Investigating quality of life in adults with epilepsy and psychogenic non-epileptic seizures

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Submitted in partial fulfilment of the requirements for the degree of

Doctorate in Clinical Psychology

Institute of Health and Wellbeing

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University of Glasgow

May 2021

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Foreword

An alternative major research project (Appendix 3) had been identified and planned between October 2018 and March 2020. In March 2020, major disruptions to NHS services occurred because of the COVID-19 pandemic and made the proposed MRP project untenable. Due to restrictions relating to the pandemic (closure of services and restriction on non-essential research) I was unable to proceed with the approvals necessary to commence recruitment within the William Quarrier Scottish Epilepsy Centre. In addition, the centre discharged all patients and halted its services for a significant period. The original project was therefore abandoned. As a result of these changes, and in line with guidance provided by the University of Glasgow, I chose to seek approval for a new project utilising an existing data set. The data provided for this study came from the William Quarrier Scottish Epilepsy Centre, it is a dataset that has not been previously used for research purposes.

Acknowledgements

I would like to say a gracious thank you to my supervisors, Professor Tom McMillan and Dr Iain Campbell for their guidance and support with the planning and completion of this research, especially as it came down to the wire.

To my family, Mom, Dad and my dearest sister Dr Zoe who have offered so much encouragement and support to get to this point, thank you for always believing in me. A special thank you goes to friends, new and old, near and far for their kindness and motivation. Gal groups, run clubs, climbing humans, and least of all flatmates; without you none of this would have been possible.

Chapter 1 Systematic Review

Associates of quality of life in individuals with psychogenic non-epileptic seizures

Prepared in accordance with the author requirements for Epilepsy and Behavior; Appendix 1.

Abstract

Background

Quality of life (QOL) in those who experience psychogenic non-epileptic seizures (PNES) is low compared to individuals with epilepsy and other clinical cohorts. Treatment should aim to improve QOL alongside reducing clinical symptoms as it has been noted that cessation of PNES symptoms does not necessarily improve quality of life significantly. There has been an expansion of the literature with a number of cross-sectional studies focusing on identifying and measuring the associations between various social and psychological factors with QOL in PNES and an updated review is warranted.

Objective

This review aims to examine the available evidence on the various psychological, social and physical factors that contribute to QOL in individuals with PNES in order to guide clinical practice and future research.

Methods

Databases were systematically searched for research published on associates of QOL in individuals with PNES. The Crowe Critical Appraisal Tool Version 1.4 was used to assess the quality of the studies by the author and a subset was examined by a second rater.

Results

Sixteen papers were identified and included. The quality of the articles was judged to be moderate to high. Methodological weaknesses identified were small sample size, failure to use appropriate diagnostic procedures (VEEG) and lack of diversity in sampling methods which largely drew on individuals in tertiary settings, limiting the generalisability of results. Seizure frequency was not found to be associated with QOL. Anxiety, depression and more generic measures of psychological distress account for a significant amount of the variance within QOL. Demographic characteristics of age and gender did not show strong evidence for association with QOL. Social factors appear to be associated with QOL and carer wellbeing has influence on QOL in the PNES

population. There is evidence for the importance of assessing patient QOL and psychological distress as it is a consistent predictor of QOL.

Conclusion

Individuals with PNES are likely to benefit from routine screening of anxiety and depression and offered suitable treatment in line with national guidance on managing anxiety and depression in the wider population, regardless of the setting. Social and carer factors appear to influence QOL and are an area for further research.

Introduction

Psychogenic Non-Epileptic Seizures (PNES) are behavioural events and experiences that typically disrupt consciousness, can cause collapse and/or produce jerking limb and body movements (Hubsch et al., 2011). The descriptive term "Non-Epileptic Seizure" refers to the absence of abnormal, evolving cortical activity that distinguishes PNES from Epileptic seizures. The term "Psychogenic" indicates that these are presumed then to originate from psychological mechanisms. One prominent theory hypothesises that PNES and their behavioural constituents (of which there are many forms) occur following the activation of a "seizure scaffold" and as a dissociative type response to threatening internal or external events (Roberts & Reuber, 2014). PNES is not a formally recognised diagnostic label but the episodes of PNES that many individuals experience often meet the diagnostic criteria of Dissociative Disorder (World Health Organization., 2005) or Conversion Disorder (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force., 2013).

Results from both quantitative and qualitative studies indicate that PNES are typically associated with a negative impact on health and wellbeing (Gregg H. Rawlings, Brown, Stone, & Reuber, 2018). Traditional outcome measures in clinical practice and research have focused on investigator reported impressions, test results or clinical indicators such as frequency, intensity, duration and onset. However, it is becoming increasingly important to acknowledge individual experiences via patient reported outcome measures when measuring the impact of PNES on physical and mental health (Devlin & Appleby, 2010). Measures can be general or disease specific and should aim to gain a representation of the patient's health status directly from the individual, without interpretation by others.

Health related quality of life or quality of life (QOL) as it may also be referred to in the literature is a construct that assesses a patient's physical functioning, emotional status and social well-being (Power et al., 1998). When compared to patients with epileptic seizures and the general population, individuals with PNES consistently report lower QOL (Al Marzooqi, Baker, Reilly, & Salmon, 2004; Myers, Lancman, Laban-Grant, Matzner, & Lancman, 2012; Szaflarski, Hughes, et al., 2003; Testa, Schefft, Szaflarski, Yeh, & Privitera, 2007). Clinical interventions for both epilepsy

and PNES often focus on reduction of seizure frequency. A systematic review by Taylor, Sander, Taylor, and Baker (2011) found that seizure frequency was the most commonly reported predictor of QOL for individuals with epilepsy. Increased seizure frequency was shown to have a negative association with QOL scores in 21 out of 26 studies. In their review, they report the negative predictive effect of increased seizure frequency on QOL appeared to be consistent across anti-epileptic drug managed and refractory populations" (p. 2171). B. Jones, Reuber, and Norman (2016a) conducted a review of QOL in individuals with PNES and found that only two out of six studies found patients with more seizures had significantly lower QOL scores. Other studies in their review found no correlation between QOL and seizure frequency and those that did, became non-significant after controlling for other variables such as depression. As such it appears that seizure reduction is not likely to have a significant impact on QOL for individuals and that as B. Jones et al. (2016a) suggest, interventions for PNES should focus on the myriad of other factors that appear to be associated with QOL.

B. Jones et al. (2016a) suggest that physical symptoms, age of PNES onset and cognitive complaints are correlated with QOL in individuals with PNES. They report finding depression to be the strongest correlate of QOL. Anxiety was found to be significantly associated with QOL in correlation analysis but not within multiple regression with covariates analysis. Dissociation was found to be negatively associated with QOL, and they also report the influence of family members to be a significant association. The authors cite limitations to these results owing to concerns about the methodological quality of the evidence identified. Almost all the studies included in the review employed a cross sectional design (which is not uncommon in PNES research) and none of the studies satisfied all three of the quality appraisal criteria applied by the authors. The quality criteria were (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 to detect a relatively small association (correlation coefficient of .3 at 5% alpha and 90% power). (3) Multivariate analysis (an index of level of confounding risk/variables). Most studies within the review did make some attempt to control for confounding variables by utilizing multiple regression analysis.

A search of the literature revealed no update on the B. Jones et al. (2016a) review. There has been an expansion of the literature with a number of cross-sectional studies focusing on identifying and measuring the associations between various social and psychological factors with QOL in PNES. This update can be used to guide clinical practice in the identification and treatment of factors which are likely to lead to the improvement in QOL in a group of individuals who are reported to have poor QOL and multiple vulnerabilities.

Research Questions:

This review updates B. Jones et al. (2016a) by investigating:

(1) What is the methodological quality of studies researching QOL in PNES?
(2) Are there seizure related or other clinical factors associated with QOL in PNES?
(3) Are there individual demographic factors associated with QOL in PNES?
(4) Are there psychological factors associated with QOL in PNES?
(5) Are there social factors associated with QOL in PNES?

Method

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). Searches of the Cochrane Database of systematic reviews were completed to find previous literature reviews on QOL in PNES. In addition, PROSPERO, the international prospective register of systematic reviews was searched for related reviews. The review protocol was then developed and registered with PROSPERO on 15th February 2021 (registration number: CRD42021234722) accessible at; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234722.

Search Strategy

The search strategy replicates that of B. Jones et al. (2016a), using APA Psyc Articles, APA Psych Info, CINAHL, Medline and Psychology and Behavioral Sciences Collection (OVID Host). EBSCO Host was used to search Chicano. Although three categories of search terms were used by B. Jones et al. (2016a) their third subject was omitted (correlation\predictor research) as this removed relevant papers in the search. The following search terms were employed:

Non-epileptic (seizure*, attack*, episode*, disorder) or psychogenic (seizure*, attack*, episode* non-epileptic) or pseudo (seizure*, attack*, episode*) or "unintended seizure*"

And

"Quality of life" or "Health related quality of life" or "quality of life measures" or HRQOL or QOL or wellbeing or "well-being", "well being"

Search terms were combined using Boolean operators "AND", "OR", "n2" and "n3". Truncations (denoted by an asterisk) were employed to ensure all search terms following the truncation were identified. A manual search of reference lists of the included articles was carried out to identify any further pertinent studies and a manual search on Google Scholar was conducted using key terms and prominent researchers in the field.

Inclusion Criteria were studies published:

(1) in English

(2) in peer reviewed journals

(3) from 1st November 2014 to 31st January 2021

(4) describing original data

(5) including individuals aged 16 years and over with a diagnosis of PNES, probable PNES or co-occurring PNES and epilepsy

(7) with any research design if assessing QOL with a validated tool and reporting an association correlation or regression with any other measured factor

Exclusion criteria were studies:

(1) investigating participants with PNES and co-occurring functional movement disorder or broader somatoform disorder

(2) including individuals below 16 years of age.

Quality Appraisal

The Crowe Critical Appraisal Tool (CCAT) was used to assess the quality of the studies (Crowe, Sheppard, & Campbell, 2011). The tool has good construct validity and inter-rater reliability with an intraclass correlation coefficient of 0.83 for combined research designs (Crowe et al., 2011). There is no specified cut-off score for the CCAT. The tool recommends consideration of individual criteria scores is important to interpretation of quality (Crowe, 2013). Brown and Reuber (2016) outlined four key aspects of study design and four key aspects of sample characteristics that are considered to be important in assessing methodological quality of PNES research. These authors designed a PNES research quality appraisal tool which went through a number of iterations before demonstrating good interrater reliability (Cohen's Kappa) of k=0.73. It has since been used in a number of systematic reviews, but not specifically in the review of QOL associations with PNES. Brown and Reuber's (2016) quality appraisal criteria were utilised within this review to further structure the "Design" and "Sampling" criteria of the CCAT.

Within the "Design" section, specific consideration was given for the following criteria:

1. Video electroencephalography (VEEG) for allocation of participants into PNES groups
2. Consecutive sampling (as opposed to convenience)
3. Standardized outcome measures
4. Matching of participants between groups on age and gender. Matched participants are defined as less than or equal to 5 years difference between mean age and less than or equal to 10% difference in number of females within the groups.

Within the "Sample" section, specific consideration was given for the following criteria:

1. Explicit reference to the exclusion of participants with epilepsy from the PNES sample
2. Explicit reference to the use of a procedure to distinguish PNES from alternative psychiatric diagnosis such as conversion disorder, syncope or anxiety.
3. Explicit reference to the exclusion of PNES from control or epilepsy samples
4. Sample size greater than 26 participants. This was decided as very few studies within the literature conduct power analysis\sample size calculations. Brown and Reuber suggest

rating sample size adequacy with reference to the commonly-used power and effect size conventions suggested by Cohen (1988). Sample sizes for case–control studies with less than 26 participants in each group (i.e., < 80% power to detect a large effect size, d = 0.8, assuming a two-tailed independent t test with alpha = .05) were not awarded a mark.

Incorporating these quality appraisal criteria does not alter the structure or scoring of the CCAT. Rather it provides specific considerations within the existing quality appraisal of design and sample and meets the recommendation that specific attention be paid to individual criteria scores within the tool. Final scores were assigned by way of CCAT scoring. The studies were rated high, moderate, low or very low quality based on arbitrary cut-offs (high: greater than 90%, moderate: 75-89%, low: 60-74%, very low: less than 60%). A second trainee psychologist rated a random subset (n=2) of the studies independently, to ensure appropriate use of the CCAT. Agreement of final scores of the CCAT was moderate as assessed by Cohen's kappa (k= .606, p=<.001). Differences in ratings were resolved via discussion.

Search Results

A total of 1046 articles were initially identified via database searches and a further five through hand search. After duplicates were removed and the remaining titles and abstracts were screened, the eligibility criteria were applied to 111 full articles. A further 95 articles were excluded and the remaining 16 were included in the review (Figure 1). Data was extracted using a tool adapted for this review (Appendix 1.2).

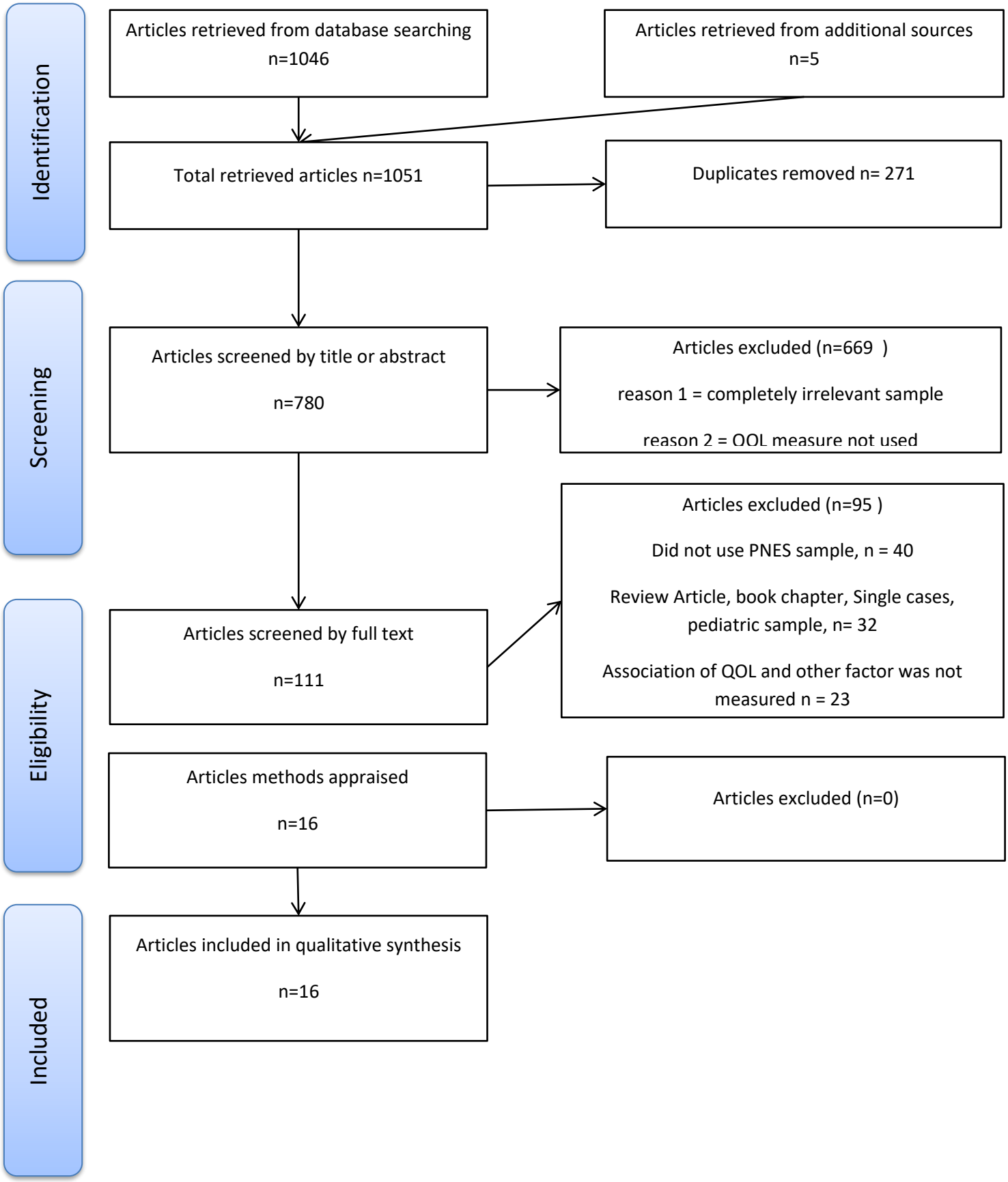

Figure 1. PRISMA Flowchart of the article identification and selection process

Results

Participants and Settings

In total, 1139 people with PNES and 45 Carers of people with PNES were reported across the 16 studies (Table 1). This number excludes studies that reported on overlapping samples (Green, Norman, & Reuber, 2017; Karakis, Janocko, et al., 2020; Karakis, Morton, et al., 2020; Wardrope, Green, Norman, & Reuber, 2019). The mean age of people with PNES across 12 studies was 39, two studies reported median age and were not included in the calculation (Novakova, Howlett, Baker, & Reuber, 2015; G. H. Rawlings, Brown, & Reuber, 2017). Across the studies, 727 participants (64%) were female.

Recruitment of participants across the studies was most frequently from general and specialist neurology settings. This was from Epilepsy Monitoring Units (EMU) in eight studies (Avalos et al., 2020; Boesten, Myers, & Wijnen, 2019; Cohen, Testa, Pritchard, Zhu, & Hopp, 2014; Karakis, Morton, et al., 2020; Latreille, Baslet, Sarkis, Pavlova, & Dworetzky, 2018; Salinsky et al., 2019; Walther et al., 2020; Wolf et al., 2015), neurology outpatient clinics in five studies (Clegg, Sirois, & Reuber, 2019; Gagny et al., 2021; Green et al., 2017; Karakis, Janocko, et al., 2020; Wardrope et al., 2019) and from both EMU and neurology outpatients in one study (Karakis, Janocko, et al., 2020). One further study recruited from a psychology clinic, treating patients referred from tertiary neurology services (Novakova et al., 2015).

The participants recruited from these settings may not be representative of the PNES population as individuals with PNES are also seen in non-specialist settings. Two studies did recruit participants from non-specialist settings; Robson et al. (2018) recruited from online support groups for people with PNES and G. H. Rawlings et al. (2017) recruited from both neurology outpatient clinics and online support groups.

Outcome Measures

Outcome measures in the reviewed studies included the epilepsy specific measures “Quality of Life in Epilepsy” (QOLIE versions 10/31) and “Quality of Life in Newly Diagnosed Epilepsy” (NEWQOL-6D). Two general measures of QOL were also used, the 36 or 12 item Short Form

Health Survey (SF-12/36) and the European Quality of Life–3 Dimensions Scale (EQ-5D-3L). Although these measures are validated and demonstrate good reliability in their intended populations, none have been validated in people with PNES and in fact no PNES specific QOL measures were identified outside of these review articles.

Study Quality

The methodological quality of the studies ranged from 63% to 93%. The majority of studies being rated as moderate or high quality. All studies scored four or five marks on the preliminary and introduction scores, indicating no major threats to quality stemming from these sections. Regarding the ethics section, one study lost marks due to the use of descriptions that could potentially lead to identification of participants (Novakova et al., 2015).

Only half the studies utilised VEEG confirmation of PNES diagnosis (Avalos et al., 2020; Boesten et al., 2019; Cohen et al., 2014; Gagny et al., 2021; Karakis, Morton, et al., 2020; Latreille et al., 2018; Wolf et al., 2015). The use of VEEG is important to the validity of results. One study (Robson et al., 2018) included participants with co-occurring epilepsy and PNES and so results in this study may not be representative of individuals with PNES only or epilepsy only. A further three studies did not indicate exclusion of those with co-occurring diagnoses (Latreille et al., 2018; Novakova et al., 2015 and Gagny et al., 2021). The PNES, epilepsy and control samples across the remaining studies were otherwise well controlled and defined.

All studies utilised consecutive sampling and standardised outcome measures which was a strength. Gagny et al. (2021) only utilised scores from the Overall Quality of Life subscale of the QOLIE-31 which only comprises two questions and note this as a limitation. Two of twelve studies that included comparison groups demonstrated matched groups as per Reuber and Brown (2016) criteria (Latreille et al., 2018; Salinsky et al., 2019). The remaining studies were marked down on this aspect of bias due to having a higher percentage of females in the PNES groups. Two studies reported a priori sample size estimation. Three studies had a low sample size according to the

Brown and Reuber (2017) criterion of n<26 (Green et al., 2017; Walther et al., 2020; Wardrope et al., 2019).

Table 1. Results

Study	Authors, Country, Date	Design, Setting, Sample, Groups, N	QOL outcome measure, Investigated Factors	Bivariate/ Multivariate Analysis conducted	Key results	Effect Size on QOL NS=Not Significant
1	Karakis et al. (2020a) USA September 2016-June 2019	Cross-sectional Epilepsy Monitoring Unit people with PNES *n=43* *Mean Age=36* *Female=33 (77%)* Caregivers of people with PNES *n=28* *Mean Age=43* *Female=17 (61%)*	QOL (QOLIE-31) Caregiver Burden (ZCBI)	Spearman correlation	ZCBI inversely correlated with QOLIE-31 total score (r=-0.69****)	Large

2	Karakis et al. (2020b) USA August 2015-June 2019	Cross-sectional Epilepsy Monitoring Unit and outpatient clinics Sample Characteristics as in Karakis et al. (2020a)	QOL (QOLIE-31) Patient Perceived Stigma (Patient LSS) Carer Perceived Stigma (Carer LSS)	Spearman correlation Stepwise multivariate regression analysis	QOLIE-31 total score was inversely correlated with LSS (r= −0.42**) caregiver stigma (r=−0.8****) Lower QOLIE-31 score predicted higher Patient LSS (partial R^2 =0.18**), it was the only predictor of Patient LSS. Lower patient QOL scores predicted higher carer LSS (partial R^2=0.08, p=0.01)	Medium Large f^2= .2195 Medium f^2= .087 Small
3	Robson et al. (2018), Online Cohort in UK and USA, 1st July - 1st October 2016	Cross-sectional Online Survey people with PNES *n= 141 (included people with co-occurring Epilepsy)* *Mean Age=37* *Female=102*	QOL (QOLIE-31) Perceived Stigma (ESS)	Spearman coefficient The coefficient of determination (r_s^2) was calculated to establish the proportion of shared variance between QoL domains and total stigma score.	QOLIE-31 total score was inversely correlated with: ESS (r_S = - 0.474***). Seizure frequency (r_s = - 0.382, ***). QOLIE-31 – showed Non-significant correlations with: Duration of PNES (r_s = 0.111 ns) Time from onset to diagnosis (r_s = 0.066 ns) Participant's age (r_s = 0.062 ns). ESS was significantly correlated with 5 of the 7 QOLIE-31 subscales: (Weight r) Seizure worry (r_s= -0.479***) Emotional Wellbeing (r_s= -0.421***)	Large Medium Large Medium

		(89%)		Bonferroni-Holm Correction	Social functioning (r_s= -0.407***) Cognitive (r_s= -0.314***) Energy and fatigue (r_s= -0.252**) QOLIE-31 was not significantly correlated with subscales: Medication effects (r_s= -0.146 ns) Overall QOL (r_s= -0.132 ns)	
4	Wardrope et al. (2019) UK July 2014-February 2015	Cross-sectional Neurology Outpatient Clinics people with PNES *N= 23* *Mean Age=38* *Female=19 (83%)* Carers of people with PNES *N= 17* *Mean Age=44*	Patient QOL (QOLIE-10) Carer Anxiety (GAD-7) Carer Depressio n (PHQ-9) Carer QOL (SF-12 subscales for mental and physical well being)	Spearman correlation	Patient QOLIE-10 was correlated with carer SF-12 (Mental Wellbeing subscale) (r= 0.646*) QOLIE-10 total score demonstrated non-significant correlations following holm-Bonferroni correction with: Carer anxiety (r = −0.025 ns) Carer Depression (r= −0.191 ns) Carer physical wellbeing r= −0.162 ns)	Large

		Female=7 (41%)			
5	Green, Norman and Reuber (2017) UK July 2014 - February 2015	Cross-sectional Neurology Outpatient Clinics people with PNES As Wardrope et al. (2019)	QOL (QOLIE-31) Duration and frequency of PNES, Severity (LSSS-3) Depression (PHQ-9), Anxiety (GAD-7), Relationship Quality (QRI) Attachment Style (ASQ-SF)	Pearson correlations	No significant correlations between QOLIE-10 and depression, anxiety, duration or frequency of PNES, relationship quality or attachment styles. Due to non-significant correlation results, no regression analyses were performed for the PNES group data.

6	Gagny, et al (2021) France January 2014 to July 2019	Cross-sectional with multiple time points (24 months) Neurology Outpatient Clinics people with PNES *n=107* *Mean Age=34* *Female=81 (76%)*	QOLIE-31, (French version, one subscale only – overall QOL) QOL (SF-36) Depression (MADRS) Anxiety (HAM-A) Dissociation (DES) Alexithymia (TAS) Trauma History (CQD)	Univariate linear regression analysis Multiple Linear Regression Multivariable logistic regression analysis to estimate predictors of change in QOL.	QOLIE-31 and SF-36 Mental and Physical Subscales not significantly correlated with gender, seizure frequency or associated epilepsy at time of diagnosis. SF-36 (Physical Scale) correlated with: Age at diagnosis, β = -.572*** IQ (β = 0.285 ns). QOLIE-31, SF-36 Mental and Physical Scales were all significantly correlated with: MADRS, All p ≤ 0.001 HAM-A, All p < 0.001 DES, P < 0.005 TAS, p ≤ 0.001 Regression Physical Health was associated with: age at diagnosis (β = -0.429*) IQ value (β = .475**) Mental and Physical SF-36 showed significant association with anxiety (respectively -0.783** and -1.012***) Depression significantly associated with QOLIE-31 (-0.863**) and SF-36 Mental Scale (-0.639*). Significant association between SF-36 and diagnosis of

					PTSD (mental SF-36: β = -13.838**, physical SF-36: β = -8.774*). A negative correlation between SF-36 Mental Scale and emotional abuse (β = -1.071**) but not in physical SF-36 dimension. No relation was found using "overall QoL" dimension of QOLIE-31 with period of life when the trauma occurred. Number of mental health consultation attended was the only significant predictor of change in "overall quality of life" of QOLIE-31 (p = 0.02). The more mental health consultations the individual attended, the greater the QoL appeared with Odds Ratio, 1.041 (CI 95 %, 1.006–1.076) per additional consultation.	
7	Rawlings, Brown & Reuber (2017) UK&USA, October 2015-July 2016	Cross-sectional Neurology Outpatient Clinics and recruitment from UK and US online support groups	QOL (NEWQOL-6D) Anxiety (GAD-7) Depressio n (NDDI-E)	Spearman's rank correlation coefficient Hierarchical Multiple Regression	No significant correlation between NEWQOL-6D and gender, age, education, duration or frequency of seizures. Significant correlation between NEWQOL-6D and: psychological distress (r=-0.58***) anxiety (r=-0.54***) depression (r=-0.54***) and illness perceptions (r=-0.42*).	 Large Large Large Medium

		people with PNES *n=45 Median Age=38 Female=41 (91%)*	Psychological Distress (GAD-7 + NNDI-E) Illness Perceptions (B-IPQ) Seizure frequency and Severity (LSSS-3)		The final model accounted for 61.9% of the variance in NEWQOL-6D scores. At stage one, demographic factors explained 3% (ns, p = 0.53) of the variance at stage two, condition factors (frequency and severity) accounted for a further 10.9% (ns, p=0.1). Psychological distress accounted for 24.8%*** and at stage four, illness perceptions accounted for 23.3%*, with personal control as a significant predictor of HRQOL.	Overall model (f^2=1.62) Large Condition Factors (f^2= .111) Medium Psychological distress (f^2= .329) Large Illness Perceptions (f^2= .303) Large
8	Avalos et al. (2020) Argentina 2017-2019	Cross-sectional Video-EEG Monitoring Unit people with PNES *n= 39 Mean Age=34 Female=34 (87%*	QOL (QOLIE- 31 Spanish) Anxiety and Depression (HADS, Spanish)	Pearson correlation coefficient Simple linear regression	A significant negative correlation between depression and QOL (r = −0.66****, r^2=0.43). A significant correlation was found between QOL and anxiety (r = −0.63****, r^2=0.40)	Large Large

9	Wolf et al (2015) USA July 2011-December 2013	Cross-sectional Epilepsy Monitoring Unit people with PNES *n=85* *Mean Age=42* *Female=56 (66%)*	QOL (QOLIE-31) Alexithymia (TAS) Somatization (PAI - somatic subscale)	Regression Mediators of the relationship between diagnosis and QOL Interactions between variables that affected QOL	QOLIE-31 was significantly correlated with: PNES diagnosis (r = -.21**) Alexithymia (r=-.39***) Somatization (r=-.64***) Abuse (r =-.13 ns) Trauma (r= -.18 ns) Alexithymia significantly predicted lower quality of life β =−.30*** CI (−.43,−.17). Across combined PNES and Epilepsy groups. Diagnosis did not predict the direct effect on quality of life, β =−2.63 (NS. p=.11) CI (−5.85, .58). In the model of somatization, diagnosis did not predict quality of life directly, β = .80 (ns, p = .61) CI (−2.27, 3.86). Diagnosis was associated with greater somatization in PNES group β = 8.82*** CI (4.73, 12.90). A one-point increase in SOM significantly decreased quality of life by .46 points, β = −.46*** CI (−.57, −.35). The total indirect effect of SOM as a mediator between diagnosis and quality of life was significant, point estimate β = −4.08, CI (–6.35,	Small Medium Large

					−2.23) indicating that SOM significantly mediated the relationship between diagnosis and quality of life.	
10	Novakova, Howlett, Baker & Reuber (2015) UK Study Approved May 2009	Cross sectional, PNES post-diagnostic psychology clinic people with PNES *n=55* *Median Age=39* *Female=47 (86%)*	QOL (SF-36 Physical Health Scale and Mental Health Scale) Psychological distress (CORE-10) Common mental disorders (PHQ-9) Illness Perceptions (BIPQ) Emotional Processing (EPS)	Spearman's correlational analyses	The SF-36 mental health Scale was correlated with all the measures: EPS (r= -.702**), PHQ-15 (r= -.478**), CORE-10 (r= -0.89**) BIPQ (r= -.697**). The SF-36 Physical Health Scale was significantly correlated with: PHQ-15 (r= -.476**) BIPQ (r=-0.442, p<0.01) but not significantly correlated with: EPS (r= 0.088 ns) CORE-10 (r=-0.085 ns) The SF-36 Mental Health Scale and Physical Health Scale were not significantly correlated (r=0.031 ns)	 Large Medium Large Large Medium Medium NS NS NS

11	Clegg et al. (2019) UK July-December 2019	Cross-sectional Outpatient appointments people with PNES *n= 46* *Mean Age=41* *Female=35 (76%)*	QOL (EQ-5D-3L) Self-Compassion (SCS-SF)	Bivariate Correlations	There was no significant correlation between Self Compassion and QOL in people with PNES (r= 0.18, p>0.05).	NS
12	Boesten, Myers and Wijnen (2019) USA, 2008-2018	Cross-sectional Epilepsy Monitoring Unit people with PNES and Trauma *n = 148* *Mean Age=39* *Female=127 (86%)*	QOL (QOLIE-31) Trauma (TSI, and TSI-2 used in later years of data collection)	Multivariate analysis of covariance (MANCOVA) between the different variables Partial Eta Squared for the proportion of variance accounted for by the trauma indicator (i.e., whether trauma	Traumatized patients on average scored lower than the non- traumatized group on the QOLIE-31 total score and Energy sub score. MANCOVA indicated a significant difference for age (p= .001) and years of education (p= .001) and not sex (p = .321) indicating poorer QOLIE-31p scores with older age and less education.	

		people with PNES No Trauma *n= 69 Mean Age=38 Female=54 (78%)*		was present or not based on self-reported data of the patients).		
13	Salinsky et al (2019), USA, Data collected over a 3-year period	Cross-sectional Epilepsy Monitoring Unit Veterans with PNES *n= 73 Mean Age=46 Female=19 (26%)*	QOL (QOLIE-31) PTSD Checklist. Depression (BDI-II), Psychiatric Diagnosis (SCID-1 &2) Personality Inventory (MMPI-II-rf)	Spearman Correlation Biserial Correlation for categorical variables Nested Multivariate Regression change-in-estimate strategy.	In veterans with PNES, QOLIE-31 scores were significantly correlated with: Employment (r= 0.32**) Years of Seizures (r=0.29**) BDI-II (r=-0.72***) PTSD Checklist (r= -0.57***) Number of axis I diagnoses (r= -0.35**) MMPI-2RF RC1 (r=-0.55***). QOLIE-31 Score was not significantly associated with age at admission, age of seizure onset, gender, education, driving ability, receipt of disability allowance, any military factors or seizure related factors (deployment, combat, years in service, combat experience scale) or the presence of any Axis II diagnoses. In the final regression Model, adjusted $r^2 = 0.65$	Medium Small Large Large Medium Large f^2=1.857 Large

					Significant predictors of QOLIE-31 were. Driving (adjusted r^2= 0.17*) BDI-II (adjusted r^2= =-0.58***) MMPI-2 RC1 (adjusted r^2= 0.29**) Age at admission, years of education, employment, number of seizures, years of seizures, PTSD Checklist, number of axis I diagnoses, and presence of axis II diagnoses were not significant predictors of QOLIE-31.	f^2=.204 Medium f^2=1.381 Large f^2=.408 Large
14	Cohen et al 2014 USA 2006 to 2013	Cross-sectional Epilepsy Monitoring Unit people with PNES *n= 46* *Mean Age=42* *Female=40 (86%)*	QOL (SF-12) QOL (LORIG) Dissociative Experiences (DES)	Regression	QOL measures only accounted for 1.2% and 5% of the variance in dissociative experiences scores. Compared to 83.3% accounted for by all the variables (BSI, BAI, BDI-II, Lorig Self-Efficacy Scale, LOT, MHLOC and MA).	

15	Latreille et al (2018) USA 3/25/2013 and 3/29/2018	Cross-sectional Epilepsy Monitoring Unit and Ambulatory Epilepsy Clinic for people with epilepsy people with PNES *n= 149* *Mean Age=38* *Female=130 (87%)*	QOL (QOLIE-31) Sleep Quality (BDI -Item 16 only)	Spearman correlation	There was a significant positive correlation between QOLIE-31 Total score and Item 16 of the BDI-II (r=0.61****) All three subscales of the QOLIE-10 correlated with BDI-II Item 16: Epilepsy effect (r= 0.33****) Mental health function (r=0.69****) Role functioning (r=0.51****)	Large Medium Large Large
16	Walther et al (2020) Germany Between 2000 and 2016	Retrospective follow-up of cross-sectional study Epilepsy Centre (telephone calls)	QOL (QOLIE-31) Depression (BDI-ii)	Logistic regression w Multiple Linear Regression (Enter Method	In the group of patients with persisting PNES, QOLIE-31 was not correlated with frequency of attacks (r=-0.27 ns) QOLIE-31 score at follow-up was associated with: Presence of PNES (β = -2.23*) depressive symptoms (β = -0.09***) economic activity (β = 1.21*) having a partner (β = 0.13 ns)	

	people with PNES cessation (minimum one year) *n= 23 Mean Age=35 Female=16(70%)* People with Persisting PNES *n= 47 Mean Age=44 Female=36(77%)*		

Notes for Table: ASQ= Attachment Style Questionnaire; BAI= Beck Anxiety Inventory, BDI= Beck Depression Inventory, B-IPQ = Brief Illness Perception Questionnaire; BSI-18= Brief Symptom Inventory – 18; CORE-10 = Clinical Outcome in Routine Evaluation, DES= Dissociative Experiences Scale; ESP-25 = Emotional Processing Scale-25; ESS= Epilepsy Stigma Scale, EQ-5D-3L = European Quality of Life – 3 Dimensions Scale, GAD-7 = Generalized Anxiety Disorder –7; LOT = Life Orientation Test; LAEP = Liverpool Adverse Events Profile; LSES = Lorig Self-Efficiency Scale; LSS= Liverpool Stigma Scale, LSSS = Liverpool Seizure Scale – Revised; MHLOC= Multidimensional Health Locus of Control; MA = Mutuality Assessment; NDDI-E = neurological disorder depression inventory for epilepsy, NEWQOL-6D = quality of life in newly diagnosed epilepsy; PHQ-9 = Patient Health Questionnaire – 9, PAI= Personality Assessment InventoryPHQ-15 = Patient Health Questionnaire – 15; PTSD-C = Post-Traumatic Symptoms Checklist; QOLIE-10 = Quality

of Life in Epilepsy –10; QOLIE-31 = Quality of Life in Epilepsy, QRI = Quality of Relationships Inventory; SCS-SF = Self compassion scale short form; SF-12 = 12 Item Short Form Health Survey, SF-36 =36-Item Short Form Health Survey, TSI -2 = Trauma Symptom Inventory - 2; TAS = 20- Item Toronto Alexithymia Scale; ZCBI = Zarit Caregiver Burden Inventory.

*p<0.05

**p<0.01

***p<0.001

****p<0.0001

ns=non-significant

Table 2. CCAT Scores

Title	Preliminaries /5	Introduction /5	Design /5	Sampling /5	Data Collection /5	Ethics /5	Results /5	Discussion /5	Total /40	Total %
Karakis et al. (2020a)	5	5	5	3	3	5	4	4	34	85
Karakis et al. (2020b)	5	5	4	3	3	5	4	5	34	85
Robson et al. (2018)	5	5	3	3	3	5	4	5	33	83
Wardrope et al. (2019)	5	5	3	2	3	5	2	5	30	75
Green et al (2017)	5	5	3	2	3	5	2	3	28	70
Gagny et al (2021	4	5	2	2	2	4	2	3	24	65
Rawlings et al. (2017)	5	5	3	3	4	5	4	5	34	85
Alvalos et al. (2020)	5	5	4	3	4	5	4	4	34	85
Wolf et al. (2015)	5	5	4	4	4	5	5	5	37	93
Novakova et al. (2015)	4	4	3	2	2	3	4	3	25	63
Clegg et al. (2019)	5	5	3	4	3	4	4	4	32	80

Boesten et al. (2019)	5	5	4	4	4	5	4	5	36	90
Salinsky et al. (2019)	4	5	3	4	4	5	4	4	33	83
Cohen et al. (2014)	4	3	3	3	2	4	3	3	25	63
Latreille et al. (2018)	5	4	2	3	3	3	4	4	28	70
Walther et al. (2020)	5	5	3	3	4	5	4	4	33	83

Is seizure frequency associated with QOL in PNES?

The studies reporting on seizure frequency were generally of moderate quality. There was no association found between seizure frequency and QOL (Gagny et al., 2021; Green et al., 2017; G. H. Rawlings et al., 2017; Salinsky et al., 2019; Walther et al., 2020). Only one study reported a weak correlation between seizure frequency and QOL (Robson et al., 2018). QOL was lower in a group of individuals with persisting PNES compared to those with PNES cessation; however the quality of this study was impaired due to small sample size.

Are demographic factors associated with QOL in PNES?

Studies looking at demographic factors were of high quality. Most studies reporting relationships between age and QoL reported no effect (G. H. Rawlings et al., 2017; Robson, Myers, Pretorius, Lian, & Reuber, 2018; Salinsky et al., 2019). Older age at the time of receiving a PNES diagnosis was associated with higher QoL in one study (Boesten et al., 2019), but not in two other studies (Gagny et al., 2021; Salinsky et al., 2019). No relationship between gender and QoL was reported (Gagny et al., 2021; Rawlings, Brown & Reuber, 2017; Salinsky et al., 2019).

Higher IQ on the WAIS-III was associated with better QOL (Gagny et al., 2021). Lower level of education was associated with a poorer QOL score in one (Boesten et al., 2019) of three studies (Rawlings, Brown & Reuber, 2017; Salinsky et al., 2019). QOL significantly correlated with employment status in veterans with PNES (Salinsky et al., 2017) and the wider adult population with PNES (Robson et al., 2018; Walther et al., 2020). The ability to drive was correlated with QOL but significance did not hold in comparison to anxiety and depression which appear to account for more variance in QOL (Salinsky et al., 2019).

Are psychological factors associates with QOL in PNES?

Quality of the studies investigating the associations between psychological factors and QOL were generally of moderate quality. Large correlations between anxiety and QOL were found (Avalos et al., 2020; G. H. Rawlings et al., 2017) and anxiety accounted for a significant proportion of the variance in QOL (Avalos et al., 2020; Gagny et al., 2021; Rawlings et al., 2017). Depression was correlated with QOL (Gagny et al., 2021; Novakova et al., 2015; G. H. Rawlings et al., 2017; Salinsky et al., 2019; Walther et al., 2020). Higher depression scores on

a range of different self-report measures predicted lower QOL, accounting for between 43% and 58% of the variance in QOL scores (Gagny et al., 2021; Salinsky et al., 2018; Walther et al 2019; Wolf et al., 2015). Depression was the highest predictor of QOL when compared to other factors (Salinsky et al., 2018).

Psychological distress, a metric created by adding scores of anxiety and depression measures together was correlated with QOL and a significant predictor of QOL, accounting for 25% of the variance (Rawlings et al. (2017). The CORE-10, a standardized measure of psychological distress was also correlated with QOL (Novakova et al. 2015).

QOL was not significantly associated with alexithymia scores in a regression model (Gagny et al., 2021). Alexithymia significantly predicted lower QOL in a sample of participants that combined people with epilepsy and people with PNES (Wolf et al., 2015). Illness perceptions were significantly correlated with QOL (Novakova et al., 2015; Rawlings et al., 2017) and accounted for 23% of the variance in QOL scores (G. H. Rawlings et al., 2017). There was no evidence of an association between attachment style and QOL (Green et al., 2017) or self-compassion and QOL (Clegg et al., 2019).

Dissociative experiences were correlated with QOL (Gagny et al., 2021; Cohen et al., 2014), but they were not predictive of QOL in multiple regression analysis (Cohen et al., 2014). In regard to these findings, not all individuals with PNES experience dissociative symptoms. Within Cohen et al. (2014) only 8 participants scored above the cut-off (>30) indicative of dissociative experiences. The methodological quality of these two studies were low owing to sampling and data collection methods.

Somatisation, or the tendency to experience unexplained medical symptoms was correlated with QOL and accounted for a significant proportion of variance (Salinsky et al., 2019; Wolf et al., 2015). Wolf et al. (2015) reported somatisation to be a mediator between diagnosis (PNES vs Epilepsy) and QOL, suggesting a strong effect of somatisation on the QOL of patients with PNES compared with patients with epilepsy. This was a study of high quality.

A history of emotional abuse was associated with QOL (Gagny et al., 2021). In a comparison of people with PNES who reported trauma and those who did not, traumatized participants on average scored lower on the QOLIE-31psub scales, indicating poorer QOL compared with the non- traumatized group (Boesten et al., 2019).

Poor sleep quality was correlated with lower QOL (Latreille et al., 2018). The quality of this study was negatively affected by the outcome measures selected for use. Sleep quality was assessed by one question on the BDI-II only.

Are social factors associated with QOL?

The quality of studies investigating the association of social factors and QOL were of variable quality; with several studies being marked down on sample size. Higher ratings of patient and carer perceived stigma were correlated with lower QOL, demonstrating medium to large correlations (Karakis, Janocko, et al., 2020; Robson et al., 2018). Higher self-reported caregiver burden (Karakis, Morton, et al., 2020) and lower caregiver QOL (Wardrope et al., 2019) was correlated with lower patient QOL.

Discussion

A wide range of psychological, demographic, seizure related, and social factors have been considered in recent research, and this highlights the complexity in assessing and caring for people with PNES. The studies reviewed were generally of good quality however not consistent in their use of outcome measures across studies. There were a vast number of unique factors investigated by the studies indicating the complexity and range of needs within the population.

Main Findings

Seizure frequency was not found to be associated with QOL; none of the studies looked at seizure reduction within their samples but associations between the number of seizures and QOL at one timepoint were not significant. Previously it has been suggested that for patients to benefit from seizure reduction, complete seizure cessation needs to occur. This is hypothesised as individuals may experience the negative impact of seizures on day-to-day

QOL with a small or large number of seizures. The negative consequences do not diminish unless seizures are eradicated completely (W. C. LaFrance, Jr., Syc, LaFrance, & Syc, 2009). Anxiety, depression and more generic measures of psychological distress were associated with QOL. These psychological factors consistently demonstrate high associations and account for a significant amount of the variance within QOL. Although the majority of research is conducted within specialist centres high levels of anxiety and depression were also demonstrated in samples drawn from online forums. The association with psychological distress further indicates why eradication of seizures in and of themselves may not improve QOL. Individuals with PNES report high levels of distress (Brown & Reuber, 2016) and it appears reducing this stress may have a positive impact on QOL.

Demographic characteristics of age and gender did not show strong evidence for association with QOL. There was some evidence for the association between being in education or employment and better QOL, even across distinct populations as in veterans and civilians. This indicates the potential utility of a multi-professional approach and perhaps indication for occupational therapy work from professionals in this population.

Psychological factors dissociation, somatisation, emotional abuse and trauma have been given consideration within the literature and the quality of studies was generally high. However, there is a paucity of research in these areas to make clinical recommendations and again a psychological formulation approach may be of benefit to working with patients in the absence of wider recommendations.

Social factors have been indicated to be associated with QOL and the role of carers is important within this population. The reviewed literature indicates potential association of caregiver burden and carer mental health with QOL in people with PNES. Patient and carer perceived stigma may also be associated with patient QOL. Due to the use of correlational analyses directionality cannot be determined, however social factors and relationships with care givers are likely to be important in the treatment of individuals with PNES.

These results are in line with the results reported by the previous review by Jones et al., (2016). There is a variation in study quality reported in the previous review. Jones et al., (2016)

noted that none of the studies satisfied all three appraisal quality criteria. The present review assessed studies on a wider range of criteria and with a standardized tool. The study quality of the present review was generally higher than that of the previous. Jones et al noted an average sample of n=45, whereas the average sample size of the 16 studies included in this review is n=71, further indicating a potential increase in the predictive power of these studies. However, post hoc power calculations have not been calculated within the present review.

This review adds to the understanding of the multitude of factors that can impact on the QOL of people with PNES. The results indicate depression and more generally psychological distress accounts for a large proportion of the variance within QOL scores. Jones et al reported only on correlations between anxiety and QOL, whereas in the present review anxiety accounted for a significant amount of the variance within QOL. Hence, more recent evidence indicates the relative importance of both depression and anxiety in the context of other factors explored. This can be contrasted with the relative unimportance of seizure frequency on QOL in people with PNES. This indicates the importance of identifying and managing symptoms of both anxiety and depression in the population.

The present review also highlights the importance of care giver mental health for quality of life for people with PNES. Jones et al. (2016) found an influence of family members on patient QOL. They found unsupportive family environments characterised by criticism and lack of interest correlated with lower QOL. A number of the studies within the present review focus on the importance of caregiver QOL and shared experience of stigmatisation on patient QOL. These results add an important concept to the literature and can focus future research with carers and family members to better understand the shared impact of difficulties on both patient and caregiver in a non-blaming atmosphere.

Moving forward from the Jones et al. (2016) there has been a considerable advance in the number and quality of studies investigating QOL in PNES. Given the continued identification of various factors and evolution of the understanding of PNES it is reasonable to suggest that an educated approach that considers the literature base coupled with patient centred care and individual psychological formulation is warranted in providing intervention to promote wellbeing and QOL in the population.

Strengths and Limitations

This review used a standardised quality appraisal tool and incorporated specific criteria relevant to the research, but this does not eliminate subjectivity of the results and possible bias. Only two studies were appraised by a second rater, meaning that there may be rater bias or unreliability. Furthermore, only one rater screened potential studies which may have resulted in missed relevant papers. Data extraction was completed by only one rater and therefore there is potential for inaccuracy to be present. The search was limited to English language studies however there may be relevant papers from other countries further limiting the scope of the results.

Clinical implications and future research

There is evidence for the importance of assessing QOL as a patient reported outcome measure and indication that this should be associated with assessment and management of psychological distress as it is a consistent predictor of QOL. Symptoms of anxiety, depression and QOL can overlap, which may account for some of the association. Using a patient centred approach to identify the most salient symptoms and difficulties within an individual is likely to be of benefit. Clinical approaches to improve patient QOL and wellbeing should acknowledge the wide range of factors identified within the literature coupled with a psychological formulation tailored to the individual. Patients with complex presentations can prioritise symptoms and identify goals for therapy within this approach.

Psychological therapies, including psychoeducation and input from the wider MDT is indicated in this complex and vulnerable population. Traditionally focus has been placed on the impact of trauma and abuse within PNES. While this may remain appropriate for a large proportion of individuals there is indication that a range of other factors are associated with QOL. Depression and anxiety commonly co-occur with the experience of previous trauma. These symptoms can be approached in the early stages or separate to trauma interventions and at may be of more relevance to individual who do not consider trauma relevant to their presentations of PNES.

There are currently no PNES specific measures of QOL; this creates difficulty in synthesising research in the population and means that the currently used tool may lack validity and

reliability in this complex population. Development of PNES specific measures would be beneficial and this has been noted by previous reviews.

Individuals with PNES and co-occurring epilepsy are largely absent within these studies. This group of individuals, although many in number tend to be excluded from cohort studies in an effort to boost methodological rigour and reduce heterogeneity of samples. Given that co-occurring epilepsy and PNES is a common presentation, future research should focus on this group to determine if QOL is affected by similar factors. These individuals should not be disadvantaged in terms of understanding QOL and clinical benefit from interventions at the benefit of other groups.

Conclusion

Individuals with PNES are likely to benefit from routine screening of anxiety and depression and offered suitable treatment in line with national guidance on managing anxiety and depression in the wider population, regardless of the setting. Individuals managed primarily by community or within GP settings may also benefit from screening and intervention.

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Chapter 2 Major Research Project

Establishing predictors of quality of life in adults with epilepsy and psychogenic non-epileptic seizures

Prepared in accordance with the author requirements for Epilepsy and Behavior. Appendix 1.1

Plain Language Summary

Title

Investigating quality of life in adults with epilepsy and psychogenic non-epileptic seizures

Background

Psychogenic non-epileptic seizures (PNES) are attacks that disrupt a person's ability to respond and can affect their level of consciousness. PNES are often linked to psychological distress and present behaviourally in a similar way to epilepsy but lack the abnormal brain activity associated with epilepsy. They are thought to result from an involuntary mechanism activated by the brain and body to deal with psychological distress. People with epilepsy and people with PNES often face challenges with physical and mental health. Seizures can be disruptive, distressing and can cause individuals to lose out on social, educational or work opportunities. As a result, many people who have seizures report many aspects of their day to day living are affected and they have a poor quality of life (QOL). One way to help people with seizures is to try and reduce the number of seizures they experience. This can be through use of medication for epileptic seizures or through education and psychological therapy for PNES. More recently clinicians have focused on exploring how else to help improve a person's QOL other than seizure reduction.

Aims and Questions

This study focused on exploring what other things affect QOL in people who experience epilepsy and PNES.

1. Do people with PNES report lower QOL than patients with Epilepsy?
2. What is associated with a person's QOL? Specifically, between the relationship with psychological distress, cognitive problems (like memory and concentration), sleep quality and QOL.
3. Does QOL improve following specialist input, assessment and diagnosis at the Scottish Epilepsy Centre (SEC)? If there is improvement, are changes in other outcomes associated with that improvement?

Methods

Routine data collected from individuals attending the SEC from March 1st 2019 to March 31st 2020 was analysed. No additional data beyond that already collected by the SEC for clinical purposes was collected. Individuals were approached as part of their admission process to the SEC. Individuals experiencing seizures and PNES were included in the analysis and formed two separate groups. Individuals with a diagnosed cognitive impairment including learning disability were excluded.

Main Findings and Conclusions

People with PNES or epilepsy rated themselves as having difficulties in QoL on a day to day basis and there was no difference in the QOL scores between the two groups. The level of psychological distress in people with epilepsy and PNES predicts how good a person's QOL is. People with high levels of psychological distress (anxiety and depression) have a lower QOL and those with lower levels of psychological distress have higher QOL. People with PNES and people with epilepsy report that their sleep quality is poor. It appears that sleep quality is linked to QOL in people with epilepsy but not for those with PNES. Cognition scores appear to predict QOL in people with PNES but not people with epilepsy.

It appears that reducing anxiety and depression or psychological distress is likely to have a positive impact on QOL for both groups of individuals. The evidence regarding the importance of sleep and cognition on QOL is limited within this study although further research may help indicate if these factors are important across both groups. Of course, if individuals feel that any of the above factors are having an impact on their QOL it is important to address this with professionals regardless of the research as each individual can have a different experience.

Abstract

Objective

This longitudinal study examined QOL in individuals with psychogenic non-epileptic seizures (PNES) and epilepsy and investigated factors associated with QOL and change in QOL from admission to discharge at a specialist epilepsy centre.

Methods

Fifty-five patients with epilepsy and 23 patients with PNES who attended the William Quarrier Scottish Epilepsy Centre (SEC) between March 1st 2019 and March 31st 2020 were included. Participants completed self-report measures in the week prior to or on the day of their admission to the SEC and again on the day of discharge.

Results

There was no significant difference between QOL scores in the PNES and epilepsy groups. Psychological distress at admission was found to be a significant predictor of QOL scores (at admission). In the epilepsy group, psychological distress accounted for 37.1% of the variance in QOLIE-31 admission scores in model one (p<.0001). Sleep Condition Indicator scores (SCI) (p=.001) and cognition scores as measured by the EpiTrack cognitive assessment (p=.167) accounted for a further 16.9% of the variance (p=.003) in model two. EpiTrack scores did not contribute significantly to the variance associated with QOLIE-31 scores. In the PNES group psychological distress accounted for 30.5% of the variance in QOLIE-31 admission scores in model one (p=.014). SCI (p=.605) and EpiTrack scores (p=.003) accounted for a further 31.5% of the variance in model two (p=.011). SCI scores did not contribute significantly to the variance associated with QOLIE-31.

QOL was improved at discharge in the PNES group (t(17) = -4.187; p=0.001), psychological distress change scores accounted for 56.6% of the variance in QOLIE-31 change scores in model one (p <.0001). QOL was also improved at discharge in the epilepsy group (t(35) = -5.875, P=0.001), psychological distress change scores accounted for 59.4% of the variance in QOLIE-31 change scores in model one. In model two of both groups, the SCI scores and EpiTrack scores did not contribute to the variance associated with QOL change scores.

Conclusion

Psychological distress is a good predictor of QOL in both patient groups. Assessment and management of anxiety and depression symptoms in both groups may enhance QOL. SCI scores made a significant contribution to the variance in QOL in the epilepsy group and EpiTrack Scores made a significant contribution to the QOL scores in the PNES group. Future research may examine the effect of sleep strategies on QOL scores and study the effect of change in cognitive scores following AED reduction on QOL.

Keywords: PNES, Psychogenic Non Epileptic Seizure, Epilepsy, Quality of Life

Introduction

Individuals with epilepsy and psychogenic non epileptic seizures (PNES) have been shown to have reduced QOL compared to other clinical populations (Al Marzooqi et al., 2004). Individuals with PNES consistently report poorer quality of life than individuals with epilepsy (Myers et al., 2012; Szaflarski, Szaflarski, et al., 2003; Testa et al., 2007). Patients with PNES have high levels of disability (Jennum, Ibsen, & Kjellberg, 2019) and outcomes in this group are relatively poor (S. G. Jones et al., 2010; Markus Reuber et al., 2003).

Studies on clinical outcomes in people with PNES and people with epilepsy have focused on reducing seizure frequency and severity. More recently there has been recognition of the impact of complex physical and mental health comorbidities and wider social/socio-economic factors and their impact on individuals. There have been a wide range of factors studied in attempts to determine the most significant associates of QOL in people with PNES.

Chapter one of this thesis, a systematic review found that seizure frequency was not associated with QOL. Anxiety, depression and psychological distress were associated with QOL and consistently account for a significant amount of the variance within QOL within the literature. The majority of research reviewed was conducted within specialist centres, however high levels of anxiety and depression were also demonstrated in samples drawn from online forums. This research suggests the importance of identifying psychological distress in individuals with PNES.

Other clinical factors, such as difficulty achieving correct diagnosis may impact on QOL. Difficulties in distinguishing between epilepsy and PNES outside of dedicated facilities can result in the misdiagnosis of PNES as epilepsy and individuals can wait an average of 7 years before receiving the correct diagnosis (M. Reuber, Fernández, Bauer, Helmstaedter, & Elger, 2002). At the point of correct diagnosis individuals and those in their social networks including families, friends, teachers or colleagues may have experienced years of conceptualising their symptoms as epilepsy resulting from brain abnormalities. Some patients can be reluctant to accept the diagnosis of PNES and view it as invalidating or confusing (Stone et al., 2003; Thompson, Isaac, Rowse, Tooth, & Reuber, 2009). Inappropriate treatment with anti epileptic

medication can produce unwanted side effects whilst having no clinical value in reducing PNES (S. G. Jones et al., 2010).

High levels of psychiatric comorbidity including depression, anxiety, post-traumatic stress and personality disorders are common in people with PNES and typically at a level greater than that of individuals with epilepsy and those in the general population (Diprose, Sundram, & Menkes, 2016). A systematic review by B. Jones, Reuber, and Norman (2016b) investigated correlates of QOL in individuals with PNES. Depressive symptoms correlated most highly. They also found that dissociation, somatic symptoms, escape-avoidance coping strategies, and family dysfunction were associated with QOL. Interestingly there was little support for an association between QOL, seizure frequency, and demographic factors. Johnstone, Malpas, Velakoulis, Kwan, and O'Brien (2021) report that psychiatric symptoms, depression and cognition were greater determinants of QOL than seizure frequency in people with PNES.

Cognitive impairment has been associated with reduced QOL in people with epilepsy (Giovagnoli & Avanzini, 2000; Giovagnoli et al., 2014) and whilst cognitive complaints are common in people with PNES, there is variability in research findings from studies investigating objective cognitive deficit in PNES (Willment, Hill, Baslet, & Loring, 2015). Cognitive impairment can be cause by a number of factors including structural abnormalities and neurodegenerative causes, psychiatric comorbidity (most notably depression) or sleep difficulties amongst others.

Sleep disturbance in people with PNES has been noted both subjectively by patient report measures and there is emerging evidence that sleep architecture may be altered in people with PNES (Vanek et al., 2021). Previous research on the association between self-reported sleep scores and QOL is sparse but one recent study in a small sample of people with PNES (n=15) found no direct correlation between sleep scores and QOL (Erickson et al., 2019). QOL in people with PNES may be increased by making improvements to sleep hygiene and treatment of sleep difficulties in this group.

A recent review by Asadi-Pooya et al. (2021) reported on the importance of attachments, marriage, social networking, stigma and education or employment in determining the QOL of

people with PNES . Individuals with PNES in Scotland have previously been reported to experience high levels of multiple deprivation (Duncan, Oto, & Wainman-Lefley, 2012). It is possible that living in circumstances with high deprivation has a negative effect on the symptoms of PNES, mental health and social supports.

Present Study

This project assesses associations between QOL and psychological symptoms, sleep quality and cognition in individuals with PNES or epilepsy using routine outcome data from inpatient admissions to the William Quarrier Scottish Epilepsy Centre (SEC). Various terms are used to describe seizure episodes not caused by abnormal brain activity. “Psychogenic Non-Epileptic Seizures” was used within the present study in correspondence with the terminology of the service where the study took place.

Research Questions:

1. Do patients with PNES report lower QOL than patients with Epilepsy?
2. What factors are associated with QOL? Do psychological, cognitive or sleep condition measures predict QOL?
3. Does patient reported QOL improve following specialist input, assessment and diagnosis?
4. If improvement in QOL does occur during admission, are changes in other outcomes associated with that improvement? Can QOL improvement be predicted by other factors?

Methods

Design

A retrospective cohort study, using routinely collected data from inpatients attending the SEC.

Ethical Approval

Research and Innovation approval for the study was granted by NHS Greater Glasgow & Clyde Health Board (GN20NE586, Appendix 2.1). Ethical approval was granted by the SEC Governance Committee (Appendix 2.2). NHS Scotland Research Ethics committee advised

application was not necessary as data were collected as part of routine processes within the SEC and were anonymised prior to being supplied to the researcher (Appendix 2.3). The University of Glasgow Medical, Veterinary and Life Sciences Ethics committee advised Ethical approval granted by the SEC was sufficient and duplication not required (Appendix 2.4).

Recruitment

Patients attending the SEC are routinely asked for their data to be used for research and/or audit on admission. Data on consecutive patients who consented and were routinely admitted to the SEC between 1st of March 2019 to 31st March 2020 was analysed.

Setting

The SEC is a national epilepsy monitoring unit for Scotland, located in Glasgow. Individuals are typically referred by the NHS to the SEC in order to: clarify diagnosis and understand the nature of seizures; record physiological and behavioural data during seizures**;** assess how seizures affect health and life**;** assess how factors in an individual's life influence their seizures and health**;** assess if seizures and illness affect an individual's mood and memory**;** make changes to treatment and medications and/or receive individual advice and support to help individuals live with epilepsy and PNES. Professionals within the centre endeavour to provide a concrete diagnosis, however due to the inherent difficulty in differentiating between PNES and epilepsy, some individuals may be discharged with an "uncertain" diagnosis.

Participants

Patients are referred from all over Scotland and some from Northern Ireland. Typically, individuals are admitted for 4 weeks, but stays from between 2 and 6 weeks are not uncommon.

Inclusion Criteria: Participants were adult inpatients (aged 16 and over), with a confirmed diagnosis of epilepsy or PNES at the time of discharge from the SEC, and fluent in English.

Exclusion Criteria: Patients who did not give consent for data to be used or those with a known moderate to severe cognitive impairment, including if resulting from learning disability or

acquired brain injury were excluded. Participants with co-occurring PNES and Epilepsy or those with uncertain diagnosis at discharge were excluded.

Diagnosis

The discharge diagnosis was made by the lead Consultant Neurologist, Neuropsychiatrist or Neurophysiologist within the SEC, involved in the patients' care. Diagnosis was based on Video Electroencephalography (EEG) monitoring in most cases. If no episodes were captured during admission, diagnosis was based on prior eyewitness description of typical events, or from video footage of typical events. Diagnoses were: "Epilepsy", "PNES", "Co-occurring PNES and Epilepsy" or "Unclear Diagnosis". "Unclear Diagnosis" included those with uncertainty within their presentation. For example, those with a confirmed diagnosis of Epilepsy but diagnostic uncertainty about the presence of co-occurring PNES or vice-versa.

Outcome Measures

Outcome measures were administered at admission and discharge. Participants were sent self-report measures prior to admission and asked to complete them in the week leading up to admission. In some cases, patients completed the measures during the first few days of admission. Cognitive screens were completed at both time points by a clinical psychologist or senior nurses under the supervision of a clinical psychologist.

Quality of Life

Quality of Life in Epilepsy (QOLIE-10/10-P/31/89; (Cramer et al., 1998)): The most commonly used tool in studies on prediction of QOL in patients with PNES (B. Jones et al., 2016b). The QOLIE-31 comprises 31 items rated on various Likert scales. The questionnaire asks patients to estimate quality of life and how they feel. It measures QOL across the domains of seizure worry, overall quality of life, emotional well-being, fatigue, cognition, medication effects, and social functioning. A weighted total QOL score is generated, and higher scores represent better QOL. The QOLIE-31 has high reliability and validity among adults with confirmed epilepsy (Devinsky et al., 1995). When used with participants with PNES the questionnaire is adapted by changing "Epilepsy" to "Seizures". Saadi, Patenaude, and Mateen (2016) estimated the worldwide QOLIE-31 average score to be 60 (range 42-82) in individuals with epilepsy.

Anxiety

Generalized Anxiety Disorder- 7 (GAD-7, (Spitzer, Kroenke, Williams, & Löwe, 2006)): This widely used screening tool for anxiety comprises 7 items with responses rated on a four-item Likert scale. Scores 5-9, 10-14 and 15 or over indicate mild, moderate and severe anxiety, respectively. The measure asks participants to consider how often they have been bothered by anxiety-related problems over the past two weeks. The GAD-7 has been validated in French patients with epilepsy and comorbid GAD and has satisfactory internal consistency (Cronbach's alpha=0.89, Micoulaud-Franchi et al., 2016). It has been used in patients with PNES (Chen et al., 2014). In primary care populations it has good psychometric properties (Cronbach's alpha=0.92; (Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007)).

Depression

Neurological Disorders Depression Inventory for Epilepsy (NDDI-E): This screening tool for major depression comprises 6 items, with responses rated on a four-point scale. Higher scores indicate a greater number of depressive symptoms. The NDDI-E is validated in patients with epilepsy and has satisfactory internal consistency (Cronbach's alpha=0.82, (Gilliam et al., 2006)). For a UK population the ideal cut-off is >15, resulting in 87% specificity and 81% sensitivity against DSM-IV major depression (Mula et al., 2016). Factor analysis of French patients with Epilepsy showed that the GAD-7 and the NDDI-E provide complementary information (Micoulaud-Franchi et al., 2016), and these authors recommend the routine use of both GAD-7 and NDDI-E in the clinical evaluation of patients with epilepsy.

Sleep Quality

Sleep Condition Indicator (SCI; Espie et al. (2014)): This eight-item screening measure for insomnia covers concerns about getting to sleep, remaining asleep, sleep quality, daytime personal functioning, daytime performance, duration of sleep problem, nights per week having a sleep problem, and extent troubled by poor sleep. Items are scored on a 5-point scale, with higher scores indicative of better sleep. Scores ≤ 16 are indicative of probable insomnia disorder. It has robust internal consistency (Cronbach's $\alpha \geq 0.86$).

Cognition

EpiTrack (Lutz & Helmstaedter, 2005): This brief screening tool assesses effects of antiepileptic drugs (AEDs) on cognition. It has been validated in patients with epilepsy but is relevant for patients with PNES who frequently prescribed AEDs prior to PNES diagnosis are. It includes six subtests assessing attention, cognitive tracking, and working memory via the Trail-Making Test (parts A and B), a test of response inhibition and motor speed, digit span backwards, written word fluency, and a maze test. EpiTrack subtest scores range from 1 to 7, with lower scores indicating poorer performance. EpiTrack total scores ≥29 indicate unimpaired performance, 26-28 are borderline and ≤25, impaired cognitive performance. The EpiTrack has satisfactory internal consistency (Cronbach's $\alpha = 0.750$) in "normal" adults. The tool has built in scoring structure to control for the effect of age on cognitive functioning.

Deprivation

Scottish Index of Multiple Deprivation (SIMD, 2020). This is a national statistics publication for Scotland. It ranks 6,976 geographical areas within Scotland on the basis of postcode. Ranks take into account income, employment, education, health, access to services, crime and housing. Ranks can be divided into vigintiles with 1, the most deprived and 20, the least deprived (SIMD Results, Scottish Government 2020).

Power and Sample Size

W. Curt LaFrance, Jr. et al. (2011) and Karakis et al. (2014) found large effect sizes when comparing QOLIE-31 scores with the Beck Depression Inventory (r=-0.73 and r=-0.77 respectively). Large correlations have been demonstrated between QOLIE-31 and the Beck Anxiety Inventory (BAI) (r= -0.66; (Karakis et al., 2014). Using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) it is estimated that n=13 is required to detect a large effect (r= 0.70) with 80% power, $\alpha = 0.05$, using correlation, two-tailed. To detect a medium effect (r=0.40) with 80% power and $\alpha = 0.05$, an n of 46 is needed again using two-tailed correlation.

Previous research using multiple linear regression analysis of QOLIE-31 scores with BDI as a predictor produced $r^2 = 0.58$ (Mitchell, Ali, & Cavanna, 2012) and multiple linear regression of QOLIE-31 scores with self-report of anxiety from the Hospital Anxiety and Depression Scale

as a predictor, demonstrated, $r^2 = 0.40$ (Avalos et al., 2020). Using G*Power (Faul et al., 2009) a sample size of 30 participants would be required to detect a large effect (f^2=0.66), with power of 80%, α= 0.05 using multiple linear regression (r^2-deviation from zero) with seven predictor variables specified. To detect a medium effect (f^2=0.31), α= 0.05, in a model with seven predictor variables, n=54 would be required. All potential participants (n=144) were considered because there could be many exclusions due to co-occurring diagnoses, learning disability and missing data. A minimum of 50 participants in each group was aimed for.

Statistical Analysis Plan

Data were analysed using IBM SPSS Statistics version 27 for Microsoft Windows. Pairwise deletion of missing data was employed throughout. Variables were checked for normality using the Kolmogorov-Smirnov (K-S) test. The significance level $p<0.05$ was used across all analyses., Corrections for multiple comparisons of t-tests and correlation analyses were not applied. This decision was taken as the outcome variables from the SCI and EpiTrack scores have not been investigated extensively in previous literature and can be viewed here as exploratory analysis. Interpretation is carried out with caution in light of this.

Differences between groups

Independent samples t-tests, Mann-Whitney U and Chi-Square test were employed to check for differences in demographic information and outcome measures of the two groups.

Correlation between QOLIE-31 admission scores and outcome measures

Correlation analysis was conducted separately for the epilepsy and PNES groups. Pearson Product Moment correlations (r) were used for normally distributed data and Spearman Rank correlations (r_s) were used for data with non-normal distribution.

Hierarchical Multiple Regression of QOLIE-31 admission scores with correlated outcome measures as independent variables.

Only variables that were significantly correlated ($p<0.05$) with QOLIE-31 admission scores were entered into the regression. In accordance with previous studies investigating the predictive value of social, psychological and clinical factors on QOL, psychological outcome

measures (anxiety and depression) were entered before cognitive and sleep measures, using the enter method. (G. H. Rawlings et al., 2017; Rizou, De Gucht, Papavasiliou, & Maes, 2015).

Change in QOLIE-31 and other outcome measures from admission to discharge

Within samples t-tests and Wilcoxon Signed Rank tests were used to measure change across admission.

Regression of change in QOLIE-31 scores

A new variable "QOLIE-31 Change Score" (QOLCS) was calculated by subtracting QOLIE-31 admission scores from QOLIE-31 discharge scores for each participant. This method was used to create Change Scores (CS) for each of the outcome measures. Normality of these variables was assessed as per the above protocol and K-S testing. Pearson and Spearman correlations were used to examine associations between the QOL-CS and GAD-7-CS, NDDI-E-CS, SCI-CS and EpiTrack-CS. Hierarchical multiple regression was conducted with QOL-CS as the dependent variable and any significantly correlated outcome measures entered into the model as per the previous method.

Data Screening

The data set provided by the SEC consisted of 144 participants, the following participants were excluded from analysis: 24 participants with learning disability, one participant discharged before diagnosis, two participants whose primary diagnosis was not epilepsy or PNES, nine participants who did not complete outcome measures, 16 participants diagnosed with co-occurring epilepsy and PNES and 14 participants with no final diagnosis at discharge. Of the 78 remaining participants included in the analysis, 55 (70%) had a discharge diagnosis of epilepsy and 23 (29%) had a discharge diagnosis of PNES.

Results

Missing values throughout the dataset resulted in varying numbers across the statistical analyses; n values are reported within all accompanying tables. The smallest sample size available within the analyses of the PNES group was 18 and the largest was 23, in the epilepsy group the smallest was 43 and the largest was 55.

Kolmogorov-Smirnov analysis indicated that several variables, were not normally distributed. In the epilepsy group these were Length of Admission, age, NDDI-E discharge, GAD-7 (admission and discharge), EpiTrack (admission and discharge), QOL-CS, NDDI-E-CS and EpiTrack-CS. In the PNES group these were SIMD, EpiTrack Discharge, NDDI-E-CS, SCI-CS and EpiTrack-CS. (see Appendix 2.5).

Age, gender and SIMD were not included in the regression model because they did not significantly correlate with QOLIE-31 (in either diagnostic group). GAD-7 and NDDI-E were entered in step one of the regressions followed by SCI and EpiTrack scores at step two. GAD-7 and NDDI-E admission scores were highly correlated in both epilepsy (rho = .658, p= 0.0000001) and PNES (r = .525, p=0.01) groups and results from multicollinearity diagnostics of the regression model (Appendix 2.6) indicated collinearity of GAD-7 and NDDI-E, in both groups. In line with previous research a new variable termed "Psychological Distress" (PD) was created by combining the scores of these two measures (Rawlings & Reuber, 2017). The equation used in the present study was PD Admission = (z-scores NDDI-E admission + z-scores GAD-7 admission) and PD Discharge = (z-scores NDDI-E discharge + z-scores GAD-7 discharge). Psychological distress was then employed as an independent variable within the regression of QOL for both groups and results displayed within the results section. Results for the regression using GAD-7 and NDDI-E can be found in Appendix 2.7.

Demographics in PNES vs. Epilepsy Groups

The demographic and psychological profile of participants with epilepsy and PNES are shown in Table 1. There were no significant differences between groups in age, gender or length of admission. SIMD vigintile scores were lower in the PNES group (median 2) than in the epilepsy group (median 8), (U=292.00, p=0.002; effect size r = 0.36). This indicates participants in the PNES group were living in more deprived areas of Scotland. The SIMD vigintile of 2 is in the 6^{th} to 10^{th} percentiles of Scotland's data zones while the epilepsy group (Vigintile 8) were living in areas falling within the 36^{th} to 40^{th} percentiles.

Research Question 1. Do PNES and Epilepsy groups differ on QOL or other outcome measures? QOL scores in the PNES (M= 31.11, SD= 12.47) and the epilepsy groups (M=32, SD= 14.87) were not significantly different (p=.807). GAD-7 scores in the PNES (Median=15) and epilepsy groups (Median=16) indicate severe anxiety and mean NDDI-E scores indicate major depression (PNES, M= 18; epilepsy, M=17). Both groups scored within the range of probable insomnia on the SCI (PNES, Median= 11; epilepsy, Median=15). PNES scores on the EpiTrack were within the unimpaired range (Median= 29) and in the impaired range in the epilepsy group (Median=27) at admission, indicating a clinical difference.

At admission, there was no significant difference between any of the outcome variables in the two groups (p>0.05, Table 1). Levene's test showed that the variances for SCI scores at admission were not equal and did not meet the assumption of homogeneity of variance. Analysis for SCI was therefore conducted with a non-parametric Mann-Whitney U test.

Table 1. Differences in demographic and psychological variables (at admission) between groups, Mean (SD) or Median (IQR)[1] and [N].

	Epilepsy [55]	**PNES [23]**	***P* value**	**Test statistic**
Demographic Variables				
Female	67% [37]	44% [10]	0.05	3.83 (Chi-Square)
Age (years)[1]	37 (27-45) [55]	40 (26-52) [23]	0.41	707 (MWU)
SIMD Vigintile Score[1]	8 (3-11) [52]	2 (1-6) [21]	0.002	292 (MWU)
Admission Length (days)[1]	21 (14-28) [55]	21 (14-28) [23]	0.93	625 (MWU)
Psychological Variables (at admission)				
QOLIE-31	32 (14.87) [50]	31 (12.47) [22]	0.81	2.45 (T-Test)
GAD-7[1]	15 (10-19) [52]	16 (9-18) [23]	0.78	573 (MWU)
NDDI-E	18 (3.94) [52]	17 (4.26) [23]	0.49	0.69 (T-Test)
EpiTrack[1]	27 (19.75-33.25) [46]	29 (26-34) [20]	0.18	555.50 (MWU)
SCI[1]	15 (7.25-22.75) [52]	11 (7-15) [23]	0.07	443 (MWU)

PNES=Psychogenic non-epileptic seizures, SIMD=Scottish index of Multiple deprivation, QOLIE-31=Quality of life in epilepsy-31, GAD-7=Generalised anxiety disorder – 7, NDDI-E=Neurological Disorders Depression Inventory, SCI=Sleep condition index, MWU= Mann Whitney U

Research Question 2. What factors are associated with QOL?

Age and SIMD scores were not significantly associated with QOL in either group (table 2). Gender was not significantly associated with QOLIE-31 scores in the epilepsy group as indicated by the QOLIE-31 scores of males (M=31.44, SD = 16.53) and females (M=32.26, SD = 14.30) in the epilepsy group t(48)=-.18, p=.858. In the PNES group the QOLIE-31 scores of males (M=26.11, SD = 9.75) was significantly lower than females (M=37.11, SD = 13.15) , t(20)=-2.251, p=.04.

Higher anxiety on the GAD-7 (p <.0001), higher depression on the NDDI-E (p<.0001) and higher insomnia on the SCI (p<.0001) was associated with lower QOL in the epilepsy group with large effect sizes. In the PNES group higher anxiety scores on the GAD-7 (p=.007) were associated with lower QOL scores and higher cognitive scores on the EpiTrack (p=.003) were associated with higher QOL scores, both with large effect sizes (table 2).

Table 2. Correlations between QOLIE-31 scores and outcome measures at admission in epilepsy and PNES groups [N].

	Age	**SIMD**	**NDDI-E**	**GAD-7**	**EpiTrack**	**SCI**
Epilepsy Group QOLIE-31	-.134[1] p= .35 [50]	-.118[2] p=.41 [47]	-.524[2] p <0.0001 [50]	-.598[1] p <0.0001 [50]	.107[1] p =.50 [42]	.516[2] p <0.0001 [50]
PNES Group QOLIE-31	-.256[2] p =.25 [22]	-.392[1] p =.09 [20]	-.397[2] p =.083 [20]	-.562[2] p= .007 [22]	.644[1] p =.003 [19]	.416[2] p =.055 [22]

[1]Spearman Correlation; [2]Pearson Correlation, PNES=Psychogenic non-epileptic seizures, SIMD=Scottish index of Multiple deprivation, QOLIE-31=Quality of life in epilepsy-31, GAD-7=Generalised anxiety disorder – 7, NDDI-E= Neurological Disorders Depression Inventory, SCI=Sleep condition index

Do psychological, cognitive or sleep condition measures predict QOL in PNES or Epilepsy groups?

A linear regression with QOLIE-31 admission scores as dependent variable, and psychological distress, SCI and EpiTrack scores as dependent variables was conducted. The regression model met assumptions for multiple linear regression (appendix 2.8). In the epilepsy group, psychological distress accounted for 37.1% of the variance in QOLIE-31 admission scores in model one (unadjusted r^2, $p<.0001$). Together SCI (β =.395, p=.001) and EpiTrack (β =.156, p=.167) scores accounted for a further 16.9% of the variance (unadjusted r^2, p=.003) in model two. EpiTrack scores did not contribute significantly to the variance associated with QOL. The final model accounted for 54% of the variance in QOLIE-31 scores (unadjusted r^2, $p<.0001$).

In the PNES group psychological distress accounted for 30.5% of the variance in QOLIE-31 admission scores in model one (unadjusted r^2, p=.014). SCI (standardised β = -.126, p=.605) and EpiTrack scores (standardised β = .575, p=.003) accounted for a further 31.5% of the variance in model two (unadjusted r^2, p=.011). SCI scores did not contribute significantly to the variance associated with QOL. The final model accounted for 62% of the variance (unadjusted r^2, p=.002) in QOLIE-31 scores (Table 3).

Table 3. Summary of hierarchical multiple regression analysis for variables predicting QOLIE-31 admission scores in Epilepsy or PNES groups.

Discharge Diagnosis		N	R	R^2	Adjusted R^2	F	Sig.	Change Statistics			Coefficients		
								R Square Change	F Change	Sig. F Change	Unstandardized B (CI 95%)	β	Sig.
Epilepsy Group	**Model 1**		.609	.371	.355	23.596	<.0001	.371	23.596	<.0001	32.344 (28.615 – 36.072)		<.0001
	PD	52									-4.884 (-6.916 – -2.852)	-.609	< .0001
	Model 2		.735	.540	.504	14.863	<.0001	.169	6.973	.003	15.005 (2.109 – 28.001)		.024
	PD	52									-4.223 (-6.069 – -2.377)	-0.527	< .0001
	EpiTrack	46									.293 (-.129 – .721)	.156	.167
	SCI	52									.624 (.261 – .986)	.395	.001
PNES Group	**Model 1**		.553	.305	.264	7.472	.014	.305	7.427	.014	30.489 (25.292 – 35.685)		<.0001
	PD	21									-3.784 (-6.704 – -.863)	-.553	.014
	Model 2		.787	.620	.544	8.161	.002	.315	6.214	.011	-4.570 (-28.847 – 19.707)		.694
	PD	21									-3.880 (-7.318 – -.443)	-.567	.029
	EpiTrack	20									1.298 (.513 – 2.084)	.575	.003
	SCI	23									-.267 (-1.347 – .813)	-.126	.605

PD=Psychological Distress, PNES=Psychogenic non-epileptic seizures, SIMD=Scottish index of Multiple deprivation, QOLIE-31=Quality of life in epilepsy-31, GAD-7=Generalised anxiety disorder – 7, NDDI-E=Neurological Disorders Depression Inventory, SCI=Sleep condition index

Research Question 3. Does patient reported QOL improve following specialist input, assessment and diagnosis?

PNES group: Mean QOLIE-31 scores were higher at discharge with a large effect size (t(17) = -4.187; p=0.001). Mean GAD-7 (t(19) = 2.415, p=0.026) and NDDI-E (t(18) = 1.968, p=0.064) were lower at discharge, showing moderate effect sizes. SCI (t(19) = -.754, p=.460) and EpiTrack (z= -1.286, p=.199) scores were higher at discharge showing small effect sizes but were not statistically significant (table 4).

Table 4. Comparison of admission and discharge scores within the PNES Group, Mean (SD) or Median (IQR)[1] [N] and Cohen's D effect size.

	Admission Scores	**Discharge Scores**	**p-VALUE**	**Effect Size**
QOLIE-31 [18]	33.09 (12.44)	50.83 (19.94)	<.001	.99
NDDI-E [19]	17.32 (4.41)	14.53 (4.16)	.06	.45
GAD-7 [20]	13.45 (5.72)	9.40 (6.46)	.03	.54
SCI[1] [20]	11 (7-15)	13 (10-19.50)	.46	.17
EpiTrack[1] [19]	29.50 (26 - 34)	34.00 (30 -35)	.20	.30

QOLIE-31=Quality of life in epilepsy-31, GAD-7=Generalised anxiety disorder – 7, NDDI-E=Neurological Disorders Depression Inventory, SCI=Sleep condition index

Epilepsy group: QOLIE-31 (t(35) = -5.875, P=0.001), EpiTrack (z= -3.44, p<0.001) and SCI scores (t(42) = -2.930, p 0.01,) were significantly higher at discharge. NDDI-E (z=-4.80, p< 0.00001) and GAD-7 (z= -4.80, p<0.00001) scores were significantly lower at discharge (Table 5). Effect sizes were moderate to large throughout. Graphical representations of the changes in scores are displayed in figures 2-5.

Table 5. Comparison of admission and discharge scores within the Epilepsy Group, Mean (SD) or Median (IQR)[1] [N] and Cohen's D effect size.

	Admission Scores	**Discharge Scores**	**p-value**	**Effect Size**
QOLIE-31 [36]	29.53 (14.93)	49.11 (19.87)	<.001	.98
NDDI-E[1] [45]	18 (16 - 21.75)	15 (10 - 18)	<.001	.72
GAD-7[1] [45]	15 (10 - 19)	8 (3-15)	<.001	.72
SCI[1] [43]	15.00 (7.25-22.75)	18.50 (11.25-25.75)	.005	.45
EpiTrack[1] [39]	27.50 (19.75 - 33.25)	29 (22.5 - 34)	<.001	.55

QOLIE-31= Quality of life in epilepsy-31, GAD-7= Generalised anxiety disorder – 7, NDDI-E= Neurological Disorders Depression Inventory, SCI= Sleep condition index

Research Question 4. If improvement in QOL does occur during admission, are changes in other outcomes associated with that improvement? Can QOL improvement be predicted by other factors?

A linear regression of QOLIE-31 scores was carried out with psychological distress change scores in model one and SCI and EpiTrack change scores added in model two (enter method). The regression met the assumptions for multiple linear regression. In the epilepsy group, psychological distress change scores accounted for 59.4% (unadjusted r^2) of the variance in QOLIE-31 change scores in model one. The final model accounted for 60.2% (unadjusted r^2) of the variance in QOLIE-31 change scores, however the change in model two was not significant (p=.77) the SCI scores (standardised β = .097, p=.479) and EpiTrack scores (standardised β = -.022, p=.865) did not contribute significantly to the variance associated with QOL change scores.

In the PNES group psychological distress change scores accounted for 56.6% of the variance in QOLIE-31 change scores in model one (unadjusted r^2, p <.0001). The final model accounted for 57.7% of the variance in QOLIE-31 change scores, however the change in model two was not significant (unadjusted r^2, p=.845) the SCI change scores (Standardised β = -.044, p=.865) and EpiTrack change scores (standardised β = .123, p=.70) did not contribute significantly to the variance associated with change in QOL (table 6).

What variables are associated with QOL discharge scores?

An additional linear regression was conducted to examine the predictive value of SCI and EpiTrack discharge scores on QOL scores at discharge. QOL at discharge was entered as the dependent variable, with psychological distress, SCI and EpiTrack discharge scores as the independent variables. The same protocol was used as in the previous regression analyses. Psychological distress score at discharge accounts for a significant proportion of the variance in QOL in model one of the epilepsy group ($t(30) = -7.079$, $p<.0001$) and model one of the PNES group ($t(16) = -5.480$, $p<.0001$). In the epilepsy group EpiTrack (Standardised $\beta = .079$, $p=.498$) and SCI (standardised $\beta = .156$, $p=.222$) did not significantly contribute to variance associated with QOL scores. In the PNES group the SCI (standardised $\beta = .462$, $p=.008$) scores contributed significantly to the variance associated with QOL scores in model 2, but EpiTrack (standardised $\beta = .189$, $p=.177$) scores did not (table 7)

Table 6. Summary of hierarchical multiple regression analysis for variables predicting change in QOLIE-31 scores between admission and discharge in Epilepsy or PNES groups

Discharge Diagnosis		n	R	R^2	Adjusted R^2	F	Sig.	Change Statistics			Coefficients		
								R^2 Change	F Change	Sig. F Change	Unstandardized B (CI 95%)	β	Sig.
Epilepsy Group	**Model 1**		.771	.594	.579	39.449	<.0001	.594	39.449	<.0001	17.528 (12.538 – 22.518)		<.0001
	PD-CS	36									-7.939 (-10.532 – 5.345)	-.771	<.0001
	Model 2		.776	.602	.55	12.607	<.0001	.008	.263	.77	16.993 (10.774 – 23.213)		<.0001
	PD-CS	36									-7.587 (-10.449 – -4.724)	-.736	<.0001
	EpiTrack-CS	39									-.121 (-1.569 – 1.327)	-.022	.865
	SCI-CS	43									.213 (-.397 – .823)	.097	.479
PNES Group	**Model 1**		.752	.566	.537	19.528	<.0001	.566	19.528	<.0001	20.437 (13.978 – 26.895)		<.0001
	PD-CS	18									-5.379 (-7.973 – -2.784)	-.752	<.001
	Model 2		.759	.577	.479	5.903	.009	.011	.171	.845	19.722 (11.655 – 27.788)		<.001
	PD-CS	18									-5.177 (-9.133 – -1.221)	-.724	.014
	EpiTrack-CS	19									.444 (-1.202 – 2.091)	.123	.70
	SCI-CS	20									-.090 (-1.207 – 1.027)	-.044	.865

PD -CS=Psychological Distress Change Score, EpiTrack -CS=EpiTrack Change Score, SCI-CS =Sleep Condition Indicator Change Score, PNES=Psychogenic non-epileptic seizures

Table 7. Summary of hierarchical multiple regression analysis for variables predicting QOLIE-31 discharge scores Epilepsy or PNES groups

Discharge Diagnosis		n	R	R^2	Adjusted R^2	F	Sig.	Change Statistics			Coefficients		
								R^2 Change	F Change	Sig. F Change	Unstandardized B (CI 95%)	β	Sig.
Epilepsy Group	**Model 1**		.796	.633	.621	50.107	<.0001	.633	50.107	<.0001	48.253 (43.805 – 52.701)		<.0001
	PD	47									-8.020 (-10.337 – -5.703)	-.796	<.0001
	Model 2		.811	.657	.619	17.239	<.0001	.024	.928	.407	34.911(11.381 – 58.442)		.005
	PD	47									-7.464 -10.035 – 4.892)	-.741	<.0001
	EpiTrack	41									.221 (-.440 – .881)	.079	.498
	SCI	44									.385 (-.246 – 1.017)	.156	.222
PNES Group	**Model 1**		.817	.667	.645	30.036	<.0001	.667	30.036	<.0001	52.328 (46.158 – 58.498)		<.0001
	PD	18									-9.562 (-13.281– 5.843)	-.817	<.0001
	Model 2		.915	.838	.801	22.417	<.0001	.171	6.864	.009	16.559 (-11.937 –45.055)		.231
	PD	18									-4.927 (-8.846 – 1.008)	-.421	.018
	EpiTrack	19									.581 (-.298 – 1.461)	.189	.177
	SCI-CS	20									1.241 (.379 – 2.102)	.462	.008

PD -CS=Psychological Distress Change Score, EpiTrack -CS=EpiTrack Change Score, SCI-CS=Sleep Condition Indicator Change Score, PNES=Psychogenic non-epileptic seizures

Discussion

Main findings

There was no difference in QOL, anxiety or depression scores in the two groups. In previous studies people with PNES reported lower QOL and scored higher on measures of psychopathology than people with epilepsy (G. H. Rawlings et al., 2017; Testa et al., 2007). It is possible that the high levels of symptoms in both groups reflect the complexity of the population served by the SEC, which may account for the difference with previous research findings.

Psychological distress was the best predictor of QOL at admission and discharge in both groups with large effect sizes. This is in concordance with previous research (G. H. Rawlings et al., 2017), including a previous review (B. Jones et al., 2016b). In the PNES group, change in psychological distress was significantly associated with change in QOL, a one unit decrease in psychological distress was associated with 7.9 points increase in QOLIE-31 score in model 1. Symptoms were significantly reduced on all measures and QOL improved at the time of discharge in the epilepsy group. At discharge, QOL improved, and anxiety symptoms reduced in the PNES group.

Insomnia scores predicted QOL in the epilepsy group at admission, but not in the PNES group. Only the change in insomnia scores was predictive of change in QOL score and this was only in the PNES group. Previous research in the area is limited but can be compared with one study that found no correlation between sleep and QOL in people with PNES (Erickson et al., 2019).

Cognition scores were associated with QOL in the PNES group at admission. . Cognitive scores improved across admission in both groups (although not statistically significant in the PNES group) and it appears that the change in score meant the measure was no longer associated with QOL at discharge. This compares with recent research that found cognitive scores were a significant predictor of QOL in people with PNES (Johnstone et al., 2021). In this study participants were assessed on a cognitive screening test during their admission and not at two time points as in the present study.

Clinical Significance

The improvement in anxiety and depression at discharge were clinically meaningful. Within both groups, the average score on the NDDI-E went from above the cut off for major depression to below the cut-off. GAD-7 scores of the PNES group reduced from moderate anxiety to mild anxiety and epilepsy group scores reduced from severe anxiety to mild anxiety. It should be noted that these changes occurred in the context of an inpatient stay; where the ward environment could have a positive or negative impact that may not translate beyond their admission. Follow-up post discharge would allow for disambiguation.

The SEC is a specialist centre providing patients with high standards of care, facilities and knowledge. It is possible that changes in scores reflect the beneficial role of admission to the SEC. Further examination of the component parts of admissions would allow for an understanding on what is impacting on psychological distress, sleep and cognition and ultimately bringing about improvements in QoL.

Standard protocol following PNES diagnosis is cessation of AEDs which can be associated with an increase in cognition scores (depending on AED). Depression is known to have an effect on cognitive functioning; thus, it is possible the change in psychological distress scores seen in both groups across admission could account for some of the variation in cognitive scores.

Strengths and Limitations

Multiple time points within the design allowed for investigation of change. The use of a control group would improve the design of the study however this would be difficult in practice. Following exclusions and pairwise comparisons, the final sample did not reach the predicted sample sizes in all analyses. The study may be underpowered to detect differences. It is unknown whether the missing data points are from a subset of participants with differences to the sampled population. These individuals represent a unique cohort of patients referred for specialist treatment. The sample is representative of individuals with PNES and epilepsy with high care needs but may not be representative of individuals who are diagnosed with PNES and epilepsy within general neurology settings.

The outcome measures are widely used in PNES samples however the QOLIE-31 has not been validated within PNES samples. This is a limitation with PNES research across the field. Although attempts were made to base diagnosis on EEG data, for some individuals there were no captured seizure events and diagnosis was made on eyewitness description of typical events. Therefore, there may be inaccuracies in the discharge diagnosis and confounding of PNES and epilepsy groups.

Clinical Implications

Clinical implications of the present study indicate screening and management of anxiety and depression is indicated for individuals with PNES and epilepsy. This should be reflected in care pathways of across all levels, not only in specialist services. Dissemination of this via guidelines and best practice could improve practice and awareness of the importance of addressing these issues.

A person centred, psychological formulation of difficulties, including the development and maintaining factors of PNES episodes and their relationship with psychological distress would be pertinent to address the needs of individuals. This could be aimed at integrating the experience of anxiety and depression with the onset of PNES and building an understanding of whether low mood or anxiety precipitate PNES events or vice versa. Building an individual's knowledge of their own difficulties through a formulation-based approach can empower people to make change and engage in treatment pathways. A formulation approach in the context of MDT working can aid individuals to engage with team members.

The high prevalence of psychopathology, sleep disturbance and poor comparative QOL in both groups indicates a need for MDT intervention, which is already indicated within SIGN guidelines for epilepsy. No such guidelines exist for PNES management and it would be pertinent for this to be included in screening and management recommendations. Clear and structured pathways within healthcare systems to address these widespread difficulties in both populations are needed. These data taken together with previous research may be useful to consider in the development of guidelines for the management of PNES within the UK.

Future research to examine the stability of changes in QOL, psychological distress, sleep and cognition following admission is recommended. Insomnia appears to be present across both groups and further research to indicate whether this can be modified via sleep intervention would be indicated. The present study excluded individuals with co-occurring PNES and epilepsy and those with learning disabilities. These individuals are often excluded from research to control for confounding effects. Future research into the associates of QOL in these groups is recommended.

Conclusions

It appears that interventions to improve anxiety, depression and sleep may benefit QOL. Sleep and cognitive scores account for a small proportion of the variance in QOL scores and further research is warranted to develop the understanding of the relationship between sleep and QOL and to further investigate the causes of poor self-rated sleep-in individuals with PNES.

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Appendices: Chapter 1

Appendix 1.1 Submission guidelines for Epilepsy and Behavior

EPILEPSY & BEHAVIOR

AUTHOR INFORMATION PACK

Epilepsy & Behavior is the fastest-growing international journal uniquely devoted to the rapid dissemination of the most current information available on the behavioral aspects of seizures and epilepsy.

Epilepsy & Behavior presents original peer-reviewed articles based on laboratory and clinical research. Topics are drawn from a variety of fields, including clinical neurology, neurosurgery, neuropsychiatry, neuropsychology, neurophysiology, neuropharmacology, and neuroimaging.

GUIDE FOR AUTHORS

INTRODUCTION

Epilepsy & Behavior has been, and still is, the fastest-growing international journal since its launch in 2000. Epilepsy & Behavior is uniquely devoted to the rapid dissemination of the most current information available on the behavioral aspects of seizures and epilepsy.
Epilepsy & Behavior presents original peer-reviewed articles based on laboratory and clinical research. Topics are drawn from a variety of fields, including clinical neurology, neurosurgery, neuropsychiatry, neuropsychology, neurophysiology, neuropharmacology, and neuroimaging.
Epilepsy & Behavior publishes papers on the study of:

- Localization of ictal and postictal behaviours
- Neuroendocrine aspects of epilepsy
- Psychiatric and psychosocial aspects of epilepsy
- Behavioral aspects of epilepsy surgery
- Cognitive and affective effects of seizure treatment
- Functional imaging
- Animal models

Types of article

Epilepsy & Behavior publishes the following types of articles:

- Original research articles (both clinical and laboratory research)
- Reviews
- Editorials
- Brief communications
- Letters
- Book reviews
- Calendar of events

PREPARATION

Peer review

This journal operates a single anonymized review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of one independent expert reviewer to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. Editors are not involved in decisions about papers which they have written themselves or have been written by family members or colleagues or which relate to products or services in which the editor has an interest. Any such submission is subject to all of the journal's usual procedures, with peer review handled independently of the relevant editor and their research groups. More information on types of peer review.

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results
Results should be clear and concise.

Discussion
The Discussion section should explore the significance of the results of the work, not repeat them. Results and Discussion should be separate and may be organized into subheadings. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Abstract
A concise and factual abstract is required. The abstract should briefly state the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Keywords
Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations
Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).
Formatting of funding sources List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa]. It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant

or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding. If no funding has been provided for the research, please include the following sentence: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication

date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

Appendix 1.2 Data extraction Tool

Data Extraction Tool

Title:

Authors:

Year:

Country:

Data Collection Period:

Study aims:

Study design:

Setting:

Sample Groups:

Number of Participants:

Quality of Life outcome Measure used:

Other Factors measured/measures used:

Analysis conducted:

Key Results:

Effect Size:

Crowe Critical Appraisal Tool Score:

Appendices: Chapter 2

Appendix 2.1: Research and Innovation Approval

Administrator: Mr Scott Broadley Telephone Number: 0141 314 4001
E-Mail: Scott.Broadley@ggc.scot.nhs.uk
Website: https://www.nhsggc.org.uk/about-us/professional- support-sites/research-development/

Research & InnovationDykebar Hospital, Ward 11
Grahamston Road
Paisley, PA2 7DE
Scotland, UK

18 December 2020

Demitra Tsivos
Mental Health and Wellbeing Research Group
1st Floor, Admin Building, Gartnavel Royal Hospital1055 Great Western Road
Glasgow, G12 0XH
NHS GG&C Board Approval

Dear Demitra Tsivos,

Study Title:	Investigating quality of life in adults with epilepsy and psychogenic non epileptic seizures who attend a national specialist epilepsy centre.
Chief Investigator:	Prof Thomas McMillan
GG&C HB site	William Quarrier Scottish Epilepsy Centre
Sponsor	NHS Greater Glasgow & Clyde
R&D reference:	GN20NE586
REC reference:	N/A
Protocol no: (including version and date)	Version 3, 03/11/2020

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the abovestudy.

Conditions of Approval
For Clinical Trials as defined by the Medicines for Human Use Clinical Trial Regulations, 2004

During the life span of the study GGHB requires the following information relating to this site
Notification of any potential serious breaches.
Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP trainingaccording to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

For all studies the following information is required during their lifespan.
First study participant should be recruited within 30 days of approval date.
Recruitment Numbers on a monthly basis
Any change to local research team staff should be notified to R&D team

Any amendments – Substantial or Non Substantial
Notification of Trial/study end including final recruitment figures
Final Report & Copies of Publications/Abstracts
You must work in accordance with the current NHS GG&C COVID19 guidelines and principles.

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.I wish you every success with this research study

Yours sincerely,

Scott Broadley

Mr Scott Broadley
Senior Research Administrator

Appendix 2.2 SEC Ethical Approval

The William Quarrier
Scottish Epilepsy Centre

20 St Kenneth Drive, Govan,
Glasgow G51 4QD
Tel: 0141 445 7750 Fax: 0141 445 7751

www.scottishepilepsycentre.org.uk

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Ms Demitra Tsivos
Trainee Clinical Psychologist
c/o The University of Glasgow
Institute of Health and Wellbeing
Gartnavel Royal Hospital
Glasgow
G12 0XH

Ref: IW/EB

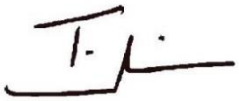
31st of July 2020

Dear Ms Tsivos,

I am writing to confirm acceptance of your evaluation proposal, assuming the necessary safeguards regarding personal identifiers are in place. You will be granted access to SEC outcome data in line with SEC patient confidentiality and research policies.

I look forward to hearing the findings from any subsequent study.

Yours sincerely



Ian Williams
Head of Epilepsy Services

Electronically verified

Appendix 2.3 NHS Ethics Advisory

GJ

Godden, Judith <Judith.Godden@ggc.scot.nhs.uk>
Mon 22/06/2020 15:18

To: Demitra Tsivos (PGR)
Cc: Emma-Jane Gault

Dear Demitra
I am also unclear whether it would be research or evaluation. I realise it is a unique model but this would not necessarily rule out research. However, you have stated that you will only be able to access fully anonymised data and this will make a difference to the requirement for NHS ethical review. In this circumstance if all of the data is supplied to the Investigator fully anonymised then NHS REC review is not required. You will require the equivalent of Caldicott Guardian approval from the person who carries out this role at the SEC. Glasgow University may also require to put it through their ethics committee and Emma-Jane can advise on that.

I hope that is helpful

Kind regards

Judith

Dr Judith Godden
Scientific Officer/ Manager
West of Scotland Research Ethics Service
07960 044211

Appendix 2.4 MVLS Ethics Advisory

RE: MVLS Research Ethics Query

MA

MVLS Ethics Admin
Mon 19/10/2020 15:22
To: Demitra Tsivos (PGR); MVLS Ethics Admin

Hi Demitra

They did, I just neglected to pass it on to you… Sorry for the inconvenience. They said that we don't need to review this as it's NHS data with Caldicot approval.

Regards
Neil

From: Demitra Tsivos (PGR) <0606906T@student.gla.ac.uk>
Sent: 19 October 2020 11:38
To: MVLS Ethics Admin <mvls-ethics-admin@glasgow.ac.uk>
Subject: Re: MVLS Research Ethics Query

Dear Neil,
Thank you for checking this out. I take it the chair ave not yet given you a reply?

Kind Regards,
Demitra Tsivos

Appendix 2.5 Normality Assessment

Table 1. D values from Kolmogorov-Smirnov Values

Variable	**Epilepsy Group**	**PNES Group**
Length of Admission (days)	.123*	.119
Age	.129*	.131
SIMD	.104	.242**
QOLIE-31 Admission Score	.088	.139
QOLIE-31 Discharge Score	.097	.107
NDDI-E Admission Score	.110	.155
NDDI-E Discharge Score	.151**	.131
GAD-7 Admission Score	.135*	.176
GAD-7 Discharge Score	.151**	.139
EpiTrack Admission Score	.144*	.103
EpiTrack Discharge Score	.152*	.225*
SCI Admission Score	.086	.080
SCI Discharge Score	.115	.109
QOL-Change Score	.154*	.135
GAD-7- Change Score	.098	.150
NDDI-E- Change Score	.133*	.198*
SCI- Change Score	.089	.197*
EpiTrack- Change Score	.202***	.239**
Psychological Distress Change Score	.107	.181*

**p <0.05, ** p <0.01, ***p<.001*

PNES= Psychogenic non-epileptic seizures, SIMD= Scottish index of Multiple deprivation, QOLIE-31= Quality of life in epilepsy-31, GAD-7= Generalised anxiety disorder – 7, NDDI-E= Neurological Disorders Depression Inventory, SCI= Sleep condition index

Appendix 2.6 Assesment OF Multicollinearity : QOL at Admission

With regards to multicollinearity within the regression models, none of the correlations within the matrix exceeded 0.80, however the correlation between GAD-7 and NNDI-E admission scores in the epilepsy group were approaching 0.80. VIF values were all <10 and the average VIF was 1.617. No tolerance values were less than 0.1. Several condition indexes were greater than 15, and one was greater than 30 indicating possible collinearity. In the epilepsy group there was a large proportion of the variance on the same small eigenvalue for GAD-7 and NDDI-E, indicating possible collinearity between the two variables. This was not present in the PNES group. Results of the Durbin Watson test indicated residuals were unlikely to be correlated. Scatterplots appeared evenly dispersed. On inspection of the histograms and P-P plots for normality of the residuals, the distribution of residuals in the PNES group looked to be non-normally distributed. Taking the above into consideration it appears multicollinearity may be present, and residuals may be non-normally distributed. Therefore, generalisation of the model outside the sample may be limited.

Appendix 2.7 Regression Values

Table 4. Summary of hierarchical multiple regression analysis for variables predicting QOLIE-31 admission scores in Epilepsy or PNES groups.

Discharge Diagnosis		n	R	R^2	Adjusted R^2	F	Sig.	Change Statistics			Coefficients		
								R Square Change	F Change	Sig. F Change	Unstandardized B (CI 95%)	β	Sig.
Epilepsy Group	**Model 1**		.621	.385	.354	12.219	<.0001	.385	12.219	<.001	61.836 (43.25 – 80.42)		<.0001
	NNDI-E	52									-.654 (-2.05 – .74)	-.173	.348
	GAD-7	52									-1.262 (-2.22 – -.30)	-.484	.011
	Model 2		.738	.545	.496	11.084	<.0001	.160	6.501	.004	42.134 (20.78 – 63.49)		<.0001
	NDDI-E										-.749 (-1.10 – .50)	-.198	.231
	GAD-7										-.976 (-1.87 – .08)	-.374	.034
	EpiTrack	46									.314 (-.12 – .75)	.165	.151
	SCI	52									.603 (.23 – .98)	.382	.002
PNES Group	**Model 1**		.574	.330	.246	3.936	.041	.330	3.936	.041	53.667 (30.64 – 76.70)		<.0001
	NNDI-E	21									-.413 (-1.90 – 1.08)	-.141	.565
	GAD-7	23									-1.106 (-2.26 – 0.05)	-.487	.060
	Model 2		.862	.743	.669	10.102	<.0001	.413	11.233	.001	3.451 (-33.34 – 40.24)		.843
	NNDI-E										.279 (-.94 – 1.50)	.095	.631
	GAD-7										-1.531 (-2.40 – 67)	-.674	.002
	EpiTrack	20									1.554 (.85 – 2.26)	.688	<.001
	SCI	23									-.143 (-1.0 – 60.78)	-.067	.744

PNES= Psychogenic non-epileptic seizures, SIMD= Scottish index of Multiple deprivation, QOLIE-31= Quality of life in epilepsy-31, GAD-7= Generalised anxiety disorder – 7, NDDI-E= Neurological Disorders Depression Inventory, SCI= Sleep condition index

A hierarchical multiple regression analysis of the epilepsy group with QOLIE-31 as the dependent variable revealed that at stage one, GAD-7 and NDDI-E explained 38.5% of the variance ($p < 0.001$). The additional outcome measures, SCI and EpiTrack were then added, explaining a further 16% ($p< 0.001$). The final model accounted for 54.5% of variance (Table 4). In the PNES group GAD-7 and NDDI-E explained 33% of the variance ($p <0.001$) as stage one. The additional outcome measures, SCI and EpiTrack were added second, explaining a further 41.3% ($p< 0.001$). The final model accounted for 74.3% of the variance.

Appendix 2.8 Multicollinearity Assessment: Psychological Distress Regression

The results from the regression model with psychological distress as the independent variable. No indication of multicollinearity between variables, all correlations < 0.70. VIF values all <10, average VIF = 1.32. No tolerance values <.10 and all index conditions were < 15. Variance proportions were satisfactorily distributed across the eigenvalues. Results of the Durbin Watson test indicated residuals were unlikely to be correlated. Scatterplots appeared evenly dispersed. On inspection of the histograms and P-P plots for normality of the residuals, the distribution of residuals in the PNES group looked to be non-normally distributed, however K-S testing of the residuals from both the epilepsy ($D(38)= .086$, $p = .254$) and PNES ($D(22)= .117$, $p = .592$) groups were non-significant.

Appendix 3: Original Research Proposal

Research Protocol Version 1

Full Title: Feasibility and acceptability of a brief psycho-education session following diagnosis of Psychogenic Non-Epileptic Seizures for patients and carers within a specialist epilepsy centre.

Short Title: Understanding PNES

Introduction

Rationale and Background

Psychogenic non-epileptic seizures (PNES) are transient paroxysmal events, characterised by altered responsiveness, motor and sensory symptoms and emotional signs. PNES appear similar to epileptic seizures but originate from psychological processes rather than abnormal brain activity (Hubsch et al., 2011). The estimated incidence of PNES is between 1.4–4.9/100,000 per year and the estimated prevalence between 2 and 33/100,000 in the general population (Asadi-Pooya & Sperling, 2015). Historically PNES has been a diagnosis of exclusion, made after ruling out neurological disorders, primarily epilepsy. The diagnosis of PNES falls within Functional Neurological Symptom (Conversion) Disorder, Somatic Symptom Disorder, Dissociative Disorder or Post Traumatic Stress Disorder in the DSM-5 (American Psychiatric Association, 2013). Within the ICD-10 classification system (World Health Organization, 1992) PNES is specified as "Conversion Disorder with seizures or convulsions", both systems accept PNES events as non-volitional, occurring without intent.

The complexities and specialist knowledge required to differentiate PNES from epilepsy means diagnosis often takes places within neurology services and specialist epilepsy centres. The gold standard for diagnosis involves the use of video electroencephalogram (VEEG) to rule out epileptic seizures. In the absence of EEG or VEEG, diagnosis can be made on review of semiological data from direct or video observation (LaFrance, Baker, Duncan, Goldstein & Reuber, 2013). Misdiagnosis is common and many individuals with PNES initially receive a diagnosis of epilepsy. Differential diagnosis is important for management of risks associated

with anti-epileptic medication and re-sective surgery for medically intractable epilepsy. It has been estimated that approximately one in five patients who first present at a specialist seizure clinic receive a diagnosis of PNES (Angus-Leppan, 2008).

Professionals can often struggle to appropriately engage and support individuals with PNES following an exclusion of neurological diagnosis. When individuals are diagnosed with PNES in neurology centres they are most often referred for psychological treatment externally as their diagnosis is not classes as a neurological/medical disorder. The distinction between psychogenic and epileptic seizures can be confusing for patients and medical professionals without specialist knowledge of the disorder (Rawlings and Reuber, 2018). Patients can be reluctant to accept that their seizures are not associated with abnormal electrical activity and may find the concept of a psychological origin to be invalidating and confusing (Stone et al., 2004). At the stage of PNES diagnosis individuals have typically experienced prolonged periods, typically years, of conceptualising their symptoms as epilepsy, generated by brain abnormality.

It has been reported that the communication style, timing and content of PNES diagnosis can have a significant impact on outcome, with evidence to suggest that good communication can lead to reduction and resolution of PNES in some individuals (Kanner et al., 1999; Hall-patch et al., 2010; LaFrance, Reuber, & Goldstein, 2013). Those who do accept PNES diagnosis demonstrate better outcomes (Ettinger, Devinsky, Weisbrot, Ramakrishna, & Goyal, 1999). However, recent evidence suggests that diagnosis and communication of PNES using standardised protocol delivered by the multidisciplinary team may not be effective at reducing the burden of PNES and patients require greater knowledge about and treatment of their disorder (Mayor et al., 2010).

This progression of knowledge surrounding the diagnosis of PNES continues to develop through research and clinical practice. A systematic review by Brown and Reuber (2016) summarised the current literature on PNES and outlined 4 overarching models (1) PNES as the activation of dissociative material, (2) PNES as a hard-wired response, (3) PNES as a physical manifestation of emotional distress and (4) PNES as a learned behaviour. The authors highlight the variable quality of studies on which these models are based and in a subsequent paper developed the Integrative Cognitive Model (ICM) of PNES. The ICM incorporates general predisposing and perpetuating factors, biological, psychological and social components with various mechanisms from the above models as the basis of understanding and managing PNES. The ICM draws upon

theory of “medically unexplained symptoms” and introduces the concept of a “seizure scaffold” which represents observable and subjective elements of PNES. The ICM suggests there are general factors that contribute to PNES dysfunction such as chronic stress. In doing so the model eliminates the presumption that abuse, especially in childhood, is the central cause of PNES. Research and understanding of PNES has advanced greatly in the past 25 years, however elements of these models tend to be mentioned only briefly in explanations of PNES and very few elements appear within protocols developed for communication of PNES to patients (Hall-Patch et al., 2010).

It is therefore important to develop communication strategies for delivering PNES diagnosis that enhance acceptance and facilitate a clear understanding of the PNES. Given the difficulties surrounding the diagnosis and diagnostic process, strategies that link in with treatment pathways and make clear as to what does and does not cause PNES are necessary to help individuals conceptualise their difficulties as distinct from epilepsy. A number of research studies have evaluated the acceptability and effectiveness of communication strategies and brief psycho-education programs in various contexts (Hall-Patch et al, 2010; Baxter et al, 2012; Chen et al, 2014; Mayor et al, 2013; Hingary et al, 2016; Wiseman et al, 2016). However, there are currently no guidelines for communication of diagnosis or treatment of PNES within the National Institute for Clinical Excellence (NICE) guidelines, the Matrix or the Scottish Intercollegiate Guidelines Network (SIGN).

A report from the International League Against Epilepsy, Nonepileptic Seizures Task Force suggests “the optimal treatment strategy, includes psychological approaches and pharmacological treatment (SSRI) in the absence of any currently available high-quality studies” (Gasparini et al, 2019). Psychological therapies indicated for the treatment of PNES include psychotherapy, “Cognitive Behavioural Therapy (CBT) and its modalities”, EMDR and family therapy (Milán-Tomás, Persyko, del Campo, Shapiro & Farcnik, 2018). A review by the International League Against Epilepsy suggests involvement of family and carers at diagnosis as favourable practice (LaFrance, Baker, et al., 2013). Individuals with PNES can have high care needs and there is evidence to suggest that caregiver attitudes impact on acceptance of PNES from a previous study by Duncan, Graham and Oto, 2014. This study assessed patient and caregiver reactions to PNES and the association between reactions and attendance of follow-up appointments and long-term outcomes. They found caregivers with favourable acceptance at 6-12 months predicted reduced health-care utilization at 5-10 years. Whitehead, Stone,

Norman, Sharpe and Reuber (2015) report psychological factors were viewed as more relevant by relatives of individuals with PNES than patients. Taken together this evidence suggests that carer perceptions of PNES may play an important role in management of PNES.

Aim/Primary and Secondary Objectives

The primary aim of this research is to investigate the acceptability of a targeted education session for patients and their carers diagnosed with PNES within the William Quarrier Scottish Epilepsy Centre, a specialist centre assessing and treating patients from across Scotland. This education session will be based on the principals of the ICM of PNES as outlined above (Brown & Reuber, 2016). The session aims to provide patients and carers with information regarding their diagnosis, offering to conceptualise symptoms and experiences by specific psychological mechanisms implicated in the development and maintenance of PNES.

The study aims to be relevant and meaningful to both patients and carers, who have in previous studies reported confusion following diagnosis (Hall-Patch et al., 2010). Based on previous research that reports benefits of brief psycho-education interventions in this population (Novakova, Harris, Rawlings, & Reuber, 2019) we predict that individuals will engage with and value the current approach. The secondary objective is to investigate the feasibility of running a pilot trial of the psycho-education session within the specialist centre, evaluating the utility of the proposed outcome measures. With reference to likely potential recruitment and retention rates of both patients and carers in this environment.

Methodology

Inclusion Criteria for Patients:

- Presence of PNES as confirmed by consultant epileptologist or clinical nurse specialist in epilepsy. Individuals who are admitted with known PNES to rule out comorbid epilepsy will also be included in the study if they have not received previous psychological input for PNES.

Inclusion Criteria for Patients and Carers:

- Individuals 16 years of age and older
- Ability to give informed consent.
- Fluent in English
- Individuals with a diagnosis of Mild learning disability will be included.

Exclusion Criteria for Patients and Carers:

- Known moderate to severe cognitive impairment including learning disability or acquired brain injury.
- Individuals who have completed previous psychological intervention for PNES.

Study Design/Plan

Patients diagnosed with PNES or comorbid PNES and Epilepsy within the WQSEC, following inpatient stay will be recruited. They will be asked to identify a family member or carer who will also be recruited into the research.

1. Following diagnosis, the consultant or relevant clinician will ask the patient if they would be interested in learning more about a study investigating the acceptability and feasibility of a brief education session of PNES for patients and carers. The Participant Information sheet (Version 1; 01/03/2020) will be given for patients to read and share with their identified carer.
2. Potential participants will then register interest by removing the tear off strip at the bottom of the information sheet (place into provided envelop) and give to a member of their clinical team to be handed to reception at the WQSEC.
3. A member of the research team will then contact the potential participant to organise a consenting visit. This will usually be with the trainee clinical psychologist during inpatient stay. The research will be summarised, and the participants will have the opportunity to ask questions about the research. Informed Consent for research will be gained and documented using the Consent Form (Version 1; 01/03/2020).
4. The trainee clinical psychologist will then administer the Patient Brief Illness Perception Questionnaire (BIPQ, Broadbent, Petrie, Main, & Weinman, 2006) and the Carer (BIPQ). This questionnaire has been adapted (with author permission) for use within PNES population. Demographic data will also be collected from both the patient and carer.
5. The patient and carer will then be invited to participate in the brief psycho-education session regarding PNES diagnosis and management. The education session will be delivered by the centres clinical psychologist and will approximately 60 minutes in duration. The session will occur during inpatient stay in one of the available clinical rooms (not patient rooms).

6. Following the education session, the Trainee Psychologist will administer the BIPQ again to both patient and carer. A feedback interview will then be conducted for both the patient and carer separately. Qualitative interview questions are outlined below.

Psycho-Education Session Details

The education session aims to provide patients and carers with a coherent understanding of the psychological mechanisms involved in PNES and how these interact with physical processes to generate various symptoms of PNES. The session will be delivered by the Centres Clinical Psychologist. It will be delivered in one session, approximately 60 minutes in length. Accompanying handouts will be provided for both the patient and carer to keep. Carers who are unable to attend the WQSEC can participate in the session via video or telephone conferencing. The material covered will be based on the following key concepts of the ICM of PNES:

- PNES develops in the context of inhibition processing dysfunction. The cause of which can be chronic stress, arousal or other factors compromising high level cognitive processing.
- PNES is understood as a conditioned reflex with contributions from inherent reflexes (freeze or startle), physical symptoms (pre-syncope, dissociation, hyperventilation and head injury) and personal knowledge or modelling. These factors come together to produce the individualised seizure scaffold.
- Behaviourally the seizure scaffold is described as the perceptions and motor activities experienced by the individual.
- PNES are non-volitional but can be inhibited with practice of specific techniques.

Outcome Measures

Acceptability will be assessed as detailed in a previous study by Saracutu, Edwards, Davies & Rance, 2018) involving qualitative questions probing education session coherence and experiences of taking part. This will be asked via the following qualitative interview questions and the answers to these questions will be transcribed and collated allowing for analysis of emerging themes present in responses.

1. What did you learn from the education session?
2. What parts of the session did you find most useful? Where there any aspects that you enjoyed?
3. What did you like least about the session? What do you think could be improved?
4. Were there any difficulties in taking part?
5. Are there any changes in how you view your PNES? If the answer is yes, what are they?
6. Is there anything you plan to do differently following the session?
7. Would you recommend this type of session to someone you cared about?

Demographic information will be collected for purposes of describing the groups. The BIPQ (Broadbent, Petrie, Main & Weinmen, 2006) will be used to measure illness perceptions in PNES. The BIPQ comprises 9 items that respondent's rate on a 10-point Likert scale, a higher total score indicates a more threatening view of the illness. There is also one causal question which is qualitative and can be analysed categorically. The questionnaire has demonstrated good internal consistency and test-retest reliability in a variety of patient populations (Broadbent et al., 2015). The BIPQ has been modified for PNES population with permission of the authors.

Data from the WQSEC research database will be used to form a comparison group, this will consist of BIPQ scores from anonymised individuals pre and post PNES diagnosis. This dataset will comprise patients who received a diagnosis of PNES within 4 months prior to the start date of the study.

Statistical Considerations

Justification of sample size

Lancaster, Dodd and Williamson (2004) suggest a sample size of 30 participants in feasibility and acceptability studies. Data from the WQSEC demonstrate that for the period April 2016 to March 2017 there were 12 patients diagnosed with PNES alone, 28 patients with mixed diagnosis (PNES and Epilepsy) and 4 patients with PNES, with unconfirmed comorbid epilepsy. A total of 44 patients for the year with confirmed PNES diagnosis (or approximately 22 over six months). Informal discussion with staff from the centre indicates that admissions have since increased. Previous studies report retention of participants following recruitment of between

56% and 90% (Mayor et al., 2012; Stone et al., 2004). We aim to recruit 30 patients to the study over a 6-month period.

Planned Data Analysis

As a feasibility study the analysis will focus on determining if the proposed psycho-education session is acceptable and would likely succeed in achieving recruitment in the current setting. As such the planned analysis will be largely descriptive in nature with features of qualitative data analysis to assess participant experiences. Feasibility will be assessed through recording the number of patients referred by their diagnosing consultant, the number who agree to participate in the research and the number who subsequently attend the session with a career. This will be used to estimate realistic recruitment rates within the centre over a given period in future research.

We will investigate if there are differences between the rates of change in illness perception between those receiving the session in the feasibility study and those diagnosed in the centre in the previous 4 months. As this is a feasibility study, we will not use this comparison for calculation of effect size.

Ethics

Health and Safety Issues

Standard personal safety risk assessment to be followed when working with patients and carers. The purpose of inpatient assessment at the SEC is to capture occurrence of seizure during admission, as such physical risks to patients will not be over and above those consented to as part of the inpatient assessment.

Criteria for discontinuation

Post diagnostic periods are a potentially sensitive time and care will be taken to ensure patients and carers are not put under any undue distress by discussing research options following their diagnosis. This will be left to the judgement of the diagnosing consultant. Patient views on their diagnosis will be handled sensitively and any monitored throughout the session. Should any of the participants become overly distressed with the presentation of information regarding PNES diagnosis or management techniques, the session will be terminated. This will be based on clinical judgement of the recruiting consultants, clinical psychologist or trainee clinical

psychologist. Debriefing will be available for participants to discuss their concerns and experiences.

Procedure for collecting data.

Data will be collected via pen and paper forms and notes taken at interview. Participants will be assigned a participant number at the time of consent and all personal information will be anonymised. Paper copies will be stored in a locked file cabinet within the WQSEC. Data will be kept in accordance with GDPR and local NHS GGC health board policies.

Ethical Issues

The principal investigator will ensure the study will be carried out in accordance with the ethical principals in the Research Governance Framework for Health and Community Care, Second Edition, 2006 and applicable legal and regulatory requirements.

Before the start of the study the protocol and informal consent form will be reviews and approved by the Ethics committee (EC). Management approval for the research study will also be obtained from the WQSEC.

Finance and Indemnity

Research costs will be funded by the University of Glasgow, for the project these are negligible costs amounting to printing of materials and outcome measures which are freely available. Research members working on the project will be covered for negligent harm through University and/or NHS indemnity schemes.

Publication

Study results will be published as part of Doctoral Thesis by the trainee clinical psychologists and will also be submitted to peer reviewed journal for publication.

Timetable

Submission Title	**Deadline Date**
Submit to R&D, Research Ethics Committee and WQSEC Research Committee.	February-March 2020
Participant Recruitment and Data Collection	April – October 2020

Data Analysis and Write Up	November – January 2021
Submission of Thesis Report	28th February 2021

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Appendix 4: Alternative Major Research Project Proposal

Research Protocol Version 3 03/11/2020

Full Title

Investigating quality of life in adults with epilepsy and psychogenic non epileptic seizures who attend a national specialist epilepsy centre.

Short Title

Scottish Epilepsy Centre Outcomes

Introduction

Epilepsy monitoring units provide specialist assessment, diagnosis and treatment for individuals with epilepsy and psychogenic non-epileptic seizures (PNES). The main aims for patients entering these centres are typically to clarify diagnosis and reduce seizure frequency. Increasingly it is being recognised that quality of life for patients comprises more than freedom from seizures. Individuals with epilepsy and PNES are affected by a complex range of biological, psychological and social factors which impact on quality of life. The association amongst various biopsychosocial factors, patient quality of life and wellbeing is emerging within the literature and will be the focus of the current research project.

Epileptic seizures and PNES appear similar in their clinical presentation, however they differ in their underlying neurophysiological processes. Epileptic seizures are characterised by abnormal neuronal discharge, whereas PNES originate from psychological processes that are not associated with abnormal brain activity (Hubsch et al., 2011). Recently there has been significant development into deriving a comprehensive understanding of the processes leading to the development and maintenance of PNES. Brown and Reuber (2016) outlined four overarching processes that are implicated in PNES. (1) PNES as the activation of dissociative material, (2) PNES as a hard-wired behavioural response, (3) PNES as a physical manifestation of emotional distress and (4) PNES as a learned behaviour. Their Integrated Cognitive Model of PNES supports an understanding of PNES as unintentional events and moves away from early conceptualisations of individuals with PNES as “hysterical” or malingering.

The complexities and specialist knowledge required to differentiate PNES from epilepsy means diagnosis often takes places within tertiary neurology services or specialist epilepsy centres. The gold standard for diagnosis involves the use of video electroencephalogram (VEEG) to rule out epileptic seizures. In the absence of EEG or VEEG, diagnosis can be made on review of semiological data from direct or video observation (LaFrance, Baker, Duncan, Goldstein & Reuber, 2013). Misdiagnosis is not uncommon, especially out with specialist centres and many individuals with PNES initially receive a diagnosis of epilepsy. Differential diagnosis is important for management of risks associated with anti-epileptic medication; appropriate response to status epilepticus and in planning resective surgery for medically intractable epilepsy. It has been estimated that approximately one in five patients who first present at a specialist seizure clinic receive a diagnosis of PNES (Angus-Leppan, 2008). Patients have many and diverse experiences within various pathways leading to a diagnosis of PNES. It can be difficult for patients to accept a diagnosis of PNES, individuals have been reported to be angry and confused with the diagnosis (Thompson et al, 2009).

The distinction between psychogenic and epileptic seizures can be confusing for patients and medical professionals who lack specialist knowledge of the disorders (Rawlings and Reuber, 2018). Misconceptions around the diagnosis of PNES may contribute to reluctant of some patients to accept the concept of psychogenic seizures and patients have been reported to see the diagnosis as invalidating and confusing (Stone et al., 2004). At the point of diagnosis individuals with PNES and their social networks including families, friends, teachers and colleagues have typically experienced years of conceptualising their symptoms as epilepsy, generated by brain abnormalities. Individuals with epilepsy experience high levels of perceived and objective stigmatization in society (Fiest et al, 2014) as do individuals with PNES, by both professionals and lay people (Karakis et al, 2020).

Research indicates that individuals with epilepsy and PNES experience higher levels of psychopathology and poorer self-reported quality of life (QoL) than the general population (Jacoby, Snape and Baker, 2008; Kobau et al, 2014; Abe et al, 2020). Furthermore, people with PNES consistently report poorer overall QoL than matched samples with epileptic seizures (Testa et al, 2007), indicating that both diagnoses are associated with a significant detriment to QoL. A systematic review by Jones, Reuber and Normal (2015) investigated for correlates of quality of life in individuals with PNES. They reported depressive symptoms to be the highest

correlate of Health Related QoL. In their review of 14 studies, they also found dissociation, somatic symptoms, escape-avoidance coping strategies, and family dysfunction to be associated with poor Health Related QoL. Interestingly they found no evidence to support the association between Health Related QoL, seizure frequency, and demographic factors. This contrasts with a previous review which found that clinical factors such as seizure frequency and severity, as well as psychological factors, impact on QOL in people with epilepsy (Taylor et al, 2011).

So, whilst seizure frequency appears to be associated with QoL at least to some degree in both individuals with epilepsy and PNES, it may have less of an impact on QoL in those with PNES. This indicates that it is important to identify other factors that contribute to and are associated with QoL in individuals with PNES only.

Study Summary

The Scottish Epilepsy Centre (SEC) is a specialist inpatient assessment and treatment centre providing services for individuals across Scotland. During inpatient stay individuals may undergo a range of specialist assessments to help diagnose and manage epilepsy and/or psychogenic non-epileptic seizures (PNES). Seizure reduction is a primary focus for patients and clinicians alike. The SEC routinely evaluates anxiety, depression and indicators of QoL at admission and discharge to help identify individuals who may benefit from additional intervention including for mental health and well-being needs.

The current research project aims to build a better understanding of the association between QoL and a range of factors in individuals with PNES and Epilepsy by investigating outcomes across inpatient admission to the SEC.

Study Aims

The primary aim of this research is to investigate factors associated with QoL in PNES and Epilepsy groups. Specifically, the association between QoL and demographic characteristics, self-reported mental health scores, sleep quality scores, screening of cognitive functioning and medication burden.

The secondary aim is to investigate if QoL ratings change during inpatient stay at the SEC and if so, are there any factors associated with this change. This will be analysed separately for

epilepsy and PNES groups. Seizure frequency does provide an important metric in terms of severity and burden of disease, seizure frequency will be analysed within groups as a descriptive statistic and change in seizure frequency will be analysed across participant groups to provide information to the SEC. Changes in seizure frequency and seizure frequency as a predictor of QoL is however not the focus of this research.

Methods

This research will be achieved by conducting a retrospective cohort analysis of routine data collected from inpatients attending the SEC. The analysis will be conducted on data which comes from an existing database, collected between 1st of March 2019 to 31st March 2020. Patients give consent for data to be used in research and/or audit at admission and all data analysis in the present study will be conducted on fully anonymised data.

Participants

Participants will be those who were admitted to the SEC within the aforementioned dates and gave consent for their data to be used in future research and audit. Inpatients at the SEC are most commonly referred in order to:

(1) clarify diagnosis and understand the nature of seizures
(2) record physiological and behavioural data during seizures
(3) assess how seizures are affecting health and life
(4) assess how factors in an individual's life influence their seizures and health
(5) assess if seizures and illness affect an individual's mood and memory
(6) make changes to treatment and medications in a safe environment
(7) provide individual advice and support to help individuals live with epilepsy

Individuals who are admitted to the SEC include those who have epilepsy only, PNES only and mixed epilepsy and PNES. Professionals within the centre endeavour to provide concrete diagnosis however due to the nature of the difficulty in differentiating between PNES and epilepsy, a number of individuals are discharged with an "uncertain" diagnosis. Participant groups within this study are

Epilepsy only
PNES only

Mixed Epilepsy and PNES (including “uncertain” diagnosis and probable mixed diagnoses)

Inclusion Criteria:

The dataset includes patients who:

- were admitted to the SEC from the time point 1st of March 2019 to 31st of March 2020 and gave consent for their data to be used for research and audit purposes
- were aged 16 and over at the date of admission
- had confirmed diagnosis or suspected diagnosis of Epilepsy or PNES
- were fluent in English

Exclusion Criteria:

The dataset excludes patients who:

- did not give consent for their data to be used for research.
- had a moderate to severe cognitive impairment including learning disability or acquired brain injury. Individuals with moderate cognitive impairment were provided with alternative outcome measures appropriate for individuals with Learning Disability. The decision to allocate patients with the alternative measures was made based on information included by the referrer or based on clinical judgement of nurse specialists within the centre, following discussion with patients and carers pre-admission.

Justification of Sample Size

Due to the nature of the data set the sample size is fixed, consisting of 85 patients with a diagnosis of epilepsy only, 26 patients with a diagnosis of PNES only and 36 patients with a mixed or unclear diagnosis. Considering those with epilepsy or PNES only the study will have 80% power to detect a standardized difference between groups (effect size) of 0.56, at a 5% significance level, for a normally distributed continuous measure.

Within the smaller diagnostic subgroup, there will be 80% power to detect a correlation of 0.25 between a continuous predictor variable and quality of life score at a 5% significance level.

Data Management

The anonymised data will be accessed and stored as per WQSEC data management guidelines. The researcher will be given an honorary WQSEC staff account within the secure Office 365 platform which the centre uses to store and share data securely. This will be accessed online via NHS computers laptops and personal devices. Data will only be stored within the WQSEC Office 365 platform.

The original file format will be an Office Excel document, the researcher will input this data to create both SPSS and "R" file documents to carry out statistical analysis. These three files will be accessible to the student research Demitra Tsivos. These files may be viewed through screen share with the academic and clinical supervisors, Thomas McMillan and Iain Campbell as well as the designated statistician Alex McConnachie. No patient identifiable data will be stored on University of Glasgow or personal computers.

Planned Data Analysis

1. The data will initially be analysed to check for normal distribution to determine if parametric or non-parametric analysis is appropriate. Descriptive data will be compiled for the dataset as a whole and per patient group, descriptive data available is:

- Age
- Gender
- Deprivation (based on postcode and Scottish Index of Multiple Deprivation). The researcher will receive the deprivation score only, not postcodes to comply with patient confidentiality and keep data anonymous.
- Diagnosis: "Epilepsy Only", "PNES Only", "Mixed and/or Unclear Diagnoses"
- Length of inpatient stay at the SEC (days)

2. In order to analyse which factors are associated with QoL on admission, a multivariable linear regression analysis will be carried out with QOLIE-31 as the dependent variable and admission measures for the NDDI-E, GAD-7, SCI, MoCA, EPItrack and deprivation index as the independent variables. This will be done first with patients condensed into one group and subsequently with three separate patient groups PNES, epilepsy and "Mixed". The reason for this is due to small patient numbers in each group.

3. An analysis of Covariance (ANCOVA) will be conducted to investigate if there is a significant difference in scores on QoL-31, NDDI-E, GAD-7, SCI, MoCA and EPItrack at admission (Time 1) and Discharge (Time 2), with the length of admission as the covariate. If there is a significant difference found in measures from admission to discharge, subsequent independent sample t-tests will be employed to identify whether there are differences between the patient groups.

4. Should there be a significant change in QoL ratings over time, it will be followed up with regression analysis to determine what factors predict change in self-reported QoL.
The total list of variables that will be supplied to the researcher is

- Date of admission and discharge
- Age
- Gender
- Scottish Index of Multiple Deprivation
- Medications on admission and at discharge (type and dose)
- Services received during admission (neurology, neuropsychiatry, neurophysiology, neuropsychology, specialist nursing)
- Neurological Disorders Depression Inventory for Epilepsy at admission and discharge
- Generalized Anxiety Disorder 7 admission and discharge
- Quality of Life in Epilepsy –31 and Quality of Life in Epilepsy –10 admission and discharge
- Brief Illness Perception Questionnaire admission and discharge
- The Sleep Condition Indicator admission and discharge
- Montreal Cognitive Assessment at admission and discharge
- EpiTrack at Admission and discharge
- Number of seizures recorded in the first week (Focal and Generalised)
- Number of seizures recorded in the last week (Focal and Generalised)
- Number of PNES recorded in the first week
- Number of PNES recorded in the last week

Ethics

There will be no novel data collection as part of this research. All data undergoing analysis has been collected as part of routine processes within the SEC. All data will be anonymised prior to being supplied to the researcher.

The SEC gave approval for the researcher to have access to the anonymised dataset and to carry out the proposed analysis. Sponsorship of the study will be provided by the University of Glasgow and the school of Medical, Veterinary and Life Sciences has been satisfied with the ethical review conducted through the SEC. It was determined that NHS GG&C Research and Development did not require to carry out ethical review as the dataset will be fully anonymised prior to reaching the researcher.

Proposed Timeline

Stage	**Date**
Submission to NHS Research and Development	November 2020
Data Analysis	November 2020 – December 2020
Writing Up	January 2021 – February 2021
Submission	February 2021

Dissemination

The research results will be published as part of the Doctoral Thesis by the trainee clinical psychologist, the results will be made available to the SEC and will be submitted to peer reviewed journal for publication. Although no conferences have been identified prospectively, it is possible that the student may present the research finding s at appropriately identified conferences.

Reference List

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