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Validity of the Neurology Quality of Life (Neuro-QoL) Measurement System in Adult Epilepsy

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Abstract

Epilepsy is a chronic neurological disorder that results in recurring seizures and can have a significant adverse effect on health related quality of life (HRQL). Neuro-QoL is an NINDS-funded system of patient reported outcome measures for neurology clinical research, which was designed to provide a precise and standardized way to measure HRQL in epilepsy and other neurological disorders. Using mixed-methods and item response theory-based approaches, we developed generic item banks and targeted scales for adults and children with major neurological disorders. This paper provides empirical results from a clinical validation study with a sample of adults diagnosed with epilepsy. One hundred twenty one people diagnosed with epilepsy participated, of which the majority were male (62%), Caucasian (95%), with a mean age of 47.3 (SD=16.9). Baseline assessments included Neuro-QoL short forms and general and external validity measures. Neuro-QoL short forms that are not typically found in other epilepsy-specific HRQL instruments include Stigma, Sleep Disturbance, Emotional and Behavioral Dyscontrol and Positive Affect & Well-being. Neuro-QoL short forms demonstrated adequate reliability (internal consistency range = .86–.96; test-retest range = .57–.89). Pearson correlations ($p<.01$) between Neuro-QoL forms of emotional distress (Anxiety, Depression, Stigma) and the QOLIE-31 Emotional Well-being Subscale were in the moderate to strong range (r's = .66, .71 & .53, respectively), as were relations with the PROMIS Global Mental Health subscale (r's = .59, .74 & .52, respectively). Moderate correlations were observed between Neuro-QoL Social Role Performance and Satisfaction and the QOLIE-31 Social Function (r's = .58 & .52, respectively). In measuring aspects of physical function, the Neuro-QoL Mobility and Upper Extremity forms demonstrated moderate associations with the PROMIS Global Physical Function Subscale (r's = .60 & .61, respectively). Neuro-QoL measures of perceived cognitive function (executive function and general concerns) produced moderate to strong correlations with the QOLIE-31 Cognition subscale (r's = .65 & .75, respectively) and moderate relations with the Liverpool Adverse Events scale (r's = .51 & .69, respectively). Finally, the Neuro-QoL Fatigue measure demonstrated moderate associations with the QOLIE-31 Energy/Fatigue subscale (r=−.65), Liverpool Adverse Events Scale (r=.69) and the Liverpool Seizure Severity Scale (r=.50). Five Neuro-QoL short forms demonstrated statistically significant responsiveness to change at 5–7 months, including Fatigue, Sleep Disturbance, Depression, Positive Affect & Well-being, and Emotional and Behavioral Dyscontrol. Overall, Neuro-QoL instruments showed good evidence for internal consistency, test-retest reliability, convergent validity and responsiveness to change over several months. These results support the validity of Neuro-QoL to measure HRQL in adults with epilepsy.

Keywords

Epilepsy; Quality of Life; Neuro-QOL; Measurement; Psychometrics; Validation

1. INTRODUCTION

Epilepsy is a chronic neurological disorder that is characterized by recurrent, unprovoked seizures that are triggered by abnormal electrical discharges in the brain [1]. Once patients are diagnosed, they have several treatment options aimed at controlling seizures and reducing symptoms [2]. Although providing satisfactory seizure control is a primary goal, epilepsy's negative effect extends beyond the duration of individual seizures. Patients may also suffer from a host of cognitive, motor, and emotional changes that may result from the same brain disease that produces the seizures, which can significantly impact one's health related quality of life (HRQL) [3–6]. Additional issues facing persons with epilepsy include

the risk of physical harm due to bone fracture, burns, drowning and unexplained death, as well as risk from surgical intervention to control intractable seizure activity [5]. Medication side effects add to the challenges faced by patients, and include sedation, nausea, double vision, tremor, cognition and memory problems. Described as a social burden as well as a chronic illness, epilepsy also contributes to psychological concerns such as anxiety and fear of seizure occurrence and related social isolation as a result of stigmatization. Adults with epilepsy experience restricted driving privileges, higher rates of unemployment and greater difficulty obtaining life or health insurance. Because of these long-term difficulties, HRQL assessment for persons with epilepsy requires attention to far more than the seizure event, medication side effects or surgical intervention.

Instruments that were designed specifically to measure HRQL of people that were diagnosed with epilepsy were not created until the 1980s [7]. Since then, there has been a growth in the development of HRQL measures that focus on epilepsy, the symptoms and other aspects of treatment. One measure called the Performance, Subjective Evaluation and Socio-Demographic Data (PESOS) was created to measure epilepsy severity, HRQL, limitations in daily living and psychosocial concerns. It is either self-administered or conducted through a face to face interview [8]. Another measure that is commonly used to measure HRQL of patients with epilepsy is the Quality of Life in Epilepsy (QOLIE-89) which has 31 and 10-item versions [9, 10]. It measures several domains including global HRQL, emotional well-being, energy-fatigue, seizure worry, medication effects, health status, cognitive functioning, and social function. Other commonly used Epilepsy-specific HRQL measures include the Well-Being Scale [11] the Liverpool Quality of Life Battery [12], the Quality of Life Assessment Schedule [13] and the Epilepsy Surgery Inventory [14].

The abundance of different generic and targeted HRQL measures that exist not only in epilepsy [15] but also in most major neurological diseases [16–22] has resulted in numerous clinical trials that lack the ability to be compared in a standardized manner. To address this, in 2005 the National Institute for Neurological Disorders and Stroke (NINDS) commissioned the creation of a new patient reported outcomes measurement system for neurological disorders called “Neuro-QoL”[23]. Neuro-QoL was developed parallel to the NIH Patient Reported Outcomes Measurement Information System (PROMIS) [24, 25], employing the same rigorous instrument development guidelines and methodologies [26] and sharing common items with PROMIS item banks. Both PROMIS and Neuro-QoL employed item response theory (IRT) modeling [27] thereby enabling unique flexibility regarding item selection and use (e.g., use of Neuro-QoL recommended short forms, or the creation of trial-specific tailored forms), administration of items (use of static short forms or dynamic computerized adaptive tests) and deeper understanding of item information (e.g., ability to evaluate each item’s information function, performance and location along a given trait’s severity continuum). The comprehensive development and initial calibration testing results of Neuro-QoL have been described previously [23, 28–30] and is beyond this scope of this clinical validation paper. The purpose of this paper is to report on the multisite validation testing results of Neuro-QoL short forms that have resulted from this work with a clinical sample of adult epilepsy patients.

2. MATERIALS AND METHODS

2.1 Participants and Procedures

Consecutive patient recruitment occurred on an ongoing basis from six participating epilepsy treatment sites (Dartmouth, University of Texas Health Science Center at San Antonio, University of Chicago, University of Puerto Rico, NorthShore University Health System and the Cleveland Clinic Foundation). Eligible patients were English speaking adults 18 years or older with a diagnosis of epilepsy. Attempts were made to proportionally

balance the level of seizure severity, from mild (no seizure within the past year) to severe (≥2 seizures per month). Patients were ineligible if they were non-English speaking, experienced non-epileptic seizures or demonstrated cognitive impairment such that it would have prevented informed consent (as determined by recruiting staff during consent process). This study was approved by participating institutional review boards.

After obtaining informed consent and explaining the study, Study personnel administered self-report measures at baseline, 7 days later, and 5–7 months after baseline. Baseline and 5–7 month assessments lasted between 60–90 minutes and were administered by computer-assisted interview in the clinic. The 7 day assessment lasted 30 minutes or less and were administered by phone interview. Physician ratings and chart review occurred at baseline and as part of the 5–7 month follow up administration. In addition to the Neuro-QoL tool, other measures included generic and epilepsy-targeted quality of life assessments, indices of seizure severity, adverse events and cognitive ability, socio-demographic and clinical questions, including well known anchor measures. This epilepsy study was a part of a larger Neuro-QoL validation study that also included recruitment of patients diagnosed with multiple sclerosis, Parkinson's disease, stroke, ALS, pediatric epilepsy and muscular dystrophies. The accrual goal for each disease was 100 people at each time point. A dedicated site monitor conducted pre, mid and end of study site visits to assure quality of data collection and other procedural compliances.

2.2 Analysis

All analyses were conducted using SPSS version 21. The internal consistency reliability of Neuro-QoL short form scores was assessed using Cronbach's alpha coefficient (coefficients of .70 or higher were considered acceptable). Test-retest reliability estimates of Neuro-QoL short form scores between baseline and 7–10 days were conducted using intraclass correlation coefficients (coefficients of .70 or higher were considered acceptable). When examining relations between Neuro-QoL scores and external measures (using Spearman's Rho), the following guidelines were used to interpret magnitude: < 0.30: Nominal; 0.30 to 0.49: Small; 0.50 to 0.69: Medium; 0.70 to 1.0: Large. We expected weaker relations between measures of dissimilar constructs and stronger associations between measures of similar or identical ones.

Descriptive statistics (frequencies/percentages for categorical data, means/standard deviations for continuous data) were calculated for Neuro-QoL and external validation measures as well as for socio-demographic and clinical variables. This included means, standard deviations, and other distributional information at the baseline and follow-up assessments. Socio-demographic and clinical information included: date of birth, gender, Spanish/Hispanic/Latino origin, racial or ethnic background, relationship status, highest grade in school completed, current occupational status, family household income, date of diagnosis, date of symptom onset, family history, co-morbid medical conditions, date of first epileptic seizure, seizure frequency, number of seizures in past 3 months, average duration of seizures (in minutes), type and duration of postictal deficit, current medication for epilepsy/seizure disorder, seizure type and sub-type, etiology of epilepsy, risk factors, seizure location, precipitating events, and seizure surgery.

Next, to examine indicators of convergent validity, baseline Neuro-QoL short form scores were correlated with scores of baseline generic validation measures and epilepsy-specific scales using Spearman rho correlations. Known groups validity comparisons were also conducted by comparing baseline Neuro-QoL and construct matching legacy measure scores between epilepsy patients grouped by seizure severity quartile groups, which were labeled "Low" (LSSS ≤ 24), "Mild" (LSSS between 25–36); "Moderate" (LSSS between 37–56)

and “Severe” (LSSS ≥ 57.5). Analysis of variance (ANOVA) with LSD post hoc comparisons were used to test for differences between groups.

Finally, to demonstrate the responsiveness of the Neuro-QoL measures for detection of change over time, we evaluated general linear models using each patient’s change score between 5–7 months since baseline. Using a 3-level Global Rating of Change (GRC) score (“better;” “about the same;” “worse”), these three categories were compared using one-way analysis of variance followed by least significant difference testing of adjacent groups when the overall F statistic was significant. For each analysis, we required that at least 5 patients be represented in each of these three categories. If fewer than five patients were represented in a category, it was collapsed with the adjacent category and the two remaining groups were compared using a t-test. There were six GRC questions. Five of them queried patients specifically about change in Physical well-being, Cognitive Well-Being, Emotional well-being, Social/Family Well-being, and Disease-related Symptoms. The sixth GRC item asked about overall quality of life. During planned comparisons no adjustments were made for multiple comparisons and no imputation of missing data was done for patients who failed to participate at the time 3 follow up.

2.3 Measures

Several measures were administered in addition to Neuro-QoL instruments, including epilepsy specific HRQL, global HRQL, cognitive performance, instrumental activities of daily living, and disease severity ratings. See Table 1 for measurement tools administered, the number of items, time required, mode of administration and assessment schedule.

2.3.1 Socio-Demographic and Clinical Data—We collected socio-demographic data (e.g., age, gender, race, ethnicity and education) at baseline using patient report and medical chart review. Clinical data (e.g., date of diagnosis, treatments) was gathered for each participant via chart review and interviews with patients at baseline and 4–6 month follow-up interviews.

2.3.2 Convergent Validity—The following instruments were used to determine convergent validity, a component of construct validity characterized by the extent to which Neuro-QoL instruments are associated in magnitude and direction with measures of similar concepts.

The Barthel Index was developed by Mahoney and Barthel [31] to assess the functional status and mobility skills of neuromuscular and musculoskeletal patients. This measure is one of the best known and most widely used instruments to assess basic activities of daily living (ADL). It has demonstrated high reliability and validity and has been used in epilepsy studies [32, 33] The Barthel Index was selected as a measure of ADLs because it is easy to administer and score, can be completed by any reliable source of information about the patient, and is reliable and valid.

Digit Symbol Coding [34] is a timed paper/pencil symbol substitution task of mental, visual and motor speed. Using a key of paired numbers and symbols, participants must draw corresponding nonsense symbols below rows of numbers.

The EQ-5D [35, 36] is a 15-item self-report measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of HRQL for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. Domains include: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

A Global HRQL Question [37] was a single item from the Functional Assessment of Chronic Illness Therapy (FACIT), “I am content with the quality of my life right now,” was used as a global measure of quality of life.

Global Ratings of Change items were created for Physical, Social/Family, Cognitive, Emotional, Symptomatic and Overall Quality of Life changes between baseline and a 5–7 month follow up assessment. This measurement strategy assumes that a patient can judge whether over the course of a specified period, their self-reported health status has changed. Typically, such questions require patients to remember a prior health state and compare it to how they are currently feeling [38, 39]. Questions were specified to the condition or domain of interest and followed the format of, “Overall, has there been any change in your condition over the past (enter time frame)?” Patients specified whether they are worse, about the same, or better using the following global rating scale: 1- a little better (or worse), 2 – moderately better (or worse) and 3 – very much better (or worse).

The Lawton Instrumental Activities of Daily Living Scale, [40] is an interviewer administered measure which includes 8 items: telephoning, shopping, food preparation, housekeeping, laundry, transportation, medications, and handling finances. Each task is graduated in a 3- or 4-level scale. The scale measures performance in contrast to ability.

The Karnofsky Performance Status Scale (KPSS) [41] is a rating of functional impairment and offers a simple if coarse breakdown of activity level across patients regardless of diagnosis. KPSS criteria are based on descriptive categories from 0–100. Ratings are traditionally made by providers.

The Liverpool Adverse Events Profile (LAEP) [42] is a 19 item self-report scale that assesses the frequency of antiepileptic drug side effects. Using a 4-point Likert scale (1= never a problem − 4=always a problem), scores are summed to create a total score (ranging from 19–76, higher scores indicating more symptoms).

The Liverpool Seizure Severity Scale (LSSS) is a 12 item scale that assesses experiences during and immediately after a seizure such as loss of consciousness and postictal confusion. Each item is scored on a Likert scale, with higher scores indicating greater seizure severity. Reported test-retest reliabilities ranged from 0.74 – 0.80.[43, 44] A modified scoring system requires patients to rate only their most severe seizure and demonstrates adequate reliability, construct validity and responsiveness to change [45].

Neuro-QoL Short Forms [46] were all between 8–10 items and provided raw scores which were converted to T-Scores; with a T = 50 indicating average function compared to the reference population and a standard deviation of 10. Neuro-QoL T-scores referenced to a general population sample are indicated by GPT (General Population T-Score) while those referenced to a clinical sample are indicated by CT (Clinical T-Score).

Oral Digit Symbol Modalities [47] is a test of speed of information processing, but is also thought to assess visual acuity and figural memory. A timed coding task using a key as reference, examinees pair specific numbers (0–9) with designated geometric figures that are matched up in the key; examinees attempt to complete as many matches as quickly as possible in 90 seconds. Written and oral forms are highly correlated (in normal adults >.78). Because some may have greater motor deficits compared to others, we administered the oral version.

Symbol Search [34] is a test of mental speed, this is a timed orthographic measure of visual attention, scanning, and motor speed. Participants must determine if a target nonsense figure

is present in a string of figures and mark a corresponding “yes” or “no” box presented at the end of each item.

A Pain numeric rating scale was a single (0–10) item that asks patients to rate, from “none” (0) to “the worst pain you can think of (“10”), the severity of their worst pain during the past week.

The PROMIS Global Health Scale [48] refers to evaluations of health in general rather than specific elements of health. The PROMIS global health items include global ratings of the five primary PROMIS domains (physical function, fatigue, pain, emotional distress, social health) and general health perceptions that cut across domains. It can be scored into a Global Physical Health component and Global Mental Health component. Global items allow respondents to weigh together different aspects of health to arrive at a ‘bottom-line” indicator of their health status. Global health items have been found to be consistently predictive of important future events such as health care utilization and mortality.

The Quality of Life in Epilepsy-31(QOLIE-31) [9, 10] is an HRQL survey for adults (>18) with epilepsy. Derived from the QOLIE-89, this scale contains domains that include seizure worry, emotional well-being, energy/ fatigue, cognition, medication effects, social effects, health status and overall quality of life. Good psychometric evidence has been reported in previous studies. This measure was administered at baseline and 4–6 months.

3. RESULTS

3.1 Sample Characteristics

Study participants were primarily male (51%), white (85%), and non-Hispanic (75%) with average age = 47.3 (Range = 18–93). Forty-seven percent were married, 67% had some college or beyond. Fourteen percent were retired, 22% on disability and 37% were employed either full or part time. Average time since epilepsy diagnosis was 18.5 years (SD=13.9). Generalized seizures were most frequently experienced (57%) followed by focal seizures (25%). Mean number of seizures in the past 3 months = 10.7 (SD=37.6). Almost everyone (95%) was taking medication for their seizure disorder, with 64% of those on polytherapy. Twelve percent (12%) had undergone surgery for their epilepsy.

Mean T-Scores and standard deviations on the short forms are shown in Table 2. Epilepsy patients reported significantly worse cognitive and social function compared to a general population reference group but similar levels of physical function and greater positive affect and well-being. When compared to a clinical neurological population, they showed similar levels of stigma, greater anxiety, but less depression, sleep disturbance, fatigue, and sense of emotional and behavioral dyscontrol.

3.2 Psychometric Characteristics

3.2.1 Reliability—Internal consistency and 7 day test-retest reliability of the short forms is shown in Table 2. Cronbach’s alphas range from .86 to .96 and Intraclass Correlation Coefficients (ICCs) from .57 to .89.

3.2.2 Convergent Validity—Spearman correlations between Neuro-QoL short forms and epilepsy-specific and global measures are shown in Tables 3 and 4, respectively.

3.2.3 Known Groups Validity—Statistically significant known group differences were observed between Leeds Seizure Severity Scale severity groups and the following Neuro-QoL short forms: Anxiety ($F=5.2$, $p<.01$), Depression ($F=5.7$, $p<.01$), Emotional and Behavioral Dyscontrol ($F=4.3$, $p<.01$), Fatigue ($F=9.1$, $p<.01$), Positive Affect and Well-

being (F=6.3, p<.01), Sleep Disturbance (F=3.4, p<.01), Stigma (F=4., 7p<.01) and Upper Extremity - Fine Motor, ADL (F=4.1, p<.01).

Compared to the EQ-5D Mobility score, the Neuro-QoL Lower Extremity Function-Mobility short form was able to successfully distinguish significantly different seizure severity scores between mild and severe ratings (F=2.5; p<.05). The Neuro-QOL Upper Extremity Function –Fine Motor/ADL short form was similar to the EQ-5D Self Care and Lawton Index of Activities of Daily Living in its ability to distinguish significant differences between low and severe seizure groups, and similar to the Lawton in being able to successfully distinguish between moderate and severe groups. It was unique, however, in its ability to distinguish between mild and severe seizure ratings (F= 4.1; p<.01), which the EQ-5D Self Care and Lawton were unable to detect.

Neuro-QoL Anxiety and Depression short forms were superior to the EQ-5D Depression/ Anxiety score in their ability to distinguish between significant seizure severity groups (Anxiety SF F=5.5; p<.001); Depression SF F=5.7; p<.001) and performed very similarly to the QOLIE-31 Seizure Worry and Emotional Distress subscales with some exceptions. Similar to the Neuro-QoL Anxiety short form, the QOLIE-31 Seizure Worry subscale could distinguish between low-moderate and low-severe seizure groups, and it was also able to distinguish between low-mild seizure groups, which the Neuro-QoL Anxiety short form did not demonstrate. However, the QOLIE-31 Seizure Worry subscale was not able to distinguish between mild-severe seizure groups, which the Neuro-QoL Anxiety short form demonstrated. The QOLIE-31 Emotional Distress and Neuro-QoL Depression and Anxiety short forms were comparable in their ability to distinguish between low-moderate and low-severe seizure groups, however only the Neuro-QoL Depression short form was able to distinguish between low-mild seizure groups.

Neither the Neuro-QoL Cognitive short forms nor the QOLIE-31 Cognition short form was able to distinguish between seizure severity groups. The NeuroQoL Satisfaction with Social Roles and Activities short form was superior to the EQ-5D Usual Activities score and similar to the QOLIE-31 Social Effects subscale in its ability to distinguish between low-moderate and low-severe seizure groups (F=2.7; p<.05). It did not distinguish between low-mild groups, which the QOLIE-31 did. Finally, the Neuro-QoL Fatigue short form was equal in performance to the QOLIE-31 Energy/Fatigue subscale (F=9.1; p<.001) in distinguishing between low-moderate, low-severe, mild-moderate, and mild-severe seizure groups.

3.2.4 Responsiveness—Physical wellbeing responsiveness was examined through planned comparisons for four Neuro-QoL measures [Lower Extremity Function-Mobility; Upper Extremity Function - Fine Motor/ADL; Fatigue; and Sleep Disturbance] and the EQ-5D's Mobility and Self Care items. Two Neuro-QOL short forms were statistically significant and one exhibited a trend toward significance, all in the predicted direction. Specifically, a trend toward significance was observed between patients who reported worse Lower Extremity Function -Mobility at 5–7 months with those who reported improved functioning (F=2.7; p=.069). Statistically significant differences were observed between patients who reported worsening at 5–7 months with those who reported staying the same or improving in both Fatigue (F=4.9; p<.01) and Sleep Disturbance (F=3.2, p<.05). The EQ-5D's Mobility and Self-care items did not demonstrate statistically significant responsiveness.

Social/Family wellbeing responsiveness was examined through planned comparisons for two Neuro-QoL short forms [Ability to Participate in Social Roles and Activities; Satisfaction with Social Roles and Activities; Stigma], the QOLIE-31 Social Function

subscale and the ED-5D Usual Activities item. A trend toward significance (F=2.6; p=.076) was observed on the Neuro-QoL form for patients who reported worse Ability to Participate in Social Roles and Activities at 5–7 months compared with those who reported improvements in this domain. No other measures (Neuro-QoL Satisfaction with Social Roles and Activities, QOLIE-31 Social Function, EQ-5D Usual Activies) demonstrated significant responsiveness over time.

Emotional wellbeing responsiveness was examined through planned comparisons for five Neuro-QoL short forms [Depression; Anxiety; Emotional and Behavioral Dyscontrol; Stigma; Positive Affect and Well-being], the EQ-5D Depression/Anxiety item, the QOLIE-31 Emotional Wellbeing subscale and the QOLIE-31 Seizure Worry subscale. Three Neuro-QOL forms were statistically significant and one exhibited a trend toward significance, all in the predicted direction. Specifically, a trend toward significance was observed between patients who reported worse Anxiety at 5–7 months with those who reported improvements in this domain (F=2.6; p=.077). Statistically significant differences were observed between patients who reported worse Depression at 5–7 months with those who reported improvements (F=4.9; p<.01); between patients who reported the same level of Emotional and Behavioral Dyscontrol with those who reported improvements (F=3.2, p<.05); and between patients who reported improved Positive Affect and Well-being with those who reported staying the same. Similarly, the EQ-5D Depression/Anxiety item was responsive (F=3.8; p−.02) between those reporting worsening and improvement over time, and the QOLIE-31 Emotional Wellbeing subscale was responsive (F=7.8, p<.01) between those reporting worsening and staying the same, as well as worsening and improving. The QOLIE-31 Seizure Worry subscale did not demonstrate significant responsiveness over time.

Cognitive wellbeing responsiveness was examined through planned comparisons for two Neuro-QoL short forms [Applied Cognition – General Concerns; Applied Cognition – Executive Function], as well as for the Oral Digit Symbol Modalities and Digit Symbol Coding, Symbol Search, and the QOLIE-31 Cognitive subscale. Neither Neuro-QOL short form exhibited statistically significant changes or trends toward significance over time. Similarly, none of the performance-based cognitive assessments (Oral Digit Symbol Modalities, Digit Symbol Coding, Symbol Search) was responsive to change over time. However, the QOLIE-31 Cognitive subscale was significantly responsive (F=3.9, p=.02) at 5–7 months between patients who reported becoming worse and those who reported staying the same or improving.

Symptomatic wellbeing responsiveness was examined through planned comparisons for five Neuro-QoL short forms [Fatigue, Sleep Disturbance, Emotional and Behavioral Dyscontrol, Depression, Anxiety], the QOLIE-31 Energy/Fatigue subscale, and the QOLIE-31 Medication Effects subscale. One Neuro-QoL form was statistically significant in the predicted direction. Specifically, differences were observed between patients who reported worse Depression at 5–7 months with those who reported staying the same or improving (F=3.9; p<.05). The QOLIE-31 Energy/Fatigue subscale was responsive at 5–7 months between patients who reported becoming worse and those who reported staying the same or improving (F=8.2, p=.00). The QOLIE-31 Medication Effects was not significantly responsive over time.

Overall Quality of Life responsiveness was examined through planned comparisons for all 13 Neuro-QoL short forms as well as for the QOLIE-31 Overall QOL subscale. Of the planned comparisons two were statistically significant and three exhibited a trend toward significance, all in the predicted direction. Specifically, a trend toward significance was observed between patients who reported staying the same and those who reported improving

in their scores of Emotional and Behavioral Dyscontrol (F=3.1, p=.051), Anxiety (F=2.9; p=.056), Fatigue (F=2.9, p=.058), and Ability to Participate in Social Roles and Activities (F=2.9, p=.061). Statistically significant differences were observed between patients who reported worse Depression over time with those who reported staying the same or improving (F=3.7; p<.05). Significant differences were also observed between patients who reported improvements in Positive Affect and Well-being at 5–7 months compared to those who reported staying the same or worsening in this domain (F=6.4, p<.01). The QOLIE-31 Overall QOL subscale was not significantly responsive over time.

4. DISCUSSION

Patients coping with a chronic condition such as epilepsy face a myriad of challenges beyond their physical impairment, and the ability to precisely measure these challenges is imperative. The psychosocial consequences of epilepsy, such as depression, anxiety, cognition and social factors, may affect a person's quality-of-life over the long or short-term, depending on the severity of the condition [49]. The Neuro-QoL measurement system uniquely offers epilepsy clinical researchers the opportunity to assess some of the most relevant and important areas of HRQL in a brief, precise and standardized way.

In addition to demonstrating high internal consistency, test-retest reliability and convergent correlations with expected legacy measures, the Neuro-QoL short forms also largely demonstrated adequate performance in distinguishing between different levels of seizure severity, as well as being responsive to change over time compared to legacy measures. Specifically, Neuro-QoL short forms in physical and social health demonstrated superior responsiveness to change compared with legacy measures, while Neuro-QoL short forms of emotional health were equally responsive to change compared with legacy measures. The QOLIE-31 Cognition and Fatigue subscales were superior to their Neuro-QOL counterparts in being responsive to change over time. Neuro-QOL short forms were also able to distinguish between varying levels of seizure severity and were largely superior or equal to the performance of legacy measures in this area. In addition to these findings of equivalence and/or superiority to existing legacy instruments, using Neuro-QoL measures also enables epilepsy researchers to benefit from its direct relationship to the larger NIH PROMIS network and existing links to PROMIS scores with similar and different patient populations. Epilepsy researchers can access information on Neuro-QOL's development and testing, as well as links to all currently available Neuro-QOL short forms and items banks by visiting www.neuroqol.org.

One domain unique to the Neuro-QoL tool compared with other epilepsy-specific or generic measures is stigma, which has a long history with this disease. Writings from as early as the 13th century indicate that people with epilepsy were perceived as possessed, sinful, sick, unclean, and contagious [50, 51]. Even today, persons with epilepsy are stigmatized to a surprising degree. A recent study reported that the stigma associated with epilepsy is very near the stigma level associated with AIDS. Another chronic condition, diabetes, was much less stigmatized [51]. Undoubtedly, stigma negatively impacts the quality of life for people with epilepsy, primarily as it relates to lowered self-esteem and self-efficacy, perceived helplessness, anxiety and depression, diminished life satisfaction, and long-term health problems [52, 53]. Additionally, people with epilepsy face stigma-related workplace disadvantages, such as being stereotyped as aggressive, antisocial, cognitively impaired, unattractive, introverted, and excessively anxious [50]. Stigma accounts for twice the amount of variance in quality of life scores as seizure frequency and antiepileptic drug side-effects [54]. The Neuro-QoL Stigma short form will provide an excellent opportunity to learn more about the role and impact of stigma with this condition and the potential

effectiveness of new treatments in helping patients adjust and experience greater levels of control.

The Neuro-QoL tool also measures commonly experienced psychological distress symptomatology, such as depression and anxiety. The prevalence of both anxiety and depression is high in people with epilepsy - between 10–25% for anxiety and between 10–60% for depression. In a large sample of adults completing the 2004 U.S. HealthStyles Survey, those with epilepsy were twice as likely to self-report anxiety or depression in the previous year compared with those without epilepsy [55]. Participants with active epilepsy (defined as having seizures in the preceding three months or taking anti-epileptic drug medication) were three times more likely [52, 54]. Investigators have found that epilepsy diagnosis, depression, and anxiety are independent predictors of HRQL. This is likely due to feelings of helplessness, heightened fear and uncertainty related to the inability to predict or control seizures [49, 56]. Neuro-QoL short forms of depression and anxiety can be useful in behavioral and mind-body medicine intervention research that focuses on uncertainty tolerance and stress reduction training.

Another psychosocial challenge, cognitive impairment, is one of the more common and debilitating conditions that affect people with epilepsy [57], which is why Neuro-QoL short forms of general and executive function-specific cognitive difficulties is a strength of this new tool. Depending on disease severity and seizure frequency, cognitive dysfunction can cause intellectual decline, reduced information processing speed, memory impairments, and attention deficits [58, 59]. Patients with epilepsy can struggle with this dysfunction their entire life because it can affect their education as a child, their social development as they grow older, and their future employment as an adult [49].

Finally, avoidance, lack of social participation and isolation are other common effects of epilepsy, which are generally related to fear of experiencing seizures in public [60]. This has significant consequences for relationship formation and maintenance, as well as satisfaction with one’s ability to participate with family and friends [61]. The Neuro-QoL tool focuses on both social participation abilities, as well as one’s satisfaction with this. Given the social aftermath of this disease, being able to measure both social participation changes and one’s satisfaction with it become very important.

In sum, the Neuro-QoL measurement system has tremendous potential to help standardize patient reported outcomes assessment in people with epilepsy. It offers patient-centered content across a host of relevant HRQL domains along with flexible administration options (e.g., short forms, computer adaptive tests) and the capacity for integration within the larger PROMIS network. Future studies should consider co-administering select Neuro-QoL item banks alongside epilepsy-specific HRQL measures (e.g., QOLIE-31, LSSS) in large samples of epilepsy patients to allow for co-calibration and common item equating between scales [62].

5. CONCLUSION

The 13 Neuro-QoL short forms demonstrated high internal consistency, ranging from .86 (Sleep disturbance) to .96 (Depression). The Intraclass Correlation Coefficients (ICC) were generally acceptable, ranging from .57 (Ability to Participate in Social Roles and Activities) to .89 (Lower Extremity Function – Mobility). Convergent validity was good, with correlations of the expected strength and in the expected direction. Neuro-QoL measures discriminated between patients at different levels of disease severity. There is initial evidence of responsiveness. Self-reported changes in physical, emotional and symptomatic well-being and overall quality of life were reflected in significant changes in theoretically-related Neuro-QoL short forms.

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Highlights

- We provide validation information on Neuro-QOL, a new health related quality of life tool in epilepsy.
- We report on Neuro-QOL's internal consistency and test-retest reliability with a sample of adult patients diagnosed with epilepsy.
- We demonstrate Neuro-QOL's comparability to existing quality of life measures in adult epilepsy.
- We report on Neuro-QOL's ability to discern between known groups of seizure severity.
- We present information on the responsiveness of Neuro-QOL short forms over time.

Table 1

Measures Administered with Adult Epilepsy Patients

Measurement Tool	# of items	Time required (minutes)	Baseline	7 Days	5–7 months	Mode of Administration
Barthel Index	10	<5	X	--	X	Interviewer
Clinical Information Form	29	<5	X	--	X	Interviewer/Chart
Digit Symbol Coding	0–133	<3	X	--	X	Self-Report/Interviewer
EQ-5D	15	<3	X	--	X	Self-report
Global HRQL Question	1	<2	X	--	X	Self-report
Global Rating of Change Scores	1	<2	--	--	X	Self-report
IADLS	8	<5	X	--	X	Interviewer
Karnofsky Performance Status	1	<2	X	--	X	Med-Professional Rated
LAEP	19	5	X	--	X	Self-report
LSSS	12	6	X	--	X	Self-report/Interviewer
Neuro-QoL Forms	100	45–60	X	X	X	Self-Report
Oral Digit Symbol Modalities	0–133	<3	X	--	X	Self-Report/Interviewer
Pain Question	1	<2	X	--	X	Self-report
PROMIS Global Health Scale	10	<2	X	--	X	Self-report
QOLIE-31	31	10	X	--	X	Self-report
Socio-demographic Form	9	<5	X	--	--	Interviewer/Chart
Symbol Search	0–60	<3	X	--	X	Self-Report/Interviewer

IADLS: Instrumental Activities of Daily Living Scale; LAEP: Liverpool Adverse Events Profile; LSSS: Liverpool Seizure Severity Scale; PROMIS: Patient Reported Outcomes Measurement Information System; QOLIE: Quality of Life in Epilepsy

Table 2

Descriptive and reliability statistics for Neuro-QoL short form T-scores

Neuro-QoL Short Form	N_{items}	$N_{persons}$	M_{GPT}	M_{CT}	*SD*	α	T-R ICCs**
Positive Affect & Well Being*	9	118	53.8		8.2	.95	.81
Applied Cognition – General Concerns*	8	119	41.9		8.7	.94	.82
Applied Cognition – Executive Function*	8	119	43.6		10.3	.94	.87
Lower Extremity Function - Mobility*	8	114	50.4		9	.92	.89
Upper Extremity Function -Fine Motor, ADL*	8	119	49		7.7	.88	.87
Ability to Participate in Social Roles and Activities*	8	119	45.3		7.2	.94	.57
Satisfaction with Social Roles and Activities*	8	119	45.9		6.5	.89	.72
Depression	8	118		47.9	8.3	.96	.82
Anxiety	8	118		52.3	8.1	.94	.81
Stigma	8	119		49.7	9.1	.91	.83
Fatigue	8	119		45.6	9.4	.95	.81
Sleep Disturbance	8	119		48.2	9.8	.86	.77
Emotional and Behavioral Dyscontrol	8	119		46.3	10.1	.93	.84

*For these banks, a high score indicates better function; for all other banks a high score indicates worse function;

**Time 1 (baseline) vs. Time 2 (7 days); M_{GPT} – Mean General Population T-Score; M_{CT}- Mean Clinical T-Score

Table 3

Correlations for Neuro-QoL short form T-scores with epilepsy-specific measures

Neuro-QoL Short Form	QOLIE-31								Liverpool Seizure Severity Scale	Liverpool Adverse Events Profile
	Total	Cognitive	Energy/ Fatigue	Emotional Well- Being	Medication Effects	Overall Quality of Life	Social Function	Seizure Worry		
Positive Affect & Well Being	.74 **	.52 **	.54 **	.67 **	.42 **	.62 **	.64 **	.52 **	−.36 **	−.60 **
Applied Cognition – General Concerns	.68 **	.78 **	.53 **	.43 **	.43 **	.42 **	.39 **	.40 **	−.19	−.70 **
Applied Cognition – Executive Function	.57 **	.67 **	.40 **	.42 **	.26 **	.41 **	.35 **	.25 **	.01	−.51 **
Lower Extremity Function - Mobility	.33 **	.34 **	.28 **	.18	.21 *	.17	.25 **	.21 *	−.20	−.39 **
Upper Extremity Function - Fine Motor, ADL	.33 **	.28 **	.27 **	.21 *	.12	.21 *	.30 **	.23 *	−.21	−.36 **
Ability to Participate in Social Roles and Activities	.65 **	.49 **	.47 **	.54 **	.42 **	.46 **	.60 **	.43 **	−.31 *	−.52 **
Satisfaction with Social Roles and Activities	.54 **	.39 **	.47 **	.46 **	.32 **	.38 **	.49 **	.41 **	−0.22	−.34 **
Depression	−.64 **	−.43 **	−.52 **	−.70 **	−.31 **	−.57 **	−.52 **	−.44 **	.39 **	.45 **
Anxiety	−.62 **	−.42 **	−.53 **	−.69 **	−.35 **	−.45 **	−.48 **	−.55 **	.44 **	.48 **
Stigma	−.58 **	−.37 **	−.42 **	−.50 **	−.37 **	−.42 **	−.57 **	−.50 **	.41 **	.48 **
Fatigue	−.59 **	−.41 **	−.67 **	−.44 **	−.38 **	−.30 **	−.50 **	−.51 **	.49 **	.61 **
Sleep Disturbance	−.53 **	−.41 **	−.46 **	−.42 **	−.37 **	−.33 **	−.43 **	−.47 **	.38 **	.63 **
Emotional & Behavioral Dyscontrol	−.58 **	−.48 **	−.45 **	−.54 **	−.34 **	−.39 **	−.48 **	−.39 **	.33 *	.55 **

* $p < .05$;

** $p < .01$

Table 4

Correlations for Neuro-QoL short form T-scores with global measures

Neuro-QoL Short Form	Barthel Index	Lawton IADL Scale	Symbol Digit Modalities # Correct	Symbol Search Raw Score	Digit Symbol Coding # Correct	PROMIS Global Physical	PROMIS Global Mental	Pain Scale 0–10	EQ-5D Index Score	Global HRQL
Positive Affect & Well Being	.19 *	.22 *	−.09	−.03	.01	.48 **	.73 **	−.40 **	.49 **	.60 **
Applied Cognition – General Concerns	.26 **	.23 *	−.09	−.077	.05	.52 **	.54 **	−.33 **	.43 **	.28 **
Applied Cognition – Executive Function	.31 **	.36 **	0.1	.09	.24 *	.44 **	.45 **	−.29 **	.43 **	.20 *
Lower Extremity Function (Mobility)	.53 **	.38 **	.15	.13	.17	.45 **	.28 **	−.33 **	.49 **	.22 *
Upper Extremity Function (Fine Motor, ADL)	.60 **	.44 **	.16	.09	.32 **	.49 **	.28 **	−.39 **	.52 **	.17
Ability to Participate in Social Roles and Activities	.36 **	.32 **	.03	−.00	.11	.49 **	.62 **	−.36 **	.50 **	.46 **
Satisfaction with Social Roles and Activities	.27 **	.15	.02	.05	.12	.46 **	.53 **	−.31 **	.43**	.57 **
Depression	−.02	−.11	.09	−.04	−.06	−.42 **	−.72 **	.29 **	−.41 **	−.64 **
Anxiety	−.05	−.08	.06	−.06	−.09	−.35 **	−.56 **	.25 **	−.34 **	−.50 **
Stigma	−.14	−.19*	.12	.013	−.06	−.37 **	−.53 **	.19*	−.34 **	−.35 **
Fatigue	−.16	−.14	.09	−.00	−.08	−.53 **	−.46 **	.26 **	−.36 **	−.28 **
Sleep Disturbance	−.12	−.11	.13	.11	.08	−.42 **	−.43 **	.17	−.34 **	−.25 **
Emotional and Behavioral Dyscontrol	−.18	−.16	.17	.08	−.01	−.30 **	−.50 **	.09	−.30 **	−.39 **

* =p< .05;

** = p< 0.01

Table 5

Known Groups Validity of Seizure Severity for Neuro-QOL and Legacy Measures

Domains	Measures	Leeds Seizure Severity Scale Groups					
		Low vs. Mild	Low vs. Moderate	Low vs. Severe	Mild vs. Moderate	Mild vs. Severe	Moderate vs. Severe
Physical	NeuroQoL Lower Extremity Function -Mobility					x	
	NeuroQoL Upper Extremity Function -Fine Motor, ADL			x		x	x
	EQ-5D Self Care			x			
	EQ-5D Mobility						
	Index of Activities of Daily Living			x			x
Emotional	NeuroQoL Positive Affect & Well Being	x	x	x			
	NeuroQoL Depression	x	x	x			
	NeuroQoL Anxiety		x	x		x	
	NeuroQoL Stigma	x	x	x			
	NeuroQoL Emotional and Behavioral Dyscontrol		x	x		x	
	EQ-5D Anxiety/Depression						
	QOLIE-31 Seizure worry	x	x	x			
	QOLIE-31 Emotional Distress		x	x			
Cognitive	NeuroQoL Applied Cognition – General Concerns						
	NeuroQoL Applied Cognition – Executive Function						
	QOLIE-31 Cognition						
Social	NeuroQoL Satisfaction with Social Roles and Activities		x	x			
	NeuroQoL Ability to Participate in Social Roles and Activities						
	EQ-5D Usual Activities						
	QOLIE-31 Social Effects	x	x	x			
Symptoms	NeuroQoL Fatigue		x	x	x	x	
	NeuroQoL Sleep Disturbance			x		x	x
	QOLIE-31 Energy/ fatigue		x	x	x	x	

LSSS Range: 0–97.5; Low: LSSS scores ≤ 24; Mild: LSSS scores between 25–36; Moderate: LSSS scores between 37–56; Severe: LSSS scores ≥ 57.5