

Parkinson's Disease and Quality of Life – A Clinician's Perspective

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Abstract

In Parkinson's disease (PD) the quality of life (QoL) of a patient is adversely affected by both the motor and non-motor symptoms of the disease. The fact that QoL is reduced in the early stages of PD may well be related to the fact that non-motor symptoms are a key factor in QoL, and these often pre-date motor symptoms. Important non-motor symptoms include depression, dementia and dribbling of saliva. The link between non-motor symptoms and reduced QoL has important implications for the management of PD because the early non-motor symptoms often appear before patients are given antiparkinsonian therapy (as motor symptoms are usually the trigger for starting therapy) and almost every patient with PD has non-motor symptoms. To improve QoL, treatment needs to be started at the point of diagnosis. Furthermore, subsequent monitoring of non-motor symptoms and choice of appropriate treatment to reduce non-motor symptoms are both key to improving QoL. Many non-motor symptoms can potentially be reduced using dopaminergic treatment, and data are beginning to emerge on the effects of continuous dopaminergic stimulation (CDS) treatment on non-motor symptoms. The rotigotine patch may improve sleep/fatigue, mood/cognition, pain and QoL; subcutaneous apomorphine infusion may improve sleep, depression/anhedonia, nocturia and pain; and intraduodenal levodopa infusion may improve cardiovascular symptoms, sleep, perception, QoL and gastrointestinal, urinary and sexual symptoms. The differences in effect on non-motor symptoms of different CDS treatments may indicate a future where treatment can be directed at improving specific non-motor symptoms and thus the QoL of people with PD.

Keywords

Parkinson's disease, quality of life, motor symptoms, non-motor symptoms, continuous dopaminergic stimulation

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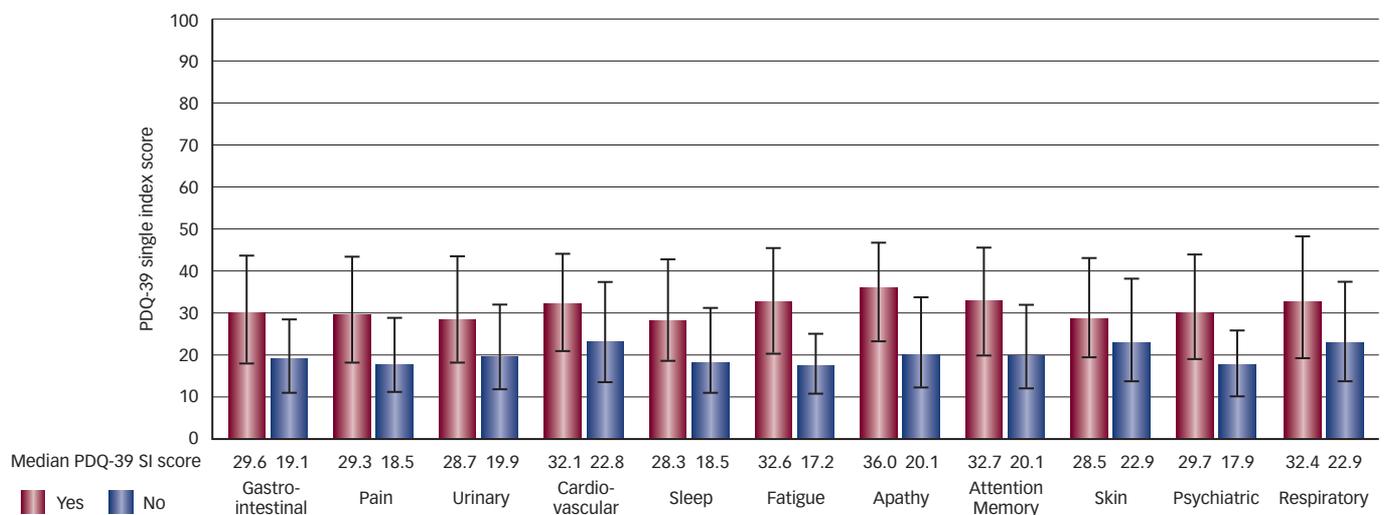
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The concept of quality of life (QoL) is multidimensional and many factors may have an effect, such as those connected to the individual, social networks, the environment and society, but health status is a key factor in determining how good a person's QoL is. In Parkinson's disease (PD), QoL is determined by the motor syndrome, non-motor syndrome and treatment effects (side effects of treatment, timing of initiation of treatment and subsequent maintenance of treatment).¹

Simpler dosing regimens of antiparkinsonian medication may improve QoL, because once-daily drug regimens are adhered to better than more frequent drug administration – total therapy adherence, total number of days adherent and adherence to dose timing are all significantly improved with once-daily medication compared with more frequent dosing.² Improved adherence results in improved motor scores, and the link between motor symptoms and QoL is well recognised. A worsening motor state leads to a poor perception of QoL by the patient and carer, dyskinesias and fluctuations reduce QoL, and treatment of motor symptoms enhances QoL. Providing more stable levodopa plasma concentrations reduces motor fluctuations and achieving this with catechol-O-methyl transferase (COMT) inhibitors improves QoL

(measured by the Parkinson's Disease Questionnaire [PDQ]-8) independently of levodopa dosing frequency.³ An increasing awareness of the non-motor symptoms of PD and their influence on a patient's QoL has highlighted the need for a more holistic approach to management. Virtually every patient with PD has non-motor symptoms. International surveys using the Non-Motor Symptom Scale (NMSS) show that patients with PD have a median of 10–12 non-motor symptoms, regardless of their nationality or disease stage.⁴ The most frequent symptoms include nocturia, dribbling saliva, urinary urgency, sexual difficulty, postural dizziness, pain and ankle swelling.^{4,5} However, the list of all non-motor symptoms is longer and includes: other neuropsychiatric disorders such as depression, psychosis, anxiety and dementia; other sleep disorders such as restless leg, rapid eye movement sleep behaviour disorder (RBD) and insomnia; sweating; orthostatic hypotension; other gastrointestinal disorders such as dysphagia, nausea, constipation and incontinence; and sensory disorders.^{6,7} Over 76 % of patients have non-motor symptoms from five or more domains.⁴ Importantly, non-motor symptoms are not just associated with advanced PD but may actually pre-date the motor manifestations of the disease. There is particularly strong evidence that this is the case for constipation, olfactory deficits, RBD and depression, and may be the case for

Figure 1: The Effect of the Presence of Non-motor Symptoms of Parkinson's Disease on Quality of Life Measured By Parkinson's Disease Questionnaire-39¹²



PDQ-39 = Parkinson's disease questionnaire-39; SI = single index. Source: Reproduced with permission from John Wiley & Sons.¹²

restless leg syndrome, apathy, fatigue and anxiety.⁷ It has been proposed that this sequence of events fits in with the neuropathology of PD, whereby the disease 'starts' in the olfactory bulb and only when it has progressed does the pathology 'spread' to the substantia nigra and cause motor symptoms.^{8,9} In the future, this could have huge implications for the early identification, treatment and prevention of PD, and assessment of the full range of non-motor symptoms will almost certainly be central to such early detection.

Despite their frequency, non-motor symptoms of PD are often under-recognised, and this article explores the evidence for non-motor symptoms being the most important determinant of QoL.

Non-motor Symptoms and Quality of Life

A survey of more than 2,000 patients by the UK Parkinson's Disease Society showed that many of the symptoms of PD that most affected people's lives were non-motor aspects such as sleep problems, depression, memory loss, anxiety, pain and balance.¹⁰ Subsequent publications have confirmed that while motor symptoms have an effect on QoL, measured by PDQ-39, non-motor symptoms such as psychiatric, autonomic and sensory symptoms also contribute significantly to reducing QoL in PD.¹¹ A large-scale study involving 1,072 patients showed that the non-motor symptoms with the largest negative impact on QoL included apathy, psychiatric symptoms including depression, fatigue, attention-memory problems, sleep problems and pain (see *Figure 1*).¹²

The development of the NMSS provides a useful tool for quantifying non-motor symptoms in patients.^{13,14} The NMSS is now accepted as a reproducible, valid and precise instrument, and a clear correlation between worsening NMSS scores and PDQ-39 scores has been demonstrated – further confirming the importance of non-motor symptoms on QoL in patients with PD.^{5,15} The correlation between NMSS scores and QoL (both PDQ-39 and PDQ-8) was greater (correlation coefficient 0.70) than the correlation between measures of motor function (Unified Parkinson's Disease Rating Scale [UPDRS] III and Hoehn and Yahr staging) and QoL (correlation coefficients ranging from 0.41 to 0.51).^{4,5,15} This strong correlation exists irrespective of the stage of PD, and scores on both the NMSS and PDQ-8 increase with the

duration of disease. Generally, non-motor symptoms that are common in advanced PD (duration >10 years) are also present at an earlier stage (disease duration <1 year).

Long-term follow-up studies show it is the non-motor symptoms such as depression, dementia, dribbling of saliva and choking that are a major cause of disability and the primary cause of hospitalisations.^{16,17} It is crucial, therefore, that both motor and non-motor symptoms are considered when aiming to improve the QoL of patients with PD.

Treatment and Quality of Life

An observational study of changes in QoL in people with PD, The audit of changes in quality of life in people with Parkinson's disease (PDLIFE), has demonstrated that initiating antiparkinsonian treatment at, or shortly after, diagnosis helps maintain the patient's QoL in the first 18 months.¹ In 188 treatment-naïve patients, 74 (39 %) started monotherapy for PD within nine months of diagnosis, 127 (68 %) started monotherapy within 18 months of diagnosis, while 61 (32 %) remained untreated. The QoL measured by PDQ-39 deteriorated significantly at nine months ($p < 0.05$) and further deteriorated at 18 months ($p < 0.05$) in patients who remained treatment-naïve. In contrast, monotherapy ensured that QoL was maintained at nine months and 18 months (see *Figure 2*).¹ All eight domains of the PDQ-39 (mobility, activities of daily living, emotion, stigma, social, cognition, communication and bodily discomfort) significantly worsened after 18 months in treatment-naïve patients with a moderate-to-large effect size – monotherapy maintained scores in most domains.¹

The findings from PDLIFE have important implications. Treatment is initiated when the physician believes the patient has deteriorated, but this belief is apparently based on the motor status of the patient. As such, QoL may deteriorate in untreated individuals owing to non-motor symptoms. Treatment initiation should therefore be based on both motor and non-motor status as both these aspects of PD have early and detrimental effects on QoL. One possible barrier to initiating treatment at diagnosis, and thus preventing rapid deterioration in QoL, is a lack of awareness and non-declaration of non-motor symptoms.¹⁸ In patients whose non-motor symptoms were assessed by the NMSS, approximately 40 % of symptoms were not declared to healthcare

professionals – the most frequently non-declared symptoms were delusions, daytime sleepiness, intense and vivid dreams and dizziness.¹⁸ There is also evidence that physicians do not always recognise non-motor symptoms of PD, fail to link them to PD or do not have time to investigate them optimally. One study showed that during routine office visits, neurologists failed to identify the presence of depression, anxiety and fatigue on >50 % of visits, and failed to recognise sleep disturbance in 40 % of patients.¹⁹

Although treatment is important for improving QoL in patients with PD, evidence for positive effects of treatment is lacking (with the possible exception of deep brain stimulation [DBS] and rasagiline).²⁰ Clearly, more research is needed on the effects of treatments on non-motor symptoms (and, in particular, level one evidence from well-designed randomised clinical trials).²¹

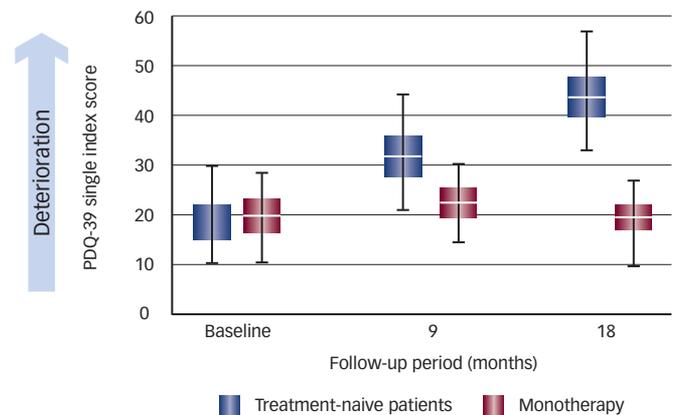
Treating Non-motor Symptoms to Improve Quality of Life

Many non-motor symptoms of PD are at least partly driven by dopaminergic mechanisms. For example, sleep-related symptoms such as RBD, depression and anhedonia, pain associated with 'wearing-off' and central pain, bowel dysfunction including constipation and unsatisfactory voiding, nocturia, erectile dysfunction and contrast sensitivity all have a dopaminergic basis.²² All these symptoms are key determinants of QoL and all can be helped using dopaminergic treatment. Other non-motor symptoms, such as dementia, may not be improved with dopaminergic treatment, and the effects of dopaminergic treatment on cognition and emotion are complex.

There are some ongoing studies designed to look at the effects of non-oral treatments of PD – including the European Parkinson Research Group (EUROPAR) and Randomised evaluation of the 24-hour coverage: efficacy of rotigotine (RECOVER)²³ studies – and initial results suggest positive effects of these continuous dopaminergic stimulation (CDS) treatments. The placebo-controlled RECOVER study indicates that the rotigotine patch may improve sleep/fatigue, mood-cognition, pain and QoL, in moderately advanced PD. As part of the EUROPAR venture, in more advanced PD patients, after three months of treatment with subcutaneous apomorphine infusion, significant improvements in the motor symptoms (measured by UPDRS), non-motor symptoms (measured by NMSS) and QoL (measured by PDQ-8) have been observed.²⁴ Whereas the control group (not treated with subcutaneous apomorphine infusion) had deterioration of non-motor symptoms and QoL,²⁴ sleep, depression/anhedonia, nocturia and pain all improved with subcutaneous apomorphine infusion, and it is thought that these changes relate not just to secondary benefits of motor symptom improvement but also to specific effects of apomorphine and CDS.²⁴

In a study involving 22 patients with advanced PD, improvements in motor and non-motor symptoms, and QoL after six months of levodopa/carbidopa intraduodenal gel infusion (Duodopa®) treatment, were observed.²⁵ Improvements of 45–81 % in the different domains of the NMSS were observed, and at least some of this improvement may have been independent of motor improvements.²⁵ In this small-scale study, 77 % of patients had improved QoL after six months (see Table 1). EUROPAR also investigates the effect of Duodopa on motor scores, non-motor scores and QoL – initial data suggest that Duodopa improved UPDRS III (motor) scores by 43.8 %, UPDRS IV (complications) scores by 52.6 % and NMSS domain scores by over 30 % (cardiovascular, sleep, perception, gastrointestinal, urinary and

Figure 2: Effect of Antiparkinsonian Treatment on Quality of Life Measured by Parkinson's Disease Questionnaire-39¹



PDQ-39 = Parkinson's disease questionnaire-39. Source: Adapted with permission from BMJ Publishing Group Limited.¹

Table 1: Change in Motor Symptoms, Non-motor Symptoms and Quality of Life in 22 Patients with Advanced Parkinson's Disease After Taking Duodopa for Six Months²⁴

Scale	Patients Worsened (%)	Patients Stable (%)	Patients Improved (%)	Effect Size
UPDRS III (motor)	13.6	18.2	68.2	0.54
UPDRS IV (complications)	0	0	100	2.03
PDQ-8	9.1	13.6	77.3	1.28
NMSS total score	4.5	0	95.5	0.89
Cardiovascular	0	40.9	59.1	0.67
Sleep/fatigue	0	13.6	86.4	0.72
Mood/cognition	18.2	22.7	59.1	0.49
Perception/hallucinations	9.1	63.6	27.3	0.30
Attention/memory	0	54.5	45.5	0.40
Gastrointestinal	4.5	27.3	68.2	0.67
Urinary	9.1	22.7	68.2	0.62
Sexual	13.6	40.9	45.5	0.48
Miscellaneous	9.1	13.6	77.3	0.97

NMSS = non-motor symptom scale; PDQ = Parkinson's disease questionnaire; UPDRS = unified Parkinson's disease rating scale.

sexual symptoms). The combined effect of these improvements resulted in a 24.4 % improvement in PDQ-8 scores.

There is insufficient evidence to conclude that specific non-motor symptoms respond to one type of treatment better than others. However, there is intriguing evidence to suggest that this may be the case (for example, levodopa-based therapies may have a better effect on some types of pain than apomorphine-based therapies), and this could help guide and individualise management decisions in the future.

Conclusions

For many patients with PD, the hardest part of living with the disease is the detrimental effect that non-motor symptoms have on their QoL. The importance of non-motor symptoms is now becoming realised among the scientific community and more data are emerging to help quantify their importance. The NMSS may be helpful in that it attempts to quantify all non-motor symptoms, but not isolated symptoms such

as depression or anxiety. It is also clear that a change in mind-set is needed, in which we move away from a reliance on the UPDRS motor score to assess PD and the effect of treatments and towards a more holistic approach that considers the assessment of non-motor symptoms as well as motor symptoms. Other factors not covered by the existing scales (such as communication) may also be important to the patient's QoL and our approach to measuring such factors will continue to evolve. Dopaminergic treatment helps reduce non-motor and motor symptoms, thus improving QoL, and the newer CDS

treatments could play a role in managing these symptoms. Indeed, this may be an important benefit of CDS treatments, to complement their effects on motor symptoms and potential benefits on adherence. However, more good quality clinical trial data are needed before this hypothesis can be proven and, thus, before recommendations can be made for early CDS treatment to improve QoL. Ongoing work will ensure a better understanding of the potential role of CDS treatments for managing non-motor symptoms and improving QoL. The aim is that the everyday lives of patients with PD will be greatly improved. ■

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