ORIGINAL CONTRIBUTION

Double-blind, Placebo-Controlled Study of Entacapone in Levodopa-Treated Patients With Stable Parkinson Disease

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**Background:** The catechol O-methyltransferase inhibitor entacapone acts by extending the elimination half-life of levodopa and is currently approved as an adjunct to levodopa for the treatment of patients with Parkinson disease (PD) with motor fluctuations.

**Objective:** To determine if the addition of entacapone administration provides benefit to levodopa-treated PD patients who have a stable response to levodopa and do not experience motor complications.

**Design:** Prospective, double-blind, placebo-controlled trial.

**Setting:** Outpatient multicenter study.

**Patients:** Female and male patients 30 years or older with idiopathic PD receiving stable doses of levodopa or carbidopa with or without other dopaminergic therapies and who did not experience motor fluctuations were eligible for the study.

**Main Outcome Measures:** Parkinsonian function and quality of life.

**Results:** The addition of entacapone did not improve motor scores on the Unified Parkinson’s Disease Rating Scale in levodopa-treated PD patients who did not experience motor fluctuations. The mean±SE adjusted change between baseline and final treatment visit was −0.9±0.35 in the entacapone group and −0.8±0.35 in the placebo group (P = .83). Significant improvement with entacapone treatment was detected in several quality-of-life measures, including the Parkinson Disease Questionnaire 39, the 36-item Short-Form Health Survey, the Parkinson’s Symptom Inventory, and investigator and subject Clinical Global Assessments. The drug was well tolerated by patients in this population.

**Conclusions:** The catechol O-methyltransferase inhibitor entacapone, used as an adjunct to levodopa in PD patients who do not experience motor fluctuations, does not improve Unified Parkinson’s Disease Rating Scale motor scores but does improve a variety of quality-of-life measures.

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**LEVODOPA IS THE STANDARD drug for the treatment of Parkinson disease (PD) and is typically administered in combination with a peripheral decarboxylase inhibitor to reduce peripheral metabolism. In the presence of a decarboxylase inhibitor, peripheral levodopa metabolism primarily occurs via catechol O-methyltransferase (COMT). The addition of a COMT inhibitor further reduces the peripheral metabolism of levodopa and extends its therapeutic effect.**

Entacapone (Comtan, Comtess; Orion Pharma, Espoo, Finland) is a selective and reversible inhibitor of COMT that in single-dose studies increases levodopa elimination half-life without altering its peak plasma concentration and time to maximal plasma concentration. Entacapone has been widely studied in PD patients experiencing levodopa-related motor fluctuations. Prospective, double-blind, placebo-controlled, multicenter studies have demonstrated that the addition of entacapone to levodopa results in increased “on” time, decreased “off” time, and enhanced motor function. Based on these clinical trials, entacapone has been approved as a treatment for end-of-dose wearing off in levodopa-treated PD patients.

The clinical benefits of entacapone are less well defined in levodopa-treated PD patients who do not have motor fluctuations but in whom it has been hypothesized that the drug might reduce the risk of developing motor complications. A placebo-controlled trial testing the COMT inhibitor tolcapone demonstrated slight, but significant, improvement in activities of...
daily living (ADL) in patients with early PD. However, the use of the drug has been restricted because of the risk of liver damage. In the present trial, we evaluated the safety and efficacy of entacapone in PD patients who were receiving stable doses of levodopa and who had not experienced end-of-dose wearing off.

METHODS

STUDY DESIGN

The study was designed as a prospective, randomized, multicenter, double-blind, placebo-controlled, parallel-group, 26-week study. The study protocol was reviewed and approved for implementation by the institutional review board at each study site.

PATIENT POPULATION

Female and male patients with idiopathic PD who were receiving stable doses of levodopa-carbidopa with or without other dopaminergic therapies were eligible for participation. Inclusion criteria included age of 30 years or older and diagnosis of PD based on a good response to levodopa and at least 2 of the following: rigidity, resting tremor, and bradykinesia. Levodopa doses had to be stable for at least 1 month, with a maximum of 4 daily doses of the regular or 3 daily doses of the controlled-release formulation. Participants could not experience end-of-dose wearing off within 4 hours of levodopa dose. Other antiparkinsonian medications were permitted, provided the dose was stable for 1 month before study entry. Exclusion criteria included previous exposure to entacapone, secondary or atypical parkinsonism, clinically significant medical or psychiatric illnesses, and dementia that precluded giving informed consent.

RANDOMIZATION AND TREATMENT

After signing informed consent approved by the institutional review board, the patients were randomized to receive entacapone, 200 mg, or matching placebo with each dose of levodopa according to a computer-generated randomization schedule. Study medication was continued until week 26 and then gradually withdrawn over 2 weeks. Patients could not increase the dose of levodopa-carbidopa or switch levodopa-carbidopa formulations during the study. The levodopa-carbidopa dose could, however, be decreased and subsequently increased back to the original baseline level if deemed necessary. Drug adjustments were performed by a blinded treatment investigator.

ASSESSMENTS AND OUTCOME MEASURES

Patients were evaluated at baseline and at weeks 1, 4, 12, 20, 26, and 28 after initiation of therapy. At each visit, parkinsonian function was evaluated with the Unified Parkinson’s Disease Rating Scale (UPDRS) and quality of life was assessed with the Parkinson Disease Questionnaire 39 (PDQ-39), the 36-item Short-Form Health Survey (SF-36), the Parkinson’s Symptom Inventory (PSI), and an investigator and subject Clinical Global Assessment. The UPDRS evaluations were performed 1 to 2 hours after the first morning levodopa dose. All patient evaluations were performed by the same blinded investigator.

The primary efficacy variable was the change from baseline to week 26 in the motor subscale scores of the UPDRS. Secondary efficacy variables included change from baseline to week 26 in ADL subscale score of the UPDRS; total UPDRS score; PDQ-39; SF-36; PSI, and investigator and subject Clinical Global

### Table 1. Demographic Summary (All Randomized Patients)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Entacapone (n = 373)</th>
<th>Placebo (n = 377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>69.8 ± 9.3</td>
<td>70.2 ± 9.4</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>72.9</td>
<td>68.7</td>
</tr>
<tr>
<td>Duration of PD, mean ± SD, y</td>
<td>4.4 ± 3.5</td>
<td>4.5 ± 3.5</td>
</tr>
<tr>
<td>Duration of levodopa prescription, mean ± SD, y</td>
<td>3.6 ± 3.1</td>
<td>3.6 ± 3.3</td>
</tr>
<tr>
<td>Levodopa dose, mean ± SD, mg</td>
<td>401.3 ± 191.9</td>
<td>406.2 ± 179.1</td>
</tr>
<tr>
<td>UPDRS score, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>19.3 ± 10.2</td>
<td>20.0 ± 9.9</td>
</tr>
<tr>
<td>ADL</td>
<td>8.9 ± 4.7</td>
<td>9 ± 4.5</td>
</tr>
<tr>
<td>Hoehn and Yahrb stage</td>
<td>2.12 ± 0.4</td>
<td>2.17 ± 0.3</td>
</tr>
<tr>
<td>Patients taking dopamine agonists, No. (%)</td>
<td>141 (37.8)</td>
<td>145 (38.5)</td>
</tr>
<tr>
<td>Patients taking selegiline</td>
<td>85 (22.8)</td>
<td>66 (17.5)</td>
</tr>
<tr>
<td>Patients taking amantadine hydrochloride, No. (%)</td>
<td>12 (3.2)</td>
<td>29 (7.7)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADL, activities of daily living; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.
STATISTICAL ANALYSIS

The primary and secondary outcome measures in the 2 treatment groups were compared using an analysis of covariance (ANCOVA), with treatment as the main effect and corresponding baseline measurement as the covariate. If assumptions of the parametric ANCOVA model of normality and constant variance were not satisfied, nonparametric Wilcoxon rank sum test, or Fisher exact test. Sample size calculations were based on the pivotal registration studies. To detect an estimated difference between groups in part 3 of the UPDRS of 2.1 ± 8.0 units with P = .05, a power of 90%, and a 20% dropout rate, a sample size of 750 was required.

Seven hundred fifty patients met entry criteria and signed informed consent. Three hundred seventy-three patients were randomized to entacapone and 377 to placebo. Two hundred eighty-one entacapone-treated patients (75.3%) and 274 placebo patients (72.7%) completed the study (Figure 1). There were no significant differences in baseline demographics between the groups (Table 1).

There was no significant difference between the 2 treatment groups with respect to the primary end point (Table 2). Mean ± SE adjusted change between baseline and final treatment visit was −0.9 ± 0.35 and −0.8 ± 0.35 in the entacapone and placebo groups, respectively (P = .83). There was similarly no significant difference between groups in the change from baseline in the ADL subscore of the UPDRS. Mean ± SE UPDRS motor and ADL scores in the entacapone and placebo groups at each visit are provided in Figure 2.

Although there was no improvement in UPDRS scores, entacapone treatment was associated with significant improvement in several quality-of-life measures compared with placebo (Table 2). There was significant improve-

### Table 2. Mean Change in Scores Between Baseline and Final Visits

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entacapone</th>
<th>Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS motor</td>
<td>19.3 ± 10.20</td>
<td>−0.9 ± 0.35</td>
<td>.83</td>
</tr>
<tr>
<td>UPDRS ADL</td>
<td>8.9 ± 4.7</td>
<td>−0.1 ± 0.19</td>
<td>.16</td>
</tr>
<tr>
<td>UPDRS total</td>
<td>29.9 ± 14.67</td>
<td>−0.9 ± 0.49</td>
<td>.42</td>
</tr>
<tr>
<td>Levodopa dose</td>
<td>401.3 ± 191.9</td>
<td>−4.9 ± 4.24</td>
<td>.004</td>
</tr>
<tr>
<td>PDQ-39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>30.2 ± 15.48</td>
<td>−0.7 ± 0.46</td>
<td>−.001</td>
</tr>
<tr>
<td>Mobility</td>
<td>29.2 ± 25.47</td>
<td>0.7 ± 0.76</td>
<td>.001</td>
</tr>
<tr>
<td>ADL</td>
<td>31.4 ± 21.60</td>
<td>−3.0 ± 0.67</td>
<td>−.001</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>25.0 ± 17.96</td>
<td>−0.9 ± 0.67</td>
<td>.13</td>
</tr>
<tr>
<td>Stigma</td>
<td>19.3 ± 20.00</td>
<td>−1.8 ± 0.68</td>
<td>.10</td>
</tr>
<tr>
<td>Social support</td>
<td>58.2 ± 20.11</td>
<td>−0.6 ± 0.90</td>
<td>.13</td>
</tr>
<tr>
<td>Cognition</td>
<td>30.1 ± 20.00</td>
<td>−0.2 ± 0.68</td>
<td>.27</td>
</tr>
<tr>
<td>Communication</td>
<td>24.8 ± 21.05</td>
<td>−0.2 ± 0.71</td>
<td>.33</td>
</tr>
<tr>
<td>Body discomfort</td>
<td>34.2 ± 21.36</td>
<td>−1.0 ± 0.78</td>
<td>.19</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>−1.1 ± 1.2</td>
<td>−0.1 ± 0.03</td>
<td>.047</td>
</tr>
<tr>
<td>Physical domain</td>
<td>−0.1 ± 1.4</td>
<td>−0.1 ± 0.05</td>
<td>.10</td>
</tr>
<tr>
<td>Bodily pain domain</td>
<td>−0.4 ± 0.99</td>
<td>0.0 ± 0.04</td>
<td>.13</td>
</tr>
<tr>
<td>General health domain</td>
<td>−0.5 ± 0.92</td>
<td>−0.1 ± 0.04</td>
<td>.45</td>
</tr>
<tr>
<td>Vitality domain</td>
<td>−0.4 ± 0.99</td>
<td>−0.0 ± 0.04</td>
<td>.94</td>
</tr>
<tr>
<td>Social functioning</td>
<td>−0.3 ± 1.05</td>
<td>−0.1 ± 0.04</td>
<td>.056</td>
</tr>
<tr>
<td>Emotional domain</td>
<td>−0.5 ± 1.22</td>
<td>−0.1 ± 0.06</td>
<td>.95</td>
</tr>
<tr>
<td>Mental health domain</td>
<td>0.1 ± 0.88</td>
<td>0.0 ± 0.03</td>
<td>.83</td>
</tr>
<tr>
<td>Physical component</td>
<td>40.2 ± 9.96</td>
<td>−0.6 ± 0.35</td>
<td>.009</td>
</tr>
<tr>
<td>Mental component</td>
<td>50.7 ± 9.35</td>
<td>−0.4 ± 0.40</td>
<td>.85</td>
</tr>
<tr>
<td>PSI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>24.0 ± 12.19</td>
<td>−1.5 ± 0.44</td>
<td>.007</td>
</tr>
<tr>
<td>Distress</td>
<td>19.3 ± 13.19</td>
<td>−1.4 ± 0.48</td>
<td>.02</td>
</tr>
<tr>
<td>Global assessment, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator improved</td>
<td>111 (39.1)</td>
<td>87 (31.3)</td>
<td>.08</td>
</tr>
<tr>
<td>Subject improved</td>
<td>140 (49.5)</td>
<td>100 (35.8)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; PDQ-39, Parkinson Disease Questionnaire 39; PSI, Parkinson's Symptom Inventory; SF-36, 36-item Short-Form Health Survey; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Change scores are given as mean ± SE; baseline visits, mean ± SD.

†P value comparing change between baseline and final visit in placebo and entacapone groups.
ment in the PDQ-39 total score, the mobility and ADL domains of the PDQ-39, the physical functioning component and vitality domains of the SF-36, and the frequency and distress measures of parkinsonian disability on the PSI. Clinical Global Assessment ratings of physicians and patients noted larger numbers of patients to be improved in the entacapone group compared with the placebo group. More patients in the placebo group (12.5%) than in the entacapone group (8.0%) required an increase in dopaminergic therapy (ie, levodopa rescue) \((P=.046)\). Similar results were obtained when the data were analyzed using a regression-based imputation model.

The most commonly observed adverse events are listed in \(\text{Table 3}\). Seven study patients died: 1 in the entacapone group and 6 in the placebo group. More patients in the placebo group (12.5%) than in the entacapone group (8.0%) required an increase in dopaminergic therapy (ie, levodopa rescue) \((P=.046)\). Similar results were obtained when the data were analyzed using a regression-based imputation model.

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The addition of entacapone to levodopa in patients with fluctuating PD has been demonstrated to reduce “off” time, increase “on” time, and enhance UPDRS motor func-

\begin{table}[h]
\centering
\caption{Adverse Events}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Event} & \textbf{Entacapone (n = 373)} & \textbf{Placebo (n = 377)} \\
\hline
Any adverse event & 339 (90.9) & 344 (91.2) \\
Nausea & 68 (18.2) & 44 (11.7) \\
Dyskinesia & 47 (12.6) & 41 (10.9) \\
Postural hypotension & 47 (12.6) & 51 (13.5) \\
Diarrhea (not otherwise specified) & 45 (12.1) & 28 (7.4) \\
Insomnia (not otherwise classified) & 39 (10.5) & 41 (10.9) \\
Fall & 36 (9.7) & 36 (9.5) \\
Dizziness (excluding vertigo) & 36 (9.7) & 34 (9.0) \\
Somnolence & 29 (7.8) & 36 (9.5) \\
Tremor aggravated & 29 (7.8) & 35 (9.3) \\
Arthralgia & 27 (7.2) & 15 (4.0) \\
Urinary tract infection (not otherwise specified) & 24 (6.4) & 12 (3.2) \\
Urinary discoloration & 24 (6.4) & 1 (0.3) \\
Fatigue & 23 (6.2) & 31 (8.2) \\
Pain in limb & 23 (6.2) & 18 (4.8) \\
Constipation & 20 (5.4) & 14 (3.7) \\
Back pain & 20 (5.4) & 19 (4.8) \\
Headache (not otherwise specified) & 19 (5.1) & 31 (8.2) \\
Sleep disorder (not otherwise specified) & 17 (4.6) & 19 (5.0) \\
Nasopharyngitis & 16 (4.3) & 20 (5.3) \\
Edema of lower limb & 8 (2.1) & 19 (5.0) \\
\hline
\end{tabular}
\end{table}

The value of a COMT inhibitor in patients with early PD who do not experience motor fluctuations is less well defined. In the present study, we assessed the effects of entacapone in levodopa-treated PD patients who do not experience motor fluctuations. We did not observe a significant benefit associated with respect to UPDRS motor score, the primary outcome measure of the study. Entacapone treatment was, however, associated with significant benefits in some quality-of-life measures, including the PDQ-39 total score, ADL and mobility domain subscores, the SF-36 physical functioning and vitality domains and physical component subscores, the PSI inventory of frequency and distress level of PD symptoms, and subject Clinical Global Assessment scores. In addition, placebo patients required levodopa rescue more often than did entacapone-treated patients. Caution must be used, however, in interpreting these secondary outcome measures. There were a large number of dropouts in this trial, for which there is no apparent explanation. More placebo patients dropped out because they required levodopa therapy, but there were no differences between groups in dropouts for adverse events. All patients were included in the intention-to-treat analysis using a last-observation-carried-forward method, which is expected to bias in favor of the placebo group (since more placebo patients dropped out because they needed further treatment and might have been expected to deteriorate even further had they stayed in the study). Identical results were obtained when the data were analyzed using other imputation strategies.

It is interesting to consider why entacapone failed to improve UPDRS motor score while providing significant benefit in quality-of-life measures. One possibility is that entacapone can provide no additional antiparkinsonian...
benefits to levodopa-treated patients. The average age of patients in this study (70.0 years) was higher than is typically encountered in clinical trials of patients with early PD. Elderly PD patients often have a less robust response to levodopa, which may make it difficult to detect subtle improvement in motor function with the addition of entacapone.15 Furthermore, the elderly age of our population raises the possibility that there was a higher-than-usual rate of misdiagnosis. A high frequency of conditions such as atypical or vascular parkinsonism, which have a limited response to levodopa, may have precluded seeing an entacapone-related benefit.

The timing of the motor examination may also have been a problem. Examinations were performed approximately 1 hour after the first morning dose of levodopa when many patients experience their best motor response.12 This may have precluded the opportunity to observe a small improvement in motor examination when entacapone was added to levodopa. It may be that it would have been easier to detect benefits if the evaluation had been performed several hours after the levodopa dose, because entacapone extends the duration of benefit following a single dose of levodopa. This may have accounted for why patients experienced enhanced quality of life and improved investigator and subject Clinical Global Assessment scores despite the lack of change in UPDRS motor scores. Finally, the small, but statistically significant, increase in the average levodopa daily dose in the placebo-treated group may have blunted detection of any differential improvement in motor function between the 2 treatment groups.

It may also have been a mistake to select the UPDRS motor subscale as the primary outcome measure. Levodopa-treated PD patients with mild disease have relatively low motor scores, and it may be difficult to detect improvement because of a floor effect. Quality-of-life scales may provide a more sensitive measure of clinical benefit in patients with early PD. Two recent clinical trials noted that UPDRS motor scores were improved to a greater degree in patients randomized to initiate therapy with levodopa compared with a dopamine agonist even though patients in both groups could receive supplemental levodopa and had comparable quality-of-life scores.13,14 This raises the possibility that dopaminergic agents affect patients with early PD in ways that are not captured by the UPDRS and emphasizes the need to use quality-of-life measures in studies of patients with early PD.15 A critique of the UPDRS also questioned its sensitivity in early PD,16 and a task force has been organized by the Movement Disorder Society to generate a revised version of the UPDRS that focuses on early disease. Despite the lack of improvement in UPDRS scores in our study, patients who received entacapone had significant benefits in quality of life compared with placebo patients. In a similar trial, the COMT inhibitor tolcapone also produced more striking improvement in quality-of-life measures than motor function.6,17 It may be that in the patients with relatively mild PD, entacapone provides clinical benefits that are subjective and more apparent to patients than physicians, although the value of these quality-of-life benefits remains unclear.

In summary, the addition of entacapone to levodopa in PD patients who do not experience motor complica-

In addition to the potential of COMT inhibitors to improve quality of life in patients with early PD, there is interest in the role these drugs might play in reducing the risk of developing the motor complications associated with levodopa therapy. A body of evidence suggests that motor complications associated with levodopa are related to abnormal pulsatile stimulation of dopamine receptors and might be prevented with therapies that deliver more continuous dopaminergic stimulation.18 In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned primates and PD patients, dyskinesias are reduced when treatment is initiated with a long-acting dopamine agonist compared with a short-acting formulation of levodopa.19,20 However, PD patients eventually require levodopa treatment, and this is associated with an increased risk of motor complications.14 We have postulated that administering levodopa with a COMT inhibitor to extend its elimination half-life might reduce the risk of pulsatile stimulation and motor complications.21 Indeed, we recently showed that adding entacapone to levodopa reduces the risk of dyskinesia in MPTP-treated primates. Clinical trials to test the capacity of entacapone to reduce the risk of levodopa-induced motor complications are currently under way.


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tions provides no measurable improvement in UPDRS scores but improves secondary measures of quality of life. Additional studies specifically designed to assess the impact of entacapone on quality of life in PD patients are needed to confirm these observations. This study underscores the complexities of conducting clinical research in levodopa-treated PD patients with mild disease.

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REFERENCES