Correlates of health-related quality of life in adults with psychogenic non-epileptic seizures: A systematic review

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Running Title: Quality of life in nonepileptic seizures

Key words: HRQoL, PNES, psychological, depression, interpersonal, coping.

Summary

Objectives. Psychogenic non-epileptic seizures (PNES) often have a debilitating impact on patients' lives. The patient, family members, and clinicians are yet to fully understand the mechanisms and treatment of this disorder. Although reviews exist about epileptic seizures, there have been no systematic reviews of studies focusing on the impact of PNES. This review considers research on factors associated with the health-related quality of life (HRQoL) of patients with PNES.

Methods. Searches of Medline, PsychInfo, CINAHL, and Cochrane Library were conducted. Search terms identified studies that examined factors associated with HRQoL in PNES. Factors fell into three categories: (1) seizure and somatic factors, (2) psychological factors and, (3) coping strategies and family functioning.

Results. Fourteen articles were included. The majority of studies were cross-sectional and were of weak to moderate quality. Depressive symptoms were negatively associated with HRQoL. Other factors associated with poorer HRQoL included dissociation, somatic symptoms, escape-avoidance coping strategies, and family dysfunction. Variables such as seizure frequency and demographic factors were not significantly associated with HRQoL.

Significance. Psychological and interpersonal factors, not seizure reduction, are important for the HRQoL of patients with PNES. The avoidance of emotions is proposed as a perpetuating factor in the difficulties associated with poorer HRQoL. A biopsychosocial approach has relevance for both the clinical and theoretical understanding of PNES. Larger scale research on psychological and relational factors is needed to inform therapeutic approaches to enhance HRQoL in patients with PNES.

Key words: HRQoL, PNES, psychological, depression, interpersonal, coping.

Key Points

- Depression was found to be the strongest correlate of HRQoL in patients with PNES.

- Other factors associated with poor HRQoL included dissociation, somatic symptoms, escape-avoidance coping strategies, and family dysfunction.
- No evidence was found to support the association between HRQoL, seizure frequency, and demographic factors.
- Services should consider treatment for depression associated with having PNES, rather than trying to treat PNES itself.
- Assessment, formulation, and intervention should monitor the role of avoidance within therapy.

Introduction

Health-related quality of life (HRQoL) is a multi-dimensional concept encompassing physical, mental, and social wellbeing.[1] Compared to epilepsy, people with psychogenic non-epileptic seizures (PNES) have consistently reported worse HRQoL, both in inpatient[2] and outpatient[3] settings. The incidence of PNES in the general population is low at 2 to 33 per 100,000, compared to 780 per 100,000 for epileptic seizures.[4] Nevertheless, PNES generate a significant health problem and cost to the patient, health system, and society.[5]

There is a high prevalence of comorbid psychiatric diagnoses in patients with PNES, including depressive (57-85%), personality (25-67%), anxiety (11-50%), dissociative (22-91%), somatoform (22-84%), and post-traumatic stress disorders (35-49%).[6] Up to 90% of PNES patients report a history of significant traumatic experiences, with rates of childhood physical abuse (0-53%) and sexual abuse (6-85%) higher than control and epilepsy populations.[7] Family dysfunction has also been indicated as contributing to poor HRQoL.[3,8] However, our understanding about the pathophysiology, perpetuating factors, and effective treatments for PNES remains limited.[9]

Although patients with PNES consistently report poorer HRQoL, systematic reviews have only considered predictors of quality of life for adults with epilepsy.[10] This review is the first to collate and critically evaluate research investigating the correlates of HRQoL in patients with PNES. In particular, the review has four aims: (i) to identify how HRQoL has been measured in research with PNES samples, (ii) to identify the strength of relationships of factors associated with HRQoL, (iii) to provide a methodological critique of studies, and (iv) to make clinical and research recommendations.

Method

Search strategy

The following electronic internet databases were searched: Medline (via OvidSP) 1946 to 21 November 2014, PsychInfo (via OvidSP) 1806 to November Week 3 2014, CINAHL via EBSCO 1982 to 21 November 2014, and Cochrane Library (Wiley) Issue 11, November 2014. The search

terms are listed in Table 1. They were a combination of search terms used within other systematic reviews on the subject of PNES[11] and HRQoL.[10] In addition, the reference lists and citations of included articles were checked to ensure no relevant articles were overlooked. The search strategy included no language restrictions.

[insert Table 1]

After removing duplicate studies, the titles and abstracts of remaining records were screened by the first author according to the following criteria, in line with a recent review of the correlates of HRQoL in patients with epilepsy.[10]

Inclusion criteria

Studies were included in the review if they met the following criteria: (i) adults (>18yrs) patient participants with a diagnosis of PNES, (ii) reported an association between any factor and HRQoL, with or without a comparator (control) population, (iii) HRQoL was assessed quantitatively using an established generic or disease-specific HRQoL measure previously validated in patient groups (not necessarily in patients with PNES), and (iv) studies of any design where the association (i.e., correlation or regression coefficient) between the factor and HRQoL was reported.

Exclusion criteria

Studies were excluded if they met the following criteria: (i) studies that considered some aspect of HRQoL but did not measure it using a validated HRQoL instrument, (ii) trials examining the impact of interventions, unless they also reported the association between factors and HRQoL, and (iii) dissertation abstracts, unpublished studies or articles.

See Figure 1 for a diagrammatic overview of the article selection procedure.

[insert Figure 1]

Data extraction

A standardised data extraction form was adapted from a review of HRQoL in patients with epilepsy.[10] For each study, the following information was extracted and summarised independently by the first author: author(s), country and year(s) of publication, study design, setting, sample size,

population characteristics, HRQoL outcome measure, correlated variables, data analysis, and quality assessment. The data was tabulated by type of statistical analyses. Studies that conducted correlation analyses only are presented in Table 2. Table 3 includes studies that also conducted regression analyses. Descriptive statistics regarding study sample sizes (e.g., sum, range, median) and participant demographics (e.g., age range, percentage female) were synthesised independently by the first author.

Quality appraisal

In line with a recent review of the correlates of HRQoL in patients with epilepsy,[10] study quality was assessed according to three criteria: (1) consecutive or random selection of patients (an index of sample and response bias), (2) statement of a formal sample size calculation or a target sample size of 115 or more (in order to detect a relatively small association, i.e., correlation coefficient of 0.3, at 5% alpha and 90% power), and (3) multivariate analysis (an index of level of confounding risk/variables). Each quality criteria was evaluated separately in each study. Categories were rated and considered ‘‘yes’’ (criteria met) or ‘‘no’’ (criteria not met), producing a quality score of 0-3. The quality appraisal process was completed by the first author and an independent rater who reviewed all 14 papers. Any disagreements were discussed until a consensus was achieved.

Results

Search results

After removing duplicates, 106 records were identified through the literature search. Titles and abstracts were examined and studies that were clearly unrelated to any seizure population were excluded. The remaining full-text articles ($N = 78$) were assessed for eligibility by the author and reasons for exclusion documented (see Figure 1). Fourteen articles were included for review.[2,3,8,12-22] The different factors assessed within the literature fell into the following categories: (1) seizure and somatic factors, (2) psychological factors, and (3) coping strategies and family functioning.

[landscape orientation]

[insert Tables 2 and 3]

Study characteristics

Thirteen studies were cross-sectional[2,3,8,12-15,17-22] and one study was an uncontrolled prospective intervention study.[16] Nine studies recruited from inpatient settings: Epilepsy Monitoring Units (n=7),[2,12-14,17,21,22] medical centre (n=1),[3] and a psychotherapeutic unit (n=1).[16] Five studies recruited participants from outpatient Neurology departments.[8,15,18-20] Two studies recruited from both outpatient and inpatient settings.[21,22]

The majority of studies were conducted in the United States of America (USA) (n=10);[2,3,8,12-14,17,18,20,21] others were carried out in the United Kingdom (UK) (n=2),[15,19] Netherlands (n=1),[16] and South Africa (n=1).[22] Four studies shared an overlapping dataset;[2,12-14] however, as they reported on different aspects of the data, these results were included in the review while acknowledging the common dataset and caution regarding repeated results. Not double counting participants from the repeated cohorts, this review includes a total of 538 individuals with PNES, with generally small sample sizes across the studies (range 22-96, median 45). Participant demographics were relatively homogenous across studies; the mean age ranged from 31-42 years and the proportion of female participants was high (range 69-100%).

Eleven studies recruited patients with PNES only[2,3,8,12-16,20-22] and three studies included patients with a comorbid epileptic seizure diagnosis.[17-19] Twelve studies recruited patients with video-electroencephalogram [vEEG] confirmed diagnoses.[2,3,8,12,13,16-22] The remaining two studies included a combination of definite (i.e., vEEG) or *highly suggestive* (i.e., witness accounts) diagnoses of PNES.[14,15] Eight studies included control samples, comparing findings with epilepsy samples (n=7)[2,3,8,12-14,21] and age and gender-matched healthy controls (n=1).[22]

Methodological quality

No studies satisfied all three quality assessment criteria. One study did not meet any of the criteria,[16] five studies met one of the criteria,[2,8,17,18,22] and eight met two of the criteria.[3,12-15,19-21] None of the studies reported a formal sample size calculation or achieved the target sample size of 115 or more. The median sample size (N = 45) is only sufficient to detect a correlation of .44 with

90% power (and 5% alpha). The use of consecutive selection of patients was reported in nine studies (64%).[3,12-15,17,19-21] The sampling method could not be determined in the remaining five studies.[2,8,16,18,22] Twelve studies carried out multivariate statistical analyses (86%).[2,3,8,12-15,18-20-22] The overall assessment suggested weak to moderate quality in the studies included in this review.

HRQoL measures used

Quality of life was most frequently measured using the seizure-specific Quality of Life in Epilepsy questionnaire (QOLIE-10/31/89) (*n*=10).[2,3,8,12,13,17-21] Other studies utilised a generic measure of HRQoL, the Short-Form Health Survey (SF-36) (*n*=4).[14-16,22]

Correlates of HRQoL

1 *Seizure and somatic factors*

(a) Seizure frequency

Six studies considered the association between seizure frequency and HRQoL.[8,15-19] Two studies reported that patients with more seizures had significantly lower summary scores on the SF-36 [15] and the subscale, *energy vitality*.[16] In contrast, a third study used the QOLIE-10 and found seizure frequency was not significantly correlated with HRQoL.[17]

Two studies conducted partial correlations and both revealed the negative relationship between seizure frequency and HRQoL summary scores became non-significant after psychological distress, physical symptoms, age, and gender had been accounted for.[15,18] Two studies conducted regression analyses and found that after controlling for other variables (e.g., depression, years with PNES), seizure frequency did not account for a significant amount of the variance in HRQoL.[8,19]

Patients who were seizure-free (i.e., no seizure for four weeks prior) had significantly higher scores on HRQoL than those who were not seizure-free.[17] At 6-month follow-up, seizure-free patients showed significant improvements in SF-36 subscales *mental health, energy vitality,* and *pain*, compared to those with continuing seizures.[16]

(b) Medication side effects

Two studies considered the association of antiepileptic drug (AED) side effects with HRQoL.[12,13] In both, regression analyses found medication side effects were a significant predictor of HRQoL; as the number of AED side effects increased, HRQoL decreased. However, caution is warranted when interpreting these results as they came from the same dataset and both combined the PNES and epilepsy data in the regression analyses. Also, AED-taking patients are one particular patient subgroup and findings may have limited generalisability.

(c) Somatic symptoms

The association between somatic symptoms and HRQoL was considered in four studies.[3,15,18,20] Using different measures, three studies found a significant association between the increased reporting of physical symptoms and lower HRQoL.[15,18,20] Symptoms included headaches, insomnia, memory difficulties, and anxiety/depression-related symptoms.[17] Daytime sleepiness and symptoms of sleep apnoea were not found to be significant correlates of HRQoL.[3]

(d) Other seizure variables

Two studies found that later age of PNES onset negatively correlated with HRQoL.[20,21] Duration of PNES, number of other medical conditions, cognitive complaints, and emotional complaints also correlated with HRQoL.[20] However, non-significant correlations were found between HRQoL and the number of AEDs or psychiatric medications taken, age of trauma, psychiatric hospitalisations, and years of education.[20] No associations were found between HRQoL and demographic variables such as employment, marital status, or religious involvement.[20]

2 *Psychological factors*

(a) Depression

Depressive symptoms were investigated in 12 studies, 11 of which reported significant associations between depression and lower HRQoL. All studies used self-report measures including the Beck Depression Inventory (BDI) (*n*=6),[3,8,16,18,19,21] Profile of Mood States (POMS) (*n*=4),[2,12-14] 10-item Clinical Outcomes in Routine Evaluation (CORE-10) (*n*=1),[15] and Minnesota Multiphasic Personality Inventory (MMPI) (*n*=1).[20]

Studies reported significant correlations between increasing depressive symptoms and lower HRQoL total, [3,8,20] or mental health component scores.[15] This relationship remained significant after controlling for age and gender.[18] One female-only study did not replicate these findings.[21]

Results from multivariate regression analyses support the above findings, suggesting that depression is a significant unique predictor of HRQoL.[8,19] Lower depression scores were found to be the only determinant of better quality of life for patients with PNES.[3]

In the studies that shared a dataset, all four regression analyses found mood to be a strong and significant predictor of HRQoL.[2,12-14] Further analyses found mood disturbance to mediate the relationship between seizure diagnosis (PNES versus epilepsy) and HRQoL.[12] In addition, mood disturbance moderated the relationship of seizure diagnosis (PNES versus epilepsy) and HRQoL.[2] That is, differences between the groups, in terms of HRQoL, were greatest when mood disturbance was reported to be minimal. However, when factors relating to somatisation (i.e., *hypochondriasis* and *hysteria* subscales of the MMPI) and psychological distress (e.g., hostility, confused thinking) were added to the model, the moderating effect of mood disturbance was no longer significant. This suggests that somatisation and psychological distress accounts for the lower HRQoL in patients with PNES when minimal mood disturbance is observed.

(b) Anxiety

Anxiety was measured in four studies using the Beck Anxiety Inventory (BAI) (n=2)[3,21] and State-Trait Anxiety Inventory (STAI) (n=2).[16,19] Anxiety was found to be negatively correlated with total HRQoL.[3] However, this association was not significant in one study, which may have lacked statistical power.[21]

After accounting for depression and dissociation, anxiety was not a significant predictor of HRQoL.[19] In addition, anxiety was not found to be a significant determinant of HRQoL in a regression model that controlled for other variables (e.g., gender, age of onset, depression).[3]

(c) Anger

Using the State-Trait Anger Expression Inventory (STAXI), one study found significant correlations between diminished quality of life and trait anger, state anger, and anger control-in (the amount one attempts to calm internal angry feelings).[20] However, of these, only trait anger was significant in the final stepwise regression model, in addition to cynicism, age at earliest trauma, and history of trauma. These findings require replication.

(d) Personality traits

Three studies administered the MMPI with mixed findings.[2,20,21] One study found significant correlations between HRQoL and emotional complaints, somatic complaints, low positive emotion, cynicism, and emotional/internalisation dysfunction.[20] However, findings were not supported by another, which may have lacked statistical power.[21]

Using subsequent multivariate analyses, 'cynicism' was found to be the only personality variable significant in the final stepwise regression model, in addition to 'trait anger', age at earliest trauma, and history of trauma.[20] In another study, scales from the MMPI-2 were combined into two factors.[2] "Somatisation" was the term used for the combined *hypochondriasis* and *hysteria* subscales, and "psychological distress" was the term for the combined subscales *depression, psychopathic deviate, paranoia, psychasthenia, schizophrenia,* and *social introversion*. Whilst the validity of grouping scales together is unknown, hierarchical regression analyses found these two factors accounted for small but significant amounts of additional variance in HRQoL (3% & 6%), above and beyond seizure type, psychiatric history, and mood state.

(e) Dissociation

Two studies assessed dissociative symptoms and found strong negative correlations with HRQoL.[16,19] After accounting for depressive symptoms, dissociative symptoms accounted for an additional 14.4% of the variance in HRQoL.[19]

3 *Coping strategies and family functioning*

(a) Coping strategies

Two studies focussed on the coping styles of patients with PNES. Patients with less active coping styles had a poorer outcome on the HRQoL subscale *energy vitality*.[16] Similarly, there was a non-significant trend for the use of *escape-avoidance* strategies associated with lower HRQoL, in a study lacking statistical power.[22]

Regression analyses indicated that *escape-avoidance* and *distancing* coping styles were negative predictors of HRQoL, whereas *confrontive coping* was a significant positive predictor of HRQoL.[22] *Planful problem solving* was not a significant predictor of HRQoL. The four subscales together accounted for 56% of the variance in HRQoL.

(b) Family functioning

Only one study investigated the influence of significant others on patient HRQoL.[8] Administering the Family Assessment Device (FAD), significant negative correlations were found between HRQoL and the *roles* and *affective involvement* subscales.[8] Subsequent regression analyses revealed that after controlling for seizure frequency, years with PNES, and depressive symptoms, the FAD subscales explained an additional 18% of the variance explained in HRQoL. Both subscales were significant predictors. This highlights the negative impact of an unsupportive and uninterested family environment on patient HRQoL.

Discussion

Summary of findings

Findings suggested that physical symptoms, age of PNES onset, and cognitive complaints are correlated with HRQoL. The increased reporting of somatic symptoms, and the tendency for patients with PNES to express psychosocial distress through unexplained somatic complaints is a consistent finding in the literature.[23] However, the Symptom Checklist 90-item (SCL-90-R) used to assess somatic symptoms is also an established screen for a broad range of symptoms of psychological distress.[24] Conceptually, somatic symptoms are also acknowledged indicators of psychological difficulties such as anxiety.[25] Therefore, it is difficult to interpret whether significant

findings are an indication of actual psychopathology or the expression of psychological distress through physical means.

Seizure reduction for patients with PNES was not found to be associated with enhanced HRQoL. This contrasts with a review on HRQoL of patients with epilepsy.[10] One potential explanation is that having fewer seizures has equivalent consequences as having many seizures (e.g., loss of driving, impact on employment and family).[18] Furthermore, the unknown causative mechanism, unpredictability, and lack of treatment may have a debilitating impact for PNES patients, regardless of frequency. Moreover, there is increasing evidence of "interictal" cognitive, emotional, and physiological dysfunction in patients with PNES which may have adverse effects on HRQoL, but may not be closely related to seizure frequency.[26,27] Therefore, seizure-reduction may not necessarily improve functioning for PNES patients; however, it may be that HRQoL is better when PNES stop completely.

This review found depression to be the strongest correlate of HRQoL in patients with PNES. Depression is cited as one of the most prevalent comorbid psychiatric diagnoses in PNES (57-85%).[6] An overlap in the constructs of HRQoL and depression may have relevance for the strong associations observed.[28] The self-evaluation of both are likely to be influenced by patients' expectations of life, cultural values, optimism, aspirations, and standards for social comparisons. Therefore, in the context of early trauma and psychopathology well-documented in the PNES population, poor outcomes on, and hence high correlations between, measures of HRQoL and depression are to be expcected.[6]

Dissociation was found to be negatively associated with HRQoL. Dissociative tendencies are highly prevalent in the PNES population and associated with poor outcomes.[29] Although widely discussed in the PNES literature, there remains ongoing debate about whether dissociative mechanisms are a precursor, expression, or means of coping with extreme physiological arousal from emotional or sensory stimuli.[30] The conceptualisation and measurement of stable dissociative tendencies in PNES remains controversial.[23]

Anxiety was only found to be significantly associated with HRQoL in correlation analyses, but not in regression analyses. This finding contrasts with results from epilepsy research.[10] Previous research suggests that in comparison to epilepsy, patients with PNES view psychological factors as less important than somatic symptoms and have a more external locus of control.[31] Also, patients with PNES have been found to have high levels of alexithymia.[32] This could denote a tendency for patients with PNES to experience and express symptoms somatically, or that patients with PNES have particular difficulty perceiving the cognitive symptoms of anxiety (i.e., realising they are anxious).

The influence of family members was found to be associated with patient HRQoL. Patients who perceived an unsupportive family environment, characterised by criticism and a lack of interest, were found to have lower HRQoL.[8] However, despite the high prevalence of family dysfunction cited in the literature, few studies have examined carer perspectives.[6] Associations have been found between the use of emotion-focussed strategies (i.e., self-orientated approaches including fantasising, self-blame, and angry outbursts) and underlying psychological difficulties.[33] Thus, avoidant approaches to stress were associated with poorer outcomes.

Methodological quality

Similar to the review of HRQoL in epilepsy,[10] the main limitation of this review concerned the methodological quality of the evidence identified. Nearly all studies included in this review employed a cross-sectional design, which means the direction of effects or causality cannot be determined. Only one study used a longitudinal prospective design allowing measurement of change across time.[16] Another important limitation relates to the HRQoL measures used. There are no disease-specific HRQoL instruments for PNES. The questionnaire most commonly used in studies, the QOLIE, is a disease-specific measure validated in patients with epilepsy. The correlations we report of QOLIE scores and other self-report measures (such as measures of depression and anxiety) suggest that its use in this setting may be valid, and patients with PNES share adverse experiences with those with epilepsy (e.g., driving restrictions, seizure worry).

Nevertheless its validity has never been determined in patients with PNES.[34] Specifically, questions about the physical and psychological effects of AEDs are not relevant to many patients with PNES. Whilst this may lead to QOLIE scores overestimating HRQoL, the scale may also fail to capture disability in other areas and underestimate HRQoL in patients with PNES. Whilst generic HRQoL measures (e.g., SF-36) are designed to be usable in any patient or healthy population and are therefore affected less by the issue of validation, they, likewise, may fail to capture disease-specific issues with marked effects on quality of life. This may be especially true if the disorder is characterised by paroxysmal symptoms. Validation studies of disease-specific versus generic measures of HRQoL are needed. Furthermore, no studies have been undertaken in patients with PNES to assess the validity of self-reported PNES frequency. With regard to external validity, the majority of reviewed studies were conducted in the USA and excluded patients with a learning disability. One study was female-only [21] and another study was completed in a pre-diagnostic inpatient setting (where there could be a strong emotional impact of not yet knowing one's diagnosis).[3] Such factors are unlikely to reflect the diversity of cultural and medical responses to PNES around the world and therefore limits the generalisability of the findings.

In terms of quality assessment, none of the studies in this review satisfied all three of the quality appraisal criteria. The main limitation was that no study reported a formal sample size or power calculation. In fact, studies typically had small sample sizes (range 22-96) resulting in reduced statistical power and an increased risk of making Type II errors. For example, the median sample size ($N = 45$) is only sufficient to detect a correlation of .44 with 90% power. Two studies were powered to detect a medium-sized correlation = .30 (>85 participants)[14,15] whereas twelve studies were powered to detect a large-sized correlation = .50 (>28 participants)[2,3,8,12-15,17-21] with two-tailed alpha = .05 and power = .80. The strengths in methodological quality included the use of multivariate analyses. Ten studies conducted regression analyses and two used partial correlation analyses. Hence, the majority of studies in this review made some attempt to control for confounding variables.

Clinical implications

Clinically, outcome is typically discussed in terms of seizure reduction; however, the relevance of PNES reduction has been questioned previously and this review emphasises the importance of other psychological and interpersonal factors for HRQoL, in particular, depression and dissociation.[35] A theme of *avoidance*, particularly of emotions, was apparent throughout a number of variables including: dissociation, somatisation, distance/escape-avoidant coping, and reduced management of internal anger - all of which have links to the avoidance or unhelpful processing of emotions. This supports existing research that found patients with PNES have high levels of experiential avoidance, work particularly hard to disconnect from uncomfortable feelings, and perceive negative emotions as damaging.[36] The role of avoidance also has strong links to the maintenance of depression[37] and as a component and a symptom of dysfunctional family processes associated with a number of clinical problems.[38] The current review suggests the importance of psychological therapies to provide a safe space to assess and make sense of emotions that can be perceived as overwhelming. However, psychological interventions may need to be framed as treating low mood/depression associated with having PNES, rather than trying to treat PNES itself given that patients with PNES have been found to be resistant to psychological explanations of their condition.[31]

The range of factors associated with HRQoL in patients with PNES indicates a need for an integrated and comprehensive approach to treatment strategies. Multimodal therapies (including those that address common comorbidities such as pain, anxiety, depression) focus on individualised symptom management and have been linked to enhanced HRQoL in other disorders.[39] Initiating psychiatric or psychological treatment for PNES and its comorbidities (i.e., pharmacotherapy, education, cognitive behavioural therapy, interpersonal or family therapy) requires further evaluation and the impact on HRQoL should be monitored.

Research recommendations

The need for larger scale research on HRQoL with PNES patients is clear. Larger samples would allow analysis of subgroups identified within PNES.[40] Future studies should include detailed reporting of power analyses and sample selection processes. Using control samples would allow inferences to be drawn about the differentiating factors that underlie PNES. Control samples should include epilepsy and/or psychiatric samples as appropriate, with a consideration of excluding patients with mixed seizure diagnoses to avoid confounding results with PNES and epilepsy presentations.

To enhance the meaningfulness and comparability of findings, PNES research would benefit from a consistent approach to the assessment of quality of life, depression, and seizure variables. The validation of a disease-specific measure with patients with PNES is a priority. The findings from the current review suggest that social (work, social and family relations, stigma) and emotional (depression, anxiety, emotional state) domains should be assessed in a HRQoL questionnaire for PNES patients. The use of self-report, carer-report, and clinician-administered measures would also allow evaluation regarding the convergent validity of the data. The inclusion of patients and caregivers is needed to explore the complex psychological and systemic factors emerging from this review. Specifically, as very little research exists about the interpersonal styles of patients with PNES, the study of patient-carer relationships would extend our theoretical understanding of factors perpetuating PNES and provide guidance for therapeutic approaches aiming to enhance patient quality of life.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication

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.

List of Abbreviations

AED – antiepileptic drugs

BAI – Beck Anxiety Inventory

BDI – Beck Depression Inventory

CORE-10 – Clinical Outcomes in Routine Evaluation

FAD – McMaster Family Assessment Device

HRQoL – health-related quality of life

PNES – psychogenic non-epileptic seizures

POMS – Profile of Mood States

QOLIE - quality of Life in Epilepsy questionnaire

MMPI - Minnesota Multiphasic Personality Inventory

PRISMA - preferred reporting items for systematic reviews and meta-analyses

SCL-90 - Symptom Checklist 90-item

SF-36 – 36-item short-form health survey

STAI - State-Trait Anxiety Inventory

STAXI - State-Trait Anger Expression Inventory

vEEG - video-electroencephalogram

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Table 1

Database Search Terms

Subject	Search terms
1	nonepileptic, psychogenic (attacks or seizures), functional, hysteri*, pseudo*, unintended (seizures), PNES, NES, NEAD
2	quality of life, value of life, quality of wellbeing, HRQOL, HQL
3	predictor*, long-term, assoc*, factor*, correlation*, correlate*, influence*, determinant*, impact, outcome*, variable*

Table 2

Summary of studies reporting correlation analyses only

Author (Year) Country and year data collected	Design / Sampling frame	Patient Population	HRQoL Outcome Factors Investigated	Bivariate and/or Multivariate Data Analysis	HRQoL Findings	Quality Rating
Kuyk et al. (2008) Netherlands 2002-2004	Prospective, uncontrolled intervention Inpatient psycho-therapeutic unit	vEEG PNES diagnosed <12 months previous *N*=26 Mean age: 30.6yrs %Female: 77.3	SF-36 Seizure frequency; Psychopathology (SCL-90); Anxiety (STAI); Depression (BDI); Coping (UCL); Dissociation (DISQ).	Wilcoxon signed-rank test. Pearson correlations.	At 6-month follow-up, patients who experienced more seizures had a lower score on the SF-36 subscale *energy vitality* (r = -56*) and showed less active coping skills (r = -.52*). Seizure-free patients had improvements in *mental health*, *energy vitality*, and *pain* subscales compared to those with continuing seizures.	0
LaFrance and Syc (2009) USA Not reported	Cross-sectional Outpatient neurology clinic	vEEG PNES and PNES+ES *N*=49 Mean age: 36.9yrs %Female: 75.5	QOLIE-31 Seizure frequency; Depression (BDI); Somatic symptoms (SCL-90).	Partial correlations.	Depressive and somatic symptoms were independently related to lower HRQoL (both r = -.73***). No significant correlation of seizure frequency with HRQoL (r = -.19).	1
Lawton, Mayor, Howlett and Reuber (2009) UK 2003-2008	Cross-sectional Specialised psychotherapy outpatient clinic	vEEG or highly suggestive accounts of PNES *N*=96 Mean age: 38.4yrs %Female: 74.0	SF-36 Seizure frequency; Psychological distress (CORE-10); Physical symptoms (PHQ-15).	Spearman and partial correlations.	Psychological distress correlated with the mental health component summary scores (r = -.66**). Physical symptoms correlated with physical health component summary scores (r = .45**). Seizure frequency was associated with HRQoL summary scores (r = -.23* & r = -.25*), but not after psychological distress and physical symptoms were accounted for.	2
Quigg, Armstrong, Farace and Fountain (2002) USA Not reported	Cross-sectional retrospective follow-up Discharged inpatients from EMU	vEEG PNES (93%) PNES+ES (7%) >6months post-diagnosis *N*=30 Mean age: 30.7yrs %Female: 77.5	QOLIE-10 Seizure frequency; Functioning (disability status).	Pearson correlations.	Higher HRQoL was associated with complete cessation of seizures. A reduction in seizures was not (r = .17).	1

Table 3

Summary of studies reporting correlation and/or regression analyses

Author (Year) Country and year data collected	Design / Sampling frame	Patient Population	HRQoL Outcome Factors Investigated	Bivariate and/or Multivariate Data Analysis	HRQoL Findings	Quality Rating
Cronje and Pretorius (2013) South Africa Not reported	Cross-sectional Inpatient and outpatient departments	vEEG PNES *N*=22 Mean age: 32.8yrs %Female: 77.27	SF-36 Coping strategies (WOC).	Pearson correlations. Multiple regression.	A non-significant trend for the use of *escape-avoidance* strategies associated with lower HRQoL (r = -.40, p = .07). Confrontive coping was a positive predictor of HRQoL (β = 2.52*). Escape-avoidance was predictive of lower HRQoL (β = -3.44**).	1
Karakis et al. (2014) USA 2009-2011	Cross-sectional Inpatient hospital and medical centre EMUs	vEEG PNES *N*=33 Mean age: 41.8yrs %Female: 78.79	QOLIE-31 Anxiety (BAI); Depression (BDI); Sleep quality (SDQ-SA).	Pearson correlations. Multiple regression.	Lower depression (r = -.77***) and anxiety (r = -.66***) scores were associated with higher HRQoL. Daytime sleepiness and sleep apnoea were not significantly correlated with HRQoL (r = -.04 & r = -.07). Depression was the only predictor of HRQoL (β = -0.85**, R^2 = .55).	2
LaFrance et al. (2011) USA Not reported	Cross-sectional Outpatient neurology clinic	vEEG PNES *N*=45 Mean age: 36.6yrs %Female: 77.8	QOLIE-31 Seizure frequency; Depression (BDI); Family functioning (FAD).	Pearson correlations. Hierarchical regression.	Depressive symptoms negatively correlated with HRQoL (r = -.73**). FAD subscales *roles* and *affective involvement* correlated with HRQoL (r = -.52** & r = -.57**). Depression (ΔR^2 = .46***) and family functioning (ΔR^2 = .18*) were predictors of HRQoL.	1
Mitchell et al. (2012) UK Not reported	Cross-sectional Outpatient neuropsychiatric clinic	vEEG PNES (78%) and PNES+ES (22%) *N*=50 Mean age: 42.0yrs %Female: 70.0	QOLIE-31 Seizure severity (NHS3); Dissociation (DES); Depression (BDI); Anxiety (STAI).	Spearman correlations. Hierarchical regression.	Negative correlation between dissociation and HRQoL (r = -.64***). Higher depressive symptoms (R^2 = .58***) and dissociation scores (ΔR^2 = .14***) predicted HRQoL.	2
Myers et al. (2012) USA 2009-2012	Cross-sectional Outpatient neurology clinic	vEEG PNES *N*=62 Mean age: 40.5yrs %Female: 87.5	QOLIE-31 Personality (MMPI-2); Anger (STAXI-2); Trauma, psychiatric and medical history (interview).	Pearson correlations. Stepwise regression.	Lower HRQoL was associated with somatic complaints (r = -.55***), low positive emotions (r = -.56***), cynicism (r = -.34**), emotional dysfunction (r = -.61***), higher trait (r = -.55**), and state anger (r = -.40**) scores. Cynicism, age at earliest trauma, history of trauma, and trait anger were significant individual predictors of HRQoL.	2

(Table 3 continued)

Strutt et al. (2011) USA Not reported	Cross-sectional Inpatient and outpatient medical settings	vEEG PNES *N*=30 Mean age: 38.9yrs %Female: 100	QOLIE-89 Anxiety (BAI); Depression (BDI); Personality (MMPI-2); Locus of control (MHLC-C); Motivation (TOMM).	Pearson correlations. Logistic regression.	Later age of PNES onset was associated with lower HRQoL (r = -.35**). HRQoL was not significantly correlated with any mood or personality measures.	2
Szaflarski and Hughes et al. (2003)* USA Jan 2001-Jan 2002	Cross-sectional Inpatient EMU	vEEG PNES *N*=40 Mean age: 37.6yrs %Female: 85	QOLIE-89 Mood state (POMS); Adverse events (AEP).	Hierarchical regression.	Seizure-related diagnosis, comorbidities, depression, and medication side effects predicted HRQoL (full model adjusted R^2 = .645).	2
Szaflarski and Szaflarski et al. (2003)* USA Jan 2001-Mar 2002	Cross-sectional Inpatient EMU	vEEG PNES *N*=53 Mean age: 36.0yrs %Female: 77.4	QOLIE-89 Mood disturbance (TMD-from POMS; Adverse events (AEP).	Hierarchical regression.	Mood disturbance and medication side effects predicted HRQoL (full model adjusted R^2 = .616).	2
Szaflarski and Szaflarski (2004)* USA Jan 2001-Jan 2003	Cross-sectional Inpatient EMU	Definite or possible PNES *N*=95 Mean age: 36.3yrs %Female: 81.1	SF-36 Mood state (POMS).	Hierarchical regression.	Seizure-related diagnosis, comorbidities, and depression predicted HRQoL.	2
Testa et al. (2007)* USA Jan 2001-Jan 2003	Cross-sectional Inpatient EMU	vEEG PNES *N*=45 Mean age: 37.4yrs %Female: 68.9	QOLIE-89 Mood disturbance (TMD-from POMS); Personality (MMPI-2).	Hierarchical regression.	Separate regression models found that mood disturbance (full model adjusted R^2 = .548) and personality characteristics (full model adjusted R^2 = .563) were related to HRQoL.	1

Note. *: Shared dataset; AEDs: anti-epileptic drugs; AEP: Adverse events profile; AN(C)OVA: analysis of (co)variance; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CORE-10: Clinical Outcomes in Routine Evaluation 10-items; DES: Dissociative Experiences Scale; DISQ: Dissociation Questionnaire; EMU: Epilepsy Monitoring Unit; ES: epileptic seizures; FAD: Family Assessment Device; MANOVA: Multivariate analysis of variance; MHLC-C: Multidimensional Health Locus of Control, Form-C; MMPI-2: Minnesota Multiphasic Personality Inventory, second edition; NHS3: National Hospital Seizure Severity Scale; PHQ-9/15: Patient Health Questionnaire 9/15; POMS: Profile of Moods States; QOLIE-10/31/89: Quality of Life in Epilepsy Inventory 10/31/89; SCL-90: Symptom Checklist 90-item; SDQ-SA: Sleep-Apnoea Disorders Questionnaire; SF-36: Short-Form Health Survey; STAI: State-Trait Anxiety Inventory; STAXI: State-Trait Anger Expression Inventory; TOMM: Test of Memory Malingering; TMD: Total Mood Disturbance; UCL: Utrecht Coping List; vEEG: video-electroencephalogram; WOC: Ways of Coping Questionnaire.

Figure 1

PRISMA Diagram: Flow chart of the literature search process