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Utilization of care among drug resistant epilepsy patients with symptoms of anxiety and depression

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ABSTRACT

Purpose: Epilepsy patients have a significantly higher rate of anxiety and depression than the general population, and psychiatric disease is particularly prevalent among drug resistant epilepsy patients. Symptoms of anxiety and depression might serve as a barrier to appropriate epilepsy care.

The aim of this study was to determine if drug resistant epilepsy patients with symptoms of anxiety and/or depression receive different epilepsy management than controls.

Method: We identified 83 patients with drug resistant focal epilepsy seen at the Penn Epilepsy Center. Upon enrollment, all patients completed 3 self-report scales and a neuropsychiatric inventory and were grouped into those with symptoms of anxiety and/or depression and controls. Each patient's medical records were retrospectively reviewed for 1–2 years, and objective measures of outpatient and inpatient epilepsy management were assessed.

Results: At baseline, 53% ($n = 43$) of patients screened positive for symptoms of anxiety and/or depression. The remaining 47% ($n = 38$) served as controls. Patients with anxiety and/or depression symptoms had more missed outpatient visits per year compared to controls (median 0.84 vs. 0.48, $p = 0.02$). Patients with symptoms of both anxiety and depression were more likely to undergo an inpatient admission or procedure (56% vs. 24%, $p = 0.02$).

Conclusion: For most measures of epilepsy management, symptoms of anxiety and/or depression do not alter epilepsy care; however, drug resistant epilepsy patients with anxiety and/or depression symptoms may be more likely to miss outpatient appointments, and those with the highest burden of psychiatric symptoms may be admitted more frequently for inpatient services compared to controls.

1. Introduction

Patients with epilepsy (PWE) suffer from depression and anxiety more than the general population.[1] Psychiatric disease is particularly prevalent among patients with localization-related epilepsy (LRE) of temporal or frontal lobe origin,[2,3] and depression and anxiety are more common in patients whose epilepsy is poorly controlled and experience at least one seizure per month.[4,5] The relationship between psychiatric illness and epilepsy is complex and bidirectional.[6–11] Stress, anxiety and depression are closely linked in the general population,[12] and these psychiatric symptoms frequently coexist in PWE as well.[13]

Identifying barriers to epilepsy care is an active area of research in light of recent attempts to establish standards of epilepsy management.[14,15] Racial minorities and the uninsured have worse access to epilepsy care, as assessed by measures such as compliance and prescriptions filled for new anti-epileptic drugs (AEDs).[16,17] These populations are also less likely to undergo resective surgery for drug resistant epilepsy[18] despite recommendations to consider surgery in all patients who have failed 2 AEDs.[19]

Although psychiatric disorders are common among drug resistant LRE patients, no study to date has examined how comorbid anxiety and depression affect these patients' epilepsy

Abbreviations: PWE, patients with epilepsy; LRE, localization-related epilepsy; AED, anti-epileptic drug; ASERT, Assessment of Suicidality in Epilepsy: Rating Tools; BDI-II, Beck Depression Inventory-II; NDDI-E, Neurologic Disorders Depression Inventory-Epilepsy; PHQ-GAD 7, Patient Health Questionnaire-Generalized Anxiety Disorder 7; MINI, Mini International Neuropsychiatric Interview; MDD, major depressive disorder; EMU, epilepsy monitoring unit; VNS, vagus nerve stimulator; IQR, interquartile range.

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care. We hypothesized that patients with symptoms of anxiety and/or depression receive substandard epilepsy care, since these patients may be more likely to avoid new therapies and invasive testing. We tested this hypothesis using a cohort of patients with active symptoms of anxiety and/or depression to determine if their outpatient and inpatient management differed from epilepsy controls without anxiety and/or depression.

2. Methods

2.1. Subjects

Subjects were recruited from the Epilepsy Center at the University of Pennsylvania. Patients had been previously enrolled in the ASERT trial, "Assessment of Suicidality in Epilepsy: Rating Tools (ASERT)".[20] Inclusion criteria for enrollment were (1) diagnosis of partial epilepsy for at least 2 years; (2) experiencing at least 1 seizure per month; and (3) receiving 1–3 AEDs. Patients with psychogenic non-epileptic seizures and those carrying a diagnosis of a major psychotic disorder were excluded. Participants signed an informed consent form approved by the Institutional Review Board. For each subject, we assessed age, gender, ethnicity, employment, education, and whether they were followed by an attending neurologist vs. a resident or nurse practitioner. We also recorded seizure characteristics, including duration of epilepsy, number of seizures per month, and presence of convulsions.

2.2. Assessment of anxiety and depression symptoms

At ASERT enrollment (baseline), participants completed a set of psychiatric questionnaires, including the Beck Depression Inventory-II (BDI-II), the Neurologic Disorders Depression Inventory-Epilepsy (NDDI-E), and the Patient Health Questionnaire-Generalized Anxiety Disorder 7 (PHQ-GAD 7). The BDI-II is a widely used self-report depression screen[21] that has been validated to screen for major depressive disorder (MDD) in PWE who score above 15.[22] The NDDI-E was developed to screen for depression among PWE and predicts MDD at a score >15.[23] Although to date, no anxiety questionnaires have been developed specifically for PWE,[24] the PHQ-GAD 7 has been used to screen for GAD and other anxiety disorders in primary care settings in patients scoring a 10 or above.[25] In addition to self-report measures, patients were also evaluated for active psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI) 5.5.0 (Version 2), which has good correlation to the Structured Clinical Interview for DSM-IV Axis I Disorders, the gold standard for identifying a comorbid mood disorder in PWE.[26]

Patients were categorized as having symptoms of depression if they had a DSM-IV diagnosis on the MINI or scored above a 15 on the BDI-II or NDDI-E. Patients were considered to have symptoms of anxiety if they had a DSM-IV diagnosis on the MINI or scored a 10 or greater on the PHQ-GAD 7.

None of the subjects had psychiatric illnesses severe enough to require admissions for their psychiatric diagnoses or housing in a psychiatric facility. Patients' anxiety and depression were managed primarily by their neurologist at the Epilepsy Center at the University of Pennsylvania. A minority of patients were referred to or seen by outpatient psychiatrists or psychologists.

2.3. Assessment of epilepsy management

Patients' medical records were retrospectively reviewed starting from the time of their enrollment in the ASERT study until August 2012. Records were no longer reviewed after a patient stopped receiving care at the Penn Epilepsy Center. Information about patients' epilepsy management was obtained mostly from their outpatient neurology notes.

Epilepsy management was divided into three categories: outpatient medical management, inpatient management, and patient adherence. Measures of outpatient medical management included number of adjustments to AED doses, starting or stopping an AED, and changes in dose or type of rescue medications or benzodiazepines. Measures of inpatient management were admissions to the epilepsy monitoring unit (EMU) for purposes of epilepsy diagnosis or surgical work-up, placement of a vagus nerve stimulator (VNS), and resective surgery. Measures of poor patient adherence included number of missed outpatient appointments and missed labs or imaging (i.e. labs or imaging were ordered for the patient but never completed). Whether or not patients achieved seizure freedom, as defined as the absence of seizures for >6 months, was also noted as a clinical outcome.

2.4. Group comparisons and statistical analysis

Since records were retrospectively reviewed for different lengths of time depending on their ASERT enrollment date, management events for a particular patient were divided by the total number of years that patient had been followed, in order to standardize outcome measures across patients. Outcome measures of epilepsy management were assessed in controls compared to patients with reported symptoms of anxiety and/or depression at enrollment. The main comparison was between controls and patients with symptoms of depression and/or anxiety, but in a secondary analysis, comparisons were conducted between controls, patients with only symptoms of depression or anxiety, and patients with symptoms of both depression and anxiety.

Group comparisons were calculated using parametric and non-parametric tests, and linear regression models were constructed to determine independent associations with each outcome measure.

3. Results

3.1. Baseline subject characteristics

Eighty-three participants were initially consented to participate, and 81 responded to all psychiatric questionnaires. At baseline, 53% ($n = 43$) of patients had either a diagnosis of anxiety or depression on the MINI ($n = 23$) and/or screened positive on any of the three screens ($n = 20$), and 47% ($n = 38$) of patients did not screen positive on any psychiatric screen or the MINI and served as controls.

Table 1 shows that patients with anxiety and/or depression symptoms were comparable with controls for all demographic variables and epilepsy history. Table 1 also outlines patients' mean scores on the three anxiety and depression screens and the percentage of patients diagnosed with depression or anxiety on the MINI.

3.2. Epilepsy management

The median length of time a patient's chart was reviewed was 19 months, with an interquartile range of 17–22 months. Table 1 compares epilepsy management and clinical outcomes in patients with symptoms of anxiety and/or depression vs. controls. For outpatient epilepsy management, patients with symptoms of anxiety and/or depression had similar numbers of AED changes per year as controls. The percentage achieving seizure freedom was similar in anxious and/or depressed patients and controls. In comparing measures of adherence, patients with depression and/or anxiety had a greater median number of missed outpatient visits per year than controls (0.84 vs. 0.48, $p = 0.02$). This effect remained

Table 1
Demographic characteristics and clinical management of patients with depressed and/or anxious symptoms compared to controls.

	Depressed and/or anxious symptoms $n = 43$	Controls $n = 38$	p value
Mean age	41	45	0.18
Minority (%)	28	26	0.87
Male (%)	42	39	0.83
Some college education (%)	60	66	0.62
Employed (%)	37	58	0.06
Receiving disability benefits (%)	28	21	0.61
Followed by attending neurologist (%)	91	90	1.00
Epilepsy history and severity			
Duration of epilepsy, median years	10	15.5	0.06
Convulsions present (%)	47	32	0.25
Seizures per month, median	6	5.5	0.44
>2 current AEDs (%)	40	37	0.81
Past epilepsy treatments			
Surgery (%)	14	18	0.59
VNS (%)	12	18	0.39
Number of AED trials, median	4	3	0.53
Comorbid medical disease			
Number of other medical conditions, median	1	2	0.91
Number of non-AED prescriptions, median	1	1	0.79
Depression and anxiety screening			
NDDI-E score	15 (IQR 12–17)	11 (IQR 9–13)	N/A
BDI-II score	17 (IQR 10–23)	5 (IQR 1–7)	N/A
PHQ-GAD-7 score	11 (IQR 8–13)	4 (IQR 2–6)	N/A
Diagnosis of depression on MINI (%)	16	0	N/A
Diagnosis of anxiety on MINI (%)	33	0	N/A
Outpatient epilepsy management			
AED changes per year, median	1.56	1.68	0.99
Inpatient epilepsy management			
Underwent surgery or VNS placement (%)	14	5	0.27
Underwent any procedure or admission (%)	37	24	0.23
Measures of patient adherence			
Number of missed outpatient visits per year, median	0.84	0.48	0.02
Missed labs, imaging, or EEG per year, median	0 (IQR 0–0.71)	0 (IQR 0–0.4)	0.91
Epilepsy control			
Achieved > 6 months of seizure freedom (%)	5	8	0.66

significant after controlling for age, gender, education, employment status, duration of epilepsy, and current convulsions.

3.3. Subgroup differences in inpatient management

Although none of the differences in inpatient management reached significance when comparing the two groups, patients with symptoms of both anxiety and depression were significantly more likely to undergo inpatient admissions and procedures than controls. Fig. 1 compares the epilepsy management of controls, patients with symptoms of only anxiety or depression, and those with symptoms of both anxiety and depression. A significantly higher proportion of anxious and depressed patients underwent any inpatient admission or procedure over the 1–2 years compared to controls (56% vs. 24%, $p = 0.02$), although the proportion with surgeries or VNS placement did not differ. In examining reasons for admissions, there were a significantly higher number of EMU admissions for diagnostic purposes per year among patients with depressed and anxious symptoms compared to controls (median 0, interquartile range 0–0.14 vs. median 0, interquartile range 0–0, $p = 0.03$), while EMU admissions for pre-surgical work-up were not significantly different between groups.

4. Discussion

Patients with active psychiatric symptoms of anxiety and/or depression did not receive a different level of epilepsy care compared to controls in most domains of epilepsy management. However, patients with symptoms of anxiety and/or depression did have more missed outpatient visits, and the more severely affected patients with symptoms of both anxiety and depression were significantly more likely to have an inpatient admission or a procedure compared to controls.

Among patients with other neurologic diseases, such as stroke, depression and anxiety are associated with increased mortality, which is thought to result in part from the psychiatric disorders disrupting the management and recovery of these patients.[27–29] Comorbid depression has been associated with worse compliance and follow-up among patients with medical disease, due to factors such as poor social support and self-motivation.[30] This is consistent with our finding that anxious and/or depressed epilepsy were more likely to miss outpatient appointments than controls. And if patients with comorbid psychiatric disease tend to have worse compliance, then it may be unsurprising that patients with symptoms of both anxiety and depression had more admissions for pre-scheduled EMU evaluations or surgical procedures. Epileptologists may be particularly likely to refer their anxious and depressed patients for inpatient evaluation, because they mistake psychiatric symptoms for peri-ictal phenomena[31] or think that these symptoms are associated with psychogenic non-epileptic events.[32] This theory is supported by our finding that anxious and depressed patients were significantly more likely than controls to be admitted to the EMU for diagnostic purposes but not for pre-surgical work-up.

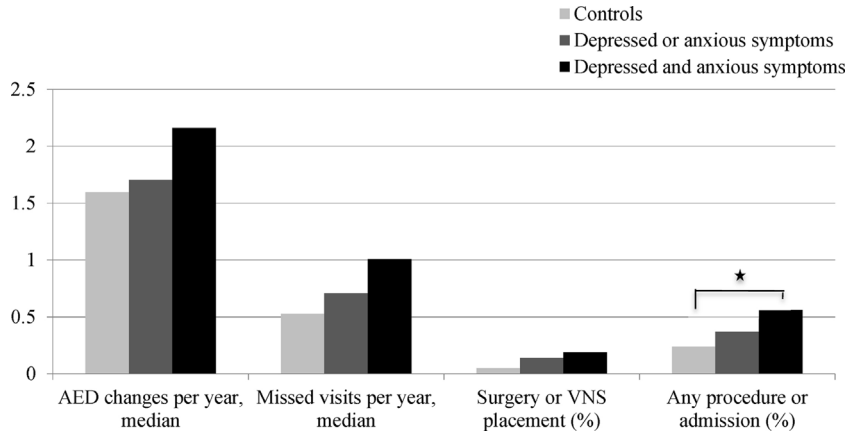

Fig. 1. Secondary analysis – subgroup comparisons. Epilepsy management in controls compared to patients with symptoms of depression OR anxiety and patients with symptoms of depression AND anxiety. $^{*}p < 0.05$ for comparison between controls and patients with depressed AND anxious symptoms.

Despite the increased rate of missed outpatient visits and inpatient admissions, it is difficult to conclude that patients with anxiety and/or depression symptoms received substandard care compared to controls. Published guidelines for epilepsy care focus on the management of epilepsy patients in a general neurology or primary care setting,[33–35] and standards of care for drug resistant LRE patients only dictate that patients who have failed 2 AEDs should be referred to specialized epilepsy centers[14–16] and considered for surgery.[19] Since our population was from a specialized center offering epilepsy surgery, the care delivered to all patients appeared to meet the minimum criteria based on these guidelines. Also, we could not ascertain whether the more frequent missed outpatient appointments and inpatient admissions made a difference in seizure frequency based on the imprecision of the data from outpatient notes, but these differences in management did not affect rates of seizure freedom.

However, we wish to highlight the finding that patients with both anxiety and depression symptoms were admitted more frequently for inpatient services than controls, since EMU admissions and carry significant iatrogenic risks. We do not believe that patients with symptoms of anxiety and depression were admitted more frequently because they had more severe epilepsy. Contrary to prior studies showing an association between a greater burden of epilepsy and psychiatric disorders,[4,5] we did not find any differences in epilepsy severity as assessed by duration of epilepsy, number of seizures per month, number of current AEDs, and presence of convulsions. One could also argue that patients with psychiatric disease may be more likely to be unemployed and therefore more available to be admitted to an inpatient unit; however, we did not find a significant difference in rates of unemployment or disability benefits among patients with anxiety and/or depression compared to controls.

There were some potential limitations of this study, which may have affected the outcome and generalizability. Instead of reassessing patients' symptoms of anxiety and depression over time, our assessment was limited to a single assessment at the time of enrollment. Also, the anxious and/or depressed patients included those who only scored positive on psychiatric screens, which is not the same as the actual DSM-IV diagnoses. To account for this, we separately examined the association between depression and/or anxiety and missed outpatient appointments among controls vs. anxious and/or depressed patients who scored positive on the MINI and vs. those who only screened positive on the psychiatric screens and found that this association was still present.

Another limitation of this study is the small sample size, which may not have allowed for enough power to detect some smaller differences in management outcomes. We only followed epilepsy patients with drug-resistant LRE treated at a tertiary care center, who were capable of answering surveys. Patients who seek treatment at a specialized epilepsy center may be more likely to take an active part in their care and comply with management decisions, and our conclusions may not generalize to epilepsy patients in the community. Also of note, we did not adjust the p value to correct for multiple comparisons in this small sample size. However, our approach was reasonable given that the study was exploratory with the purpose of generating hypotheses.[36] Future studies can be more directed with fewer comparisons.

This study illustrates that co-morbid anxiety and depression may lead to differences in epilepsy management. Our findings highlight the importance of identifying and adequately treating psychiatric disease to prevent inequalities in epilepsy care, especially given the prevalence of anxious and depressed symptoms among epilepsy patients.

5. Conclusions

This is the first study to explore how comorbid psychiatric disease affects epilepsy care. Although we had hypothesized that symptoms of anxiety and depression would serve as a barrier to appropriate epilepsy care, our findings suggest that patients with symptoms of anxiety and/or depression are not receiving substandard care in most domains of epilepsy management. However, based on our results, epileptologists should be aware that they may be admitting patients with symptoms of anxiety and depression symptoms more frequently than their other patients.

Our results are limited by a small sample size and short follow-up period. In addition, it is difficult to conclude how a higher rate of inpatient admissions may ultimately affect epilepsy outcomes. A prospective study that includes assessments for seizure frequency and increases the frequency of screens for anxiety and depression should be conducted to confirm our conclusions.

Ethical approval

The study was approved by the US institutional review board and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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