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Sociodemographic and Clinical Factors Associated with Depression in Epilepsy

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Abstract

The impact of mood disorders on patients with epilepsy is an important and growing area of research. If clinicians are adept at recognizing which patients with epilepsy are at risk for mood disorders, treatment can be facilitated and morbidity avoided. We completed a case-control study (80 depressed subjects, 141 non-depressed subjects) to determine the sociodemographic and clinical factors associated with self-reported depression in people with epilepsy. The Patient Health Questionnaire-9 was used to determine clinically significant depression. In multivariate analyses, depressed subjects with epilepsy were significantly less likely than non-depressed subjects to be married or employed and more likely to report comorbid medical problems and active seizures in the past six months. Adjusted for all other variables, subjects with epilepsy reporting lamotrigine use were significantly less likely to be depressed [OR = 0.4 (95% CI: 0.2 -- 0.8)] compared to those not reporting lamotrigine use.

Keywords

Epilepsy; Depression; Seizures; Case-control; Epidemiology

INTRODUCTION

Depression is a common disorder with lifetime prevalence in the United States of approximately 16% [1]. Depression is more common in women, the poor, those with less education, those with more severe adverse life events, and those with medical illness [2]. Epilepsy is also a common disorder with lifetime prevalence estimated at 0.5% [3]. The two conditions are often comorbid and prior studies report a prevalence of major depression in people with epilepsy of 20–55% in those with uncontrolled epilepsy and between 3–9% in those with controlled epilepsy [4].

Patients with epilepsy have a higher risk of suicide compared to the general population [5] and those with epilepsy who suicide have higher rates of comorbid psychiatric illness [6]. Depression in patients with epilepsy is associated with a lower quality of life [7] with one study finding depression to be the only predictor of quality of life [8]. Patients with epilepsy and depression also utilize more health resources compared to patients with epilepsy alone [9] and

most patients with epilepsy and depression do not have depression diagnosed or adequately treated [10].

Many biopsychosocial factors have been associated with increased depression in patients with epilepsy including being male [11], having a low IQ or learning disability [12], having an “external locus of control” [13], having a family history of major depression [14], and being less physically active [15]. Patients with epilepsy experience stigma in social and vocational areas of life [16] and stigma may be a risk factor for depression [17]. A left-sided seizure focus may place a patient at higher risk for depression [18] and those who have more frequent seizures also appear at risk [19]. A relationship also exists between depression and the use of more than one antiepileptic drug (AED) or taking certain AEDs (e.g. phenobarbital) [20]. The following report adds to work in this area by describing a case-control study reporting the sociodemographic and clinical factors associated with depression in patients with epilepsy.

RESEARCH DESIGN AND METHODS

This study was designed as a multidisciplinary effort between the neurologists, neuropsychologists, and psychiatrists caring for patients through the University of Washington Regional Epilepsy Center (UW REC), primarily through Harborview Medical Center, the King County Washington safety net hospital. The study was approved by the Institutional Review Board at the University of Washington and all subjects provided informed consent prior to participation.

Project PEARL (People Encouraging Active Rewarding Lives) is a CDC-funded randomized controlled trial investigating an intervention for subjects 18 years and older with epilepsy and comorbid depression who are treated at the UW REC or the University of Washington general neurology clinics. Patients enrolled in that trial must have epilepsy (defined by being enrolled at the UW REC or neurology clinics with an ICD-9 diagnosis of epilepsy) and meet criteria for major depression, minor depression, or dysthymia based on the Patient Health Questionnaire-9 (PHQ-9), a valid screen for depressive disorders [21]. Though the PHQ-9 has not been validated as a screening tool in patients with epilepsy, it has been validated in patients with traumatic brain injury [22], stroke [23], and chronically ill elderly patients [24]. Subjects must speak and read English and have been seen by a UW neurologist in the past two years. Exclusion criteria included being pregnant or nursing, having a bipolar or psychotic disorder, seeing a psychiatrist, screening positive for substance abuse on the CAGE questionnaire [25], or having severe cognitive deficits (defined as correctly answering less than three of five orientation and memory recall questions taken from the Mini-Mental Status Exam [26]). Recruitment for Project PEARL involved a two-stage process detailed in Figure 1. In stage one, potential cases were given a two-item screen (the screening questionnaire 1, or SQ1) containing the cardinal symptoms of depression (depressed mood or anhedonia) from the PHQ-9. Anyone with a positive SQ1 was asked to complete the second screening questionnaire (SQ2) containing the full PHQ-9 and items necessary to determine eligibility. Those ultimately enrolled as cases completed a baseline questionnaire containing demographic, behavioral, and clinical questions. For Project PEARL, the SQ2 was administered face-to-face or over the phone and the baseline questionnaire was filled out face-to-face.

Using the PHQ-9, major depression is defined by having five or more depressive symptoms more than half the days for at least two weeks, with at least one symptom being depressed mood or anhedonia [21]. Minor depression is defined as having two to four depressive symptoms for nearly half the days over two weeks with at least one of the symptoms being depressed mood or anhedonia while not meeting criteria for dysthymia [27]. Dysthymia was diagnosed if a subject answered positively one of two dysthymia screening questions and had at least three depressive symptoms for nearly half the days over the past two weeks with one

of them being depressed mood. Of the 80 depressed cases in Project PEARL, 49 (61.25%) met criteria for both major depression and dysthymia (“double depression”), 6 (7.5%) met criteria for major depression only, 15 (18.75%) met criteria for dysthymia only, and 10 (12.5%) met criteria for minor depression. For the purposes of this study, all four groups were combined and are called “depressed.”

Project PRIDE (Predictors of Depression in Epilepsy), a sub-study of Project PEARL, involved recruiting controls from the group of subjects who screened negative for depression on the SQ1 screening for Project PEARL. Controls met all criteria for the PEARL study with the exception of depression diagnosis and cognitive screen. Because the cognitive screen must be done in person or over the phone, this was not completed on potential controls. However, only 0.8% of subjects were ineligible for the PEARL study based on this cognitive screen (see Figure 1). Of the 333 potential controls, 185 responded (response rate of 55%) and 141 were eligible to be used as control subjects for the data analysis (see Figure 1 for details). All respondents received \$10. Compared to the subjects who either did not respond or did not meet criteria to serve as a control ($n=218$), controls were more likely to be married ($\chi^2(1) = 13.38, p<0.001$) or white ($\chi^2(1) = 12.47, p<0.001$) but were not different with respects to age or gender.

Cases with depression (from Project PEARL) and controls (from Project PRIDE) answered identical baseline questions regarding age, gender, education, employment, marital status, and race. Other baseline measures included the Rapid Assessment of Physical Activity (RAPA) [28] and, based on the methods of Wells et al. [29], we estimated non-epilepsy medical comorbidity by having subjects answer yes or no to a list of 18 possible medical conditions. Baseline clinical questions included self-reports of both seizure type (with or without loss of consciousness (LOC)) and frequency and current medications. This case-control study only involved the comparison of baseline data between the cases and controls. There was no intervention involved in any part of this study.

STATISTICAL ANALYSIS

After institutional review board approval was obtained, we examined the deidentified data to compare differences in sociodemographic and self-reported clinical factors between the two groups. Statistical analyses were performed using Intercooled Stata version 10.0 (StataCorp LP, College Station, TX). Questionnaire items included multiple categories for many demographic questions such as highest level of education, marital status, current work status, and race. Binary variables were created for these demographic variables including “college or more,” “married or living as married,” “white,” and “employed.” The RAPA is a brief screener that categorizes subjects as “active,” “underactive,” or “sedentary.” A binary physical activity variable was created indicating whether a subject was “active” or not. The number of “other health problems” answered positively by subjects was summed and treated as a continuous variable. Each subject was asked to report if he or she had a seizure with or without LOC in the past month. Subjects were then asked to write down the number of seizures with or without LOC experienced over the past month and six month periods. Due to the wide variability in the number of seizures reported, binary categories were created for “more than one seizure in the past month” and “more than six seizures in the past six months” for those who reported any number of seizures in the past month or six months. Subjects reported the name of any psychotropic or antiepileptic drug being taken. This drug information was all self-report and used as binary variables. Continuous variables were analyzed using two-group t-tests and chi-square tests were used to examine categorical data.

A logistic regression analysis was performed using the unadjusted variables significantly associated with depression in the bivariate analyses ($p<0.05$). The one month binary seizure

variables were not added to the model due to collinearity with the six month binary seizure variables.

RESULTS

Table 1 details the demographic, physical activity, and other health problem differences between the depressed and non-depressed subjects. Compared to non-depressed controls, depressed subjects report less education, are less likely to be married or employed, are less likely to be categorized as “active” on the RAPA, and report significantly more comorbid medical problems. There was no age or gender difference between groups.

Figure 2 demonstrates that subjects with depression were more likely than those without depression to report having had seizures with or without LOC in the past month and past six months. As detailed in Table 2, among those subjects reporting any seizures with or without LOC in the past month or six months, there were no group differences regarding the number of seizures reported. In other words, depressed subjects were more likely than non-depressed subjects to report any seizure activity, however, depressed subjects reporting active seizures do not report a significantly higher seizure frequency compared to non-depressed subjects reporting active seizures.

Table 3 details the analysis of medication use between the two groups. Benzodiazepines (prescribed either on a schedule or as needed to treat acute seizures) were separated from other antiepileptic drugs (AEDs) due to their potential use for both seizures and psychiatric symptoms. Antidepressant drug use is a binary variable that is positive if the subject reported taking any medicine that is classified as an antidepressant (including low doses of trazodone or tricyclic antidepressants used for sleep). There was no relationship between presence of depression and the number of non-benzodiazepine AEDs reportedly used. When binary categories were created comparing taking none or one AED to taking two or more AEDs, there was also no relationship ($\chi^2(1) = 0.26$, $p=0.6$). Subjects with depression were significantly more likely than those without depression to report benzodiazepine and antidepressant use. Among AEDs taken by more than 10 subjects, non-depressed subjects were more likely to report taking lamotrigine ($\chi^2(1) = 4.6$, $p = 0.03$).

The logistic model shown in Table 4 indicates that, after adjusting for other variables, being married (or living as married) and being employed full or part time is associated with lower odds of being depressed compared to those who are unmarried or not employed. The odds of depression also increased with the number of reported chronic medical problems. Regardless of seizure type (i.e. with or without LOC), subjects reporting active seizures in the past six months have a higher odds of depression compared to subjects reporting no seizures. Those reporting active seizures with loss of consciousness appear to be at higher risk of depression (OR = 5.69) compared to those reporting active seizures without loss of consciousness (OR = 2.22). Adjusted for all other variables, taking antidepressants is associated with higher odds of depression and lamotrigine use was associated with lower odds of depression.

A sensitivity analysis was completed that found no significant difference in results when the minor depressed group (N=10) was excluded. There was also no significant sociodemographic or clinical difference between groups (major depression and dysthymia compared to minor depression) when analysis of variance or chi-square group comparisons were performed. Supplemental Tables 1 through 3 contain analysis results comparing subjects taking lamotrigine (N=87) to those not taking lamotrigine (N=134) on all of the sociodemographic and clinical variables addressed in this study. The only difference found was that subjects taking lamotrigine were significantly more likely to be taking two or more non-benzodiazepine anticonvulsants compared to those not taking lamotrigine ($\chi^2(1) = 12.21$, $p < 0.001$).

DISCUSSION

The relationship between psychiatric disorders and epilepsy has been observed since the time of Hippocrates. Recent epidemiologic studies have confirmed both the association between the two disorders and the bidirectional nature of that association. For example, Kobau and colleagues studied 4,345 surveys from a population-based sample of US households. After adjusting for income and ethnicity, adults reporting an epilepsy diagnosis (2.9% of the sample) were 2.5 times more likely to report depression in the previous year [30]. Also, depression has been found to be a risk factor for seizures, possibly due to neurochemical changes in the brain [31]. Our cross-sectional case-control study corroborates the known association between seizures and depression [32], but offers no insight into the direction of that relationship.

Consistent with existing literature about the epidemiology of depression in the general population, this study suggests that people with epilepsy who are unmarried, unemployed, and have comorbid medical problems are more likely to have depression. However, in this study, those who participated as controls in the non-depressed group were more likely to be married than those who did not participate as controls. This may bias the finding that those with depression and epilepsy were less likely to be married. The unadjusted analysis showed a relationship between lack of physical activity and depression. This is consistent with previous research in people with epilepsy associating decreased levels of physical activity with depression [15]. Unlike depression in the general population, this study found no relationship between depression and age or gender, replicating a finding from other studies of depression in people with epilepsy [33].

Another potentially clinically relevant finding from this study is that, after adjusting for sociodemographic and clinical factors, subjects with epilepsy reporting treatment with lamotrigine had odds of depression half that of subjects not reporting lamotrigine use. This finding supports other research suggesting lamotrigine may function as an antidepressant in patients with epilepsy [34-36]. However, this finding must be tempered by the fact that lamotrigine has not demonstrated efficacy as a treatment for acute bipolar depression [37] and has shown little promise as a treatment for acute unipolar depression [38]. This may be because people with epilepsy experience distinct mood difficulties (e.g. the well-described interictal dysphoric disorder [39]) compared to the major depressive episodes experienced by those without epilepsy but with bipolar and unipolar mood disorders. This study supports that idea. While we did not use an interictal dysphoric disorder screen, our “depressed” group of 80 subjects included 64 (80%) who reported significant dysphoric symptoms over the past two years.

In this study, there are many unmeasured factors such as epilepsy type (e.g., generalized versus focal), comorbid neurologic conditions (e.g. head injury, brain surgery), lamotrigine dose, length of time on a particular AED, and AED adherence that may confound the relationship between lamotrigine use and depression. Our analysis did not demonstrate that subjects taking lamotrigine had less active seizures and, in fact, demonstrated that subjects taking lamotrigine were more likely to be prescribed at least one other AED. The non-depressed subjects were more likely, after adjusting for seizure frequency, to be on lamotrigine, and those on lamotrigine were more likely than those not on lamotrigine to be on at least two or more total non-benzodiazepine AEDs. This might suggest that subjects on lamotrigine actually had more difficult to treat epilepsy though that is not supported by our data in Supplemental Table 2. Alternatively, it could be that the treating neurologists kept patients on lamotrigine because of perceived beneficial effects on mood, even in situations where other AEDs had to be added to improve seizure control.

In what may appear to be a counterintuitive finding, these data showed that subjects using antidepressants were significantly more likely to report depression. However, research has demonstrated that depressed patients in primary care who are accurately diagnosed and receive antidepressants are often those with the most severe depressions and treatment is frequently inadequate [40]. This “severity confound” indicates that these subjects were getting treated for depression but treatment was either ineffective or it was too early in treatment to show benefit. This study is strengthened by the use of ambulatory subjects and a control group that closely resembles the cases. One limitation is the lack of a formal diagnostic interview to define the presence or absence of a depressive disorder. While the PHQ-9 has been validated against gold-standard interviews like the Structured Clinical Interview for the DSM (SCID), it has not been validated in people with epilepsy. For this reason, the depression and non-depression diagnoses may not be valid and other diagnoses such as dysthymic disorders may not have been defined accurately. Another significant limitation is the lack of more detailed clinical information such as epilepsy type. The apparent differences between those with and without depression might be more clinically relevant if analyses could be stratified by epilepsy type. Other limitations include the use of subjects enrolled at a tertiary care specialty epilepsy program, limiting generalization to patients with epilepsy in the general population. In addition, there is selection bias as those who ultimately served as the controls may differ from those who did not in other ways besides the few demographic characteristics (age, gender, and marital status) we were able to compare. Also, while cases and controls were asked the same questions, controls completed a mailed questionnaire while cases were interviewed in person. In addition, the clinical information was based on self-report and, as noted, many clinical factors were not studied and case and control definition was not based on a clinical interview. Overall, these findings add to the understanding of depression in patients with epilepsy and highlight the need to investigate this further with well-designed, population-based, prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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¹ Subjects eligible for the PEARL Study were referred back to the study. Six of these subjects were ultimately randomized

² 22 subjects met only one exclusion criteria while five others met two criteria

Figure 1.
PEARL and PRIDE Study Recruitment

☐	Not Depressed	
☒	Depressed	
¹	12.8% vs. 28.9%	$\chi^2(1) = 8.6$
²	19.2% vs. 51.3%	$\chi^2(1) = 24.7$
³	20.6% vs. 40%	$\chi^2(1) = 9.65$
⁴	34.8% vs. 56.3%	$\chi^2(1) = 9.65$

Figure 2.
Self-Reported Seizure Frequency By Group

Table 1
Demographic and Clinical Characteristics By Depression Grouping

	Not Depressed (N=141)	Depressed (N=80)	Test Statistic
Age	43.9 ± 15.2	43.9 ± 11	t = 0.02 ; df = 219
Women	74 (52.5)	42 (52.5)	$\chi^2(1) = 0.00$
College or more	109 (77.3)	39 (48.8)	$\chi^2(1) = 18.81$ ***
Married or living as married	69 (48.9)	25 (31.3)	$\chi^2(1) = 6.53$ *
White	129 (91.5)	67 (83.8)	$\chi^2(1) = 3.0$
Living alone or single with children	40 (28.4)	27 (33.8)	$\chi^2(1) = 0.7$
Employment: full or part time	73 (51.2)	19 (23.8)	$\chi^2(1) = 16.5$ ***
Mean number of reported medical problems ¹	1.4 ± 1.6	2.9 ± 2.3	t = -5.8 ; df = 219 ***
"Active" level of physical activity ²	70 (49.7)	20 (25)	$\chi^2(1) = 12.8$ ***

Data are n (%) or mean ± SD

** p<0.01

p<0.001

*
p<0.05

¹ Subjects answered "yes" or "no" to 18 different chronic medical conditions

² Physical activity level based on answers to the Rapid Assessment of Physical Activity Questionnaire

Table 2
Self-Reported Seizure Frequency by Depression Grouping

Seizures with Loss of Consciousness (LOC)			
	Not Depressed (N=141)	Depressed (N=80)	Test Statistic
Any seizures <i>with</i> LOC in the past month?	18 (12.8)	23 (28.9)	$\chi^2(1) = 8.6^{**}$
• More than one seizure with LOC reported in the past month ¹	9 (50)	10 (43.5)	$\chi^2(1) = 0.17$
Any seizures <i>with</i> LOC in the past six months?	27 (19.2)	41 (51.3)	$\chi^2(1) = 24.7^{***}$
• More than six seizures with LOC reported in the past six months ²	7 (25.9)	5(12.2)	$\chi^2(1) = 2.11$
Seizures without Loss of Consciousness (LOC)			
	Not Depressed (N=141)	Depressed (N=80)	Test Statistic
Any seizures <i>without</i> LOC in the past month?	29 (20.6)	32 (40)	$\chi^2(1) = 9.65^{**}$
• More than one seizure without LOC reported in the past month ³	19 (65.5)	24 (75)	$\chi^2(1) = 0.65$
Any seizures <i>without</i> LOC in the past six months?	49 (34.8)	45 (56.3)	$\chi^2(1) = 9.65^{**}$
• More than six seizures without LOC reported in the past six months ⁴	20 (40.82)	22 (48.9)	$\chi^2(1) = 0.62$

Data are n (%)

* p<0.05

p<0.001

**
p<0.01

¹ Calculated only for those who reported any seizures *with* LOC in the past month; comparison is between those who reported more than one seizure and those who reported only one

² Calculated only for those who reported any seizures *with* LOC in the past six months; comparison is between those reporting more than six seizures and those reporting six or fewer

³ Calculated only for those who reported any seizures *without* LOC in the past month; comparison is between those reporting more than one seizure and those reporting only one

⁴ Calculated only for those who reported any seizures *without* LOC in the past six months; comparison is between those reporting more than six seizures and those reporting six or fewer

Table 3

Medication Use by Group

	Not Depressed (N=141)	Depressed (N=80)	Test Statistic
Total Non-benzodiazepine Anticonvulsants¹			$\chi^2(4) = 3.2$
• None	1 (0.7)	0 (0)	
• One	78 (55.3)	42 (52.5)	
• Two	42 (29.8)	28 (35)	
• Three	20 (14.2)	9 (11.3)	
• Four	0 (0)	1 (1.3)	
Any Antidepressant Use	24 (17)	34 (42.5)	$\chi^2(1) = 17.1$ ***
Any Benzodiazepine Use	12 (8.5)	14 (17.5)	$\chi^2(1) = 4$ *
Specific Anticonvulsant Use²			
• Carbamazepine	27 (19.2)	18 (22.5)	$\chi^2(1) = 0.4$
• Lamotrigine	63 (44.7)	24 (30)	$\chi^2(1) = 4.6$ *
• Levetiracetam	39 (27.7)	18 (22.5)	$\chi^2(1) = 0.7$
• Phenytoin	21 (14.9)	11 (13.8)	$\chi^2(1) = 0.1$
• Pregabalin	11 (7.8)	9 (11.3)	$\chi^2(1) = 0.7$
• Topiramate	19 (13.5)	16 (20)	$\chi^2(1) = 1.6$
• Valproic Acid	12 (8.5)	13 (16.3)	$\chi^2(1) = 3.0$
• Zonisamide	11 (7.8)	5 (6.3)	$\chi^2(1) = 0.2$

Data are n (%) or mean $\pm$ SD

** p<0.01

p<0.001*
p<0.05

¹When binary categories were compared for taking two or more anticonvulsants (compared to only one or none) or three or more anticonvulsants (compared to taking none, one, or two), there were also no significant associations by depression grouping

²Calculations performed only for drugs taken by >10 subjects; excluded were acetazolamide, ethosuximide, felbamate, gabapentin, oxcarbazepine, phenobarbital, primidone, and tiagabine

Table 4
Logistic Regression Model of Depression versus No Depression

Independent Variables	Odds Ratio	95% CI
College or more	0.80	0.36 -- 1.80
Married or living as married	0.43 *	0.20 -- 0.93
Employment: full or part time	0.41 *	0.18 -- 0.91
Number of other health problems		
• 1 vs. 0	1.46 ***	1.19 -- 1.80
• 2 vs. 0	2.14 ***	1.41 -- 3.25
• 3 vs. 0	3.14 ***	1.68 -- 5.86
"Active" level of physical activity	0.58	0.27 -- 1.24
Seizures <i>with</i> LOC in the past six months	5.69 ***	2.54 -- 12.77
Seizures <i>without</i> LOC in the past six months	2.22 *	1.06 -- 4.66
Any Antidepressant Use	3.03 **	1.35 -- 6.79
Any Benzodiazepine Use	2.54	0.86 -- 7.54
Lamotrigine Use	0.39 *	0.18 -- 0.83

p<0.001

**
p<0.01

*
p<0.05