Longitudinal Change in Quality of Life in Neurological Disorders Measures Over 3 Years in Patients with Early Parkinson's Disease

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ABSTRACT: Background: The Quality of Life in Neurological Disorders (Neuro-QoL) is a publicly available health-related quality-of-life measurement system.

Objective: The aim of this study was to evaluate the utility of Neuro-QoL item banks as outcome measures for clinical trials in Parkinson's disease.

Methods: An analysis of Neuro-QoL responsiveness to change and construct validity was performed in a multicenter clinical trial cohort.

Results: Among 310 participants over 3 years, changes in five of eight Neuro-QoL domains were significant ($P < 0.05$) but very modest. The largest effect sizes were seen in the cognition and mobility domains (0.35–0.39). The largest effect size for change over the year in which levodopa was initiated was −0.19 for lower extremity function–mobility. For a similarly designed clinical trial, estimated sample size required to demonstrate a 50% reduction in worsening ranged from 420 to more than 1000 participants per group.

Conclusions: More sensitive tools will be required to serve as an outcome measure in early Parkinson's disease. © 2021 International Parkinson and Movement Disorder Society

Key Words: quality of life; measurement; Parkinson's disease; Neuro-QoL

Measuring disease progression in Parkinson's disease (PD) in a way that captures the full breadth of clinical change and reflects what is meaningful to patients is challenging. The US Food and Drug Administration guides industry in their drug labeling claims to assess efficacy using patient-reported outcomes (PROs) when measuring a concept best known by the patient or best measured from the patient perspective, such as symptom burden and functional status.[1] This includes symptom burden and functional status. To this end, PROs are useful in clinical trials and observational outcomes research, but they must be responsive to change over the duration of a disease-modifying clinical trial.

The Quality of Life in Neurological Disorders (Neuro-QoL) measurement system consists of item banks addressing 13 domains across physical, mental, and social health[2] that are not disease specific. The Neuro-QoL measures have been little studied in PD.[3] The International Parkinson and Movement Disorder Society (MDS) Task Force for Rating Scales has rated the disability-related item banks as "recommended" for use in PD for the evaluation of disability.[4] The last comprehensive review of Health-Related Quality of Life (HR-QoL) scales in PD by the MDS Task Force (2011)[5] did not evaluate the Neuro-QoL measures. Based on longitudinal change of the Neuro-QoL measures over a 3-year period in patients with early PD enrolled in a disease-modifying clinical trial, we evaluated their responsiveness to change, construct validity,

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Lisa M. Shulman and Tanya Simuni should be considered joint senior authors.

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 12 January 2021; **Revised:** 12 April 2021; **Accepted:** 15 April 2021

Published online 13 May 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28641

and the feasibility of using the Neuro-QoL item banks as outcome measures in clinical research based on sample sizes required.

Patients and Methods

Data Collection

The Safety, Tolerability, and Efficacy Assessment of Dynacirc CR in PD study (STEADY-PD, reported previously) was a multicenter randomized double-blind placebo-controlled clinical trial of isradipine in early PD.[6,7] At enrollment, participants were required to have Hoehn and Yahr stage ≤2 and to be within 3 years of diagnosis. They could not be currently receiving dopaminergic therapy. Ninety-five percent of participants completed the 3 years of follow-up. Participants completed eight short form paper versions of the Neuro-QoL item banks (Table 1) annually. They also completed the PD-specific HR-QoL measure at the same visit: Parkinson's Disease Questionnaire-39 (PDQ-39),[8] Unified Parkinson's Disease Rating Scale (UPDRS), and MDS-UPDRS.[9]

Statistical Analysis

Isradipine was not found to have an influence on the progression of PD as measured by total UPDRS parts I to III scores,[7] so isradipine and placebo groups were combined in this analysis. The Neuro-QoL measures were compared with conceptually similar PDQ-39 subscores and MDS-UPDRS item 1.1 (cognitive impairment). Correlations were assessed using Spearman's correlation coefficients. Effect sizes were calculated as follows: (mean [3 years] − mean[baseline])/SD(3 years − baseline). Conditional minimal detectable change (which determines whether an observed change for an individual exceeds measurement error) reference values were taken from Kozlowski et al.[10] Responsiveness to treatment was assessed by evaluating the change in Neuro-QoL scores before and after initiation of levodopa. P values <0.05 were considered statistically significant. Sample size calculations for a hypothetical clinical trial were modeled using data from STEADY-PD III and based on a 2-sided test with alpha = 0.05 and beta = 0.2.

Results

At baseline, the mean age of the 336 individuals enrolled in STEADY-PD was 62 years (SD 9, range 31–83 years), mean disease duration 10 months (SD 9, range 1–39 months), mean total UPDRS 23 (SD 9, range 6–52) (see Supporting Information Table S1 for full characteristics). The following results are based on 310 individuals who completed the full 3 years of follow-up (visit 10), including completing the Neuro-QoL measures.

Correlations of the changes over 3 years between Neuro-QoL and commonly used measures are shown in Table 1. All correlation coefficients were significant and ranged from absolute values of 0.19 to 0.53.

Neuro-QoL scores at the 3-year visit in the Neuro-QoL domains of anxiety, lower extremity–mobility, upper extremity–fine motor, executive function, and applied cognition–general concerns were statistically significantly worse compared with baseline. Effect sizes for these changes were small to moderate; the largest effect sizes were seen in the cognitive and mobility domains (0.35–0.39). Effect sizes for change in the comparison measures were similar in magnitude (Table 2).

For worsening, the largest proportion of scores exceeding the conditional minimal detectable change threshold was in the applied cognition–general concerns domain (19%). For improvement, the largest proportion was seen in the domain of positive affect (15%) (Supporting Information Table S2).

A total of 114 individuals started levodopa therapy over the course of the trial and had pre- and post-levodopa assessments with Neuro-QoL measures approximately 1 year apart. Compared with the 69 individuals who were deemed to require symptomatic treatment but were not receiving levodopa at the visit following this, the mean MDS-UPDRS part III score change was significantly different (improved): −6.35 (95% CI: −7.84 to −4.85) for those starting levodopa therapy versus −0.36 (95% CI: −2.22 to 1.50) for those not starting levodopa. In contrast, there were no statistically significant differences in Neuro-QoL changed score between those starting and not starting levodopa (Supporting Information Table S3). Effect sizes ranged from −0.007 for positive affect and well-being to −0.19 for lower extremity function–mobility. Treatment of half of the cohort with isradipine without benefit but with a proportion experiencing adverse effects[7] could affect Neuro-QoL change scores in some domains. To address this, we repeated both the 3-year analyses and the pre- and post-levodopa analyses within the placebo group only and found very similar results (data not shown).

Sample Size Estimates

Supporting Information Table S4 shows the required sample sizes for a putative 3-year clinical trial testing a disease-modifying intervention for early-stage PD, using change scores of the Neuro-QoL measures or the corresponding comparison measures as endpoints. To demonstrate a 50% reduction in the rate of worsening, the estimated sample size required was smallest for the Neuro-QoL cognition and lower extremity function (400–500 participants per group) and 1000 or greater participants per group for upper extremity function and emotional symptom-related domains. The sample size

TABLE 1 *Correlations of the changes over 3 years between Neuro-QoL item bank scores and comparison measures*

Measures (Neuro-QoL item bank/ comparison measure)	Expected correlation direction[a]	Spearman's correlation coefficient	*P* value
Neuro-QoL Anxiety/PDQ-39 Emotional Well-Being	Positive	0.50	<0.0001
Neuro-QoL Depression/PDQ-39 Emotional Well-Being	Positive	0.53	<0.0001
Neuro-QoL Lower Extremity Function–Mobility/PDQ-39 Mobility	Negative	−0.45	<0.0001
Neuro-QoL Upper Extremity Function–Fine Motor, ADL/PDQ-39 ADL	Negative	−0.53	<0.0001
Neuro-QoL Stigma/PDQ-39 Stigma	Positive	0.41	<0.0001
Neuro-QoL Executive Function/MDS-UPDRS 1.1[b]	Negative	−0.25	<0.0001
Neuro-QoL Applied Cognition General Concerns/MDS-UPDRS item 1.1[b]	Negative	−0.19	0.0009
Neuro-QoL Positive Affect and Well-Being/ PDQ-39 Emotional Well-Being	Negative	−0.42	<0.0001

[a]For the PDQ-39, higher scores indicate worse health status, whereas for the Neuro-QoL item banks, higher scores indicate more of the construct being measured (ie, better function or worse symptom). For example, higher scores on the Neuro-QoL Positive Affect and Well-Being item bank are better, whereas for Anxiety, higher scores are worse.
[b]MDS-UPDRS item 1.1 = patient or caregiver-reported cognitive impairment.
Neuro-QoL, Quality of Life in Neurological Disorders; PDQ-39, Parkinson's Disease Questionnaire-39; ADL, activities of daily living; MDS, Movement Disorder Society; UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 2 *Mean change and effect size of each Neuro-QoL domain and comparison measure over 3 years*

Measure	Mean change, baseline to year 3 (SE)	*P* value[a]	Effect size[b] for 3-year change
Neuro-QoL Anxiety	0.73 (0.37)	0.05	0.11
Neuro-QoL Depression	0.50 (0.31)	0.10	0.09
Neuro-QoL Positive Affect and Well-Being	0.34 (0.49)	0.49	0.04
PDQ-39 Emotional Well-Being	1.67 (0.80)	0.04	0.12
Neuro-QoL Lower Extremity Function–Mobility	−2.02 (0.33)	<0.0001	−0.35
PDQ-39 Mobility	3.84 (0.66)	<0.0001	0.34
Neuro-QoL Upper Extremity Function–Fine Motor	−1.91 (0.43)	<0.0001	−0.25
PDQ-39 ADL	5.08 (0.80)	<0.0001	0.36
Neuro-QoL Stigma	0.41(0.30)	0.17	0.08
PDQ-39 Stigma	0.15 (0.85)	0.86	0.01
Neuro-QoL Executive Function	−2.75 (0.41)	<0.0001	−0.38
Neuro-QoL Applied Cognition–General Concerns	−2.57 (0.38)	<0.0001	−0.39
MDS-UPDRS 1.1[c]	0.17 (0.04)	<0.0001	0.27

[a]*t* test for change >0.
[b]Mean difference/SD change.
[c]Cognitive impairment.
Neuro-QoL, Quality of Life in Neurological Disorders; PDQ-39, Parkinson's Disease Questionnaire-39; ADL, activities of daily living; MDS, Movement Disorder Society; UPDRS, Unified Parkinson's Disease Rating Scale.

requirements for the corresponding comparison measures were similar with the exception of measures related to activities of daily living (ADL) and cognition. The PDQ-39 ADL subscore required a smaller sample size than the Neuro-QoL upper extremity function (473 vs. 960). The sample size required to detect a

50% reduction in worsening of either of the Neuro-QoL cognitive domains was less than that which would be required for MDS-UPDRS 1.1 (400 vs. 848).

Discussion

Examining the evolution of Neuro-QoL scores in the context of a negative clinical trial serves as a model for what can be expected in placebo arms or when starting dopaminergic therapy. Statistically significant correlations that are low to moderate in magnitude between the Neuro-QoL changed scores and those of conceptually related measures support the conceptual relatedness of the comparison measures but also suggest that the Neuro-QoL scores are capturing something different from the corresponding PDQ-39 score or MDS-UPDRS item. For some comparisons, this is expected because the concepts covered are either more specific (eg, anxiety [Neuro-QoL] vs. general emotional well-being [PDQ-39]) or different (positive affect and well-being [Neuro-QoL] vs. negative emotions [PDQ-39]).

Over the 3-year period, changes are of low magnitude with correspondingly small-to-moderate effect sizes. For all domains, only a small proportion of change scores exceeded the conditional minimal detectable change threshold. Effect sizes for the comparison measures are of similar magnitude. This may reflect the fact that there is not a great deal of change in performance of daily activities in early PD,[11,12] which is the emphasis of the physical function-related Neuro-QoL measures. Similar modest changes and substantial floor effects are seen with the MDS-UPDRS part II in early PD as well, particularly after initiation of dopaminergic treatment.[13] The relatively stable HR-QoL scores over time in this cohort might be related to "response shift," in which patients with chronic conditions adapt their internal standards and values over the course of disease.[14] It has been demonstrated that people with PD tend to minimize assessments of change in HR-QoL over time.[15]

The ability of the Neuro-QoL to detect the effect of levodopa appears to be poor. It is important to acknowledge that the Neuro-QoL measures were administered only annually, and the long interval between the preceding off-drug and the subsequent on-drug assessments may dilute change scores related to starting symptomatic therapy.[15] The larger effect sizes over the 3-year period compared with before/after levodopa may also reflect the fact that responsiveness to improvement is not necessarily the same as responsiveness to decline. Our finding was similar to Lamichhane et al.,[16] whereby disability and HR-QoL measures were less responsive to improvement than they were to decline.

Using any of the Neuro-QoL measures, we found that the sample sizes required to show a substantial 50% reduction in worsening are larger than the size of the original trial and substantially larger than the vast majority of most previous disease-modifying clinical trials in PD.[17] The STEADY-PD trial of isradipine was powered to detect a 25% reduction in worsening of the sum of the UPDRS parts I to III from baseline to 3 years,[6] a magnitude of effect that would require more than 1000 participants given the distribution of change in Neuro-QoL scores seen over the course of the study. Sample size requirements for a shorter trial (as for most disease-modifying studies in PD to date) would be even larger. This calls into question the practicality of using Neuro-QoL (or other HR-QoL measures) as an outcome measure in similarly designed early PD disease-modifying trials.

Limitations of this study include the lack of a true gold standard of change against which to compare the Neuro-QoL measures. To our knowledge, there is no established minimal clinically important difference for the Neuro-QoL measures in PD, so we could not assess the clinical importance of the longitudinal Neuro-QoL changes in this cohort.

Conclusions

The minor changes over time in Neuro-QoL measures in early PD do not imply that the instruments are not useful outcomes research tools in PD. There is a movement in clinical trials research to emphasize endpoints that are meaningful to patients and reflect how they value outcomes as opposed to the outcome itself.[18,19] Measuring HR-QoL in PD is important, but to serve as an outcome measure for clinical trials, more sensitive tools will be required, at least in early PD. The performance of Neuro-QoL measures in studies testing therapies in cohorts with more advanced disease should be further explored, because studies of outcomes relevant to mid- and later-stage PD, such as cognition, may find Neuro-QoL to be a more informative measure. Furthermore, the Neuro-QoL instruments may have an important place in observational and cross-disease studies. Future research should seek to define clinically important differences in the Neuro-QoL measures to inform their interpretation.

Financial Disclosure

Authors Marras, Mills, Eberly, Oakes, Chou, Halverson, Parashos, Tarolli, Suchowersky, Farbman, Shulman and Simuni received compensation for their roles in the STEADY-PD-III clinical trial.

Acknowledgments: This study was conducted with financial support from National Institutes of Neurological Disorders and Stroke (NINDS) grants U01NS080818 and U01NS080840.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.