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Development of a Health-Related Quality of Life Measure for Peripheral Neuropathy

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Statement of Problem: To develop and evaluate a self-administered health-related quality of life (HRQOL) measure for peripheral neuropathy. *Methods:* A field test measure of 162 items was developed that included the RAND-36 Health Survey as a generic core and a neuropathy-targeted supplement whose content was driven by results from three focus groups with 22 adults having peripheral neuropathy. It was administered at baseline and at 3- and 6-month follow-ups to 80 adult clinical trial enrollees with diabetic neuropathy. Item reduction and placement into scales, reliability, construct validity, responsiveness, and HRQOL comparisons to a general U.S. population were conducted. *Results:* The final 97-item instrument includes 16 multi-item scales and 6 single items. Internal consistency reliabilities ranged from 0.67 to 0.93 (median = 0.88); intraclass correlation coefficients for those reporting no change in health between baseline and 3 months ranged from 0.42 to 0.84 (median = 0.77). Factor analysis of scales revealed physical and mental health as the two underlying dimensions. Correlations between selected HRQOL scales and sociodemographic variables were modest; there were more noteworthy associations between HRQOL scales and employment, disability days, and neurologic symptom ratings. Associations of HRQOL with neurologic examination (strength and reflexes) and with electrophysiologic findings were nonsignificant (all $p > 0.10$). Responsiveness of a physical health summary score relative to a criterion of change in subject's ratings of neuropathy symptom severity yielded a moderate effect size (= 0.60) and a Guyatt statistic exceeding 1.0. *Conclusions:* Results provide preliminary support for the measure's reliability and validity among adults with diabetic peripheral neuropathy. HRQOL was more strongly associated with symptom ratings than with examination and electrophysiologic test results. **Key Words:** Health-related quality of life—Peripheral neuropathy—SF-36—RAND-36—Relative validity—Responsiveness.

As new treatments are developed for chronic neurologic conditions such as peripheral neuropathy, outcome measures are needed that assess the patient's perception of their functioning and well-being (1,2). The goal is to extend the evaluation of outcomes beyond the traditional focus on disease symptoms, signs, and test results to also include patient-centered assessments (3). Health researchers over the past 15 years have established a methodologic foundation for the process of developing reliable and valid measures of health-related quality of life (HRQOL) (4).

Peripheral neuropathies have a wide range of causes, with the commonality of damage to or degeneration of peripheral nerves. Clinical effects can include weakness, pain, impaired sensation, decreased autonomic function, or some combination. The impact of neuropathy on day-

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to-day functioning and well-being is potentially substantial and includes impairment of activities such as bathing and dressing to more vigorous activities (5). In addition, people with neuropathy may experience anxiety, depression, low self-esteem, and feelings of stigma because of their neuropathy or its cause or both (6–9). The most commonly encountered peripheral neuropathy in developed countries is that due to diabetes. In one population-based cohort of adults with diabetes, the prevalence of diabetic polyneuropathy (either asymptomatic or symptomatic) was 48 per 100, and the prevalence of symptomatic diabetic polyneuropathy was 14 per 100 (10).

A literature review revealed few instances of standardized assessment of HRQOL in people with neuropathy. In one study HRQOL was assessed in adults having peripheral neuropathy secondary to cisplatin chemotherapy for testicular and ovarian cancer and in remission (11). Thirty subjects were administered an eight-item peripheral neuropathy symptom scale developed by the investigators and the European Organization for Treatment of Cancer (EORTC) questionnaire, which assesses fatigue and malaise, psychological distress, well-being, social support, and activities of daily living. Content validity was assessed by reviewing it with two patients and two physicians; reliability was not reported. Pearson product-moment correlations between the neuropathy symptom scale and the five EORTC scales ranged from 0.36 to 0.77 (all $p < 0.05$), except for social support ($r = 0.10$; $p > 0.05$).

In another study, HRQOL was measured before and after a treatment for neuropathic limb pain in 33 diabetics (12). There were single-item ratings of appetite, mobility, mood, sleep, and discomfort with the treatment, and a visual analogue pain item. Neither the item development procedure nor reliability or construct validity was reported; however, significant improvements from before to after the intervention were reported for all ratings.

A clinical trial of the impact of a home exercise program on HRQOL in 28 people with peripheral neuropathies used the SF-36, a well-established generic HRQOL measure, and found no differences between intervention and control groups. Investigators also compared SF-36 scores with that of the general population, noting them to be lower in this sample of people with neuropathy (13). The SF-36 has also been used as a secondary outcome measure in a treatment trial of 165 diabetics with painful neuropathy (14). The intervention group scored significantly better than the control group on three of the eight SF-36 scales (pain, emotional well-being, energy/fatigue), but the two groups did not differ on the other five scales. In addition, disease-targeted measures assessing pain and sleep interference had stronger associations with differences between treatment and control groups than did those three SF-36 scales.

Thus the literature on HRQOL assessment in neuropathy lacks sufficient information about evaluation of reliability and validity in people with neuropathy. While one study used an established HRQOL measure and supplemented it with a neuropathy symptom scale, there was limited input from patients in identifying relevant dimensions and in the generation of potential items. The results of the two studies that used generic instruments suggest that these did not capture all the important aspects of HRQOL for this population. Because of this and evidence from other chronic conditions that generic "off-the-shelf" measures may not capture all of the important dimensions of HRQOL important to people with those chronic conditions (15), we undertook the initial phase of the development of an HRQOL instrument for adults having peripheral neuropathy. The ultimate goal was to develop a measure that could be used for any chronic peripheral neuropathy, but we also wanted to be able to compare HRQOL of samples from this clinical population with samples having other chronic conditions or to a general population. Thus we selected an existing generic measure as a core, then created or adapted a set of disease-targeted items from people having different kinds of neuropathy. Development of the final instrument and preliminary assessment of its measurement properties were based on data from a sample having diabetic peripheral neuropathy.

Methods

Development of an HRQOL Field Test Measure

Because the literature review on HRQOL aspects of peripheral neuropathy revealed a paucity of data on this topic, we conducted a series of focus groups with adults having peripheral neuropathy. Focus groups are designed to provide in-depth, fundamental information about experiences and perceptions in a "focused" area among people who share a common characteristic, such as peripheral neuropathy. This methodology is useful for gaining an understanding of the essential ingredients of HRQOL for a targeted subgroup (16). A total of three focus groups of 22 adults (14 female, 8 male) with peripheral neuropathy were held. Participants were recruited from the practices of a general internist, an endocrinologist, and a neurologist, representing both academic and community practices in southern California. Focus groups were run by the same moderator, who had extensive experience with this qualitative methodology. Semistructured protocols were developed by study investigators as a focus group guide; audiotaped recordings were made of each group.

Two of the three groups consisted of people with diabetic neuropathy, and one group had people with neuropathies of various etiologies (e.g., Charcot Marie Tooth and paraprotein-related). Duration of neuropathy ranged from 1 year to 30 years. Three participants needed to use a wheelchair, three required the assistance of a cane to ambulate, and the remainder needed no assistance to walk.

Information was elicited from the first two focus groups (one diabetic and one multiple etiologies) about the following: daily activities and neuropathy symptoms, and how neuropathy symptoms and other conditions affect daily activities; feelings about neuropathy, including effects on self-esteem and self-consciousness; and the impact of neuropathy on relationships. Participants in the third focus group completed a draft questionnaire containing questions developed by study investigators based on results of the previous focus groups, as well as items drawn from existing measures whose relevance was suggested by those focus groups. After each questionnaire section, the moderator asked participants a series of questions about their reactions to the items they had just completed. After completing the questionnaire, subjects were asked about any domains missed or any irrelevant domains that should be excluded.

The moderator's written summaries of the focus groups (available upon request) were reviewed by study investigators (two of whom each observed a different focus group) to identify specific content areas relevant to people with peripheral neuropathy. Examples of neuropathy-targeted HRQOL topics identified as key based on these focus groups are ambulation, balance, and fear of falling; ability to handle objects such as change or utensils; numbness and hypersensitivity or pain in both upper and lower extremities; sleep disturbances; and self-esteem. Based on the focus group data and on the available published literature, a field test measure was assembled. The RAND Health Survey 1.0 (a.k.a. RAND-36 and SF-36) was selected as the generic core, having eight multi-item scales assessing physical function, pain, role limitations due to physical health problems, energy/fatigue, role limitations due to emotional problems, emotional well-being, social function, and general health perceptions (17,18). To supplement this generic core, items tapping self-consciousness, self-esteem, optimism, stigma, control, social isolation, health distress, cognitive function, sleep, sexual function, social support, disability days due to health, and additional emotional well-being items were drawn from existing measures or created. In addition, items were created that asked about the impact of neuropathy on daily activities, work, physical function, pain, energy, sleep, relationships, social activities, and days of work or school missed in the prior month. Items about symptoms of neuropathy and an overall rating of severity of neuropathy symptoms over the prior 3 months were developed. Finally, the EQ-5D item on overall health was selected for the field test measure, with the adaptation that subjects were asked to write in a number between 0 and 100 on the thermometer to indicate their own health that day (19). The final field test instrument contained a total of 162 items, with the SF-36 placed at the beginning of the questionnaire, with items in their standard order.

Development and Evaluation of the Final HRQOL Measure

Samples

Subjects in the field test sample included 80 adults (56 male, 24 female) enrolled in a multicenter, randomized trial of an experimental treatment for diabetic peripheral neuropathy (20). All enrollees had an established diagnosis of either insulin-dependent or non–insulin-dependent diabetes mellitus, evidence of large-fiber neuropathy by abnormal tendon reflexes or quantitative sensory testing, and at least 4 points out of 30 on a scale reflecting neuropathy impairment in either symptoms, examination findings, tests, or some combination (higher scores = more impairment). Individuals having a malignancy or clinically important major organ dysfunction were excluded from the trial, as were those with a psychiatric disorder or cognitive deficits that could interfere with the ability to give informed consent.

Mean age of subjects was 52 years (range = 27 to 65). Average number of years with diabetes was 16 (range = 1 to 58) and with symptomatic neuropathy was 5.5 (range = < 1 to 31).

Measures

In addition to the HRQOL instrument, subjects were asked about their education, income, and employment status. Subjects indicated whether they had ever been diagnosed with each of 22 medical conditions: hypertension, heart attack, congestive heart failure, angina, cancer, migraines, eye disease, sinus trouble, hay fever, arthritis, sciatica, chronic pulmonary disease, liver trouble, dermatitis, stomach trouble, deafness or trouble hearing, kidney problems, limitation in use of an arm or leg, trouble seeing, epilepsy, thyroid problems, and prostate problems (for males) or abnormal vaginal bleeding (for women). A sum of the "yes" responses was used as a summary comorbidity indicator.

Clinical parameters, including symptoms, neurologic examination, quantitative sensory testing, and electrophysiologic tests, were also assessed (21). Participants were rated by clinicians on scales of (1) the presence

and/or degree of neuropathy symptoms: sensory (0–12 points), motor (0–32 points), and autonomic (four items for all subjects yielding 0–4 possible range; a fifth item on impotence is assessed only for males, yielding 0–5 point possible range for subgroup analysis within males only), and (2) neurologic examination findings: sensation (0–32 points), strength (0–64 points), and reflexes (0–20 points) (22). Higher ratings indicate more deficits. Summary scores for symptoms and examination findings are determined as sums of the individual scales in each area. Quantitative sensory testing (vibration, heat/pain, and cooling detection thresholds) and electrophysiologic tests including nerve conduction studies were carried out according to standardized protocols (22,23).

Data Collection

HRQOL, clinical, and test data were collected at baseline, 3 months, and 6 months at study sites, and then delivered to Amgen, Inc. Data were entered as ASCII files for transfer to investigators for analysis after the clinical trial ended.

Institutional review board approval was obtained at each site before subject recruitment; UCLA Human Subjects Protection Committee approval for the HRQOL analyses was obtained.

Analysis Plan

All analyses were conducted using PC-SAS or BASIC programs written by the investigators.

Item placement into scales and item reduction. Items were grouped into hypothesized scales based on content. Multitrait scaling analysis was performed to evaluate the extent to which each item correlated more highly with its hypothesized scale than with other scales, and factor analyses of subgroups of items were also used to better define the underlying structure of sets of items (24,25). Multitrait scaling was used to identify items with low item-scale correlations (i.e. < 0.30) or lack of discrimination across scales, which were omitted from the final instrument; some additional items were removed based on consideration of content and review of item analyses. A target length of approximately 100 items was sought for the final instrument.

Descriptive statistics and reliability. Scores on all multi-item scales represent the average of the answered items. These scores were transformed linearly to a possible 0–100 range, such that higher values indicated better HRQOL. Means, standard deviations, ranges, and percentages of subjects scoring the highest and lowest possible scores were calculated to evaluate baseline scale score distributions. Internal consistency reliabilities were estimated for multi-item scales with Cronbach's alpha coefficient (26). Using intraclass correlation coefficient (two-way random effects model), test-retest reliability was estimated for subjects reporting "no change" in overall health between baseline and the 3-month follow-up (27). (This is an imperfect criterion for stability but probably yields conservative estimates).

Content validity. Content validity refers to the extent to which an instrument represents the range of the domain it is designed to measure and how well it reflects that domain (28). The content validity of these instruments was supported by work carried out in the development process for the draft instrument, which involved a literature review and patient focus groups.

Construct validity. Construct validity was evaluated in multiple ways. First, common factor analysis using squared multiple correlations as communality estimates was performed to summarize the intercorrelations among the scales (29). Common factor analysis has been shown to be more accurate than principal components analysis in reproducing the underlying population correlation matrix (30). Factor rotation was conducted to achieve simple structure, and several criteria were examined to evaluate the appropriate number of factors to rotate, including Guttman's weakest lower bound (31), Cattell's screen test (32), and parallel analysis (33). A Promax oblique rotation (34) was employed to enable evaluation of the reasonableness of the orthogonal assumption and to produce a more realistic representation of the factors (35). Our sample size was sufficient to yield a ratio of five cases per scale, which is above the acceptable minimum ratio (36).

The associations of HRQOL scales with selected sociodemographic and clinical parameters (education, income, employment, duration of diabetes, duration of peripheral neuropathy, disability days, comorbidities, symptom assessments, neurologic examination findings, and quantitative sensory and electrophysiologic tests) were examined with correlations (Spearman and product moment) and analyses of variance (t-statistics and F-ratios). We hypothesized positive associations between HRQOL and education, income, and employment, and negative associations between HRQOL and longer duration of disease, more disability days or comorbidities, and worse symptoms, examination findings, and test results. Relative validity analysis was employed to estimate the sensitivity of different HRQOL scales to selected parameters (37). Relative validities were generated by calculating ratios of the F-ratios of each scale to the F-ratio of a designated reference scale (the HRQOL scale with the smallest F-ratio).

Responsiveness. Responsiveness to change was assessed two ways (27): the effect size and the Guyatt statistic. Effect size is the ratio of mean score change from one point in time to a later time point, to the standard

deviation of scores at the earlier time (38), among subjects determined by some external criterion to have changed ("unstable" subjects). The Guyatt statistic (39) is determined by the ratio of the mean difference in score changes from one point in time to another among "unstable" subjects, to the standard deviation of the difference in scores between those same time points in "stable" subjects (i.e., those judged by an external criterion as not having changed).

We used the difference between two time points in subjects' ratings of severity of neuropathy symptoms over the prior 3 months (rated on a 5-point scale, from "no symptoms" to "extremely severe symptoms") as an external criterion of change. This measure was used because we were interested in change detectable by the person with neuropathy on a measure targeting his or her condition (i.e., a change in neuropathy). Thus subjects having different severity ratings for neuropathy at baseline and at 6 months were classified as "unstable" for these analyses, and all other subjects were "stable." The sign of change scores was reversed for subjects whose criterion severity rating was lower at the later time point relative to the earlier time point; thus "unstable" subjects included both those who improved and those who worsened on the criterion rating.

Development of physical and mental health summary scores for peripheral neuropathy-targeted measure. We derived physical and mental health factor scores from an oblique (Promax) rotated solution (Table 2) and labeled these physical and mental health summary scores.

Comparison of peripheral neuropathy-targeted measure to generic measure. Construct validity and responsiveness of the physical and mental health summary scores of the SF-36 were determined and compared with results for the physical and mental health summary scores of the peripheral neuropathy-targeted measure (40).

Comparison of HRQOL to the general U.S. population. Scale scores on the generic core (the SF-36) were compared with predicted scores for an age- and gender-adjusted sample based on published data from the 1990 U.S. National Survey of Functional Health Status (41).

Results

Item Placement into Scales and Item Reduction

Items were placed into hypothesized clusters by study investigators (excluding items intended to be single items) and analyzed as described in "Methods." The final instrument included 97 items, with 91 items distributed among 16 multi-item scales (Table 1): physical functioning (11 items), role limitations due to physical health problems (6), pain (7), energy/fatigue (5), upper extremities (6), balance (8), self-esteem (6), emotional well-being (7), stigma (3), cognitive function (3), role limitations due to emotional problems(3), general health perceptions (7), sleep (5), social functioning (9), sexual function (2), and health distress (3). In addition, there were six single items: severity of neuropathy symptoms over the prior 3 months (adapted from another source) (42), number of days missed from work or school in prior month due to neuropathy and due to health, change in health over prior 3 months (modified time frame from standard SF-36 change in health item), the EQ-5D rating of overall health (19), and satisfaction with sexual functioning (43).

The SF-36 was retained in the final measure. The health perceptions scale was expanded by two items, and four of the five sleep scale items were derived from longer instruments in the Medical Outcomes Study (MOS); the cognitive functioning and health distress scales each consist of 3 MOS items (44–46). An item on stiffness or tightness of hands or feet (pain scale) and an item on difficulty feeling the shape of objects in your hand (upper extremities scale) were adapted from a neuropathy symptom scale (10). An item on difficulty working buttons, zippers, or laces in the upper extremities scale was derived from a multiple sclerosis instrument (47), and a balance scale item on carefulness to avoid falling when moving was drawn from another multiple sclerosis measure (48). The self-esteem scale includes five items adapted from the Rosenberg Self-esteem Scale (49). The emotional well being scale is expanded by 2 items derived from the Center for Epidemiologic Studies–Depression (CES-D) index (50). The stigma scale consists of three items adapted from Jacoby's work (51), and the sexual function scale consists of two items adapted from the Kidney Disease Quality of Life Instrument (43). A set of neuropathy-targeted items that were created based on focus group comments were also retained in the final measure. Examples are an item on amount of difficulty holding onto or using small objects such as keys, pens, or coins; and an item on the amount the individual is bothered by their ability to walk on slick or slippery surfaces. A copy of the final instrument and all scoring procedures are available on request from the first author at no charge.

Descriptive Statistics and Reliability

Means of the 16 scales range from 57 for energy/fatigue to 94 for stigma, with nearly 80% scoring the possible maximum on the stigma scale (i.e., less stigma; Table 1).

Table 1. *Descriptive statistics and reliability of peripheral neuropathy health-related quality of life measure*

Scale or Item	Number of items	Mean[a]	Standard Deviation	Minimum score	Maximum score	% of patients scoring at floor	% of patients scoring at ceiling	Cronbach's Alpha	Test-Retest Reliability[b] (n=42)
Physical Functioning	11	73.0	25.7	7	100	0.0	18.8	0.93	0.83
Role Limitations–Physical Health	6	65.8	33.3	3	100	0.0	31.3	0.87	0.72
Pain	7	65.5	21.9	15	100	0.0	6.3	0.91	0.84
Energy/Fatigue	5	56.8	23.4	4	100	0.0	1.3	0.93	0.80
Upper Extremities	6	91.9	11.2	42	100	0.0	37.5	0.80	0.84
Balance	8	79.2	19.1	18	100	0.0	18.8	0.89	0.77
Self-esteem	6	79.9	16.9	42	100	0.0	15.0	0.81	0.82
Emotional Well Being	7	71.4	17.2	20	94	0.0	0.0	0.91	0.83
Stigma	3	93.5	14.8	50	100	0.0	78.8	0.88	0.42
Cognitive Functioning	3	76.8	20.1	20	100	0.0	20.0	0.88	0.68
Role Limitation - Emotional	3	66.7	38.6	0	100	15.0	51.3	0.76	0.61
General Health Perceptions	7	58.6	20.3	18	100	0.0	1.3	0.81	0.77
Sleep	5	71.1	18.4	19	100	0.0	3.8	0.67	0.63
Social Functioning	9	80.5	19.6	19	100	0.0	17.5	0.89	0.69
Health Distress	3	68.3	25.5	7	100	0.0	11.3	0.93	0.79
Sexual Function	2	68.7	34.2	0	100	10.1	40.5	0.76	0.72
Physical Health Summary Score[c]	—	50.0	10.0	26.3	64.6	0.0	0.0	0.97[d]	0.83
Mental Health Summary Score[c]	—	50.0	10.0	28.2	64.3	0.0	0.0	0.95[d]	0.82
Satisfaction with Sexual Function	1	55.1	38.0	0	100	20.5	25.0	n/a	0.79
Overall Health	1	70.5	17.7	20	99	0.0	0.0	n/a	0.56

[a]Means and standard deviations at baseline QOL.

[b]The test-retest reliability estimate is the intraclass correlation from a two-way random effects model. When n=42, only patients who completed both the baseline and first follow-up and answered that their health has been "about the same" at the first follow-up compared to three months previously are included in the analysis. Mean test-retest interval = 91 days. While this criterion for stability is not optimal, it yields test-retest reliability estimates that are likely to be conservative.

[c]The overall, physical, and mental health summary scores were converted to T-scores; these summary scores included contributions across all scales and were based on factor analyses and regression analyses.

[d]Internal consistency reliability of the physical and mental health summary scores was estimated with Mosier's formula.[49]

Internal consistency reliabilities for multi-item scales ranged from 0.67 to 0.93 and exceeded 0.70 on all but the sleep scale. Reliability estimates (using Mosier's formula) (52) for the two summary scores exceeded 0.94. Test-retest reliability among the 42 subjects reporting no change in health at 3 months relative to baseline ranged from 0.42 to 0.84, with a median of 0.77; all estimates exceeded 0.60 except for stigma.

Construct Validity

Factor Analysis

Exploratory factor analysis provided support for physical and mental health dimensions of the 16 multi-item scales (Table 2). The physical health dimension is defined primarily by physical functioning, pain, and balance. The mental health dimension is defined primarily by self-esteem, emotional well-being, and cognitive function. The estimated correlation (Promax rotated solution) between physical and mental health factors was 0.57, supporting the use of an oblique factor model.

Associations with Sociodemographic and Clinical Measures

Higher educational attainment and higher income were both associated with better physical functioning, fewer role limitations due to physical health problems, freedom from pain, more energy, better social functioning, and higher physical summary scores (Spearman correlations; p's < 0.05). Higher educational attainment was also associated with better sleep; higher income was related to better balance and self-esteem, and less perceived stigma (Spearman correlations; p's < 0.05). People who were working for pay had higher HRQOL scores than those not working for pay on 11 of 16 scales and on both summary scores (p's < 0.05; Table 3).

Table 2. *Promax rotated two-factor solution for HRQOL scales*[a,b]

Scale	Factor 1 (Physical)	Factor 2 (Mental)
Physical Functioning	**0.92**	−0.10
Role Limitations–Physical Functioning	**0.63**	**0.34**
Pain	**0.92**	−0.03
Energy/Fatigue	**0.63**	**0.31**
Upper Extremities	**0.57**	0.00
Balance	**0.87**	−0.10
Sleep	**0.60**	0.06
Self-esteem	−0.05	**0.75**
Emotional Well Being	−0.19	**1.02**[c]
Stigma	0.12	**0.45**
Cognitive Functioning	0.00	**0.76**
Role Limitations–Emotional	0.27	**0.58**
Health Distress	0.27	**0.59**
Sexual Function	0.27	**0.32**
Social Functioning	**0.64**	**0.34**
General Health Perceptions	**0.49**	**0.43**

[a]Estimated correlation between physical and mental health factors was 0.57

[b]Standardized regression coefficients of the factors on the scales

[c]A coefficient greater than 1.0, while unlikely, is possible in the rotated factor solution.

Duration of diabetes was not associated with any measure except for pain, where less pain was related to greater duration (i.e., higher pain scale scores; Pearson r = 0.24, $p < 0.05$). Other results were all in the expected direction. Longer duration of symptomatic neuropathy was related to worse upper extremity functioning (i.e., lower scale scores; Pearson r = –0.38, p = 0.0004) and not to other HRQOL dimensions. Twenty-two percent of subjects reported being unable to work or attend school because of their health, and 15% because of their neuropathy for 1 or more days in the prior month. Scale scores were lower for 15 of 16 scales due to any health-related disability days and for 14 of 16 scales due to any neuropathy-related disability days, relative to those without disability days (p's < 0.05); the strongest associations were with social functioning. Disability days for either reason were strongly related to HRQOL physical and mental health summary scores (lower; p's < 0.01; Table 4). An increasing number of comorbidities was associated with lower summary scores and lower scores for 12 of 16 scales (Table 4; Spearman correlations; p's < 0.05).

Clinician ratings of sensory and motor symptoms were significantly related to the physical health summary score (Spearman correlation = –0.46 and –0.47; p's $<$ 0.0001) but unrelated to the mental health summary score (Table 5). Autonomic symptoms were significantly related to both the mental and physical health summary scores. There was a modest relationship between more sensory examination deficits and lower physical health summary scores; sensory examination ratings were unrelated to mental health summary scores. No statistically significant relationships were identified between physical and mental health summary scores and the strength examination, reflexes, or quantitative sensory or electrophysiologic test results.

Responsiveness (Table 6)

Effect sizes for the physical health summary score and for the pain, upper extremity, physical functioning, role limitations—physical, and balance scales were in the moderate range (0.40–0.60) (53). (Effect size for the stigma scale was moderate but attributable to very little variability in baseline scale scores). All other effect sizes for HRQOL scales were small. By comparison, effect size for the summary neurologic symptom score was moderate (magnitude = 0.45) and for the summary neurologic exam rating was small (magnitude = 0.19).

The largest Guyatt responsiveness statistic was for the physical health summary score (= 1.04), followed in magnitude by the upper extremity and pain scales, which all exceeded 0.90. The magnitude of the Guyatt responsiveness statistic for the summary neurology symptoms score was 0.78, comparable to that of the role limitations due to physical health problems scale (= 0.71).

Comparison to the SF-36

Analyses of relationships between the SF-36 physical and mental health summary scores and variables such as disability days and employment status showed that associations were not as strong as those between the corresponding physical and mental health summary scores for the peripheral neuropathy-targeted measure and those variables. For example, the F-ratio for the association between disability days due to health and the SF-36 physical health summary score was 9.7, which compares to an F-ratio of 18.8 for the association between disability days due to health and the peripheral neuropathy-targeted summary physical health score. In another example, in contrast to the statistically significant associations between the peripheral neuropathy-targeted mental health summary scores and autonomic symptoms, associations of the SF-36 mental health summary score and autonomic symptoms were nonsignificant. Responsiveness indices, including both effect sizes and the Guyatt statistic, were also lower for the SF-36 summary scores relative

Table 3. *Relationships between HRQOL scale scores and employment status*

Scale	Working for pay full or part-time (range n=55–56)	Not working for pay (n=19)	F[c]	Relative Validity[d]
Physical Functioning	75.8[a]	60.5[b]	5.2	103.1
Role Limitations–Physical Health	73.5[a]	46.1[b]	11.2	224.5
Pain	68.8[a]	56.4[b]	4.7	93.3
Energy/Fatigue	60.5	49.1	3.4	68.5
Upper Extremities	91.9	91.2	0.1	1.0
Balance	82.1[a]	69.5[b]	6.7	134.2
Self-esteem	84.2[a]	69.7[b]	12.4	247.8
Emotional Well Being	74.9[a]	63.5[b]	7.2	144.7
Stigma	97.2[a]	81.1[b]	8.6	171.7
Cognitive Functioning	79.6[a]	68.4[b]	4.5	89.0
Role Limitations–Emotional	75.0[a]	47.4[b]	8.0	160.2
General Health Perceptions	61.0[a]	49.9[b]	4.4	87.4
Sleep	74.1	68.5	1.5	29.8
Social Functioning	84.8[a]	68.7[b]	6.8	135.2
Health Distress	69.6	63.9	0.7	14.5
Sexual Function	71.3	60.3	1.5	29.3
Physical Health Summary Score	51.7[a]	45.2[b]	6.2	124.0
Mental Health Summary Score	52.5[a]	43.7[b]	12.9	257.8

[a,b]Means within a row with different superscripts differ significantly ($p < 0.05$; t-test).

[c]F-ratio = T-squared, from t-test of difference in means

[d]Relative validities were calculated as the ratios of the F-ratios of each scale to the F-ratio of the scale with the smallest F-ratio (the upper extremities scale), which is set to 1.

to corresponding indices for the peripheral neuropathy-targeted measure's summary scores.

Comparison to the General Population

Figure 1 illustrates age- and gender-adjusted T-scores (mean of 50 and S.D. of 10 in the U.S. general population) of the diabetic peripheral neuropathy clinical trial enrollees relative to the U.S. national sample. All SF-36 scale scores for the neuropathy sample were significantly lower than the general population means (z-statistics; all $p < 0.02$); physical function, role limitations (physical), pain, and health perceptions scores were more than a half standard deviation lower for the neuropathy sample than for the general population.

Discussion

This study describes the development of a comprehensive measure of HRQOL for peripheral neuropathy, which includes a generic core and a neuropathy-targeted supplement. Use of focus groups of people with neuropathy to explore relevant HRQOL issues was an invaluable source of data for the creation of items in the field test measure. Focus groups are increasingly recognized as a desirable component of the HRQOL instrument development process, and they are critical for certain conditions such as neuropathy, where the existing literature was scant.

Results from data collected in this diabetic neuropathy sample provide preliminary support for the reliability and validity of the 97-item measure. (We estimate that at a rate of five items per minute this instrument takes about 20 minutes to complete). However, further evaluation in other populations with diabetic neuropathy is needed. In addition, even though item development was based on input from people with neuropathy of various etiologies, further evaluation of psychometric properties of the full 97-item measure should be conducted with samples having neuropathy of other causes before its routine application in studies of such populations. While there were ceiling effects for the stigma scale in this sample having diabetes, in a sample with leprous neuropathy the scale may have more variability in scores. Similarly, sexual satisfaction score distributions might show more variability in samples having more prominent autonomic involvement, and upper extremity scale scores could show greater variability among those having more

Table 4. *HRQOL scale scores and number of days in the past month unable to work or attend school because of health or because of peripheral neuropathy; correlations between HRQOL scale scores and number of comorbidities*

	Disability days due to health				Disability days due to neuropathy				
Scale	None N = 60–61	At least One day N=17	F[c]	Relative Validity[d]	None N=67–68	At least one day N=12	F[c]	Relative Validity[d]	Comorbidity (Spearman correlations) N = 79–80
Physical Functioning	78.0[a]	55.7[b]	11.4	9.6	77.8[a]	45.8[b]	19.3	10.9	−0.32[e]
Role Limitations–Physical Health	74.8[a]	38.6[b]	20.1	16.9	73.2[a]	24.2[b]	30.3	17.1	−0.40[e]
Pain	70.0[a]	52.0[b]	10.4	8.7	69.2[a]	44.5[b]	15.2	8.6	−0.38[e]
Energy/Fatigue	61.3[a]	43.8[b]	8.4	7.1	59.4[a]	42.3[b]	8.4	4.7	−0.31[e]
Upper Extremities	94.0[a]	85.8[b]	6.4	5.4	92.9	86.5	3.4	1.9	−0.35[e]
Balance	83.2[a]	65.4[b]	13.3	11.2	82.2[a]	61.9[b]	13.3	7.5	−0.32[e]
Self Esteem	83.1[a]	66.9[b]	14.1	11.8	82.6[a]	64.9[b]	12.7	7.1	−0.31[e]
Emotional Well Being	75.7[a]	55.5[b]	23.8	20.0	73.8[a]	58.1[b]	9.4	5.3	−0.16
Stigma	96.9[a]	80.9[b]	8.1	6.8	96.9[a]	74.3[b]	10.7	6.0	−0.22
Cognitive Functioning	80.8[a]	62.0 [b]	13.6	11.4	79.3[a]	62.2[b]	8.1	4.5	−0.27[e]
Role Limitations–Emotional	76.0[a]	37.3[b]	15.8	13.3	73.5[a]	27.8[b]	17.3	9.7	−0.14
General Health Perceptions	63.2[a]	44.7[b]	12.7	10.6	61.2[a]	44.2[b]	7.8	4.4	−0.28[e]
Sleep	74.9[a]	60.5[b]	9.3	7.8	73.5[a]	57.9[b]	7.9	4.5	−0.26[e]
Social Functioning	86.5[a]	58.8[b]	25.2	21.2	85.7[a]	51.5[b]	50.2	28.2	−0.23[e]
Health Distress	71.6[a]	57.6[b]	4.1	3.5	70.8[a]	53.9[b]	4.7	2.6	−0.29[e]
Sexual Function	71.0	58.3	1.2	1.0	70.8	56.6	1.8	1.0	−0.21
Physical Health Summary Score	52.6[a]	42.0[b]	18.8	15.8	52.0[a]	38.8[b]	22.6	12.7	−0.38[e]
Mental Health Summary Score	52.8[a]	40.2[b]	27.6	23.2	51.9[a]	39.2[b]	20.6	11.6	−0.27[e]

[a,b]Means within a row with different superscripts differ significantly ($p < 0.05$; t-test).

[c]F-ratio = T-squared, from t-test of difference in means

[d]Relative validities were calculated as the ratios of the F-ratios of each scale to the F-ratio of the scale with the smallest F-ratio (the sexual function scale), set to 1.

[e]$p < 0.05$

Table 5. *Relationships between HRQOL summary scores and neurologic symptoms, neurologic examination findings, and electrophysiologic tests (N range from 75 to 79)*

	Symptoms				Neurologic Examination			Electrophysiologic tests	
HRQOL Scale	Sensory symptoms	Motor symptoms	Autonomic symptoms	Autonomic symptoms (males only)[1]	Sensory exam	Strength exam	Reflexes	Sural nerve conduction amplitude	Peroneal nerve conduction amplitude
Mental Health Summary									
Spearman correlation	−0.11	−0.15	−0.25	−0.37	0.09	−0.11	0.08	0.04	−0.06
p-value	0.35	0.19	0.02	0.005	0.45	0.32	0.49	0.71	0.59
Physical Health Summary									
Spearman correlation	−0.46	−0.47	−0.24	−0.35	−0.23	−0.18	−0.06	0.04	−0.004
p-value	0.0001	0.0001	0.03	0.01	0.04	0.11	0.58	0.74	0.97

[1]N=56; scale includes one additional item on impotence that was assessed in male study subjects.

Table 6. *Responsiveness statistics for HRQOL and neurologic symptoms and exam ratings*

	"Unstable" Group (n=18–19)		"Stable" Group (n=37–38)		
HRQOL Scale or Neurologic Rating	Mean score change	sd of change	sd of change	Effect Size	Guyatt Statistic
Physical Functioning	12.42	27.24	20.55	0.46	0.60
Role Limitations–Physical Health	14.08	32.76	19.78	0.43	0.71
Pain	12.56	20.56	13.42	0.61	0.94
Energy/Fatigue	7.37	26.57	14.84	0.28	0.50
Upper Extremities	7.39	13.41	7.87	0.55	0.94
Balance	6.44	16.17	11.12	0.40	0.58
Self Esteem	−2.41	19.20	11.14	−0.13	−0.22
Emotional Well Being	3.16	18.60	10.15	0.17	0.31
Stigma	1.32	1.91	20.40	0.69	0.06
Cognitive Functioning	2.46	11.41	17.21	0.22	0.14
Role Limitations–Emotional	7.02	36.14	38.46	0.19	0.18
General Health Perceptions	7.96	21.56	11.70	0.37	0.68
Sleep	5.30	21.46	11.79	0.25	0.45
Social Functioning	6.11	17.93	14.02	0.34	0.44
Health Distress	7.02	24.50	15.08	0.29	0.47
Sexual Function	3.07	36.91	17.85	0.08	0.17
Physical Health Summary Score	5.58	9.33	5.37	0.60	1.04
Mental Health Summary Score	1.22	9.32	5.22	0.13	0.23
Summary Neurologic Symptoms	2.00	4.41	2.56	−0.45	−0.78
Summary Neurologic Exam	1.44	7.58	7.00	−0.19	−0.21

[1]Criterion for classification in "unstable" group is a difference in a patient's ratings of severity of neuropathy symptoms over prior 3 months as reported at baseline and at 6 months.

advanced neuropathies or neuropathies with more prominent upper extremity involvement.

Test-retest reliability estimates exceeded the standard of 0.70 for group comparisons for 11 of 16 scales and for all summary scores (54). Although these estimates were below the cutoff for five scales, we note that four of those five exceeded 0.60. In addition, these estimates represent lower bound estimates of reliability, due to the long interval (mean = 91 days) between test-retest dates. Estimates need to be obtained in stable subjects in the future based on shorter intervals. The test-retest reliability estimate for the stigma scale is relatively low, but there were significant ceiling effects on this scale. Given the potential importance of this construct in some neuropathy populations, we recommend keeping it in the instrument until additional studies can be undertaken.

Because of the small sample, estimates of responsiveness based on these data are preliminary. However, results reported here provide evidence supporting the utility of the instrument's physical health summary scores, as well as selected scales tapping aspects of physical health, for detecting change in neuropathy symptom severity. These HRQOL measures were more strongly related to self-reports of differences over time in neuropathy symptom severity ratings than were clinician ratings of symptoms. Examination and test findings were little related to self-reports of temporal differences in symptom severity. Future work should incorporate current proposed standards for determining minimally important differences in clinical measures of neuropathy over time, to more definitively evaluate responsiveness of this HRQOL instrument, using larger samples (27).

Comparisons to predicted HRQOL SF-36 scale scores for an age- and gender-adjusted general population sample reveals that this diabetic neuropathy sample's physical health status is markedly lower. Although some decrements in health may be attributable to diabetes, it is likely that neuropathy has a unique additional impact on HRQOL, and we note that similar findings were obtained in a sample of mixed chronic neuropathies (13).

The combination of a generic HRQOL measure with a neuropathy-targeted supplement is an advantage for assessing interventions because it ensures that HRQOL is comprehensively assessed yet is likely to target areas of particular clinical relevance and likely to change with treatment. The generic core allows for comparing the rel-

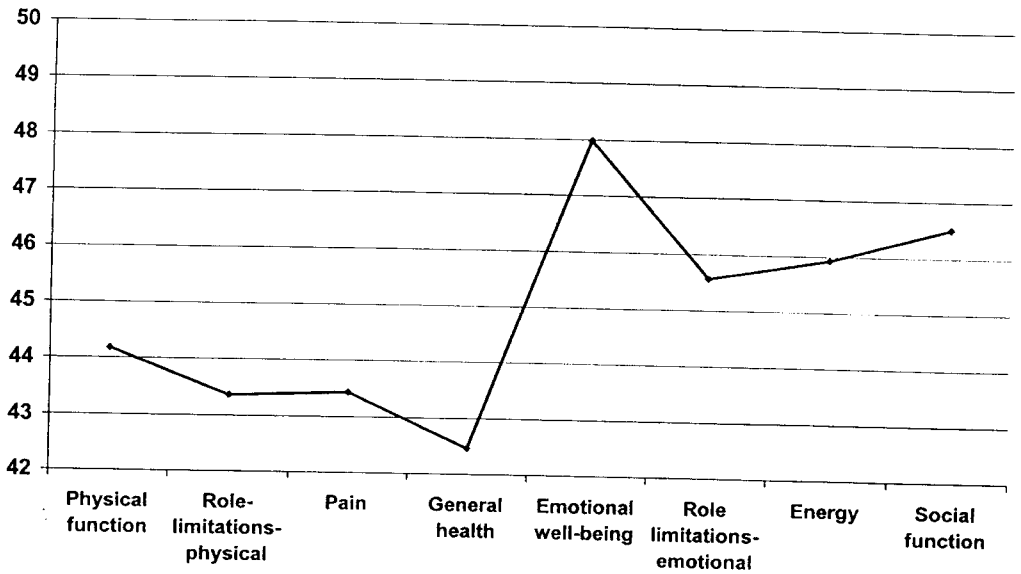

Figure 1. SF-36 Health Survey T-scores for the peripheral neuropathy sample (N=80). Mean T-score for each scale is 50 (SD=10) in general US population and is age- and gender- adjusted.

ative burden of neuropathy with other diseases and to the general population. However, our findings support that the addition of peripheral neuropathy-targeted items to the generic measure resulted in improved construct validity and responsiveness. Given the worldwide prevalence of neuropathy and its morbidity, and the growing pursuit of new approaches to therapy (55,56), further evaluation of the utility of this HRQOL instrument for peripheral neuropathy seems desirable.

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