Author/s:
Welton, JM;Walker, CJ;Riney, K;Ng, A;Todd, L;D'Souza, W

Title:
Quality of life and its association with comorbidities and adverse events from antiepileptic medications: Online survey of patients with epilepsy in Australia

Date:
2020-03-01

Citation:
Welton, J. M., Walker, C. J., Riney, K., Ng, A., Todd, L. & D'Souza, W. (2020). Quality of life and its association with comorbidities and adverse events from antiepileptic medications: Online survey of patients with epilepsy in Australia. Epilepsy and Behavior, 104 (Pt A), https://doi.org/10.1016/j.yebeh.2019.106856.

Persistent Link:
https://hdl.handle.net/11343/273785

Epilepsy & Behavior 104 (2020) 106856

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Quality of life and its association with comorbidities and adverse events from antiepileptic medications: Online survey of patients with epilepsy in Australia

Jeremy M. Welton [a,*], Christine Walker [b], Kate Riney [c,d], Alvin Ng [e], Lisa Todd [f], Wendyl J. D'Souza [g,h]

[a] UCB Pharma, Level 1/1155 Malvern Rd, Malvern, VIC 3144, Australia
[b] Chronic Illness Alliance, 587 Canterbury Rd, Surrey Hills, VIC 3127, Australia
[c] Queensland Children's Hospital, 501 Stanley St, South Brisbane, QLD 4101, Australia
[d] University of Queensland School of Clinical Medicine, Brisbane, Queensland, Australia
[e] Costello Medical Singapore Pte Ltd, 133 New Bridge Road #23-01/02, Chinatown Point, 059413, Singapore
[f] Epilepsy Action Australia, 1/1 Lucknow Rd, North Ryde, NSW 2113, Australia
[g] The Department of Medicine, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, VIC 3065, Australia
[h] The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia

ARTICLE INFO

Article history:
Received 13 November 2019
Revised 12 December 2019
Accepted 12 December 2019
Available online 15 January 2020

Keywords:
Quality of life
Comorbidities
Antiepileptic drugs
Adverse events
Australia
Cross-sectional

ABSTRACT

Objective: This study aimed to explore the quality of life (QoL) of adult patients with epilepsy (PwE) in Australia and its relationship with comorbidities and adverse events (AEs) from antiepileptic drugs (AEDs).
Methods: Cross-sectional surveys were completed by PwE, or carer proxies, recruited via the online pharmacy application MedAdvisor and Australian PwE Facebook groups from May to August 2018. Data were collected on demographics, epilepsy severity and management, AEs, comorbidities, and QoL (using the Patient-Weighted Quality of Life in Epilepsy Inventory [QOLIE-10-P] total score). Two linear regression models were constructed to explore associations between AEs or comorbidities and QOLIE-10-P score, with possible confounders determined using stepwise selection.
Results: Nine hundred and seventy-eight of 1267 responses were eligible (mean age of respondents: 44.5 years, 64% female, 52% employed). Recent AED use was reported by 97%; 47% were on AED monotherapy, 35% had ≤2 lifetime AEDs, and 55% were seizure-free for >1 year. After stepwise selection, control variables included in both models were time since diagnosis, employment status, seizure frequency, number of currently prescribed AEDs, and number of general practitioner (GP) visits per year. In the model for comorbidities, "psychiatric disorders" was associated with the largest QOLIE-10-P score decrease (−23.14, $p < 0.001$). In the model for AEs, which additionally controlled for depression and anxiety disorder, self-reported "memory problems" was associated with the largest decrease in QOLIE-10-P score (−14.27, $p < 0.001$).
Conclusions: In this survey of Australian PwE, many of whom had relatively well-controlled epilepsy, psychiatric and self-reported memory problems were common and associated with the greatest detrimental impact on QoL. Further research is needed to better understand the underlying causes of impaired QoL and thereby improve its management.

1. Introduction

Quality of life (QoL) in patients with epilepsy (PwE) may be affected by numerous complex factors, including the severity of epilepsy, antiepileptic drug (AED) treatment, as well as felt and enacted stigma [1]. Epilepsy is often associated with comorbid health conditions [2]; in particular, studies have pointed to a high prevalence of neuropsychiatric conditions and pain disorders in PwE, which are reported more frequently than in the general population [3]. These comorbidities can affect QoL even in the absence of active seizures, and may be stronger predictors for QoL than seizure-related factors [4,5].

Furthermore, up to 40–50% of PwE may experience adverse events (AEs) from AEDs [6,7]. Thus, aside from the main goal of seizure control, the tolerability of AEDs is a major consideration in evaluating the effectiveness of antiepileptic therapy. This is supported by several studies demonstrating that AEs are important determinants of QoL, and that reducing side effects may be key to improving the QoL of PwE [1,7].

* Corresponding author.
E-mail addresses: Jeremy.Welton@ucb.com (J.M. Welton), cwalker@chronicillness.org.au (C. Walker), drkateriney@qldkidsneuro.com (K. Riney), alvin.ng@costellomedical.com (A. Ng), LTodd@epilepsy.org.au (L. Todd).

https://doi.org/10.1016/j.yebeh.2019.106856

Observational studies on the prevalence of comorbidities and AEs typically recruit more easily accessed patients, such as through patient organizations for epilepsy or tertiary hospitals; these usually represent a population of PwE in the more severe end of the disease spectrum [8,9]. Such patients may not be representative of a broader population of PwE, which includes those who are well-controlled with one AED or who do not regularly access tertiary hospital services or patient organizations. Identifying and recruiting patients with less severe epilepsy outside these settings can be challenging, and consequently, less is understood about these patients and the impact of epilepsy on their QoL.

The Internet has become a common source of health information and social support; in Australia, up to 80% of Internet users seek medical information online [10]. People with epilepsy and other conditions use online tools to improve disease self-management, or to connect with others through online communities [11]. Using novel online recruitment methods, including surveying patients accessing a pharmacy medication app, the objective of this exploratory study was to investigate relationships between QoL and the presence of comorbid conditions or AEs in a broad sample of PwE in Australia, in order to better understand how these important factors may contribute to QoL.

2. Participants and methods

2.1. Participants and recruitment

The survey was administered online through SurveyMonkey® (www.surveymonkey.com) and was completed by either PwE or their carers by proxy. Respondents were recruited through the posting of invitation links to the public Facebook groups of Epilepsy Australia, Epilepsy Action, and Epilepsy Foundation, and on MedAdvisor, an Australian personal medication management mobile application.

Eligible patients were those who were residing in Australia, were ≥18 years of age, reported having a seizure disorder or epilepsy using a validated epilepsy screening question, and who had not completed the survey before [12] (Fig. 1). The study was approved by the Bellberry Human Research Ethics Committee (Application No: 2018-01-038) before commencement.

2.2. Data collection and measures

The survey was open for data collection for 13 weeks from 28 May 2018 to 28 August 2018. It consisted of five main sections: demographics, epilepsy severity and management, AEs, comorbidities, and QoL. Adverse event items were adapted from the Liverpool Adverse Events Profile [13]; some items were removed to avoid overlap with the comorbidities question, and only dichotomized Yes/No responses were allowed. Comorbidities were adapted from items used in the Epilepsy Comorbidities and Health (EPIC) survey conducted in the US [3]. In addition, the standardized Generalized Anxiety Disorder 7-item (GAD-7) scale was used to determine the presence of GAD in respondents, with scores of ≥10 validated as the cutoff point for identifying cases [14], and the presence of comorbid depression was evaluated using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), where scores of >15 are indicative of major depression disorder (MDD) in PwE [15]. Quality of life was measured using the validated Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE-10-P), a 10-item questionnaire covering the domains of epilepsy, mental health, and role functioning, which are then weighted by an item measuring overall distress [16]. Final QOLIE-10-P total scores range from 0 to 100, with a higher score indicating better QoL [17].

Postcodes were categorized into 5 remoteness categories (Major Cities of Australia; Inner Regional Australia; Outer Regional Australia; Remote Australia; Very Remote Australia) according to Australian Statistical Geography Standard (ASGS) data published by the Australian Bureau of Statistics (ABS) [18]. Where possible, postcodes that did not appear in the database were conservatively recoded to adjacent postcodes, e.g., from 4001 to 4000 for Brisbane City.

Postcodes were also stratified according to socioeconomic status quintiles using their Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) score, based on the most recent available (2016) Socio-Economic Indexes for Areas (SEIFA) data published by the ABS [19]. Responses with postcodes that could not be mapped to any socioeconomic category in the database were removed from the analyses.

Although respondents could exit the survey at any point, questions required a mandatory response in order to proceed to the next section of the survey. Questions on AEs were omitted for respondents who

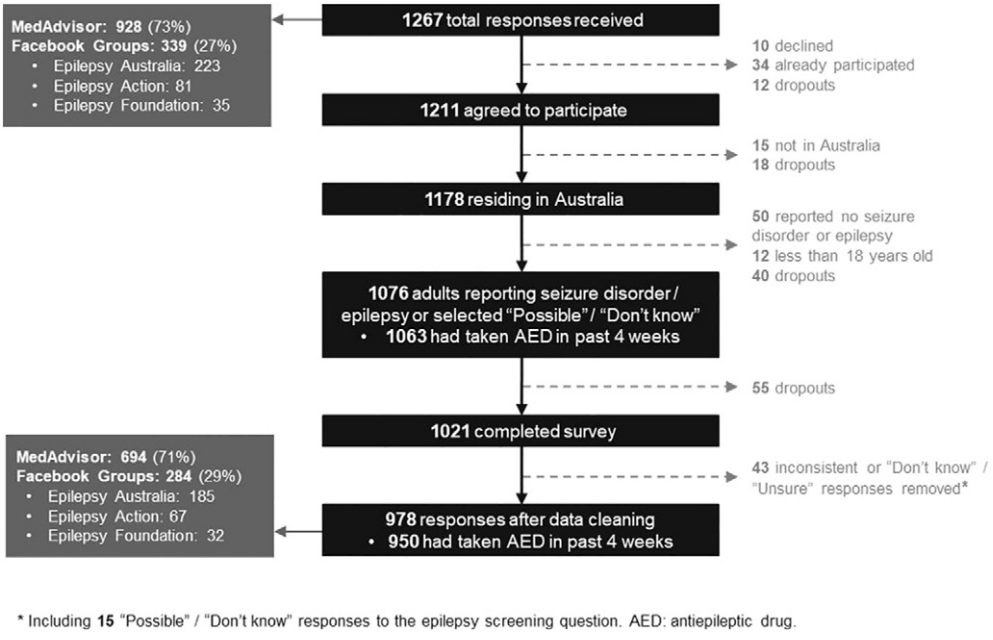

Fig. 1. Survey respondent eligibility flowchart.

Table 1
Summary characteristics of survey respondents.

	All PwE (N = 978)	AED Group (N = 950)
Age (years), mean ± SD	44.47 ± 14.14	44.43 ± 14.14
Time since diagnosis (years), mean ± SD	21.57 ± 15.56	21.47 ± 15.50
Gender, n (%)		
Female	626 (64.0%)	605 (63.7%)
Male	346 (35.4%)	339 (35.7%)
Other	6 (0.6%)	6 (0.6%)
Employment, n (%)		
Employed (including part-time, self-employed)	506 (51.7%)	493 (51.9%)
Not looking for work (including retired, student)	238 (24.3%)	227 (23.9%)
Unable to work	181 (18.5%)	178 (18.7%)
Looking for work	53 (5.4%)	52 (5.5%)
Socioeconomic status		
Quintile 1 (poorest)	142 (14.5%)	137 (14.4%)
Quintile 2	189 (19.3%)	184 (19.4%)
Quintile 3	185 (18.9%)	180 (19.0%)
Quintile 4	215 (22.0%)	210 (22.1%)
Quintile 5 (richest)	247 (25.3%)	239 (25.2%)
Remoteness of residence		
Very remote	2 (0.2%)	2 (0.2%)
Remote	8 (0.8%)	8 (0.8%)
Outer regional	69 (7.1%)	68 (7.2%)
Inner regional	230 (23.5%)	220 (23.2%)
Major cities	669 (68.4%)	652 (68.6%)
NDDI-E score[†], mean ± SD	14.37 ± 4.52	14.33 ± 4.52
GAD-7 score[‡], mean ± SD	6.18 ± 5.77	6.12 ± 5.76
Current number of prescription drugs for seizures, n (%)		
None	21 (2.2%)	12 (1.3%)
1	459 (46.9%)	452 (47.6%)
2	289 (29.6%)	283 (29.8%)
3 or more	209 (21.4%)	203 (21.4%)
Number of seizure medications taken in entire life, n (%)		
None	1 (0.1%)	0 (0%)
1	140 (14.3%)	133 (14.0%)
2	199 (20.3%)	195 (20.5%)
3 or more	638 (65.2%)	622 (65.5%)
Seizure frequency, n (%)		
Seizure-free for >1 year	538 (55.0%)	525 (55.3%)
Seizures experienced every 3–12 months	184 (18.8%)	176 (18.5%)
Seizures experienced every month	144 (14.7%)	141 (14.8%)
Seizures experienced every week or every day	112 (11.5%)	108 (11.4%)
Primary health practitioner, n (%)		
Neurologist	586 (59.9%)	572 (60.2%)
GP	376 (38.4%)	364 (38.3%)
Other	16 (1.6%)	14 (1.5%)
Perception of epilepsy as well-controlled, n (%)		
Yes	726 (74.2%)	705 (74.2%)
No	130 (13.3%)	128 (13.5%)
Unsure	122 (12.5%)	117 (12.3%)
Selected healthcare utilization rates in the past 12 months		
Visits to emergency department due to epilepsy, mean ± SD	0.54 ± 1.47	0.54 ± 1.48
Times seizure rescue medication administered outside of hospital/clinic, mean ± SD	0.76 ± 6.33	0.78 ± 6.42
Visits to GP regarding epilepsy management, mean ± SD	3.20 ± 7.68	3.25 ± 7.77
Visits to specialist regarding epilepsy management, mean ± SD	1.86 ± 4.48	1.88 ± 4.53

[†]NDDI-E: Neurological Disorders Depression Inventory for Epilepsy (scores >15 indicated MDD); [‡]GAD-7: Generalized Anxiety Disorder 7-item scale (scores ≥10 indicated GAD); AED group: respondents who had taken at least one antiepileptic drug in the past four weeks; GAD: generalized anxiety disorder; GP: general practitioner; MDD: major depression disorder; PwE: patients with epilepsy; QOLIE-10-P: Patient-Weighted Quality of Life in Epilepsy Inventory; SD: standard deviation.

indicated that they had not taken any seizure medication in the past four weeks.

2.3. Statistical analysis

The survey data were analyzed using R versions 3.5.0–3.5.2 [20]. A p-value less than 0.05 was considered statistically significant in all analyses. No sample size calculations were performed as all analyses were considered exploratory.

To avoid collinearity between variables in the analyses, AEs and comorbidities were grouped by type based on clinical rationale. The grouped variables remained binary; a "yes" response to each domain was determined by a "yes" response to any individual variable in that group.

Descriptive summary statistics were generated for demographic and clinical variables as well as for individual and grouped AEs and comorbidities, in order to observe the contributions of individual variables towards each AE or comorbidity group. To explore sample characteristics, descriptive statistics were also stratified by recruitment channel (MedAdvisor/Facebook) and the respondents' geographic remoteness, with the groups compared using chi-squared, Kruskal–Wallis H, or Mann–Whitney U tests.

As QoL scores were not normally distributed, we conducted Mann–Whitney U tests to determine univariable associations between grouped AEs and QoL (for respondents who had taken at least one AED in the past four weeks, "AED group"), and between grouped comorbid conditions and QoL (for all respondents).

Multivariable analyses were conducted to determine relationships between QoL and AEs or comorbidities after adjusting for control

variables that may improve the goodness of fit of the model. Two multivariable linear regression models were constructed, with grouped comorbidities as compulsory independent variables in the first model and grouped AEs as compulsory independent variables in the second model. Total QOLIE-10-P score was the outcome variable in both models.

Control variables for each model were determined using bidirectional stepwise selection. Variables available for selection in each model are listed in Supplementary Table 1. Each stepwise selection was performed based on Akaike information criterion (AIC), where a lower AIC indicates a better fitting model. When there were <10 cases for a given category, some categories within a variable were combined to increase counts; when merging was not possible, categories with low counts were removed. In some cases, variables were also recategorized to aid interpretation of the analysis. Once a final model was determined, multicollinearity was assessed by calculating the variance inflation factor (VIF) of each variable in the final model, with VIFs greater than 5 or 10 indicating moderate and severe multicollinearity, respectively. The R command "stepAIC" from the MASS package was used to perform the stepwise selection analysis [21].

To explore any effect of proxy responses by carers, a sensitivity analysis was performed where carer responses were excluded. A second post hoc sensitivity analysis was also performed where only neurologist-managed PwE were included, to investigate potential differences in the reporting of comorbidities and AEs between PwE managed by general practitioners (GPs) and specialists.

3. Results

3.1. Respondent characteristics

A total of 1267 responses were received. After data cleaning, 978 complete responses were included in subsequent analyses, of which 950 were in the AED group (Fig. 1). Characteristics were similar between the AED group and respondents overall (Table 1).

The mean age of all respondents was 44.5 years; approximately 47% were from higher socioeconomic households (quintiles 4 and 5), and more than half of respondents were employed (including part-time and self-employed, Table 1). The majority reported being seizure-free for >1 year, and three-quarters perceived their epilepsy as being well-controlled; 21% of respondents had >2 AEDs currently prescribed, and 65% had >2 different seizure medications prescribed over their lifetime (Table 1).

Most respondents were recruited from MedAdvisor (71%), with the remaining from Facebook. Stratifying by source of response, we found that respondents from MedAdvisor tended to be older and reported generally better-controlled epilepsy compared with respondents from Facebook (Supplementary Table 2). Seizure frequency was significantly different across the strata ($p < 0.001$); more MedAdvisor respondents were seizure-free for >1 year (61.7% vs. 38.7%), while a higher percentage of Facebook respondents experienced seizures every day to every month (37.7% vs. 21.5%). Respondents from Facebook also generally had more seizure medications currently prescribed and over their lifetime, and had made more visits to the emergency department, GPs, and specialists ($p < 0.05$, Supplementary Table 2). MedAdvisor respondents reported a higher mean QoL than the Facebook-recruited group by more than 15 points (48.6 vs. 32.3, $p < 0.001$).

Comparing respondents residing in different remoteness areas, there were significant differences across strata in the type of primary healthcare practitioner (HCP) managing their epilepsy; almost two-thirds of PwE living in major cities had a neurologist as their primary HCP, while only about half of PwE living in more remote areas were managed by neurologists, with more being managed by a GP ($p < 0.05$, Supplementary Table 3). Furthermore, PwE in more remote regions had a significantly higher number of seizure rescue medications administered outside of a clinical setting in the past year ($p < 0.05$, Supplementary Table 3).

Table 2
Summary of mean QOLIE-10-P scores by domains and individual items.

	All PwE (N = 978)	AED group (N = 950)
Total QOLIE-10-P, mean ± SD	43.9 ± 28.9	44.1 ± 28.9
Role functioning domain, mean ± SD	66.7 ± 29.2	66.9 ± 29.2
Epilepsy effects domain, mean ± SD	59.3 ± 30.2	59.4 ± 30.2
Mental health domain, mean ± SD	53.5 ± 19.9	53.6 ± 20.0
Question item 1: Energy/fatigue	38.2	38.4
Question item 2: Depression/emotional worry	61.8	62.0
Question item 3: Driving limitations	75.6	75.6
Question item 4: Work limitations	63.6	63.8
Question item 5: Social limitations	63.3	63.6
Question item 6: Memory difficulties/cognition	49.3	49.6
Question item 7: Physical effects of medications	63.7	63.6
Question item 8: Mental effect of medications	65.0	64.9
Question item 9: Seizure worry	64.5	64.5
Question item 10: Overall quality of life	60.6	60.4
Question item 11: Distress (weight)	0.64	0.64

AED group: respondents who had taken at least one antiepileptic drug in the past four weeks; PwE: patients with epilepsy; QOLIE-10-P: Patient-Weighted Quality of Life in Epilepsy Inventory; SD: standard deviation.

3.1.1. Quality of life of respondents

Among all survey respondents, the mean QOLIE-10-P score was 43.9 (standard deviation (SD): 28.9; minimum: 0.0; maximum: 100.0; Table 2). Respondent scores were well-spread in frequency between 0 and 100, with a slightly higher frequency at the extreme lower end (scores <10). Mean scores were lowest in the mental health domain (53.5) and highest in the role functioning domain (66.7; Table 2). Examining individual items, relatively low mean scores were observed for "memory difficulties/cognition" (49.3) and "energy/fatigue" (38.2) compared with "driving limitations" (75.6) and "mental effect of medications" (65.0; Table 2).

3.2. Prevalence of comorbidities and associations with QoL

Psychiatric disorders were the most commonly reported comorbidities (46%), followed by pain (44%), respiratory issues (39%), and cardio- or cerebrovascular disease (27%, Table 3). Of 16 comorbidities listed in the survey, the mean number reported was 2.5, with 73.6% reporting ≤3, and 16.9% reporting none at all (Fig. 2).

In the univariable analyses, there were significant differences in mean QoL for respondents with psychiatric disorders, respiratory issues, movement disorder/tremor, attention-deficit hyperactivity disorder (ADHD), and pain, compared with those without these grouped comorbidities ($p < 0.05$, Table 4).

After removing responses where categories with low cell counts were selected, 977 eligible responses were used to build the multivariable regression model. Control variables included in the model via bidirectional stepwise selection were seizure frequency, time since diagnosis, current number of AEDs prescribed, employment status, number of AEDs prescribed over entire lifetime, number of GP visits, and number of visits to the emergency department due to epilepsy in the past year. The final model accounted for approximately 52% of the variability in QoL, and only three grouped comorbidities were significantly associated with QoL ($p < 0.05$, Table 4). Psychiatric disorders were associated with the largest difference in QoL score (−23.14 [95% confidence interval (CI): −25.93, −20.34]), followed by movement disorder/tremor (−5.08 [−8.95, −1.21]), and pain (−4.94 [−7.62, −2.26]).

In the sensitivity analysis where carer responses were excluded (n = 855), results were similar (i.e., all significant variables remained significant). However, in the sensitivity analysis where only PwE managed

Table 3
Frequency of grouped and individual comorbidities.

Grouped comorbidity	n (%)	Individual comorbidity	n (%)
Psychiatric disorders	449 (46%)	Major depression disorder (from NDDI-E)[†]	397 (41%)
		Generalized anxiety disorder (from GAD-7)[‡]	247 (25%)
		Bipolar disorder	43 (4%)
Pain	428 (44%)	Migraine headache	305 (31%)
		Chronic pain	195 (20%)
		Neuropathic pain	99 (10%)
		Fibromyalgia	38 (4%)
Respiratory issues	385 (39%)	Asthma	244 (25%)
		Sleep disorder/apnea	193 (20%)
Cardio-/cerebrovascular disease	266 (27%)	High blood pressure	229 (23%)
		Stroke	60 (6%)
Movement disorder/tremor	134 (14%)	–	–
Severe head injury	100 (10%)	–	–
Diabetes	76 (8%)	–	–
Congenital birth defect	55 (6%)	–	–
Attention-deficit hyperactivity disorder (ADHD)	47 (5%)	–	–

Respondents were asked: "Have you ever been told by a health professional that you have…?"; [†]NDDI-E: Neurological Disorders Depression Inventory for Epilepsy (scores >15 indicated MDD); [‡]GAD-7: Generalized Anxiety Disorder 7-item scale (scores ≥10 indicated GAD).

by neurologists were included (n = 586), the association of QoL with pain became statistically insignificant (p = 0.120), while respiratory issues became significant (p = 0.042), with an associated change in QoL of −3.78 (95% CI: −7.43, −0.14; Supplementary Table 4). Psychiatric disorders and movement disorder/tremor remained significantly associated with QoL, with slightly larger estimated decreases (Supplementary Table 4).

3.3. Prevalence of reported AEs and associations with QoL

Sleep problems were the most-reported AE among survey respondents (89%), followed by memory problems (68%), headache (54%), and unsteadiness (50%, Table 5). Of the 11 individual AEs listed in the survey, the mean number per respondent was 5.1, with 7.4% reporting none, and no respondents reporting all 11 (Fig. 2).

In the univariable analyses, significant differences in mean QoL were found between respondents with and without any of all seven grouped AEs (p < 0.001, Table 6).

In the multivariable linear regression model, four AE groups showed a significant impact on QoL score (p < 0.05, Table 6). Self-reported memory problems were associated with the largest difference in QoL (−14.27 [95% CI: −17.02, −11.53]), followed by unsteadiness (−4.89 [−7.53, −2.26]), sleep problems (−4.68 [−8.75, −0.60]), and gastrointestinal issues (−3.79 [−6.41, −1.17]). Control variables included the presence of MDD or GAD, seizure frequency, employment status, time since diagnosis, current number of AEDs prescribed, and number of GP visits due to epilepsy in the past year. The model accounted for approximately 62% of the variability in QoL (Table 6).

In the sensitivity analysis where carer responses were excluded (n = 831), the results were similar (i.e., significant variables and control variables were the same), except for sleep problems, which became statistically insignificant (p = 0.134).

4. Discussion

This online survey, which aimed to obtain a more representative sample of the population of Australian PwE, found a high rate of reported comorbidities and AEs, even though respondents appeared to have relatively well-controlled epilepsy. Approximately half of respondents reported comorbid psychiatric disorders and pain, while more than two-thirds reported sleep and memory problems arising from AED use. In multivariable models, a number of comorbidities and AEs were significantly associated with decreased QoL; in particular, the largest decreases were observed in respondents who reported psychiatric comorbidities and memory issues.

4.1. Internet-recruited cohort

Using novel online recruitment methods, this survey accessed a sample of PwE with less severe epilepsy than typically recruited in other published surveys, with 55% of respondents reporting >1 year of seizure freedom and nearly half reporting treatment with AED monotherapy. In comparison, 42% were seizure-free for 12 months and 37%

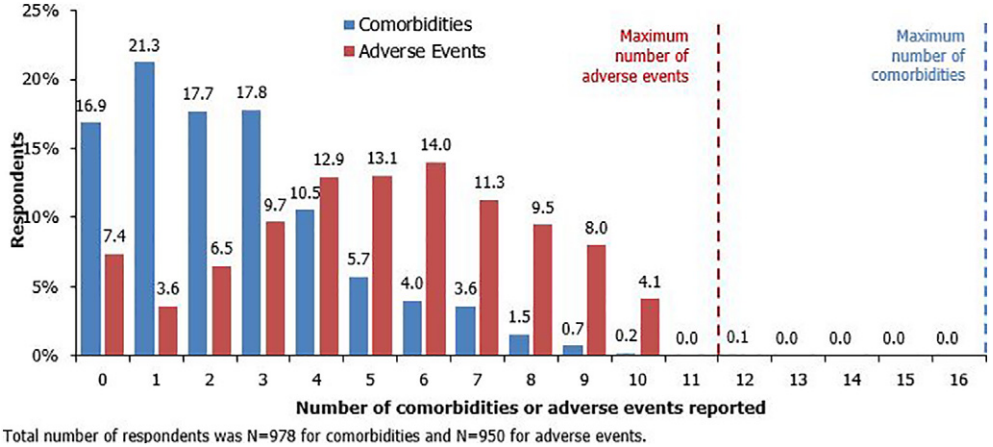

Fig. 2. Number of individual comorbidities and adverse events reported by respondents. Total number of respondents was N = 978 for comorbidities and N = 950 for adverse events.

Table 4
Results of univariable analysis and multiple regression model for comorbidities.

Independent variable	Univariable analysis	Multivariable regression model		
	p-Value*	Estimate (95% CI)†	p-Value	VIF
(Intercept)	–	76.94 (67.03, 86.85)	<0.001	–
Psychiatric disorders	<0.001	−23.14 (−25.93, −20.34)	<0.001	1.11
Movement disorder/tremor	<0.001	−5.08 (−8.95, −1.21)	0.010	1.06
Pain	<0.001	−4.94 (−7.62, −2.26)	<0.001	1.06
Respiratory issues	<0.001	−1.52 (−4.22, 1.18)	0.269	1.05
ADHD	0.004	−1.85 (−7.96, 4.25)	0.552	1.03
Diabetes	0.885	−0.19 (−5.08, 4.70)	0.938	1.04
Cardio-/cerebrovascular disease	0.839	0.66 (−2.31, 3.64)	0.662	1.06
Severe head injury	0.330	−0.18 (−4.48, 4.12)	0.935	1.04
Congenital birth defect	0.056	−0.86 (−6.48, 4.77)	0.765	1.03
Adjusted $R^2 = 0.52$, AIC = 5875.59				

*From Mann–Whitney U tests; †Estimates provided are vs. without specific comorbidity present; N = 978 responses were included in the univariable analyses; N = 977 responses were included in the multivariable regression model; ADHD: attention-deficit hyperactivity disorder; AIC: Akaike information criterion; CI: confidence interval; VIF: variance inflation factor.

were on monotherapy in the 2017 survey of the community-based Australian Epilepsy Research Register [22]. Additionally, there was a high rate of employment among PwE in this survey (51.7%), which was comparable with the Australian labor force participation rate of 47.7% for people with disabilities as recorded by the ABS [23]. The mean QOLIE-10-P score in our respondents (43.9) was higher than that of PwE cohorts recruited from hospitals and epilepsy clinics in the USA (33.3–36.7) and Ireland (37.3–39.2) [24–26].

The differences we found between Facebook and MedAdvisor respondents suggest that recruitment via MedAdvisor allowed us to reach a relatively unique community sample of PwE; the digital nature of the health app may have skewed the selection of survey respondents towards younger people with higher socioeconomic status [27], who may be more likely to be high-functioning, working adults. In contrast, recruitment via social media or patient organizations may reach a different population of PwE; among patients with cancer or chronic diseases, different characteristics and situations can increase motivation to seek out and actively participate in patient groups both offline and on social media [28]. For instance, those struggling to cope with more severe disease may be more likely to reach out to patient organizations for social support [29].

4.2. Comorbidities

The high rates of comorbid psychiatric and pain-related issues reported in this cohort of PwE, whose seizures were largely well-controlled, align with the findings of a recent community-based survey in Norway, in which the majority reported issues such as tiredness, memory and concentration problems, headache, and feeling depressed, despite over 40% of respondents having been seizure-free for at least one year [30].

Psychiatric comorbidities had the largest association with QoL in multivariable analyses. At 46%, the high rate of psychiatric comorbidities reported was internally consistent with the low mean scores found in the mental health domain of the QOLIE-10-P. Rates of depression and anxiety are known to be elevated in PwE: the prevalence of depression and GAD among PwE has been estimated at 9.6% and 12.5%, respectively [31], and 24% reported high or very high levels of psychological distress in the Tasmanian Epilepsy Register, a community-based cohort which recruited patients based on AED prescriptions in the Australian National Prescription Database [32]. In contrast, in 2007, 2.7% and 4.1% of the general Australian population reported having GAD or a depressive episode in the past year, respectively [33].

Rates of psychiatric comorbidities in our community-based sample (46%) were similar to those found by Gandy et al. among PwE from a tertiary epilepsy hospital in Sydney [9,34,35], where 39% of a cohort of 130 PwE had at least one psychiatric disorder [9]. The rate of MDD, measured through NDDI-E score, was 41% in our survey, vs. 30.6% of 147 PwE in the Sydney tertiary hospital [34], and 53.3% in a broader sample of 2254 patients with neurological disorders, including 676 with epilepsy [35]. Furthermore, although seizure-related factors and AED treatment have been previously identified as risk factors for depression [2], Gandy et al. found no statistically significant differences in the rates of any category of mood or anxiety disorders between those with well-controlled and refractory epilepsy [9]. The comparable rates of psychiatric comorbidities in our study with those of more severe patients recruited from tertiary institutions support the finding that both well-controlled and treatment-resistant forms of epilepsy are associated with equally high risk of mental health disorders [9].

In our analysis, the association between psychiatric comorbidities and decreased QoL was significant even after controlling for seizure frequency, the number of current and lifetime AEDs prescribed, and other proxies for disease severity. One multinational, phase IV clinical study

Table 5
Frequency of grouped and individual adverse events.

Grouped adverse events	n (%)	Individual adverse events	n (%)
Sleep problems	844 (89%)	Sleepiness	656 (69%)
		Tiredness	779 (82%)
		Disturbed sleep	625 (66%)
Memory problems	643 (68%)	Memory problems	643 (68%)
Headache	516 (54%)	Headache	516 (54%)
Unsteadiness	471 (50%)	Unsteadiness	383 (40%)
		Dizziness	352 (37%)
Gastrointestinal issues	340 (36%)	Upset stomach	340 (36%)
Weight gain	339 (36%)	Weight gain	339 (36%)
Visual disturbance	254 (27%)	Double or blurred vision	254 (27%)

Respondents were asked: "Questions about unwanted effects you may have experienced from your seizure medication: Over the past four weeks, have you had any of the problems listed below?"

Table 6
Results of univariable analysis and multiple regression model for adverse events.

Independent variable	Univariable analysis	Multivariable regression model		
	p-Value*	Estimate (95% CI)†	p-Value	VIF
(Intercept)	<0.001	81.89 (70.84, 92.95)	<0.001	–
Memory problems	<0.001	−14.27 (−17.02, −11.53)	<0.001	1.13
Unsteadiness	<0.001	−4.89 (−7.53, −2.26)	<0.001	1.16
Sleep problems	<0.001	−4.68 (−8.75, −0.60)	0.025	1.13
Gastrointestinal issues	<0.001	−3.79 (−6.41, −1.17)	0.005	1.11
Visual disturbance	<0.001	−1.94 (−4.97, 0.91)	0.182	1.12
Headache	<0.001	−0.87 (−3.57, 1.83)	0.526	1.19
Weight gain	<0.001	−0.74 (−3.20, 1.73)	0.557	1.04
Adjusted $R^2 = 0.62$, AIC = 5489.05				

*From Mann–Whitney U tests; †Estimates provided are vs. without specific adverse event present; N = 950 responses were included in both univariable and multivariable analyses; AIC: Akaike information criterion; CI: confidence interval; VIF: variance inflation factor.

that excluded patients with any serious psychiatric disorders within the past five years recorded a higher mean baseline QOLIE-10-P score of 56.3 among 152 Australian patients who had a similar mean epilepsy duration (22 years) and a much higher AED polytherapy rate of 67.8% at study entry than our sample, suggesting a more refractory group of PwE [36,37]. The comparatively high QOLIE-10-P scores found in this sample of patients further reinforce the notion that QoL may be greatly affected by factors other than seizure severity.

Indeed, previous studies have found that the impact of psychosocial factors on health-related QoL is independent from disease-specific variables and may even have a greater impact than disease severity [38–40]. It has been suggested that PwE whose seizures are well-controlled may place greater importance on coping with other impacts of their treatment and the psychosocial consequences of their epilepsy, instead of focusing on minimizing seizures [1].

At 44%, pain disorders were the second-most reported comorbidity type in our sample, with most respondents in this group reporting migraine headache and/or chronic pain. The prevalence of chronic pain and reoccurring pain (over a 6-month period) is 15.4% in the general Australian population based on the 2011 to 2012 Australian National Health Survey [41], while the estimated migraine prevalence is between 2.6% and 21.7%, with an average of ~12% [42]. The occurrence of migraines is known to be increased in PwE compared with the general population, though the nature of and basis for the association remains unclear [2].

Pain disorders were significantly associated with a decrease in QoL, suggesting that the known negative impact of migraines and chronic pain on QoL in the general population [43,44] is also applicable to PwE who are relatively well-controlled. However, in the sensitivity analysis including only neurologist-managed PwE, pain was no longer a significant predictor of QoL. The explanation for this is unclear; there may be demographic differences between neurologist-managed PwE and the GP-treated cohort, such as having higher socioeconomic status or more refractory epilepsy. Alternatively, as chronic pain is known to be associated with psychiatric disorders and psychological distress [45], there may be further unexplored interrelationships between pain and the other comorbidities in the model. We also note that although 54% of the AED group reported "headache" as an AE of AEDs, this was not significantly associated with a decrease in QoL in the multivariable model for AEs.

Finally, movement disorder/tremor was also significantly associated with a decrease in QoL. Other studies have reported a higher prevalence of movement disorder/tremor among PwE, possibly attributed to the use of valproate, which is known to cause tremors as an AE [3]. It is unclear if the presence of tremors as an AE could have been misclassified or misdiagnosed as a sign of a separate comorbid movement disorder in our survey. We considered that this may be particularly true in PwE primarily managed by GPs, who may not be aware of the association between valproate use and tremors. However, in a sensitivity analysis where only neurologist-managed PwE were included, this variable remained significant, with the estimate increasing slightly. Further studies would be needed to confirm if a primary movement disorder unrelated to medication use may be a common comorbidity affecting QoL among PwE.

4.3. Adverse events

While multiple studies have investigated the prevalence of various AEs of AEDs [1,6], and the association between the number of AEDs and QoL [46], there is a lack of evidence on the impact of different types of AEs on QoL among PwE.

Memory-related AEs were reported by 68% of respondents, and were associated with the largest decrease in QoL in our study. The low mean score we found for the "memory difficulties/cognition" item of the QOLIE-10-P was internally consistent with the high rate of memory-related AEs in our sample. Memory problems are one of the more common AEs reported by PwE [1,13]. Comparatively, the prevalence of self-reported memory problems in other populations ranges from 9% in US adults aged ≥40 years [47] to 33.5% among older adults (aged 65–85 years) in Australia [48].

It is important to note the possibility of other factors influencing the self-reporting of AEs by patients; a previous study of the Liverpool Adverse Events Profile found that comorbid depression, rather than AED exposure, was the strongest predictor for more patient-reported AEs [49]. Previous studies have found that both objective cognitive function (determined by memory, verbal ability, psychomotor, and processing speed tests) and self-reported cognitive functioning are significant predictors of QoL in PwE [50]. However, there is evidence that self-reported memory difficulties do not correlate highly with objective memory tests but are more closely related to mood [51]. Thus, although our multivariable analysis controlled for depression and anxiety, it is important to note that the effects of self-reported cognitive deficits on QoL may be confounded by mood disturbance [50]. Our study highlights that memory problems can remain a significant concern even among relatively well-controlled PwE; one possible interpretation is that high-functioning or reasonably controlled PwE may be more sensitive to cognitive issues, and are thus more likely to report and be affected by them than a more severe sample who are more focused on managing seizure control [1].

Sleep problems were the highest-reported AE in our sample, with 89% of respondents indicating tiredness, sleepiness, and/or disturbed sleep. This contrasts with the general Australian population, where the reported prevalence of excessive daytime sleepiness was between 10.4% (male) and 13.6% (female) [52], and 13–20% of adults from Adelaide reported sleeping difficulties [53]. The increased rate of sleep disorders in PwE is commonly attributed to both seizures and the effect of AEDs [54] and has previously been associated with significantly lowered QoL [54,55]. Our results align with what is known in the literature, although a relatively small decrease in QoL was observed. As sleep problems have been widely associated with memory issues and mood/anxiety disorders [56,57], this also further reinforces the possible negative effects of these interrelated issues among PwE.

4.4. Limitations of the study

This study reached a large sample of PwE with relatively well-controlled epilepsy, a group that is underrepresented in other studies of QoL among clinically recruited PwE. However, as noted in previous sections, digital recruitment may also limit the generalizability of our results; users of the MedAdvisor app and epilepsy Facebook groups who would have seen the survey invitation link may be more likely to be younger, working adults with higher socioeconomic status. There may furthermore be voluntary response bias, as all responders were self-selected and responses from noncompleters were discarded. Different characteristics and situational factors may affect motivation to actively participate in patient groups and likelihood of responding to the survey [28]; for instance, those who have already opted into the MedAdvisor app may be more amenable to sharing personal health data by participating in research.

In addition, there may have been recall bias, as survey questions required the retrospective recall of earlier diagnoses and medication history. Although the presence of GAD and MDD were evaluated via validated instruments within the survey, because these were screening tools and not diagnostic tests, the data may not represent the true rate of GAD or MDD diagnoses in the sample. Furthermore, other reported comorbidities may not have still been present at the time of the survey. As the classification of a symptom as a "comorbidity" or "adverse event" was self-reported, definitions may overlap or be inconsistent between respondents. In addition, since even *untreated* PwE may report AEs at the same rate as individuals newly started on AED treatment, some overrating of self-reported AEs may have occurred [49]. On the other hand, Bianchi et al. suggest that self-reported questionnaires may

allow better and more complete information to be collected on the medical history of PwE, with less bias from clinician judgment on the reporting of certain symptoms and signs considered more clinically important [58].

The use of stepwise selection for control variables in the multivariable analyses allowed for the systematic selection of predictors that are most likely to affect the outcome variable. However, only a single model is selected in this method, and if more than one equally well-performing model existed, it was not possible to assess how estimates may have changed according to different variables selected by other models.

While the survey was focused on collecting data on comorbidities and AEs that were potentially relevant to QoL based on prior research, other important variables may have been omitted, resulting in possible residual confounding. For instance, no information was collected on education level, and we also omitted questions on epilepsy etiology or seizure type because of difficulties ascertaining these accurately via patient self-report. As no data on specific medications were collected in our survey, we were also unable to control for the effect of comedications in our models, such as accounting for the use of valproate in evaluating the impact of tremors as a comorbidity.

Finally, as the survey was cross-sectional and only looked at a single timepoint for each responder, it is not possible to infer causal relationships using these data.

4.5. Implications and future directions

This study suggests that psychiatric disorders and memory problems are common, and a significant burden in well-controlled epilepsy.

To determine the appropriate management strategies to maximize QoL in PwE, further research is needed to explore the complex interrelationships between symptoms; for example, relationships between epilepsy and comorbidities such as migraine headaches may be bidirectional [2,40]. Future prospective studies would help to further clarify causality between the variables, including relationships between possibly interrelated or overlapping symptoms, and to account for individual medication effects.

Finally, preliminary additional analyses of our survey data provided some evidence that PwE living in rural or suburban areas are less likely to be managed by neurology specialists and may experience poorer outcomes, likely amplifying the negative effects of comorbidities and AEs on QoL among PwE. These rural–urban health disparities have been previously documented in Australia, with higher mortality and morbidity in remote communities compared with metropolitan areas, partially attributable to inequalities in access to care [59,60]. Further research should explore the need for improved access to epilepsy specialist services in remote regions, as rural PwE may face a lack of availability of specialized health professionals nearby and have difficulties traveling to faraway cities to reach appointments [61].

5. Conclusions

This online survey accessed a novel pool of relatively well-controlled PwE in Australia. In this sample, comorbidities and AEs were common, and psychiatric and memory problems were associated with the greatest detrimental impact on QoL. These results suggest the importance of evaluating even seemingly well-controlled PwE for comorbidities and AEs that may be impacting QoL.

Funding

This study was sponsored by UCB Pharma. Support for statistical analysis provided by Alvin Ng from Costello Medical, Singapore and third-party writing assistance for this article provided by Wee Yan Ran from Costello Medical, Singapore were funded by UCB Pharma in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Declaration of competing interest

JW is an employee of UCB Pharma. CW is CEO of Chronic Illness Alliance Inc. Australia and Board member of Epilepsy Foundation Australia. CW has received funding from UCB Pharma to contribute to this research. KR has received speaker honoraria, travel support, advisory board honoraria, and/or research funding from: UCB Pharma, Eisai Australia, Novartis Pharmaceuticals, Zogenix International Inc., AFT Pharmaceuticals Ltd., LivaNova Australia Pty Ltd., and Janssen-Cilag Pty Ltd. AN is an employee of Costello Medical Singapore Pte Ltd., which provided data analysis and editorial services for the study. LT is an employee of Epilepsy Action Australia and has no disclosures to declare. WD's salary is part-funded by The University of Melbourne. He has received travel, investigator-initiated, and speaker honoraria from UCB Pharma; investigator and speaker honoraria from Eisai Australia; educational grants from Novartis Pharmaceuticals, Pfizer Pharmaceuticals, and Sanofi-Synthélabo; educational, travel, and fellowship grants from GSK Neurology Australia; advisory board honoraria from LivaNova PLC and Tilray Inc.; and honoraria from ScieGen Pharmaceuticals.

Acknowledgments

This study was funded by UCB Pharma. The authors thank the respondents who took part in this survey, as well as Epilepsy Australia, Epilepsy Action Australia, Epilepsy Foundation, and MedAdvisor for their support in distributing the survey. The authors also acknowledge Wee Yan Ran from Costello Medical, Singapore, for medical writing and editorial assistance based on the authors' input and direction.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106856.

References

[1] Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia 1997;38:353–62.
[2] Seidenberg M, Pulsipher DT, Hermann B. Association of epilepsy and comorbid conditions. Future Neurol 2009;4:663–8.
[3] Ottman R, Lipton RB, Ettinger AB, Cramer JA, Reed ML, Morrison A, et al. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey. Epilepsia 2011;52:308–15.
[4] Canuet L, Ishii R, Iwase M, Ikezawa K, Kurimoto R, Azechi M, et al. Factors associated with impaired quality of life in younger and older adults with epilepsy. Epilepsy Res 2009;83:58–65.
[5] Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia 2011;52:2181–91.
[6] Bazil CW. Comprehensive care of the epilepsy patient—control, comorbidity, and cost. Epilepsia 2004;45:3–12.
[7] St. Louis EK. Minimizing AED adverse effects: improving quality of life in the interictal state in epilepsy care. Curr Neuropharmacol 2009;7:106–14.
[8] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. Anxiety in epilepsy: a neglected disorder. J Psychosom Res 2015;78:149–55.
[9] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. Rates of DSM-IV mood, anxiety disorders, and suicidality in Australian adult epilepsy outpatients: a comparison of well-controlled versus refractory epilepsy. Epilepsy Behav 2013;26:29–35.
[10] Cheng C, Dunn M. Health literacy and the Internet: a study on the readability of Australian online health information. Aust N Z J Public Health 2015;39:309–14.
[11] Wicks P, Keininger DL, Massagli MP, de la Loge C, Brownstein C, Isojarvi J, et al. Perceived benefits of sharing health data between people with epilepsy on an online platform. Epilepsy Behav 2012;23:16–23.
[12] Ottman R, Barker-Cummings C, Leibson CL, Vasoli VM, Hauser WA, Buchhalter JR. Validation of a brief screening instrument for the ascertainment of epilepsy. Epilepsia 2010;51:191–7.
[13] Panelli RJ, Kilpatrick C, Moore SM, Matkovic Z, D'souza WJ, O'brien TJ. The Liverpool Adverse Events Profile: relation to AED use and mood. Epilepsia 2007;48:456–63.

[14] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.
[15] Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. Rapid detection of major depression in epilepsy: a multicentre study. Lancet Neurol 2006;5:399–405.
[16] Cramer JA, Perrine K, Devinsky O, Meador K. A brief questionnaire to screen for quality of life in epilepsy the QOLIE-10. Epilepsia 1996;37:577–82.
[17] Cramer JA, Van Hammée G, N132 Study Group. Maintenance of improvement in health-related quality of life during long-term treatment with levetiracetam. Epilepsy Behav 2003;4:118–23.
[18] Australian Bureau of Statistics. Correspondence, 2017 postcode to 2016 remoteness area. http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.005July%202016?OpenDocument. [Accessed 20 June 2018].
[19] Australian Bureau of Statistics. Postal area, indexes, SEIFA 2016. http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012016?OpenDocument. [Accessed 21 August 2018].
[20] R Core Team. R: a language and environment for statistical computing. https://www.R-project.org/. [Accessed 23 August 2018].
[21] Venables WN, Ripley BD. Modern applied statistics with S. . 4th ed.New York: Springer; 2002.
[22] Peterson C, Piccenna L, Walker C. Summary of the Australian Epilepsy Longitudinal Survey — Wave 4. https://www.epilepsyfoundation.org.au/wp-content/uploads/2017/01/Wave-4_Report-summary.pdf. [Accessed 23 July 2019].
[23] Australian Bureau of Statistics. 4433.0.55.006 - Disability and Labour Force Participation. http://www.abs.gov.au/ausstats/abs@.nsf/mf/4433.0.55.006#1; 2012. [Accessed 23 July 2019].
[24] Alexander HB, Broshek DK, Quigg M. Quality of life in adults with epilepsy is associated with anticonvulsant polypharmacy independent of seizure status. Epilepsy Behav 2018;78:96–9.
[25] Quigg M, Gharai S, Ruland J, Schroeder C, Hodges M, Ingersoll KS, et al. Insomnia in epilepsy is associated with continuing seizures and worse quality of life. Epilepsy Res 2016;122:91–6.
[26] Higgins A, Downes C, Varley J, Tyrell E, Normand C, Doherty CP, et al. Patients with epilepsy care experiences: comparison between services with and without an epilepsy specialist nurse. Epilepsy Behav 2018;85:85–94.
[27] Krebs P, Duncan DT. Health app use among US mobile phone owners: a national survey. JMIR Mhealth Uhealth 2015;3:e101.
[28] Han JY, Kim J-H, Yoon HJ, Shim M, McTavish FM, Gustafson DH. Social and psychological determinants of levels of engagement with an online breast cancer support group: posters, lurkers, and nonusers. J Health Commun 2012;17:356–71.
[29] Antheunis ML, Tates K, Nieboer TE. Patients' and health professionals' use of social media in health care: motives, barriers and expectations. Patient Educ Couns 2013;92:426–31.
[30] Henning O, Landmark CJ, Henning D, Nakken KO, Lossius MI. Challenges in epilepsy—the perspective of Norwegian epilepsy patients. Acta Neurol Scand 2019;140:40–7.
[31] Rai D, Kerr MP, McManus S, Jordanova V, Lewis G, Brugha TS. Epilepsy and psychiatric comorbidity: a nationally representative population-based study. Epilepsia 2012;53:1095–103.
[32] Lacey CJ, Salzberg MR, Roberts H, Trauer T, D'Souza WJ. Psychiatric comorbidity and impact on health service utilization in a community sample of patients with epilepsy. Epilepsia 2009;50:1991–4.
[33] Australian Bureau of Statistics. 4326.0 - National survey of mental health and wellbeing: summary of results. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4326.0Main+Features32007?OpenDocument; 2007. [Accessed 7 October 2019].
[34] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, et al. Assessing the efficacy of 2 screening measures for depression in people with epilepsy. Neurology 2012;79:371–5.
[35] Gandy M, Karin E, Fogliati VJ, Meares S, Nielssen O, Titov N, et al. Emotional and cognitive difficulties, help-seeking, and barriers to treatment in neurological disorders. Rehabil Psychol 2018;63:563.
[36] Steinhoff BJ, Somerville ER, Van Paesschen W, Ryvlin P, Schelstraete I. The SKATE™ study: an open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. Epilepsy Res 2007;76:6–14.
[37] Somerville ER, McLaughlin DB, Robinson MK, Berkovic SF, Australian SKATE Study Group. Adjunctive therapy of uncontrolled partial seizures with levetiracetam in Australian patients. Epilepsy Behav 2007;11:338–42.
[38] Pulsipher DT, Seidenberg M, Jones J, Hermann B. Quality of life and comorbid medical and psychiatric conditions in temporal lobe epilepsy. Epilepsy Behav 2006;9:510–4.
[39] Hackett ML, Glozier NS, Martiniuk AL, Jan S, Anderson CS. Sydney epilepsy incidence study to measure illness consequences: the SESIMIC observational epilepsy study protocol. BMC Neurol 2011;11:3.
[40] Kwan P, Yu E, Leung H, Leon T, Mychaskiw MA. Association of subjective anxiety, depression, and sleep disturbance with quality-of-life ratings in adults with epilepsy. Epilepsia 2009;50:1059–66.
[41] Miller A, Sanderson K, Bruno R, Breslin M, Neil AL. The prevalence of pain and analgesia use in the Australian population: findings from the 2011 to 2012 Australian National Health Survey. Pharmacoepidemiol Drug Saf 2017;26:1403–10.
[42] Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? Brain Behav 2018;8:e00950.
[43] Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. J Pain Res 2016;9:457.
[44] Guitera V, Muñoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: a study in a general population. Neurology 2002;58:1062–5.
[45] Institute of Medicine (US) Committee on Pain. Disability, and chronic illness behavior. 9 psychiatric aspects of chronic pain. Pain and disability: clinical, behavioral, and public policy perspectives. National Academies Press (US); 1987.
[46] Thomas SV, Koshy S, Nair CS, Sarma SP. Frequent seizures and polytherapy can impair quality of life in persons with epilepsy. Neurol India 2005;53:46.
[47] Jean-Pierre P, Winters PC, Ahles TA, Antoni M, Armstrong FD, Penedo F, et al. Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study. J Oncol Pract 2011;8:30–4.
[48] Mewton L, Sachdev P, Anderson T, Sunderland M, Andrews G. Demographic, clinical, and lifestyle correlates of subjective memory complaints in the Australian population. Am J Geriatr Psychiatry 2014;22:1222–32.
[49] Perucca P, Jacoby A, Marson A, Baker G, Lane S, Benn E, et al. Adverse antiepileptic drug effects in new-onset seizures: a case–control study. Neurology 2011;76:273–9.
[50] Perrine K, Hermann BP, Meador KJ, Vickrey BG, Cramer JA, Hays RD, et al. The relationship of neuropsychological functioning to quality of life in epilepsy. Arch Neurol 1995;52:997–1003.
[51] Elixhauser A, Leidy NK, Meador K, Means E, Willian MK. The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. Epilepsy Res 1999;37:13–24.
[52] Hayley AC, Williams LJ, Kennedy GA, Berk M, Brennan SL, Pasco JA. Prevalence of excessive daytime sleepiness in a sample of the Australian adult population. Sleep Med 2014;15:348–54.
[53] Lack L, Miller W, Turner D. A survey of sleeping difficulties in an Australian population. Community Health Stud 1988;12:200–7.
[54] Piperidou C, Karlovasitou A, Triantafyllou N, Terzoudi A, Constantinidis T, Vadikolias K, et al. Influence of sleep disturbance on quality of life of patients with epilepsy. Seizure 2008;17:588–94.
[55] De Weerd A, De Haas S, Otte A, Trenité DKN, Van Erp G, Cohen A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. Epilepsia 2004;45:1397–404.
[56] Kyle SD, Crawford MR, Morgan K, Spiegelhalder K, Clark AA, Espie CA. The Glasgow Sleep Impact Index (GSII): a novel patient-centred measure for assessing sleep-related quality of life impairment in insomnia disorder. Sleep Med 2013;14:493–501.
[57] Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. Depress Anxiety 2015;32:664–70.
[58] Bianchi E, Erba G, Beghi E, Giussani G. Self-reporting versus clinical scrutiny: the value of adding questionnaires to the routine evaluation of seizure disorders. An exploratory study on the differential diagnosis between epilepsy and psychogenic nonepileptic seizures. Epilepsy Behav 2019;90:191–6.
[59] Dixon J, Welch N. Researching the rural–metropolitan health differential using the 'social determinants of health'. Aust J Rural Health 2000;8:254–60.
[60] Thomas SL, Wakerman J, Humphreys JS. Ensuring equity of access to primary health care in rural and remote Australia-what core services should be locally available? Int J Equity Health 2015;14:111.
[61] England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy across the spectrum: promoting health and understanding: a summary of the Institute of Medicine report. Epilepsy Behav 2012;25:266–76.