INVITED REVIEW

QUALITY OF LIFE AND MEASURES OF QUALITY OF LIFE IN PATIENTS WITH NEUROMUSCULAR DISORDERS

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ABSTRACT: In this review we present an overview of quality of life (QOL) and QOL measures in neuromuscular disorders. We discuss the characteristics of QOL measures used in neuromuscular research, highlighting differences between generic versus disease-specific and global versus health-related QOL instruments. The phenomenon of response shift is reviewed. Commonly used QOL instruments are reviewed for amyotrophic lateral sclerosis, muscle diseases, myasthenia gravis, and polyneuropathy. We also review some of what is known about QOL for patients with these neuromuscular disorders. Muscle Nerve 46: 9–25, 2012

This review is intended to provide the reader with an overview of quality of life (QOL) and QOL measures in neuromuscular disorders and to equip the reader with an understanding of what we believe are important aspects of QOL measures, particularly with respect to neuromuscular disorders, so that the reader can more effectively interpret the QOL literature and appropriately use QOL measures for patient care and clinical research.

QUALITY OF LIFE

The concept of QOL is a difficult one to grasp because of the widely varying ways in which the acronym “QOL” is defined and used. As defined by the World Health Organization, QOL is “...a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment.”1,2

To get a sense of how an individual views his or her QOL, we must have an instrument with which it can be measured. If such a measure is to be useful in understanding those factors that contribute to an individual’s QOL, it is necessary to ask the patient to rate not only overall QOL, but the importance of individual items. These items usually are contained within several broad areas, called domains, which might include but are not limited to, physical, psychological, social, existential, and spiritual. The large number of potential domains, and the enormous choice of items within each domain, has led to the development of a large number of QOL instruments, which differ in the domains emphasized, the specific items within each domain, and the format of the questions. On the most fundamental level, the primary determinants of the usefulness of a particular QOL measure are the content (i.e., items) of the measure and the population in which it is used.

QOL is determined by health-related factors (physical, functional, emotional, and mental well-being) and non–health-related factors (jobs, family, friends, spirituality, other life circumstances). Health-related QOL (HRQOL) is more narrowly defined than global QOL. It is largely viewed from a medical perspective, and so it usually does not include non-medical concepts, such as family, support systems, friends, etc., unless these domains are directly affected by the health status of the patient. HRQOL theoretically differs from global QOL in that it seeks to address those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment. However, this distinction between QOL and HRQOL is often blurred; in many instances, the categorization of a measure as being a global QOL measure or an HRQOL measure depends on whether those using the measure believe that changes in scores will correlate with changes in disease status. To illustrate, the 15-item Myasthenia Gravis QOL (MG-QOL15) measure might be considered an HRQOL measure, because the items on

Abbreviations: ADL, Activities of Daily Living; ALS, amyotrophic lateral sclerosis; ALSAQ-40, 40-item ALS Assessment Questionnaire; CHQ, Child Health Questionnaire; CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth (disease); DLOI, Dermatology Life Quality Index; EMG, electromyography; FACT-GOG-Ntx, Functional Assessment of Cancer–Gynecologic Oncology Group, Neurotoxicity; FDA, U.S. Food and Drug Administration; FFS, Functional Rating Scale; GBS, Guillain–Barré syndrome; HRQOL, health-related quality of life; INQoL, Individualized Quality of Life (questionnaire); IRT, item response theory; IVg, intravenous immunoglobulin; MOS, mental component scale; MD, muscular disease; MG-MMT, Myasthenia Gravis–Manual Muscle Testing; MG-QOL15, 15-item Myasthenia Gravis Quality of Life (instrument); MGQ, Myasthenia Gravis Questionnaire; MCGQOL, McGill Quality of Life (questionnaire); MRC, Medical Research Council; MSG, Muscle Study Group; NHIP, Nottingham Health Profile; NIS, neuropathy impairment score; PCS, physical component scale; PRO, patient-reported outcome; QMG, Quantitative Myasthenia Gravis (score); QOL, quality of life; SEIQOL-DW, Schedule for Evaluation of Individual Quality of Life, direct-weighting form; SF-36, 36-item Short Form; SIP, Sickness Impact Profile; SIS, single-item score; SOLE, Strips of Life with Emoticons

Key words: health-related QOL; neuromuscular disorders; HRQOL; QOL; quality of life; response shift

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mediated polyneuropathies, for example,10–15 but appears to be particularly suitable for the immune-globulin QOL, irrespective of disease status. 4 Cella reflects ALS patients’ own assessments of their global QOL measure, because it was designed to be a global QOL measure, because it was designed to reflect ALS patients’ own assessments of their global QOL, irrespective of disease status. 4 Cella and Tulsky stated that HRQOL “refers to patients’ appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal.”5 There are two notable facets to this definition: (1) the patient’s appraisal of the extent of dysfunction; and (2) the patient’s degree of satisfaction or dissatisfaction with that dysfunction. The patient’s appraisal is critical because “the person wearing the shoe is the one who knows where it pinches.” The degree of patient satisfaction or dissatisfaction is necessary, because it provides information about the tolerability of the dysfunction; some patients can tolerate severe impairment and disability, whereas others are extremely dissatisfied with minimal manifestations. 5 HRQOL measures are more likely to be used in clinical trials in order to assess for changes in the patient’s perspective related to any effect of treatment.

Some important considerations for the clinician when assessing the value and appropriateness of a particular QOL measure include: (1) whether the measure is a global QOL or an HRQOL measure; (2) whether the measure is disease-specific or generic; (3) which life domains (e.g., psychological well-being, social functioning) are being studied and which are not; (4) population and setting for which the measure is intended; (5) psychometric properties (e.g., validity, reliability, responsiveness, item response theory analyses); (6) ease of administration and interpretation; (7) who completes the measure (e.g., self-administered); and (8) how the results are intended to be used (e.g., to improve the patient’s QOL). What follows is a discussion of these important characteristics of QOL measures.

COMMENTS ABOUT THE APPROPRIATENESS OF A QOL MEASURE FOR A PARTICULAR PATIENT POPULATION

Some QOL measures are disease-specific and others are generic. For example, the 36-item Short Form (SF-36) is an example of a generic HRQOL measure that is frequently used in neuromuscular research, with varying success. 7–9 The SF-36 appears to be particularly suitable for the immune-mediated polyneuropathies, for example,10–15 but it is less suitable for many other neuromuscular disorders. Fortunately, there are now many recently validated QOL measures that are specific for various neuromuscular diseases, including ALS, myasthenia gravis (MG), inherited polyneuropathy, myopathies, and muscular dystrophies. One advantage of using a disease-specific HRQOL measure over generic measures is that the disease-specific measures include only items (and thus life domains) that are relevant to an illness and/or treatments and exclude items (and domains) that are not. An investigator should read the individual items of a QOL scale with a particular patient population in mind to estimate the scale’s suitability for that population. For example, the SF-36, which has been used for studying the HRQOL of patients with MG, contains several that items address “bodily pain,” but no items that directly address vision, speaking, chewing, or swallowing—the most common and bothersome manifestations of MG. 5–9

The specificity of a disease-specific QOL measure allows for optimal psychometric properties, avoids creating added burden on patients and staff caused by lengthy scales containing items that miss the mark, and avoids the inclusion of items that run the risk of being viewed by patients as unnecessarily intrusive. 5 If the QOL measure is a burden because it is unnecessarily lengthy and viewed as being partly irrelevant, it is unlikely to be taken seriously by the patient or used by the health-care professional. Thus, a disease-specific QOL scale of appropriate length and breadth should be more valuable and appropriate in most instances. On the other hand, one advantage of generic measures is that they provide insight on where a neuromuscular disease stands in comparison to other conditions that have been assessed with the same measure.

The life domains that should be included in a disease-specific QOL measure should also be determined by the objective of the measure. Is the objective to capture information that will likely change if the disease changes? This is often the goal of HRQOL measures for treatable diseases. Or, is the QOL measure trying to capture information about additional life domains that are not necessarily treatable with pharmacotherapy but are nevertheless important for the overall care of the patient? The use of global QOL measures may be particularly appropriate for: (1) progressive diseases where steadily deteriorating physical domains might overshadow changes in other domains (e.g., ALS); (2) the development of coping strategies for patients; (3) end-of-life counseling; and (4) diseases in which physical dimensions are assessed accurately in other non-QOL measures (e.g., functional rating scales such as the ALSFRS). 4,16,17 In these instances, one objective might be to identify life domains that are important to the patient for which an intervention might be helpful. For example, could the intervention of a social worker...
improve the social support of a patient (and thus the QOL of the patient)? Or could family counseling improve QOL for a particular patient? Furthermore, there are other HRQOL scales that focus on other sequelae of disease rather than the neuromuscular disease per se, such as respiratory, cardiac, and cutaneous scales. For example, the QOL impact of the cutaneous symptoms evident in dermatomyositis can be evaluated using the Skin-dex-1618 or Dermatology Life Quality Index (DLQI).19 The respiratory consequences of ALS and its response to non-invasive ventilation has been assessed using a respiratory-specific QOL (e.g., Sleep Apnea Quality of Life Index).20

**COMMENTS ABOUT OTHER IMPORTANT ATTRIBUTES OF QOL MEASURES**

QOL instruments often use multiple-item ordinal scales. The test items of a QOL measure should meet generally accepted criteria, including the ability to give rise to illuminating responses, to be shorter rather than longer, avoid double negatives, ask about a single issue/facet, and use simple language that avoids ambiguity.1 It is important to note that some items in QOL scales are designed to measure the “symptom impact” of a disease, whereas other items are designed to measure the impact of the disease on certain life domains. QOL scale scores can usually be summed as a total score and sometimes be broken into meaningful subscores that assess specific domains. Some QOL scales can be calculated immediately by the clinician, allowing for easy interpretation and use in the clinical setting, whereas other scores are more difficult to calculate and interpret and thus perhaps are better reserved for clinical trials; however, this gap between degrees of difficulty in the interpretation of summed QOL scores will narrow as implementation of electronic medical records and availability of helpful applications becomes more widespread and user-friendly.

QOL items are patient-reported and usually self-administered. Although physicians and other evaluators are capable of estimating, to some extent, the degree of dysfunction experienced by a patient, the patient’s appraisal of this dysfunction and the extent of tolerability of this dysfunction, viewed through the lens of multiple dimensions (e.g., psychological, social), are what QOL measures attempt to measure.1,5,21 QOL measures are designed to “gain access to the subjective.”22 QOL assessment by proxy may be the only way to assess QOL in children, but they run the risk of underestimating children’s perception of their QOL. The generic PedsQOL and its muscle disease–specific add-on module take the approach of having both child and parent versions.23 There are differing child versions with items and responses that are tailored to different age ranges. The version for the very youngest age range uses emoticons to capture the child’s responses to the questions. This approach is also used by the Strips of Life Emotions (SOLE) generic pediatric QOL scale.24

There is sometimes confusion about what constitutes a subjective measure and what can be considered to be objective. Patient-reported items are certainly subjective, but it must be remembered that physician-reported items are almost always also subjective, because these estimates (e.g., examination findings) also require human judgment. For example, Medical Research Council (MRC) strength scoring requires evaluator judgment and is thus a subjective measure. It is true, however, that some subjective data are more subjective than others. For example, a test item in a scale that assesses a patient’s level of frustration with weakness is prone to be more subjective than direct examination of that weakness. However, rather than dichotomize outcome measures as being subjective or objective, it is generally more useful to think in terms of who reports the findings: patients, physicians, or others. For instance, many scales are patient-reported and others are physician-reported. QOL measures are one type of patient-reported outcome. In December 2009, the U.S. Food and Drug Administration (FDA) published guidance for industry on use of patient-reported outcomes (PROs) to support labeling claims of medical products.25 There were a number of important points in this guidance that are relevant to this review, including: (1) A PRO “is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.” (2) The findings measured by a valid and reliable PRO instrument can be used to support a claim in medical product labeling. (3) “Use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective.” The subjective nature of PROs raises the issue of whether the scores they produce can be regarded as an interval scale. Item response theory (IRT) model (e.g., Rasch) analysis may be able to address this issue by checking whether the scale items and the scale responses create a hierarchical continuum with reasonably regular scaling responses that conform to one’s expectation of how such scales should work. Rasch analysis (or other IRT analysis) may be less applicable in QOL scales that are multidimensional, as the different dimensions (i.e., domains) may change in different directions. Nevertheless, Rasch analysis can be used to explore linear behavior of domains (e.g.,
physical functioning) within a multidomain measure (SF-36). Most of the items in some HRQOL measures, such as the MG-QOL15, are closely related to MG disease status, making the use of Rasch analysis appropriate.

It is generally believed that QOL measures that have been “validated” are preferable over measures that have not been. It is worth noting that there are many caveats to the wholesale branding of a scale as “validated.” One important caveat is that validation of a scale is not an “all-or-none” process but is rather an ongoing, iterative process that is specific to particular populations and settings. Also, there are different types of definitions of the various types of validity (criterion validity, construct validity, discriminant validity, etc.) and reliability (test–retest and internal consistency) that may be found on-line or in numerous excellent review articles. Despite the caveats, all things being equal, “validated” scales are desirable over non-validated ones. The investigators recommend that anyone considering developing or modifying a PRO measure, such as a QOL scale, consult the FDA’s 2009 guidance on this subject.

QOL scales should also be sufficiently sensitive to meet the needs of the investigator. This, too, depends on what the scale is meant to measure. For example, is the QOL scale only meant to be an indicator of how the patient currently perceives the disease? Is the QOL measure expected to also be responsive to clinical change in an individual? HRQOL scales generally function well as indicators of how an individual patient is feeling about the disease at that given moment, but an HRQOL measure might be less valuable for providing information about a particular individual’s response to an intervention (e.g., drug), in large part due to other variables, including emotional state and the possible effects of “response shift” (discussed in what follows). In the neuromuscular clinic at the University of Virginia, for example, the MG-QOL15 is administered to patients with MG, because it provides real-time information about a patient’s estimate of his or her MG-related dysfunction and the tolerability of that dysfunction. This can be helpful information when trying to make the most informed decision about the patient’s care. For example, if a patient has manifestations (e.g., diplopia and ptosis) that are not overly bothersome, the treating physician might be less inclined to escalate treatment, whereas escalation of treatment would more likely be indicated for the patient who is troubled by those same manifestations.

QOL can also be conceptualized as the discrepancy between individuals’ hope/expectations and present experiences. Thus, the greater the undesirable discrepancy between expectation and experience, the worse the QOL. What we find in practice is that individuals undergoing a serious health threat amend or reassess their expectations in light of new possibilities and new priorities, resulting in a relative, and often surprising, sparing of QOL. This adaptive change is referred to as the “response shift.” It is defined as a change in the meaning of one’s self-evaluation of a target construct (e.g., QOL). It is thought to arise from three major sources: (1) a change in a patient’s internal standards of measurement; (2) a change in the patient’s values; and (3) a redefinition of the target construct. These three sources of response shift are likely interconnected. There are also three broad components that contribute to a response shift and adjustment in perceived QOL: (1) a catalyst (e.g., diagnosis of disease); (2) antecedents (i.e., the dispositional characteristics of the individual patient; e.g., personality, expectations, and spiritual identity); and (3) mechanisms (i.e., behavioral, cognitive, and affective processes to deal with the illness; for example, coping abilities, spiritual beliefs). As a simplistic example, when judging QOL, an individual in good health is more likely to place importance on domains that are associated with intact physical function and strength, such as exercise or employment, whereas an individual with ALS may come to eventually judge QOL based more on interactions with family and friends, enjoyment of the beauty of one’s surroundings, or existential factors such as meaning and purpose in life. With regard to neuromuscular diseases as the catalyst, all catalysts are obviously not created equally. Qualities of the catalyst that are likely important are disease severity, pace of onset, duration, prognosis, and direction (i.e., improving, worsening, not changing). For example, the catalytic effect from the diagnosis and manifestations of Duchenne muscular dystrophy will be much more powerful than that from a diagnosis of carpal tunnel syndrome. Response shift may somewhat limit the usefulness of HRQOL measures for following individuals over time to assess efficacy of an intervention. On the other hand, one could exploit the phenomenon of response shift to improve the QOL of those with untreatable neuromuscular disease by harnessing and magnifying the response shift.

AMYOTROPHIC LATERAL SCLEROSIS
Understanding QOL in ALS can be daunting, because much of the literature is quantitative, involving the testing of various psychometric properties, such as reliability, validity, and responsiveness. It may thus be difficult for many neuromuscular clinicians to grasp intellectually or to appreciate the clinical
relevance. Those who wish to learn more about this field often find themselves confronted by two additional barriers: (1) there is no agreed-upon definition of QOL in ALS; and (2) both generic and disease-specific QOL instruments have been used. Clarification of the latter two points is necessary not only for understanding the basis for much of the literature on QOL in ALS, but also for forming a foundation for appropriate use of QOL measurements in clinical care and research. Psychometric properties of the instruments, although of interest and importance, are outside the scope of this review, and can be found within the references cited in what follows.

**Health-Related QOL Instruments.** Early attempts to measure QOL in patients with ALS utilized instruments that were heavily weighted toward physical function and failed to fully capture other factors that contribute to QOL. Examples of this include the Sickness Impact Profile (SIP),\textsuperscript{31–35} SF-36,\textsuperscript{7–9,35–38} and EuroQoL EQ-5D,\textsuperscript{39–42} SIP/ALS-19,\textsuperscript{43} all of which are HRQOL instruments whose scores decline as physical strength and function decline in patients with ALS.

The 40-item ALS Assessment Questionnaire (ALSAQ-40) was a major breakthrough. It contains 5 domains—physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional reactions—and has been demonstrated to have good psychometric properties.\textsuperscript{44,45} Nonetheless, it is heavily weighted toward physical function; the first 20 questions pertain to upper and lower extremity function, and the next 10 to bulbar function. Thus, it is best considered to be a scale of HRQOL, and scores decrease with worsening strength and physical function. A shortened version, the ALSAQ-5, uses one question from each domain of the longer instrument, and was found to produce results similar to that of the 40-item version.\textsuperscript{46} Versions of the ALSAQ-40 in Japanese, Dutch, Spanish, and Italian appear to share properties of the English-language version.\textsuperscript{36,47–49} The ALSAQ-40 remains in active use as a valid disease-specific HRQOL measure for individuals with ALS.

**Global QOL Instruments.** One shortcoming of HRQOL instruments is that, although HRQOL in patients with ALS declines over time, global QOL, as determined by these patients, does not appear to do so. A number of studies have demonstrated that QOL in patients with even advanced ALS may be high.\textsuperscript{16,50–52} In further support of this, QOL, depression, hopelessness, and psychological well-being of patients with ALS who were on ventilator support were not significantly different from those not receiving mechanical ventilation.\textsuperscript{52–54}

The finding of high QOL self-assessment ratings by those with ALS serves to emphasize that QOL is a judgment of the individual and not of the observer. It has been demonstrated repeatedly that physicians, other health-care providers, and those in good health frequently underestimate the QOL of seriously ill patients with chronic diseases, often by making assumptions about the importance of strength and physical ability.\textsuperscript{21,55–58} As a consequence, HRQOL instruments, as designed by those without disease, do not measure many factors that contribute to QOL in patients with life-threatening illnesses but which often are not obvious to observers.\textsuperscript{59–61} These observations brought about the realization that global QOL instruments should reflect overall QOL as judged by the patient, rather than reflecting either the more limited construct of HRQOL or the (usually) inaccurate assessment of global QOL as judged by an observer. This led to the development or use of instruments for assessment of global QOL in patients with ALS.

Trailblazing work came from Cohen and colleagues using the McGill Quality of Life questionnaire (MQOL).\textsuperscript{62–65} They noted that existing QOL instruments overemphasized the physical domain and underemphasized other domains such as the psychological, in particular the existential, which they defined as “perception of purpose, meaning in life, and capacity for personal growth and transcendence.”\textsuperscript{62} Existential concerns are of great importance to people with life-threatening illnesses. Examples of choices that tap into existential concepts on the MQOL questionnaire are: (1) life is “a burden” vs. “a gift”; (2) my life has been “meaningless and without purpose” vs. “very purposeful and meaningful”; and (3) “no progress” in achieving life goals vs. “complete fulfillment” of life goals.

The MQOL consists of 16 items, each of which is rated 0 (worst) to 10 (best). These scores are grouped into five subscales: physical symptoms; physical well-being; psychological symptoms; existential well-being; and support. Scores on the 5 subscales range from 0 (worst) to 10 (best), and are each calculated as the mean of the items contributing to that scale. The MQOL total score is the mean of the 5 subscales again calculated from 0 (worst) to 10 (best). There is also a single-item score (SIS) that asks patients to rate their overall QOL. The SIS correlates well with the total MQOL score. MQOL was found to be valid and reliable for measuring QOL in patients with cancer, human immunodeficiency virus/acquired immunodeficiency disease, and other life-threatening illnesses, and for those in palliative care. The importance of the existential domain is emphasized.
by the correlation between the existential well-being subscale and the SIS. The SIS also correlated with psychological symptoms and support, but not with physical symptoms.

For individuals with ALS, self-rated global QOL, as measured by the MQOL, was correlated with the total MQOL score, and with psychological, existential, and support subscores. But, QOL as measured by the MQOL-SIS and the total MQOL score did not correlate with measures of physical strength and function in a cross-sectional study, and QOL as measured by the MQOL questionnaire remained relatively stable over time as patients weakened. Others have also found QOL as measured by the MQOL questionnaire to be stable in ALS patients over time. Thus, the MQOL was an early instrument that appeared to capture global QOL, as judged by the patient.

The Schedule for the Evaluation of Individual Quality of Life (SEIQoL) and the related direct-weighting form (SEIQoL-DW) begin with the same important concept shared by other global QOL instruments: a person’s QOL is what he or she determines it to be. The difference from other global QOL instruments is the underlying principle that factors that determine individual QOL should be elicited individually. Thus, each individual to whom the questionnaire is administered creates his or her own unique version of it. The SEIQoL is based on a method known as judgment analysis and is administered using a standardized semistructured interview. Individuals name 5 areas of life (cues) most important to their QOL, determine the level of functioning on each cue on a 0–100 scale (rangeing from as bad as could possibly be to as good as could possibly be), and determine the relative importance (weight) of each of these cues to that individual’s QOL. The level of functioning is multiplied by weight for each cue, and the sum of these 5 values is added to produce an index score of QOL, ranging from 0 (worst) to 100 (best). The SEIQoL-DW can be administered more quickly. Cues weights are determined by the use of a pie chart with sections whose size the individual can adjust to reflect the relative importance (weight) of the 5 cues. Both versions have been found to be valid and reliable. They have been widely used in individuals with a variety of non-neurological disorders, individuals with neurological disorders other than ALS and their caregivers, and healthy elderly persons.

There are a number of studies using the SEIQoL or SEIQoL-DW in ALS. As with MQOL, physical strength and function did not correlate with SEIQoL or SEIQoL-DW index scores. Also, similar to findings with the MQOL, the SEIQoL-DW in patients with ALS did not decline over time, despite declines in physical function.

Those cues associated with strength and function—often given as the cue “health”—did not appear to play the major role in determining QOL. The cue most often named or given highest weight, or both, in most studies was “family.” Although “health” was commonly named, it was well behind family in frequency or weighting in most series, and it was one of many other factors identified by patients as determining QOL, including friends, social life, profession/occupation, finances, entertainment/leisure activity, spiritual life/religion, and psychosocial/existential.

An ALS-Specific Global QOL Instrument. It is clear from studies of the MQOL instrument and the SEIQoL that individuals identify many non–health-related factors as being important to their QOL. Although MQOL and the SEIQoL appeared to be very useful at measuring QOL in patients with ALS, there were some shortcomings. Spiritual or religious factors appeared to play a role in preserving QOL in some individuals, but were not explicitly investigated by the MQOL instrument. Also, a number of other factors were identified in the SEIQoL-DW as being important to the maintenance of QOL in patients with ALS, which were not necessarily covered by the MQOL. However, the SEIQoL-DW, although of great value in identifying factors that contribute to the psychosocial well-being of individuals with ALS, was of uncertain value in reflecting aggregate QOL of groups of patients, thus raising concerns about its suitability for use in clinical treatment trials and other studies of groups. The authors of the SEIQoL have themselves noted that it is best suited for use in single-subject and within-subject designs. This led to the development of the ALS-Specific Quality of Life Instrument (ALSSQOL).

The ALSSQOL is a disease-specific QOL instrument designed to reflect ALS patients’ own assessments of their global QOL, and to be suitable for use in individuals, yet valid and reliable across large samples. Development was based on 3 major building blocks: (1) the MQOL questionnaire, including reviews of the responses of a subset of patients to an open-ended question asking them to describe the things that had the greatest effect on their QOL in the past 2 days; (2) data collected on religiosity and spirituality, and (3) items that patients with ALS identified in semistructured interviews as being of importance to their QOL. The instrument was then reformatted to increase ease of administration, and 3 questions in the MQOL that ask the individual to identify 3 troublesome symptoms were removed and replaced with a list of 10 problems assembled from those
symptoms listed most commonly by ALS patients. The result of this process was the 59-item ALSSQOL.4 Each item of the ALSSQOL is scored on a 0–10 scale, with 0 the least desirable situation and 10 the most desirable. An average ALSSQOL score for each individual ranging from 0 to 10 can be determined by summing the scores for all questions for that individual and then dividing by the number of questions answered by that individual. A prospective, multicenter study of 342 patients was carried out to evaluate the psychometric properties of the ALSSQOL. Six domains were identified into which 46 of the questions could be grouped: (1) negative emotion—13 items; (2) interaction with people and the environment—11 items; (3) intimacy—7 items; (4) religiosity—4 items; (5) physical symptoms—6 items; and (6) bulbar function—5 items. The ALSSQOL inquires more broadly than the MQOL into religiousness and asks about intimacy, loneliness, relationships, environment, social interaction, values, coping, interest, and desires/goals. The ALSSQOL was found to be an acceptable and valid instrument for assessing QOL in individuals with ALS, and it appears to be valid and useful across large samples. Scores correlated well with MQOL-SIS, but poorly with measures of strength and function, consistent with results expected for a global QOL instrument. As in previous ALS QOL studies, QOL scores were generally high, with a mean ALSSQOL score of 7.1/10. A multicenter validation of the 46-item version, the ALSSQOL-R, has been completed.87

One strength of the ALSSQOL lies in the insight it provides into a wide array of important variables that can form the basis for appropriate interventions by a multidisciplinary team. Another benefit is that subscale scores can be used to track domains of QOL time, and thus to understand the trajectory of specific factors contributing to QOL. The negative emotion subscale is a broad measure of psychological health that assesses sadness, anxiety, depression, helplessness, purpose, control, and thoughts about the future, illness, and self. When it was followed in ALS patients over a 3- or 6-month period, this subscale was found to be stable despite a clear decline in strength and physical function.88

Understanding the Stability of Global QOL in ALS. The dissociation between chronically ill patients’ own ratings of their QOL and the assessment of a patient’s QOL by those in good health is a key to understanding the relative stability of QOL during the disease trajectory by some individuals with ALS and other life-threatening disorders. The underlying principle likely is the “frame shift” or “response shift” that occurs during the course of such an illness, as discussed in previous studies.34,37,82,89,90 Using the SEIQoL-DW as a measure of individual QOL, such shifts have been demonstrated. For example, in 1 study, the level and weight for “family” increased over time, and the importance attached to “sport” decreased.65 Similarly, it has been found that ALS patients are more likely to list “partner” and less likely to list “health” as areas of importance to the construct of “meaning in life.”91 Multidisciplinary ALS clinics may play a role in these complex dynamics. Previous studies have shown that patients who attend such clinics appear to have a higher overall mental QOL than patients who do not receive such care.92 Multidisciplinary clinics may influence expectations and facilitate response shift. This response shift is not unique to ALS. For example, it has also been described in individuals with advanced cancer55 and has been identified, to a limited extent, in MG.

Although patients with ALS rate their own QOL higher than might be expected by those in good health, it is important to realize that the high overall QOL ratings do not mean that those with ALS are free from psychological morbidity. As would be expected in a population of individuals coping with a fatal disease, psychological health in ALS patients differs from those who are in good health, and many ALS patients experience psychological distress of various types. When assessed with the Brief Symptom Inventory, a self-report measure of symptoms of psychological distress, scores of ALS patients were comparable to distressed psychiatric outpatients and significantly higher than those of non-patient adults on several global measures (global severity index and positive symptom distress index) and some subscales (anxiety, depression, phobic anxiety, and somatization).93 Thus, it is important to assess and treat the mental health of ALS patients broadly, despite their relatively high overall QOL measurements. And it is also important for the clinician to keep in mind that studies such as these, useful as they are, do not permit us to identify the highly negative impact on an individual’s self-perceived QOL and psychological state that can result from a careless statement or thoughtless treatment by a physician or other health-care worker. Clinicians have great power to positively or negatively impact their patients’ QOL and psychological well-being.94 Although it may be obvious, it cannot be overstated that this should not be lost in the sea of questionnaires, analyses, and psychometric discussions that characterize the literature on QOL in ALS.

Choosing an ALS QOL Instrument. There is no “best” QOL instrument for use in ALS. The choice of the optimum instrument depends on whether
QOL is being assessed in an individual or a group, and what the goal is for measuring QOL. In the setting of patient care, it is likely that global QOL is the most useful measure because it assesses such a wide spectrum of domains that contribute to overall QOL as judged by the patient. Thus, instruments such as the MQOL questionnaire, the SEIQoL-DW, or the ALSSQOL-R generally provide the type of information that is most useful for individual assessment and for designing an individual management and treatment plan. In contrast, if the goal is the quantification of QOL as an outcome measure of a therapeutic intervention for a group of patients in a study, then global measures are likely to be less useful because they include factors that are outside the scope of the intervention, such as psychological support, existential factors, religion, and finances. In such cases, HRQOL measures such as the ALSAQ-40, which deal more specifically with variables likely to be influenced by the treatment, would be more useful.

These measures provide information beyond that which can be obtained from direct measures of function, such as the ALSFRS-R or manual muscle testing, because well-designed QOL measures assess domains that, although largely function-based, are perceived as being meaningful to patients. This is in contrast to function-based measures whose significance to patients is less clear, such as a 2-point increase in ALSFRS-R or a 2-kg increase in elbow flexion. The utility of measuring QOL in treatment trials will likely increase as treatments for ALS become more effective. However, as long as our therapeutic armamentarium is limited to measures that at best slow disease progression but do not alter the inevitable downward physical course, QOL likely will continue to be determined largely by non-medical factors that are not directly affected by the therapeutic intervention. Thus, QOL instruments that measure global QOL are unlikely to be shown meaningful changes as a result of such interventions, and those that measure HRQOL are likely to show declines. In such a world, clinicians can facilitate maintenance of QOL in their patients by altering expectations, facilitating response shifts, and providing patients with the tools to best cope, emotionally and physically, with this devastating illness. More effective therapeutics, as they are developed, will result in a need to re-think which instruments will be most valuable in assessing our patients, both individually for patient-care purposes, and more broadly to assess changes in outcomes in groups.

MUSCLE DISEASES
Measuring QOL in muscle diseases (MDs) has added to our understanding of the patient experience of these diseases. It may have particular utility for the hereditary MDs, most of which at present lack any effective medical treatment. As is the case with ALS, measuring QOL may identify areas at which to direct interventions that might help retain QOL despite illness progression. Studies of QOL in MD have identified several useful interventions, including fatigue management, tailored orthoses, and rehabilitative strategies for pain resulting from posture or gait.

Measuring QOL in MD. QOL has been assessed in adults with MDs using a variety of generic measures, including Index of Domain Satisfaction and the Life Satisfaction Index-A.97 SIP,98–100 Nottingham Health Profile,101 Arthritis Impact Scale 1,102 and the 36-item Short Form (SF-36). 101–103 The most frequently used generic measures have been the SF-36104 and SIP.105 Unfortunately, as with other neuromuscular diseases, generic measures of QOL do not capture all the issues relevant for people with MD. For example, clinical factors such as myotonia or weakness are usually omitted from these measures. Also, many items included in generic measures are superfluous when applied to MD. For example, for wheelchair-dependent people with MD, many items related to ability to walk long distances and climb stairs are not applicable.

QOL assessment by proxy may be the only way to assess QOL in young children, but they run the risk of underestimating a child’s perception of QOL. The generic PedsQL, SOLE, and Child Health Questionnaire take the approach of having both child and parent versions.23,24 PedsQL has a muscle disease-specific add-on module that has been validated for Duchenne muscular dystrophy and spinal muscular atrophy. The PedsQL and SOLE have differing child versions with items and responses that are tailored to different age ranges. The versions for the very youngest age range use emoticons to capture the child’s responses to the questions.106–108

Symptom-specific QOL measures have also been applied to MD populations.18,19,109 Specifically, the Skindex-16 and DLQI have been used to isolate the QOL impact of the cutaneous symptoms evident in dermatomyositis.109 The investigators reported poorer QOL related to cutaneous symptoms in women and disabled patients (compared with “not disabled” patients). However, no significant difference in QOL related to cutaneous symptoms was found between patients with myositis and those without myositis. This suggests that, although these questionnaires may be successful in isolating QOL related to the cutaneous symptoms of dermatomyositis, they may be missing the additional impact of myositis on QOL.
Measures that assess exclusively psychosocial areas have also been studied in relation to MD.\textsuperscript{105} These tend to focus on well-being, affect, interpersonal, and emotional aspects of QOL in MD. However, excluding assessment of symptom impact or physical aspects of QOL in MD may be unwise. This is because impaired physical functioning should be expressed in changes in psychosocial domains (e.g., reduced mobility should negatively impact mood and psychosocial functioning), but the opposite relationship may also be true with the effect of mood, emotion, and psychosocial functioning on physical QOL.\textsuperscript{105} Thus, failing to measure physical QOL in MD may exclude useful information about patients’ perceptions of the physical impact of their disease. Of course, measuring physical QOL may be particularly important in isolating the efficacy of a given treatment, because it would allow investigators to ascertain whether a patient actually experiences a meaningful improvement in physical functioning. Small improvements in function may not make a meaningful difference to patients, and even significant physical changes may take a while to be reflected in non-physical aspects of QOL.

In response to these problems, a disease-specific measure of QOL for MD has been developed: the Individualized Quality of Life Questionnaire (INQoL).\textsuperscript{110} It has been translated and validated for U.S. English, Italian,\textsuperscript{111} and Serbian versions and also has translations into French and German. It was derived from qualitative analysis of data generated from semistructured interviews with MD patients. Items were then constructed for the questionnaire based on the ICIDH-2 model of disease, incorporating the concepts of impairment, activities, and participation. These items were verified by a postal survey and, following this, test–retest reliability, validity, and responsiveness to change were all satisfactorily appraised. INQoL consists of 45 questions within 10 sections. Four of these sections focus on the impact of key muscle disease symptoms [weakness, fatigue, pain, and locking (i.e., myotonia)], 5 look at the impact (degree and importance of impact) of MD on particular areas of life (activities, independence, social relationships, and body image), and 1 section asks about the effects of treatment. Participants respond using a 7-point Likert scale. This results in a profile of 10 scores, 9 of which represent the sections of the INQoL, and a composite score based on scores from the 5 life domains. These categories were created so that it would be possible to attribute change in QOL either to an actual change in symptom impact or to a change in perceived QOL. This design may also allow researchers to ascertain whether a change in QOL after treatment has resulted from a “bottom-up” change in patient symptoms or a “top-down” change (response-shift) caused by patients’ re-evaluation of their goals. Thus, scores related to symptoms’ severity and their impact (“bottom-up”) can be separated from life domains (“top-down”), and we can therefore better understand the nature of any changes over time or in response to interventions. The INQoL has now been used in several studies and continues to show good validity. Indeed, in 1 study, many of the physical domains of INQoL showed a better association with manual muscle testing than did the physical domains of the most widely used generic measure of QOL in MD, the SF-36.\textsuperscript{111}

**The Impact of MD on QOL.** Unsurprisingly, MD has a significant negative impact on QOL when compared with healthy controls. In 12 studies that compared people with MD and healthy controls, all reported poorer scores for the MD groups on 1 or more of the QOL domains.\textsuperscript{96,97,103,104,112–120} Currently, there is little evidence to suggest a meaningful difference in QOL between individual MD diagnosis groups; however, larger sample sizes for each of the MDs might change this view.\textsuperscript{105} The 2 largest studies of QOL in MD reported that patients with myotonic dystrophy experience a better QOL than the other MD subjects,\textsuperscript{111} and those with limb-girdle muscular dystrophy experience a worse QOL than other MD subjects (Rose, personal communication).

One might anticipate that the acquired inflammatory myopathies (e.g., dermatomyositis) should be considered apart from inherited MD as they respond to treatment and may pursue a relapsing–remitting course. Thus, QOL in both the physical and psychosocial domains may be differently affected in this group. Although QOL in acquired inflammatory myopathies may be better than that experienced in limb-girdle MD\textsuperscript{111} and worse than that experienced by those with myotonic dystrophy, no study has yet reported a specific profile of QOL in the inflammatory myopathies compared with other MDs. Four studies\textsuperscript{109,114,119,120} have looked specifically at QOL in this group, but it is still unclear whether inflammatory myopathies exert a different influence on QOL, or if QOL in these MDs is mediated by factors different from those evidenced for inherited MD.

**Factors that Affect QOL in MD.** Many factors may affect QOL in MD populations. Those with the greatest empirical support to date include mood; disease severity, pain, and fatigue.\textsuperscript{105} We focus here on the effects of the 2 most salient factors that affect QOL in MD: disease severity and mood.
Seven studies that have assessed associations between measures of disease severity (e.g., manual muscle testing or the Health Assessment Questionnaire)\textsuperscript{96,98,99,104,117,119} Rose et al. (personal communication) reported strong and/or significant associations between physical domains and function. Of these 7 studies,\textsuperscript{98,99} reported that the strength of the correlations between function and psychosocial status was small to medium; the other studies reported no significant associations between these domains. These findings may reflect the more ephemeral nature of psychological/emotional functioning and may also illustrate the “disability paradox”; QOL in these non-physical areas being retained, in part as patients adjust to their illness. Similar findings have also been reported in a study of DMD patients\textsuperscript{121} and, as discussed earlier, also in ALS. In DMD, QOL was found to be independent of the degree of disability and respiratory impairment. These findings are important, as the underrating of QOL by health-care professionals and caregivers may occur if QOL is based on judgments of severity of physical functioning. If not recognized, the result may be an inaccurate estimate of QOL and an unwanted impact on care decisions.\textsuperscript{122} This highlights again the importance of seeing beyond disease severity and the need to take into account psychosocial aspects of QOL in health-care decisionmaking.

Mood is strongly associated with QOL in MD. The relationship between mood and physical functioning is bidirectional, with physical functioning affecting mood and mood affecting physical functioning. Two studies have observed that measures of mood are the best predictors of QOL ahead of measures of severity\textsuperscript{104} (Rose, personal communication; Sadjadi et al., 2010). As increased rates of depression are reported in MD, clinicians should take time to assess affect disturbance in MD patients.\textsuperscript{123,124} These findings give reason for optimism, however, as low mood is amenable to improvement through psychotherapy. Finally, it should be noted that mood is not just a surrogate measure for QOL; the profile of the effects of mood on QOL differs from that of disease severity, and mood is only loosely correlated with the severity of MD.\textsuperscript{104}

In summary, QOL is reduced in MD, and more factors than just disease severity may explain this reduction. There is strong evidence of associations between mood, pain, fatigue, and QOL in MD. These findings offer additional hope, as therapies aimed at addressing these factors (e.g., psychotherapy) may help improve QOL despite the current lack of any effective drug treatment for most of the inherited MDs.

\textbf{MYASTHENIA GRAVIS}

QOL has been assessed in adults with MG using a variety of measures. The SF-36 has frequently been used as an HRQOL measure for MG.\textsuperscript{125–129} However, the SF-36 includes items not relevant to MG and leaves out other domains that should be assessed. Despite these limitations, QOL studies of MG patients that used the SF-36 have demonstrated modest correlations of HRQOL subscores and disease status. In 1 study, subscales related to physical role capacity (e.g., role–physical) weremeaningfully different between controls and MG patients.\textsuperscript{125} In another study, significantly lower ratings for all subscale scores of the SF-36 were observed for MG patients compared with healthy controls.\textsuperscript{126} Measures of disease severity correlated with the physical aspects (e.g., physical functioning, role–physical) of the SF-36. Physical composite scores of the SF-36 have also been shown to correlate with single-fiber electromyography (EMG) abnormalities in the deltoid muscle of MG patients.\textsuperscript{127} In the Muscle Study Group (MSG) trial of mycophenolate mofetil, changes in SF-36 total scores (between weeks 0 and 12) correlated with changes in the Myasthenia Gravis–Activities of Daily Living (MG-ADL) scale (a patient-reported outcome measure that assesses MG symptoms and daily activities) but not physician-reported measures of manifestations.\textsuperscript{128}

The MG Questionnaire (MGQ) is a disease-specific, validated QOL scale made up of 25 items.\textsuperscript{126,127} For some of the items, patients are asked to rate whether they are “very limited,” “somewhat limited,” or “not at all limited” in performing certain activities, such as going up a flight of stairs. For other items, patients are asked to respond “yes” or “no” to questions about possible modifications made at work or with other activities. For example, patients are asked if they have reduced the time spent at work. The MGQ is easy to use and has demonstrated excellent test–retest reliability. In terms of the responsiveness of the MGQ, in 10 patients who experienced clinical improvement, the mean global score of the MGQ was also improved (21.9 vs. 25.6).\textsuperscript{126}

Another MG-specific measure of QOL was validated during the MSG trial of mycophenolate mofetil for MG.\textsuperscript{126,130} This 60-item, disease-specific survey assesses the domains of mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns. In the MSG trial, MG-QOL60 scores correlated with changes in the Quantitative Myasthenia Gravis (QMG) scale (a disease-specific scale measuring weakness and neuromuscular fatigue) and MG-ADL, but not manual muscle testing (MG-MMT). At baseline, MG-QOL60 scores
correlated significantly with SF-36, QMG, MG-ADL, and MG-MMT. The MG-QOL60 outperformed the SF-36 in this trial, notably by demonstrating higher correlations with changes in QMG and MG-ADL and higher correlations at baseline with QMG and MG-MMT.

A 15-item MG-specific QOL scale (MG-QOL15) was derived from the 60-item QOL scale in order to offer a more user-friendly instrument, both in terms of time spent administering the instrument and time spent analyzing the results. In the MSG trial of mycophenolate mofetil, the MG-QOL15 correlated as highly as the 60-item MG-QOL60 for physical and social domains of the SF-36, the two domains most relevant to MG. Other domains of the SF-36 (e.g., bodily pain) did not correlate with the MG-QOL15 scores, suggesting the MG-QOL15 captured clinical information that it was designed to capture and avoided capturing superfluous clinical information. Correlation coefficients for the MG-QOL15 were similar to the 60-item MG-QOL for the QMG, MG-MMT, and MG-ADL at week 0 and also for changes in scores. The MG-QOL15 also demonstrated high sensitivity. The MG-QOL15 has been further validated in an 11-center scale validity study of 175 patients with MG. Score distributions of the items of the MG-QOL15 and mean scores correlated with disease severity and distribution. Test–retest reproducibility of the MG-QOL15 has been shown to be excellent in 38 patients followed at the University of Virginia. The MG-QOL15 is particularly well suited for informing the physician in real time of the patient’s appraisal of and tolerability with MG-related dysfunction, particularly in light of its ease of use and ease of interpretation. In the clinical setting, the MG-QOL15 often confirms the physician’s clinical impression. It is of interest that the items most significantly scored abnormal in the 11-center scale validation study were the items that do not directly assess physical manifestations but rather assess psychological, social, and occupational domains. These items include, “I am frustrated by my MG,” “My MG limits my ability to enjoy hobbies and fun activities,” “I have limited my social activity because of my MG,” and “I have to make plans around my MG.” This finding is significant because these issues, which are meaningful to the patient, are not easily estimated on routine history-taking or examination, and, thus, they are often not considered during evaluation and decisionmaking. Occasionally, the MG-QOL15 assessment can tip the scale on treatment decisions. For example, a patient with ocular MG who is not bothered by the ocular dysfunction might merit less aggressive treatment than one who is troubled and even disabled by these manifestations. In many instances, an individual’s MG-QOL15 score correlates with the clinical impression, providing reassurance that the patient and physician are similarly assessing the disease status. Rarely, the MG-QOL15 scores do not parallel other measures of disease and the physician’s clinical impression. When this happens, the physician should investigate why the MG-QOL15 scores are discordant with other assessments.

The MG-QOL15 can also be used to follow a patient over time. Various cut-points in change of MG-QOL15 scores have been provided, but a single cut-point to indicate MG-QOL improvement is not recommended due to the many factors that go into determining whether or not an individual’s MG-QOL has improved. These factors might include, but are not limited to: (1) the initial MG-QOL15 score; (2) the patient’s “antecedents”; (3) the duration and past course of the patient’s disease (e.g., prior myasthenic crisis); (4) secondary gain (e.g., patient seeking disability); and (5) the presence or absence of effective response shift. Furthermore, specific changes in items and subscores of the MG-QOL15 must be considered in the context of the individual, the setting and the clinical status of the patient. A third function of the MG-QOL15 might be to assist in following groups of MG patients over time in a clinical trial.

POLYNEUROPATHIES

There is considerable heterogeneity in manifestations of polyneuropathy, in large part due to the many etiologies of polyneuropathy and the specific effects these etiologies have on nerve. Some polyneuropathies manifest predominantly with pain, whereas others present with weakness and paresthesias and still others with ataxia or autonomic impairment. The disease course also varies considerably, from a rapidly progressive but self-limited course (e.g., Guillain–Barré syndrome) to a more insidious-onset and chronic, progressive course (e.g., Charcot–Marie–Tooth disease). Age of onset and severity also vary considerably among patients. In this section, we make general comments about QOL and polyneuropathy, before focusing on the polyneuropathies that tend to be most frequently encountered and managed by the neuromuscular specialist.

Most of the outcome measures of HRQOL used for polyneuropathy have been generic, and the generic HRQOL scale that has been used the most is the SF-36. Other generic HRQOL scales used for various polyneuropathies include the SIP, Nottingham Health Profile, and Euro-QOL. An HRQOL measure specific for
polyneuropathy has been developed but appears to be rarely utilized, possibly because of its length (97 items).\textsuperscript{136} The Functional Assessment of Cancer–Gynecologic Oncology Group, Neurotoxicity (FACT-GOG-Ntx) is frequently used to assess HRQOL in patients with chemotherapy-induced polyneuropathy.\textsuperscript{157}

Patients with polyneuropathy, like other neuromuscular disorders, often report worse QOL scores than normal controls, and these QOL scores generally worsen as the severity of polyneuropathy worsens.\textsuperscript{10–15,138–149} HRQOL also worsens as neuropathic pain worsens and improves with effective pain control.\textsuperscript{159} Some components of QOL, such as the role–physical subscale of the SF-36, may improve with home exercise programs.\textsuperscript{151}

**Immune-Mediated Polyneuropathies.** The generic SF-36 has been most often applied for studying HRQOL of patients with immune-mediated polyneuropathies [e.g., chronic inflammatory demyelinating polyneuropathy, Guillain–Barré syndrome (GBS)] and it appears to be better suited for use in these disorders than most other neuromuscular disorders.\textsuperscript{10–15} In a study of 114 patients with immune-mediated polyneuropathies and a stable clinical condition, all of the mean subscale scores of the SF-36 were significantly lower than those of the control group.\textsuperscript{10} The more physically oriented domains were more significantly abnormal. SF-36 subscale scores were significantly lower for non-ambulatory patients compared with ambulatory patients. General strength and sensory disturbance partially explained the physical component summary score on the SF-36. SF-36 scores and subscale scores improved for a cohort of 20 patients followed longitudinally who improved clinically. For these patients, domain subscores reached the normal range for all individuals, except for domain subscores “physical functioning” and “role functioning—physical.” The SF-36 was also used in an international, randomized, controlled trial (the “ICE Study”) that compared intravenous immunoglobulin (IVIg) to placebo in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).\textsuperscript{11,32} In this study, all the mean SF-36 subscale scores were lower than normative data at enrollment (117 patients), changes in physical component summary (PCS) and mental component summary (MCS) scores were significantly better for the IVIg group, and the following subscale scores were significantly better for the IVIg group during the first phase: physical functioning; role–physical; social functioning; and mental health. Results were similar during the crossover phase and extension phase. General deterioration of mean scores occurred in the extension phase for patients re-randomized to placebo. Fifty percent of the variance in HRQOL component measures (PCS and MCS) was explained by a combination of impairment and activity and participation measures.\textsuperscript{12} An earlier study of 97 patients with acquired neuropathies (9 with CIDP, 29 with GBS, 2 with multifocal motor neuropathy, and 2 with polyneuropathy associated with a monoclonal protein) reported that 41% of the HRQOL variance could be explained by neuropathy symptoms and signs.\textsuperscript{151} The SF-36 was also used in a smaller study of patients with severe fatigue (16 GBS, 4 CIDP) who underwent a 12-week bicycle exercise program.\textsuperscript{155} In that study, the PCS of the SF-36 improved with training. In a Danish study of 14 CIDP patients, SF-36 physical functioning and vitality subscale scores were significantly different compared with those of a control population.\textsuperscript{14} Strength assessed by dynamometry correlated with the PCS. The neuropathy impairment score (NIS) correlated with the PCS and MCS. EuroQOL, another HRQOL measure, was used in a randomized trial of interferon-beta1a in CIDP.\textsuperscript{135}

**Diabetic Polyneuropathy and Other Acquired Polyneuropathies.** Generic measures and disease-specific measures have been used to study QOL in patients with diabetic polyneuropathy. The SF-36 is the most frequently used generic HRQOL, whereas the Norfolk QOL-DN and NeuroQOL measures are 2 disease-specific QOL scales sometimes used in diabetic polyneuropathy research.\textsuperscript{144,145,154} Numerous prospective, symptomatic treatment trials of painful diabetic polyneuropathy have been carried out, and some of these trials have studied HRQOL along with other outcomes. These studies, among others, demonstrated that QOL is impaired in diabetics with polyneuropathy, particularly patients with painful polyneuropathy. The studies also showed that successful treatment of the pain improves HRQOL.\textsuperscript{150} Pharmacological and non-pharmacological interventions in diabetic neuropathy that have been shown, in at least one class I or class II trial, to improve QOL include pregabalin, venlafaxine, duloxetine, dextromethorphan, morphine sulfate, and percutaneous electrical nerve stimulation. Of the QOL measures, bodily pain, mental health, social functioning, and sleep interference tend to improve the most with effective treatment of pain.\textsuperscript{150}

One study from the UK used the Nottingham Health Profile (NHP) to measure HRQOL in patients with diabetic polyneuropathy.\textsuperscript{133} The NHP is a validated measure of 38 items that assesses six domains: energy; sleep; pain; physical mobility; emotional reactions; and social isolation. Diabetics with painful neuropathy scored worse on the NHP.
in 5 domains, the exception being social isolation, compared with diabetics without pain and non-diabetic controls. Another study from the UK demonstrated that all QOL measures (EuroQOL, SF-36, QOL-DN) deteriorated with worsening of severity of diabetic polyneuropathy. 134

HRQOL is significantly impaired in patients with neuropathic pain regardless of the etiology. 133,139,143,150,152 For example, in one study of 120 consecutive patients with polyneuropathy, PCS and MCS scores of the SF-36 correlated with presence of pain. 139 A multicenter study of over 500 polyneuropathy patients (44% with diabetes mellitus) reported significantly worse SF-36 scores compared with norms. 141 General disability scales were related to all SF-36 domain scores. PCS scores correlated more closely with disability measures than did MCS. A study of 90 patients with chronic axonal polyneuropathy demonstrated worse HRQOL scores for neuropathy patients. 140 The differences were most significant for social functioning, pain, and physical functioning. Patients with worse disability scores scored poorer for physical functioning and for role limitations due to physical problems.

Inherited Polyneuropathies. CMT disease causes physical disability, which can affect the choice of profession, slow down important activities, create a need for help in everyday life, and cause emotional distress. Disease perception and coping with the diagnosis can depend on many things, including the patient’s experience with the disease, personality, family and social support network, accessibility, and knowledge of medical professionals. 135

Studies of QOL in CMT consistently demonstrate lower mean QOL scores compared with normative data. For example, all domains of the SF-36 were significantly lower for patients compared with norms in 2 Italian studies of CMT. HRQOL mean scores were not worse at 2-year follow-up for the cohort of 137 CMT1A patients, in contrast to worsening in mean values for distal muscle strength, sensory testing, and walking disability. 148,149,156,157

The ability to stand and toe- or heel-walk were shown to correlate most strongly with SF-36 results in 1 study of 89 patients with CMT1A. 149 Although cohorts of CMT patients generally demonstrate worse mean scores, it must also be remembered that many individuals with CMT will register normal QOL scores.

The ascorbic acid treatment trials of adults with CMT1A have used the SF-36 as the measure of HRQOL. 158,159 There were no significant differences in SF-36 scores between treatment groups followed over 1 year 158 or 2 years 159 of treatment. The Australian ascorbic acid trial in children with CMT1A identified no change in QOL scores after 12 months of treatment. 160,161 The Child Health Questionnaire (CHQ) used in that study is a proxy measure of QOL, as parents fill it out on behalf of their children. 161 The children with CMT1A (age 5–16 years) demonstrated lower mean scores than age-matched population norms in 11 of 12 CHQ domains (except family cohesion). Leg cramps, tremor, and gross motor function correlated with many CHQ domains, whereas distal motor latency and nerve conduction velocity were found to be significant independent predictors for 3 of 12 CHQ domains. 165

Some implications of the QOL research in CMT include confirmation that CMT is generally not a benign disease and recognition of the need for including responsive QOL measures in future CMT trials so that investigators can better estimate what might constitute clinically meaningful change of an intervention. 162 The development of a disease-specific CMT QOL measure would be valuable for future trials, as the responsiveness of the SF-36 in CMT is questionable.

CONCLUSIONS
As evident in this review, the field of QOL research in neuromuscular disease is complex and challenging for many reasons, including the large number of neuromuscular diseases under study, the large number of QOL outcome measures in use, our imprecise understanding of what makes up QOL, and the ever-changing, dynamic nature of all that contributes to one’s QOL. Despite these inherent challenges, understanding QOL to the extent possible is essential to understanding patients with neuromuscular disorders. Fortunately, significant progress in QOL research for neuromuscular disease has occurred over the past few decades, in part because of the emergence and use of disease-specific, validated QOL measures. More detailed information about QOL and QOL measures in neuromuscular disease may be found in the referenced material and on-line, such as at www.researchROM.com.

REFERENCES


