ORIGINAl ARTiCLE

Factors determining when to start levodopa/carbidopa/entacapone treatment in Spanish patients with Parkinson’s disease

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KEYWORDS
Parkinson’s disease; Levodopa/carbidopa/entacapone

Abstract
Introduction: Several therapeutic options are available for the symptomatic treatment of Parkinson’s disease (PD). There is no reliable information about which factors are involved in the choice of treatment.

Objective: To identify factors contributing to the decision to start treatment with levodopa/carbidopa/entacapone (LCE) in patients with PD.

Patients and methods: We completed a descriptive cross-sectional retrospective multicentre study of patients with idiopathic PD receiving LCE. Clinical data were collected with special attention to factors that could potentially determine when to initiate treatment with LCE in normal clinical practice.

Results: We studied 1050 patients with a mean age of 71.3 ± 8.7 years (58.2% men). Average time from the onset of symptoms to diagnosis was 13.8 ± 12.9 months, with a latency time of 74.5 ± 53.6 months before starting LCE treatment. The most common initial symptoms were tremor (70.6%), reduced dexterity (43.2%) and slowness of movement (41.5%). At the start of LCE treatment, most patients were in Hoehn and Yahr stage 2 (57.5%), with an average rating of 73.4% on the Schwab and England scale. Eight hundred twenty-two patients (78.3%) received treatment with other drugs before starting LCE (mean time between starting any PD treatment and starting LCE was 40.5 ± 47.2 months). Clinical factors with a moderate, marked, or crucial effect on the decision to start LCE treatment were bradykinesia (84.7%), daytime rigidity (72.2%), general decline (72.2%), difficulty walking (66.4%), tremor (62.7%), nocturnal rigidity (56.1%), and postural instability (53%). Difficulty performing activities of daily living was the only psychosocial factor identified as having an influence on the decision (84.3%).

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Introducción
Parkinson’s disease (PD) presents with both motor symptoms (resting tremor, bradykinesia and rigidity) and nonmotor symptoms. In Spain, PD prevalence is estimated at 1.7% among patients older than 65 years, although there are significant regional variations. Idiopathic PD accounts for approximately 85% of all the cases of parkinsonism diagnosed annually. Its complex aetiology is linked to environmental and genetic factors, which probably explains the disease’s heterogeneous progression profiles. Within this context, patient subgroups with different pathogenic mechanisms may exist, and each group may require a personalised treatment approach. While there is currently no proven neuroprotective treatment, powerful and efficient symptomatic treatments are available, but there is no consensus on when or how to start pharmacological treatment. Some studies suggest that early onset of treatment is beneficial to the patient’s quality of life, while most clinical practice guidelines recommend starting therapy when the first symptoms affecting daily life appear. Furthermore, treatment choice is based on several factors that are related to the drug itself (efficacy, complications, safety, etc.), the patient profile (symptoms, age, occupation, comorbidity, etc.) and other circumstances (e.g., socioeconomic status). This situation promotes uncertainty among patients and variability in clinical practice which has to do with lack of evidence.

Since not enough information is available on the factors influencing some therapeutic decisions made during the course of PD, performing studies to identify such influences seems to be justified. There is currently no consensus on which factors are involved in the decision to start combination treatment with set doses of levodopa/carbidopa/entacapone (LCE), which is one of the more frequently used PD treatments. This retrospective study aims to identify the factors affecting the decision by Spanish neurologists to prescribe this treatment in normal clinical practice. To our knowledge, no other study with a similar aim has been carried out in our setting, and the results of our study may be useful for increasing knowledge in this field.

Resultados: Se estudió a 1.050 pacientes (edad media 71,3 ± 8,7 años; 58,2%, hombres), con 13,8 ± 12,9 meses de evolución hasta el diagnóstico y 74,5 ± 33,6 meses hasta el momento del inicio del tratamiento con LCE. Los síntomas iniciales incluyeron: temblor (70,6%), reducción de destreza (43,2%) y leitud de movimientos (41,5%). El estadío de Hoehn y Yahr mayoritario al inicio de LCE fue 2 (57,5%), mientras que la escala de Schwab y England presentó una puntuación media de 73,4%. Ochocientos veintidós pacientes (78,3%) recibieron otros fármacos antes de LCE (tiempo medio entre inicio de tratamiento e inicio con LCE: 40,5 ± 47,2 meses). Los factores clínicos determinantes para iniciar el tratamiento con LCE fueron la presencia de bradicinesia (84,7%), rigidez diurna (72,2%), empeoramiento general (72,2%), dificultad marcha (66,4%), temblor (62,7%), rigidez nocturna (56,1%) e inestabilidad postural (53%). El único factor psicosocial determinante identificado fue la dificultad para realizar las actividades habituales de la vida diaria (84,3%).

Conclusiones: En la EP, el inicio del tratamiento con LCE viene determinado fundamentalmente por los déficits motores y la discapacidad asociada.
was calculated based on the precision considered acceptable for the worst-case scenario (from a precision of ±3% points for a proportion of 50%, to a precision of ±1.8% points for a proportion of 10% in one response category). We included patients aged 18 years and older with idiopathic PD treated with LCE during a minimum of 3 months before inclusion in the study. Patients were excluded if they were participating in a clinical trial during treatment with LCE and if their state of health, in the researcher’s opinion, would not permit them to be included in the study.

We collected clinical data from the patients by reviewing their medical histories, paying special attention to the factors determining when LCE treatment was started in normal clinical practice. The study protocol was approved by the Ethics Committee at Hospital Clinic in Barcelona.

In addition to the clinical symptoms specific to PD, we recorded time since diagnosis, initial symptoms, Hoehn and Yahr scale score,15 parts 2 (activities of daily living) and 3 (motor examination) of the Unified Parkinson Disease Rating Scale (UPDRS),16 Schwab and England Activities of Daily Living Scale,17 any previous treatments, and the start date for the different treatments. Furthermore, we analysed associations between the demographic and clinical variables recorded and pathological factors linked to disease progression and to onset of LCE treatment. A clinical or psychosocial factor was considered a determinant in the decision to start LCE treatment if the sum of 2% of patients in the categories ‘moderate influence’ and ‘crucial and determining’ represented more than 50% of the total patients presenting that factor.

Typical descriptive statistics were used according to the characteristics of the variables (categorical or continuous). Parametric (t-test or ANOVA) or non-parametric tests (Mann–Whitney or Kruskal–Wallis) were used to make comparisons. The Chi-square test was used with qualitative variables.

After identifying the clinical and psychosocial determinants, we established the association between these factors and the sociodemographic characteristics of the patients. To do so, we applied a logistic regression model for each determinant (as the dependent variable) using backward stepwise selection of the non-significant sociodemographic variables (independent variables). Results were expressed as odds ratios with their respective 95% confidence intervals.

Statistical analyses were performed using SAS statistical software, version 9.1.3 or later.

Results

The sample consisted of 1050 patients (58% men; mean age: 71.3 ± 8.7 years), assessed by 102 neurologists. The baseline condition of the patients at the start of LCE treatment was as follows. Hoehn and Yahr scale (available for 97.1% of patients): stage 1, 14.9%; stage 2, 57.5%; stage 3, 23.1%; and stage 4, 4.5%. Mean score on UPDRS part II (ADL): 12.8 ± 7.0; UPDRS part III motor examination, 25.7 ± 13.2 (UPDRS parts II and III available for 62.7%). Mean score on the Schwab and England scale (available for 76.5%): 73.4 ± 15.7. Table 1 displays other sociodemographic and medical history data for the sample.

Table 1  Sociodemographic characteristics of patients at the start of LCE treatment.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No studies</td>
<td>600</td>
<td>100.0</td>
<td></td>
<td>432</td>
<td>100.0</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Some primary studies</td>
<td>36</td>
<td>6.0</td>
<td></td>
<td>41</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed primary studies</td>
<td>158</td>
<td>26.3</td>
<td></td>
<td>161</td>
<td>37.3</td>
<td></td>
<td></td>
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<tr>
<td>Secondary studies</td>
<td>197</td>
<td>32.8</td>
<td></td>
<td>142</td>
<td>32.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher education</td>
<td>146</td>
<td>24.3</td>
<td></td>
<td>71</td>
<td>16.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household composition</td>
<td>63</td>
<td>10.5</td>
<td></td>
<td>17</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>592</td>
<td>100.0</td>
<td></td>
<td>425</td>
<td>100.0</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>With domestic partner</td>
<td>26</td>
<td>4.4</td>
<td></td>
<td>28</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With relatives</td>
<td>411</td>
<td>69.4</td>
<td></td>
<td>221</td>
<td>52.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In an institution</td>
<td>142</td>
<td>24.0</td>
<td></td>
<td>164</td>
<td>38.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.1586</td>
</tr>
<tr>
<td>Rural area (pop. &lt;5000)</td>
<td>581</td>
<td>100.0</td>
<td></td>
<td>420</td>
<td>100.0</td>
<td></td>
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</tr>
<tr>
<td>Suburban area (pop. 5000–19 999)</td>
<td>97</td>
<td>16.7</td>
<td></td>
<td>70</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban area (pop ≥20 000)</td>
<td>110</td>
<td>18.9</td>
<td></td>
<td>100</td>
<td>23.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Employed</td>
<td>584</td>
<td>100.0</td>
<td></td>
<td>418</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>60</td>
<td>10.3</td>
<td></td>
<td>21</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>68</td>
<td>11.6</td>
<td></td>
<td>33</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pensioner</td>
<td>1</td>
<td>0.2</td>
<td></td>
<td>248</td>
<td>59.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>455</td>
<td>77.9</td>
<td></td>
<td>116</td>
<td>27.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LCE: levodopa/carbidopa/entacapone.

* Chi-square test.
The time elapsed between the onset of typical PD symptoms and the time of the study was 6.21 ± 4.47 years and 5.18 ± 4.40 years from time of diagnosis. Table 2 displays other time data having to do with medical and treatment history.

Initial characteristic symptoms included tremor (70.6%), decreased ability and dexterity (43.2%), slow movement (41.5%), rigidity (17.6%) and impaired balance (12.1%). As shown in Table 3, most patients started treatment with levodopa (53%), a dopaminergic agonist (40%), and/or MAO inhibitors (19%).

Clinical and psychosocial factors

Table 4 summarises all the clinical and psychosocial factors assessed at the start of LCE treatment. The assessed clinical factors included typical signs of PD (tremor, rigidity, and bradykinesia), difficulty walking, loss of manual dexterity, motor fluctuations, and general clinical decline. Some of the most important clinical factors affecting the decision to start LCE treatment were bradykinesia (84.7%), general clinical decline (72.2%), and daytime rigidity (72.2%) (Table 4 and Fig. 1). Other clinical factors were decisive for some patients (wearing-off: 96%; motor fluctuations: 88%), but due to their limited representation in the sample (<5%), they have not been studied exhaustively or taken into account in secondary analyses.

Among the psychosocial factors considered, clumsiness and difficulty performing activities of daily living were determinants in the decision to start LCE treatment in 84.4% of the cases.

Association between sociodemographic characteristics and determinants

The summary of the association between the identified determinants and the sociodemographic characteristics is as follows. (a) No demographic characteristics linked to bradykinesia were identified as determinants in the decision to start LCE treatment; (b) the probability of presenting postural instability as the determinant was lower in patients younger than 65 years than in those older than 75 (OR: 0.48; CI 95%, 0.31-0.74); (c) the probability of presenting difficulty walking as the determinant was higher among patients younger than 65 years than in those older than 75 years (OR: 2.24; CI 95%, 1.49-3.35); (d) the probability of presenting a general clinical decline as the determinant in the decision to start treatment was lower among rural patients than among urban patients (OR: 0.57; CI 95%, 0.39-0.85); and (e) the probability of presenting difficulty with activities of daily living as the determinant was significantly lower among unemployed patients than among pensioners (OR: 0.29; CI 95%, 0.17-0.48).

Discussion

This study enables us to define the baseline clinical profile of Spanish PD patients started with LCE treatment. The main aim of the study included identifying clinical and psychosocial factors with a potentially significant effect on the neurologist’s decision to begin LCE treatment for PD.

Most of the PD patients who started LCE treatment presented motor symptoms at the approximate age of 65 years. They were mainly men with a primary or secondary education, retired, and living with a domestic partner. This demographic profile coincides with profiles described by other series on specialised care. The mean time elapsed from diagnosis to the first PD treatment was approximately 1.5 months, with a high variability (SD = 6.6 months); mean time elapsed between first-line treatment and the start of LCE treatment was approximately 3.5 years.

Levodopa (excluding LCE) and dopaminergic agonists were the drugs most frequently used as first-line treatment. In 40% of the cases, the dopaminergic agonist selected as first-line therapy coincides with the criteria established by most clinical guidelines. Although levodopa is effective for improving motor performance,15 doctors prescribing this drug should be aware that it is associated
Table 4  Factors influencing the decision to start LCE treatment.

<table>
<thead>
<tr>
<th>Presence (%)</th>
<th>Influence on the decision (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Slight</td>
</tr>
</tbody>
</table>

**Main clinical factors**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presence (%)</th>
<th>Influence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>90.5</td>
<td>15.4</td>
</tr>
<tr>
<td>Daytime rigidity</td>
<td>96.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Nocturnal rigidity/insomnia</td>
<td>89.1</td>
<td>16.8</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>97.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Postural instability</td>
<td>78.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>88.4</td>
<td>15.3</td>
</tr>
<tr>
<td>Symptoms affecting the dominant hand</td>
<td>88.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Fear of losing balance</td>
<td>80.7</td>
<td>29.3</td>
</tr>
<tr>
<td>Overall clinical decline</td>
<td>89.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Motor fluctuations</td>
<td>2.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>2.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>3.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Psychosocial factors**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presence (%)</th>
<th>Influence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty with activities of daily living</td>
<td>98.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Difficulty driving</td>
<td>69.5</td>
<td>44.8</td>
</tr>
<tr>
<td>Difficulty with job performance</td>
<td>65.6</td>
<td>45.6</td>
</tr>
<tr>
<td>Symptoms are embarrassing for the patient</td>
<td>77.9</td>
<td>34.5</td>
</tr>
<tr>
<td>Altered mood</td>
<td>82.6</td>
<td>24.9</td>
</tr>
<tr>
<td>Limitations on leisure activities</td>
<td>80.7</td>
<td>35.2</td>
</tr>
<tr>
<td>Impact on relationships</td>
<td>80.1</td>
<td>34.0</td>
</tr>
<tr>
<td>Secondary sexual dysfunction</td>
<td>66.7</td>
<td>61.6</td>
</tr>
<tr>
<td>Requested by patient</td>
<td>65.2</td>
<td>47.6</td>
</tr>
<tr>
<td>Intolerance to other drugs</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Simplification of treatment</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Side effects</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Lack of efficacy of other treatments</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Difficulty managing treatment</td>
<td>0.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

a Percentage calculated based on the total assessable patients (n = 1050).
b Percentage calculated based on the total patients presenting the symptom.

Figure 1  Clinical determinants in the decision to start LCE treatment.
with motor complications in more than half of the patients after the first 5 years of treatment. First-line treatment with a dopaminergic agonist aims to lower the risk of such complications. However, the development of new levodopa formulations, particularly the LCE combination studied here, has allowed us to optimise the pharmacodynamic profile and the bioavailability of the active ingredient (levodopa). Consequently, these formulations have become useful alternatives for treating motor manifestations and subsequent disability, and generally speaking, they show better tolerability than dopaminergic agonists. Nevertheless, use of the LCE formulation as first-line treatment is limited due to the recommendations listed above and the results of studies such as STRIDE-PD. This study demonstrated that starting levodopa treatment with LCE did not delay or decrease the frequency of dyskinesias (and may even increase them).

Among those patients for whom we have data on the start of LCE treatment, 80.6% presented a Hoehn and Yahr stage of 2.0 or 3.0, with mean scores on the Schwab and England scale and the UPDRS (parts II and III) that indicate general moderate impairment. Most of these patients were not fully independent for activities of daily living or else performed tasks slowly and with difficulty. These findings provide evidence that Spanish patients with PD begin LCE treatment relatively late, despite the proven efficacy of LCE in both stable and fluctuating patients and the demonstrated improvement in some areas of quality of life.

Analysis of clinical factors involved in the start of LCE treatment found that the main determinants were bradykinesia, general clinical decline, and daytime rigidity, followed by difficulty walking, tremor, nocturnal rigidity, and postural instability. Wearing-off and other motor fluctuations were determining factors for the patients presenting them. The only determinant among the psychosocial factors was difficulty performing activities of daily living. These factors coincide with the areas that improve the most with LCE therapy in patients experiencing the wearing-off effect, according to a recent post hoc analysis.

However, the decision of when to start this treatment depends on the highly idiosyncratic relationship between the patient and the disease. Once doctors decide to start treatment for PD, they must choose among different strategies (MAO inhibitors, dopaminergic agonists, and levodopa in combination with a decarboxylase inhibitor). The most suitable treatment must be chosen based on the patient’s characteristics (age, level of disability, occupation, etc.), the expected benefit (i.e., functional improvement) and the potential risks (i.e., development of dyskinesias and motor fluctuations). In any case, it should be noted that levodopa as first-line treatment not only increases the risk of motor complications in the short and medium term, but also involves a higher functional gain. This circumstance must be considered alongside the patient’s age and functional requirements.

The different regression models developed indicated that age, residential setting, and employment status were associated with different clinical determinants. This creates a complex framework of individual, clinical, and social interrelationships in which overall mobility and functional capacity differ between subgroups and are relevant when making treatment decisions.

Of the study’s limitations, the following are especially important: (a) its retrospective character; (b) the small percentage of patients presenting wearing-off in this series, a phenomenon whose cause could not be determined due to the study design; (c) the fact that influence of nonmotor symptoms on the decision to prescribe LCE was not taken into account (based on data in the ‘Psychosocial factors’ section in Table 4, these symptoms seem to have a low relevance); and (d) lack of analysis of the potential differences in the prescription of drugs due to socioeconomic factors linked to geographical and political situations.

The main contribution of this study, despite the limitations mentioned above, is that it demonstrates that LCE treatment onset is linked to functional decline and more noticeable signs of neurological impairment in the patient. Future studies focusing on quality of life may be able to evaluate the benefits of LCE treatment and the possible decrease of that benefit if the start of the appropriate therapy is delayed.

**Conflicts of interest**

This study received financial support from Novartis Farmacéutica, S.A. PMM received professional fees (as speaker or collaborator in different studies) from Novartis, Britainia, Orion Pharma, Abbott, UCB, and the Movement Disorder Society. He also received research grants from the FIS-ISCIII, IMERSO, Université Clermont-Ferrand (France), the Movement Disorder Society, Michael J. Fox Foundation (USA), and Queen Sofia Foundation. BH and JR are employed by Novartis Farmacéutica, S.A.

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