Validation of a simple disease-specific, quality-of-life measure for diabetic polyneuropathy

CAPPRI

Kelly G. Gwathmey, MD, Reza Sadjadi, MD, William B. Horton, MD, Mark R. Conaway, PhD, Carolina Barnett-Tapia, MD, Vera Bril, MD, James W. Russell, MBChB, MS, FRCP, Aziz Shaibani, MD, Michelle L. Mauermann, MD, Michael K. Hehir, MD, Noah Kolb, MD, Jeffrey Guptill, MD, Lisa Hobson-Webb, MD, Karissa Gable, MD, Shruti Raja, MD, Nicholas Silvestri, MD, Gil I. Wolfe, MD, A. Gordon Smith, MD, Rabia Malik, MD, Rebecca Traub, MD, Amruta Joshi, MS, Matthew P. Elliott, MD, Sarah Jones, MD, and Ted M. Burns, MD

Correspondence

Dr. Burns
tmb8r@virginia.edu

Neurology® 2018;90:e2034–e2041. doi:10.1212/WNL.0000000000005643

Abstract

Objective

We studied the performance of a 15-item, health-related quality-of-life polyneuropathy scale in the clinic setting in patients with diabetic distal sensorimotor polyneuropathy (DSPN).

Methods

Patients with DSPN from 11 academic sites completed a total of 231 Chronic Acquired Polyneuropathy Patient-Reported Index (CAPPRI) scales during their clinic visits. Conventional and modern psychometric analyses were performed on the completed forms.

Results

Conventional and modern analyses generally indicated excellent psychometric properties of the CAPPRI in patients with DSPN. For example, the CAPPRI demonstrated unidimensionality and performed like an interval-level scale.

Conclusion

Attributes of the CAPPRI for DSPN include ease of use and interpretation; unidimensionality, allowing scores to be summed; adequate coverage of disease severity; and the scale's ability to address relevant life domains. Furthermore, the CAPPRI is free and in the public domain. The CAPPRI may assist the clinician and patient with DSPN in estimating disease-specific quality of life, especially in terms of pain, sleep, psychological well-being, and everyday function. The CAPPRI may be most useful in the everyday clinical setting but merits further study in this setting, as well as the clinical trial setting.

Podcast

Dr. Alex Menze interviews Dr. Kelly Gwathmey on the CAPPRI quality-of-life measure for diabetic polyneuropathy.

NPub.org/wiy6sj

From the Departments of Neurology (K.G.G., A.J., M.P.E., S.J., T.M.B.), Internal Medicine (W.B.H.), and Public Health Sciences (M.R.C.), University of Virginia, Charlottesville; Massachusetts General Hospital/Harvard Medical School (R.S.), Boston, MA; Division of Neurology (C.B.-T., V.B.), Department of Medicine, The Ellen and Martin Prosserman Centre for Neuromuscular Diseases, University of Toronto and University Health Network, Toronto, Canada; Department of Neurology (J.W.R.), University of Maryland, Baltimore; Department of Neurology (A.S.), Baylor St. Luke's Medical Center, Houston, TX; Department of Neurology (M.L.M.), Mayo Clinic, Rochester, MN; Department of Neurology (M.K.H., N.K.), University of Vermont, Burlington; Department of Neurology (J.G., L.H.-W., K.G., S.R.), Duke University Medical Center, Durham, NC; Department of Neurology (N.S., G.I.W.), University at Buffalo, SUNY, Buffalo, NY; Department of Neurology (A.G.S.), Virginia Commonwealth University, Richmond; Department of Neurology (R.M.), Rush University Medical Center, Chicago, IL; and Department of Neurology (R.T.), University of North Carolina, Chapel Hill.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CAPPRI = Chronic Acquired Polyneuropathy Patient-Reported Index; **CI** = confidence interval; **DIF** = differential item functioning; **DSPN** = distal sensorimotor polyneuropathy; **HRQOL** = health-related quality of life; **INCAT** = Inflammatory Neuropathy Cause and Treatment; **MNSQ** = mean square; **ODSS** = Overall Disability Sum Score; **RPCM** = Rasch partial credit model.

The World Health Organization estimates that >400 million people worldwide have diabetes, of which >30 million are living in the United States.^{1,2} Diabetes is a major cause of polyneuropathy with a lifetime prevalence approaching 50%.^{3,4} Distal sensorimotor polyneuropathy (DSPN) is the most common neuropathy of diabetes.³⁻⁵ Pain, paresthesias, imbalance, and impaired dexterity are common manifestations of DSPN, negatively affecting daily function, sleep, mental health, and patient safety.³⁻⁶

Patient-reported outcome measures may be used in everyday clinic and clinical studies to estimate symptoms, function, and health-related quality of life (HRQOL).⁷ HRQOL measures are well-suited for acquired polyneuropathy, such as DSPN, because many of the manifestations are more evident to the patient and often provide important information about what it is like to live with the disease. Numerous studies have demonstrated that HRQOL is impaired in DSPN.^{6,7} To date, both generic measures and disease-specific measures have been used to study HRQOL in DSPN.⁸ One limitation of these scales is they are generally not user-friendly in the everyday clinic setting, often because they do not provide immediately available, clinically practical data that inform at the time of the visit, and/or because they are too time-consuming for a busy clinic setting.

We set out to validate an easy-to-use and easy-to-interpret, 15-item, disease-specific HRQOL scale for patients with chronic, acquired polyneuropathy, including patients with diabetic DSPN (figure 1). The Chronic Acquired Polyneuropathy Patient-Reported Index (CAPPRI; CAP-PRI) has previously been validated in immune-mediated polyneuropathy.⁹ In this study, we prospectively validate the CAPPRI for DSPN.

Methods

Investigators with expertise in DSPN were recruited from 11 academic sites in the United States and Canada to participate in our study. The study was performed in the everyday clinic setting at each site from January 2016 to October 2017.

Standard protocol approvals, registrations, and patient consents

Each site received institutional review board approval to participate in this study.

Patients and measures

The following data were collected for consented patients with chronic, noninherited (e.g., acquired) polyneuropathy:

age, sex, etiology of neuropathy, CAPPRI, Inflammatory Neuropathy Cause and Treatment (INCAT) score, and Overall Disability Sum Score (ODSS). The diagnosis of diabetic DSPN was made by a neuromuscular specialist or endocrinologist familiar in the care of the patient with DSPN. Diagnosis was made on the basis of clinical manifestations (e.g., distal, symmetric sensory or sensorimotor symptoms and signs in a patient with a diagnosis of diabetes), often with supportive electrodiagnostic testing.

Rasch partial credit model

The Rasch partial credit model (RPCM) was conducted for the CAPPRI responses using Winsteps software (version 3.70.0.5) to explore data for item-person targeting, item fitting, dependency, dimensionality, category response functioning (thresholds), and differential item functioning (DIF). Item and person separation indexes represent item and person hierarchy. The RPCM compares the probabilistic expectations of “item difficulty,” including relative ability of each individual test item to differentiate between patient disability levels, and “person ability,” which is the relative patient disability rank measured by the outcome measure, on a common logarithmic scale. A more difficult item is more likely to be abnormal in more disabled patients but less so in less disabled patients. This technique allows measuring how sensitive items are to pick up differences between different disability levels and also whether items are covering an appropriate range of disability. Person reliability index indicates the replicability of person ordering we could expect if this sample of persons were given another parallel set of items measuring the same construct. Item reliability index indicates the reproducibility of items placement along the same pathway if the same items were given to another sample of the same size that behaved the same way. Person and item separation indices are estimated as adjusted person or item standard deviation divided by the average measurement error, where measurement errors are the total variance that are not accounted for in the Rasch analysis. Separation indices represent the spread of persons or items on the measured variable.

Item fitting, dependency, and dimensionality

Fit statistics examine the observed data in comparison with the expectations of the RPCM. Item fitting is calculated using χ^2 statistics, and in Winsteps is reported as mean square (MNSQ), which is the unstandardized average value of squared differences between the RPCM's expected and actual values for an item. The MNSQ value for each item should ideally fall between 0.50 and 1.70 for clinical tools. Item

Figure 1 The Chronic Acquired Polyneuropathy Patient-Reported Index (CAPPRI)

Chronic acquired polyneuropathy – patient-reported index (“CAP-PRI”) scale

Patient instructions: Please indicate how true each statement has been
(for example, over the past few weeks)

	Not at all 0	A little bit 1	A lot 2
1. I am frustrated by my neuropathy.			
2. I am bothered by pain from neuropathy.			
3. I am off balance when walking because of my neuropathy.			
4. I have trouble getting dressed because of my neuropathy.			
5. I have trouble sleeping because of my neuropathy.			
6. I am bothered by limitations in performing my work (include work at home) because of my neuropathy.			
7. I have trouble driving because of my neuropathy.			
8. I am dependent on others because of my neuropathy.			
9. I am depressed about my neuropathy.			
10. I am falling because of my neuropathy.			
11. I am preoccupied with my neuropathy.			
12. I am unable to do all the leisure activities that I want to do because of my neuropathy.			
13. I am worn out because of my neuropathy.			
14. I have trouble eating because of my neuropathy.			
15. I have trouble doing activities around the house.			

Total score: _____

dependencies represent the correlation between item difficulties, identifying items potentially measuring the same concept, which could form a subdimension, thereby affecting overall unidimensionality of the test. In addition, the Rasch model assumes that the measure is unidimensional. To test this assumption, we used principal component analysis of the differences between the observed and expected scores or residuals, to reveal contrasting items, which can potentially breach the unidimensionality of the outcome measure. We considered evidence of sufficient unidimensionality if the variance in the first contrast was less than 2 eigenvalues, with interitem correlations below 0.33.

Category response functioning

The RPCM compares the probability of endorsing the different response options within one item, whereby patients with more disability are more likely to endorse the option reflecting more severity than patients with less degree of disability. If these probabilities do not follow the expected order, it might indicate that the response options are not adequate and need to be revised.

Differential item functioning

DIF statistics compare how people belonging to different groups (e.g., males/females) answer each item. In an ideal

measure, items should be free from DIF, that is, the probabilities of answering each item should be independent from the population tested. Winstep software reports the Mantel method, which is log-odds estimators of DIF size and significance from cross-tabs of observations of the 2 groups using *t* test (2-tailed). We considered a *p* value of <0.01 as significant, adjusting for multiple comparisons.

We also performed more traditional parametric and non-parametric biostatistics to test the construct validity of the CAPPRI in patients with DSPN. We analyzed the concurrent validity of the CAPPRI by comparing it with the INCAT ODSS (upper limb, lower limb, total) by calculating Pearson correlation coefficients, including for each item of the CAPPRI. We assumed moderate correlations (*r*: 0.4–0.7). In addition, we calculated the percentage of missing answers and the response patterns for each item. Finally, we calculated Cronbach α as a measure of internal consistency, where values >0.8 are considered adequate for individual use.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

The CAPPRI (figure 1) was completed by 668 patients with chronic, acquired, or idiopathic polyneuropathies seen in clinic at 11 academic centers. Etiologies of polyneuropathy included DSPN, chronic inflammatory demyelinating polyneuropathy, idiopathic painful neuropathy, idiopathic painless neuropathy, chemotherapy-induced polyneuropathy, and alcohol-related neuropathy, among others.

In this cohort, 235 patients had polyneuropathy diagnoses of DSPN only, of whom 231 completed all 15 items of the CAPPRI scale. Three participants omitted 1 item only (2 omitted item 11 and 1 omitted item 9) and 1 participant did not respond to 2 items (items 10 and 11). Form completion per site ranged from 1 to 161. The majority of patients with DSPN were seen at the University of Virginia (69%). Fifty-three percent were men. Mean age was 59.3 years (SD 13.5).

RPCM calculation demonstrated good person (0.88) and item (0.99) reliability with adequate item (9.1) and person (2.7) separation indices. There was no major floor or ceiling effect for the overall scale, and items covered a good range of person ability (figure 2). Items “trouble eating” (item 14) and “falling” (10) were more sensitive for detecting differences in clinical status of more disabled patients, and items “bothered by pain” (2) and “frustrated” (1) were more sensitive in lower levels of disability. All items had good fit, based on the MNSQ values, with the exception of item 5 (sleep), for which the MNSQ value was slightly elevated (MNSQ: 1.72 and *z* score 5.1) (figure 2). There were no significant item dependencies, with only mild

Figure 2 Developmental pathway map of the CAPPRI in distal sensorimotor polyneuropathy

The pathway maps out items of the CAPPRI (circles with numbers). Item difficulty is mapped on the vertical axis, with more difficult items (e.g., “trouble eating” and “I am falling”) located near the top and easier items near the bottom (e.g., “I am frustrated” and “bothered by pain”). Thus, this figure allows one to visualize on the vertical axis which items are most useful in discriminating severity at different levels of overall disease severity. The horizontal axis maps how well the items fit under one construct. The item’s proximity to the midline on the horizontal axis represents how well the item contributes to what the outcome is intending to measure (i.e., the construct). For example, item 3 (“off balance”) is located close to the midline. In contrast, item 5 is borderline misfitting (“trouble sleeping”). CAPPRI = Chronic Acquired Polyneuropathy Patient-Reported Index.

correlation between items 2 (pain) and 5 (sleep) ($\rho = 0.2$). Principal component analysis of misfitting portions of items showed 40% variance unexplained by items, of which only 5.8% (less than 2 item eigenvalue) could be explained by possible first subdimension, composed of mainly items 2 and 5. Items 1, 11, and 9 were minor contributors. Category responses were well ordered and organized for all items (figure 3). DIF statistics showed only significant difference in the response pattern to item 5 (sleep) between male and female respondents. Compared to men, women scored sleep higher earlier in terms of HRQOL severity as measured by CAPPRI.

For patients with DSPN, the Pearson correlation coefficient for CAPPRI with INCAT ODSS (total) was 0.39 (95% confidence interval [CI] 0.27–0.49; $p < 0.001$). Pearson correlation

Figure 3 Category responses (i.e., patient choices) for each item of the CAPPRI in distal sensorimotor polyneuropathy, organized by most difficult (“trouble eating”; item 14) to least difficult (“frustrated”; item 1)

The dots represent the threshold for patient responses: “none” (green) to “a little” (blue) to “a lot” (red). This figure illustrates acceptable order of response options and adequate approximation of an interval-level scale. CAPPRI = Chronic Acquired Polyneuropathy Patient-Reported Index.

coefficient with INCAT lower limb was 0.37 (95% CI 0.26–0.48; $p < 0.001$), and was 0.24 (95% CI 0.11–0.36; $p = 0.002$) for INCAT upper limb. CAPPRI items with the highest correlations for INCAT total scores were: dependent on others (0.46; $p < 0.001$), trouble doing activities around the house (0.40; $p < 0.001$), off balance when walking (0.39; $p < 0.001$), unable to do leisure activities (0.36; $p < 0.001$), and falling (0.36; $p < 0.001$). CAPPRI items with the highest correlations for INCAT lower limb were the same as for total INCAT score correlations: dependent on others (0.46; $p < 0.001$), trouble doing activities around the house (0.39; $p < 0.001$), off balance when walking (0.38; $p < 0.001$), unable to do leisure activities (0.35; $p < 0.001$), and falling (0.33; $p < 0.001$). CAPPRI items with the highest correlations for INCAT upper limb were as follows: trouble getting dressed (0.32; $p < 0.001$), falling (0.33; $p < 0.001$), trouble doing activities around the house (0.23; $p < 0.001$), dependent on others (0.21; $p < 0.001$), off balance when walking (0.38; $p < 0.001$), and unable to do leisure activities (0.20; $p < 0.001$). Item response frequencies are illustrated in figure 4. Raw and standardized Cronbach α scores for each item were all >0.91 (range 0.911–0.919).

Discussion

The CAPPRI is an HRQOL scale specifically developed for patients with chronic, acquired polyneuropathy. In this study, we used both conventional and more modern psychometric

techniques to validate the CAPPRI specifically for patients with DSPN. The CAPPRI met Rasch expectations, indicating, among other attributes, that the scale acts like an interval-level scale, rather than only an ordinal scale. As such, the difference between points on the CAPPRI is measurable and approximately equal, thereby allowing for summation of item scores (i.e., is unidimensional), as well as for biostatistical analyses in other cohorts of patients with DSPN. The items of the CAPPRI scale adequately cover a wide range of DSPN disease severity (figure 2). Our analysis also revealed no major misfitting CAPPRI items in DSPN. The one borderline misfitting item was “trouble sleeping” (item 5). We consider this item to be important for the overall content validity of the scale, in large part because of many years of cumulative clinical experience caring for patients with DSPN and also given the significance of sleep for health and quality of life.¹⁰ Our analysis demonstrated a mild dependency between the pain item (item 2) and sleep item (item 5), a finding not unexpected based on clinical experience and an association worth remembering when trying to judiciously treat pain. This minimal interitem dependency is unlikely to significantly affect the interpretation of the CAPPRI. The Pearson correlation coefficients with the INCAT total and subscores were slightly low. These findings are of unclear psychometric significance to us, in large part because the INCAT is only a 2-item scale designed for immune-mediated polyneuropathy that estimates only upper limb and lower limb manifestations and not the experience of living with DSPN. On balance, the results of the traditional and more modern psychometric (Rasch) analyses validate the CAPPRI for use in patients with DSPN.

This initial work with the CAPPRI in DSPN teaches us more about the challenges for our patients with DSPN. It was of interest that certain CAPPRI items correlated significantly with the INCAT ODSS (disability) scale. For instance, the items that correlated highest with total INCAT disability score were “dependent on others,” “trouble doing activities around the house,” “off balance when walking,” “unable to do leisure activities,” and “falling.” CAPPRI items with the highest correlations for INCAT lower limb were essentially the same as for total INCAT score. It was interesting but not surprising that the CAPPRI item with the highest correlation for INCAT upper limb was “trouble getting dressed.” It is also noteworthy that more than half of the patients with DSPN scored “a lot” on items “I am frustrated” (item 1) and “I am bothered by pain” (2); more than one-third also scored “a lot” on items “unable to do all the leisure activities that I want” (12), “off balance when walking” (3), “bothered by limitations in performing my work” (6), “trouble with activities around the house” (15), and “trouble sleeping” (item 5) (figure 4). These findings illustrate that patients with DSPN are frustrated, affected by pain and limitations of everyday activities, and at risk of falls, illustrating many challenges and unmet needs for patients with DSPN.

Following are some of the positive attributes of the CAPPRI for DSPN: (1) ease of use; (2) ease of interpretation with

Figure 4 Proportion of patients with distal sensorimotor polyneuropathy who scored “none” (green), “a little” (blue), or “a lot” (red) for each of the 15 items of the CAPPRI

CAPPRI = Chronic Acquired Polyneuropathy Patient-Reported Index.

results immediately available in clinic; (3) it is free and in the public domain; (4) it addresses various life domains, including physical and social functioning, pain, and emotional well-being; (5) the scale appears to be unidimensional, allowing scores to be summed; (6) the items appear to cover well the various degrees of disease severity; and (7) it can be considered a validated scale for patients with DSPN. Furthermore, the individual item responses can each be easily interpreted and likely followed longitudinally.⁹ For example, the CAPPRI may assist the clinician and patient in estimating efficacy of a newly prescribed symptomatic treatment, e.g., regarding pain and secondary effects on sleep, psychological well-being, and function. We believe this everyday clinical setting is probably where the power of the CAPPRI will best be realized. This is because patient-reported measures, especially validated, disease-specific measures for chronic, symptomatic diseases such as DSPN, can supplement the interview and examination and assist in informed decision-making.¹¹

The selection of measures for clinical use should consider statistical performance and other factors, including ease of use, ease of interpretation, why the measure is being used (e.g., to assist diagnosis or to estimate clinical status),¹² other logistical considerations such as time available, and, for

patient-reported measures, the clinician's estimate of the reliability of the responses, judged patient by patient. Clinician judgment of reliability of item scores can be a challenge but should not be an excuse for reluctance to incorporate patient-reported surveys into clinical practice. We know there is no substitute for placing patient responses in their proper clinical context and for judging their reliability and accuracy during every encounter—as we already do this with any patient interview. Throwing out unreliable responses, such as sometimes happens with a patient seeking secondary gain or someone with significant comorbidities, is part of everyday patient care and is not unique to patient-reported measures, such as the CAPPRI.

“Real-world evidence” has an increasing role in the development and regulatory decision-making of medical products and for those who study, deliver, or pay for health care.¹³ Real-world evidence may complement traditional clinical trials, substitute for clinical trials, especially in rare diseases, point out unmet needs in health care, and assist in any value estimate. Any value payment system is predicated on an accurate estimate of value, which should include disease-specific quality of life whenever reasonable. We think the CAPPRI may be well-positioned as a tool to provide real-world

evidence from the patient perspective for those suffering from DSPN and for clinicians, investigators, and other stakeholders. In addition to its validity as an interval-level scale for DSPN, a major advantage of the CAPPRI is its ease of use, which is especially important for creation of real-world evidence. Furthermore, the CAPPRI is practically useful for informing clinicians and patients in the everyday clinic setting.

Further study is necessary to better understand its value, particular strengths, and limitations. Future study of the CAPPRI might include correlation studies with well-established outcome measures, test-retest evaluation, assessment of responsiveness following symptomatic treatment intervention, and estimates of meaningful, clinically significant differences in scores for individuals with DSPN. The CAPPRI might also be useful in the clinical trial setting. We have not yet studied the psychometric properties of the CAPPRI in any clinical trial setting, including participants with DSPN.

There are several limitations of our study. These include the relatively small numbers for such a common disorder, preponderance of data originating from one center, diagnosis of DSPN solely based on clinical grounds, study of patients undoubtedly of different symptom durations and on different treatments including symptomatic treatments, limited study of correlations with other measures, including electrodiagnostic data, and original development and validation of the scale first for chronic, immune-mediated polyneuropathy.⁹ Regarding this last limitation, it is worth mentioning that the investigators' decision-making based on earlier analyses considered more widespread utility of the scale (and hence choice of the name, Chronic Acquired Polyneuropathy Patient-Reported Index). Despite these limitations and especially in light of our DSPN study results, we believe the CAPPRI is validated and useful in patients with DSPN. More study and scrutiny, however, are warranted, particularly in different settings, such as other everyday clinic settings, in clinical studies, and in other languages and cultures.

Author contributions

Dr. Gwathmey: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Sadjadi: analysis and interpretation, critical revision of the manuscript for important intellectual content, study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Horton: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Conaway: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Barnett-Tapia: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Bril: acquisition of data, critical revision of the manuscript for important

intellectual content. Dr. Russell: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Shaibani: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Mauermann: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Hehir: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Kolb: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Guptill: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Hobson-Webb: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Gable: acquisition of data. Dr. Raja: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Silvestri: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Wolfe: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Smith: critical revision of the manuscript for important intellectual content. Dr. Malik: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Traub: acquisition of data, critical revision of the manuscript for important intellectual content. Amruta Joshi: acquisition of data, study supervision. Dr. Elliott: acquisition of data. Dr. Jones: acquisition of data. Dr. Burns: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

Study funding

No targeted funding reported.

Disclosure

K. Gwathmey, R. Sadjadi, and W. Horton report no disclosures relevant to the manuscript. M. Conaway reports consulting support from CSL Behring. C. Barnett-Tapia has received compensation from CSL Behring for speaking engagements and from UBC from consulting. She has received research support from Octapharma for clinician-initiated research and a new initiatives grant from the Division of Neurology, University of Toronto. V. Bril reports scientific advisory board support from CSL Behring, Baxalta, Grifols, Argenx, Octapharma, Alpha Technologies, Powell Mansfield Inc.; funding for travel or speaker honoraria from CSL Behring; *PLoS One* editorial board; consultancy support from CSL Behring, Grifols, BioNevia, Octapharma, Powell Mansfield Inc., Argenx, Alpha Technologies, Baxalta; research support, commercial entities, from CSL Behring, Grifols, BioNevia, Octapharma, Baxalta, Argenx; research support, foundations and societies, from Toronto General/Toronto Western Hospital Foundation GBS/CIDP Foundation International. J. Russell is supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases, NIH 1R01DK107007-01A1, the Office of Research Development, Department of Veterans Affairs (Biomedical and Laboratory Research Service and Rehabilitation Research and Development, 101RX001030), and the Diabetes Action Research and Education Foundation. He reports grant support

from NIH NIDDK 1R01DK107007-01A, Department of Veterans Affairs Rehabilitation Research & Development Service, and Biomedical and Laboratory Research Service, grant award to the University of Maryland from Impeto Medical, and a grant to the University of Maryland from the Diabetes Action Research and Education Foundation. A. Shaibani reports no disclosures relevant to the manuscript. M. Mauermann reports having received honoraria from the AANEM and AAN for lectures, honoraria from *Continuum* journal for manuscript, scientific advisory board for IONIS Pharmaceuticals for TTR amyloid clinical trial, royalties from *Autonomic Disorders* book published by Oxford, travel and honoraria from BMT InfoNet for lecture. She is section editor for *Mayo Clinic Proceedings*. M. Hehir reports consulting for Octapharma and CSL Behring. He is receiving a clinician scientist scholarship from the American Brain Foundation/AAN and Myasthenia Gravis Foundation of America. N. Kolb reports serving on an advisory board for Octapharma, and has received a grant from the Lake Champlain Cancer Research Organization Inc. J. Guptill has received personal compensation for consulting and serving on a scientific advisory board, DSMB, speaking engagement, or other activities with Alexion, Argenx, Becton Dickinson, and Grifols. Dr. Guptill has received research support from Grifols Foundation, Bioverativ, Myasthenia Gravis Foundation of America, the Alzheimer's Association, and NIH (K23NS085049). L. Hobson-Webb reports receiving support from Genzyme, a Sanofi Company; research funding for investigator initiated study in Pompe disease; one time speaker honorarium for neurologic complication of lysosomal storage disorders; Aerpio Therapeutics, Inc.: spouse employment and stock options; CSL Behring; research support as site investigator for PATH study; National Institute of Aging Claude D. Pepper Older Americans Independence Center 1 K23 AG23621-01A1. K. Gable and S. Raja report no disclosures relevant to the manuscript. N. Silvestri reports having received personal compensation from Alexion Pharmaceuticals for consulting and speaking, Strongbridge Pharmaceuticals for speaking, OptionCare for consulting, and CSL Behring for consulting. Dr. Silvestri is also on the editorial board for the *Journal of Clinical Neuromuscular Disorders*. G. Wolfe reports receiving personal compensation for consulting from Alexion

Pharmaceuticals, Grifols, Shire; consulting compensation from Grifols, Syntimmune, Argenx, Marathon; and research funding from Alexion, Argenx, Ra, CSL Behring, NINDS/NIH, and the MGFA. A. Smith and R. Malik report no disclosures relevant to the manuscript. R. Traub reports commercial research support from Vertex Pharmaceuticals. A. Joshi, M. Elliott, and S. Jones report no disclosures relevant to the manuscript. T. Burns has received personal compensation for consulting from CSL Behring, GLG, and Clearview Health. He received travel and lodging support for an advisory board meeting from Alexion Pharmaceuticals. He is the Deputy Editor of the *Neurology*[®] Podcast. Go to Neurology.org/N for full disclosures.

Received December 22, 2017. Accepted in final form March 20, 2018.

References

1. World Health Organization. Diabetes Fact Sheet [online]. 2017. Available at: who.int/mediacentre/factsheets/fs312/en/. Accessed December 2017.
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.
3. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154.
4. Barrett EJ, Liu Z, Khamaisi M, et al. Diabetic microvascular disease: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2017;102:4343–4410.
5. Dyck PJ, Albers JW, Anderson H, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. *Diabetes Metab Res Rev* 2011;27:620–628.
6. Bril V, England J, Franklin GM, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758–1765.
7. Burns TM, Graham CD, Rose MR, Simmons Z. Quality of life and measures of quality of life in patients with neuromuscular diseases. *Muscle Nerve* 2012;46:9–25.
8. Trikkalinou A, Papazafropoulou AK, Melidonis A. Type 2 diabetes and quality of life. *World J Diabetes* 2017;8:120–129.
9. Gwathmey KG, Conaway MR, Sadjadi R, et al. Construction and validation of the chronic acquired polyneuropathy patient-reported index (CAP-PRI): a disease-specific, health-related quality of life instrument. *Muscle Nerve* 2016;54:9–17.
10. Devine EB, Hakim Z, Green J. A systematic review of patient-reported outcome instruments measuring sleep dysfunction in adults. *Pharmacoeconomics* 2005;23:889–912.
11. Burns TM. The best of both worlds: using patient-reported plus physician-scored measures during the evaluation of myasthenia gravis. *Muscle Nerve* 2016;53:3–4.
12. Zilliox LA, Ruby SK, Singh S, Zhan M, Russell JW. Clinical neuropathy scales in neuropathy associated with impaired glucose tolerance. *J Diabetes Complications* 2015;29:372–377.
13. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence: what is it and what can it tell us? *N Engl J Med* 2016;375:2293–2297.