Received: 9 March 2021 | Revised: 7 July 2021 | Accepted: 8 July 2021

DOI: 10.1111/epi.17012

Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Quality of Life in Epilepsy: Same questions, but different meaning to different people

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Funding information
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Abstract

Objectives: Patient-reported outcome measures (PROMs) are used widely to elicit patient's self-appraisal of their health status and quality of life. One fundamental assumption when measuring PROMs is that all individuals interpret questions about their health status in a consistent manner. However, subgroups of patients with a similar health condition may respond differently to PROM questions (ie, differential item functioning [DIF]), leading to biased estimates of group differences on PROM scores. Understanding these differences can help inform the clinical interpretation of PROMs. This study examined whether DIF affects 10-item Quality of Life in Epilepsy (QOLIE10) scores reported by patients with epilepsy in outpatient clinics.

Methods: Data were from the Calgary Comprehensive Epilepsy Program, a prospective registry of patients with epilepsy in Calgary, Alberta. Latent variable mixture models (LVMMs) based on standard two-parameter graded response models with increasing numbers of latent classes were applied to QOLIE10 item data. Model fit was assessed using the Bayesian Information Criterion (BIC) and latent class model entropy. Ordinal logistic regression was used to identify QOLIE10 items that exhibited DIF.

Results: In this cohort of 1143 patients, 567 (49.6%) were female and the median age was 37.0 (interquartile range [IQR] 27.0) years. A two-class LVMM, which provided the best fit to the data, identified two subgroups of patients with different response patterns to QOLIE10 items, with class proportions of 0.62 and 0.38. The two subgroups differed with respect to antiseizure polytherapy, reported medication side effects, frequency of seizures, and psychiatric comorbidities. QOLIE10 items on the physical and psychological side effects of medication exhibited large DIF effects.

Significance: Our study revealed two different response patterns to quality-of-life instruments, suggesting heterogeneity in how patients interpret some of the questions. Researchers and users of PROMs in epilepsy need to consider the differential interpretation of items for various instruments to ensure valid understanding and comparisons of PROM scores.

KEYWORDS

differential item functioning, health-related quality of life, latent class analysis, latent variable mixture models, QOLIE10

1 | INTRODUCTION

Epilepsy accounts for a quarter of the global disability-adjusted life-years for neurological conditions,[1–2] and it has significant impact on different aspects of the lives of patients with epilepsy, including social functioning (eg, relationships, ability to work), psychological health, emotional well-being, and cognitive functioning.[3–6] Although seizure control remains the primary goal of treatment interventions (eg, surgery and antiseizure medications [ASMs]) in epilepsy, measures of health-related quality of life (HRQOL) are used to quantify the impact of epilepsy on several aspects of patients' lives in clinical trials and epidemiological studies.[7] For example, these patient-reported outcomes measures (PROMs) are used as secondary end points to evaluate the efficacy of treatment interventions, compare health status of population groups, and to monitor changes in patients' disease trajectory.[8–10]

The Quality of Life in Epilepsy inventory is a family of validated PROMs for assessing HRQOL in patients with epilepsy.[11–14] In particular, the short version (10-item) Quality of Life in Epilepsy (QOLIE10) is increasingly being used to assess HRQOL in adult patients with epilepsy, especially in clinical trials and busy clinical settings.[6,15] Although much attention has been paid to psychometric evaluations of QOLIE10 with respect to construct validity, test-retest reliability, and cultural translations/adaptions in several populations,[16–21] one important but frequently overlooked aspect of PROM validation is the establishment of its measurement invariance across subgroups of patients with epilepsy.[22,23] That is, are subgroups of respondents with the same diagnosis but underlying clinical differences consistent in their interpretations of QOLIE10 items? This assumption of measurement invariance determines the extent to which a PROM construct is comparable across groups of interest. Violation of this assumption, which is also known as differential item functioning (DIF), can lead to biased conclusions about population group differences. Although DIF is known to be associated with patients' demographic characteristics, such as sex, age, ethnicity, and education, differences in clinical and psychosocial characteristics of patients with epilepsy, which are known to be predictors of HRQOL, may be associated with DIF. This is particularly important because of the well-established, and indeed bidirectional, association between epilepsy and depression,[24] as well as the fact that epilepsy is a disease comprising heterogenous groups of patients with varying etiologies, seizure types, and syndromes who can be clustered into unique groups with defining psychosocial characteristics.[25–26] In addition, learning about how DIF relates to different clinical characteristics can have important implications for interpreting PROM scores and informing decisions in different patient groups.

The purpose of this study was to assess whether DIF impacts QOLIE10 scores in a cohort of patients with epilepsy in an outpatient clinic. This study is particularly important because QOLIE10 is widely used in busy clinical settings, where patient populations might differ with respect to their demographic and clinical features characteristics, resulting possibly in differential responses to individual QOLIE10 items. The objectives of this study are to (1) examine the presence of heterogeneity in patients' responses to QOLIE10 items in a cohort of adults with epilepsy, (2) investigate several demographic and clinical characteristics that might explain the sources of heterogeneity among subgroups, and (3) identify items on which these subgroups of patients differ in their response patterns.

Key Points

- We identify subgroups of patients with epilepsy with different response patterns to the 10-item Quality of Life in Epilepsy (QOLIE10) items, suggesting that some items are interpreted differently by different subgroups of patients, even though they have the same medical condition.
- Latent variable mixture models uncovered two subgroups of patients with different response patterns to QOLIE10 items.
- Heterogeneity of responses has implications for the interpretation of patient-reported outcomes scores and their application to inform clinical decisions.

2 | METHODS

2.1 | Data source

Data were obtained from the Calgary Comprehensive Epilepsy Program (CEP) database, a cohort-based registry of all adults with epilepsy seen at the Foothills Medical Center, a tertiary care center in Calgary, Alberta, Canada. The registry collects data of patients' demographic, clinical, and self-reported data at every clinical encounter, which are stored and extracted using REDCap electronic capture tools hosted at the University of Calgary's Clinical Research Unit. Our cohort included data from the initial clinical encounter of adult patients since inception until June 2018 and who completed the Patient-weighted 10-item Quality of Life in Epilepsy (QOLIE10-P) measure. QOLIE10 items are derived from the first 10 items on QOLIE10-P. Diagnoses of anxiety and depression were based on physician interviews; comorbidity was assessed through physician interviews and chart reviews by the consulting epileptologist and categorized using the Epilepsy Comorbidity Index[27]; ASM side effects were

determined based on patients' report of at least one side effect attributable to any ASM they are on.

2.2 | Statistical analysis

As a first step, parallel analysis and exploratory factor analyses (EFAs)[28] of QOLIE10 items were conducted to assess the unidimensionality of the QOLIE10 items. The number of positive eigen values of the corresponding factors/principal components corresponds to the number of dimensions in the data. Essential unidimensionality was considered present if the ratio of the first and second eigen values was greater than 4.0.[29–30] We did not examine the factorial structure of the QOLIE10-P in these analyses. The 11th item (distress) merely serves to transform (weight) the total score (based on the 10 items). Thus it is not defensible to include the 11th item together with the other 10 items in a unidimensional factor structure. Therefore, for reasons of parsimony, only results based on the original measurement structure of the QOLIE10 will be reported. Latent variable mixture models (LVMMs) with incremental numbers of latent classes were applied to address the first objective.[31–33] Item response theory (IRT) was applied using Samejima's graded response model (GRM) to specify the one-class LVMM, which assumes no heterogeneity in the data. Subsequent LVMMs with increasing numbers of latent classes were specified by allowing the GRM parameters (difficulty and discrimination parameters) to vary across the latent classes, thereby modeling heterogeneity in the data.[33] Model fit was evaluated using several measures,[34–37] including (1) Bayesian Information Criterion (BIC); (2) Vuong-Lo-Mendel-Rubin likelihood ratio test (VLMR),[34] which compares goodness of fit of models with k and (k+1) latent classes; and (3) model entropy, which assesses certainty of class membership (values >0.8 indicate high confidence in latent class assignment).[38–40] For the BIC, the optimal model has the smallest BIC value, whereas a nonsignificant VLMR test ($p > .05$) indicates that the model with the smaller number has a better fit. Logistic regression based on auxiliary variables in mixture modeling[41] was used to determine the extent to which latent classes differed with respect to patients' demographic (sex, age, marital status, education), clinical (epilepsy type, childhood epilepsy onset, number of comorbid conditions, number of ASMs, seizure frequency, reported medication side effects, anxiety and depression), and psychosocial (employment, ability to drive) characteristics. These demographic, clinical, and psychosocial characteristics are known predictors of HRQOL or confounders of the association between exposures and HRQOL in patients with epilepsy.[39–42] Age was categorized as younger (18–54 years) and older (55+ years) to distinguish between young and older adults. Depression and anxiety variables were derived from clinician diagnoses.

To identify DIF in QOLIE10 items, we adapted the logistic regression DIF procedures for LVMMs,[33,43] in which two models where each item was regressed on (1) the latent factor score (based on the LVMM) and (2) the factor score plus the latent class membership (to test for uniform DIF), and the latent class by latent factor interaction (to test for nonuniform DIF). The magnitude of DIF was evaluated based on the difference in the Nagelkerke R^2 comparing models (1) to (2), for each item. A change in R^2 (ΔR^2) below .035 is indicative of ''negligible'' DIF, a ΔR^2 between .035 and .070 indicates ''moderate'' DIF, and a ΔR^2 above .07 indicates a "large" DIF effect.[44] The latent variable analyses were conducted in Mplus v8.4,[45] whereas other analyses were conducted in R v4.1.[46]

3 | RESULTS

The characteristics of the patient cohort are described in Table 1. Of the 1143 patients included in this analysis, 567 (49.6%) were female, 495 (43.3%) were married or in a common-law relationship, 552 (48.3%) had post-secondary education, and 618 (54.1%) were employed. The median age was 37.0 (interquartile range [IQR] 27.0) years.

Table 2 describes the frequency distributions of patients' responses for all QOLIE10 items. More than 12% of the patients reported feeling downhearted and low most or all of the time (item 2); and nearly 23% reported that seizures or the effects of ASMs affected their ability to drive and other means of transportation (item 3) all or most of the time. More than half of the cohort was bothered by the physical or psychological effects of ASMs (items 7 and 8) all of the time. Overall, more than 65% reported pretty good or very good quality of life (item 10). For many of the items, some of the response options were endorsed by only a few patients, creating a sparse cells issue. For these items, the response categories endorsed by less than 7% of the patients were collapsed with the adjacent response category.

Parallel analysis and EFAs revealed that the first three factors had positive eigen values but only one factor had an eigen value greater than 1.0. The ratio of the first and second eigen values is 24.1, an indication that there is essential unidimensional structure for the QOLIE10 item data in this population (Figures S1–S2).

Results of the LVMMs suggest that a two-class model provided the best fit to the data; class 1 consisted of 429 patients (37.5%), whereas class 2 consisted of 714 patients (62.5%). The two-class model had the highest model entropy (0.79), the lowest BIC value, and a statistically significant VLMR test when comparing two-class model vs one-class models, but a nonsignificant VLMR test when comparing two and three-class models (Table 3).

The logistic regression results indicate that the two latent classes differed with respect to driving status, employment,

TABLE 1 Descriptive characteristics of the study cohort

Patient characteristics	*n* (%)
Overall age (median [IQR])[a]	37.0 (27.0)
[18–34) years	24.00 (9.0)
[35–44) years	39.00 (4.0)
[45–54) years	50.0 (5.0)
[55–64) years	59.0 (4.0)
65+ years	72.0 (8.0)
Sex (*n*, % female)	567 (49.6)
Marital status (*n*, % married/Common law)	495 (43.3)
Education (*n*, % post-secondary)	552 (48.3)
Employment (*n*, % employed)	618 (54.1)
Driving status (*n*, % driving)	505 (44.2)
Childhood onset epilepsy (*n*, % yes)	565 (49.4)
Focal epilepsy (*n*, % yes)	775 (67.8)
Total seizure frequency (*n*, % ≥2 seizures/per year)	406 (35.5)
Depression (*n*, % yes)	191 (16.7)
Anxiety (*n*, % yes)	169 (14.8)
Number of ASMs (*n*, % ≥2 ASMs)	358 (31.3)
Epilepsy-specific comorbidity Index (*n*, % >1)	112 (9.8)

$N = 1143$.

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

[a]Reported as median and IQR.

childhood-onset epilepsy, depressive symptoms, anxiety symptoms, seizure frequency, reported side effects from medications, and use of multiple ASMs. Specifically, patients in class 1 were general younger, were less likely to drive, were less likely to have had childhood-onset epilepsy, and were less likely to be employed; but they were more likely to be taking multiple ASMs, report two or more seizures per month, report more side effects from ASMs, and report more depression and anxiety symptoms than patients in class 2 (Table 4). Patients in class 1 reported a significantly lower median predicted QOLIE10 factor score than patients in class 2 (Figure 1).

DIF analyses with respect to the latent classes revealed that QOLIE10 items on the physical and psychological effects of the ASMs (items 7 and 8) exhibited large DIF effect sizes across the latent classes (Table 5). In particular, patients in class 1 reported more bothersome physical and psychological effects of the ASMs (items 7 and 8) than patients in class 2.

4 | DISCUSSION

This study examined heterogeneity in how patients with epilepsy respond to questions about their quality of life. The findings highlight important novel aspects in our understanding of how patients view their quality of life and factors that influence their perception and PROM self-ratings. First, we identified two subgroups of patients who view and respond differently to QOLIE10 items in a consistent manner. The subgroups differed with respect to disease severity, related disability, and most sociodemographic factors. In particular, compared to those in latent class 2, patients in latent class 1 were younger, but had features of more disabling epilepsy, more polypharmacy, and worse depression and anxiety, and they endorsed more side effects from ASMs. This novel finding provides new information about the clustering of specific clinical variables with a direct bearing on quality of life, and it can alert clinicians to address comorbidities to improve quality of life.

Our second notable finding is a significant difference between the two groups of patients in the way they respond to two QOLIE10 items, namely the physical effects of ASMs (item 7) and the psychological effects of ASMs (item 8), but not other items. Patients with worse epilepsy and depression view and respond to these two items about side effects differently from those with milder or better controlled epilepsy. These findings highlight the impact of disease severity and related disability on how patients with epilepsy view and rate the side effects of ASMs.

Our findings are consistent with previous reports of an association between reports of worse side effects of ASMs and mood and behavioral problems,[47] highlighting the importance of a comprehensive approach to epilepsy care, including psychosocial aspects and optimization of ASM therapy. However, we also demonstrate the impact of these factors on specific aspects of HRQOL, and their importance in patient care.

An important question raised by our findings pertains to the interpretation and comparison of QOLIE10 scores across groups of patients with different levels of drug resistance and disability. We do not believe that our new finding of DIF in two items of the QOLIE10 detracts from the validity of the instrument because the remaining eight items demonstrated adequate item invariance across the two populations. However, the results raise questions about the inclusion and wording of items pertaining to ASM side effects in QOLIE10 instruments. The latent class analyses demonstrate that responses to these items are not only determined by epilepsy-related quality of life, but also other differences among respondents (such as their younger age, features of epilepsy disability, polypharmacy, depression and anxiety, and ASM side effects). At a basic level, this finding shows that when HRQOL is measured, the domains of epilepsy severity/disability, mood, and perception of side effects are intertwined. At a deeper level it raises methodological questions regarding the use of patient-reported outcome measures (PROMs). For example, is such intertwining correctable by refining questionnaire items? LVMMs could be used to identify invariant items[33]; however, the meaning of summary scores may be altered if potentially relevant

TABLE 2 Distribution of study cohort responses to QOLIE10 items

Item #	QOLIE10 item	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
1	Did you have a lot of energy?	100 (8.7)	366 (32.0)	220 (19.3)	252 (22.1)	151 (13.2)	54 (4.7)
2	Have you felt downhearted and low?	31 (2.7)	111 (9.7)	126 (11.0)	255 (22.3)	351 (30.7)	269 (23.6)
		A great deal	A lot	Somewhat	Only a little	Not at all	
3	How much of the time during the past 4 weeks your epilepsy or antiepileptic drugs have caused trouble with driving (or other transport…)	234 (20.5)	25 (2.2)	37 (3.2)	55 (4.8)	792 (69.3)	NA
		Not all bothersome				Extremely bothersome	
4	During the past 4 weeks, how much do your work limitations bother you?	670 (58.6)	134 (11.7)	110 (10.4)	74 (6.5)	146 (12.8)	NA
5	During the past 4 weeks, how much do your social limitations bother you?	643 (56.3)	171 (15.0)	148 (13.0)	105 (9.2)	76 (6.7)	NA
6	During the past 4 weeks, how much do your memory difficulties bother you?	399 (34.9)	247 (21.6)	189 (16.5)	143 (12.5)	165 (14.5)	NA
7	During the past 4 weeks, how much do physical effects of antiepileptic drugs bother you?	628 (54.9)	204 (17.8)	153 (13.4)	91 (8.0)	67 (5.9)	NA
8	During the past 4 weeks, how much do psychological effects of antiepileptic drugs bother you?	662 (57.9)	167 (14.6)	153 (13.4)	92 (8.1)	69 (6.0)	NA
		Very afraid	Somewhat afraid	Not very afraid	Not afraid at all		
9	During the past 4 weeks, how afraid are you of having a fit during the next 4 weeks?	139 (12.1)	202 (17.7)	242 (21.2)	560 (49.0)	NA	NA
		Very good	Pretty good	Good & bad about equal	Pretty bad	Very bad	
10	During the past 4 weeks, how has your QUALITY OF LIFE been 1 (that is, how have things been going for you)?	259 (22.7)	492 (43.1)	262 (22.9)	109 (9.5)	21 (1.8)	NA

$N = 1143$.

Abbreviation: NA, not applicable; QOLIE10, 10-item Quality of Life in Epilepsy.

TABLE 3 Fit statistics and latent-class estimation for conventional item response theory model and latent variable mixture models for the QOLIE10 items

Fit statistics	1-class IRT	2-class IRT	3-class IRT	4-class IRT
LL	−12 159.90	−11 853.48	−11 675.32	−11 551.25
BIC	24 608.50	24 397.02	24 435.23	24 581.19
Entropy	-	0.79	0.77	0.75
VLMR	-	0.00	0.14	0.82
Class proportions				
Class 1	1.0	0.38	0.25	0.32
Class 2	-	0.62	0.23	0.21
Class 3	-	-	0.52	0.20
Class 4	-	-	-	0.27

$N = 1143$.

Abbreviations: BIC, Bayesian Information Criterion; IRT, item response theory model; LL, Loglikelihood; QOLIE10, 10-item Quality of Life in Epilepsy; VLMR, Vuong-Lo-Mendel-Rubin likelihood ratio test p value.

TABLE 4 Association between latent classes and characteristics of the study cohort

Characteristic	Class 1 ($N_1 = 429$)	Class 2 ($N_2 = 714$)	Odds ratio [95% CI]
Age (n, % >55 years)	74 (17.3)	185 (25.9)	0.45 [0.29, 0.69]*
Sex (n, % female)	227 (52.9)	340 (47.6)	1.09 [0.80, 1.47]
Marital status (n, % married/ common-law)	172 (40.0)	323 (45.2)	1.35 [0.95, 1.90]
Epilepsy type (n, % focal epilepsy)	306 (71.3)	469 (65.7)	0.84 [0.50, 1.18]
Childhood onset epilepsy (n, % yes)	206 (48.0)	359 (50.3)	0.57 [0.40, 0.81]*
Education (n, % post-secondary)	172 (40.0)	380 (53.2)	0.83 [0.60, 1.16]
Employment (n, % yes)	168 (39.2)	450 (63.0)	0.48 [0.35, 0.67]*
Driving (n, % yes)	85 (19.8)	420 (58.8)	0.21 [0.15, 0.30]*
Polytherapy (n, %2+ ASMs)	191 (44.5)	167 (23.4)	1.72 [1.24, 2.39]*
Seizure frequency (n, %1+ seizures)	238 (55.5)	168 (23.5)	2.83 [2.06, 3.89]*
Comorbidity index (n, % 1+)	51 (11.9)	61 (8.5)	1.57 [0.92, 2.68]
Depression (n, % depressed)	140 (32.6)	51 (7.1)	4.27 [2.66, 6.86]*
Anxiety (n, % anxiety)	120 (28.0)	49 (6.9)	2.91 [1.79, 4.75]*
ASM side effects (n, % yes)	238 (55.5)	233 (32.6)	2.26 [1.66, 3.07]*

$N = 1143$.

Abbreviations: ASM, antiseizure medication; 95% CI, 95% confidence intervals.

*$p < .05$.

items were to be removed. Another option is to develop adjusted scoring algorithms, based on LVMM results.[48] LVMMs could be implemented in automatic (computerized) scoring to obtain adjusted predictor factor scores without having to remove/delete any item. On a pragmatic level, even without having the calculated adjusted scores, the results of this study provide information for clinicians to consider whether scores may be positively or negatively biased, by taking into account information about the predictors of latent class membership. This information could be included on the forms themselves, to cue clinicians to the likely class to which the patient belongs, thereby refining interpretation according to their perceived impact of ASM adverse effects.

The two items about ASMs in the QOLIE10 are worded in the same manner as the three preceding items, asking how much the person "is bothered by…", and they have the same response options. It is important to note that the items exploring energy (which is a prominent side effect of ASMs), mood (an important determinant of HRQOL), and seizures (a marker of severity and drug-resistance), all of which explore aspects that are different between the two groups, did not demonstrate DIF (ie, they were invariant across both groups). On the other hand, items 7 and 8, which demonstrated a high DIF, are the only items in the questionnaire that explore the negative effect of an intervention, that is, something the patient is subjected to (ASMs). It is possible,

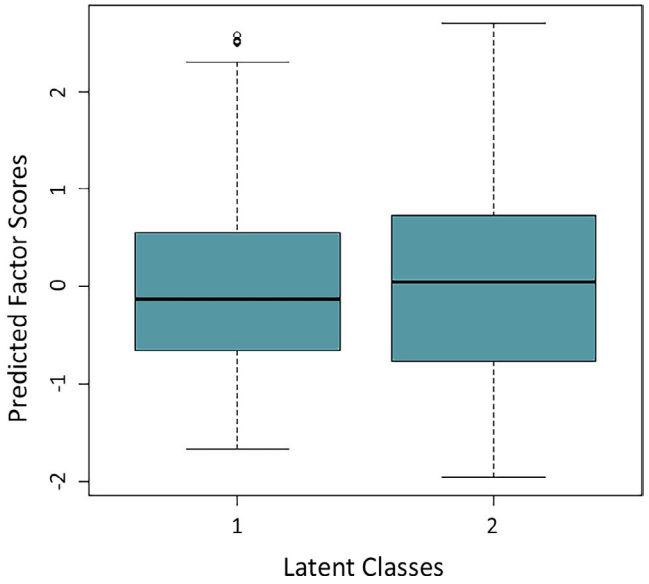

FIGURE 1 Distribution of 10-item Quality of Life in Epilepsy (QOLIE10) total scores across latent classes. Patients in class 1 were younger, were less likely to drive, were more likely to be taking multiple antiseizure medications (ASMs), to report two or more seizures per month, to report more side effects from ASMs, and to endorse more depression and anxiety symptoms than patients in class 2

therefore, that patients who share features of those in class 1, interpret these QOLIE10 items through a heightened sense of harm of interventions in a setting of poor health, a more external health-related locus of control, and an increase in psychological reactance (an aversive affective reaction in response to interventions or impositions), all of which have shown to impact perception and adherence to prescribed treatment.[49,50] Clinicians need to be mindful of the implications of item-level DIF on the ability to interpret and compare scores across groups, when assessing the impact of ASM side effects. It is notable that in light of these findings, clinicians should be encouraged to systematically assess patients for psychological morbidity, and treat accordingly, as this is likely to impact not only mood, but also patients' perceptions of ASM side effects, their adherence to medications, and potentially their seizure control.

This study is not without limitations. First, responses were collapsed on some items with few responses. It is not clear how this might have influenced the detection of DIF on some of the items. Second, nearly 50% of the patients self-reported their epilepsy as "not severe," and less than 20% had a formal diagnosis of depression and/or anxiety, which is lower than the reported population prevalence of depression in individuals in epilepsy.[51,52] It is not clear how much our study findings can be generalized to cohorts with more severe epilepsy and higher rates of depression. Future research will seek to replicate these findings in other population-based cohorts of patients with more severe epilepsy. Third, LVMM, like most IRT models, assume unidimensionality of the PROM items (ie, only one latent factor underlies the PROM items), which was not tenable in our data. Instead, we could establish only essential dimensionality (ie, one dominant latent factor) in QOLIE10 items. Future research will use computer

TABLE 5 Differential item function analysis (DIF effect size) of the QOLIE10 items

Item	Item description	DIF effect size (ΔR^2)
1	Did you have a lot of energy?	Invariant
2	Have you felt downhearted and low?	Invariant
3	How much of the time during the past 4 weeks your epilepsy or antiepileptic drugs have caused trouble with driving (or other transport…)	Invariant
4	During the past 4 weeks, how much do your work limitations bother you?	Invariant
5	During the past 4 weeks, how much do your social limitations bother you?	Invariant
6	During the past 4 weeks, how much do your memory difficulties bother you?	Invariant
7	During the past 4 weeks, how much do physical effects of antiepileptic drugs bother you?	0.14
8	During the past 4 weeks, how much do psychological effects of antiepileptic drugs bother you?	0.18
9	During the past 4 weeks, how afraid are you of having a fit during the next 4 weeks?	Invariant
10	During the past 4 weeks, how has your QUALITY OF LIFE been (that is, how have things been going for you)?	Invariant

Note: N = 1143.

ΔR^2 = difference in the Nagelkerke R^2 of model in which each item regressed on the factor score (model 1), and the model where each item is regressed on the factor score, latent class membership, and their interaction (model 2). Invariant items are those that have a $\Delta R^2 \leq 0.035$.

simulations to examine the accuracy of latent class recovery when strict unidimensionality cannot be established in PROMs.

In conclusion, this study revealed heterogeneity in how patients with epilepsy responded to QOLIE10 questions about their HRQOL. LVMM identified two subgroups of patients with different response patterns to the QOLIE10 items pertaining to the impact of side effects of ASMs. These analyses have important implications for the comparability of QOLIE10 scores in the presence of substantial heterogeneity in item responses, and the use of these scores to provide personalized clinical decisions for disease management, especially as pertains to psychological morbidity and perception of ASM adverse effects. We recommend that routine DIF analyses be conducted to identify heterogeneous subgroups to aid accurate interpretation of PROM scores in clinical and epidemiological studies.

ACKNOWLEDGMENTS

This research is supported by a Canadian Institutes of Health Research (CIHR) Operating Grant (# 122110) to TTS, RS, and LML. LML is supported by a CIHR Canada Research Chair in Methods for Electronic Data Quality and RS is supported by a CIHR Canada Research Chair in Person-Centered Outcomes.

CONFLICT OF INTEREST

SW's institution received unrestricted educational grants from UCB Pharma, Eisai, and Sunovion. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sajobi TT, Josephson CB, Sawatzky R, Wang M, Lawal O, Patten SB, et al. Quality of Life in Epilepsy: Same questions, but different meaning to different people. Epilepsia. 2021;62:2094–2102. https://doi.org/10.1111/epi.17012