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Clinical experience with the novel levodopa formulation entacapone + levodopa + carbidopa (Stalevo®)

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Levodopa is the main pharmacologic treatment for Parkinson's disease. However, the long-term administration of levodopa is associated with the development of motor complications which can seriously compromise patient function. Increasing evidence indicates that such problems are related to abnormal pulsatile stimulation of striatal dopamine receptors and that treatments providing more continuous stimulation reduce the risk of motor complications. It is possible that administering levodopa with a reversible catechol-*O*-methyl transferase inhibitor at frequent intervals might reduce the risk of these complications. Stalevo® (Orion) combines levodopa, the dopa-decarboxylase inhibitor carbidopa and the catechol-*O*-methyl transferase inhibitor entacapone in a single tablet. This review provides an overview of the initial clinical experience gained with Stalevo during clinical trials, including several case studies.

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Since its introduction in the 1960s, levodopa (administered in combination with a dopa-decarboxylase inhibitor [DDCI]) has remained the single most efficacious therapeutic regimen for Parkinson's disease (PD) [1–3]. Although a number of novel therapies have been developed in an attempt to improve PD management, most patients still depend on levodopa due to its superior ability to control the spectrum of PD signs and symptoms [4]. All patients with idiopathic PD have a robust therapeutic response to carbidopa/levodopa. However, long-term therapy with traditional levodopa formulations is associated with the development of motor complications. All major advances to levodopa therapy over the past 40 years have been driven by the need to deliver a more consistent long-term therapeutic response to levodopa, without the development of treatment-associated complications. With this aim in mind the novel preparation of levodopa, the DDCI carbidopa and the selective, reversible catechol-*O*-methyl transferase (COMT) inhibitor entacapone – Stalevo® (Orion) – has recently been made available. It represents the latest advance in the development of levodopa therapies. From here on in it shall be called Stalevo. Stalevo is presented in one tablet and available in three commonly used levodopa doses (50, 100 and 150 mg). Combining levodopa with entacapone (Comtess®, Orion) has been shown to be an effective, powerful and well-tolerated strategy in the management of patients with PD experiencing wearing-off fluctuations [5–8]. Based on the extensive clinical experience with levodopa and entacapone, Stalevo has been recently approved in the USA and the European Union to treat patients with PD who are experiencing a wearing-off effect. Currently, clinical experience with Stalevo is limited, most clinical experience comes from recently conducted randomized clinical trials [9–11]. The aim of this article is to review the initial experience of Stalevo gained during these clinical trials, including specific case studies to aid discussions of the practical considerations when administering this important new drug. The theoretical advantages of extending the half-life of levodopa in the plasma and hence reducing possibly the pulsatile stimulation at the postsynaptic receptor site is also discussed.

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Development of levodopa

During the first years of its use, large amounts of levodopa were required to produce a good clinical response, as only 1% of levodopa in the plasma was able to reach the brain [12]. These larger doses were associated with the development of severe peripheral dopaminergic side effects such as nausea, vomiting and orthostatic hypotension. It was quickly realized that reducing the peripheral metabolism of levodopa with a DDCI such as carbidopa enabled more (~5%) levodopa to reach the brain and allowed a 70% reduction in the amount of levodopa needed, thus reducing the severity of peripheral side effects [12]. Consequently, the coadministration of a DDCI with levodopa was almost immediately adopted as routine practice and it is now standard procedure to combine levodopa with DDCI in one tablet. Hence, when levodopa is required in levodopa-naive patients, DDCI with levodopa is used as the initial drug. There are two commercially available DDCIs – carbidopa and benserazide – only carbidopa is approved for use in the USA. With the issue of peripheral side effects generally resolved, maintaining the therapeutic efficacy of levodopa over the course of the day has now become the greatest challenge in the treatment of PD.

A variety of strategies have been employed to improve the delivery of oral carbidopa/levodopa without the development of motor complications. The classic approach is to manipulate the levodopa regimen, either by increasing the size of the levodopa dose or by titrating the levodopa regimen to provide smaller, more frequent levodopa doses (fractionating). However, these modification strategies, although initially effective, often fail quite quickly [1]. For example, increasing the size of individual levodopa doses often leads to an increased severity of dyskinesia, and although fractionating the levodopa dose may reduce dyskinesia, it is often at the expense of a re-emergence of symptoms due to suboptimal levodopa exposure. In recognition of these limitations, controlled release (CR) levodopa preparations were developed in the hope of achieving better levodopa pharmacokinetic profiles. However, although they can be a useful additional levodopa therapy, CR preparations are associated with erratic absorption and unstable plasma levels and therefore, have not provided the long-term solution that was originally hoped [13]. A clinical study which evaluated the effects of immediate release (IR) and CR levodopa/carbidopa (Sinemet® CR Bristol–Myers Squibb) in levodopa-naive patients found no therapeutic benefit of CR levodopa over traditional IR formulations, with no significant differences in the proportion of patients experiencing motor fluctuations or dyskinesia between the treatment groups [14]. Similar results from a clinical study of identical design which evaluated the effects of IR and CR levodopa/benserazide (Madopar® HBS, Roche) over a 5-year period, also found no therapeutic benefit of CR over IR levodopa [15]. An increasingly popular alternative is to combine levodopa with a COMT inhibitor such as entacapone, to extend the elimination half-life of levodopa and thereby reduce the risk that levodopa treatment will induce motor complications.

Levodopa-associated motor complications

In most patients, the therapeutic response to DDCI/levodopa during the first few years of treatment is consistent and long-lasting, and a regimen of two or three or more daily doses usually results in sustained symptomatic improvement [13]. At this stage, motor complications such as wearing-off are not apparent. This is due to the capacity of the remaining nigral dopamine neurons to store and release dopamine, so as to buffer fluctuations in plasma levodopa and ensure a more continuous dopaminergic stimulation (CDS) [16]. As the disease progresses there is loss of presynaptic neuronal capacity and hence loss of buffering capacity. However, long-term administration of levodopa is frequently limited by the development of an inconsistent therapeutic response and the development of motor complications, which can seriously compromise patient function and limit their ability to fully benefit from the drug [17,18]. Often, the first of these motor complications to emerge is wearing-off where there is a loss of benefit from each dose of levodopa before the next dose [19–21]. Another common complication is morning off, in which symptoms are often worse upon awakening but subside after morning administration of levodopa. On–off fluctuations, delayed on and failure to switch on usually occur as the disease progresses [22–24]. In addition to the re-emergence of typical motor symptoms, such as tremor, rigidity and bradykinesia, the signs of wearing-off can include more subtle nonmotor symptoms such as mood changes, pain, cognitive changes (e.g., mental slowing and sensory problems), panic attacks, anxiety and episodic sweating [25,26]. The emergence of wearing-off can also often be accompanied by the development of a variety of dyskinesia and dystonias. Peak-dose dyskinesia is the most common manifestation and tends to occur at the time of the peak plasma concentration of the drug and the maximal clinical response.

It was previously believed that 30–50% of patients experience motor complications after approximately 5 years of levodopa therapy [27]. However, recent well-designed clinical studies have reported wearing-off to occur earlier in the course of the disease, often within 1–2 years of initiating levodopa treatment (FIGURE 1) [19,28]. For example, in the Comparison of the Agonist pramipexole versus Levodopa on Motor complications in Parkinson Disease (CALM-PD) study, which compared levodopa treatment with pramipexole (Mirapexin®, Pfizer Inc.), 38% of patients had experienced wearing-off and 31% of patients had experienced dyskinesia within 2 years of initiating levodopa treatment [19]. Similarly, in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study, after 18 months of therapy, 50 and 30% of levodopa-treated patients were experiencing wearing-off and dyskinesia, respectively [28].

Although the exact mechanisms underlying levodopa-related motor complications are not completely understood, the pharmacokinetic limitations of levodopa, in particular its short elimination half-life of only 1–1.5 h, have been identified as a major contributor [15,28]. This short half-life means that oral levodopa administration results in fluctuating plasma levels and ultimately leads to the intermittent pulsatile stimulation of

dopamine receptors in the striatum. It is now believed that long-acting therapies that provide more continuous dopaminergic stimulation may provide a way of ameliorating the oscillations in striatal dopaminergic delivery, thereby avoiding the generation of dyskinesia (and possibly other types of motor complication) [16,18,29,30]. This belief has provided the impetus for the early use of long-acting dopamine agonists, especially in young-onset patients who are most at risk of developing disabling motor complications and then using levodopa when a more robust therapeutic effect is required. This notion has been tested in several long-term clinical trials with long-acting dopaminergic agonists. One of the most extensive of these is the 5-year, 056 study which compared the effects of levodopa or ropinirole in drug-naive PD patients [31]. Similarly, the 4-year CALM-PD study examined patients randomized to treatment with levodopa or pramipexole [19]. In both studies, monotherapy with levodopa and dopamine agonists provided significant symptomatic improvement, as measured by the Unified Parkinson Disease Rating Scale (UPDRS), but the degree of improvement was greater in the subjects assigned to the levodopa treatment groups. Although there were far fewer incidences of dyskinesia in ropinirole- (Requip®, GlaxoSmithKline) and pramipexole-treated patients, most of the patients in both studies were receiving supplemental levodopa by the study end (~70% in each study) [19,31]. Similar findings have been reported by other double-blind clinical investigations performed with other dopaminergic agonists [32,33]. Consequently, dopamine agonists have not offered a complete practical long-term alternative to levodopa and attention has refocused on strategies to improve the long-term administration of levodopa.

Benefits of combining levodopa with a COMT inhibitor in PD patients experiencing motor fluctuations

Drugs that inhibit COMT were developed as a means of blocking the peripheral metabolism of levodopa and thereby modifying levodopa pharmacokinetics so as to extend its plasma half-life and provide a more continuous availability of levodopa to the brain [34]. Two COMT-inhibitor compounds have been introduced into clinical practice, tolcapone in 1997 and entacapone in 1998. Due to rare cases of fatal liver toxicity, the marketing authorization for tolcapone (Tasmar®, Roche) was suspended in the European Union in 1997, while in the USA tolcapone is now recommended only for patients with motor fluctuations who are not candidates for other therapies [35,36]. Consequently, entacapone is currently the most widely available and employed agent of this type. Entacapone is a nitrocatechol compound. It has similar T_{max} and half-life values as levodopa (1–2 and 0.4–0.9 h, respectively) and accordingly is routinely administered in combination with each dose of levodopa to extend the drug's elimination half-life. When given in combination with a single dose of levodopa/carbidopa, entacapone 200 mg increases the levodopa half-life from 1.3–2.4 h, increases the plasma levodopa area under the curve by 35–40% and decreases the peak–trough variations in the daily plasma levels by 30–50% [34,37,38].

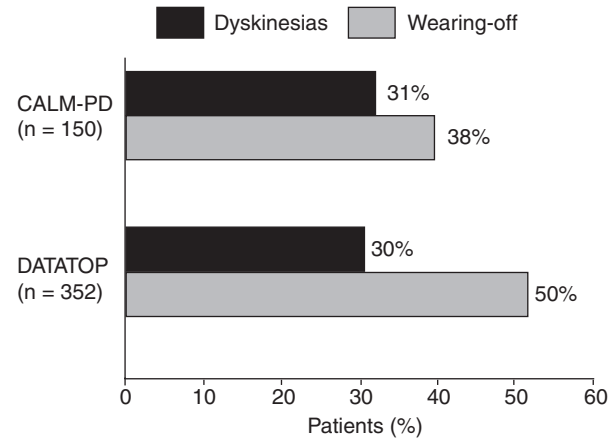

Figure 1. Incidence of motor complications after 2 years of levodopa therapy.
CALM-PD: Comparison of the Agonist pramipexole versus Levodopa on Motor complications in Parkinson Disease; DATATOP: Deprenyl And Tocopherol Antioxidative Therapy of Parkinsonism.

The efficacy and safety of entacapone given in combination with levodopa and a DDCI has been proven in five prospective, randomized, double-blind, placebo-controlled Phase III studies performed in over 1000 PD patients worldwide TABLE 1 [5–8,39]. In these studies, levodopa given in combination with a DDCI and entacapone increased daily on time by an average of 1–1.7 h and decreased off time by an average of 1.1–1.5 h. Statistically significant improvements in UPDRS motor and activities of daily living scores during on time were also observed. Another consistent result observed in all studies was the reduction in the total daily levodopa dose [5,6,40]. Whereas patients receiving placebo had to increase their mean daily levodopa dose by 100 mg over the course of these studies, patients in the entacapone group decreased their daily dosage of levodopa by 85–90 mg. To better assess the long-term efficacy and safety of entacapone, 132 patients who had successfully completed the previous NOMECOMT study received open-label therapy with levodopa plus entacapone, irrespective of whether they had initially been randomized to receive placebo or entacapone during the original double-blind study [6]. Patients were followed for 3 years in what was referred to as the NOMESAFE study [41]. In this long-term study, treatment with entacapone increased the mean period of benefit from the first morning dose of levodopa from 2.1 h at baseline (without entacapone) to 2.5 h at 3 years ($p < 0.01$). Furthermore, at 3 years, more than 90% of patients maintained or improved their daily off time compared with baseline without having to increase their mean daily levodopa dose [41].

Clinical experience with levodopa in combination with DDCI and entacapone spans more than 300,000 patient years of safety data, including trial data up to 5 years. Results from several randomized, placebo-controlled studies show the most common dopaminergic side effects to be dyskinesia, nausea and dizziness. The most common

Table 1. An overview of studies undertaken with entacapone + levodopa + carbidopa (Stalevo®).

Study	Study design	Objective	Efficacy results	Safety results
SIMCOM	Open-label, single-group, cross-over, multicenter, 4-week study	To investigate the initiation of Stalevo in 52 PD patients previously treated with an IR DDCI/levodopa preparation plus separate entacapone	• 69% preferred Stalevo or considered it as equivalent to their previous treatment • Patients' clinical condition was similar or better in 85% of patients evaluated by investigators and in 75% of patients evaluated by themselves • The UPDRS motor score (part 3) and total scores (parts 1–3) were reduced at week 4 by 1.9 ± 4.9 and 2.5 ± 6.0 points ($p < 0.01$ for both) from baseline • 86% of all levodopa doses used at baseline were directly replaceable by Stalevo tablets containing the same amount of levodopa	• Only one serious adverse event was reported (dyspnea, dizziness) • Three patients discontinued due to an adverse event • Other treatment-related adverse events were reported in nine patients; these were mild-to-moderate in nature
TC-INIT	Open, randomized, parallel-group, multinational, 6-week study	To compare the switch from IR DDCI/levodopa to either DDCI/levodopa plus entacapone administered separately or to Stalevo tablets in 200 PD patients with wearing-off	• >80% of patients were assessed to be in better clinical condition at week 2 in the Stalevo group (82% assessed by investigators and 81% by patients) compared with 76 and 73% of patients receiving entacapone separately • The UPDRS part 2 and 3 and total (1–3) were decreased in both groups at week 2 compared with baseline, by an average of 2.5, 4.2 and 7.1 points in patients receiving entacapone separately and 2.5, 4.8 and 7.9 points in patients receiving Stalevo • The proportions of patients experiencing motor fluctuations were reduced in both groups and particularly among patients receiving Stalevo	• Both treatments were well-tolerated • Three patients receiving DDCI/levodopa plus entacapone individually (intermittent confusion, nausea and diarrhea) and one patient in the Stalevo group (light headedness) discontinued due to adverse events • One serious adverse event was reported in the group receiving DDCI/levodopa plus entacapone individually (panic attack-like syndrome)
SELECT-TC	An open-label, multicenter, single-arm, 4-week study	To evaluate the tolerability, safety and efficacy of switching from an IR DDCI/levodopa preparation to Stalevo in 169 consecutive PD patients experiencing wearing off, with and without mild dyskinesia	• Stalevo resulted in significant improvements in PDQ-39 and UPDRS (1 plus 2 plus 3) scores, $p < 0.001$ • Assessment of off time demonstrated a reduction in off time in 32% of patients, compared with an increase in 7% of patients	• Adverse events were infrequent and mild, the most common being nausea (12.4%), dizziness (6.5%) and somnolence (6.5%) • 14 patients (8%) discontinued treatment with Stalevo; 12 (7%) due to adverse events • 11 out of 130 (8.5%) patients developed new onset dyskinesia • 17 out of 39 (43.6%) patients had worsening of existing dyskinesia

DDCI: Dopa-decarboxylase inhibitor; IR: Immediate release; PD: Parkinson's disease; PDQ: Parkinson`s Disease Questionnaire; UPDRS: Unified Parkinson Disease Rating Scale.

nondopaminergic side effects are diarrhea and urine discoloration [42]. Moreover, controlled clinical trials have found no evidence of liver toxicity, as measured by liver enzyme activity, with treatment with levodopa and a DDCI in combination with entacapone [42].

With a wealth of clinical evidence clearly demonstrating the long-term efficacy and safety of entacapone in reducing motor fluctuations, the concept of combining entacapone with carbidopa and levodopa in one tablet became popular among movement disorder specialists.

Development of Stalevo

Taking into consideration the most commonly prescribed DDCI/levodopa and entacapone doses, Stalevo has been made available in dose combinations of carbidopa/levodopa/entacapone 12.5/50/200 mg (Stalevo 50), 25/100/200 mg (Stalevo 100) and 37.5/150/200 mg (Stalevo 150). Since the efficacy and safety of entacapone given in combination with levodopa and a DDCI had already been established, the development and registration programs for Stalevo were based mainly on demonstrations of bioequivalence to conventional carbidopa/levodopa formulations plus entacapone, administered simultaneously [43]. These four bioequivalence studies were conducted with the Stalevo formulations to be marketed. The reference product was carbidopa/levodopa IR (Sinemet) 25/100 mg tablets in dosages of 12.5/50 mg (half tablet), 25/100 mg (one tablet) and 37.5/150 mg (1.5 tablets) administered with entacapone (Comtess®, Orion) 200 mg. With Stalevo, these dosages are provided in single tablets so there is no need to break tablets. These bioequivalence studies led to the availability of Stalevo much earlier than if extensive clinical trials had been required [43].

Stalevo has recently been approved in the USA to treat patients with PD who are being treated with levodopa and are experiencing the signs and symptoms of wearing-off. Stalevo will most commonly be introduced in two clinical circumstances: switching from carbidopa/levodopa IR plus entacapone and switching from carbidopa/levodopa formulations alone [43]. In the USA, in the simplest scenario, Stalevo is indicated for patients who are already receiving IR carbidopa/levodopa in combination with entacapone, as a substitute for their current therapy with equivalent strengths of the three individual components. Therefore, one Stalevo 50 tablet can be substituted for a carbidopa/levodopa 25/100 mg half-tablet plus 200 mg entacapone, one Stalevo 100 tablet can be substituted for one carbidopa/levodopa 25/100 mg tablet plus 200 mg entacapone and one Stalevo 150 tablet can be substituted for one and a half carbidopa/levodopa 25/100 mg tablets plus 200 mg entacapone. It is recommended that no more than one Stalevo tablet be taken at each dosing administration in order that the entacapone dose is not increased beyond 200 mg per dosage. Since clinical experience with daily doses of entacapone above 1600 mg is limited in the USA, the maximum recommended daily dose of Stalevo is eight tablets per day. Due to the way that the Stalevo tablet has been formulated, it also recommended that it should not be cut or broken [43]. Consequently, there will be many combinations of medications where a more complex regimen will have to be considered. In some instances, supplemental levodopa alone (without entacapone) may also need to be administered with the Stalevo tablet in order to provide more than 150 mg of levodopa per dose and obtain a more robust clinical response. The best combination of dosing regimens with Stalevo will become more apparent as both the patient and doctor become more familiar with this new product. It is also important that patients are educated on the signs and symptoms of wearing-off and dyskinesia. Patients and caregivers are encouraged to discuss them with their doctor so that any necessary dose adjustments can be made.

Stalevo is also indicated in the USA for patients taking IR carbidopa/levodopa preparations not currently receiving entacapone therapy and who are experiencing the symptoms of wearing-off. However, on-label use indicates that this does not include patients who are receiving more than 600 mg of levodopa per day or who have a history of moderate or severe dyskinesia. This restriction is due to the fact that clinical studies have shown that the presence of dyskinesia and higher daily levodopa dose at baseline were associated with an increased likelihood of levodopa dose reduction after entacapone initiation. The presence of dyskinesia was a stronger predictor of levodopa dose reduction than daily levodopa dose [44]. Since dose adjustments are more difficult with Stalevo, it is recommended that if a patient is receiving more than 600 mg levodopa per day and/or is experiencing dyskinesia, then the patient should first be titrated individually with carbidopa/levodopa and entacapone, and then switched to Stalevo once stabilized. It is important to remember that even though clinical benefits are seen relatively quickly, it may take several weeks to develop a stable clinical response to Stalevo. During this time transient dyskinesia may occur and then resolve or lessen but improvement of rigidity, akinesia and tremor will be maximal usually in 2 or more weeks.

Clinical experience with Stalevo

Currently, three clinical trials have been undertaken with Stalevo. The first study (SIMCOM), was an open-label study undertaken to evaluate the initiation of Stalevo in patients with PD previously treated with an IR DDCI/levodopa preparation plus separate entacapone [10]. By contrast, TC-INIT and SELECT-TC evaluated the effects of initiating Stalevo in PD patients experiencing wearing-off who were receiving IR DDCI/levodopa without entacapone. TC-INIT was a randomized, parallel-group, multinational study undertaken in Europe [9], while the SELECT-TC study was an open-label muticenter study undertaken in the USA [11].

Substituting for IR carbidopa/levodopa & entacapone previously administered as individual products

The simplest way to introduce Stalevo is to patients who are already receiving IR carbidopa/levodopa and entacapone and are stabilized on these individual products.

The ease and tolerability of switching from a DDCI/levodopa preparation plus entacapone to Stalevo was evaluated in the open-label, single-group, crossover study, SIMCOM [10]. This study included PD patients who were being treated with an IR DDCI/levodopa preparation plus entacapone. All patients (n = 52) were switched from their current DDCI/levodopa therapy to the corresponding dose of Stalevo. Following 4 weeks of treatment with Stalevo, most (69%) of the subjects either preferred treatment with Stalevo or considered it as equivalent to their previous treatment. The patients'

clinical condition was similar or better in 85% of patients evaluated by investigators and in 75% of patients evaluated by themselves. Importantly, the switch from DDCI/levodopa and entacapone to Stalevo was well-tolerated, with a low incidence of adverse events. Overall, Stalevo was considered easier to handle (by 84% of patients), easier to remember (67%) and swallow (59%), more simple to dose (94%) and more convenient to use (84%) than the previous treatments administered individually [10].

Substituting IR carbidopa/levodopa therapy (without entacapone) when patients experience the signs & symptoms of wearing-off

The second scenario where Stalevo can be introduced is to patients receiving IR carbidopa/levodopa therapy at the first signs and symptoms of wearing-off. However, as mentioned, this does not include patients who are receiving more than 600 mg of levodopa per day or who have a history of moderate or severe dyskinesia. Initiating Stalevo in patients who are not already taking entacapone may require more consideration in order to ensure that the patient becomes stabilized appropriately on this new levodopa product. In the TC-INIT study, 200 PD patients being treated with three to six daily doses of IR levodopa/DDCI and experiencing symptoms of wearing-off, were randomly assigned to receive either 200 mg of entacapone taken separately with each dose of their DDCI/levodopa therapy or in Stalevo tablets. The results of this study demonstrated that treatment with Stalevo was as easy to initiate as treatment with DDCI/levodopa and entacapone individually. Stalevo provided improved symptom control and was well-tolerated. Over 80% of patients were assessed to be in better clinical condition at week 2 in the Stalevo group (82% assessed by investigators and 81% by patients) compared with 76 and 73% of patients receiving entacapone separately [9]. Like TC-INIT, the SELECT-TC study was also designed to evaluate the ease of switching from traditional DDCI/levodopa to Stalevo. During this study, patients were switched from the most commonly prescribed dose of IR carbidopa/levodopa 25/100 mg to Stalevo for 4 weeks. The results of this study have not yet been published, however, a preliminary evaluation of this study has shown that the transfer from carbidopa/levodopa therapy to Stalevo was well-tolerated [11]. In addition, the UPDRS scores (parts 2, 3, 2 plus 3 and question 39) and Parkinson's Disease Questionnaire (PDQ)-39 total scores were shown to be significantly improved from baseline to study end with Stalevo treatment.

Two case studies from the SELECT-TC study demonstrate how transferring patients from carbidopa/levodopa therapy to Stalevo was easily managed by the clinician and well-tolerated by the patient while resulting in improvements of patient function.

A 49 year old female who had been diagnosed with PD 1 year previously was enrolled in the SELECT-TC study. This patient was already experiencing wearing-off after just 1 year of levodopa therapy. At study initiation the patient was also experiencing early morning dystonia, sleep disturbances and joint pain and had Hoehn and Yahr stage 1.5.

This patient was switched from her current dose of Sinemet IR 600 mg/day (1.5 tablets, four-times daily) to Stalevo 150 (one tablet four-times daily). She did not receive any other concomitant PD medication during the study period. Following 4 weeks of treatment, UPDRS question 39, which measures the average proportion of the waking day in which the patient is off, showed that the patient's off time had decreased from 26–50% of the waking day at baseline to 1–25%. Subjective evaluations showed that the patient considered herself very much improved while the investigator considered her much improved. The patient tolerated Stalevo well, reporting no incidences of dyskinesia and no adverse events. The patient continued into the extension phase of this study where she continued to have a good response to Stalevo with no reported incidences of dyskinesia. Although this patient had a mild hallucination for 1 day which was thought to be related to Stalevo, no action was taken.

A second case study from the SELECT-TC study is that of a 62 year old male who had been diagnosed with PD 5 years previously and who had been taking levodopa for 2 years. At study initiation the patient was experiencing wearing-off and sleep disturbances, and had Hoehn and Yahr stage 2.0. During the study, the patient was switched from his current dose of Sinemet 25/100 IR 400 mg/day (100 mg four-times daily) to alternate doses of Stalevo 100 (two tablets daily) and Stalevo 150 (two tablets daily). This patient was also receiving ropinirole 2 mg four-times daily throughout the study. Following 4 weeks of treatment, the patient's total UPDRS score was improved from baseline, although there was no overall change in off time or the total PDQ-39 total score. At the study end, the patient considered himself much improved and the investigator was of the same opinion. The patient tolerated Stalevo well, reporting no incidences of dyskinesia and no adverse events. The patient continued into the extension phase of the study.

These two case studies demonstrate the relative ease of initiating Stalevo. However, an important consideration when administering levodopa is the transient increase in dyskinesia that can be observed in some patients who are receiving more than 600 mg of levodopa per day or who have a history of dyskinesia. A third case study from the SELECT-TC study is that of a 67 year old male who had been diagnosed with PD 3 years previously and who had been taking levodopa since diagnosis. At study initiation the patient was experiencing wearing-off, early morning dystonia, sleep disturbances and symptomatic orthostasis (Hoehn and Yahr stage 3.0). During the study, the patient was switched from his current dose of Sinemet IR 500 mg/day (one tablet five-times daily) to Stalevo 100 (one tablet, five-times daily). He did not receive any other concomitant PD medication during the study period. Following 4 weeks of treatment, the patient's total UPDRS score and PDQ-39 were improved from baseline. Moreover, UPDRS

question 39 showed that the patient's wearing-off had decreased from 26–50% of the waking day at baseline to 1–25% at the end of the study. The patient also reported that his tremor had stopped. Subjective evaluations showed that the patient considered himself very much improved while the investigator considered him much improved. Although this patient developed mild dyskinesia when lying down (1–25% of the day), he did not want to lower his dose of Stalevo. This patient also continued into the extension phase of this study where he continued to have a good response to Stalevo. Although he experienced a slight increase in dyskinesia towards the end of the extension phase, no action was taken.

Considerations when initiating Stalevo in patients who may be experiencing dyskinesia

It is recommended that patients who are experiencing moderate-to-severe dyskinesia on levodopa therapy should first be titrated individually with carbidopa/levodopa and entacapone 200 mg and then switched to Stalevo once stabilized. Patients with mild dyskinesia were also permitted to enrol into the SELECT-TC study. One such patient was a 64 year old male who had been suffering from PD for 10 years. This patient had been receiving levodopa therapy since his diagnosis. In addition to wearing-off, at study initiation the patient was experiencing dyskinesia related to wearing-off, stiffness and rigidity, and difficulty walking. During the study, the patient was switched from his current dose of Sinemet IR 550 mg/day (1.5 tablets, three-times daily and one tablet once-daily) to comparable dosages of Stalevo 150 (one tablet, three-times daily) and Stalevo 100 (one tablet daily). This patient was also receiving ropinirole 4 mg three-times daily and selegiline (Zelapar®, Athena) 5 mg four-times daily throughout the study. Following treatment with Stalevo, his dyskinesia had reduced from 26–50% of the day at baseline to 1–25% of the day at week 4. The patient's total UPDRS score was improved from baseline, as was the total PDQ-39 total score. Overall, the patient considered himself very much improved and the investigator agreed with this self-assessment. On entry to the extension phase, the patient discontinued ropinirole therapy and increased their Stalevo dosing regimen to Stalevo 150 (one tablet, four-times daily) and Stalevo 100 (one tablet at the end of the day). Interestingly, the patients' dyskinesia continued to improve throughout the extension phase and by the last study visit, the patient was classified as having no dyskinesia (UPDRS question 34, duration of dyskinesia). It is recognized in this case that selegiline 5 mg four-times daily is a higher dose than that which is usual.

Considerations when initiating Stalevo in patients already receiving CR levodopa formulations

Although there is currently limited clinical experience, the PD physician will probably wish to consider the possibility of switching patients receiving CR carbidopa/levodopa with or without entacapone directly to Stalevo. Stalevo has similar T_{max} and half-life values as levodopa CR and improves the pharmacokinetics of standard oral levodopa formulations, stabilizing the therapeutic response and enhancing the symptomatic benefits. Pharmacokinetic data and clinical experience has estimated that the bioavailability of levodopa from carbidopa/levodopa CR is approximately 70–75% that of carbidopa/levodopa IR. This means that the levodopa area under the curve produced by carbidopa/levodopa CR 50/200 plus entacapone 200 mg should be approximately comparable with Stalevo 150 [43]. However, the levodopa absorption profiles for Stalevo and levodopa/carbidopa CR are different. Levodopa from Stalevo has a T_{max} similar to that of levodopa/carbidopa IR (0.5–1.5 h), whereas absorption is more delayed from levodopa/carbidopa CR (T_{max} 1.5–3 h). These differences should be considered when patients are switched from levodopa/carbidopa CR to Stalevo. In general, a shorter levodopa T_{max} is desirable in patients with motor fluctuations to minimize the time from medication administration to onset of clinical effect. It is important to remember that those patients first stabilized on levodopa CR may not always tolerate the more rapid onset of action of IR levodopa with Stalevo. In the TC-INIT study, patients who were receiving Sinemet CR as part of their levodopa regimen were permitted to switch to Stalevo.

One such example is that of a 65 year old female who had been diagnosed with PD 7 years previously and had been receiving levodopa therapy for 5 years. At study initiation the patient was not suffering from dyskinesia (Hoehn and Yahr stage 2.0). Her medication at baseline consisted of Sinemet (IR) 25/100 mg (one tablet, three-times daily), Sinemet (CR) 25/100 mg (one tablet alone at night) and pergolide 1 mg (four-times daily). During this study, all the patients' levodopa doses were switched to Stalevo including Sinemet CR which was replaced with Stalevo 100. Dosing adjustments were permitted during the study and the daily levodopa dose was increased from 400 to 500 mg/day at week 1 (with the addition of an extra Stalevo 100 tablet). Hence the patient was taking Stalevo 100 five times a day. After 2 weeks of treatment, the clinical global impression of change score was assessed as much improved by both patient and the investigator. In addition, the clinician found Stalevo easy to initiate. Although mild dyskinesia began to occur by week 4 (<25% of the day), the patient expressed a preference for remaining on Stalevo.

Considerations when initiating Stalevo in patients receiving benserazide/levodopa

A further consideration is the initiation of Stalevo in patients who are receiving a levodopa regimen that contains the DDCI benserazide, such as Madopar, rather than carbidopa. A number of patients enrolled in the TC-INIT study received Madopar. One such patient was a 57 year old male who had been diagnosed with PD 12 years previously, at which time he was started on levodopa therapy. At study initiation the patient was not suffering from dyskinesia and was at Hoehn and Yahr stage 2.5. His medication at baseline consisted of Madopar (IR) 25/100 mg (one tablet, five-times daily) Madopar CR 25/100 mg (one tablet at night) and pramipexole 1.5 mg (three-times daily). Madopar CR was

taken at night as it is believed that a dose of levodopa CR on retiring to bed may improve night time mobility and hence sleep. During the study the patient was switched from his current levodopa regimen (including Madopar CR) to Stalevo 100 (one tablet five-times daily). Although permitted, no dosing adjustments were felt to be required during the study. After 2 weeks of treatment, the clinical global impression of change score was assessed as much improved by both patient and the investigator. The clinician also found that Stalevo was easy to initiate. Replacement of Madopar CR with Stalevo was well-tolerated and the patient expressed a preference for remaining on Stalevo.

These trials with accompanying case studies clearly demonstrate that patients can be easily switched from traditional DDCI/levodopa preparations, with or without previous entacapone therapy, to Stalevo. Treatment with Stalevo improved symptom control comparable with treatment with DDCI/levodopa and entacapone taken separately. Most patients preferred treatment with Stalevo, finding it more convenient to use and handle than their previous treatments. Stalevo was also found to be well-tolerated with minimal adverse events.

Summary

As always, in the journey of treating a PD patient, a knowledgeable physician will be crucial to the management of the patient and their medication. It is also very important for the patient to be knowledgeable about the disease and educated as to its symptoms – particularly wearing-off and dyskinesia. Despite the availability of an increasing array of novel alternative therapies, levodopa remains the most effective agent in the treatment of PD. In patients already receiving levodopa, switching to the corresponding Stalevo tablet is analogous to adding entacapone. Stalevo can also be introduced to patients who are already receiving IR carbidopa/levodopa and entacapone and are stabilized on these individual products. In this instance, Stalevo offers the increased convenience of taking only one tablet in place or two (or more) separate tablets. These advantages are particularly desirable for patients taking many pills each day and those who may inadvertently mix up medications or have difficulty adhering to complex treatment regimens. By ensuring the simultaneous administration of carbidopa/levodopa and entacapone, Stalevo simplifies therapy. An additional advantage is that Stalevo 50 and 100 tablets are smaller than entacapone tablets. This may be particularly beneficial for patients with swallowing difficulties. For patients already receiving levodopa therapy, either with or without entacapone, clinical experience indicates that Stalevo is easy to initiate, well-tolerated and preferred by patients. An important treatment decision in the management of early patients is when to initiate levodopa therapy. If the hypothesis that entacapone reduces the pulsatility of levodopa therapy (and thereby reduces the risk of long-term complications) can be substantiated in long-term clinical trials, introducing Stalevo will simplify administration and enhance the benefits of levodopa from the time it is first employed. This in turn would allow for a review of the current treatment algorithm for the management of PD as well as a re-evaluation of the cost-effectiveness of the various treatment options available for PD [45,46]. It is clear that combination therapy will be needed for the most ideal and individualized treatment for most patients.

Expert opinion

Stalevo is an important advance in the development of levodopa therapies and it is my belief that it will be an extremely useful addition to the therapies available to treat PD. Stalevo provides a robust therapeutic effect and is well-tolerated with a low incidence of adverse events. Furthermore, patients have found Stalevo easier to handle, remember and swallow, more simple to dose and more convenient to use. Consequently, Stalevo offers a significant opportunity for many patients to improve their quality of life and activities of daily living. There is a strong belief that long-acting therapies that provide more CDS may provide a way of ameliorating oscillations in striatal dopaminergic delivery, thereby reducing the risk of motor complications. Since Stalevo provides levodopa in a more pharmacokinetically optimized manner there is much anticipation that this drug will give added benefits to patients' quality of life and well-being.

Five-year view

As we gain a greater understanding of the underlying mechanisms of levodopa-related motor complications, increasing attention has focused on the use of dopaminergic therapies that provide a more continuous delivery of levodopa to the brain [16,18,47,48]. Under normal physiological circumstances, striatal dopamine receptors are stimulated in a mainly continuous manner; tonic stimulation occurs continuously at a low frequency, whereas phasic stimulation occurs in high-frequency bursts associated with rewards or movement planning [49,50]. However, nigrostriatal degeneration causes disruption in the normally efficient dopamine production and reuptake system and any excessive fluctuations in striatal dopamine levels can no longer be buffered. Under these circumstances, the level of dopaminergic stimulation more closely reflects the half-life of the exogenous drug [29,51]. Consequently, short-acting dopaminergic therapies stimulate striatal dopamine receptors in a pulsatile or burst pattern, thus inducing an abnormal physiological state [16]. This pulsatile stimulation at the postsynaptic dopamine receptor induces long-lasting gene and hence protein changes downstream in the basal ganglia and can also lead to glutamate-induced excitotoxicity [16]. Ultimately, these downstream changes result in signaling problems in the spiny neurons of the striatum and the likely subsequent development of abnormal motor outputs, such as dyskinesia. D1 receptors and presynaptic receptors may also play a role in motor complications.

The importance of CDS has been substantiated by the ability of continuous infusions of levodopa to maintain antiparkinsonian activity while leading to a lessening of dyskinesia intensity [52–54]. However, it is in preclinical models of PD that the validity of the

concept of CDS as a means to avoid dyskinesia induction has been most fully tested [55]. In methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP)-treated primates, repeated administration of traditional levodopa formulations or other short-acting dopamine agonists leads to the onset of marked involuntary movements [56]. In contrast, treatment with doses of long-acting dopamine agonists such as bromocriptine [57], ropinirole [58] and cabergoline (Cabaser®, Pfizer Inc.) [59] has been demonstrated to result in a much lower incidence of dyskinesia than that produced by equivalent antiparkinsonian doses of levodopa. Furthermore, recent studies in the MPTP marmoset model have demonstrated that extending the half-life of levodopa with entacapone not only improves symptomatic control but also reduces the risk of inducing dyskinesia compared with the same dose of regular levodopa [60]. In addition, clinical trials in a limited number of patients with a stable response to levodopa have shown that the coadministration of levodopa and a DDCI with entacapone can provide a number of additional benefits, including improvements in motor symptoms and activities of daily living [61].

These positive findings suggest that levodopa should be routinely administered in combination with a DDCI and a COMT inhibitor. The recent approval of Stalevo, which combines levodopa with the two enzyme inhibitors in a single tablet, will facilitate this treatment approach. Interestingly, it has been proposed that Stalevo, which provides levodopa in a more pharmacokinetically optimized manner, may have a role in the early treatment of PD and may even be the preferred manner of administering oral levodopa [29]. Maybe even using Stalevo as the first drug when levodopa is first initiated in a patient with PD. When more clinical evidence has been gathered, it is probable that this theoretical consideration of CDS with Stalevo will drive its earlier use in patients who are not experiencing motor fluctuations. Thus, we eagerly await the results of the long-term clinical studies now underway. Historically levodopa, administered in combination with the DDCI carbidopa, was well accepted and it soon became standard procedure to combine levodopa with carbidopa in one tablet. It is my belief that most levodopa-naive PD patients will be able to start treatment directly with Stalevo.

Key issues

- Since its introduction in the late 1960s, levodopa administered in combination with a dopa-decarboxylase inhibitor (DDCI) remains the single most efficacious therapeutic agent for Parkinson's disease (PD).
- Long-term administration of levodopa is frequently limited by the development of an inconsistent therapeutic response and the development of motor complications, which can seriously compromise patient function and limit their ability to fully benefit from the drug.
- Extensive clinical experience demonstrates that entacapone, given in combination with levodopa and a DDCI, increases on time, decreases off time, improves parkinsonian motor status and improves activities of daily living.
- Stalevo is a combination of levodopa, the DDCI carbidopa and the catechol-*o*-methyl transferase inhibitor entacapone presented in one tablet and available in the three commonly used levodopa doses (50, 100 and 150 mg).
- Stalevo has recently been approved to treat patients with PD who are being treated with levodopa (with or without entacapone) and are experiencing the signs and symptoms of wearing-off.
- Clinical studies have shown that patients can be easily switched from traditional DDCI/levodopa or a DDCI/levodopa preparation plus entacapone to Stalevo in a number of different scenarios.

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