

## Effect of Therapeutic Interventions on Health-related Quality of Life in Parkinson's Disease

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### Abstract

Health-related quality of life (HRQoL) used to be considered a secondary parameter in clinical trials of Parkinson's disease (PD) and in routine clinical practice, but is now increasingly recognised as an important measure of patient status. A number of studies have shown that the severity of PD is strongly associated with poor HRQoL scores and that measuring HRQoL domains provides a valuable assessment of overall patient status. Current guidelines from the Movement Disorder Society Task Force and the European Parkinson's Disease Association recommend the use of HRQoL measures in the diagnosis and monitoring of patients. The European Medicines Agency PD Guidelines, however, do not yet recommend the use of such indirect endpoints in clinical trials. A series of phase III and post-marketing studies evaluating the selective monoamine oxidase type B inhibitor, rasagiline in PD, including between 404 and 1,176 patients, showed that treatment with rasagiline leads to significant improvements in HRQoL parameters such as the Parkinson's Disease Quality of Life questionnaire (PDQUALIF), the 39-Item Parkinson's Disease Questionnaire (PDQ-39), the PDQ-8 and other HRQoL-related parameters. Other clinical trials have shown significant improvements in parameters including: Short-Form-36, EuroQuol 5D, PDQUALIF, PDQ-39 and HRQoL-related parameters in PD patients treated with dopamine agonists, selegiline, tocopherol or levodopa/carbidopa/entacapone or levodopa/carbidopa combinations. Experience gained with these instruments is likely to increase the attention paid to HRQoL in PD assessment and could improve diagnosis and monitoring of PD and may ultimately improve patient outcomes.

### Keywords

Parkinson's disease, health-related quality of life, treatments, guidelines, clinical trials

**Disclosure:** The authors received an honorarium from Teva and Lundbeck for their participation in the symposium held at the 20th World Congress on Parkinson's Disease and Related Disorders in Geneva, Switzerland in December 2013, which preceded the development of this article. Heinz Reichmann has served on Advisory Boards, given lectures for and received research grants from Abbott, AbbVie, Bayer HealthCare, Boehringer Ingelheim, Britannia, Cephalon, Desitin, GSK, Lundbeck, Medtronic, Merck-Serono, Novartis, Orion, Pfizer, Teva, UCB Pharma and Valeant. Pablo Martínez-Martin participates on an Advisory Board for AbbVie and has performed lectures or serves on the speakers' bureaus for UCB, AbbVie, Italfarmaco, Britannia, Novartis and the Movement Disorder Society. Fabrizio Stocchi is a consultant for Lundbeck, Teva, UCB, Merck, Novartis, GSK, Chiesi, IMPAX and Britannia and has performed lectures or serves on the speakers' bureaus for Lundbeck, Teva, UCB, Merck, Novartis, GSK, Chiesi and Britannia.

**Acknowledgements:** Editorial assistance was provided by James Gilbert at Touch Medical Media.

**Received:** 2 May 2014 **Accepted:** 12 May 2014 **Citation:** *European Neurological Review*, 2014;9(1):19–26

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**Support:** The publication of this article was supported by H Lundbeck A/S and Teva Pharmaceuticals. The views and opinions expressed are those of the authors and not necessarily those of H Lundbeck A/S or Teva Pharmaceuticals.

In Parkinson's disease (PD) the assessment of quality of life (QoL) using various measures is increasingly important to determine disease status and to assess the efficacy of new and existing treatments from the patients' point of view. In the past, health-related quality of life (HRQoL) measures using generic and specific instruments such as the SF-36 and the PDQ-39 were mostly used as secondary endpoints for clinical trials but are now becoming recognised as notable arbiters of improvement across a range of patient parameters. The use of these measures as endpoints in clinical trials of PD treatments and their recognition by some regulatory authorities (including the US Food and Drug Administration [FDA] and the European Medicines Agency [EMA]) highlights their increasing importance.<sup>2–4</sup> The need to monitor

HRQoL parameters in individuals with PD in regular clinical practice is also becoming accepted. Several clinical trials of new PD treatments have included HRQoL measures among the primary endpoints and some have shown marked improvements on these criteria.<sup>5–9</sup>

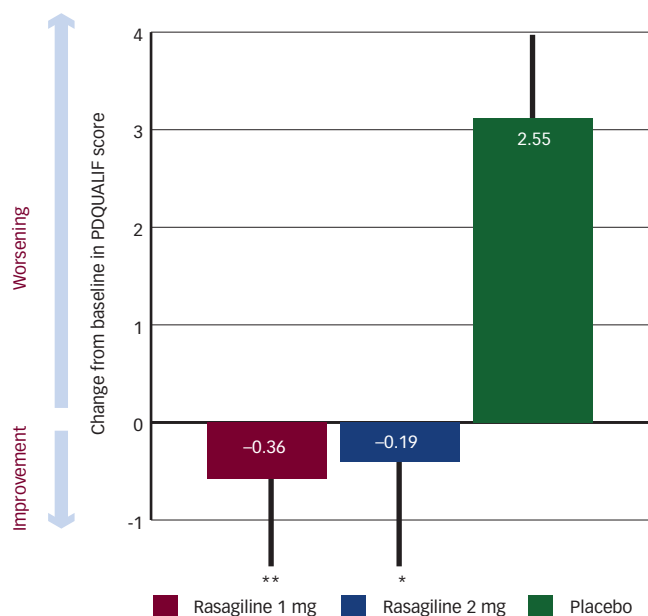
This article continues the theme of a companion article in this issue<sup>10</sup> by reviewing the effect of treatments in clinical trials on HRQoL in PD as discussed in an expert panel session on HRQoL in PD that took place at the 20th World Congress on Parkinson's Disease and Related Disorders, Geneva, December 2013. For more information on QoL, HRQoL and its assessment tools, please refer to the companion article.<sup>10</sup>

**Table 1: Level of Evidence Supporting Early Parkinson's Disease Drugs Based on Efficacy Against Motor Symptoms\***

Effective (Level A)	Effective (Level B)	Effective (Level C)	Insufficient Data
Levodopa (CR)	Bromocriptine (DA)	Piribedil (DA)	Entacapone (CI)
Dihydroergocriptine (DA)	Cabergoline (DA)		Tolcapone (CI)
Pergolide (DA)	Lisuride (DA)		
Pramipexole (CR/DA)	Amantadine (wNMDA-A)		
Ropinirole (CR/DA)	Anticholinergics (ACh-B)		
Rotigotine (DA)			
Rasagiline (MAO-BI)			
Selegiline (MAO-BI)			

\*As given in the European Federation of Neurological Societies/Movement Disorder Society–European Section (EFNS-MDS-ES) guidelines.<sup>16,49</sup> ACh-B = acetylcholine blocker; CI = catechol-O-methyltransferase inhibitor; CR = controlled release; DA = dopamine agonist; MAO-BI = monoamine oxidase B inhibitor; wNMDA-A = weak N-methyl-D-aspartate receptor antagonist/increases dopamine release/decreases dopamine reuptake. Sources: Oertel et al., 2011, Elmer et al., 2013, Koller et al., 2004, Ferreira et al., 2013, Fox et al., 2011.<sup>16–20</sup>

**Figure 1: Effect of Rasagiline on Quality of Life in Early Parkinson's Disease as Shown in the TEMPO Study Comparing Rasagiline Doses with Placebo**



\*p<0.05; \*\*p=0.01 versus placebo. PDQUALIF = Parkinson's Disease Quality of Life questionnaire. Source: Biglan et al., 2006.<sup>5</sup>

**How do Treatments for Parkinson's Disease Impact Patients' Quality of Life?**

PD features numerous motor and non-motor symptoms that can negatively impact HRQoL. This was highlighted in an extensive systematic review, conducted in 2011, that included 29 clinical studies showing that depression was the most frequently identified determinant of a poorer HRQoL in PD.<sup>11</sup> Disease severity and disability were also associated with poor HRQoL outcomes. In addition, gait impairments and complications of medication therapy were most likely to affect overall QoL. The review concluded that the effects of demographic factors, motor and non-motor symptoms all contribute to QoL deterioration and strategies should be implemented to address them in order to minimise the impact of PD. As discussed in the companion article, HRQoL questionnaires have been developed to encompass, in one assessment tool, all the factors that meaningfully impact QoL for most patients, at all stages of the disease. HRQoL scores worsen as disease progresses and the evaluation is closely related with

many aspects of the disease such as depression, motor symptoms and non-motor symptoms and this can evolve over time. HRQoL evaluation shows how the clinical symptoms impact on patients' daily lives, and is therefore a measure that goes beyond clinical assessment.

Various drug treatments have been shown to improve both motor and non-motor symptoms in PD and can be used as monotherapy or as adjuncts with other treatments and can have a marked impact on HRQoL.<sup>12,13</sup> A systematic review of 61 clinical trials, however, showed that the evidence supporting the use of many treatments to improve HRQoL in PD was variable.<sup>14</sup> The review found insufficient evidence of HRQoL improvement after treatment with amantadine, anticholinergics, cabergoline, entacapone, pramipexole, selegiline and tolcapone. In addition, insufficient evidence was found supporting the efficacy of surgical interventions such as unilateral thalamotomy, unilateral and bilateral pallidal stimulation and unilateral thalamic DBS. This systematic review, however, found good evidence of HRQoL improvement in PD following treatment with the selective monoamine oxidase type B inhibitor, rasagiline and following two surgical procedures, deep brain stimulation (DBS) of the subthalamic nucleus and unilateral pallidotomy. More recent reviews have also found good evidence of HRQoL improvement in PD for rotigotine<sup>15</sup> and pramipexole.<sup>13</sup>

Various medications with different modes of action have shown efficacy against many of the motor symptoms of PD. The European Federation of Neurological Societies/Movement Disorder Society–European Section (EFNS-MDS-ES) 2010 treatment-based guidelines<sup>16,17</sup> give levels of efficacy evidence supporting the use of medications in early PD (see Table 1). These guidelines give level A evidence (established as effective, and having at least one convincing class I study or at least two consistent, convincing class II studies) supporting treatments such as levodopa, pramipexole, ropinirole, rotigotine, rasagiline and selegiline. The guidelines give level B evidence (probably effective and having at least one convincing class II study or overwhelming class III evidence) supporting anticholinergics, cabergoline and amantadine.<sup>16–20</sup> Some guidelines also give guidance on the use of adjunct therapy in PD.<sup>19</sup> Such adjunct therapies include the use of entacapone with levodopa in non-fluctuating patients and in the prevention/delay of motor complications or rasagiline as a symptomatic adjunct. Whilst improvements in measures of efficacy in PD as described in the guidelines do not always directly equate to improvements in measures of HRQoL, the criteria are closely related.

In treating PD, non-motor symptoms are often ignored in favour of motor symptoms that are more visible; many patients do not regard non-motor

**Table 2: Major Clinical Studies of Rasagiline in Parkinson's Disease Using Quality of Life and Related Endpoints**

Study Name and Reference	Number and Type of Patients	Treatments	Quality of Life Endpoints Included	Major Quality of Life Findings
TEMPO <sup>5</sup> (US)	404 early PD patients	1 mg and 2 mg rasagiline/day or placebo over 26 weeks	Change in UPDRS score and in PDQUALIF	Significant changes in both scales versus placebo (p=0.05 and p=0.01 for 1 mg and 2 mg/day doses) Significant effects on HRQoL seen in elderly (≥65 years) and younger patients (<65 years) – considered due to the symptomatic benefits of rasagiline
Post-marketing study <sup>40</sup> (Germany)	754 patients with idiopathic PD	1 mg rasagiline/day as monotherapy or combination therapy over 4 months	PDQ-39 subscales	PDQ-39 QoL total scores and subscale scores were significantly improved by rasagiline p<0.001. Significantly improved all PDQ-8 single item scores and WHO-5 single item scores
Post-marketing study <sup>41</sup> (Germany)	871 patients with idiopathic PD on monotherapy or combination therapy	1 mg rasagiline/day over 6 months	CURS, UPDRS fluctuation subscale, daily OFF time, PDQ-8 novel Parkinson syndrome score PS-23, WHO-5 patient-reported outcome and AEs	Treatment significantly improved all PDQ-8 single-item scores (p<0.001 versus baseline) between baseline and the final evaluation. Treatment significantly improved all WHO-5 single item scores (p<0.001 versus baseline). A subgroup of patients receiving combination therapy (n=227) showed marked reductions in daily OFF times, particularly in morning
ADAGIO substudy on fatigue <sup>35,36</sup> (Europe)	1,176 previously untreated patients with PD	Rasagiline 1 mg/day (n=270) or 2 mg/day (n=277) or placebo (n=558) over 36 weeks	16-item PFS	A substudy (n=1,105) showed significant lower PFS scores after 36 weeks compared with placebo (p<0.01 and <0.0001 for 1 mg and 2 mg/day doses, respectively). Rasagiline also delayed the need for symptomatic anti-parkinsonian drugs
LARGO <sup>37</sup> (Israel, Argentina and Europe)	687 outpatients with PD	Rasagiline 1 mg/day (n=231), entacapone 200 mg/day (n=227) with every levodopa dose, or placebo (n=229) over 18 weeks	Change in total daily OFF time	Significant improvement in daily OFF time for rasagiline and entacapone versus placebo (p<0.001) In a substudy, rasagiline produced a –5.64 UPDRS unit change in motor symptom score (p<0.05 versus placebo) <sup>42</sup>
PRESTO <sup>38</sup> (US)	472 patients with PD at least 2.5 hours of daily OFF	Rasagiline, 0.5 or 1.0 mg/day, or placebo over 26 weeks	Change in total daily OFF time	Significant improvement in daily OFF time for rasagiline doses versus placebo (p<0.05 and p<0.001). PDQUALIF summary scale results showed a trend towards improvement for 0.5 mg for rasagiline (p=0.07 versus placebo), but not for 1.0 mg dose (p=0.22 versus placebo). PDQUALIF social subscale showed improvements for rasagiline dose levels over placebo. A pooled analysis of the LARGO and PRESTO study results showed significant differences for rasagiline versus placebo for UPDRS subscores for bradykinesia, rigidity and tremor <sup>18</sup>

AE = adverse event; CURS = Columbia University Rating Scale; HRQoL = health-related quality of life; PD = Parkinson's disease; PDQ = Parkinson's disease questionnaire; PDQUALIF = Parkinson's Disease Quality of Life questionnaire; PFS = Parkinson Fatigue Scale; UPDRS = Unified Parkinson's Disease Rating Scale; WHO = World Health Organization.

symptoms as a direct manifestation of the disease and therefore do not report them. Frequently used treatments for motor symptoms in PD include dopamine agonists (DAs), such as pramipexole, pergolide, ropinirole, rotigotine and the monoamine oxidase inhibitor, rasagiline, but these are also effective against non-motor symptoms, such as depression and sleep disorders.<sup>21</sup> The DA ropinirole, for example, has shown efficacy in treating non-motor symptoms. In a US study of 393 patients with PD who were inadequately controlled with levodopa, treatment for 24 weeks with a 24-hour long-acting ropinirole formulation produced significant improvements on the Beck Depression Inventory-II, emotional well-being, stigma and communication, and on the PD Sleep Scale.<sup>22</sup>

Musculoskeletal, visceral and neuropathic pain is a persistent problem in PD that diminishes QoL. The benefit of addressing this problem on HRQoL was shown in a study in Sweden that included 57 patients with PD. Rapid diagnosis and prompt treatment with drugs produced significant improvements in all SF-36 criteria, including pain (p<0.001) compared with control individuals.<sup>23</sup>

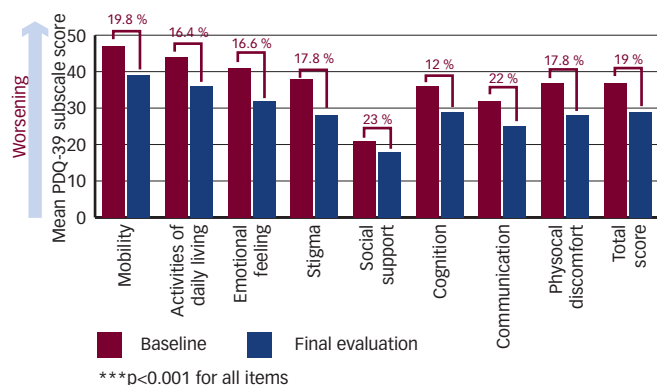
Numerous other treatment approaches to PD have been taken with variable degrees of success. These include DBS, stem cell implantation, medications and exercise. A systematic review of 14 suitable randomised

controlled trials found that exercise programmes have a positive effect on HRQoL (and other parameters) in PD.<sup>24</sup> However, exercise had little apparent effect on depression and it was not clear what the optimal exercise content should be and at what stage of the disease it is most effective. Currently there is little or no available evidence of HRQoL improvement following transplantation of mesencephalic cells. Such treatment has not shown consistent efficacy on stated endpoints in PD including measures of HRQoL.<sup>25</sup>

### Guidelines and Recommendations for Quality of Life in Parkinson's Disease

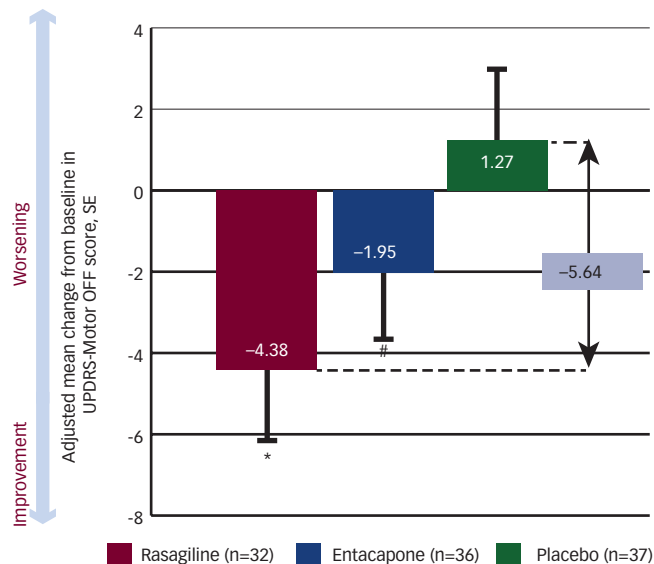
HRQoL is increasingly included in guidelines and recommendations as an essential aspect to assess in patients with PD. This was emphasised by a Movement Disorder Society Task Force that was commissioned to rate the psychometric quality of available HRQoL scales as applied to Parkinson's disease. The task force determined that several assessment scales reached the level of 'recommended'.<sup>26</sup> These scales include four generic scales (EuroQoL, Nottingham Health Profile, 36-item Short-Form Health Survey and Sickness Impact Profile) and five specific scales (39-Item Parkinson's Disease Questionnaire [PDQ-39], 8-item Parkinson's Disease Questionnaire Short Form [PDQ-8], Parkinson's Disease Quality of Life Questionnaire

**Figure 2: Effect of Rasagiline on Quality of Life in Parkinson's Disease as Shown in a German Post-marketing Study**



PDQ = Parkinson's disease questionnaire. Source: Reichmann and Jost, 2010.<sup>40</sup>

**Figure 3: Change in Motor Symptoms during Early Morning OFF (UPDRS-Motor OFF Score) at Week 18 in the LARGO Substudy**



Bars = standard error (SE). UPDRS = Unified Parkinson's Disease Rating Scale. Source: Stocchi and Rabey 2011.<sup>42</sup>

[PDQUALIF], Parkinson's Impact Scale [PIMS] and Scales for Outcomes in Parkinson's Disease – Psychosocial [SCOPA-PS]). The Task Force asserted that prompt and consistent use of these scales is likely to provide clinicians with a more accurate and timely diagnosis of PD and enable better monitoring of disease/patient and treatment.

The theme of promoting HRQoL in PD has also been highlighted by the European Parkinson's Disease Association (EPDA) European Standards of Care Consensus Statement (2012), which states: 'early drug treatment combined with therapeutic interventions can reduce the economic impact of Parkinson's and in some cases delay the progression of the disease, which maintains a person's HRQoL for a longer period of time.'<sup>27</sup> The UK Parkinson's Disease National Guidelines for Diagnosis and Management in Primary and Secondary Care (2006) goes further by stating that the choice of therapy in PD should 'aim to optimise the HRQoL over the whole expected lifespan of an

individual'.<sup>28</sup> The EMA Guidelines (2008), however, do not recommend the use of indirect efficacy variables (such as HRQoL endpoints) as primary efficacy variable in pivotal studies unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proved.<sup>29</sup> It is possible that such regulatory directives may change in the future as HRQoL measures are increasingly recognised as critical endpoints in the treatment of PD.

**Clinical Trials in Parkinson's Disease with Quality of Life Measures as Major Endpoints**

Many pharmacological treatments have shown efficacy in terms of improving motor symptoms, but the effect on HRQoL has generally been less pronounced. Various dopaminergic drugs such as levodopa, pramipexole, cabergoline, ropinirole and rotigotine are effective against motor symptoms but do not always improve non-motor symptoms.<sup>30,31</sup> These drugs, however, have common side effects such as nausea, vomiting, constipation, headaches, drowsiness, sudden attacks of sleepiness, fainting due to low blood pressure, hallucinations, delusions and confusion. Further side effects include existing dyskinesias and impulsive/compulsive behaviours that may become more troublesome.<sup>30,31</sup> Several reasons for the relatively reduced effect on HRQoL measures include limitations of the methods or scales used, the design of trials and the lack of clinical improvement from the patients' point of view. The lack of apparent improvement in HRQoL in some cases has been attributed by some authors to the use of certain scales that are complex (such as PDQ-39) and that the meaning of the resultant scores is unclear and could lead to misinterpretation.<sup>15,32</sup> A literature review on the effects of PD treatments found 14 double-blind, placebo- or active comparator-controlled trials that used HRQoL instruments as outcome measures.<sup>15</sup> Among these, entacapone showed HRQoL improvements in non-fluctuating patients but benefits were not so apparent in patients with fluctuations.<sup>15</sup> Rasagiline has improved HRQoL as monotherapy in early Parkinson's disease.<sup>14,15</sup> Rotigotine improved HRQoL in both early Parkinson's disease and more advanced disease with motor fluctuations.<sup>13,33</sup>

**Clinical Trials of Rasagiline with Health-related Quality of Life or Related Endpoints**

In addition to having positive effects on motor symptoms, rasagiline has significantly improved non-motor symptoms in PD including fatigue, attention deficits, executive function and cognition in different randomised clinical trials.<sup>34-36</sup> Rasagiline was evaluated in a series of large randomised double-blind clinical trials that are summarised in Table 2. Several of these trials used HRQoL endpoints. A major example was the pivotal trial phase III Early Monotherapy for Parkinson's Disease Outpatients (TEMPO) study (n=404, rasagiline 2 mg, 1 mg or placebo) in which the change in total PDQUALIF total scores after 6 months improved for both rasagiline doses but worsened for placebo (p=0.01 for 1 mg and p<0.05 for 2 mg) (see Figure 1).<sup>5</sup> The phase III Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily (LARGO) (n=687)<sup>37</sup> and Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'OFF' (PRESTO) (n=472)<sup>38</sup> studies showed significant improvements produced by rasagiline versus placebo in terms of OFF times and Unified Parkinson's Disease Rating Scale (UPDRS) motor symptom scores (see Table 2). A post-hoc analysis of these two trials showed that rasagiline was an effective first adjunct therapy in levodopa-treated patients and improved symptoms in patients showing early wearing off, improved all characteristic PD symptoms and was beneficial in patients already receiving other adjunctive dopaminergic treatment.<sup>18</sup>

A further notable study was the Double-blind, Delayed-start Trial of Rasagiline in Parkinson's disease (ADAGIO) trial (n=1,176) in which untreated PD patients were randomised to 1 mg or 2 mg rasagiline/day for 72 weeks (early treatment) or placebo for 36 weeks followed by a switch to 1 mg or 2 mg rasagiline/day for a further 36 weeks (delayed treatment).<sup>35</sup> Although no HRQoL endpoints were specified, a post-hoc analysis<sup>36</sup> (n=1,105) notably revealed that progression of Parkinson's Fatigue Scale (PFS) scores was significantly reduced by rasagiline. At Week 36 in the 1 mg and 2 mg/day rasagiline-treated groups, PFS scores had progressed from a baseline score of  $2.2 \pm 0.9$  units by 0.03 and -0.02 units, respectively, compared with 0.17 units for placebo ( $p < 0.01$ ). Fatigue is important from the patient's perspective, it is well-known as a disabling PD symptom that has a significant impact on QoL and consequently should be monitored and appropriately treated.<sup>39</sup> In the ADAGIO trial, patients treated with rasagiline 1 mg also showed improvements in the scale for non-motor experiences of daily living scale (nM-EDL) compared with those receiving placebo (mean difference -0.33;  $p = 0.049$ ). This indicated a general improvement in patient capability to participate in regular activities.

A German post-marketing study investigated the efficacy and safety of rasagiline 1 mg/day in combination with other treatments in regular clinical use. Diary entries for patients with idiopathic PD (n=754) showed significant improvements in health and overall well-being (PDQ-39 scores) ( $p < 0.001$ ).<sup>40</sup> From baseline to 4 months, rasagiline treatment significantly improved PDQ-39 total scores (by 19 %) and all eight PDQ-39 subscores (mobility, activities of daily living, emotion, stigma, cognition, communication, social support and physical discomfort) by 12–23 % (see *Figure 2*). It was concluded that monotherapy or combination therapy with rasagiline can improve PD symptoms, reduce OFF time, and improve QoL with favourable tolerability in daily clinical practice.

In a more recent post-marketing study conducted in Germany, patients (n=871) with idiopathic PD receiving monotherapy (33 %) or combination therapy (67 %) were treated with rasagiline 1 mg/day over 6 months.<sup>41</sup> This produced improvements in symptom severity and HRQoL (measured using the PDQ-8) in patients at stages over the entire course of the disease. Patients receiving combination therapy also showed reductions in daily OFF time, especially in the morning. Symptom improvements were more notable in patients receiving rasagiline in combination with levodopa. Early morning OFF times were also investigated in a substudy of the LARGO trial that compared patients who were treated with rasagiline (n=32), entacapone (n=36) and placebo (n=37) and monitored during the practically defined OFF state. After 18 weeks, there was a 5.64 unit improvement for rasagiline in UPDRS motor OFF score ( $p = 0.013$ ) and a 3.22 unit improvement for entacapone ( $p = 0.14$ ) compared with placebo (see *Figure 3*).<sup>42</sup> This indicated that rasagiline provides significant efficacy on motor symptoms during early morning OFF time.

Rasagiline has also shown significant improvements in measures of cognition and in non-motor EDL assessments. In a study conducted in Turkey, patients with PD and impairments in two of four cognitive domains (attention, executive functions, memory, visuospatial functions) (n=55) were randomised to rasagiline or placebo for 3 months.<sup>34</sup> Patients treated with rasagiline showed significant improvement in digit span backwards (memory) measures ( $p = 0.04$ ) and verbal fluency ( $p = 0.038$ ) compared with placebo.

Thus, these trials indicate that rasagiline can improve various measures of HRQoL and related measures in PD patients. The greater use of

HRQoL measures in ongoing PD trials emphasises the increasing importance of these parameters as measures of efficacy in assessing new and existing treatments.

### Clinical Trials of Other Parkinson's Disease Treatments using Health-related Quality of Life and Related Endpoints

During the past decade numerous studies have investigated the efficacy and safety of other treatments in PD and have included HRQoL-related measures as pre-specified endpoints. These studies have demonstrated that different treatment approaches directly improve measures of HRQoL or improve parameters that affect HRQoL. Some notable studies are summarised in *Table 3*. An example of a trial with planned HRQoL endpoints was the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial, which was a retrospective cohort study conducted by the Parkinson Study Group in the US and Canada that used the SF-36 to investigate the factors affecting worsening HRQoL in PD.<sup>7</sup> A group of 362 patients with early PD were given selegiline and tocopherol and monitored for 5–6 years after enrolment. The results showed that depression, poor cognitive function and reduced functional independence were predictive of worsening HRQoL at a later stage. These results suggested that clinical care should be expanded beyond the most visible effects of PD and should recognise the impact of mood, cognition and function on HRQoL.

Another major trial was the Early Detection of Wearing off in Parkinson disease (DEEP) study. This investigated the problematic effects of wearing-off in which low plasma levels of levodopa between doses leads to a return of symptoms with low mobility and dyskinesias, which negatively impacts HRQoL.<sup>43</sup> In a population of 617 patients with PD, wearing-off was identified in 351 patients (56.9 %) by neurologists but in 415 patients (67.3 %) by a self-administered questionnaire. The most common symptoms of wearing-off were: 'slowness of movements' (55.8 %) and 'reduced dexterity' (48.8 %). Significant factors in wearing-off were shown to be younger age, female gender, increasing UPDRS part II scores and longer duration of anti-Parkinson treatment. The number of motor and non-motor wearing-off symptoms were correlated with the PDQ-8 total score ( $p < 0.0001$  for both). Wearing-off therefore tends to increase with PD duration, has a negative effect on HRQoL and is frequently underestimated by neurologists.

The long-term effects of PD treatments on HRQoL have been rarely studied and are largely unknown. The Parkinson Study Group in the US sought to address this deficiency in 301 patients with PD who received either initial pramipexole or initial levodopa and were subsequently followed for over 4 years.<sup>9</sup> Scores on EQ-5D, PDQUALIF and the accumulated difference in the total HRQoL total scores improved over the first 3–6 months but then gradually worsened. These parameters, however, were significantly better for pramipexole-treated patients compared with levodopa-treated patients after 3–4 years ( $p = 0.03$  for the difference between pramipexole after 3 years and  $p = 0.04$  for the difference after 4 years). An analysis indicated that the drugs affect different domains within the instruments: pramipexole improved HRQoL by its effect on non-motor functions while levodopa mainly improved the motor domains of the HRQoL.

A further effect of PD is comorbid depression, which is a common and debilitating symptom affecting up to 50 % of patients and has a severely negative effect on the HRQoL.<sup>44</sup> There is little published evidence supporting treatment efficacy for depression in PD;<sup>45</sup> however, a few

**Table 3: Major Clinical Studies of Other Parkinson's Disease Treatments Using Quality of Life and Related Endpoints**

Study Name and Reference	Number and Type of Patients	Treatments	Quality of Life and Related Endpoints	Major Quality of Life Findings
DATATOP <sup>7</sup> (Canada/US)	362 patients with early PD	Patients with PD given selegiline and tocopherol and monitored 5–6 years after enrolment (retrospective cohort study)	SF-36 scores	Depression, cognitive function and degree of functional independence were predictive of worsening HRQoL at a later stage. Clinical care should be expanded beyond the most visible effects of PD and recognise the impact of mood, cognition and function on HRQoL.
DEEP <sup>43</sup> (Italy)	617 patients with PD	Self-administered questionnaire	Investigated effects of wearing-off in patients treated with levodopa and the effect on HRQoL	Wearing-off identified in 351 patients (56.9 %) by neurologists but in 415 patients (67.3 %) by questionnaire. Most common wearing-off symptoms: 'slowness of movements' (55.8 %) and 'reduced dexterity' (48.8 %). Significant factors were: younger age, female gender, UPDRS Part II score and duration of treatment. Wearing-off increases with PD duration, is frequently underestimated and has a negative effect on HRQoL.
Parkinson Study Group (US) <sup>9</sup>	301 patients with PD	Initial pramipexole or initial levodopa and were followed for over 4 years	EQ-5D, PDQUALIF and accumulated difference in the total HRQoL	EQ-5D, PDQUALIF and accumulated difference in total HRQoL scores improved in first 3–6 months but worsened after that. These parameters were significantly better for pramipexole after 3–4 years (p=0.03 for difference after 3 years and p=0.04 for 4 years). Analysis suggested that the drugs affect different domains of the instruments: pramipexole improved non-motor functions but levodopa mainly improved the motor function HRQoL domains.
Non-comparative study (Italy) <sup>6</sup>	151 patients with PD and major depressive disorder	Duloxetine (60 mg/day) for 12 weeks	17-item Hamilton Rating Scale for Depression, PDQ-39 total score, Beck Depression Inventory, CGI-S and PGI	Duloxetine significantly improved HRQoL measures. Improvements were seen in the 17-item Hamilton Rating Scale for Depression (p<0.001), PDQ-39 total score and individual domains (p<0.001), Beck Depression Inventory (p<0.001), Clinical Global Impression of Severity (p<0.001) and Patient Global Impression of Improvement total scores (p<0.001). Duloxetine was well tolerated and had no detrimental effect on PD symptoms.
Comparative study (France) <sup>8</sup>	80 patients with PD	Levodopa (n=40) or DBS (n=40)	PDQ-39, Ways of Coping Checklist and Coping with Health, Injuries and Problems Scale	Depression and anxiety were not significantly different with levodopa or DBS. Both DBS and levodopa had significant effects on coping strategies (greater for levodopa). Communication domains of QoL were poorer for DBS. There were significant correlations between coping strategies and QoL dimensions with levodopa but not with DBS.
PRACTICOMT <sup>51</sup> (Spain)	Patients with PD and 'end-of-dose' motor fluctuations	3 months of treatment with entacapone added to levodopa	PDQ-8 and 'End-of-dose' motor fluctuations	Treatment significantly increased on-time by 21 % (p<0.0001) and by 23 % after 12 months (p<0.0001) and induced significant reductions in the UPDRS scores for subscales II and III and improved PDQ-8 scores (significant differences between visits at 3, 6, 9 and 12 months versus baseline; p<0.0001).
16-week randomised, open-label study (US) <sup>52</sup>	350 patients with PD receiving LC treatment and end-of-dose wearing-off	Patients either switched immediately to LCE (n=177) or switched after a delay of 4 weeks (n=173)	PDQ-39 and PDQUALIF	Week 4: Significantly larger improvements in mobility and activities of daily living PDQ-39 sub-scores for immediate treatment versus delayed treatment (p=0.0331 and p=0.0125, respectively). Week 8 significant total score decreases in PDQUALIF (p=0.0133) and PDQ-39 (p=0.0001). Wearing-off with long-term levodopa treatment can be minimised with the early use of combination therapy with other drugs such as entacapone or rasagiline and can keep levodopa doses low.
Single group study (Czech Republic) <sup>53</sup>	Patients with PD before and after DBS treatment	Increase in DBS amplitude (0.35 V)	PDQ-39 and UPDRS III questionnaires	DBS amplitude increase produced a 22.9 % improvement in PDQ-39 scores. Emotions, stigma and communication subscales were improved after the increase but there was no further change in UPDRS III scores. Amplitude increase had potential to improve some non-motor functions and aspects of HRQoL in some patients.
RECOVER <sup>47,33</sup> (International)	287 patients	Patients randomised 2:1 to receive 2–16 mg rotigotine/24 hour (titrated over 1–8 weeks with a 4-week maintenance period) or placebo	Morning UPDRS OFF scores (morning akinesia)	Rotigotine produced significant improvements in morning UPDRS OFF scores (morning akinesia) versus placebo; p<0.001. Post-hoc analysis showed rotigotine may benefit sleep, pain, mood limb pain, discomfort in bed, difficulty dressing, feeling depressed, getting around in public and being embarrassed in public due to PD.
STRIDE-PD <sup>48,50</sup> (US)	745 patients with early PD	Patients randomised to LC or LCE or 134 to 208 weeks	Risk of developing motor complications, wearing-off and dyskinesia	Factors predictive of dyskinesia: levodopa dose and UPDRS Part II scores. Wearing-off of levodopa efficacy was lower for 400 mg/day dose than dose levels up to 600 mg/day. Overall trend was significantly different (p<0.001, log rank test). Minimum effective dose should be used to reduce the risk of dyskinesias and wearing-off.

CGI-S = Clinical Global Impression of Severity; DBS = deep brain stimulation; LC = levodopa/carbidopa; LCE = levodopa/carbidopa/entacapone; PD = Parkinson's disease; PDQ = Parkinson's disease questionnaire; PGI = Patient Global Impression of Improvement total score; UPDRS = Unified Parkinson's Disease Rating Scale.

studies have shown the efficacy of some treatments for this symptom including pramipexole<sup>46</sup> and duloxetine.<sup>6</sup>

Numerous further studies that assessed treatments in PD included parameters that affect various aspects of HRQoL in their design rather than specific HRQoL endpoints (see *Table 3*). An example was the rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER) in which 287 patients with advanced PD were randomised 2:1 to receive 2–16 mg rotigotine/24 hour (titrated over 1–8 weeks with a 4-week maintenance period) or placebo. Patients treated with rotigotine showed a significant 3.1 UPDRS unit improvement: ( $p < 0.001$ ) in morning UPDRS OFF motor scores (morning akinesia) compared with placebo.<sup>47</sup> A post-hoc analysis of the RECOVER trial showed that rotigotine may benefit patients with sleep, pain, mood and other symptoms that might affect HRQoL such as limb pain, discomfort in bed, difficulty dressing, feeling depressed, getting around in public and being embarrassed in public due to PD.<sup>33</sup>

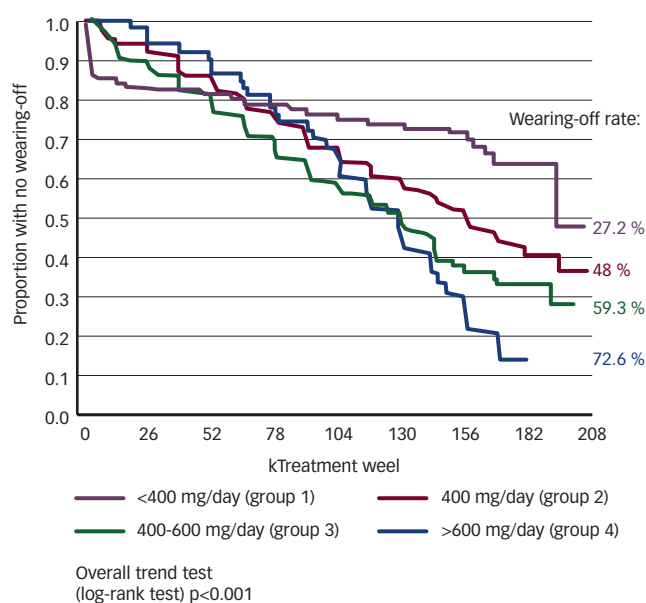
A further key study that measured endpoints that may affect HRQoL was the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study, which investigated whether administering a combination of levodopa/carbidopa/entacapone (LCE) would decrease the risk of developing motor complications, wearing-off and dyskinesia.<sup>48</sup> Patients with early PD ( $n=745$ ) were randomised to receive levodopa/carbidopa (LC) or LCE for 134 to 208 weeks. In the main study, factors predictive of dyskinesia included levodopa dose and UPDRS Part II scores. Wearing-off of levodopa efficacy was lower in patients receiving a 400 mg/day dose than in patients receiving dose levels more than 400 mg/day (see *Figure 4*).<sup>48</sup> The overall trend was significantly different ( $p < 0.001$ , log rank test). This suggested that the minimum effective dose should be used to reduce the risk of dyskinesias and wearing-off.

These varied studies have shown that treatments in PD including levodopa and other medications improve generic measures of HRQoL, such as SF-36, and also improve specific measures of HRQoL, such as domains of PDQ-39, EQ-5D and PDQUALIF. Other interventions such as DBS can also improve aspects of HRQoL and are recommended by numerous investigators. Some treatments have also been shown to improve aspects such as wearing-off, UPDRS scores, mobility, pain and depression. While these are not strictly measures of HRQoL they are associated with it and should be considered when assessing patient well-being.

## Future Developments

The value of HRQoL measures is being increasingly recognised by regulatory authorities and it is likely that they will eventually be specified as required endpoints in clinical trials. As a result, preferred and validated HRQoL endpoints may be incorporated into more guidelines and increasingly standardised to ensure consistency between trials and

**Figure 4: Dose-dependent Wearing-off of Levodopa Effect in Parkinson's Disease in the STRIDE-PD Study**



Source: Olanow et al., 2013.<sup>48</sup>

treatment centres. In regular practice, treatment choices may be more informed by their effects on patient HRQoL in addition to their effects on motor function and non-motor symptoms. Subsequently, HRQoL measures would likely be more actively monitored during treatment as part of the normal routine. This will enable improved understanding of patient responses and enable better targeted treatment approaches.

## Conclusion

In some studies and in regular clinical practice in patients with PD, measures and assessments of HRQoL and non-motor symptoms continue to be regarded as secondary parameters and are frequently not monitored. This results in a poor holistic view of patients, a limited appreciation of the disease impact and possibly the use of treatments that are insufficient to manage the patient and reduce the burden on their caregivers.

Several sets of scales provide valuable and reliable measures for assessing HRQoL in PD and some, particularly the PDQ-39, are now widely used to assess different domains within HRQoL. Evidence supporting the use of HRQoL instruments has been provided by various clinical trials of PD treatments, some of which used HRQoL measures as primary endpoints. Many clinical trials using HRQoL measures as major endpoints are also currently in progress. Experiences from these and the trials outlined above will increase attention paid to HRQoL matters in PD and will ultimately benefit patient outcomes and potentially reduce the burden on caregivers. ■

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