Accepted Date : 02-Dec-2015

What factors contribute to the risk of depression in epilepsy? - The Tasmania Epilepsy Register Mood Study (TERMS)

Cameron J Lacey FRANZCP [ab]
Michael R Salzberg MD [a]
Wendyl J D'Souza PhD [b]

[a] Department of Psychiatry, St Vincent's Hospital Melbourne, The University of Melbourne, Melbourne, Victoria, Australia
[b] Department of Medicine, St Vincent's Hospital Melbourne, The University of Melbourne, Melbourne, Victoria, Australia

Corresponding Author Dr Cameron Lacey
Present address Department of Psychological Medicine
University of Otago, Christchurch
PO Box 4345
Christchurch, New Zealand
Email cameron.lacey@otago.ac.nz
Phone: +64 3 3720400
Fax: +64 3 3720407

Running Title	Risk factors for depression in epilepsy
Key Words	Risk Factors, Epilepsy, Seizures, Depression, Community studies
Number of Pages	21
Word Count	3284
Number of References	41
Number of Figures	Nil
Number of Tables	2 plus 1 supplementary table

Objective: To model factors associated with depression in a community sample of people with epilepsy. The factors investigated were derived from proposed risk factors for depression from patients with epilepsy, other chronic illness and the general population.

Methods: Multivariate analysis using general linear regression models of factors associated with depression in the Tasmanian Epilepsy Register Mood Study (TERMS), a cross-sectional community sample of 440 patients with epilepsy.

Results: A model with acceptable fit was created that explained 66% of the variance of depression. Associated factors included in this model were neuroticism, physical functioning, social support, past history of depression and stressful life events.

Significance: In this cross-sectional study specifically designed to investigate depression in epilepsy, we showed that general risk factors for depression in other illness and in the general population are also important in patients with epilepsy, with little support for disease-related risk factors.

KEY WORDS Risk Factors, Epilepsy, Seizures, Depression, Community studies

Introduction

Systematic reviews support an increased prevalence of depression in patients with epilepsy and suggest a broad biopsychosocial approach is necessary to better understand the factors associated with depression.[1; 2] Comorbid depression has a range of adverse consequences for the patient and implications for clinical practice. These include decreased quality of life, diminished medication adherence, poorer treatment outcomes, increased health service use,[3] increased cognitive complaints, increased risk of other chronic diseases such as cardiovascular disease, and suicide.[4] However the risk factors that contribute to this important comorbidity remain uncertain. Better identification of these factors is needed to advance treatment and prevention of depression in patients with epilepsy.

Conceptual models of the complex interaction between risk factors for major depression and chronic medical conditions have been proposed.[5] Recent models increasingly utilize a lifespan approach by linking established risk factors for depression (genetics, early life adversity and stressful life events) with subsequent maladaptive relationship attachments (including with health service providers), biobehavioural risks for chronic disease, consequences of chronic disease and a person's ability to self-manage this disease. A similar theoretical approach based on a diathesis-stress model has recently been described with regard to epilepsy.[6]

The rate of depression appears to rise as one moves from primary care to secondary and tertiary care.[3] This suggests that ascertainment bias may limit the generalizability of findings from secondary-tertiary samples to community treated people with epilepsy. With this in mind, this study was designed to identify factors associated with depression in a community sample of people with epilepsy.

METHODS

Population

The Tasmanian Epilepsy Register Mood Study (TERMS) was designed specifically to investigate depression in patients with epilepsy. TERMS was a cross-sectional mail survey of a community sample of patients with epilepsy previously recruited onto the Tasmanian Epilepsy Register (TER). The TER is a predominantly primary care treated cohort of patients with epilepsy, invited from the Australian National Prescription Database, diagnosed using a validated seizure interview interpreted by an epilepsy specialist using standardized guidelines. Details of the methodology of TER have been previously published.[7] Inclusion criteria for this study were participants who remained enrolled on the TER; aged 16 years or above; able to provide informed consent.

Depression Assessment

The Center for Epidemiologic Studies Depression Scale (CES-D) was the primary measure of depression (defined as those with a score of 15 or higher).[8] The CES-D is a reliable measure of depression in patients with epilepsy[9] and has been used in multiple epilepsy studies.[6] The CES-D has comparable sensitivity (0.985), specificity (0.791) and predictive values to another widely used depression self report instrument, the Beck Depression Inventory II (BDI-II).[9]

Associated Variables

Variables were selected to provide as comprehensive coverage as possible of the proposed and established risk factors derived from our previous systematic review.[2]

Sociodemographic Variables

Participants' socioeconomic status was assessed using level of education and occupation. Highest educational level was coded as a four point ordinal variable: "Up to year 10 or equivalent", "Up to year 12 or equivalent", "Trade, Certificate or Diploma", and "Tertiary Degree or Higher Degree". An ordinal occupation level for the participant and partner was created based on previous studies of associations with socioeconomic status in the Australian population.[10] A combined education-household occupation variable was created in a similar manner to a previous examination of the impact of socioeconomic status on mental disorder in the Australian population.[11]

Disease-Related Variables

Some epilepsy diagnostic information was available from the TER. When possible, both the patient and a witness were questioned by the interviewer. Previous research established that use of the TER diagnostic epilepsy interview, when interpreted with standardized diagnostic guidelines, produced close agreement with an epilepsy specialist's clinical assessment in diagnosing the presence of epilepsy (K=0.94), seizure-onset type (K=0.84), and the presence of Idiopathic Generalised Epilepsy or Genetic Generalised Epilepsy under the new terminology (IGE/GGE) (K=0.82) when evaluating patients with suspected seizures in a outpatient setting.[12] When examining the idiopathic generalized epilepsy syndromes, given the small numbers with generalized epilepsy with febrile seizures plus, epilepsy with myoclonic absences syndromes and IGE unspecified, these were combined into 'idiopathic generalized other' for subsequent analyses. Participants who reported taking two or more medications taken for epilepsy (anticonvulsant medications) in the previous four weeks were categorized as AED polytherapy. The Short Form 12 Health Survey (SF12) – Physical Component Summary score subscale was used as a combined measure of physical impairment that could incorporate impairment from participants' seizures as well as other physical comorbidities.

Psychological Variables

Early environment stress was examined in two questionnaires. First, the Measure of Parenting Style (MOPS) assessed perceived parenting experience in the first 16 years of life.[13] Second, the Global Perceived Early Life Stress (GPELS) provided a

brief two-item assessment of overall early life-stress.[14] Stressful life events were measured using the List of Threatening Experiences Questionnaire.[15] Both severity and number of threatening experiences were combined by summing the subjective rated impact of all events to create the LTE-Q variable. Past history of major depression was assessed using a general screening question designed to detect any significant lifetime episode of two weeks or more.[16] The personality construct of neuroticism was assessed with the International Personality Item Pool - Neuroticism Scale (IPIP-N), which consists of questions that measure characteristics such as tenseness, self-doubt and pessimism.[17] Social support was assessed using the Modified Measure Of Social Support Survey (MSSS-5).[18]

Statistical analysis

Univariate associations between depression and associated variables are presented using the CES-D total score and tested using Spearman correlation, independent *t* tests and ANOVA tests for continuous, dichotomous and categorical variables respectively. Associations were tested using data from all available participants, noting that not all participants answered all questions. Multivariate analysis used stepwise linear regression models (IBM SPSS Statistics, version 22) to estimate the association between depression and associated variables. Any variable with a p value of <0.1 was entered in the regression analysis.

This study was granted ethical approval by the University of Tasmania Human Research Ethics Committee.

RESULTS

Sociodemographic and disease characteristics

The demographic and disease characteristics of the included sample are presented in Table 1. 74% (440/597) of eligible TER participants responded and the final sample comprised 212 men and 228 women with a mean age of 52 years (SD 16 years). Most participants were married or in a de facto relationship (58%). More than half (59%) of all participants were not employed. Using the CES-D, almost half (44%) of the sample had depression. Most participants (56%) had not experienced a seizure in the previous two years. The majority (299; 68%) of participants reported (or 'were classified as having') a focal seizure onset and 98 (22%) an Idiopathic Generalised Epilepsy syndrome (IGE). Of those with IGE, 29 had juvenile absence, 27 had childhood absence, 26 had juvenile myoclonic epilepsy and 23 had other IGE syndromes.

INSERT TABLE 1 APPROX HERE

Univariate associations

Significant associations between and depressive symptoms and associated variables are highlighted in Table 1. There was no significant correlation between depressive symptoms and age (r=0.05, p=0.26). There was no significant difference in depressive symptoms between males and females (p=0.07). When the relationship between age and depression was examined in males and females separately there remained no significant relationship. A higher level of depressive symptoms was seen in participants not currently in a relationship (p=0.001). Lower combined household socioeconomic status was significantly associated with higher depressive symptoms (p=0.036).

There was a significant relationship between increasing seizure frequency and greater depressive symptoms p<0.001). There was no significant relationship between depressive symptoms and different types of seizure onset. There was no difference in depressive symptoms in those with IGE syndrome and without IGE. There were no significant group differences in depressive symptoms between the different idiopathic generalized epilepsy syndromes (F=1.62, df=4, p=0.17). The majority of participants (64%) reported taking only one anticonvulsant medication in the previous four weeks. Participants receiving more than one anticonvulsant were more likely to report more depressive symptoms (p=0.04). There was a significant inverse correlation between SF12 Physical (PCS) and depressive symptoms (r=-0.31, p<0.001). All psychological variables examined were associated with depressive symptoms (additional details presented in supplementary table e-1). There was a significant association between MOPS Negative Parenting and higher depressive symptoms (p<0.001). Greater perceptions of birth – preteen life stress (GPELS) were associated with greater depressive symptoms (p<0.001). Experience of at least one stressful life event was very common and only 17% reported no stressful life event in the previous five years. There was a significant association between depressive symptoms and the LTE-Q Total (p<0.001). Almost half (48%) of participants reported a previous depressive episode and those with a past history of depression were more likely to report greater current depressive symptoms (p<0.001). There was a strong correlation between depressive symptoms and neuroticism (r=0.78, p<0.001). There was a significant relationship between less social support and increasing depressive symptoms (p<0.001).

Multivariate analysis

All variables with $p<0.1$ in univariate associations with depression were entered into the general linear regression. The following variables met this threshold: gender, combined SES, relationship status, seizure frequency, SF12 PCS, MOPS negative parenting, GPELS, LTE-Q, past history of depression, neuroticism, MSSS-5 and anticonvulsant polytherapy. The final model (see table 2) showed that depression was significantly associated with neuroticism, physical functioning, social support, past history of depression and stressful life events. The model was significant ($F=119.675$, $p<0.001$) and accounted for approximately 66% of the variance of CES-D ($R^2 =.665$, adjusted $R^2 =.659$). Depressive symptoms were primarily predicted by higher levels of neuroticism which uniquely accounted for approximately 52% of the variance of depressive symptoms.

INSERT TABLE 2 APPROX HERE

DISCUSSION

Depression was common in this community-based cohort and our linear regression model demonstrated that depression was associated with neuroticism, physical functioning, level of social support, past history of depression and stressful life events. These five factors explained 66% of the variance of depressive symptoms. Although systematically examined, epilepsy-related factors had minimal explanatory effect.

The proportion of depression in our study was slightly higher than a US community-based sample of people with epilepsy that used the same screening tool and grade for depression (35% mild-severe depression vs 44% in our sample).[8] In 2001, when this cohort was initially recruited, Tasmania was the most disadvantaged state in Australia with a smaller proportion of residents classified in the higher socioeconomic ranks,[19] which may partially explain the observed higher depression rate.

Although our study was one of the few community studies primarily designed to investigate depression in epilepsy, there is considerable research available from epilepsy samples in other settings. We found little evidence of a relationship between age or gender and presence of depression, however a previous systematic review suggested the most likely candidates for risk factors for depression were female gender, younger age, lower socioeconomic status and single or divorced relationship status.[2] Contrary to this, some non-community based samples have found higher risk of depression in males.[20] Other studies have found either female gender[21] or neither gender was associated with depression.[22] It is possible that selection bias contributed to the discrepancies in the hospital derived studies of people with epilepsy. However the failure to consistently establish a relationship between gender and depression in people with epilepsy is strikingly different to that seen in depression in the general population[23] and other chronic disease[24] and suggests there may be significant differences in the development of depression in patients with epilepsy although the direction remains unclear.

The relationship between age and psychiatric comorbidity is inconsistent. The average age of this sample was older than in most studies included in our previous systematic review,[2] which may contribute to the lack of association with depression in our study. Across most studies of depression in people with epilepsy, other chronic

illness and the general population, younger patients are more at risk of depression with gender differences also declining with advancing age.[25] Relationship status (being single, divorced, widowed) has also been reported in some epilepsy studies using other sampling methods[22] and is consistent with an extensive literature on depression in the general population.[23]

Whilst socioeconomic status was associated with increased rate of depression in univariate analysis it did not remain significant in the multivariate analysis. The reasons for this lack of association remain unclear. The association between depression and individual socioeconomic status has been a consistent finding in the large literature on the impact of socioeconomic status on depression in the general population.[23] In addition, markers of socioeconomic status such as employment and financial strain were predictive of depression in a hospital derived prospective epilepsy study.[26]

No epilepsy-related variable was retained in the final model and only seizure frequency was significant in univariate analysis, consistent with the conclusion that seizure frequency was commonly associated with depression, although in a previous systematic review[2] the overall contribution to risk of depression was small. Although, there is some support for increasing illness severity as a risk factor for depression in people with stroke and cancer,[27] seizure type and syndrome are often poorly addressed in community epilepsy studies, with few studies attempting this and most relying on the imprecision of patient self-report[28] or clinical record review.[29] One potential problem with these methods is the likely inclusion of patients with conditions that mimic seizures such as psychogenic non-epileptic seizures and the inability to define diagnosis at a higher syndrome level. There is a much larger literature derived from more highly selected samples with more accurate seizure type and epilepsy syndrome characterisation, with many advocating that depression is more common in focal epilepsy than in other types and syndromes,[21] although this is also debated.[6; 26] Others have proposed that the type of seizure experienced may also be important, with generalized tonic clonic, myoclonic and partial seizures suggested as risk factors for depression.[30] An important strength of this study is our standardized validated methods to classify patients' epilepsy using direct interviews, diagnostic guidelines and an epilepsy specialist.[12] Therefore, the lack of an association between depression and epilepsy variables in this community study is more persuasive than in

previous studies; and strengthens the case that there are likely to be significant problems with selection bias in the highly selected hospital samples.

Greater physical comorbidity was associated with increased risk of depression. This is consistent with emerging awareness of the prevalence and importance of the range of comorbidities in addition to neuropsychiatric comorbidity that is seen in people with epilepsy. Comorbidities of epilepsy (other than depression) such as other chronic illnesses have been associated with depression in previous studies.[31] Other studies derived from non-community sources also support the impact of comorbidities on depression in people with epilepsy.[22]

All psychological and personality variables were associated with depression in univariate analysis and comprised four of the five variables retained in the regression model. Neuroticism has been considered in various personality construction theories using different instruments. One of the more common personality construction theories is the five-factor model and our study used a questionnaire which aims to assess a similar concept of neuroticism.[17] Neuroticism had the strongest weight in our model which is consistent with extensive evidence demonstrating that neuroticism is a risk factor for the development of depression in the general population.[32] Whilst possible that the presence of depression itself may lead to participants erroneously reporting their premorbid personality, there is evidence of consistency of personality self-reports including neuroticism.[33] The experience of stressful life events in the previous five years was strongly associated with depression. No previous community epilepsy study examined stressful life events. However there are reports demonstrating a strong effect of stressful life events on risk of depression using other disease samples.[34] There is also an extensive literature in general depression[15] and other chronic diseases on the association between depression and stressful life events.[23] In a small hospital based sample of people with epilepsy the final linear regression model included mostly psychological variables (stress, social support, self-efficacy) in a model that accounted for 54.7% of the variance.[35] Another hospital-based study also found that similar psychological variables (social support and stigma) were included in a regression model that accounted for up to 46% of the variance of depression at baseline.[26] These are similar to the psychological variables retained in the linear regression model in our study (stressful life events, a past history of depression, neuroticism, social support), which explained 66% of the variance and

is the best predictive model available to date. Although our study did not include stigma much of the literature about the importance of perceived stigma in patients with epilepsy and subsequent risk of depression relies on predominantly tertiary or highly selected samples and cross-sectional associations.[36] Limitations in the link between stigma and risk of depression include considerable variability in perceived stigma in epilepsy across cultures[37] and inconsistent findings when confounding factors were included.[38]

The importance of psychological variables in our study has potential implications for treatment of depression in epilepsy. Psychological factors are potential targets for intervention using standardized psychotherapeutic approaches and arguably are more modifiable than many socio-demographic and disease-related variables. Furthermore, similar links between depression and social support have also been reported in other chronic conditions and social support has been the target of controlled intervention trials.[39]

Clearly the problem of depression comorbidity is not unique to epilepsy but whether depression is more common in people with epilepsy compared to other neurological disorders remains uncertain. Furthermore the risk factors for depression in this epilepsy population were broadly similar to those in other chronic diseases and in the general population. Further research is required to determine if differing prevalence of these risk factors in patients with epilepsy compared to other chronic disease contributes to the difference in prevalence of depression.

Ultimately there is a need to adopt a lifespan approach to understand these two chronic diseases and their overlapping aetiologies. For example, the complex changing patterns of neurogenesis over time in both epilepsy and depression underscores the need to consider a lifespan approach.[40]

There are several limitations to this study. The main drawback is the prevalent cross-sectional design resulting in the examination of factors associated with depression by retrospective recall in established epilepsy. The prevalent cohort design also has limitations as participants may be captured at different stages of their illness. It is possible the patients at different stages of the condition, may have different risk factors for depression. A longitudinal design, considerably more expensive and lengthier to conduct, would have offered the advantage of probing incident depression as well as risk factors. Nevertheless, the results from cross-sectional analyses can

generate valuable insights that can inform prospective studies. The sample utilized for this study was not a random sample and may does not reflect the diversity of patients with epilepsy and their severity in the population. It may be that patients with epilepsy, treated by community physicians, have less severe forms of epilepsy which may explain the limited explanation of seizure related variables in the analysis. A further limitation is the reliance on self-rated/report instruments for many of the factors assessed in this study: the assessment of depression, parenting, neuroticism, social support, life experiences and personal and family psychiatric history. Additionally the CES-D is a self-report screening test of depressive symptoms and there may be discrepancies between symptoms of depression identified with this questionnaire and a diagnosis of major depression as made by structured clinical assessment. Although limited non-invasive alternative methods are currently available, accurately determining frequency of seizures is challenging, particularly when loss of awareness during events affects recall.[41]

In this cross-sectional study specifically designed to investigate depression in epilepsy, we found that risk factors in current multi-step modeling of depression in chronic disease and general populations were also associated with depression in patients with epilepsy. Further, incident, prospective designed studies need to focus on these factors and not be constrained to epilepsy-related factors if we are to improve our understanding of this important comorbidity in patients with epilepsy.

Key Points

- General linear regression was used to model factors associated with depression in a cross-sectional community sample of 440 patients with epilepsy.
- Factors associated with depression were neuroticism, physical functioning, social support, past history of depression and stressful life events.
- This model explained 66% of the variance of depressive symptoms.

DISCLOSURES

This study was supported by a Pfizer Neurosciences Grant.

Assoc Prof D'Souza has received support from travel, investigator-initiated, and speaker honoraria from ***UCB Pharma***; educational grants from ***Novartis Pharmaceuticals, Pfizer Pharmaceuticals*** and ***Sanofi-Synthelabo***; educational, travel and fellowship grants from ***GSK Neurology Australia***, and honoraria from ***SciGen Pharmaceuticals***. Dr. Cameron Lacey has received a research grant from **Pfizer Pharmaceuticals**. The remaining author has no conflicts of interest.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Funding

This study was supported by a Pfizer Neurosciences Grant.

Contributions of authors

CL designed the study, conducted the analysis, interpreted the data, drafted the manuscript. WD assisted with conception and design of the study, interpreting the data, and revising the manuscript. MS assisted with conception and design of the study, interpreting the data, and revising the manuscript. All authors approved the version to be published.

REFERENCES

1. Fiest KM, Dykeman J, Patten SB, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80:590-599.

2. Lacey C, Salzberg M, D'Souza W. Risk Factors for Depression in Community Treated Epilepsy: Systematic Review. Epilepsy Behav 2015;43:1-7

3. Lacey CJ, Salzberg MR, Roberts H, et al. Psychiatric comorbidity and impact on health service utilization in a community sample of patients with epilepsy. Epilepsia 2009;50:1991-1994.

4. Barry JJ, Ettinger AB, Friel P, et al. Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. Epilepsy Behav 2008;13 Suppl 1:S1-29.

5. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216-226.

6. Hoppe C, Elger CE. Depression in epilepsy: a critical review from a clinical perspective. Nature Reviews Neurology 2011;7:462-472.

7. D'Souza WJ, Fryer JL, Quinn SJ, et al. The Tasmanian Epilepsy Register--a community-based cohort. Background and methodology for patient recruitment from the Australian national prescription database. Neuroepidemiology 2007;29:255-263.

8. Ettinger A, Reed M, Cramer J, et al. Depression and comorbidity in community-based patients with epilepsy or asthma. Neurology 2004;63:1008-1014.

9. Jones JE, Hermann BP, Woodard JL, et al. Screening for major depression in epilepsy with common self-report depression inventories. Epilepsia 2005;46:731-735.

10. Ball K, Mishra GD. Whose socioeconomic status influences a woman's obesity risk: her mother's, her father's, or her own? Int J Epidemiol 2006;35:131-138.

11. Taylor R, Page A, Morrell S, et al. Socio-economic differentials in mental disorders and suicide attempts in Australia. Br J Psychiatry 2004;185:486-493.

12. D'Souza WJ, Stankovich J, O'Brien TJ, et al. The use of computer-assisted-telephone-interviewing to diagnose seizures, epilepsy and idiopathic generalized epilepsy. Epilepsy Res 2010;91:20-27.

13. Parker G, Roussos J, Hadzi-Pavlovic D, et al. The development of a refined measure of dysfunctional parenting and assessment of its relevance in patients with affective disorders. Psychol Med 1997;27:1193-1203.

14. Carpenter LL, Tyrka AR, McDougle CJ, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. Neuropsychopharmacology 2004;29:777-784.

15. Brugha TS, Cragg D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. Acta Psychiatr Scand 1990;82:77-81.

16. Gladstone GL, Parker GB. Is behavioral inhibition a risk factor for depression? J Affective Disord 2006;95:85-94.

17. Goldberg LR, Johnson JA, Eber HW, et al. The international personality item pool and the future of public-domain personality measures. Journal of Research in Personality 2006;40:84-96.

18. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32:705-714.

19. Australian Bureau of Statistics. Population by Age and Sex, Australian States and Territories. Canberra: Australian Bureau of Statistics 2003. Report No.:Cat. No.3201.0

20. Altshuler L, Rausch R, Delrahim S, et al. Temporal lobe epilepsy, temporal lobectomy, and major depression. J Neuropsychiatry Clin Neurosci 1999;11:436-443.

21. Kimiskidis VK, Triantafyllou NI, Kararizou E, et al. Depression and anxiety in epilepsy: the association with demographic and seizure-related variables. Annals of General Psychiatry 2007;6:28.

22. Thompson AW, Miller JW, Katon W, et al. Sociodemographic and clinical factors associated with depression in epilepsy. Epilepsy Behav 2009;14:655-660.

23. Goodwin R, Jacobi F, Bittner A, et al. Epidemiology of Mood Disorders. In DJ S (Ed) The American Psychiatric Publishing Textbook of Mood Disorders, American Psychiatric Publishing: Arlington, Va; 2006:33-54.

24. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry 2007;29:409-416.

25. Surtees PG. Psychosocial aetiology of chronic disease: a pragmatic approach to the assessment of lifetime affective morbidity in an EPIC component study. J Epidemiol Community Health 2000;54:114-122.

26. Reisinger EL, DiIorio C. Individual, seizure-related, and psychosocial predictors of depressive symptoms among people with epilepsy over six months. Epilepsy Behav 2009;15:196-201.

27. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. The Medical Journal of Australia 2009;190:S54-60.

28. Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. Epilepsy Behav 2009;14:134-140.

29. Stefanello S, Marin-Leon L, Fernandes PT, et al. Psychiatric comorbidity and suicidal behavior in epilepsy: a community-based case-control study. Epilepsia 2010;51:1120-1125.

30. de Souza EAP, Salgado PCB. A psychosocial view of anxiety and depression in epilepsy. Epilepsy & Behavior 2006;8:232-238.

31. Naess S, Eriksen J, Tambs K. Psychological well-being of people with epilepsy in Norway. Epilepsy Behav 2007;11:310-315.

32. Kendler KS, Gatz M, Gardner CO, et al. Personality and major depression: a Swedish longitudinal, population-based twin study. Arch Gen Psychiatry 2006;63:1113-1120.

33. Costa PT, Bagby RM, Herbst JH, et al. Personality self-reports are concurrently reliable and valid during acute depressive episodes. J Affect Disord 2005;89:45-55.

34. Wiegartz P, Seidenberg M, Woodard A, et al. Co-morbid psychiatric disorder in chronic epilepsy: recognition and etiology of depression. Neurology 1999;53:S3-8.

35. Lee SA, Lee SM, No YJ. Factors contributing to depression in patients with epilepsy. Epilepsia 2010;51:1305-1308.

36. Whatley AD, DiIorio CK, Yeager K. Examining the relationships of depressive symptoms, stigma, social support and regimen-specific support on quality of life in adult patients with epilepsy. Health Educ Res 2010;25:575-584.

37. Baker GA, Brooks J, Buck D, et al. The Stigma of Epilepsy: A European Perspective. Epilepsia 2000;41:98-104.

38. Hermann BP, Whitman S, Wyler AR, et al. Psychosocial predictors of psychopathology in epilepsy. Br J Psychiatry 1990;156:98-105.

39. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA 2003;289:3106-3116.

40. Danzer SC. Depression, stress, epilepsy and adult neurogenesis. Exp Neurol 2012;233:22-32.

41. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol 2013;12:563-571.

Table 1 Characteristics of TERMS sample and p-value of univariate association with depressive symptoms

Variable	n, percentage	Mean CES-D	p-value
Male	212 (48%)	14.4	0.07[a]
Female	228 (52%)	16.4	
Relationship Status			
Never Married	102 (23.2%)	15.8	0.001[b]
Married/De Facto	257 (58.4%)	14.0	
Divorced/Separated	55 (12.7%)	21.0	
Widowed	20 (4.8%)	15.7	
Combined Household SES			
1 (Low)	108 (24.5%)	17.5	0.036[b]
2	74 (16.8%)	16.9	
3	75 (17.0%)	15.8	
4	35 (8.0%)	14.9	
5	42 (9.5%)	14.9	
6	30 (6.8%)	13.2	
7	25 (5.7%)	11.2	
8 (High)	31 (7.9%)	10.1	
Seizure Frequency (in the last two years)			
None	236 (54.4%)	12.9	<0.001[b]
Once	30 (6.8%)	14.9	
More than 1 but not monthly	90 (20.5%)	17.1	
Monthly-weekly	51 (11.6%)	20.2	
At least weekly	27 (6.1%)	23.5	
Seizure Onset Type			
Generalized	102 (23.2%)	15.4	0.99[b]

Focal	300 (68.2%)	15.4	
Uncertain	38 (8.6%)	15.3	
Epilepsy Syndrome			
Idiopathic Generalized Epilepsy	98 (22%)	15.7	0.97[a]
Other	343 (78%)	15.3	
Anticonvulsant Medication			
Monotherapy	272 (64%)	14.6	0.04
Polytherapy	151 (34%)	17.0	

[a] Independent t test. [b] ANOVA. CES-D - Center for Epidemiologic Studies Depression Scale.

Table 2 Stepwise regression results

Model	Unstandardized Coefficients		Standardized Coefficients			
	B	Std. Error	Beta	t	Sig.	sr^2
(Constant)	9.167	3.847		2.383	.018	
Neuroticism	.819	.053	.628	15.594	<.001	.520
Physical functioning (PCS)	-.139	.034	-.139	-4.044	.<001	-.135
Measure of social support (MSSS-5)	-1.972	.503	-.137	-3.919	<.001	-.131
Previous depression	-2.986	.867	-.129	-3.444	.001	-.115
Stressful life events (LTE-Q)	.817	.385	.077	2.119	.035	.071

Dependent variable was depressive symptoms (CES-D). sr^2 squared semipartial correlation. PCS: Physical Component Summary score of Short Form Health Survey (SF12), MSSS-5: Modified Measure Of Social Support Survey, LTE: List of Threatening Experiences Questionnaire.