randomised, double-blind, placebo-controlled phase III efficacy studies involving over 1,000 patients worldwide have demonstrated that adding entacapone to conventional levodopa/DDCI significantly improves motor fluctuations.[7–10] The severity of motor fluctuations was assessed through the home diaries of patients. Patients recorded 'on' and 'off' times and 'on' times with dyskinesia experienced every hour. The extent of therapeutic response was also determined by Unified Parkinson's Disease Rating Scale (UPDRS) scoring by an examiner. In NOMECOMT (the Nordic Multicenter Study on Entacapone, the Catechol-O-Methyltransferase Inhibitor Trial),[8] the addition of entacapone to levodopa–carbidopa significantly increased the mean daily 'on' time by 1.2 hours compared with placebo (see *Figure 2*). In CELOMEN, a six-month randomised, placebo-controlled, double-blind study conducted in Germany and Austria,[9] the addition of entacapone to each daily dose of standard or controlled-release levodopa significantly decreased the 'off' time by 1.6 hours compared with 0.9 hours in the placebo-treated group (see *Figure 3*).

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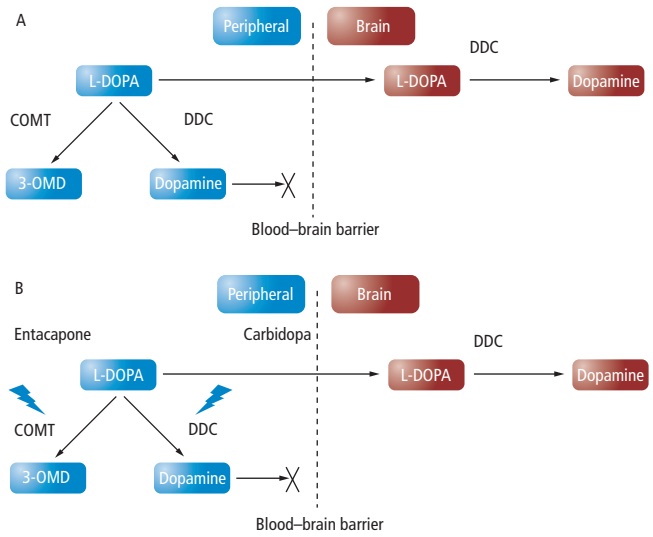
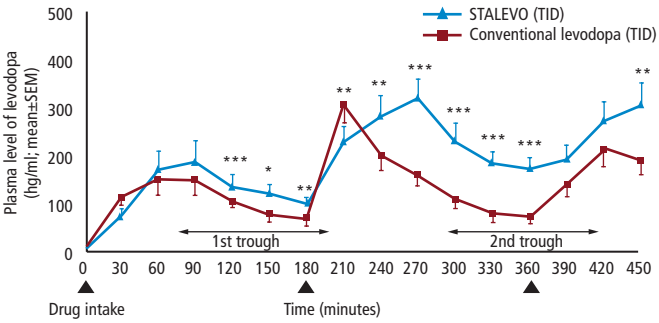
The reduction of motor fluctuations leads to significant improvements in patient function. In the NOMECOMT study, motor scores decreased (i.e. improved) in the patients treated with levodopa–DDCI and entacapone from 25.5 to 22.5 points. In comparison, conventional levodopa plus placebo resulted in a decrease from 24.6 to 23.8 points; the difference between the groups was statistically significant ($p<0.05$). In the CELOMEN study, activities of daily living (ADL) scores improved in fluctuating patients

Figure 1: Metabolism of Levodopa – Levodopa–Carbidopa–Entacapone Increases the Availability of Dopamine in the Brain



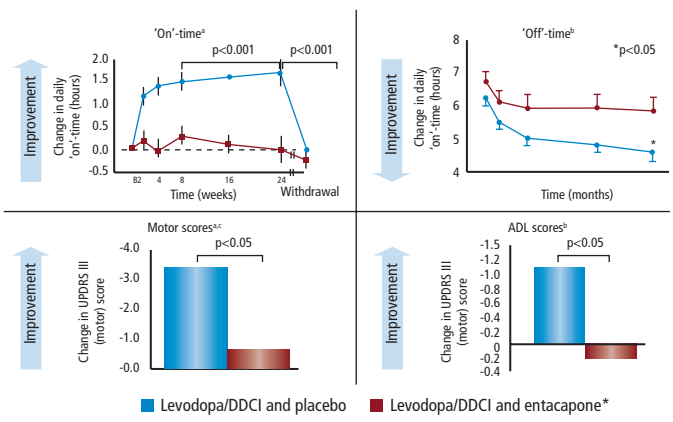
COMT = catechol-omethyl transferase; 3-OMD = 3-omethylevodopa; DDC = dopa decarboxylase; L-DOPA = levodopa.

Figure 2: Entacapone Leads to a Less Pulsatile Plasma Levodopa Profile by Avoiding Deep Troughs



Source: Muller et al., J Neural Transm, *2006;113(10):1441.*
**p<0.05; **p<0.01; ***p<0.001; TID = three times daily.*

Figure 3: Effect of Entacapone on Motor Fluctuations



Sources: a. Rinne et al., Neurology, *1998;51(5):1309; b. Poewe et al.,* Acta Neurol Scand, *2002;105:245; c. Stalevo US prescribing information.*
**Levodopa–carbidopa–entacapone is available as Stalevo®.*

treated with levodopa–DDCI and entacapone by -1.1 points and deteriorated with levodopa–DDCI plus placebo by 0.2 points; again, the difference between the groups was statistically significant (p<0.05).

Safety data demonstrate that concomitant entacapone with levodopa–DDCI is well tolerated. The majority of the safety data have been derived from analysis of the adverse events reported in: the four main phase III, double-blind, placebo-controlled efficacy studies;[7–10] NOMESAFE, a three-year open-label extension of the NOMECOMT study with up to five years of follow-up;[11] the long-term phase III safety study FILOMEN;[12,13] and post-marketing surveillance studies representing over one million patient-years of exposure.

Two categories of side effects can be determined: dopaminergic adverse events, which include dyskinesias, nausea and vomiting, and non-dopaminergic events, which include urine discolouration, diarrhoea, abdominal pain and constipation. A retrospective analysis of pooled data from the four comparative phase III studies[7–10] and the FILOMEN safety study[12,13] showed that approximately 30% of patients administered levodopa–DDCI and entacapone developed dyskinesias as an adverse event. However, the number of patients who dropped out of trials as a result of an increase in dyskinesias was only 1–2%. Approximately 10% of patients reported urine discolouration. Diarrhoea occurred in 10% of patients, but resulted in withdrawal of study medication in only 2.5–3% of cases (see *Table 1*).

In the NOMESAFE study,[11] all patients received open-label levodopa–DDCI and entacapone. Over three years, levodopa–DDCI and entacapone were found to maintain a good tolerability profile. The mean duration of benefit self-reported by patients from first morning dose with levodopa–DDCI and entacapone increased from a mean of 2.1 hours at baseline to 2.8 hours at three months and remained significantly above baseline at three years (p<0.001 in all cases). The NOMESAFE study also indicated no significant deterioration in UPDRS scores with levodopa–DDCI and entacapone, demonstrating preservation of patient function at three years compared with baseline. There were no significant changes in mean UPDRS I scores, while mean UPDRS II (ADL) and III (motor) scores improved significantly (p<0.05) from 10.5 to 9.8 during the first 12 months and from 28.4 at baseline to 26.9 at month three, respectively. By month 36, both UPDRS II and III scores were similar to baseline.

These data on the efficacy and safety of COMT inhibition in the treatment of patients experiencing re-emergence of symptoms due to wearing-off were given a level A status by the joint European Federation of Neurological Societies (EFNS), the Movement Disorder Society–European Section (MDS-ES) 2006 guidelines[14] and the quality standards subcommittee of the American Academy of Neurology (AAN).[15]

Current Therapeutic Options to Reduce Motor Fluctuations

Several therapeutic options can be considered in a patient treated with conventional levodopa and suffering from motor fluctuations. The first strategy is to increase the levodopa dose frequency. This choice has the advantage of not introducing a new drug, but renders the daily treatment more cumbersome because while drug intake at each meal is easy to organise, the added pill burden required to increase drug intake every three hours is more complicated. Another option is to use a sustained-release form of levodopa,[16,17] although such a strategy has a limited effect in reducing motor fluctuations.[18] From a practical point of view, the sustained-release form appears to be beneficial as a late-evening dose for improving night and early-morning akinesia.[19]

Adding a dopamine agonist or increasing the dosage of a dopamine agonist, if the patient is already being prescribed this option, is a possibility that has been shown to be effective in reducing motor fluctuations;[20–24] however, this strategy increases the risk of dopamine-agonist-related side effects. Such antiparkinsonian drugs could induce hallucination/delusion, especially in aged patients or in patients with cognitive decline.[25] This renders such an option difficult to consider in these patients. Dopamine agonists can also be responsible for increased daytime somnolence, accompanied in certain cases by narcolepsy.[26] Recently, dopamine agonists have been recognised as being associated with rare cases of complex behaviour disorders, such as the impulse control behaviour syndrome, with gambling, compulsive shopping and hypersexuality.[27] Such side effects, which can lead to major social repercussions, may affect up to 14% of patients treated by dopamine agonists. With the ergot-derived dopamine agonists, an increased risk of cardiac valvular fibrosis has also been reported.[28]

The use of a monoamine oxidase-B (MAO-B) inhibitor is another option that has been investigated as a treatment option for reducing motor fluctuations associated with conventional levodopa therapy. MAO-B is an enzyme that catabolises brain dopamine, consequently increasing and prolonging its action. Several controlled studies have confirmed the efficacy of MAO-B inhibitors to decrease the severity of motor fluctuations.[29–31] MAO-B inhibitors are usually well tolerated, but the amphetamine metabolite of the MAO-B inhibitor selegiline can lead to hallucination or delirium, especially in aged patients.[32]

The demonstrated efficacy in correcting motor fluctuations and the good tolerability of levodopa–carbidopa–entacapone makes its choice pertinent in the management of such complications. Levodopa–carbidopa–entacapone provides an option that does not require the addition of a drug with neurological effects, since the action of entacapone is exclusively at a peripheral level. Levodopa–carbidopa–entacapone optimises levodopa, the natural agonist, and reduces the number of drug administrations required (see *Table 2*).

Table 1: Levodopa–DDCI plus Entacapone Is Well Tolerated without Marked and Frequent Side Effects Compared with Treatment with Conventional Levodopa–DDCI Alone

	Patients (%)	
Adverse Events*	Levodopa–DDCI plus Entacapone (n=806)	Levodopa–DDCI plus Placebo (n=497)
Dyskinesia/hyperkinesia	30.4	17.5
Nausea	13.6	7.4
Parkinsonism aggravated	13.5	15.3
Urine discolouration	10.8	0.0
Diarrhoea	10.3	3.8
Dizziness	7.9	5.6
Abdominal pain	7.3	4.2
Constipation	7.2	4.2
Hypokinesia	6.9	6.2
Fatigue	6.1	3.6

Adapted from Parkinson Study Group, 1997;[7] Rinne et al., 1998;[8] Poewe et al., 2002;[9] Brooks, 2003;[10] Haapaniemi et al., 2001;[12] Myllyla et al., 2001.[13]
**Occurring in >6% of patients in the levodopa–DDCI plus entacapone arm.*

Table 2: Different Therapeutic Options for a Parkinsonian Patient Suffering from Motor Fluctuations

Option	Advantages	Disadvantages
Increase levodopa dose frequency	No risk of introducing a new drug; treatment with the natural agonist	Daily treatment more constrained
Sustained-release form of levodopa	Treatment with the natural agonist Potential for late-evening administration	Limited impact for reducing motor fluctuations
Dopamine agonists	Effective for decreasing motor fluctuations Good efficacy to decrease the severity of dyskinesia	Introduction of a non-natural agonist Risk of side effects
Monoamine oxidase-B inhibitors	Effective for decreasing motor fluctuations	Risk of side effects linked to the amphetamine (especially catabolite of selegiline)
Levodopa–carbidopa–entacapone combined form	Optimisation of the natural agonist Effective for decreasing motor fluctuations	Caution needed when used in patients with dyskinesia

Practical Management of STALEVO to Decrease Motor Fluctuations

Detecting Motor Fluctuations

Motor fluctuations reduce quality of life and may also be responsible for a harmful plasticity within the basal ganglia; thus, early detection of levodopa-related complications for early treatment is mandatory. The detection of motor fluctuations is usually achieved by interviewing the patient and/or the patient's care-giver. Specific questions may help enhance early detection of motor fluctuations; these include enquiries on changes in motor state (i.e. impairment of gait or of hand movement, occurrence of tremor) during the day; the patient's condition in the early morning before the first antiparkinsonian drug intake and one hour after drug intake; whether the motor state worsens before drug intake; and what happens when there is a delay in the drug intake.

Non-motor fluctuations can also occur in PD, and these complications may be more difficult to demonstrate;[33] however, non-motor fluctuations also lead to disability and reflect non-optimal functioning of the basal ganglia. Accordingly, the detection and correction of non-motor fluctuations is also an important clinical consideration. Three main categories of non-motor fluctuation can be differentiated: psychiatric, vegetative and sensory. Depressive mood or anxiety, palpitation, dyspnoea, sweating, numbness or miscellaneous pain can be reported in the hypodopaminergic state. All of these symptoms have the specificity of being non-permanent during the day, and when carefully analysed appear to fluctuate in relation to the level of efficacy of the antiparkinsonian treatment.

Analysing Motor Fluctuations

Once motor fluctuations have been detected in a patient, these complications require careful analysis before initiating treatment. Again, the main analytical tool is to interview the patient or care-giver. The goal for the practitioner is to attempt to establish the patient's 'typical day'. The analysis needs to focus particularly on the patient's condition the morning before the first dose of the antiparkinsonian drug, the time taken for the first dose to act and the duration of its effects, the time of the 'bad periods' (i.e. tremor, movement disability, gait impairment) and the quality of sleep. Furthermore, the analysis needs to take into consideration any co-existing dyskinesia. The use of a home diary offers an interesting tool for analysing motor fluctuations.[34] Patients are asked to indicate their condition hourly,

i.e. sleep, 'off', 'on' and 'on' with troublesome dyskinesia. A diary over three consecutive days provides a good period of observation to obtain pertinent information. In the most difficult cases, brief hospitalisation may help, and medical staff can fill in a similar hourly diary. A levodopa challenge is a useful complement (and is also particularly useful to analyse dyskinesia).[35] A levodopa challenge provides information on the severity of the morning 'off' period, the time of effect and the duration of levodopa (the dosage is the levodopa equivalent of the morning dosage of the first intake of antiparkinsonian drugs +50mg, given in liquid levodopa while the patient fasts and after overnight withdrawal of antiparkinsonian drug).

> Levodopa–carbidopa–entacapone is an effective and well-tolerated treatment option in Parkinson's disease patients suffering from motor fluctuations.

Treating Motor Fluctuations

If the patient is suffering from isolated fluctuations, such as the lack or the poor efficacy of a given intake of treatment, the correction will be restricted to that sole intake, i.e. increasing the drug dosage or changing the time of administration, for example a few minutes earlier or sometimes longer before a meal. The presence of regular motor fluctuations requires treatment optimisation, such as the introduction of levodopa–carbidopa–entacapone. Currently, the recommended method is a day-to-day switch from conventional levodopa to levodopa–carbidopa–entacapone. Each intake of conventional levodopa is changed to levodopa–carbidopa–entacapone with the corresponding dosage of levodopa. To reduce the risk of an increase of dopaminergic adverse effects, careful titration of the levodopa dose may be necessary in cases where increased exposure to levodopa is expected. Caution is mandatory in patients suffering from dyskinesia, as the switch may result in a worsening of the complication. When dyskinesia is severe, levodopa first needs to be reduced (even if this leads to a worsening of the motor fluctuation), before the switch to levodopa–carbidopa–entacapone is made.

Conclusion

Levodopa–carbidopa–entacapone is an effective and well-tolerated treatment option in PD patients suffering from motor fluctuations. Early detection of fluctuation is important for prompt treatment, which in turn will improve the quality of life of the patients. Moreover, addressing levodopa-related motor fluctuations early may also be beneficial for basal ganglia function, which, ultimately, will benefit the patient. ■

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