Pramipexole versus Levodopa in Patients with Early Parkinson’s Disease: Effect on Generic and Disease-Specific Quality of Life

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ABSTRACT

Objective: Although health-related quality of life (HRQOL) has been included in multiple Parkinson’s disease (PD) clinical trials, little is known about how HRQOL responds to treatments over time. Here we assess the effect of therapy on HRQOL and explore factors that influence the HRQOL profiles and subdomains.

Method: A total of 301 subjects with early PD were randomized to either initial pramipexole or initial levodopa and followed every 3 months over a 4-year period. To estimate health outcomes, we used EQ-5D and PDQUALIF. We calculated the incremental effectiveness as the accumulated difference in the total HRQOL over time between treatments. The subgroup analyses (by sex, race, age, baseline patient characteristics, and occurrence of adverse events) were conducted using the same approach. Sensitivity analysis was performed to test the effect of missing data imputation on the results.

Results: All three HRQOL measures resulted in similar profiles over time characterized by initial improvement over the first 3 to 6 months and followed by a gradual decline in years 2, 3, and 4. The difference in HRQOL between the treatment arms widened in favor of pramipexole in years 3 and 4 for all HRQOL measures used (EQ-5D: Y3 0.048, \( P = 0.03 \); Y4 0.071, \( P = 0.04 \)). Our analyses suggested that the effect of pramipexole on HRQOL was mediated through nonmotor functions, whereas levodopa improved primarily motor domains of HRQOL.

Conclusion: Our results suggest that pramipexole and levodopa affect patient HRQOL via improvement on different domains of well-being: nonmotor effect for pramipexole and mobility improvement for levodopa.

Keywords: health-related quality of life, levodopa, longitudinal assessment, Parkinson’s disease, pramipexole.

Introduction

Recent clinical trials comparing initial treatment with dopamine agonists to initial levodopa therapy in early Parkinson’s disease (PD) have shown that each treatment policy generates distinct effect profiles [1–3]. Initial use of dopamine agonists compared with initial use of levodopa results in reduced risk of developing dyskinesias and wearing off over the first 4 to 5 years of treatment. Initial use of levodopa compared with dopamine agonists, however, results in a sustained five- to seven-point improvement on the Unified Parkinson’s Disease Rating Scale (UPDRS) [1,2] and significantly less somnolence and edema. Treatment guidelines have stated that both are options as initial therapy and the available evidence does not favor one treatment option over another.

Several types of outcomes are used in patient outcomes research, including cost-effectiveness studies.

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10.1111/j.1524-4733.2006.00078.x

The concept of health-related quality of life (HRQOL) was developed to evaluate quantitatively person’s well-being [4, 5]. Utility scores reflect person’s preferences for health states. Utilities are used as weights when calculating quality-adjusted life-years (QALYs) that capture both duration of life in a particular health state and utility of that state [6–8]. Health states could be defined by their HRQOL. Utilities are assessed using preference-based methods, such as time trade-off for EQ-5D [9]. Visual analog scale is often used for simplicity but it does not provide utility values. HRQOL and utility evaluations are different from the assessment of health status that is typically performed via health status questionnaires [10].

Prior studies have shown that HRQOL is correlated with important aspects of PD. Cross-sectional studies in PD have shown that HRQOL is influenced by age, disease severity, depression, sleep-related events, and motor fluctuations [11–14]. Longitudinal studies [15,16] have shown that quality of life in PD patients decreases as the disease progresses. Although HRQOL assessments have been included in multiple PD clinical trials, little is known about differential effects of treatments on HRQOL of PD population over time.
The 4-year trial [2] comparing initial pramipexole and initial levodopa showed that between the treatment arms there was no difference in the mean changes in the HRQOL scores from the 48-month visit to the baseline visit. In this study, we estimate longitudinal models to characterize HRQOL profiles taking into account the HRQOL values for all visits and accumulate gains and losses over time, by treatment arm [17]. This approach takes into account the transient interim values of HRQOL during the trial rather than ignoring dynamic patterns in HRQOL between randomization and the end of the trial. This may be of particular relevance given that the beneficial quality of life effects associated with delaying dopaminergic complications by using initial dopamine agonists instead of levodopa may be delayed and accrue over years of therapy [2].

Using this method, we address the following questions: 1) in early PD patients, which treatment alternative generates more benefit in terms of HRQOL, and 2) how does the difference in HRQOL gains between treatments change as time goes on. In addition, we explore whether patients who experience adverse events (dyskinesias, edema, and somnolence) have worse quality of life than patients who do not experience adverse events.

Methods
Overview of Clinical Trial
The trial was a randomized, double-blinded, placebo-controlled study that randomly assigned 301 subjects with early PD to either initial levodopa (n = 150) or initial pramipexole (n = 151) with the option in both arms of adding open-label levodopa for emerging disability [18]. Eligible subjects were persons 30 years or older who had PD for less than 7 years, Hoehn and Yahr scale (HY) [19] stage I–III, and who required dopaminergic anti-PD therapy at the time of enrollment [18]. Enrollment occurred between October 1996 and August 1997 at 22 academic movement disorder clinics in the United States (17 sites) and Canada (five sites). The 2- and 4-year trial results are reported elsewhere [1,2,18,20].

Health-Related Quality of Life assessments
The HRQOL was measured using generic (EuroQol group instrument including EQ-5D and EQ-VAS) [9, 21] and PD-specific (PDQUALIF [22]) instruments at baseline and 10, 26, 52, 78, 102, 130, 156, 182, and 208 weeks after randomization. The HRQOL instruments were self-administered during the face-to-face study visit in a quiet clinic room, and were the first instruments administered during the study visits.

We chose EQ-5D as the primary HRQOL measure because this instrument provides a measure of utility and, hence, allow us to estimate effectiveness in QALY units. In addition, EQ-5D has been tested for use in the elderly with PD [23,24]. ED-VAS and PDQUALIF do not yield utility values but were included 1) to examine similarities and differences between HRQOL values obtained via different tools; and 2) to reemphasize trends. Changes in the EQ-5D over time were denoted as QALYs gained or lost. Changes in the EQ-VAS and PDQUALIF over time are referred to as VAS-t and PDQUALIF-t.

EQ-5D. The EQ-5D consists of two main components: patient health state classification component with a set of weights to assign a utility value (denoted here as EQ-5D) to each health state and a visual analog scale (EQ-VAS). The health classification component is defined over five domains of health: mobility, self-care, usual activity, pain, and depression/anxiety. Each of the five domains is categorized into three severity levels and responses are combined by a scoring algorithm to produce a summary score between –0.594 (the worst health state) and 1.0 (the best health state), with 0 anchored at death. Utility values for health states are based on time-trade-off responses taken from a sample of the UK population. The EQ-VAS is a thermometer-type scale with 101 tick marks on which the subject rates his or her current health state on a scale from 0 to 100, with 0 corresponding to the lowest score (worst imaginable health) and 100 corresponding to the best imaginable health.

The Parkinson’s disease quality of life scale (PDQUALIF). The PDQUALIF is a disease-specific HRQOL instrument, which consists of 33 patient self-administered questions. The questions evaluate changes in person’s severity of disease, independence in performing activities of daily living (ADLs), social interactions and emotional status as perceived by the patient. Preliminary reliability and validity have been demonstrated on a sample of PD patients with varying severity of PD symptoms [22]. In the original instrument, higher PDQUALIF scores represent greater disability. To make the interpretation consistent with the EQ-5D, we reversed the scoring of the PDQUALIF by dividing the score by 100 and subtracting that from 1 so that higher scores represent better HRQOL.

Imputation of Missing HRQOL Data
Overall, 18% of HRQOL data were missing (547 out of 3010 observations), either in the middle of the trial (intermittent missing, 1%) or at the end of the 4-year period as a result of early study termination (dropout missing, 17%). In the pramipexole group, 11 subjects withdrew for somnolence, five for edema, and one for both. In the levodopa group, three withdrew for dyskinesias, and one for somnolence. For patients who died during the study (three deaths in the levodopa group and two in the pramipexole group were not treatment-related), HRQOL for all visits after death...
was assigned to zero. For each dependent measure (EQ-5D, EQ-VAS or PDQUALIF), missing data were imputed using a multivariate fixed-effect (FE) model similar to the approach recommended by Engels and Diehr [25]. The dependent variable, \( Y_{it} \), was the difference between the baseline HRQOL score and the score for each following visit. Independent variables included treatment, baseline patient characteristics, a set of variables describing baseline health status, trial-related variables, a series of indicators for each study visit (number of weeks after randomization), and a fixed individual component used to account for individual patient trends in HRQOL over time. Health status at baseline included the number of self-reported comorbidities and a proxy for mental health problems (depression/anxiety) based on the Anxiety/Depression item of the EQ-5D questionnaire (answer of 0 = none, 1 = some, 2 = severe). Trial-related variables included treatment assigned at randomization, trial completion status, whether the subject was on open-label levodopa at the time of the visit, and markers indicating whether the subject dropped-out by the next visits and whether the previous visit was missing. Originally we included the independent variables describing adverse events (presence of dyskinesias, somnolence, edema, wearing offs or on/off effects) in the model. But because these variables and their interactions with treatment and time were not significant, independently or jointly, at \( P = 0.05 \) level, they were omitted from the final model.

We imputed \( Y_{it} \) for missing data by calculating prediction \( \hat{Y}_{it} \) using the above independent variables, all of which were observed, and \( \mu_{it} \), the estimated individual-level FE. We assumed that HRQOL data were missing at random (MAR), conditional on observed subject characteristics and individual FE. All the results presented include all 301 subjects. We used STATA Statistical Software Release 8.0 (STATA Corporation, College Station, TX, 2003) for the modeling and SAS for Windows Version 8 (The SAS Institute, Cary, NC, 2001) for data manipulations.

**Determining the Effectiveness of Treatment Strategies**

We generated normalized quality of life profiles for each treatment group by plotting the mean change in the HRQOL score from baseline to each study visit using the EQ-5D, the EQ-VAS, and the PDQUALIF [26,27]. We estimated the effectiveness of the intervention as the difference in areas under the normalized HRQOL profile between the treatments, \( \Delta \hat{E} = \text{pramipexole} - \text{levodopa} \). To obtain the present discounted values of HRQOL, all measures were discounted at 3% annually. We generated bootstrapped (1000 iterations resampled by person) standard errors of the areas under the appropriate HRQOL profiles and of the estimate of incremental effectiveness (\( \Delta \hat{E} \)). With each redrawn sample of the bootstrap, we estimated the imputation model and recalculated the point estimates. Thus, the reported standard errors incorporated uncertainty due to the imputation as well as uncertainty due to sampling.

To identify subpopulations with differential treatment effects, we examined the effect of the 4 years of therapy on HRQOL in the following groups: males, females [13], subjects age 65 and over, subjects under 65 years of age, subjects with the lowest baseline HRQOL score and the highest baseline HRQOL scores (for each of the EQ-5D, EQ-VAS, PDQUALIF) [11, 15], and those with self-reported depression/anxiety as measured by the EQ-5D. Areas under each treatment HRQOL profile and the difference between the treatment arms were estimated as described above.

**Exploratory EQ-5D Analyses**

**Sensitivity analyses on imputation of missing data.** We conducted sensitivity analyses to assess the consequence of imputation on the HRQOL estimates. In particular, we varied assumptions about the quality of life profiles immediately after dropout. We considered four scenarios: 1) quality of life profiles improved for both treatments; 2) quality of life deteriorated for both treatments; 3) quality of life improved for those in the pramipexole group and deteriorated for those in the levodopa group; and 4) quality of life improved for those in the levodopa group and deteriorated for those in the pramipexole group. Scenarios in which a subject’s quality of life improves after dropout include “treatment-related” dropouts when side effects of medication result in treatment termination and, on drug discontinuation, quality of life improves. Scenarios in which a subject’s quality of life deteriorates further after dropout reflect “disease progression-related” dropouts. To quantify the improvement or deterioration in HRQOL in each of the scenarios, we estimated regression models that identified a decline before dropout (a deterioration of 0.078 QALY in the pramipexole arm and 0.065 QALY in the levodopa arm), and we assumed that the decline either continued (further deterioration of the same amounts after dropout) or reversed (improvements of the same amounts after dropout) until the 48th month’s visit.

In addition to the FE approach for imputing missing data as described above, we also tested standard methods for the imputation of missing data: 1) imputation of the mean (IOM); 2) last observation carried forward (LOCF); and 3) imputation conditional on individual baseline characteristics but without the individual FE component (OLS) [28].

**Association between EQ-5D and adverse events.** To explore the relationship between the treatments, adverse events (dyskinesias, wearing off, somnolence, and edema), and HRQOL, we compared the total gain in HRQOL over 4 years in subjects who had and did
not have specific complications at least once during the trial. The presence of dyskinesias and wearing off was determined by one investigator at each site and based on direct observation or historical report. The presence of edema or somnolence was determined by open-ended questioning of subjects at each study visit. The findings were considered significant at P-values less than 0.05.

**EQ-5D and UPDRS subscale analysis.** To provide insights into the health status domains that constitute HRQOL, we performed a subscale analysis of the EQ-5D and the UPDRS [20]. We calculated the incremental 4-year gains for each of the five EQ-5D items: mobility, self-care, usual activity, pain, and depression/anxiety. We also applied the imputation model to the UPDRS and calculated the incremental 4-year gains for the total score as well as its three subscales: mental (part I), ADLs (part II), and motor (part III). The subscale gains are estimated using different scales and, hence, they cannot be compared directly. Nevertheless, the direction of the difference and statistical significance of these estimates provide useful information about treatment effect.

**Results**

**Subject Characteristics**

Baseline characteristics of patients randomized to either levodopa or pramipexole are presented in Table 1. When measured via PDQUALIF and EQ-5D, the baseline HRQOL scores were significantly higher for patients randomized to levodopa (P < 0.05). Close to a third of all subjects reported some level of depression/anxiety at randomization, which was more prevalent in the pramipexole arm (38% vs. 22% in levodopa arm, chi-square = 0.002). In addition, subjects in pramipexole group on average had more comorbidities (4.84 vs. 4.32 in levodopa group, P = 0.04). Patients in the levodopa group, on average, were diagnosed with PD for a longer period of time before enrolling in the study (1.8 vs. 1.5 years for pramipexole subjects, P = 0.03).

Prevalence of in-trial complications varied between the treatment arms. Subjects randomized to pramipexole reported higher occurrence of somnolence (38.4% vs. 19.3% in levodopa group, P < 0.001) and edema (41.1% vs. 13.3% in levodopa arm, P < 0.001), whereas levodopa subjects experienced more dyskinesias (50.7% vs. 21.9% among pramipexole subjects, P < 0.001) and wearing offs (59.3% vs. 45% in pramipexole arm, P = 0.01) (Table 1).

**Estimating HRQOL Gain over Time**

The HRQOL profiles over the 4 years for each of the three measures were similar (Fig. 1). The profiles showed an immediate gain in HRQOL in year 1 followed by a decline over the next 3 years. The subjects randomized to pramipexole experienced greater cumulative gains over the 4 years, but the difference in total gains did not reach statistical significance. The incremental effectiveness of pramipexole compared with levodopa increased over time, with the largest benefits observed during the last 2 years of the trial. The difference in QALY gain between pramipexole and levodopa groups was statistically significant in the years 3 and 4 of the trial (year 3, 0.048 QALY, P = 0.03; year 4, 0.071 QALY, P = 0.04).

Table 2 shows the incremental HRQOL gains by baseline characteristics. Males tended to have significant incremental gains in QALY due to pramipexole, whereas females did not. Those subjects who self-reported lower HRQOL anxiety and depression at baseline tended to demonstrate greater gains in

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**Table 1  Characteristics of trial cohort**

<table>
<thead>
<tr>
<th>Category name</th>
<th>Variable</th>
<th>Levodopa mean/percent n = 150</th>
<th>Pramipexole mean/percent n = 151</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>Age (year)</td>
<td>60.9 (10.5)†</td>
<td>61.5 (10.1)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Sex (male)</td>
<td>66.0%</td>
<td>63.6%</td>
<td>0.66</td>
</tr>
<tr>
<td>Health status</td>
<td>PD duration</td>
<td>1.8 (1.7)</td>
<td>1.5 (1.4)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Depression/anxiety‡</td>
<td>22.0%</td>
<td>38.4%</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Number of comorbidities†</td>
<td>4.34 (2.35)</td>
<td>4.84 (2.44)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>UPDRS total</td>
<td>31.1</td>
<td>32.6</td>
<td>0.30</td>
</tr>
<tr>
<td>HRQOL</td>
<td>PDQUALIF</td>
<td>0.73 (0.11)</td>
<td>0.71 (0.12)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>EQ-5D</td>
<td>0.78 (0.18)</td>
<td>0.72 (0.21)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>EQ-VAS</td>
<td>0.78 (0.12)</td>
<td>0.75 (0.16)</td>
<td>0.12</td>
</tr>
<tr>
<td>In-trial adverse events</td>
<td>Somnolence</td>
<td>19.3%</td>
<td>38.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>13.3%</td>
<td>41.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Dyskinesias</td>
<td>50.7%</td>
<td>21.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Wearing off</td>
<td>59.3%</td>
<td>45.0%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Chi-square for comparison of frequency and t-test for comparison of means, levodopa versus pramipexole.

†Values in parentheses are SD.

‡Subjects who answered “I am not anxious or depressed” were classified into “no depression/anxiety” group. Subjects who answered “I am moderately/extremely anxious or depressed” were classified into “depression/anxiety” group.

†Includes cardiovascular, pulmonary, allergic, gastrointestinal, metabolic/endocrine, renal, reproductive, musculoskeletal, dermatologic, and psychiatric categories.

HRQOL, health-related quality of life; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.
Figure 1 Total 4-year gains in health-related quality of life (HRQOL): PDQUALIF, EQ-5D, EQ-VAS. The mean change in HRQOL from baseline was calculated at each visit (10, 26, 52, 78, 102, 130, 156, 182, and 208 weeks) for each treatment arm using EQ-VAS (A), EQ-5D (B), and PDQUALIF (C). The incremental differences ($\Delta$) in HRQOL between pramipexole and levodopa, by year, were estimated as the area between the two treatment profiles. The size of each graph was scaled to reflect the differences in the instrument scale ($-0.594$ to 1 for EQ-5D and 0 to 1 for EQ-VAS and adjusted PDQUALIF).
HRQOL if in the pramipexole group compared with the levodopa group, but the differences did not reach statistical significance for all instruments. No clear pattern of incremental HRQOL gains or losses emerged by age.

Sensitivity Analysis on Imputation of Missing EQ-5D Data

Under all four scenarios, the cumulative QALY gains were greater in the pramipexole group compared with the levodopa group (Table 3). Only under the scenario where quality of life improves after withdrawal for those in the pramipexole group and deteriorates for those in the levodopa group did the incremental gains in QALY reached statistical significance (QALY gained 0.216, \( P = 0.01 \)). When we assumed that EQ-5D would improve for all subjects after dropping out, treating with pramipexole resulted in the incremental gain of 0.143 QALY (\( P = 0.09 \)) compared with treating with levodopa.

Using standard methods for missing data imputation also demonstrated a nonstatistically significant difference in QALY's gain by treatment arm over 4 years of therapy, and the estimates of health gains were smaller (LOCF 0.084 QALY [SD 0.074], IOM 0.083 QALY [SD 0.077], OLS 0.082 QALY [SD 0.071]) (Fig. 2). We also performed another sensitivity analysis by repeating the analysis after removing the four patients with the lowest baseline EQ-5D scores, which were all in the pramipexole arm. Neither point estimates nor statistical significance were substantively affected by exclusion of the four subjects.

Association between EQ-5D and Adverse Events

There were no statistically significant differences in QALY gained or lost for subjects who experienced an adverse event compared with those who did not experience an adverse event (Table 4). Nevertheless, several themes emerged. For the subjects in the levodopa group, the presence of dyskinesias and wearing off were associated with greater gains in HRQOL compared with the subjects who did not experience dyskinesias. For the subjects in the pramipexole group, however, the relationship between HRQOL and dyskinesias was reversed. Pramipexole subjects who experienced dyskinesias had smaller gains in HRQOL compared with the subjects who did not have dyskinesias. Subjects who experienced somnolence and edema experienced smaller gains in HRQOL compared with subjects who did not experience these events but the differences were not statistically significant.

EQ-5D and UPDRS Subscale Analysis

In general, subjects randomized to initial levodopa tended to show more improvements on physical function domains of motor and ADLs, whereas subjects randomized to initial pramipexole tended to show improvements in mental health domains. For example,
there is some evidence that those subjects randomized to initial levodopa compared with initial pramipexole had incremental gains on the mobility and self-care items of the EQ-5D (mobility item: 0.603, \( P < 0.01 \), self-care item: 0.164, \( P = 0.43 \)). Those subjects randomized to initial levodopa compared with initial pramipexole also had incremental gains on the Motor and ADL sections of the UPDRS (Motor component: 17.567, \( P < 0.01 \), ADL component: 2.849, \( P = 0.13 \)). There was less difference between the two groups on the usual activities item of the EQ-5D (0.072, \( P = 0.79 \)).

On the other hand, those subjects randomized to initial pramipexole compared with initial levodopa had incremental gains on the anxiety/depression item and the pain/discomfort items of the EQ-5D (anxiety/depression item: 0.509, \( P = 0.13 \), pain/discomfort item: 0.387, \( P = 0.21 \)). These subjects also had incre-

\[\text{Table 4} \quad \text{Incremental changes in EQ-5D over 4-years by treatment assignment and adverse events}\]

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Pramipexole</th>
<th>(\Delta \text{QALY (SD)})</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesias</td>
<td>N=76 (0.077)</td>
<td>33 (0.112)</td>
<td>0.018 (0.074)</td>
<td>0.81</td>
</tr>
<tr>
<td>No dyskinesias</td>
<td>N=74 (0.135)</td>
<td>118 (0.079)</td>
<td>0.220 (0.135)</td>
<td>0.10</td>
</tr>
<tr>
<td>Difference</td>
<td>0.092 (.115)</td>
<td>-0.110 (0.129)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wearing off</td>
<td>N=89 (0.095)</td>
<td>68 (0.095)</td>
<td>0.104 (0.036)</td>
<td>0.00</td>
</tr>
<tr>
<td>No wearing off</td>
<td>N=61 (0.117)</td>
<td>83 (0.084)</td>
<td>0.226 (0.161)</td>
<td>0.16</td>
</tr>
<tr>
<td>Difference</td>
<td>0.150 (0.097)</td>
<td>0.029 (0.112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>N=29 (0.151)</td>
<td>58 (0.095)</td>
<td>0.197 (0.064)</td>
<td>0.00</td>
</tr>
<tr>
<td>No somnolence</td>
<td>N=121 (0.092)</td>
<td>93 (0.295)</td>
<td>0.163 (0.128)</td>
<td>0.20</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.138 (0.129)</td>
<td>-0.104 (0.103)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>N=20 (0.136)</td>
<td>62 (0.078)</td>
<td>0.131 (0.192)</td>
<td>0.50</td>
</tr>
<tr>
<td>No edema</td>
<td>N=130 (0.102)</td>
<td>89 (0.094)</td>
<td>0.169 (0.115)</td>
<td>0.14</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.015 (0.153)</td>
<td>-0.053 (0.109)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\text{QALY}, \text{quality-adjusted life-year}\).
mental gains on the Mental component of the UPDRS (1.303, \( P = 0.07 \)). There were no significant differences on any of the seven PDQUALIF subscales over time.

**Discussion**

This study demonstrates that patients treated with initial pramipexole compared with initial levodopa may have different trends in HRQOL over the first 4 years of treatment. After an initial HRQOL increase with both treatments during the first year of therapy, there was a decline in HRQOL over the next 3 years. The HRQOL pattern was similar for three separate measures, two generic preference-based measures and a disease-specific quality of life measure. Even though none of the 4-year changes in HRQOL reached statistical significance level of 95\%, the consistency of the results across the HRQOL instruments and the direction of change that supported our hypotheses suggested that our observations were not random.

Our results suggest that initial pramipexole may be improving HRQOL compared with initial levodopa through nonmotor mechanisms. The observed HRQOL differences in favor of pramipexole occurred despite a persistent five-point UPDRS benefit favoring levodopa (mediated via the Motor and ADL components). The mobility item of the EQ-5D also favored levodopa. Pramipexole is known to be effective for treating restless leg syndrome, depression, schizophrenia, and possibly fibromyalgia [29–32]. It is possible that PD treatment with pramipexole may be providing symptom relief or prevention through these nonmotor mechanisms (e.g. interaction with dopaminergic D2 and D3 receptors [33,34]), which in turn may be improving self-reported HRQOL. Although not statistically significant, the Mental component of the UPDRS as well as the depression/anxiety and pain/discomfort items on the EQ-5D favored pramipexole. More research is needed to measure nonmotor symptoms and their possible contributions to HRQOL, because they may be more important than the contributions of the constructs in the commonly used motor scales that do not concentrate on the mental health, such as the UPDRS. The new UPDRS has a major emphasis on nonmotor features and so it may be able to assay the differences in these domains more effectively than the currently used version.

Although not statistically significant, our results also provide insights into the relationship between side effects and treatment. Dyskinesias are associated with levodopa therapy but not with pramipexole therapy. In addition, during the first 2 years of therapy, dyskinesias in the levodopa arm were associated with improved HRQOL [12]. Pramipexole subjects had an option of taking open label levodopa if the original treatment was not effective. Thus, dyskinesias in pramipexole group occurred only in subjects for whom the treatment did not work well and were thus associated with lower HRQOL. We concluded that in levodopa arm, dyskinesias were indicative of successful treatment and higher HRQOL although in pramipexole group dyskinesias signaled the failure of the original pramipexole therapy and, consequently, lower QALY gains over the 4 years. Our data also show that the common pramipexole-associated side effects of somnolence and edema were not associated with significant decrements in HRQOL. This may be similar to the “quality of life paradox” reported in breast cancer patients when estimated effect of therapy side effects on HRQOL may be attenuated if patient adapts to treatment toxicities [35–37]. Also, the HRQOL questionnaires used in the study asked subjects to describe their health “today.” Hence, transient health states (e.g. adverse events resolved by the time of assessment) would not be captured unless they produce a lingering effect on HRQOL (e.g. depression).

The deterioration of HRQOL after the first year of treatment was greater in patients treated with levodopa compared with those treated with pramipexole. In fact, HRQOL gains, measured using EQ-5D, in years 3 and 4 for those treated with pramipexole were significantly greater \((P < 0.05)\) than for those treated with levodopa. What are the possible explanations for these observed differences in HRQOL gains over time?

One possible factor that may contribute to the observed difference in HRQOL by treatment arm is differential, by treatment, dropout: more subjects in pramipexole group \((n = 67)\) prematurely withdrew compared with subjects in levodopa group \((n = 49)\). A widening difference in HRQOL profiles could be explained if relatively more dropouts in the pramipexole group were “treatment-related” whereas in the levodopa group relatively more dropouts were primarily “disease progression-related.” As a consequence of this, after dropout, the pramipexole subjects would experience relative improvements compared with levodopa subjects. There is some evidence for that. Except for somnolence and edema (16 people in pramipexole arm vs. one in levodopa arm), other reasons for leaving the trial were distributed similarly between the treatment arms [2]. Notably, even under the assumptions that are most favorable to levodopa (that quality of life worsens after dropout in the pramipexole arm and improves in the levodopa arm), we find greater HRQOL gains in the pramipexole group (although not statistically significant). Under the opposite set of assumptions (those that relatively favored pramipexole), the differences in HRQOL between the treatment arms were even greater and statistically significant. This confirms that the cause of dropouts matters.

Differences in the levels of HRQOL at randomization could be another possible explanation of the relatively larger gains among those in the pramipexole
group. Because subjects in the pramipexole group had lower HRQOL at baseline, their relative improvement compared with those in the levodopa group could be explained by regression to the mean. There were, however, only four subjects, all in the pramipexole group, that had particularly low HRQOL at baseline. Analyses that excluded these four subjects found both that, among the remaining subjects, HRQOL were balanced at baseline, and that the main substantive results were not changed, suggesting that regression to the mean is unlikely to explain our findings.

Comparison across various imputation techniques revealed that regardless of the imputation approach, HRQOL was higher in pramipexole arm during the 4 years of therapy, but the QALY gain was not significant. The FE imputation approach had a more pronounced effect on the pramipexole arm compared with other approaches. One explanation for that is that the individuals who dropped out of the pramipexole arm had overall good health that declined right before the dropout (the last visit). Hence, incorporating the individual “fixed effect” component along with baseline patient information brought the imputed values up compared with other methods. One can see the trend that as the imputation technique becomes more sophisticated (from LOCF to IOM to LOS to FE), the treatment arms grow further apart. This trend indicates that in addition to MAR; the basic assumption for all utilized imputation techniques, there is a systematic component of HRQOL that is conditional on observed subject characteristics. To utilize more fully the available information, the FE approach seems appropriate.

These results are in line with the earlier study [2] that defined and measured treatment effectiveness as the difference between the baseline and final (at 208 weeks) EQ-5D scores, delta EQ-5D, and concluded that there was no difference, by treatment. Our approach estimates treatment effectiveness using QALY, the product of EQ-5D and time. This approach takes advantage of the entire EQ-5D profile, rather than using only two data points (the first and the last). Nevertheless, the results of both approaches, as well as of all other imputation methods we tested, concluded that there was no statistically significant difference in HRQOL over 4 years. Our study explores the HRQOL profiles to examine the dynamic differences in HRQOL over time because one of the a priori assumptions about pramipexole is that it may have a long-term effect by delaying use of levodopa and related dyskinesias. Using several approaches, including the FE imputation, we found statistically significant differences in the annual QALY gains in the later years, by treatment.

Further research is also needed to better understand the meaning of incremental changes in preference-based health measures, and to help understand the strengths and weakness of various HRQOL measures [38]. What does a gain in 0.149 QALY mean over a 4-year period? Using willingness-to-pay approach as one benchmarking method, 0.149 QALY would be valued at $7450 using $50,000/QALY or approximately $30,000 assuming a more realistic societal value of $200,000 per QALY gained based on historical spending patterns [39,40]. Other anchor-based methods can be used to help establish the meaning of gains and losses of HRQOL over time [38]. Our results suggest that preference-based measures can provide valuable information beyond traditional disease-specific impairment and disability scales.

Because preferences incorporate patient’s perspective on all aspects of therapy, physicians should take patient’s preference into account especially when there is no clear medical evidence or recommendation about the preferred choice. Although it appears that these two treatment options are differentially affecting HRQOL over time, more work is needed to determine whether the magnitude and strength of these changes represent clinically meaningful differences to help guide treatment decisions.

In summary, subjects randomized to initial pramipexole compared with initial levodopa in early PD showed distinct HRQOL profiles over time. The HRQOL gains associated with pramipexole become more apparent in years 3 and 4 after initiation of the therapy that certainly raises the possibility that a longer-term study would show even larger gains. Our results also raise the possibility that pramipexole may be improving HRQOL through nonmotor mechanisms. The common pramipexole-associated side effects of somnolence and edema did not have significant negative effects on HRQOL. Continued follow-up of this cohort may help determine whether the relative improvements due to pramipexole are lasting and help unravel the pathways through which these two treatment options are differentially affecting HRQOL over time.

The earlier version of the article was presented at the 25th Annual Meeting of the Society for Medical Decision Making in Chicago, Illinois, October 2003. The authors would like to thank Cornelia Kamp and Drs Karl Kieburtz, Anthony Lang, and Michael McDermott for their comments on the article, Carolynn O’Connell and Patricia Klein with assistance in preparing the article, and all participating sites for collecting quality of life data.

Source of financial support: The randomized clinical trial was supported by Pharmacia, Corp. (Peacock, NJ)/Pfizer (New York, NY) and Boehringer Ingelheim Pharma (Ingelheim, Germany). The additional analyses and research efforts for the quality of life study were supported by research grants K01 AG 20980 from the National Institute of Aging (Katia Noyes) and K24 NS42098 from the National Institute of Neurological Disorders and Stroke (Robert Holloway).
Quality of Life in CALM-PD

References


Appendix: Parkinson Study Group

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