

# Practical Guidance for the Management of Parkinson's Disease with Levodopa – Proceedings of the Neuronet-PD Working Group



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## Introduction

Despite being the most efficacious dopaminergic treatment, there is still debate as to how best to use levodopa for the treatment of Parkinson's disease (PD). There are large amounts of data on levodopa obtained from clinical trials; however, practical guidance on how to use levodopa optimally throughout the course of the disease is scarce. In order to capture the various clinical experiences and practices of a group of experts working in the field of PD, a workshop was held at a meeting of the Neuronet-PD working group in August 2008. Neuronet-PD is an Advisory Committee on PD composed of European experts and is supported by Novartis Pharmaceuticals AG (see Acknowledgements). The objective of the meeting was to gain practical recommendations on the optimal use of levodopa, in its various standard (levodopa/dopa decarboxylase inhibitor) and combination (levodopa/dopa decarboxylase inhibitor/catechol-O-methyltransferase inhibitor) formulations, based on the personal experiences of the working group. Specifically, the role of the combination formulation, levodopa/carbidopa/entacapone (LCE; Stalevo<sup>®</sup>, Orion Pharma, Espoo, Finland) was discussed. This article aims to capture the recommendations that resulted from these discussions on such issues as initiation and optimisation of levodopa therapy, management of side effects and optimising compliance. The recommendations, practices and guidance described here are all experience- rather than evidence-based and, thus, instead of having a consensus on all issues, the purpose of this review is to reflect all the individual experiences and strategies being used by the different experts.

Since its introduction in the 1960s, levodopa has transformed the treatment of PD, resulting in dramatic improvements in patient quality of life and reductions in disability, and has remained unrivalled in its symptomatic control.<sup>1,4</sup> However, despite its superior symptomatic benefits, long-term use of the drug is associated with the development of motor complications, such as wearing-off and dyskinesia,<sup>5</sup> which can occur as early as 6 months after the initiation of levodopa.<sup>6</sup> In the past, fear of these complications has often led physicians to delay the initiation of levodopa, giving priority to dopamine agonists, and to prescribe suboptimal doses once initiated.

Regardless of which therapy is initially given, as the disease progresses the majority of patients will require levodopa, either as a supplemental therapy or a monotherapy.<sup>3,4,7</sup> Recent studies have also demonstrated that, in the long term, the choice of initial treatment may not alter the ultimate risk of developing troublesome dyskinesias once levodopa is initiated,<sup>8</sup> or the incidences of motor complications.<sup>9,10</sup>

## Initiation of levodopa therapy

### Background

Levodopa is administered with a dopa-decarboxylase inhibitor (DDCI), such as benserazide (Madopar<sup>®</sup> and Prolopa<sup>®</sup>, Roche Products Ltd, Welwyn Garden City, UK) or carbidopa (Sinemet<sup>®</sup>, Merck, Sharp & Dohme, Haarlem, The Netherlands and Parcopa<sup>®</sup>, Schwarz Pharma, Monheim, Germany; Figure 1). Inhibition of dopa decarboxylase (DDC), one of the major routes of peripheral levodopa metabolism, helps to increase the half-life and bioavailability of levodopa.<sup>11,16</sup> Despite an improvement in the pharmacokinetic profile of levodopa through this combination, it is still characterised by fluctuations and deep troughs in plasma levodopa levels. Thus, a third, pharmacokinetically enhanced formulation of levodopa, LCE (levodopa/carbidopa/entacapone), has recently been developed, which provides dual-enzyme inhibition of both DDC and catechol-O-methyltransferase (COMT), the second enzyme involved in the peripheral metabolism of levodopa.<sup>17</sup>

### Recommendations of the Neuronet-PD members

Levodopa can be initiated in various ways and will differ between individuals. In general, patients should start on low doses of levodopa and titrate up until an efficacious dose is reached. The two most common strategies for initiating levodopa therapy are at doses of 50 or 100 mg, with variations of these summarised below. Age is an important consideration when deciding on the best strategy to initiate levodopa. In elderly patients (aged >65 years) levodopa may be used as first-line therapy. In contrast, the first-line therapy in young-onset patients is predominantly dopamine agonists with levodopa often only initiated as an adjunct when symptomatic control becomes insufficient. As such, lower initial










Levodopa dose (mg)	Sinemet	Madopar	Stalevo equivalent
50			
100			
150			
200			

Figure 1: Levodopa formulations and their currently available dosing strengths.

## Optimisation of levodopa therapy

### Background

Once initiated on levodopa, modifications to the dosing regimen will eventually be required to help maintain optimal symptom control and manage motor complications. Commonly employed strategies for maintaining symptom control include increasing the total daily dose and the unit dose of levodopa, increasing the number of daily doses, using controlled-release levodopa or switching to Stalevo. Increasing the dose strength or frequency of levodopa doses does not fully address the high peaks and low troughs in plasma levodopa levels, although frequent dosing can achieve higher plasma levodopa concentrations for longer periods of time.<sup>18</sup> In addition, high doses of levodopa are associated with an increased risk of dyskinesia.<sup>19,20</sup> Controlled-release formulations have an unpredictable pharmacokinetic profile with erratic absorption and delayed ON-time,<sup>16</sup> and do not reduce the risk of dyskinesia compared with immediate-release formulations.<sup>21</sup> Despite this, controlled-release formulations may be of some benefit during the night-time.

Stalevo has been shown to reduce the deep troughs in plasma levodopa levels associated with conventional levodopa in studies with both healthy subjects and patients with PD (Figure 2), as well as to increase the half-life and bioavailability of levodopa.<sup>18,22</sup> The improved pharmacokinetic profile associated with dual-enzyme inhibition has been demonstrated to increase ON-time, decrease OFF-time and improve motor scores in patients experiencing advanced wearing-off.<sup>23,26</sup> Benefits can also be seen in patients with early signs of wearing-off or who require the initiation of levodopa. In patients with early wearing-off, Stalevo provides improvements in motor function, activities of daily living, patient-assessed

doses of levodopa should be employed (i.e. 50 mg unit dose may be preferable to 100 mg). However, levodopa may be initiated as first-line therapy in younger patients if they suffer from disabling side effects with dopamine agonists.

### Direct initiation of 100 mg levodopa three times daily

This is a common strategy for the initiation of levodopa in patients who are not experiencing motor fluctuations and who are at a low risk of developing dyskinesia. A three times daily (tid) dosing regimen may be the most convenient for patients as doses can be scheduled around mealtimes, and 100 mg levodopa allows most patients greater symptom control than if they were initiated at lower doses.

### Initiation of 50 mg levodopa four times daily

Initiating patients on a four times daily (qid) regimen may allow for a better coverage throughout the day compared with a three times daily regimen. The additional benefit of this strategy is the use of lower individual doses of levodopa in patients who may be at risk of developing adverse events. This strategy is mainly used in order to reduce possible adverse events seen with 100 mg levodopa and to reduce the fluctuations in plasma levels, which may, in the long term, lead to the pulsatile stimulation of striatal dopamine receptors. However, 100 mg levodopa qid should also be considered if 50 mg levodopa doses provide insufficient symptom control. There are limitations to this strategy; namely, patients may have greater difficulty adhering to a four times daily dosing regimen, as it does not revolve around mealtimes. Thus, unless the patient is awake long hours, this strategy may be difficult to adhere to. Additionally, there is still a lack of clinical data to support the superiority of this strategy over a three times daily regimen.

### Slow, gradual titration to levodopa three times daily

Further variations of the gradual titration up to 100 mg levodopa include starting at 50 mg levodopa once daily and adding another 50 mg dose every 3 days until 50 mg tid is reached, and starting with a 100 mg levodopa dose in the morning and two additional 50 mg doses that would gradually be replaced by two 100 mg doses over the period of a week. These strategies may aid the physician in the individual optimisation of therapy on a patient-by-patient basis, as therapy can be stabilised at any stage depending on the patient's response to each step. In addition, these strategies may be more suitable for patients at risk of poor drug tolerance and could also incorporate an intermediate step of 75 mg levodopa.

**Table 1: Response of wearing-off symptoms following a switch to Stalevo (SENSE trial)**

Symptom	Symptom classification	Present at screening n=113, %	Improved at Week 6 n=113, %
Q1. Tremor	Motor	81	74
Q2. Any slowness of movement	Motor	91	60
Q3. Mood changes	Non-motor	43	52
Q4. Any stiffness	Motor	76	62
Q5. Pain/aching	Non-motor	50	32
Q6. Reduced dexterity	Motor	90	53
Q7. Cloudy mind/slowness of thinking	Non-motor	54	34
Q8. Anxiety/panic attacks	Non-motor	20	30
Q9. Muscle cramping	Motor	53	60
<b>Any motor symptom</b>	<b>Motor</b>	<b>100</b>	<b>62</b>
<b>Any non-motor symptom</b>	<b>Non-motor</b>	<b>82</b>	<b>38</b>

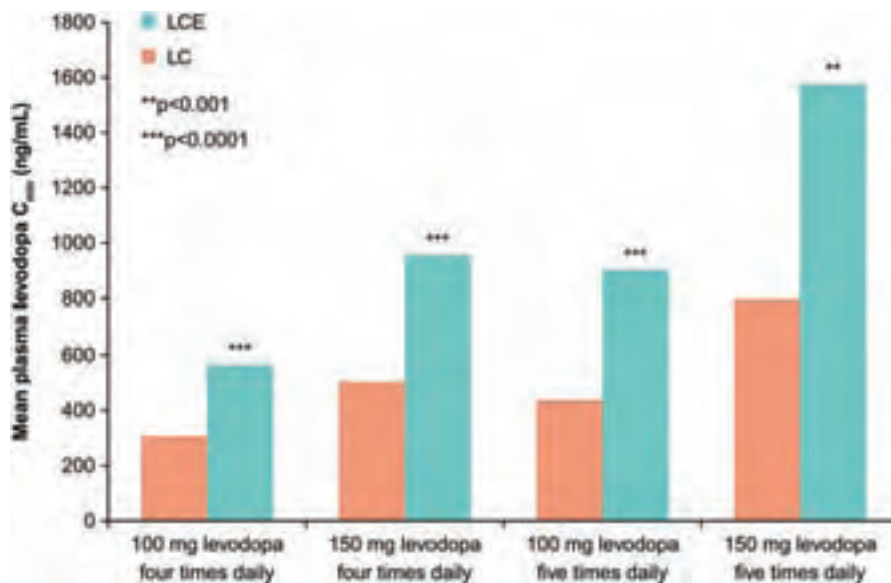


Figure 2: Minimum levodopa concentrations of Stalevo compared with conventional levodopa in healthy volunteers (the KINESTA study)<sup>8</sup> LCE=levodopa/carbidopa/entacapone; LC=levodopa/carbidopa; C<sub>min</sub>=minimum levodopa concentration.

Clinical Global Impression of Change [CGI-C]), and motor and non-motor wearing-off symptoms, regardless of whether patients had previously received levodopa/benserazide or levodopa/carbidopa (Table 1).<sup>27</sup> In addition, the benefits of Stalevo compared with conventional levodopa on health-related quality of life have been demonstrated in the QUESTAP study in patients with PD experiencing no, or minimal, non-disabling motor fluctuations.<sup>28</sup> Finally, the use of high doses of Stalevo (200 mg levodopa) may be of benefit for night-time use. A recent pharmacokinetic study demonstrated greater levodopa bioavailability and a longer half-life with Stalevo compared with controlled-release levodopa, commonly used at night, when given as a single night-time dose.<sup>29</sup>

#### Recommendations of the Neuronet-PD Working Group

The modification of a patient's levodopa dose is necessary to maintain symptom control and to manage motor complications. To maintain symptom control, the most common modification strategy is to increase the individual levodopa dose, either by an increase from 100 to 150 or 200 mg of conventional levodopa or an increase in dose frequency from three to four times daily dosing. Once patients begin to experience wearing-off, a switch to Stalevo is often the most beneficial strategy. The switch to Stalevo can be implemented in a number of ways, and the most efficacious switching strategy depends on the profile of the patient. In general, when switching to Stalevo, the number of doses per day should remain the same unless the patient is receiving five or six doses per day. In this case, a reduction in the number of daily doses to four or five is recommended.

#### Direct switch to Stalevo

The most commonly used strategy for patients experiencing predictable motor fluctuations

and who are not at risk of dyskinesias is a direct overnight switch to Stalevo with equivalent levodopa dose.

#### Gradual switch to Stalevo

A more gradual switch using lower levodopa doses is advised for patients at risk of dyskinesia or those with severe motor fluctuations. The gradual switch can be carried out by switching from conventional levodopa dose by dose to equivalent doses of Stalevo, or by the use of entacapone. Use of entacapone means the addition of an extra tablet to each dose of conventional levodopa, which would then be replaced by a single, equivalent tablet of Stalevo. Adherence may be an issue with this strategy, as an increase in the patient's pill burden occurs in the intermediate stage of the switch. It is worth noting that although a switch to equivalent doses of Stalevo would be suitable for most patients, those receiving high daily doses of levodopa may benefit from a gradual, stepped switch to a lower Stalevo strength to minimise any dyskinesia or worsening of parkinsonian symptoms.

In Europe, Stalevo is available in three different dose strengths containing 50, 100 and 150 mg levodopa. In addition, a 200 mg levodopa dose strength, has recently become widely available throughout Europe. However, two new strengths have recently been made available in the USA containing 75 and 125 mg levodopa, and these will also soon be available in most European countries. The flexible dose range may be advantageous in the gradual switch to Stalevo, as it allows for the up- or down-titration of therapy in small levodopa increments, thus allowing the effective management of side effects without compromising efficacy. The range also allows the simplification of the dosing regimen without the need for breaking tablets.

#### Switch to a combination of Stalevo and Sinemet/Madopar

In countries where Stalevo 200 is not yet available, physicians may need to consider combining Stalevo with low doses of Sinemet or Madopar to provide adequate symptom control in patients requiring a high total daily levodopa dose. In addition, extra doses of levodopa (controlled- and immediate-release) to supplement Stalevo at night-time and for the first morning dose is also recommended in some cases to help maintain symptomatic control and minimise wearing-off.

Dose fractionation is generally thought to be a strategy best suited to patients at a more advanced disease stage, as a less frequent dosing regimen could be harder to maintain symptomatic control throughout the day. Although certain European countries do use controlled-release levodopa more than others, in general, the sole use of controlled-release formulations during the daytime are avoided due to their unpredictable response. However, they may be of use at night-time.

#### Maintaining patients on optimal therapy

##### Background

Adherence and compliance to medication is important in PD to maintain function and to prevent the development of motor complications.<sup>30,31</sup> However, studies in patients with PD have shown poor medication compliance, especially with regard to the timing of each dose of medication. With advancing disease, the increasingly complex dosing regimens have been shown to negatively impact on patient adherence.<sup>32,33</sup> A number of interventions have been suggested to help maintain patients on optimal therapy. These include advanced warning of side effects, the addition of an anti-emetic during the initiation or dose titration phase, PD nurse/physician follow-up visits or phone calls and computer-based patient information. Informing the patient of potential adverse events; for example, prior warning of chromaturia with Stalevo (a harmless discoloration of urine), may help increase patient compliance if they are made aware that this is a harmless chemical effect of the drug. Active counselling about therapy has been shown to improve a patient's timing adherence to treatment.<sup>34</sup> Similarly, a follow-up call has been demonstrated to be useful in reducing discontinuation rates of patients with PD who had begun therapy with levodopa/DDCI and entacapone. A phone call 2 weeks after therapy initiation significantly decreased discontinuations for up to 6 months of therapy.<sup>35</sup>

##### Recommendations of the Neuronet-PD Working Group

Patient contact following the initiation of levodopa is essential for patient compliance; however, its success depends on available resources and in some cases may prove impractical if physicians do not have access to adequate services. Specialist PD nurses are

available in certain countries to provide patient support and education, via follow-up calls. Alternatively, the use of a specific helpline number or a special weekly outpatient clinic, which the patients could call or visit in the event of experiencing any adverse events, may help patients to maintain their levodopa therapy. It is also worth highlighting the use of computer-based patient information, via memory sticks or web-based programs, such as Google Health, as potentially useful therapy maintenance strategies.

## Conclusions

Levodopa is still the gold standard in the medical treatment of PD. The fear of motor complications, however, has led to its delayed initiation or its suboptimal administration. Conventionally, levodopa is given with a DDCI (carbidopa [Sinemet] or benserazide [Madopar]) and more

recently a combined formulation (Stalevo) has been developed that inhibits both DDCI and COMT in a single tablet. Stalevo provides an improved pharmacokinetic profile, which translates into clinical benefits compared with conventional levodopa. Strategies for the initiation of levodopa therapy vary between physicians, although initiation of either a 50 or 100 mg levodopa tid dosing regimen is most commonly used. With advancing disease, physicians commonly increase the dose or dose frequency of conventional levodopa or switch to Stalevo. Strategies for switching to Stalevo depend on the patient profile, levodopa dose and disease stage. At all stages of disease it is essential to maintain patients on optimal levodopa and to keep them informed of potential side effects. This can often be challenging, and such strategies as patient education and early follow-up may be of use to help patients gain optimal benefit from their levodopa therapy with minimum side effects. ♦

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