Positive anxiety or depression screen despite ongoing antidepressant prescription in people with epilepsy: A large cross-sectional analysis

Samantha Ongchuan Martin a, Fatemeh Sadeghifar b, Beverly M. Snively c, Halley Alexander b, James Kimball a, Kelly Conner b, Cormac A. O’Donovan d, Heidi M. Munger Clary b,*

a Department of Psychiatry, Wake Forest University School of Medicine, Winston-Salem, NC, USA
b Department of Neurology, Wake Forest University School of Medicine, Winston-Salem, NC, USA
c Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, NC, USA
d Department of Neurology and Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Article info

Article history:
Received 23 July 2022
Revised 30 October 2022
Accepted 5 November 2022
Available online 7 November 2022

Keywords:
Antidepressant
Anxiety
Depression
Psychiatric comorbidity
Mental health
Neurology clinic

Abstract

Purpose: While antidepressants are recommended to manage anxiety or depression in epilepsy, limited effectiveness data exist in real-world epilepsy samples, and prior work indicated frequent positive screens despite antidepressant prescription. In response, this study evaluates factors associated with positive anxiety or depression screen during ongoing antidepressant prescription.

Methods: Clinical and sociodemographic characteristics were collected among consecutive adult epilepsy clinic patients completing validated anxiety and depression instruments. The sample was divided by presence vs absence of existing antidepressant prescription at time of screening. Among those on an antidepressant, multivariable logistic regression was performed on pre-selected characteristics to evaluate for association with positive anxiety and/or depression screen. Pre-selected characteristics included: antidepressant dose, antidepressant prescriber specialty, antiseizure medications (number, potential psychotropic effects), seizure frequency, employment, visit no-shows, and medical insurance.

Results: Of 563 people with epilepsy, 152 had evidence of antidepressant prescription at time of screening and 73/152 (48%) had positive anxiety and/or depression screen. Multivariable modeling demonstrated low antidepressant dose and no-show visit(s) were associated with positive screens (adjusted OR 2.29, CI 1.00–5.48 and 3.11, 1.26–8.22 respectively).

Conclusion: Low antidepressant dose and factors potentially associated with adherence (visit no-shows) may contribute to persistent anxiety and/or depression among epilepsy patients on an antidepressant.

1. Introduction

Anxiety and depression in people with epilepsy (PWE) are prevalent and associated with poor quality of life, increased healthcare utilization, medication side effects, drug-resistant epilepsy, and premature mortality [1]. Despite high prevalence [2–5], substantial morbidities, and public health implications [4], depression and anxiety in PWE continue to be under-recognized and undertreated [6,7]. Reasons for under-treatment include insurance-related factors, mental health provider shortages, limited communication between psychiatrists and neurologists, mental health stigma and reluctance to seek psychiatric care [6–10]. A solution may be for neurologists to screen and treat mental health comorbidities.

Recent quality improvement efforts and publications support screening and treatment by neurologists for anxiety and depression in epilepsy clinics [11,12]. A survey of leading epileptologists indicated most were willing to prescribe an antidepressant [13], and brief, freely available depression and anxiety screeners have been validated in epilepsy [14,15]. In a recent study, most patients preferred neurologists to prescribe for anxiety and depression symptoms in an epilepsy clinic [16]. Studies in primary care demonstrate non-psychiatrists can manage anxiety and depression safely and effectively, particularly using validated screening instruments [17,18]. However, despite recognition and treatment of depression, symptoms may persist after first-line therapeutics. In the STAR*D trial, remission of depression was only 26.6% in primary care and 28% in psychiatry settings after 14 weeks of citalopram [18]. Treatment-resistant depression is defined by a
lack of response to adequate dose and duration trials of at least 2 antidepressants and affects approximately-one-third of individuals with depression [19,20]. Treatment-resistant depression leads to increased healthcare utilization, increased suicide risk, and impaired psychosocial functioning; also, decreased remission rates are associated with concurrent anxiety, substance use disorder, general medical disorders, unemployment, and low education [18].

Prior work in a real-world clinic sample demonstrated over 40% of individuals with positive anxiety or depression screens were on an antidepressant [21], suggesting affective symptoms may be prevalent in patients with epilepsy despite antidepressants. A recent study in epilepsy revealed remission in just over half of participants following 16 weeks of sertraline or cognitive behavioral therapy [22]. However, data is lacking on clinical and demographic variables associated with persistent symptoms despite antidepressant treatment in PWE. Additionally, factors such as antidepressant dosing in real-world epilepsy clinic settings have not been well-studied. In a retrospective observational study in PWE, antidepressants yielded good therapeutic response for psychiatric symptoms independent of seizure frequency and were associated with possible decrease in seizure frequency [23]. It would be beneficial if neurologists could identify patients with epilepsy at risk for persistent affective symptoms despite treatment, warranting further intervention such as medication adjustment or psychiatric referral.

Thus, our objectives were to do the following in a large consecutive epilepsy clinic sample: 1. To describe clinical, sociodemographic, and health utilization characteristics of those with positive vs negative anxiety/depression screens overall, and among those with an ongoing antidepressant prescription. 2. To evaluate a combination of a priori selected factors for association with positive anxiety and/or depression screen among those receiving an antidepressant (primary objective).

2. Methods

A prospective anxiety and depression screening was conducted among consecutive patients in clinics of three tertiary care epileptologists from April 30, 2018 to June 6, 2019, for clinical care and randomized pragmatic trial eligibility assessment [24]. Research use of clinical information was approved by the institutional review board, and information on the parent study design is found at clinicaltrials.gov (NCT03464383). This study sample includes all consecutive unique individuals with epilepsy who completed anxiety and depression screening instruments for the first time in study period. Those with epileptiform discharges or seizures on prior electroencephalography(EEG), or with epilepsy as the leading epileptologist-documented diagnosis met inclusion for diagnosis of epilepsy. To subdivide the sample for this cross-sectional analysis, participants were defined as being on an antidepressant if the electronic health record(EHR) on date of anxiety and depression screening indicated an antidepressant as a current ongoing medication (see Table S1 for full list of included antidepressants).

Anxiety and depression screening instruments were completed by self-report on a tablet (Generalized Anxiety Disorder–7, GAD-7 and Neurological Disorders Depression Inventory-Epilepsy, NDDI-E), with GAD-7 ≥ 10 and NDDI-E ≥ 16 considered positive screens [14,25]. Psychiatric symptoms and treatment characteristics were collected via self-report among those with positive screens, including history of psychiatric hospitalization and screen for past manic episode via Mini-International Psychiatric Interview for DSM IV (MINI-IV) past manic episode module, which was added to study procedures later than other items. Passive suicidal ideation was assessed via NDDI-E item 4 [26]. Current antidepressant, dosing, and prescriber type (neurologist vs non-neurologist: psychiatrist, primary care provider, other specialties) were collected by chart abstraction. Antidepressants were categorized by class (selective serotonin reuptake inhibitor—SSRI, serotonin and norepinephrine reuptake inhibitor—SNRI, or other: mirtazapine, bupropion, buspirone, vortioxetine) and dose level (low, medium, high). To assign antidepressant dose categories, we used dose ranges based on the dose category component of the Antidepressant Treatment History Form Short Form(ATHF-SF) [27,28]. ATHF-SF scores of 1 or 2 indicate insufficient dose, scores of 3 correspond to an established minimally effective dose, and scores of 4 imply use of medication above established minimally effective dose. Thus, we categorized ATHF-SF dose ranges 1 and 2 as low, 3 as medium, and 4 as high for each antidepressant (Supplemental Table S1). Dose levels for vortioxetine (no published ATHF-SF dose range available) were defined based on FDA dose range and clinical expertise of the study psychiatrist, with doses < 10 mg classified as low, 10–20 mg as medium, and > 20 mg as high [29,30].

The following clinical and demographic variables were collected by chart abstraction: sex, age, race, ethnicity, marital status, education, insurance type (proxy for socioeconomic status), epilepsy type, seizure frequency, seizure freedom (≥ 6 months), and antiseizure medications(ASM). We categorized ASM as potentially beneficial for mood and anxiety if they are commonly used to treat primary psychiatric conditions in clinical practice and have evidence to benefit mood and anxiety: valproic acid, lamotrigine, carbamazepine, and oxcarbazepine [31–34]. Levetiracetam, zonisamide, topiramate, and perampanel were classified as potentially harmful for mood/anxiety, based on evidence from multiple studies in PWE [31–37]. The other antiseizure medications in this sample, with literature supporting mixed responses (eg. potentially beneficial for anxiety but harmful for depression), or having minimal effect on mood or anxiety, were classified as “other” and included: gabapentin, pregabal, clobazam, clonazepam, diazepam, lorazepam, felbamate, phenobarbital, primidone, lacosamide, brivaracetam, phenytoin, acetazolamide, ethosuximide, and eslicarbazepine [31–34].

Regarding health utilization, the number of no-show appointments to neurology during twelve months prior to anxiety and depression screening was collected, along with overall health system no-show rate. Between-visit patient encounters with neurology (telephone calls and patient portal messages) were counted in the year prior to screening.

2.1. Analyses

Study data were managed using Research Electronic Data Capture (REDCap) [38] and analyses were conducted using SAS 9.4. Descriptive statistics were calculated among the entire sample by symptom screening and antidepressant prescription status. Two-sample t tests and chi-square tests were used to test for statistical significance of bivariate relationships as appropriate. Prior to multivariable logistic regression modeling of the primary outcome of persistent symptoms (GAD-7 ≥ 10 and/or NDDI-E ≥ 16), clinically relevant and potentially associated covariates were selected by a ranked selection process among covarouis, with an appropriate number of covariates selected for the sample size (i.e., individuals with antidepressant prescription). Covariates selected for modeling were: antidepressant dose, potential mood/anxiety effects of ASM, neurologist vs other antidepressant prescriber, number of ASM prescribed, seizure frequency, system no-show visits, employment status, and insurance type. Results are reported for both simple logistic regressions with individual covariates and for the full model. Individuals with missing data were excluded in modeling: one individual had missing seizure frequency and one was missing employment. Sensitivity analyses were conducted on full model results by (1) removal of covariates one at a time, and (2) adding potential confounders: sex, education, epilepsy type, and married/partnered status, one at a time.
3. Results

3.1. Characteristics of entire screened epilepsy sample

Of 884 clinic visits screened, 563 unique individuals with epilepsy were included in this analysis; as shown in Fig. 1, most of the exclusions were because these were follow-up visits, but others were excluded due to lack of an epilepsy diagnosis. Table 1 shows sociodemographic and clinical characteristics of the sample by antidepressant prescription and anxiety/depression screening status. The overall sample (N = 563) had mean age of 43.7 years (range 17–101), were 49.4% women, 83.1% White, 36.3% employed, and 45.1% had private or commercial insurance. Overall 30.2% had a positive screen for symptoms of anxiety and/or depression, with 64 individuals (11.4%) screening positive for both anxiety and depression, 71 (12.6%) for anxiety alone, and 35 (6.2%) for depression alone. At the time of symptom screening, there was evidence of ongoing antidepressant prescription in 27.0% (152/563), with rates of prescription higher in White (30.0%) and non-Hispanic/Latino (27.5%) participants compared to Black (11.8%) and Hispanic/Latino (13%) participants (ratio of rates = 2.5 for White vs Black and 2.1 for non-Hispanic/Latino vs Hispanic/Latino).

3.2. Epilepsy characteristics

Table 2 demonstrates clinical characteristics of the sample, by screen results and antidepressant prescription status. A majority (71.1%) had focal epilepsy, and only 53.3% were seizure-free ≥ 6 months (Table 2). Among individuals with prior epilepsy surgery or neurostimulation therapy (N = 81), 35 (43.2%) had vagal nerve stimulator (VNS) alone, 20 (24.7%) had a laser ablation (two after a phase II intracranial evaluation), 16 (19.8%) had a temporal lobectomy (two of these also had a VNS), 5 (6.2%) had a responsive neurostimulator, 2 (2.5%) had hemispherectomy, 2 (2.5%) had a phase II intracranial evaluation and VNS, and one (1.2%) had a tailored resection.

While nearly all in the sample (552/563 or 98.0%) were on ASM, 20.3% were on three or more. Among those on ASM, 200 (36.2%) were on at least one medication with potentially harmful psychiatric effects (Table 2), and 137 (24.8%) were exclusively taking potentially harmful ASM (levetiracetam, zonisamide, topiramate, and/or perampanel) [31–37]. Of 189 (34.2%) taking ASM with potentially beneficial psychiatric effects, 127 (23.0% of those on ASM) were exclusively on this category (lamotrigine, valproic acid, oxcarbazepine, and/or carbamazepine) [31–34]. The proportion of individuals taking exclusively beneficial or harmful ASM was similar among those with positive vs negative symptoms and those prescribed antidepressants vs not prescribed antidepressants.

3.3. Factors associated with positive anxiety or depression screen

Among those on antidepressants, positive anxiety/depression screen was associated with unemployment (p = 0.005). As expected, the proportion reporting passive suicidality was higher in the positive screen group (p < 0.0001). There were no other significant differ-
ences between those with positive vs negative anxiety/depression screen among the antidepressant prescription sub-sample.

### 3.4. Antidepressant type

Among those with ongoing antidepressant prescription (N = 152), 81.6% were prescribed SSRI, while 13.8% were prescribed SNRI (Table 3). Overall, 144 individuals were on antidepressant monotherapy, 7 on dual antidepressant, and 1 was prescribed three antidepressants (buspirone, mirtazapine, and citalopram). The dual antidepressant combinations included buspirone, mirtazapine, and bupropion (in 4, 2, and one individual, respectively). These medications were combined with SSRI (in 5/7), or with venlafaxine or vortioxetine. Among 124 on SSRI, 54 (43.5%) screened positive. However, positive screens were 13/21 (61.9%) for those prescribed SNRI and 12/14 (85.7%) for those on other antidepressants. Among individuals on antidepressant monotherapy (N = 144), those prescribed SNRI or other antidepressant had positive screen rate 1.67 times the rate in those prescribed SSRI. This ratio of rates was also examined with duloxetine excluded, since it may have been prescribed for a non-psychiatric indication more often than the other SNRIs; the ratio with duloxetine excluded was 2.04 (N = 131).

### 3.5. Antidepressant dosing

Twenty-three percent of patients were prescribed sub-therapeutic doses of antidepressants (low category; Table 3). The rate of low doses was 17.9% (10/56) among patients with prescriptions by neurologists and 26.0% (25/96) among those by non-neurologists. Among 34 individuals on monotherapy with sub-therapeutic doses, 21 (61.8%) screened positive, in contrast to 46 of 110 (41.8%) on a therapeutic dose. This difference in positive screens by dosing category was most pronounced for SSRI monotherapy: 56.5% on low doses had a positive screen (13/23), compared to 37.9% of those in the medium/high dose category (36/95). On the other hand, most of those prescribed SNRI or other antidepressant monotherapy had positive screens regardless of dosing level (57.1%, 4/7 for low dose SNRI vs 61.5%, 8/13 for medium/high dose SNRI).

### 3.6. Other psychiatric medications

Eight psychiatric medications

Eight patients (1.4%) were on trazodone; six had positive anxiety and/or depression screen, and four of these were also on an SSRI, SNRI, or other antidepressant. Six individuals were prescribed tricyclic antidepressants(TCA), with positive anxiety and/or depression screens among three, only one of which was also prescribed SSRI, SNRI, or other antidepressant.

### 3.7. Other psychiatric symptoms/history

Among patients with positive screen, 36/170 (21.2%) reported past psychiatric hospitalization, while 18/106 (16.9%) completed the MINI past manic episode questions, 13/125 (10.4%) met criteria for a past manic episode. Among individuals with past manic episode, 7/13 were prescribed an antidepressant: one by neurologist, one by primary care provider, two by psychiatrist, and three by non-neurology provider of uncertain specialty. Psychogenic nonepileptic seizures(PNES) were present along with epilepsy in 12 (2.1%) of 563 participants in the overall sample, and 4 (0.7%) had suspected PNES but lacked EEG monitoring-based diagnosis.
3.8. Health utilization and prescriber

Table 4 shows no-show visits and between-visit neurology encounters by antidepressant status and prescriber type. There were close to twice as many between-visit neurology encounters (phone calls and patient portal messages) among those with a neurologist antidepressant prescriber than others on or off antidepressants. Among those not receiving an antidepressant prescription from a neurologist, those with positive screens had more between visit encounters with neurology than those with negative screens.

3.9. Multiple logistic regression: Positive screens among those on antidepressant

Among factors selected a priori for multivariable modeling (Table 5), presence of at least one no-show visit to any specialty in the institution and low antidepressant dose were significantly associated with positive symptom screen. Having any health system no-show was associated with 3-fold increased odds of positive screen, and low antidepressant dosing (vs medium or high) was associated with 2-fold increased odds of positive screen (Table 5). Other factors yielded odds ratios in directions expected a priori, but were not statistically significant. In sensitivity analyses, removal of covariates from the main model one at a time did not change the findings; similarly, addition of sex, education, epilepsy type, and married/partnered status one at a time did not change the findings from the main model (data not shown). This was despite a strong relationship observed between screen status and epilepsy type, with odds ratio for a positive screen among individuals with unknown epilepsy type vs focal or generalized epilepsy of 3.69.

4. Discussion

Although recommended first line treatment for depression in epilepsy includes antidepressants or psychotherapy [39], 48% of those prescribed antidepressants screened positive for depression and/or anxiety despite the antidepressant, and 33.6% had positive screens despite adequate antidepressant dosing. Below we discuss findings and potential implications from our main objective to evaluate associations of pre-selected factors with positive anxiety or depression screen during antidepressant treatment.

4.1. Epilepsy-related factors

In a priori specified multivariable modeling, neither seizure frequency nor psychiatric effect profile of antiseizure medications (ASM) were associated with positive anxiety or depression screen.
under ongoing antidepressant prescription. While previous studies demonstrated association of seizure frequency with anxiety or depression symptoms [40, 41], and multiple studies support beneficial and harmful psychiatric effects of antiseizure medications grouped as potentially beneficial and harmful, respectively [31–37], our analysis is unique in examining associations specifically with presence of positive anxiety/depression screen during ongoing antidepressant treatment. The results may suggest a lack of impact of seizure frequency and ASM psychiatric effect profile on response to antidepressants among PWE, and thus support medication treatment approaches for PWE similar to general population for anxiety and/or depression. However, the ASM side effect profile analysis may be limited by potential opposite direction psychiatric effects in different individuals (eg. if some individuals experienced mood worsening on topiramate while others had improved mood).

4.2. Neurologist practice habits and care implications

4.2.1. Antidepressant dosing, type

In our study, 23% of individuals prescribed an antidepressant were on sub-therapeutic doses, 63% of whom had positive screens for anxiety/depression, and low dosing was associated with two-fold increased odds of positive symptom screen in multivariable modeling. In the study sample, 18% of neurologist-prescribed antidepressants were low doses, as were 26% of antidepressants prescribed by non-neurologists. Optimizing antidepressant dosing

| Table 3 | Treatment characteristics among those on antidepressants*. |
|---------|------------------------------------------------------------|
| Overall | Positive screen | Negative screen |
| Count (row %) | 152 (100%) | 73 (48.0%) | 79 (52.0%) |
| SSRI prescribed | 124 (81.6%) | 54 (74.0%) | 70 (88.6%) |
| SNRI prescribed | 21 (13.8%) | 13 (17.8%) | 8 (10.1%) |
| Another antidepressant prescribed | 14 (9.21%) | 12 (16.4%) | 2 (2.33%) |
| Escitalopram* | 38 (25.0%) | 20 (27.4%) | 18 (22.8%) |
| Sertraline | 31 (20.4%) | 12 (16.4%) | 19 (24.1%) |
| Citalopram† | 28 (18.4%) | 14 (19.2%) | 14 (17.7%) |
| Antidepressant(s) prescribed by neurologist | 36 (36.8%) | 26 (35.6%) | 30 (38.0%) |
| Highest antidepressant dose level category; N = 56 | |
| Low | 35 (23.0%) | 22 (30.1%) | 13 (16.5%) |
| Medium | 63 (41.5) | 21 (28.8) | 42 (53.2) |
| High | 54 (35.5) | 30 (41.1) | 24 (30.4) |
| Highest dose neurologist-prescribed; N = 56 | |
| Low | 10 (17.9%) | 6 (23.1%) | 4 (13.3%) |
| Medium | 25 (44.6) | 7 (26.9) | 18 (60.0) |
| High | 21 (37.5) | 13 (50.0) | 8 (26.7) |
| Highest dose non-neurologist-prescribed; N = 96 | |
| Low | 25 (26.0%) | 16 (34.0%) | 9 (18.4%) |
| Medium | 38 (39.6) | 14 (29.8) | 24 (49.0) |
| High | 33 (34.4) | 17 (36.2) | 16 (32.7) |

SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors
*Count of individuals (column %) unless otherwise specified
†Most frequently used among participants
*Individuals on multiple antidepressants are included under highest dosing category among their prescribed antidepressants.

| Table 4 | Health utilization by antidepressant prescription and prescriber status, and by results of the depression-anxiety screen*. |
|---------|------------------------------------------------------------|
| Overall | Current antidepressant prescription | No current antidepressant prescription |
| Count (row %) | 563 (100%) | 26 (4.62%) | 30 (5.33%) | 47 (8.35%) | 49 (8.7%) | 97 (17.2%) | 314 (55.8%) |
| No-show visit percent among all visits and among neurology clinic visits at institution: | |
| All visit % | 7.1 ± 8.5 | 8.7 ± 9.1 | 4.6 ± 5.9 | 7.9 ± 7.4 | 7.0 ± 7.6 | 8.9 ± 10.5 | 6.6 ± 8.2 |
| 0% | 163 (29.0%) | 5 (19.2%) | 11 (36.7%) | 5 (10.0%) | 12 (24.5%) | 28 (28.9%) | 102 (32.5%) |
| >0 to 10 | 263 (46.7) | 11 (50.0) | 15 (50.0) | 31 (66.0) | 25 (51.0) | 38 (39.2) | 141 (44.9) |
| >10 | 137 (24.3) | 8 (30.8) | 4 (13.3) | 11 (23.4) | 12 (24.5) | 31 (32.0) | 71 (22.6) |
| Neurology clinic %† | 3.7 ± 12.1 | 7.7 ± 15.9 | 1.9 ± 6.0 | 4.1 ± 12.2 | 1.8 ± 7.8 | 3.4 ± 11.6 | 3.8 ± 12.8 |
| Encounters in neurology clinic at institution, expressed as count during previous 12 months: | |
| All encounters | 4.6 ± 6.0 | 8.0 ± 7.8 | 10.1 ± 11.2 | 5.4 ± 5.4 | 4.2 ± 6.0 | 4.9 ± 6.5 | 3.2 ± 4.4 |
| 0 | 133 (23.6%) | 2 (7.7%) | 1 (3.3%) | 9 (19.2%) | 10 (20.4%) | 18 (16.8%) | 91 (29.6%) |
| >0 to 5 | 285 (50.6) | 12 (46.2) | 14 (46.7) | 21 (44.7) | 26 (53.1) | 52 (53.3) | 160 (51.0) |
| >5 to 10 | 82 (14.6) | 5 (19.2) | 4 (13.3) | 10 (21.3) | 9 (18.4) | 14 (14.4) | 40 (12.7) |
| >10 | 63 (11.2) | 7 (26.9) | 11 (36.7) | 7 (14.9) | 4 (8.2) | 13 (13.4) | 21 (6.7) |

*Mean ± SD and median [interquartile range], or count (column %), unless otherwise specified
†No-show visits among neurology clinic visits at institution during previous 12 months, expressed as percentage of visits.
is crucial in treating depression, and these results highlight a potential opportunity to improve anxiety and depression treatment outcomes via adequate receiving antidepressants in primary care are on lower than guideline-recommended doses [42], and about 16% of patients prescribed antidepressants from 1996 to 2015 were on lower than approved-range doses [43]. While low dosage could reflect an area of practice improvement for prescribers, low dosage could reflect patient reluctance to take higher doses, side-effect limited dosing, or other factors beyond provider preference. Given that our analysis was cross-sectional, in our sample it is unclear whether individuals were in initial stages of treatment, rather than on stable, longer-term dosing plans (especially for non-neurologist prescribers). Further research should examine responsiveness of PWE to moderate and higher dose antidepressants and examine efforts to optimize antidepressant dosing in managing anxiety and/or depression among PWE. While antidepressant type was not selected for multivariable analysis, those prescribed SSRI in this sample were less likely to screen positive for anxiety or depression symptoms from missed treatment, while these results may indicate substantial increased care intensity burden when neurologists prescribe antidepressants in addition to managing epilepsy, which could lead to untenable workloads, and may highlight a need to develop and evaluate collaborative or multidisciplinary models to overcome this.

### 4.3. Treatment adherence

In general samples, odds of non-adherence to treatment are three times greater in depressed or anxious patients than non-depressed or non-anxious patients [47]. In this study, no-show rates across all health system appointments were examined as a proxy for adherence. Having any no-show visit was associated with nonshows across all health system appointments were examined as a proxy for adherence. Having any no-show visit was associated with nonadherence directly impacting care intensity/costs [46]. In our study, those with fewer between-visit encounters (phone calls, portal messages) were less likely to screen positive, as 22% of patients with no phone calls or portal messages in the year prior to screening having anxiety or depression symptoms, compared to 43% of those with > 10 encounters. Additionally, those prescribed an antidepressant by the neurologist had twice as many pre-visit telephone and patient portal encounters as those with another prescriber or no antidepressant, regardless of symptom screen status (Table 4). Our prior work in this clinic setting demonstrated patients preferred their neurologist to prescribe antidepressants [16], but the data in this study on pre-visit telephone and portal encounters suggests potential added provider burden of care for multimorbidity in this sample. If generalizable, these results may indicate substantial increased care intensity burden when neurologists prescribe antidepressants in addition to managing epilepsy, which could lead to untenable workloads, and may highlight a need to develop and evaluate collaborative or multidisciplinary models to overcome this.

#### 4.2.2. Multimorbidity and care intensity

Depression is 2–3 times more likely in people with multimorbidity than people without multimorbidity or chronic physical conditions [45]. In a systematic review, multimorbidity significantly impacted disability, poor quality of life, and high healthcare utilization/costs [46]. In our study, those with fewer between-visit encounters (phone calls, portal messages) were less likely to screen positive, as 22% of patients with no phone calls or portal messages in the year prior to screening having anxiety or depression symptoms, compared to 43% of those with > 10 encounters. Additionally, those prescribed an antidepressant by the neurologist had twice as many pre-visit telephone and patient portal encounters as those with another prescriber or no antidepressant, regardless of symptom screen status (Table 4). Our prior work in this clinic setting demonstrated patients preferred their neurologist to prescribe antidepressants [16], but the data in this study on pre-visit telephone and portal encounters suggests potential added provider burden of care for multimorbidity in this sample. If generalizable, these results may indicate substantial increased care intensity burden when neurologists prescribe antidepressants in addition to managing epilepsy, which could lead to untenable workloads, and may highlight a need to develop and evaluate collaborative or multidisciplinary models to overcome this.

#### Table 5

Univariate and multivariate logistic regression results for positive versus negative screen among those with current antidepressant prescription*.  

| Percentage Screen + | Univariate results | Multivariate results |
|---------------------|--------------------|----------------------|
|                     | Odds ratio | 95% CI | Odds ratio | 95% CI |
| Highest antidepressant dose level category* | Low | 62.9 | 2.19 | (1.02, 4.87) | 2.29 | (1.00, 5.48) |
|                     | Medium or High | 43.6 | Ref | – | Ref – |
| Potential psychiatric effects of antiseizure medication | Beneficial effects | 38.3 | 0.62 | (0.28, 1.37) | 0.59 | (0.25, 1.40) |
|                     | Harmful effects | 54.9 | 1.22 | (0.57, 2.64) | 1.35 | (0.57, 3.22) |
|                     | Beneficial & harmful, other only, or none | 50.0 | Ref | – | Ref – |
| Antidepressant(s) prescribed by neurologist | No | 49.0 | Ref | – | Ref – |
|                     | Yes | 46.4 | 0.90 | (0.47, 1.75) | 0.97 | (0.46, 2.03) |
| Antiseizure medication number | None or monotherapy | 44.0 | Ref | – | Ref – |
|                     | Dual therapy | 50.0 | 1.27 | (0.60, 2.71) | 1.29 | (0.55, 3.08) |
|                     | 3 + medications | 50.0 | 1.27 | (0.55, 2.95) | 1.16 | (0.43, 3.15) |
| Seizure frequency | Seize free > 1 year | 44.3 | Ref | – | Ref – |
|                     | Less than weekly | 51.5 | 1.34 | (0.68, 2.64) | 1.38 | (0.65, 2.95) |
|                     | At least weekly | 53.3 | 1.44 | (0.47, 4.52) | 1.54 | (0.46, 5.28) |
| Any no-show visits† | No | 30.3 | Ref | – | Ref – |
|                     | Yes | 52.9 | 2.59 | (1.16, 6.13) | 3.11 | (1.26, 8.22) |
| Employed | No | 52.4 | 1.74 | (0.88, 3.52) | 1.27 | (0.55, 2.90) |
|                     | Yes | 38.8 | Ref | – | Ref – |
| Medicare/Medicaid only or no insurance | No | 42.4 | 0.67 | (0.35, 1.28) | 1.03 | (0.47, 2.31) |
|                     | Yes | 52.3 | Ref | – | Ref – |

*N = 152, except one observation was excluded in models with covariate seizure frequency due to missing data.† Individuals on multiple antidepressants are included under highest dosing category among antidepressants.

#### Notes

- The relationship between persistent symptoms and adherence could be bidirectional, with nonadherence directly impacting anxiety and depression symptoms from missed treatment, while...
anxiety and/or depression symptoms may also lead to non-adherence as observed in other conditions [49–51]. Although psychosocial variables examined in the multivariable and sensitivity analyses did not demonstrate significant association with persistent anxiety/depression symptoms, visit no-shows could also partially reflect other unmeasured psychosocial factors contributing to persistent anxiety or depression despite prescribed therapy. Nevertheless, non-adherence is a potentially intervenable factor with some likely direct impact on anxiety and depression treatment outcomes, which merits further investigation.

4.4. Sociodemographic factors, healthcare disparities

In this study, although more unemployed individuals (46%) screened positive than employed individuals (25% positive screens), there was no independent association of unemployment with positive screens among those prescribed antidepressants. We also found no significant association of insurance type (socioeconomic status proxy) with positive screens. Thus, our results did not duplicate general population and epilepsy studies demonstrating associations of these factors with anxiety or depression symptoms [52–56]. Our study may have been too small to duplicate prior findings, and these prior studies did not specifically examine associations with symptom screens under antidepressant treatment, which is novel in the present study. Future work should examine direct measures of socioeconomic status and other social determinants of health for association with antidepressant effectiveness in epilepsy.

Health disparities in depression/anxiety remission rates may occur via mechanisms including reduced service provision. In our study, Blacks and Hispanic/Latinos were less often prescribed antidepressant(s) than Whites (12% and 13% respectively, in contrast to 30% of Whites). The reasons for this are unclear, and subgroups are too small to support any definitive conclusions, but these findings are similar to treatment patterns identified in other studies. For example, Quinones et al. demonstrated nearly all minority groups had lower odds of adequate antidepressant use compared to Whites [57]. Racial and ethnic minorities are disproportionately affected by adverse outcomes of epilepsy [58,59]. It is important for future mental health care research in epilepsy to evaluate health disparities and design interventions to eliminate disparities.

4.5. Strengths, limitations and generalizability

While this study is novel in examining associations of clinical and sociodemographic factors with anxiety and depression symptoms specifically in the setting of real-world antidepressant prescribing conditions and a first step toward examining potential antidepressant resistance in epilepsy, the study design has limitations and findings should be interpreted with caution. A major limitation is lack of longitudinal data to thoroughly explore response to antidepressants over time; our analysis documents a single snapshot in time regarding the presence or absence of a positive symptom screen with pre-existing antidepressant prescription of unspecified prior duration that may or may not have been optimized by the prescriber. We acknowledge our analysis does not consider baseline severity, treatment course of individual patients, potential concomitant treatment such as psychotherapy, or appropriateness of doses prescribed to each individual. We also acknowledge limitations of screening instruments; while these do not reflect definitive psychiatric diagnoses, screening tools are often used in clinical practice to monitor therapy response [17,18]. Another limitation is that we placed psychiatrists and primary-care providers in one category of non-neurologist prescribers. We were unable to explore practice habits of these two specialties because the EHR system did not enable prescriber type identification when antidepressants were prescribed outside the health system. Finally, data on localization of focal epilepsy were not available, so we could not evaluate for an association of temporal lobe epilepsy with persistent symptoms in the setting of antidepressant.

This analysis is likely generalizable to similar clinics, as significant efforts were made to screen and include as many consecutive patients from the clinics as possible, though the tertiary care setting may have biased the sample toward more severe, and potentially more treatment-resistant individuals than may have been observed in a community setting. Future work should include multiple centers and non-tertiary settings to enhance generalizability. Despite the limitations, this consecutive real-world sample with a priori modeling plan explores a unique topic in the epilepsy literature, reflecting real-world care scenarios faced by neurologists adhering to quality measures for anxiety and depression screening at every visit [11] when patients have positive screens during ongoing antidepressant therapy from varied sources.

5. Conclusion

This large consecutive analysis of clinic patients screened for anxiety and depression demonstrated high prevalence of positive screens despite existing antidepressant prescriptions, indicating lack of adequate symptom relief among many patients in this care setting. Among a priori factors examined, low antidepressant dose was associated with 2-fold increased odds of positive screen, and prior missed visits, reflecting potential adherence, were associated with 3-fold increased odds of positive screen. The findings demonstrate a need for clinical improvement efforts to optimize antidepressant dosing for people with epilepsy and enhance adherence. Future longitudinal studies are needed to evaluate interventions to improve antidepressant care delivery and further evaluate factors associated with antidepressant responsiveness among people with epilepsy. The study results also suggest greater between visit care intensity for neurologists among patients with positive anxiety or depression screens, and when antidepressants are prescribed by the neurologist. Strategies to meet this clinical care burden should be evaluated.

Funding

Supported by the National Center for Advancing Translational Sciences and National Institute of Neurological Disorders and Stroke of the National Institutes of Health [Grant No R25 NS088248; UL1 TR001420, U24 NS107197, 2KL2TR001421.] The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Sponsor had no role in study design, collection, analysis and interpretation of data, writing this report, or the decision to submit for publication.

Ethical statement

This research was approved by the Wake Forest University Health Sciences Institutional Review Board and was carried out in accordance with the Declaration of Helsinki. As part of a prospective assessment of consecutive patients in tertiary care clinics of three epileptologists from April 30, 2018 to June 6, 2019, individuals completed anxiety and depression screening (with dual purpose of quality measure-satisfying clinical care and research eligibility assessment for a related intervention study, NCT03464383). Research use of the existing clinical screening information and other clinical information present in the electronic
health record was approved by the institutional review board with waiver of informed consent, and the research was conducted with robust measures to protect privacy/confidentiality in place. Because this was an observational study (non-experimental) involving analysis of existing clinical information, waiver of informed consent was deemed appropriate by the institutional review board.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Conner has served as a paid consultant and on a speaker’s bureau for SK Life Sciences, Inc. She is an advisory board member for Neurelis, Inc. Dr. O’Donovan has received research support from Sunovion, has served as a consultant for Bioserenity, and has served as an expert witness. No other conflicts of interest declared by the authors.

Acknowledgements

The authors would like to thank Mingyu Wen, Daena Oates, Rachel Croxton, Brittany Briceno, Matthew Wong and Joseph Kaizer for contributions to data collection and the overall parent study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejbr.2022.100572.

References

[1] Kanner AM. Anxiety disorders in epilepsy: the forgotten psychiatric comorbidity. Epilepsy Curr 2011;11(3):90–1.
[2] Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80(6):596–9.
[3] Gulpe D, Bolat E, Mete L, Arici S, Celebiyoz M. Psychiatric comorbidity, quality of life and social support in epileptic patients. Nord J Psychiatry 2011;65:57–60.
[4] Scott AJ, Sharpe L, Hunt C, Cundy M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. Epilepsy 2017;58(6):973–82.
[5] England MJ, Liverman CT, Schultz AM, Strawbridge LM. Summary: a reprint of the 2015 Institute of Medicine report Neurology and Epilepsy Across the Spectrum: Promoting Health and Understanding. Baltimore, MD 2019.
[6] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. A randomized trial of second-generation antidepressants in the treatment of refractory depression. Arch Gen Psychiatry 2006;63(1):28–40.
[7] Fristoe KM, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163(1):28–40.

Munger Clary HM, Croxton RD, Allan J, Lovato J, Brenes G, Sinvely BM, et al. Who is willing to participate in research? A screening model for an anxiety and depression trial in the epilepsy clinic. Epilepsy Behav 2020;104(Pt A):106907.
[8] Gilliam FG, Black KJ, Carter J, Freedland KE, Sheline YI, Tsai WY, et al. A trial of sertraline or cognitive behavior therapy for depression in epilepsy. Ann Neurol 2007;56(4):545–56.
[9] Ribot R, Ouyang B, Kanter AM. The impact of antidepressants on seizure frequency and depressive disorders in patients with epilepsy: Is it worth investigating? Epilepsy Behav 2017;70(Pt A):5–9.
[10] Rush AJ, Croxton RD, Allan J, Lovato J, Brenes G, Sinvely BM, et al. Is it time to train neurologists in the management of mood and anxiety disorders in epilepsy? Epilepsy Behav 2016;55:184–8.
[11] Munger Clary HM, Croxton RD, Allan J, Lovato J, Brenes G, Sinvely BM, et al. To what extent are patients’ needs and preferences for anxiety and depression management in a symptomatic epilepsy clinic? Epilepsy Behav 2022;114:PT 1057–63.
[12] Zupancic M, Yu S, Kandukuri R, Singh S, Tumanyan A. Practice-based learning and systems-based practice: detection and treatment monitoring of generalized anxiety and depression in primary care. J Grad Med Educ 2010;2(3):474–7.
[13] Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163(1):28–40.
[14] Fristoe KM, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al. Treatment-refractory depression trial in the epilepsy clinic. Epilepsy Behav 2020;104(Pt A):106907.
[15] Gilliam FG, Black KJ, Carter J, Freedland KE, Sheline YI, Tsai WY, et al. A trial of sertraline or cognitive behavior therapy for depression in epilepsy. Ann Neurol 2007;56(4):545–56.
[16] Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163(1):28–40.
Barkil-Oteo A. Collaborative care for depression in primary care: how psychiatry could “troubleshoot” current treatments and practices. Yale J Biol Med 2013;86(2):139–46.

Luo Y, Kataoka Y, Ostinelli EG, Cipriani A, Furukawa TA. National Prescription Patterns of Antidepressants in the Treatment of Adults With Major Depression in the US Between 1996 and 2015: A Population Representative Survey Based Analysis. Front Psychiatry 2020;11:35.

Thase ME. Are SNRIs more effective than SSRIs? A review of the current state of the controversy. Psychopharmacol Bull 2008;41(2):58–85.

Read JR, Sharpe L, Modini M, Dear BF. Multimorbidity and depression: A systematic review and meta-analysis. J Affect Disord 2017;223:36–46.

Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Carmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011;10(4):430–9.

DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160(14):2101–7.

Hamilton KT, Anderson CT, Dahodwala N, Lawler K, Hesdorffer D, French J, et al. Utilization of care among drug resistant epilepsy patients with symptoms of anxiety and depression. Seizure 2014;23(3):196–200.

Dempe C, Junger J, Hoppe S, Katzenberger ML, Moltner A, Lodwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res 2013;74(2):122–7.

Bautista LE, Vera-Cala LM, Colombo C, Smith P. Symptoms of depression and anxiety and adherence to antihypertensive medication. Am J Hypertens 2012;25(4):505–11.

Alosaimi FD, Asiri M, Alsuwayt S, Alothaim T, Bin Muqren M, Almufarrih A, et al. Psychosocial predictors of nonadherence to medical management among patients on maintenance dialysis. Int J Nephrol Renovasc Dis 2016;9:263–72.

Zisook S, Johnson GR, Tal I, Hicks P, Chen P, Davis L, et al. General Predictors and Moderators of Depression Remission: A VAST-D Report. Am J Psychiatry 2019;176(5):548–57.

Lorant V, Deliege D, Eaton W, Robert A, Philippot P, Anseau M. Socioeconomic inequalities in depression: a meta-analysis. Am J Epidemiol 2003;157(2):98–112.

Lorant V, Croux C, Wexch S, Deliege D, Mackenbach J, Anseau M. Depression and socio-economic risk factors: 7-year longitudinal population study. Br J Psychiatry 2007;190:293–8.

Kobau R, Ditorio CA, Price PH, Thurman DJ, Martin LM, Ridges DL, et al. Prevalence of epilepsy and health status of adults with epilepsy in Georgia and Tennessee: Behavioral Risk Factor Surveillance System, 2002. Epilepsy Behav 2004;5(3):358–66.

Wiebe S, Bellhouse DR, Falloway C, Eliasziw M. Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci 1999;26(4):263–70.

Quinones AR, Thielke SM, Beaver KA, Trivedi RB, Williams EC, Fan VS. Racial and ethnic differences in receipt of antidepressants and psychotherapy by veterans with chronic depression. Psychiatr Serv 2014;65(2):193–200.

Kumar N, Aebi M, Lu E, Burant C, Sajatovic M. Ethnicity and health outcomes among people with epilepsy participating in an epilepsy self-management RCT. Epilepsy Behav 2019;101(Pt A):106469.

Burneo JG, Jette N, Theodore W, Begley C, Parko K, Thurman DJ, et al. Disparities in epilepsy: report of a systematic review by the North American Commission of the International League Against Epilepsy. Epilepsia 2009;50(10):2285–95.