



## Health-related quality of life in Veterans with epileptic and psychogenic nonepileptic seizures

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### ARTICLE INFO

#### Article history:

Received 31 December 2018

Revised 6 February 2019

Accepted 7 February 2019

Available online 17 March 2019

#### Keywords:

Epilepsy  
Psychogenic seizures  
Veterans  
Quality of life

### ABSTRACT

**Rationale:** Health-related quality of life (HRQoL) is compromised in civilians with epileptic seizures (ES) or psychogenic nonepileptic seizures (PNES). U.S. Veterans are a distinct patient group with regard to gender, age, and background. We studied HRQoL in Veterans and asked the following: (1) Is there a difference in HRQoL in Veterans with ES vs. PNES?; (2) What factors influence HRQoL in each group?; (3) What factors influenced the difference between seizure groups?

**Methods:** We studied consecutive Veterans entering the epilepsy monitoring units (EMUs) of three VA Epilepsy Centers of Excellence. Patients underwent continuous video-EEG monitoring. Seizure diagnoses followed established criteria. Health-related quality of life was measured with the Quality of Life in Epilepsy Inventory-31 (QOLIE-31). Evaluations included the Structured Clinical Interview for Diagnostic and Statistical Manual-IV (DSM IV), the posttraumatic stress disorder (PTSD) Checklist (PCL), the Beck Depression Inventory II (BDI-II), and the Minnesota Multiphasic Personality Inventory-2 Restructured form (MMPI-2RF). Between-group differences were tested with Wilcoxon tests. Nested regression analysis was used to evaluate the influence of demographic, social, military, seizure-related, and psychological factors on QOLIE-31 scores.

**Results:** The median QOLIE-31 total score was 14 points lower in Veterans with PNES vs. ES ( $p < 0.001$ ; Cohen's  $d = 0.73$ ). Within each seizure group, psychological factors accounted for  $\geq 50\%$  of the variance in QOLIE scores while combined demographic, social, and seizure-related factors accounted for 18% (group with ES) and 7% (PNES). Psychological measures, particularly PCL and the BDI-II scores, accounted for all of the difference in QOLIE-31 total scores between Veterans with ES and those with PNES.

**Conclusions:** Health-related quality of life as measured by the QOLIE-31 is worse in Veterans with PNES as compared with those with ES. Psychological factors account for the most of the variance in QOLIE-31 scores regardless of seizure type and also account for the difference between groups with PNES and ES. Demographic, military, social, and seizure-related factors have minimal influence on HRQoL. These results in U.S. Veterans are similar to those found in civilians despite differences in patient age, gender, and background.

Published by Elsevier Inc.

### 1. Introduction

Health-related quality of life (HRQoL) is a multidimensional clinical construct that attempts to summarize a patient's subjective experience regarding the impact of health conditions on their everyday function. Specific scales have been developed for measuring HRQoL in patients

with seizure disorders, the most widely used being the Quality of Life in Epilepsy Inventory (QOLIE) [1,2]. Health-related quality of life is adversely affected by both epileptic seizures (ES) and psychogenic nonepileptic seizures (PNES) [3,4]. Quality of Life in Epilepsy Inventory scores are commonly used to supplement traditional clinical outcome measures such as seizure frequency, and appear to measure a distinct aspect of the patient experience [3,4].

Civilian studies have attempted to determine factors associated with higher or lower HRQoL scores in patients with ES [5–12]. In general, these studies have shown that psychological factors, particularly depression, have the strongest association with HRQoL scores (reviewed by Taylor et al., 2011) [3]. Seizure frequency had less overall influence.

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Similarly, studies of civilians with PNES have shown that HRQoL scores are primarily correlated with psychological factors as opposed to demographic, social, or seizure-related factors (reviewed by Jones et al., 2016) [4,13–17]. These observations are important for the design and assessment of therapies for seizure disorders where a goal is to improve quality of life (QoL) rather than seizure frequency alone. Whether these general observations hold true for specific patient populations is unclear.

Veterans with seizure disorders differ from civilians in a number of ways. They are predominately male and have higher rates of traumatic brain injury as the proposed cause for seizures [18,19]. For Veterans diagnosed with PNES, the strong association with posttraumatic stress disorder (PTSD) also differs from civilians [20]. Because of these and other differences, the factors influencing HRQoL may be different in Veterans. We studied HRQoL in a well-characterized group of Veterans with epilepsy monitoring unit (EMU)-proven ES or PNES and asked three questions: (1) Is there a difference in HRQoL in Veterans with ES vs. PNES?; (2) What factors are associated with HRQoL in each group?; (3) What factors influence the difference in HRQoL between these two groups?

## 2. Methods

### 2.1. Patients

We studied consecutive patients admitted to the EMUs of the San Francisco California, Portland Oregon, and Madison Wisconsin VA Epilepsy Centers of Excellence, over a three-year period. Detailed characteristics of the study population, and inclusion/exclusion criteria, have been presented [19]. A total of 333 patients met inclusion criteria, consented to study participation, and underwent research testing. At the conclusion of EMU evaluation, patients were assigned one of the following discharge diagnoses by the site principal investigator, using specified criteria: (1) *ES only*; (2) *PNES only*; (3) *'Mixed' ES and PNES* (ES and PNES, or PNES and interictal epileptiform activity); (4) *Other nonepileptic seizures* (physiologic events confused with ES); or (5) *Inconclusive*. Definitions for these diagnoses are similar to those used nationally by the VA Epilepsy Centers of Excellence and are detailed elsewhere [18]. This report concerns exclusively patients with confirmed diagnoses of ES only or PNES only.

### 2.2. Research evaluations

Interviews were performed and questionnaires were collected prior to completion of video-EEG monitoring and debriefing of the patient regarding their seizure diagnosis (to minimize reporting bias). Evaluations included the following:

**Quality of Life in Epilepsy Inventory-31 (QOLIE-31):** A multidimensional measure of HRQoL in patients with seizures, derived from the larger QOLIE-89 [2]. In addition to the total score (primary measure), there are 8 subscales (Table 1). The QOLIE-31 is the most commonly used research instrument for measuring HRQoL in research studies of patients with ES or PNES [3,4].

**PTSD Checklist (PCL; civilian version):** A self-report measure of the severity of current PTSD symptoms [21]. Results are highly correlated to those obtained with the Clinician Administered PTSD Scale.

**Beck Depression Inventory II (BDI-II):** A commonly used self-report inventory measuring the severity of current depression symptoms [22].

**Structured Clinical Interview for Diagnostic and Statistical Manual IV (DSM IV) (SCID I and II):** SCID I is a semi-structured interview for determining axis I mental disorders as classified by the DSM IV. Interviews were performed by study psychologists/psychiatrists. The SCID II evaluates thirteen Axis II personality disorders using DSM IV criteria. To ensure reliability of administration and scoring across

**Table 1**

QOLIE-31 total score and subscales for the groups with ES and PNES. *p* values are from Wilcoxon tests comparing groups with ES and PNES. IQR – interquartile range (75th–25th).

	PNES n = 73	ES n = 64	<i>p</i>	Effect size
QOLIE-31 (median, IQR)				
Total score	39.6 (49.4–27.2)	53.9 (60.9–40.5)	<0.0001	0.73
Energy score	35.0 (45.0–20.0)	45.0 (60.0–32.5)	0.002	0.55
Emotion score	48.0 (64.0–32.0)	64.0 (76.0–52.0)	0.0005	0.61
Daily activity score	27.0 (45.0–13.0)	47.5 (66.0–27.5)	<0.0001	0.77
Mental activity score	36.4 (55.6–20.8)	45.6 (66.5–33.3)	0.007	0.47
Medication effects score	55.6 (77.8–27.8)	50.0 (72.2–25.0)	0.39	–0.16
Seizure worry score	24.0 (40.3–10.0)	43.3 (59.2–22.3)	0.0003	0.64
Overall QoL score	50.0 (65.0–32.5)	60.0 (72.5–42.5)	0.07	0.30
Distress score	39.3 (57.1–25.0)	46.4 (67.9–35.7)	0.02	0.20

sites, the principal psychologist (EG) trained clinicians from all sites and conducted blind practice ratings.

**Minnesota Multiphasic Personality Inventory-2 Restructured form (MMPI-2RF):** A 338-question personality/psychopathology inventory [23]. For the planned analysis, we utilized only the RC1 scale that measures a patient's tendency to somatization (unexplained medical symptoms). Consistent with recommended guidelines, we excluded MMPI results for patients who were unreliable, or provided an excessive number of unscorable response (Variable Response Inconsistency (VRIN-r) or True Response Inconsistency (TRIN-r)  $\geq 80$ ; Cannot Say (CNS)  $\geq 15$ ) [23]. These exclusions applied to two patients with ES and 6 patients with PNES.

### 2.3. Analyses

Patient demographic, social, military, seizure, and psychological factors were summarized with medians and interquartile ranges. The significance of differences between the groups with ES and PNES for QOLIE-31 total scores and subscales was determined using the Wilcoxon test, two-tailed (several QOLIE-31 subscales had nonnormal distributions; Shapiro–Wilk test). Effect sizes were calculated as Cohen's *d*.

To determine clinical factors/test scores that influenced the QOLIE-31 total score, we performed a nested multivariate regression analysis. Candidate clinical characteristics and test scores were selected based on review of the literature. We screened these candidate variables for inclusion in the regression by examining Spearman correlations with the QOLIE-31 total score [8,9]. We screened candidate categorical variables using biserial correlation. We included in the regression all candidate measures that had a correlation *p* value of  $\leq 0.1$  for either the group with ES, the group with PNES, or both groups combined. After selecting variables for the regression, we grouped them into 5 categories: demographic, social, military, seizure-related, and psychological. As there were no military factors selected for inclusion, this reduced to 4 categories. Regression for demographic variables was performed first, and each successive category was entered with inclusion of the previous categories. The same measures were used for the groups with ES and PNES, though the analyses were conducted independently. For each set of measures, we calculated the regression coefficient (*R*), the adjusted coefficient (*R*<sup>2</sup>), and the ANOVA *F* value and its associated *p* value.

To assess the influence of these factors on the difference in the QOLIE-31 total score between the groups with ES and PNES, we utilized a change-in-estimate strategy. Covariates with known relationships to the QOLIE-31 total score were entered one at a time to determine their effect on the association of seizure group with the QOLIE-31 total score (using estimated standardized coefficients). We determined which models brought the estimated coefficient for seizure type (ES vs. PNES) as close as possible to the null. All analyses were conducted using SAS software v9.4.

## 2.4. Standard protocol approvals, registrations, patient consents, disclaimer

This study was approved by the ethical standards committee and central institutional review board (CIRB) for the U.S. Veterans Administration. Written consent was obtained from all study participants. The contents of this manuscript do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

## 3. Results

### 3.1. QOLIE-31 scores in Veterans with verified ES and PNES

Valid QOLIE-31 scores were available for 64 of 70 patients diagnosed with ES only (91%) and 73 of 81 patients with PNES only (91%). The remaining patients either refused to complete the QOLIE-31 or had an excessive number of incomplete items (not scorable). Patients in the groups with PNES and ES were similar with regard to age at the time of EMU evaluation, gender, education, and age at seizure onset (Table 2).

The QOLIE-31 total scores and subscales for the patient groups with ES and PNES are charted in Table 1. The QOLIE-31 total score was higher in patients with ES as compared with those with PNES. The median difference between groups was 14 points ( $p < 0.001$ ; effect size  $d = 0.73$ ). Differences between the two groups were significant for all subscales except medication effects and overall QoL. The daily activity score, seizure worry score, emotion score, and energy score had the largest effect sizes for difference between seizure groups. The higher medication effects score in the group with PNES (ns) may in part be related to a lower percentage of patients receiving Anti-epileptic medications (AEDs) at the time of EMU admission (65% of patients in the group with PNES vs. 95% in the group with ES;  $p < 0.001$ ; Table 2). The QOLIE-31 total score for seven patients with documented mixed ES and PNES was 42.5.

**Table 2**

Clinical characteristics/test scores for the groups with PNES and ES. For continuous measures: median (IQR). Years of seizures = time interval between seizure onset and EMU evaluation. N for the MMPI-RC1 scale was 66 (PNES) and 61 (ES). The combat experience scale was administered only to patients reporting military combat (N = 21 and 29 for the groups with ES and PNES respectively). w – Wilcoxon test; f – Fisher's exact test. Significant  $p$  values ( $\leq 0.05$ ) are bolded for emphasis.

	PNES n = 73	ES n = 64	$p$
<b>Demographics</b>			
Age at admission (years)	46.0 (53.0–34.0)	44.5 (60.0–35.0)	0.30 (w)
Seizure onset age (years)	29.5 (45–25)	32.0 (47.0–22.0)	0.49 (w)
Gender (% male)	74.3	84.4	0.21 (f)
Education (years)	14 (14–14)	14 (14–12)	0.13 (w)
<b>Social</b>			
Working (%)	23.0	34.4	0.13 (f)
Driving (%)	21.6	17.2	0.67 (f)
Receiving disability (%)	81.1	65.6	<b>0.05 (f)</b>
<b>Military</b>			
Deployed to war zone (%)	57.5	47.6	0.30 (f)
Combat exposure (%)	43.8	34.4	0.38 (f)
Combat experience scale	18 (26–12)	14 (24–8)	0.30 (w)
Years in service	4.0 (9.0–3.5)	5.0 (6.0–3.0)	0.15 (w)
<b>Seizure</b>			
Disabling seizures/month	8.0 (16.0–2.2)	2.3 (6.0–1.0)	<b>&lt;0.001 (w)</b>
Years of seizures	3.5 (14.0–1.0)	7.0 (20.0–3.0)	<b>0.03 (w)</b>
AED prescribed (current) (%)	64.9	95.3	<b>&lt;0.0001 (f)</b>
Seizures attributed to TBI (%)	46.0	25.0	<b>0.01 (f)</b>
<b>Psychological</b>			
Beck Depression Inventory II	24 (35–14)	13 (22–7)	<b>0.0001 (w)</b>
PTSD Checklist	60.0 (67.5–43.5)	34.5 (48.5–29.5)	<b>&lt;0.0001 (w)</b>
Number of axis I diagnoses	3 (5–2)	1 (2–0)	<b>&lt;0.0001 (w)</b>
Any axis II diagnosis (%)	41.8	23.0	<b>0.03 (f)</b>
MMPI-2RF RC1 scale	79 (86.0–72.0)	63 (74–56)	<b>&lt;0.0001(w)</b>

### 3.2. Correlation of clinical characteristics/test scores with the QOLIE-31 total score

Table 2 lists factors of interest with regard to explaining the variation in individual QOLIE-31 scores within the groups with ES and PNES (candidate measures for regression analysis). The two groups were similar with regard to demographic, military, and social measures. Veterans diagnosed with PNES had a higher frequency of seizures and were more likely to indicate that the cause of seizures was a traumatic brain injury (TBI). Veterans with ES had seizures for a median of seven years at the time of EMU admission, vs. 3.5 years in the group with PNES. This may reflect earlier EMU referral of patients with atypical events. All of the included psychological measures showed greater psychopathology/psychological distress in Veterans diagnosed with PNES vs. ES (BDI-II, PCL, number of axis I diagnoses, presence of an axis II diagnosis, MMPI-RC1). The BDI-II and PCL scores were highly correlated (Spearman correlations 0.74 and 0.71 for the groups with ES and PNES respectively).

Table 3 summarizes correlations between the QOLIE-31 total score and patient characteristics/test scores. Correlations are shown for the groups with ES and PNES separately, and jointly. As per the analysis plan, measures with  $p \leq 0.1$  for either seizure group (or both combined) were included in the regression analysis. These included age at admission, years of education, current employment, current driving, disabling seizures/month, years of seizures, BDI-II and the PCL scores, number of axis I diagnoses (from the SCID), the presence of a personality disorder (from the SCID II), and the MMPI-RC1 scale score. Military factors did not correlate with the QOLIE-31 total score and were not included in the regression analysis. Scatter plots of BDI-II vs. QOLIE-31 scores and seizure frequency vs. QOLIE-31 scores are shown in Supplementary Fig. E-1.

### 3.3. Regression analyses

Results of the regression analyses are shown in Table 4. Demographic, social, and seizure-related factors combined accounted for 18% of the variance in QOLIE-31 total scores within the group with ES and 7% within the group with PNES (adjusted  $R^2$ , model 3). In models 2 and 3, age at EMU admission and employment status each showed modest associations with the QOLIE-31 total score ( $p \leq 0.05$ ), but only for the group with ES. In model 2, driving was associated with a higher QOLIE-31 total score, but only in the group with PNES. Seizure frequency had a weak negative association (ns) with the QOLIE total score in model 3, but only for patients with ES.

In contrast, there was a marked increase in adjusted  $R^2$  when psychological measures were included (model 4). An increase in total adjusted  $R^2$  by more than 0.5 was seen for both seizure groups (total adjusted  $R^2$  of 0.68 and 0.65 for the groups with ES and PNES respectively).

To better understand which psychological measures had the greatest influence on regression model 4, we added these to model 3 one at a time (Supplementary Table E-1). The largest increase came from adding the BDI-II score to model 3 (adjusted  $R^2$  increased to 0.56/0.60 for groups with ES and PNES respectively). Adding only the PCL score increased adjusted  $R^2$  to 0.53/0.42. Lesser increases resulted from adding only the MMPI-2 RC1 (adjusted  $R^2$  increased to 0.38/0.38), or the number of axis I diagnoses (0.34/0.14). Adding 'any axis II diagnosis' alone did not improve on model 3.

### 3.4. Factors influencing the difference in QOLIE-31 total scores between groups with ES and PNES

We evaluated factors that accounted for the observed difference in QOLIE-31 scores between groups with ES and PNES. Standardized coefficients were calculated for the effect of seizure type on QOLIE-31 total score. We then added each regression measure, one at a time, and observed which ones decreased the standardized coefficient for seizure

**Table 3**  
Correlations for clinical/test factors with the QOLIE-31 total score. *p* values ≤0.1 are bolded for emphasis.

	PNES (N = 73)		ES (N = 64)		PNES + ES	
	Correlation	<i>p</i>	Correlation	<i>p</i>	Correlation	<i>p</i>
<b>Demographics</b>						
Age at admission	0.08	0.52	0.16	0.20	0.15	<b>0.09</b>
Age at seizure onset	−0.15	0.19	0.04	0.74	−0.08	0.33
Gender	−0.06	0.62	0.02	0.86	−0.05	0.53
Education	−0.17	0.16	−0.17	0.18	−0.19	<b>0.02</b>
<b>Social</b>						
Employment	0.32	<b>0.01</b>	0.19	0.11	0.29	< <b>0.001</b>
Driving	0.19	0.13	0.23	<b>0.05</b>	0.18	<b>0.03</b>
Receiving disability	0.12	0.35	−0.12	−0.30	−0.05	0.53
<b>Military</b>						
Deployment	−0.02	0.86	−0.10	0.42	−0.09	0.31
Combat	−0.08	0.52	−0.13	0.27	−0.13	0.13
Years in service	−0.07	0.58	−0.09	0.45	−0.12	0.18
Combat Experience scale (CES) total score	−0.20	0.29	−0.06	0.78	−0.15	0.31
<b>Seizure-related</b>						
Seizure/month	−0.17	0.15	−0.25	<b>0.05</b>	−0.30	< <b>0.001</b>
Years of seizures	0.29	<b>0.01</b>	0.13	0.30	0.28	<b>0.001</b>
Number of AEDs	−0.09	0.44	−0.03	0.81	0.07	0.45
Current AED use	−0.07	0.59	−0.04	0.77	0.09	0.29
<b>Mental health</b>						
Beck Depression Inventory II	−0.72	< <b>0.001</b>	−0.67	< <b>0.001</b>	−0.76	< <b>0.001</b>
PTSD Checklist	−0.57	< <b>0.001</b>	−0.70	< <b>0.001</b>	−0.70	< <b>0.001</b>
# of axis I diagnoses	−0.35	<b>0.004</b>	−0.43	< <b>0.001</b>	−0.51	< <b>0.001</b>
Any axis II diagnosis	−0.11	0.39	−0.11	0.36	−0.17	<b>0.05</b>
MMPI-2RF RC1	−0.55	< <b>0.001</b>	−0.49	< <b>0.001</b>	−0.62	< <b>0.001</b>

type towards the null (Table 5). Inclusion of the PCL score had the largest effect, reducing the standardized coefficient for seizure type to near zero. Other psychological factors (MMPI-2RF RC1, BDI-II, number of axis I diagnoses) also reduced the standardized coefficient for seizure type to levels that were no longer significant. Demographic, social, and seizure-related factors had essentially no effect.

**4. Discussion**

We studied groups of Veterans who were well characterized with regard to the diagnoses of ES and PNES. With regard to HRQoL, there are three main conclusions: (1) HRQoL as measured by the QOLIE-31 was better in Veterans with ES as compared with those with PNES.

(2) The major factors driving QOLIE-31 total scores in both the patient groups with ES and PNES were psychological, with only small effects of demographic, social, or seizure-related factors. (3) The observed difference in QOLIE-31 scores between the groups with ES and PNES was accounted for by psychological factors with scores on the PTSD Checklist having the strongest effects. Demographic, social, and seizure-related factors had essentially no effect.

Previous civilian studies have consistently shown that HRQoL is better in patients with ES than in those with PNES, despite the use of different instruments and inpatient vs. outpatient populations [9–11, 13,17,24]. Our Veteran groups were older than the reported civilian study groups, were predominately male, and had somewhat different backgrounds particularly with regard to military experience, TBI as

**Table 4**  
Regression models for factors associated with QOLIE-31 total scores; patient groups with ES and PNES. Standardized estimates for each measure and model. Change in adjusted R<sup>2</sup> is the difference from the previous model.

	Model 1		Model 2		Model 3		Model 4	
	ES	PNES	ES	PNES	ES	PNES	ES	PNES
<b>Demographic</b>								
Age at admission	0.19	0.10	0.28*	0.12	0.24*	0.04	0.07	−0.04
Years of education	−0.16	−0.12	−0.12	−0.18	−0.18	−0.13	−0.09	−0.12
<b>Social</b>								
Employed (Y,N)			0.29*	0.16	0.27*	0.19	0.02	0.17*
Driving (Y,N)			0.19	0.24*	0.10	0.17	0.24*	0.11
<b>Seizure-related</b>								
Disabling seizures/month					−0.18	−0.04	−0.14	0.04
Years of seizures?					0.18	0.19	0.10	0.06
<b>Psychological</b>								
Beck Depression score							−0.37**	−0.58***
PTSD Checklist score							−0.35**	−0.03
Number of axis I diagnoses							0.12	−0.10
Any axis II diagnosis (Y,N)							0.10	0.15
MMPI-2RF RC1 scale							−0.30**	−0.29**
F value (ANOVA)	2.03	0.82	3.29*	2.24	3.20**	1.84	11.58***	10.72***
R <sup>2</sup>	0.06	0.02	0.19	0.12	0.26	0.14	0.74	0.72
Adjusted R <sup>2</sup>	0.03	−0.01	0.13	0.06	0.18	0.07	0.68	0.65
Change in adjusted R <sup>2</sup>			0.10	0.07	0.05	0.01	0.50	0.58

\* *p* ≤ 0.05.  
\*\* *p* ≤ 0.01.  
\*\*\* *p* ≤ 0.001.

**Table 5**  
Estimated standardized coefficients for the regression of QOLIE-31 scores by seizure type (ES vs. PNES), and by seizure type plus additional single factors.

	Standardized coefficients	
	Factor	Seizure type
Seizure type only		−0.347***
Seizure type + factor		
PTSD Checklist score	−0.695***	−0.003
MMPI-2RF RC1 score	−0.597***	−0.075
Beck Depression score	−0.712***	−0.112
Number of axis I diagnoses	−0.416***	−0.122
Disabling seizures per month	−0.166	−0.326***
Seizure duration	0.185	−0.322***
Driving	0.200	−0.355***
Employment	0.245	−0.312***
Education	−0.125	−0.323***
Age at admission	0.0116	−0.335***

\*\*\*  $p \leq 0.001$ .

a proposed mechanism for seizures, and the frequency of a PTSD diagnosis in patients with PNES [18,19]. Despite these differences, our findings were similar to those of civilian studies; QOLIE-31 scores were higher in Veterans with ES vs. PNES, and the effect size (0.73) was within the range reported in civilians studied using either the QOLIE-31 or QOLIE-89 [10,11,24,25]. The observed difference in median scores between the groups with ES and PNES was 14 points. Although it is difficult to assign importance of this difference when comparing two patient groups, it is well above the threshold of 11.8 points proposed for a clinically significant change in QOLIE-31 scores [26].

Factors influencing HRQoL in patients with ES and PNES have been reviewed, and in general, psychological factors have had the greatest effects [3,4]. Taylor et al. reviewed 53 civilian studies examining predictors of HRQoL in patients with ES. Demographic factors such as age, gender, and marital status did not influence HRQoL, and social factors such as working and education had inconsistent associations. Seizure frequency had a negative association with HRQoL in most but not all studies. However, psychological factors, particularly depression, were consistently associated with the strongest effects on HRQoL [5,8–10]. For example, Loring et al. reported that BDI scores alone accounted for 45% of the variance in QOLIE-89 total scores [5]. Similar results were reported by others [8–10].

Our findings in Veterans with ES are consistent with the civilian studies. We found a weak negative association between seizure frequency and HRQoL [27]. However, seizure frequency explained only an additional 5% of the variance in QOLIE-31 scores in our model 3. The relatively weak association between seizure frequency and QoL may in part reflect our population; all patients were admitted to EMUs for poorly controlled seizures. None were completely seizure-free. Because seizure freedom may have more dramatic effects on activities and psychological well-being, inclusion of seizure-free patients might have resulted in greater effects on HRQoL [28–31]. Employment and driving were associated with positive effects on QOLIE-31 scores, though these were relatively small and model dependent. Together, demographic, social, and seizure-related measures explained only 18% of the variance in QOLIE-31 total scores for patients with ES. In contrast, inclusion of psychological measures added another 50%. The BDI-II scores alone increased the explained variance to 56% and PCL scores alone to 53%. Results for the PCL may be unique to this Veteran population where PTSD is much more common than in civilians [32,33]. Because PTSD and depression were highly correlated, disentangling the contribution of each measure is problematic. Overall, our model 4 accounted for 68% of the variance in QOLIE-31 scores for patients with ES, similar to civilian studies [9,10,12,25].

Results for Veterans with PNES were broadly similar to those for Veterans with ES. Demographic, social, and seizure-related factors

together accounted for only 7% of the variance in the QOLIE-31 total score. Seizure frequency had essentially no influence on QOLIE-31 in the group with PNES, consistent with civilian studies and different from observations in patients with ES [4,9,14]. As in the group with ES, psychological factors were most important in explaining QOLIE-31 scores, accounting for 58% of the variance in model 4. The BDI-II scores alone increased the adjusted  $R^2$  value from 0.07 to 0.60. In a review of 14 studies of patients with PNES, Jones et al. concluded that depression was the strongest correlate for HRQoL, and our findings are consistent with that conclusion [4].

Lastly, we examined factors that explained the difference in QOLIE-31 scores between Veterans with ES and PNES. These may be different from the factors explaining variance within each group. For example, a study of alexithymia in civilians with ES and PNES showed an association with worse QOLIE-31 scores in both groups but no contribution to differences in scores between groups [11]. In the same study, somatization (Somatic Complaints Scale of the Personality Assessment Inventory) was demonstrated to be a significant mediator between seizure type and QoL. In the current study, several psychological measures influenced the difference in QOLIE-31 scores between seizure groups whereas demographic, social, and seizure-related factors did not. Scores on the PCL had the largest effect, eliminating the observed difference between groups. This is perhaps not surprising given the marked difference in PCL scores between Veterans diagnosed with ES vs. PNES [19,20]. However, scores on the BDI-II or the MMPI-2RF RC1 also accounted for much of the difference between groups. This latter measure of somatization is similar to the Somatic Complaints Scale of the Personality Assessment Inventory and supports the concept that somatization not only influences QoL in each seizure group, but also the difference in QoL between groups [11,24]. Because several of the psychological measures used in this study are highly correlated with one another, it is difficult to tease apart contributions of a particular scale to group differences in QoL.

#### 4.1. Study strengths and weaknesses

To our knowledge, only one previous study has examined HRQoL in Veterans with seizures. Using a large national survey database, Zeber et al. demonstrated that Veterans with epilepsy and comorbid psychiatric disorders (schizophrenia, bipolar disorder, PTSD, depression, anxiety disorder, substance abuse, other) had lower Short-form Health Survey (SF-36) scores than patients without these disorders [34]. Posttraumatic stress disorder and depression had the greatest effects.

This study benefitted from a well-characterized group of Veterans diagnosed with ES only and PNES only by EMU monitoring and meeting research diagnostic criteria. Interviews and questionnaires were completed prior to debriefing of patients so as to minimize patient reporting bias. Patient demographics and the distribution of EMU discharge seizure diagnoses were representative of the population of patients studied by the 15 national VA Epilepsy Centers of Excellence [35].

This study also has important limitations. The study groups may not be representative of the VA outpatient population. All patients were referred to EMUs because of poorly controlled seizures, primarily for diagnostic evaluation. Also, because Veterans seeking care at Veterans Affairs Medical Centers are less than half of all Veterans, these results can only be considered valid for VAMC patients. Another limitation was reliance on a limited set of measures. Civilian studies have identified several additional factors that could impact QoL in patients with seizure including illness perception, locus of control, alexithymia, personality traits, and dissociative symptoms [9,11,16,24,36,37]. Inclusion of one or more of these might have helped explain the remaining 30% of QoL variance not explained in our models. We relied on the QOLIE-31 as the sole measure of HRQoL. As observed by Jones et al., the strength of association between the QOLIE and depression scores may in part be related to an overlap in the constructs for these measures [4].

## 5. Conclusions

Health-related quality of life is worse in Veterans diagnosed with PNES as compared with those diagnosed with ES. The median difference of 14 points is explained by psychological factors. Demographic, social, and seizure-related factors have little influence. Similarly, within each patient group, psychological factors have far more influence on QoL than does seizure frequency or other factors. These results suggest that optimizing outcomes for Veterans with ES or PNES will require attention to psychological status as well as seizure control.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2019.02.010>.

## Acknowledgments

The authors thank Eilis Boudreau MD, PhD for comments on this manuscript.

Supported by grant 5101cx000721-04 from the US Department of Veterans Affairs.

Part of this work was presented at the annual meeting of the American Epilepsy Society, New Orleans, La.; December, 2018.

## Declarations of interest

None.

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