CHARACTERIZING SCREENING METHODS AND MANAGEMENT PLANS AMONG PATIENTS WITH ANXIETY OR DEPRESSION IN EPILEPSY CLINIC

BY

JIANYI LI

A Thesis Submitted to the Graduate Faculty of
WAKE FOREST UNIVERSITY GRADUATE SCHOOL OF ARTS AND SCIENCES

in Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

Neuroscience program

December, 2019

Winston-Salem, North Carolina

Approved By:

Heidi Munger ClARY, MD, MPH, Advisor

Emilio Salinas, PhD, Chair

Scott D. Rhodes, PhD
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>II. INTRODUCTION</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric disorders and epilepsy</td>
<td>2</td>
</tr>
<tr>
<td>Screening for psychiatric disorders of PWE by neurologists</td>
<td>5</td>
</tr>
<tr>
<td>Identifying and managing psychiatric disorders in PWE in practice</td>
<td>9</td>
</tr>
<tr>
<td>III. METHODS</td>
<td>13</td>
</tr>
<tr>
<td>Setting, participants, and design</td>
<td>13</td>
</tr>
<tr>
<td>Demographic and clinical variables</td>
<td>13</td>
</tr>
<tr>
<td>Validated screening tools and informal screening for anxiety and depression</td>
<td>15</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>17</td>
</tr>
<tr>
<td>Data Management</td>
<td>17</td>
</tr>
<tr>
<td>IV. RESULTS</td>
<td>19</td>
</tr>
<tr>
<td>Characteristics of the study population</td>
<td>19</td>
</tr>
<tr>
<td>Assessment of screening methods</td>
<td>21</td>
</tr>
<tr>
<td>Characterizing management plans and assessing their outcomes</td>
<td>25</td>
</tr>
<tr>
<td>V. DISCUSSION AND CONCLUSION</td>
<td>28</td>
</tr>
</tbody>
</table>
VI. REFERENCES

VII. CURRICULUM VITAE
LIST OF ILLUSTRATIONS AND TABLES

Table 1. Characteristics of the 565 Subjects Enrolled in the Baseline Visit by Psychiatric Symptoms..................................................................................................................................................20

Table 2. Screening methods of 106 subjects with identified symptoms of anxiety or depression at visit..............................................................................................................................................21

Figure 1A. Distribution of standardized instrument among 565 subjects enrolled in the baseline visit....................................................................................................................................................22

Figure 1B. Distribution of detected methods among 106 subjects whose symptoms of anxiety or depression were identified at baseline visits.................................................................23

Table 3. Frequencies, proportions of positive screens and scores by different screening methods..................................................................................................................................................24

Table 4A. Comparison of NDDI-E with PHQ-2 among 29 individuals who completed both instruments........................................................................................................................................25

Table 4B. Comparison of informal screening with PHQ-2 among 29 individuals who completed both instruments........................................................................................................................................25

Table 5. Description of the outcomes of the management plan in follow up visits among 63 Individuals with identified symptoms of anxiety or depression in baseline visits......27
LIST OF ABBREVIATIONS

GAD-7: The Patient’s Health Questionnaire – Generalized Anxiety Disorder-7

NDDI-E: The Neurological Disorder Depression Inventory for Epilepsy

PCP: Primary-care Physician

PHQ-2: The Patient’s Health Questionnaire–2

PHQ-9: The Patient’s Health Questionnaire-9

PNES: Psychogenic Nonepileptic Seizures

PWE: People with Epilepsy
ABSTRACT

People with epilepsy have a higher chance of developing depression and anxiety than general population. Psychiatric comorbidities in PWE are detrimental because they impact quality of life of PWE and management plans for epilepsy. Therefore, neurologists are essential for detecting anxiety and depression in PWE in outpatient clinics. Validated screening instruments including PHQ-2, PHQ-9, NDDI-E and GAD-7 can efficiently detect positive symptoms. However, they are not widely applied. There are limited studies describing screening methods and management plans in real practice. Therefore, this study was designed to characterize screening methods and describe the management plans of epilepsy providers. This study enrolled 565 individuals and collected their demographic and clinical variables. Usage of several screening methods and management plans of individuals with positive symptoms were obtained. Results showed that although PHQ-2 was the most frequently applied screening tool in outpatient clinic, it had a very low detection rate. Clinicians tended to use informal screening to identify most symptoms. Medication prescription and psychiatry referral were the two most common management plans, and the combination of those two actions resulted in the highest percentage of patients with improved symptoms. Results also indicated the potential need to adjust optimal cut-points of GAD-7 and NDDI-E.
INTRODUCTION

1. Psychiatric disorders and epilepsy

Epilepsy is a prevalent, chronic neurological disorder. It is the fourth most prevalent neurologic disorder after migraine, stroke, and Alzheimer disease, affecting nearly 50 million people in the world. According to the results of several epidemiological studies of populations from various regions and countries, people with epilepsy (PWE) had higher chance of developing depression and anxiety compared with the general population. In other words, the prevalence of psychiatric comorbidities is high in PWE. Epidemiological studies on the association between epilepsy and psychiatric disorders have found that epilepsy can precede, co-occur with or follow the diagnosis of a psychiatric disorder. A systematic review and meta-analysis of population-based studies in 2013 demonstrated the depression in PWE was common across numerous studies. This review examined 23 articles which were based on 14 distinct populations. According to the results derived from the 9 depression-focused studies investigating 29891 PWE, the estimated prevalence of active depression symptoms (current or past-year) was 23.1%. According to the results derived from 4 studies investigating 5454 PWE, the risk of lifetime depression was estimated at 13%. The results of a Korean hospital-based study in 2013 showed the prevalence of depression in PWE was 27.8%, which was 3.16 times higher than that of the general population.

Although anxiety in epilepsy is less well studied than depression, several studies demonstrated that the prevalence of anxiety in PWE was high. According to the population-based study by Tellez-Zenteno et al. in 2007, estimates of the lifetime prevalence of anxiety in the population with epilepsy is potentially as high as 22.8%. In
the general population without epilepsy, this number is 5.6\% \textsuperscript{8}. The odds of anxiety symptoms in the population with epilepsy compared to the healthy general population were estimated to be a 2.4 \textsuperscript{6}. Another Canadian population-based study in 2007 demonstrated that 24.4\% of PWE showed symptoms of psychiatric disorders. And this prevalence rate was 1.85 times higher than that of healthy controls. Another study demonstrated that the prevalence rate of anxiety disorder was 14.1\%, which was 1.26 times higher than healthy controls \textsuperscript{7}. The results of another Korean hospital-based study showed the prevalence of anxiety in PWE was found to be 15.3\%, which was 4.78 times higher than that of people without epilepsy \textsuperscript{9}.

The relationship between psychiatric comorbidities and epilepsy is bidirectional \textsuperscript{10}. Not only PWE have an increased risk of developing psychiatric disorders, but patients suffering from a primary psychiatric disorder also have an increased risk of developing epilepsy \textsuperscript{10}. The results of several epidemiologic studies showed that depression and anxiety were risk factors for epilepsy. A matched longitudinal cohort study in 2012 examined 3773 PWE, compared them with 14025 controls and found that first occurrences of psychiatric disorders increased significantly both before and after epilepsy diagnosis, concluding that psychiatric disorders increase the risk for developing epilepsy, and epilepsy increases the risk for developing the psychiatric disorders \textsuperscript{11}.

Psychiatric comorbidities in PWE are detrimental in that they can not only impact the quality of life of PWE, but disturb the management plan of the epilepsy at various levels as well \textsuperscript{10}. The life of PWE can be affected in three ways \textsuperscript{10}. First of all, anxiety and depression are leading predictors of poor quality of life. A study in 2004 investigated the effects of anxiety and depression on health-related quality of life (HRQOL). The results
indicated that depression and anxiety were associated with reduced HRQOL, and psychiatric comorbidity had a more serious effect on reduced HRQOL than clinical seizure or demographic variables did. Secondly, current psychiatric disorders are related to high frequency of medical services use, resulting in higher economic stress for the patient, family and society. Thirdly, anxiety and depression are related with higher risk of unexpected death (such as accidents and suicide) by external causes. A population-based case-control study in 2007 examined 21169 suicide cases in Denmark from 1981 to 1997. Among these cases, patients with epilepsy and comorbid psychiatric disorders had the highest risk of suicide, even excluding socioeconomic factors. The results of a population study in 2013 showed that psychiatric comorbidity plays an essential part in the premature death of PWE. The study examined all Swedish with epilepsy born between 1954 and 2009 and aimed to investigate risks and causes of premature mortality. 75.2% of the PWE who died from external causes had comorbid psychiatric disorders.

The management plan for epilepsy is impacted by anxiety and depression at various levels. First of all, a psychiatric history prior to the onset of epilepsy seems to have association with a higher risk of treatment-resistant epilepsy. A study in 2007 analyzed 780 patients in the West of Scotland who were diagnosed with epilepsy and followed up them over a 20-year period to find out the clinical factors that predicted pharmacoresistance. This study demonstrated that there was a correlation between a psychiatric history and resistance to antiepileptic drug (AED) therapy. Secondly, a psychiatric history of a patient and/or his/her family have been shown to be related with a higher risk of non-psychiatric and psychiatric adverse events to AEDs. A study in 2003
investigated psychopathologic features of psychiatric adverse events in 517 patients who took levetiracetam to treat epilepsy. And the results showed that the association between previous psychiatric history and psychiatric adverse events was significant, indicating that a psychiatric history potentially increases the risk of psychiatric adverse events to AEDs. Thirdly, current psychiatric disorders and/or a psychiatric history are associated with stress, which may increase seizure frequency. A prospective diary study in 2007 collected the information including seizure occurrence, stress, and anxiety from 71 subjects on 15179 completed diary days. The results showed that seizure occurrence was more likely to occur when high stress levels existed. Another survey in 2003 assigned a questionnaire to patients in the outpatient epilepsy department to assess their perceptions about stress and seizures, and 64% of those reported that the stress due to psychiatric condition increased their seizure frequencies. Because anxiety and depression affect the quality of life of PWE and impact the management plan for epilepsy, neurologists need to pay attention to the psychiatric comorbidities in epilepsy. They ought to come up with approaches to rapidly detect anxiety and depression in PWE in a busy outpatient clinic.

2. Screening for psychiatric disorders of PWE by neurologists

There are many methods to detect depression and anxiety, including standardized interviews and self-report screening tools. Composite International Diagnostic Interview (CIDI) and SCID are two examples of fully structured and semi-structured interviews. Mini-International Neuropsychiatric Interview (MINI) is another example of standardized interviews, which was designed for clinical use and is commonly used by psychiatrists and mental care professionals in clinical care. Clinicians commonly use
these formal interviews to assess the performance of screening instruments like self-reported rating scales. However, because standardized interviews such as CIDI and SCID are time-consuming and require much training that is not included in neurology training programs or medical school, they are not practical in neurology clinics.\textsuperscript{21}

Screening tools, on the other hand, are commonly brief, standardized and requiring fewer resources to carry out, thus using them can be very effective in neurology clinic setting.\textsuperscript{20} Commonly used and validated self-report tools for screening anxiety and depression in epilepsy include Generalized Anxiety Disorder-7 item scale (GAD-7), Patient Health Questionnaire (PHQ), and Neurologic Disorder Depression Inventory for Epilepsy (NDDI-E). Among those screening tools, only GAD-7 is used to identify anxiety, and all the rest of them are used to identify depression.

2.1. Screening for depression in epilepsy

According to the International League Against Epilepsy Commission on the Neuropsychiatric Aspects of Epilepsy, the most recommended screening tools for detecting depression in clinic are PHQ-2 and NDDI-E.\textsuperscript{21} Although PHQ-9 is less frequently used than PHQ-2 and NDDI-E, it has comparable validity, sensitivity and specificity with other screening instrument.\textsuperscript{22}

PHQ-9 contains 9 questions related to depression from the full PHQ, which are (1) “little interest or pleasure in doing things”, (2) “feeling down, depressed, or hopeless”, (3) “trouble falling asleep, staying asleep, or sleeping too much”, (4) “feeling tired or having little energy”, (5) “poor appetite or overeating”, (6) “feeling bad about yourself – or
that you are a failure or have let yourself or your family down”, (7)“trouble concentrating on things, such as reading the newspaper or watching television”, (8)“moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual”, and (9) “thoughts that you would be better off dead, or of hurting yourself in some way”. For each question, there are four options for the patient to choose: (1) not at all, (2) several days, (3) more than half the days, and (4) nearly every day. The patient is required to answer how often each situation was encountered in the past 2 weeks. If 5 or more of the 9 scenarios have been encountered at least “more than half the days” in the past 2 weeks, then the patient is diagnosed as major depression. Each item of PHQ-9 have a score from 0 (not at all) to 3 (nearly every day), thus the PHQ-9 scores range from 0 to 27. Severity of depression can be interpreted as negative (if score equals zero), minimal (if score ranges from 1 to 4), mild (if score ranges from 5 to 9), moderate (if score ranges from 10 to 14), moderately severe (if score ranges from 15 to 19), and severe (if score ranges from 20 to 27). The patient who checked off any problems also needs to answer an additional overall impact question: how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? The answers for selection are “not difficult at all”, “somewhat difficult”, “very difficult” and “extremely difficult”.

Due to the busy nature and competing demands of primary care practice, a briefer measure of depression was desired for use in busy clinic settings. Therefore, the PHQ-2 was adopted as an efficient measure for depression screening. The PHQ-2 includes first two questions of the PHQ-9. The stem question of PHQ-2 is “Over the past 2 weeks, have you been bothered by any of the following problems?” The patient is required to
answer yes or no. If the patient answers “yes” to one problem, then he/she will get 1 point, thus scores of PHQ-2 range from 0 to 2. The PHQ-2 is briefer and more efficient than PHQ-9, thus it is widely applied in outpatient clinic for depression screening. Patients will be screened by PHQ-9 if only their answers of PHQ-2 are positive.

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is another validated screening tool for depression. It is a rapid and reliable screening method for detecting depression. One notable characteristic of NDDI-E is that it is an instrument specifically designed detection of depression in epilepsy, and it can identify depressive symptoms which can be separated from antiepileptic drug side effects 20. Similar to PHQ-2 and PHQ-9, NDDI-E also consists of different questions, and patients are required to answer how often they have encountered those situations in the past two weeks. There are 6 different items that compose the NDDI-E, which are “everything is a struggle”, “nothing I do is right”, “feel guilty”, “I’d be better off dead”, “frustrated”, and “difficulty finding pleasure”. Each item of the NDDI-E has a score from 1 (never) to 4 (always or often), thus scoring of NDDI-E ranges from 6 to 24. Scores ranging from 6 to 15 are interpreted as not being suggested of major depression, though significant mood disorder cannot be excluded. scores ranging from 16 to 24 are interpreted as having signs or symptoms that may indicate major depression 20.

2.2. Screening for anxiety in epilepsy

Consensus guidelines have not recommended screening tools for anxiety yet 21, but GAD-7 is a commonly used screening instrument in clinic setting. In the 2017
Epilepsy Quality Measurement Set, GAD-7 was listed as a potential validated instrument which met quality measurement requirement. It is a valid and reliable screening method and has been validated for detecting anxiety in PWE. Because it is simple, straightforward and efficient, GAD-7 has been widely adopted by primary physicians. The study by Seo indicates that application of GAD-7 brings about higher detection rate of anxiety in PWE. GAD-7 is a brief questionnaire which contains 7 questions and requires less than 3 minutes to complete. Patients are required to answer how often have they been bothered by 7 different symptom dimensions which are “feeling nervous, anxious, or on edge”, “not being able to stop or control worrying”, “worrying too much about different things”, “trouble relaxing”, “being so restless that it’s hard to sit still”, “becoming easily annoyed or irritable”, and “feeling afraid as if something awful might happen”. Scores of answers to each question range from 0 (not at all sure) to 3 (nearly every day), thus final scores range from 0 to 21. The condition of patient is interpreted as normal (if score ranges from 0 to 4), mild anxiety (if score ranges from 5 to 9), moderate anxiety (if score ranges from 10 to 14) and severe anxiety (if score ranges from 15 to 21).

3. Identifying and managing psychiatric disorders in PWE in practice

Although screening tools for anxiety and depression have many advantages, they are not widely applied in all neurology clinics. Therefore, despite depression and anxiety being common in PWE, they are often undiagnosed and/or untreated by neurologists. Prior studies indicate that only half of PWE suffer from depression are under mental health care. And only one-third of youth with epilepsy who have
psychiatric disorders have received mental health treatment. A study in 2014 determined the proportion of PWE who received depression-related treatment. And the results showed that among all subjects with current depression, 70.3% of them did not receive any treatment to alleviate depression. 37.2% of the individuals with a past history of depression but no current episode received depression-related treatment.

In 2013, the American Academy of Neurology (AAN) established an Epilepsy Update Quality Measurement Set workgroup in order to review the quality measures in the previous year, and to introduce new quality measures for the purpose of improving outcomes for PWE. In this updated quality measurement set, Screening for Psychiatric or Behavioral Health Disorders (Measure 5 in the 2014 version) was invented in order to solve the problem of undiagnosed and untreated psychiatric comorbidities in epilepsy.

In 2016, a survey by Munger Clary published in a commentary asked epileptologists about their opinions towards actions and barriers to assessing anxiety and depression in PWE. According to the results, most neurologists in this survey claimed that they regularly assessed depression (65.7%) at initial visit and at every follow-up visit. Approximately half of the respondents answered that they routinely addressed anxiety (47.5%) at every clinic visit. When faced with a patient with depressive symptoms, 70% of neurologists would further screen the patient to identify the symptoms, about 60% preferred to prescribe an antidepressant, 90% preferred to refer the patient to a mental health provider, and only 12% believed referring to a primary care provider (PCP) would be beneficial. When presented with a patient with symptoms of anxiety, 53.9% of respondents would further screen the patient, 33.7% preferred to prescribe an anxiolytic, 95.1% preferred a referral to a mental health care provider, and 14.9% preferred a referral
to a PCP. Only 11.8% preferred to administer a validated screening instrument for depression and only 4.9% for anxiety. Participants of this survey also identified several barriers to screening for depression and anxiety in the clinic. The most identified barrier was insufficient available mental health providers. From their perspectives, the availabilities of either psychiatrists or counseling/psychotherapy services were inadequate. However, this is a survey-based study. Studies investigating the proportion of validated instrument usage and the approaches of neurologists when faced with patients with positive psychiatric symptoms in real practice are limited.

Due to the negative effects of anxiety and depression on the life of PWE and on the management plan of the epilepsy, it is necessary for researchers to conduct interventional studies which use pragmatic trials in real clinical settings in order to investigate treatments for anxiety and depression in epilepsy. Since pragmatic trials are derived from usual care practice, it is essential to understand and obtain characteristics of usual care practice. Characterizing usual care practice can not only create preliminary data for designing interventions, but also provide basic information of usual care control group in future interventional studies. In order to find out the real situation of usual care of anxiety and depression in PWE and to provide valuable preliminary data for grounding new ideas for psychiatric intervention, this thesis was conducted to characterize screening measurement and management plan of neurologists while dealing with anxiety and depression comorbidities in PWE. The purpose of this study was two-fold: during usual care practice among multiple providers at a single tertiary care epilepsy center in 2017 (1) to assess the proportion of individuals who were screened for anxiety or depression by any method, and to further characterize method used, and (2) to describe the management
plans carried out by epilepsy providers in the baseline visit and investigate the outcomes in the follow up visit.
METHODS

1. Setting, participants, and design:

This is a longitudinal, retrospective study of all adults who had a clinic visit at the Wake Forest Comprehensive Epilepsy Center from March 1st to May 31st 2017. The baseline visit was defined as the first epilepsy clinic visit from March 1st to May 31st 2017, and the follow up visit was defined as the next clinic visit following the baseline visit. All participants completed a baseline visit with 1 of 5 neurologists or 1 of 2 Advanced Practice Providers (APPs). Outcomes of participants were assessed at the follow up visit. This study includes 565 individuals out of 573 total seen in the clinic during the baseline study period. Eight individuals were excluded because they were younger than 18 years old. There were 565 adults who completed a baseline visit, and 433 individuals who completed a follow up visit by February 11, 2019. The Wake Forest Comprehensive Epilepsy Center is an academic medical center located in Winston Salem, serving a diverse population. All data were collected by electronic medical chart review. This study was approved by IRB with waiver of informed consent and the study ID is IRB00046507.

2. Demographic and clinical variables

Demographic variables which were collected included age, sex, race/ethnicity, psychiatric history of anxiety or depression (documented in problem lists, medical history, or described as ongoing comorbidities of the subjective portion of the provider notes), the scores of completed screening methods by specific instrument, management
plan for anxiety and depression carried out by epilepsy providers. Race/ethnicity was classified into six categories: White, Black, Asian, American Indian/Alaska Native, Hispanic and Others. Screening tools for depression included PHQ-2, PHQ-9, NDDI-E and GAD-7 was a screening tool for anxiety. Clinical variables which were collected included certainty of epilepsy diagnosis, epilepsy diagnosis, active anxiety or depression symptoms identified at visit (defined below), psychogenic nonepileptic seizures (PNES), and history of anxiety or depression. Certainty of epilepsy diagnosis was categorized into three levels of certainty (1) EEG with epileptiform discharges or seizure recording, (2) non-epileptiform EEG and remission with antiepileptic drug and (3) epilepsy diagnosis based on clinical impression alone. Epilepsy type was categorized into three groups by 2017 International League Against Epilepsy criteria: (1) focal epilepsy, (2) generalized epilepsy, and (3) uncertain type. Active symptoms identified at visit were determined to be positive if clinician indicated that a patient showed positive symptoms of anxiety or depression in interval history, assessment, or plan section of the progress notes, or the results of screening instrument were positive. Positive history of anxiety or depression was determined based on past medical history column and problem list column of electronic medical chart and description of psychiatric history of patients by providers in progress note from visit (key words included “history of anxiety/depression”, “positive past medical history of anxiety/depression”, “had symptoms of anxiety/depression in the past”, etc.). Management plan carried out by neurologists was classified into six categories: no management plan was made but symptoms of anxiety/depression were identified; Providers prescribed medications to treat symptoms; The patient was referred to primary care physicians; The patient was referred to psychiatrists/counselors; The
patient was referred to a psychologist for relaxation training; And no management plan was made due to no symptoms. Baseline variables were collected at initial visit, and outcome variables were collected at follow up visit. Outcomes assessed in follow up visits were: (1) if the scores of specific screening instruments improved and (2) if the identified symptoms improved based on mention in the progress note at follow up (in interval history or assessment sections).

3. Validated screening tools and informal screening for anxiety and depression

There were four validated screening tools for anxiety and depression in this study: PHQ-2, PHQ-9, NDDI-E and GAD-7. PHQ-2, PHQ-9 and NDDI-E are three screening methods aiming for detecting and evaluating severity of depression. And GAD-7 is a validated screening tool for identifying anxiety in PWE. Several studies have demonstrated the validity and reliability of these four screening tools in terms of detecting depression and anxiety in PWE.9 28 35 36 According to the institutional protocol, nursing stuff collected the answers of PHQ-2 by interviewing patients. A total PHQ-2 score of larger than zero was considered as positive. If a positive response to the PHQ-2 was provided by patients, electronic medical record system would automatically open up PHQ-9 for potential further screening. Based on a validation study by Kroenke, a PHQ-9 score of 5 or higher was considered as having a positive screen for depressive symptoms23. NDDI-E and GAD-7 were administered by providers as paper forms based on their clinical judgement and were scanned to medical record system. Based on a validation study, the patient who had a NDDI-E score of 16 or higher was considered as having a
positive depressive symptoms \(^{36}\), and the patient who had a GAD-7 score of 10 or higher was considered as having a positive anxiety symptoms \(^{9}\).

According to the systematic review of several screening tools (including NDDI-E, PHQ-2 and PHQ-9) in PWE by Gill et al. in 2017, NDDI-E was the most commonly used validated screening tool for depression in epilepsy \(^{37}\). For exploratory analysis of sensitivity and specificity of the PHQ-2 brief depression screener, we considered the NDDI-E to be the ‘gold standard’.

Not only the frequencies of validated screening instrument were determined, the frequencies of informal screening were also obtained in this study. Informal screening represented some informal screening questions which aimed to identify symptoms of anxiety or depression but were integrated into clinical interview by providers. Since it was difficult to determine whether informal screening was routinely completed merely based on medical chart documentation, we could only obtain those patients who were determined to have positive symptoms of anxiety or depression by informal screening. In this study, informal screening was determined positive based on the following criteria: (1) a patient did not complete any screening instrument but his/her active symptoms of depression/anxiety were identified by provider at visit. (2) A patient was screened negative by PHQ-2/PHQ-9/NDDI-E, but his/her depression was identified by providers at visit. (3) A patient was screened negative by GAD-7, but his/her anxiety was identified by providers at visit. If a patient with documented positive symptoms of anxiety or depression had negative results of validated standardized instrument or was not screened by standardized screening tools, then we could infer that informal screening identified the symptoms of anxiety or depression of this patient. In other words, the patients who
received informal screening but were not determined to have positive symptoms were unknown in this study.

4. Statistical analysis

Analyses were conducted by using RStudio 1.2. This study compared the descriptive variables of the patients who had active symptoms of anxiety/depression at visit with those who did not have active symptoms in order to explore which variable could be associated with symptoms of anxiety/depression based on a series of chi-square analysis (for categorical variables) and t-test (for quantitative variable). The main objective of this study was to compare the usage and the proportion of positive results of four different screening tools based on chi-square tests. Another goal was to investigate whether the proportions of the individuals with improved symptoms were associated with different management plans. Chi-square analysis was conducted to investigate whether the proportion of people with improved symptoms was associated with specific management plans. Another chi-square analysis was performed to compare expected percentages of management plans claimed by neurologists in the survey by Munger Clary and observed percentages in this study. A p value of < 0.05 was considered statistically significant.

5. Data Management

Study data were collected and managed using REDCap electronic data capture tools hosted at Wake Forest University School of Medicine. REDCap (Research
Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.  

Confidentiality of patients was protected by collecting only information needed to assess study outcomes. Only a unique study identification number appeared on the data collection form in order to help ensure subject privacy and confidentiality. Any collected patient identifying information was maintained on a linkage file which was stored separately from the data. Data access was limited to study staff, protected by secured password.
RESULTS

1. Characteristics of the study population

Table 1 shows several descriptive variables of 565 subjects enrolled in baseline visits. Except age, all variables are categorical and their proportions were listed in Table 1. In order to investigate the association between identified psychiatric symptoms either by standardized screening or informal screening reflected in documentation and several factors including sex, age, epilepsy diagnosis, PNES (psychogenic epilepsy), and psychiatric history, the overall population was divided into two groups. There were 459 individuals without symptoms of anxiety or depression identified at visit, and there were 106 individuals with those symptoms identified either by standardized screening or informal screening recorded in progress notes at visit. In this baseline population, the prevalence of anxiety and depression by either standardized instrument or informal screening was 18.8%. Of the baseline population, the prevalence of anxiety was 13.63%, and the prevalence of depression was 10.97%. Table 1 compares characteristics of individuals with identified symptoms of anxiety or depression at visit and individuals without those symptoms. Based on the results of chi-square analyses and two sample t-test, PNES (χ²=4.96, p=0.03) was associated with positive symptoms. And positive history of anxiety or depression was also associated with positive symptoms (χ²=159.73, p<0.00001). Nearly all people with symptoms identified have a documented medical history of anxiety or depression. The following factors were not associated with identified psychiatric symptoms: sex (χ²=2.67, p=0.10), race (χ²=3.08, p=0.55), epilepsy diagnoses (χ²=3.78, p=0.051), and age (t=-0.93, p=0.35).
<table>
<thead>
<tr>
<th></th>
<th>Overall (N=565)</th>
<th>No symptoms of anxiety or depression identified (N=459)</th>
<th>Identified symptoms of anxiety or depression (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex</strong></td>
<td>248 (43.9)</td>
<td>206 (45.5)</td>
<td>39 (36.8)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>42.3 ± 16.9</td>
<td>42.0 ± 17.1</td>
<td>43.7 ± 16.0</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>432 (76.5)</td>
<td>347 (75.6)</td>
<td>85 (80.2)</td>
</tr>
<tr>
<td>Black</td>
<td>100 (17.7)</td>
<td>83 (18.1)</td>
<td>17 (16.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (1.1)</td>
<td>6 (1.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (3.5)</td>
<td>18 (3.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (1.1)</td>
<td>4 (0.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td><strong>Certainty of epilepsy diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed with epilepsy</td>
<td>468 (82.8)</td>
<td>387 (84.3)</td>
<td>81 (76.4)</td>
</tr>
<tr>
<td>EEG with epileptiform discharge</td>
<td>213 (37.7)</td>
<td>136 (40.5)</td>
<td>27 (25.5)</td>
</tr>
<tr>
<td>Non-epileptiform EEG and remission with AED</td>
<td>132 (23.4)</td>
<td>107 (23.3)</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td>Epilepsy diagnosis based on clinical impression alone</td>
<td>123 (21.8)</td>
<td>94 (20.4)</td>
<td>29 (27.4)</td>
</tr>
<tr>
<td>No diagnosis of epilepsy</td>
<td>97 (17.2)</td>
<td>72 (15.7)</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td><strong>Epilepsy type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>314 (57.1)</td>
<td>264 (57.5)</td>
<td>50 (47.2)</td>
</tr>
<tr>
<td>Generalized</td>
<td>120 (25.6)</td>
<td>98 (21.4)</td>
<td>22 (20.9)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>34 (6.1)</td>
<td>25 (5.4)</td>
<td>9 (8.5)</td>
</tr>
<tr>
<td>No diagnosis of epilepsy</td>
<td>97 (17.2)</td>
<td>72 (15.7)</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td>PNES</td>
<td>29 (5.1)</td>
<td>19 (4.1)</td>
<td>10 (9.4)</td>
</tr>
<tr>
<td><strong>Completed any standardized screening instrument?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>379 (67.1)</td>
<td>298 (64.9)</td>
<td>81 (76.4)</td>
</tr>
<tr>
<td>PHQ-2</td>
<td>370 (65.5)</td>
<td>296 (64.5)</td>
<td>74 (69.8)</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>3 (0.5)</td>
<td>0 (0)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>NDDLE</td>
<td>38 (6.7)</td>
<td>8 (1.7)</td>
<td>30 (28.3)</td>
</tr>
<tr>
<td>GAD-7</td>
<td>38 (6.7)</td>
<td>9 (2.0)</td>
<td>29 (27.4)</td>
</tr>
<tr>
<td>Not screened by any standardized instrument</td>
<td>186 (32.9)</td>
<td>161 (35.1)</td>
<td>25 (23.6)</td>
</tr>
<tr>
<td><strong>Positive history of anxiety or depression?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>240 (42.5)</td>
<td>137 (29.8)</td>
<td>103 (97.2)</td>
</tr>
<tr>
<td>In past medical history column of medical chart</td>
<td>139 (24.6)</td>
<td>95 (20.7)</td>
<td>44 (41.5)</td>
</tr>
<tr>
<td>In problem list column of medical chart</td>
<td>113 (20.0)</td>
<td>68 (14.8)</td>
<td>43 (42.5)</td>
</tr>
<tr>
<td>In progress notes from visit</td>
<td>145 (25.7)</td>
<td>43 (9.4)</td>
<td>102 (96.2)</td>
</tr>
<tr>
<td>No</td>
<td>325 (57.5)</td>
<td>322 (70.2)</td>
<td>3 (2.8)</td>
</tr>
</tbody>
</table>
Table 2. Screening methods of 106 subjects with identified symptoms of anxiety or depression at visit

<table>
<thead>
<tr>
<th>Screening methods</th>
<th>Overall (N=106)</th>
<th>Both anxiety and depression (N=33)</th>
<th>Depression only (N=29)</th>
<th>Anxiety only (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected by instrument</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected by PHQ-2 (depression)</td>
<td>28 (26.4)</td>
<td>15 (45.5)</td>
<td>6 (20.7)</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td>Detected by PHQ-9 (depression)</td>
<td>4 (3.8)</td>
<td>0</td>
<td>4 (13.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Detected by GAD-7 (anxiety)</td>
<td>21 (19.8)</td>
<td>14 (42.4)</td>
<td>NA</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td>Detected by NDDI-E (depression)</td>
<td>15 (14.2)</td>
<td>12 (36.4)</td>
<td>3 (10.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Detected by informal screening</td>
<td>78 (73.6)</td>
<td>18 (54.5)</td>
<td>23 (79.3)</td>
<td>37 (84.1)</td>
</tr>
</tbody>
</table>

2. Assessment of screening methods

Table 2 compares screening methods of individuals identified as anxiety and those identified as depression. There were three types of screening methods: (1) An individual was only screened by informal screening and did not receive any standardized instrument. (2) An individual was screened by at least one standardized instrument but had negative results, and his/her symptom was identified by informal screening. (3) Symptoms of an individual were identified based on positive results of at least one standardized instrument.

Table 2 also compares screening methods of individuals identified as anxiety only (N=44), depression only (N=29) and both anxiety and depression (N=33). Their symptoms were either identified by standardized instruments or by informal screening. Proportions of individuals whose symptoms identified by either screening method are listed in Table 2. Of all 565 individuals enrolled in this study, only 38 people were screened by GAD-7. Among those 38 individuals, the percentage of those whose anxiety were identified by instrument (GAD-7) was 55.3%. Of the 28 individuals whose symptoms of anxiety or depression were detected by standardized instrument, 4 had positive PHQ-2 scores. Of those 4 individuals, 3 completed PHQ-9 and 2 (66.7%) of
them had positive PHQ-9 scores. Of the 78 individuals whose symptoms of anxiety or depression were detected by informal screening, 25 (32.1%) did not receive any standardized instrument, and 53 (67.9%) were screened by standardized instrument but had negative results. Of these 53 individuals, 51 had negative PHQ-2 results, 7 had negative GAD-7 results and another 7 had negative NDDI-E results. Of all the 7 individuals with negative GAD-7 results, they had a mean score of 4.4 ± 4.16. Of all the 7 individuals with negative NDDI-E results, the mean score was 12.0 ± 3.29.

**Figure 1A.** Distribution of standardized instrument among 565 subjects enrolled in the baseline visit
Figure 1B. Distribution of detected methods among 106 subjects whose symptoms of anxiety or depression were identified at baseline visits.

Figure 1A shows the distribution of standardized instrument among 565 individuals enrolled in baseline visit. Of the whole population, 186 (32.92%) patients were not screened by any kind of standardized instrument, Figure 1B shows the distribution of detected methods among 106 individuals whose symptoms of anxiety or depression were identified at baseline visits.

Frequencies and proportions of positive screens of each method were demonstrated in Table 3. A chi-square test was performed in order to investigate whether the proportion of positive screens was significantly associated with different screening methods. The results of the chi-square test demonstrated that the proportion of positive screens was significantly related to different screening methods ($\chi^2=283.07$, $p<0.00001$). Of the 370 individuals who were screened by PHQ-2, 4 (1.4%) had positive PHQ-2
scores, 70 (18.9%) had negative scores but depressive symptoms were identified by informal screening. Of the 38 individuals who were screened by NDDI-E, 15 (39.5%) had positive NDDI-E scores, 14 (36.8%) had negative scores but depressive symptoms were identified by informal screening. Of the 38 individuals who were screened by GAD-7, 22 (57.9%) had positive GAD-7 scores, 9 (23.7%) had negative scores but symptoms of anxiety were identified by informal screening.

**Table 3.** Frequencies, proportions of positive screens and scores by different screening methods

<table>
<thead>
<tr>
<th></th>
<th>PHQ-2</th>
<th>PHQ-9</th>
<th>NDDI-E</th>
<th>GAD-7</th>
<th>Informal screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usage counts (ⅰ% of all baseline visits)</td>
<td>370 (65.5)</td>
<td>3 (0.5)</td>
<td>38 (6.7)</td>
<td>38 (6.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Positive screens (ⅰ% of all individuals receiving specific screenings)</td>
<td>4 (1.4)</td>
<td>2 (66.7)</td>
<td>15 (39.5)</td>
<td>21 (55.3)</td>
<td>78</td>
</tr>
<tr>
<td>Scores (Mean ± SD)</td>
<td>0.02 ± 0.19</td>
<td>7.67 ± 4.51</td>
<td>13.65 ± 4.49</td>
<td>8.82 ± 6.74</td>
<td>NA</td>
</tr>
</tbody>
</table>

*In this study, it was unclear whether informal screening was routinely recorded in documentation, thus the total number of people who received informal screening was unknown. We could only obtain the number of individuals who had positive results of informal screening.*

Table 4 compares several pairs of screening methods among individuals who completed both, including PHQ-2 vs. NDDI-E, and PHQ-2 vs. informal screening. For an exploratory comparison with PHQ-2, NDDI-E was considered “gold standard” in terms of identifying depressive symptoms. Zero individual out of 11 with positive NDDI-E was determined to be positive by PHQ-2, thus the sensitivity of PHQ-2 was 0 when compared with NDDI-E. 17 individuals out of 18 with negative NDDI-E were determined to be negative by PHQ-2, thus the specificity of PHQ-2 was 94.4% when compared with NDDI-E. For an exploratory comparison with PHQ-2, informal screening was considered “gold standard”. According to Table 4b, zero individual out of 29 with positive informal screening was determined to be positive by PHQ-2. In other words, among 29 people who had positive symptoms of depression and completed PHQ-2, PHQ-2 detected none
of the depressive symptoms which were detected by informal screening. Therefore, when compared with informal screening, the sensitivity of PHQ-2 was zero.

3. Characterizing management plans and assessing their outcomes

Of the 106 subjects whose psychiatric symptoms were identified by providers at visit, 6 (5.7%) were referred to PCP, 24 (22.6%) were referred to psychiatry care, 10 (9.4%) were referred to counseling service, 5 (4.7%) were referred to a psychologist for relaxing training, 40 (37.7%) were prescribed medication, and 40 (37.7%) were not treated by providers. Among these 106 individuals, 20 (18.9%) were referred to psychiatry and prescribed medication at the same time. Chi-square tests were performed between the percentages of management plans that were observed in this study and expected percentages of management plans in the survey by Munger Clary. Results indicated that the differences between observed and expected percentages of several management plans (PCP, psychiatry referral, and prescribed medication) were all significant (PCP: $\chi^2=24.60$, $p=10^{-6}$; Psychiatry referral: $\chi^2=184.79$, $p<0.001$; Prescribed medication: $\chi^2=99.51$, $p<0.001$). Of the 565 subjects enrolled in baseline visits, 106 (18.8%) of them had symptoms of anxiety or depression which were identified at baseline.
visits. Among those 106 individuals, 84 (79.2%) of them completed follow up visits before February 11th, 2019. Of these 84 patients, there were 21 individuals whose psychiatric conditions were unknown in follow up visits. We could not find any information from medical charts about whether their identified symptoms improved or not in follow up visits. Among 63 individuals whose symptoms were either improved or not in follow up visits, outcomes of their previous management plan carried out by neurology providers were listed in Table 5. Those 63 individuals had received 4 different management plans. Of the individuals who received prescribe only, 57.1% had improved symptoms; Of the individuals who were referred to psychiatry only, 50.0% had improved symptoms; Of the individuals who received plans of both psychiatry referral and prescription, 80.0% had improved symptoms; Only 1 individual received plans of both PCP referral and prescription and his symptom improved in the follow up visit. Of 17 individuals who were untreated in baseline visit, 64.7% had improved symptoms. In order to find out whether proportion of improved symptoms was significantly related with different management plans, a chi-square test was performed. The results of chi-square analysis show that distinct management plans were not significantly associated with proportions of improved symptoms ($\chi^2=3.10$, $p=0.54$). In order to find out whether receiving any management plan was associated with higher proportion of improved symptoms, another chi-square test was performed. The results indicate that higher proportion of improved symptoms was not significantly associated with receiving management plans or not ($\chi^2=0.0002$ $p=0.99$).
Table 5. Description of the outcomes of the management plan in follow up visits among 63 Individuals with identified symptoms of anxiety or depression in baseline visits

<table>
<thead>
<tr>
<th>Management plan</th>
<th>Patients with improved symptoms (N=39)</th>
<th>Patients with unimproved symptoms (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received any management plan (N=46)</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Prescribe only (N=21)</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Psychiatry referral only (N=14)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Prescribe &amp; psychiatry referral (N=10)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Prescribe &amp; PCP (N=1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No action (N=17)</td>
<td>11</td>
<td>6</td>
</tr>
</tbody>
</table>
DISCUSSION

This is one of a few studies characterizing the application of the validated screening instruments for anxiety and depression and assessing the outcomes of management plans made by epilepsy providers in real clinic settings. There were about 67% individuals screened by validated standardized instrument in spite of the fact that the protocol requires all providers use screening tools for identifying potential anxiety and depression. The results demonstrate that when compared with other screening instruments, the most frequently used screening tool was PHQ-2, and the least frequently used screening instrument was PHQ-9. The frequencies of GAD-7 and NDDI-E being applied in clinic were lower than those of PHQ-2, but much higher than those of PHQ-9. PHQ-2 is a required screening tool based on the institutional protocol. Ideally, each patient should be screened by PHQ-2 by nursing staff before visiting epilepsy providers, but patients have right to refuse PHQ-2 screening. Therefore, the frequency of PHQ-2 being applied should be the highest among all four screening instrument. Since electronic medical record system would only automatically open up PHQ-9 if a patient has positive response of PHQ-2, and there were only a few positive screens of PHQ-2 in this study, it is reasonable that the frequency of PHQ-9 being used was significantly lower than that of PHQ-2. The frequencies of NDDI-E and GAD-7 being applied were the same (both 6.7%). For the 41 individuals who were screened by NDDI-E, GAD-7 or both, 35 (85.3%) of them were screened by both NDDI-E and GAD-7, which was significantly higher than the proportions of them being screened by only NDDI-E or only GAD-7. This result indicates that when presented with a patient with symptoms of either anxiety or depression, providers tended to apply NDDI-E and GAD-7 together. The high
tendency of providers combining NDDI-E with GAD-7 when presented with patient with anxiety or depression can be explained by a prior study. According to a study by Micolaud-Franchi, factor analysis demonstrates that GAD-7 and NDDI-E provide complementary information of the psychiatric conditions of PWE. This study also suggests that epilepsy providers should consider applying both GAD-7 and NDDI-E while assessing psychiatric conditions of PWE.

The proportion of positive PHQ-2 results was 1.4%, which was significantly lower than the proportions of positive PHQ-9, NDDI-E, and GAD-7 (66.7%, 39.5%, and 55.3% respectively). PHQ-2 was applied on most patient in epilepsy clinic, no matter whether patients have active psychiatric symptoms or not. NDDI-E and GAD-7, on the other hand, were administered by providers based on their impressions and psychiatric conditions of patients. Therefore, the proportion of positive PHQ-2 results should be lower than that of NDDI-E or GAD-7. Given the fact that PHQ-9 was only screened by nursing stuff when a patient had positive PHQ-2 results, the proportion of positive PHQ-9 should also be higher than that of PHQ-2. However, the proportion of positive PHQ-2 results was still lower than expectation. It was surprising that there were only 4 patients had positive PHQ-2 scores.

In this study, the sensitivity and specificity of PHQ-2 were calculated when NDDI-E and informal screening were considered as the gold standard. When NDDI-E was considered as the gold standard, the sensitivity of PHQ-2 was extremely low (equaled zero), but the specificity of PHQ-2 was extremely high (94.4%). This result indicated that in this study, PHQ-2 was able to correctly classify most of the individuals who were determined to be depression free by NDDI-E, but PHQ-2 was unable to
correctly discriminate the individuals who were determined to have depressive symptoms by NDDI-E. In this study, NDDI-E detected more patients with positive depressive symptoms than PHQ-2. It was surprising that PHQ-2 had such low positive rate (only 1.4%) in spite of the fact that it is a recommended and validated screening tool for detecting depression based on several studies. Such significant deviation of positive rate of PHQ-2 between this study and other studies could due to two factors: study population and the format of PHQ-2. Most of the studies which demonstrate the validation of PHQ-2 are based on general population instead of the population with epilepsy. For example, a study in 2010 demonstrated that PHQ-2 and PHQ-9 are both validated to screen for major depression. However, the study population was primary care population. The prevalence of epilepsy in the population was unknown. Another study in 2016 found out that the PHQ-2 had great overall accuracy relative to PHQ-9 in terms of detecting depression. However, the study population was also general population. 3636 adults who attended 12 Australian general practices were enrolled and the prevalence of epilepsy in this population was low. There was one study by Margrove which aimed at epilepsy population and demonstrated the validation of PHQ-2. However, the format of PHQ-2 applied in that study was different from what was used in this thesis. In the study of Margrove, the PHQ-2 used was a two-question questionnaire but each question had 4 possible answers and had a scale from 0 to 3. The total score ranges from 0 to 6 and a score higher than 2 is considered as positive depression. The patient would describe the frequency of experiencing each question from “not at all” (0 point) to “nearly every day” (3 points). However, in our study, each question of PHQ-2 only had two answers: “Yes” (1 point) or “No” (0 point).
The total score has a range of 0 to 3 which is narrower than the range in Margrove’s study. Each question may have led to the higher chance of false negative answers. A patient who has experienced one symptom described in PHQ-2 not so frequently might get 1 point for this question in Margrove’s study but get 0 points in our study due to the limited options of each question. Therefore, the percentages of positive screens of PHQ-2 were lower than expected. The higher chance of false negative answers could also explain why there were several individuals who were screened negative by PHQ-2 but depressive symptoms were detected by informal screening.

In this study, we only obtained positive results of informal screening. Among those individuals whose symptoms were identified by informal screening, they either had negative results of standardized screening instrument or did not receive any screening tools. Therefore, when informal screening was considered as the gold standard, the sensitivity of PHQ-2 was zero. Since the results of informal screening were all positive in this study, specificity of PHQ-2 did apply in this study because informal screening did not identify anybody with negative symptoms. It was notable that there were 7 individuals who had negative GAD-7 results and 7 individuals who had negative NDDI-E results, but their symptoms of anxiety or depression were determined by informal screening. This finding may indicate the potential needs of adjusting optimal cut points of GAD-7 and NDDI-E. According to a systematic review by Kroenke, the optimal cut point of GAD-7 is 10\(^4\). However, of the 9740 patients involved in this systematic review, the prevalence of epilepsy was unknown and the study population was general population. This cut point of 10 may not be the optimal one when the prevalence of epilepsy in population is high. In our study, of these 7 individuals who had negative
GAD-7 but positive symptoms of anxiety were identified by informal screening, 1 individual had a score of 7, 1 individual had a score of 7 and 1 individual had a score of 9. Those scores were close to the original cut point of 10 and those three patients all had mild anxiety based on the interpretation of GAD-7 scores. Therefore, the cutpoint of GAD-7 should be a little bit smaller than 10. According to another systematic review by Gill, although the NDDI-E cutpoint of 15 was recommended by many studies, a cutpoint of 13 was also optimal for detecting depression in patients with epilepsy. The optimal cutpoint of 13 explains why there were 7 individuals who had negative NDDI-E results but were identified as positive depression by informal screening. Among those 7 individuals, 4 of them had a NDDI-E score between 13 and 15. Therefore, they should be identified positive by NDDI-E if the cutpoint of 13 were applied in this study.

The prevalence of anxiety in our study population was 13.63%, and the prevalence of depression was 10.97%. According to a study in 2018, the prevalence of anxiety disorders in PWE was 16.7%, which was higher than our study population. According to a meta-analysis in 2013, the prevalence of depression in PWE was 23.1%, which was also higher than our population. The lower prevalence of anxiety and depression in our study population may lead to lower detection rate of standardized screening instrument than expected.

This study describes the management plan of epilepsy providers in real practice. Among all management plans they carried out, prescribing medication is the most common action (37.7%), then the psychiatry referral (22.6%) and counseling referral (9.4%). PCP referral only occurred 5.7% of all times, and 37.7% of the patients were untreated even though their symptoms had been identified. This is an interesting finding.
in that it differs with the results of a survey by Munger Clary in 2016. According to this survey, while dealing with patients suffering from depression, about 60% of the epileptologists participated stated that they were comfortable prescribing an antidepressant, 52% of them believed a referral to psychiatry was a good idea, 39.2% believed that they should referral the patients to mental healthcare professional, and 12% thought PCP would be a good answer to this problem. While dealing with patients with anxiety, 61.4% thought a referral to psychiatry might be a good idea and 33.7% preferred a referral to mental health professional. Instead, in actual practice which was observed from this study, only 22.6% of all times, epilepsy providers actually referred patients to psychiatry department. 9.4% of all times, they referred patients to counseling service, and only 4.7% of all times they referred patients to psychological service. 37.7% of the patients did not receive any management plan. According to the results of several chi-square tests, there were significant differences between expected and observed percentages of management plans (PCP: $\chi^2=24.60$, p=10^{-6}; Psychiatry referral: $\chi^2=184.79$, p<0.001; Prescribed medication: $\chi^2=99.51$, p<0.001). However, the percentage of PCP referral in this study was consistent with that in the survey. In that survey, only 14.9% of respondents would like to refer patients with anxiety to PCP and only 12% would like to refer patients with depression to PCP. In this study, only 5.8% of the patients with anxiety or depression were referred to PCP. Both percentages were the lowest among all possible management plans in that survey and this study, indicating that epilepsy providers do not tent to refer patients to PCP and they actually do not do this in real practice.
This study demonstrates the outcomes of the management plans carried out by epilepsy providers. Compared with other management plans, the patients who received the plan of prescription and psychiatry referral had the highest percentage in terms of improved symptoms (the plan of prescription and PCP referral was excluded because there was only one patient who received this management plan). However, according to the results of chi-square test, there was no significant association between improved symptoms and different management plan. Interestingly, there was also no significant association between improved symptoms and whether receiving management plan or not. Since there were 23 individuals whose symptoms were inaccessible from medical charts, we cannot conclude that whether different management plan had effect on alleviating symptoms of anxiety or depression. It is possible that most of these 23 individuals actually had improved symptoms, or vice versa.

This study also investigates the possible association between identified psychiatric symptoms and several factors including sex, age, epilepsy diagnosis, PNES, completed screening methods, and psychiatric history. Results of chi-square tests and t-test indicate that PNES and psychiatric history were significantly associated with identified psychiatric symptoms. This result makes sense in that a patient with PNES and positive psychiatric history psychiatric conditions would be associated with higher tendency of having active symptoms of anxiety or depression. Insignificant association between age, sex and positive psychiatric symptoms indicates that age and sex are not related with active symptoms of anxiety or depression in this sample.

Overall, the results of this study provide insight into potential improvement and adjustment of usual care in future epilepsy clinic. In this study, although the usage rate of
PHQ-2 was relatively high, the detection rate of it was very low. According to the results of this study, it seems that applying PHQ-2 in epilepsy clinic was not very effective in terms of identifying depressive symptoms of PWE. However, it does not mean that PHQ-2 should not be applied in epilepsy clinic. Due to its briefness and easiness, PHQ-2 fits perfectly in busy outpatient clinic. In order to increase the detection rate of PHQ-2 in the future, another version of PHQ-2 should be considered. Instead of using the PHQ-2 which scoring ranges from 0 to 2, applying an alternative version of PHQ-2 with wider scoring range might decrease the chance of false negative answers and identify more patients with depression. Besides, neurologists or nursing stuff should keep track of “informal screening questions” during clinical interviews in the future. In this study, the symptoms of most patients were identified by informal screening. Undoubtedly, clinicians tend to use the method of informal screening to identify potential psychiatric symptoms. Therefore, to better understand what kind of informal questions clinician asked during clinic visits and to provide more specific data for future interventional studies, providers and nursing staff could consider document more details in medical charts in the future.

This study has several strengths. First of all, this is one of a few studies which concentrates on characterizing the usage of multiple screening methods and management plan of providers in real epilepsy clinic. Characterizing usual care practice provides demographic and clinical information of usual care control groups which could be used in future interventional studies. Secondly, this is a retrospective study which major content was reviewing medical charts. Chart review studies have relatively low cost to perform and is able to be accomplished rapidly and conveniently.
This study also has several limitations. First of all, the retrospective nature of this study led to less accurate data about patient history. The transfer of information from the patient to the physician or nurse who documented it into the medical record cannot be completely accurate. According to a study, it showed that a physician could only obtain 68% of the information about the conditions of injury from trauma patients. And only 67% of the information which the physician obtained was finally documented into the medical chart. In this study, there were 21 (25.0%) individuals in follow up visits whose conditions of psychiatric symptoms were either inaccessible or missing. Under extreme conditions, symptoms of those 21 individuals might all have improved or might all be unimproved in follow up visits, thus chi-square statistics and corresponding p-value would greatly change. In other words, the results of chi-square tests could have been biased by missing data.

Secondly, the sample size of this study was limited. Although there were 565 individuals who completed baseline visit, only 433 of them completed follow up visits. Given that the latest follow up date was February 2019, there are over 100 individuals have not completed their follow up visits in approximately two years. Relatively low follow up rate results in limited samples of follow up patients who were identified with active psychiatric symptoms at baseline visits. The power of statistical tests (such as chi-square test) was also lowered due to low sample size. Therefore, in future study, more samples should be collected in order to increase the follow up rate.

Thirdly, only positive results of informal screening can be obtained in this study. Due to the limitation of progress notes and electronic medical chart system, it was difficult to find relevant information about whether a physician asked informal screening
questions during clinical interview. Future studies need to concentrate on finding approaches of obtaining the variable of informal screening and locating all possible individuals who were asked informal screening questions by providers.
CONCLUSION

Overall, this study characterizes the application of validated screening instruments for anxiety and depression and describes management plans and their outcomes carried out by epilepsy providers in a real clinic setting. Although PHQ-2 was the most frequently applied screening tool in outpatient clinic, it had a very low detection rate. NDDI-E and GAD-7 were commonly applied by providers when presented with patients with active symptoms of anxiety or depression. Clinician tended to use informal screening to identify most symptoms. Medication prescription and psychiatry referral were the two most common management plans, and the combination of those two actions resulted in the highest percentage of patients with improved symptoms. Although most epilepsy providers tended to screen patients for anxiety or depression, there were still many patients with active psychiatric symptoms untreated by neurologists. Due to missing data, the association between management plan and improved symptoms cannot be determined. Future work should concentrate on eliminate missing data and finding ways of locating all patients who are asked informal screening questions by clinician. Besides, future study should also focus on how to increase the application of validated screening instruments and how to address the untreated psychiatric symptoms of certain patients.
REFERENCES


Jianyi Li  
131 Crowne Court • Winston Salem, North Carolina 27106  
Phone: (336) 997-6042 Email: jianyi.li@alumni.wfu.edu  

CURRICULUM VITAE

EDUCATION

**Wake Forest University**, Winston Salem, NC  
Master of Science in Neuroscience  
Graduated in Dec, 2019  
GPA: 3.83

**Wake Forest University**, Winston Salem, NC  
Bachelor of Science, Biology Major  
Graduated in May, 2016  
GPA: 3.27

**Harbin No.3 High School**, China  
High School Diploma, 2012  
GPA: 3.9 Top 10 % of Class of 440 students

AWARDS/HONORS

**Dean’s List**: 4 semesters  
**Partial Tuition Scholarship**: 2017-2018, 2018-2019  
**Individual Patent**: Designation of central air-conditioning receiver mutual obstruction

EXPERIENCE

**Brain Awareness Council**, Winston Salem, NC  
*Student director*, Jan 2019 – May 2019  
During this scientific outreach volunteering activity, I was able to interact with the community members of various age and understanding levels. I communicated with basic neuroscience knowledge and research practices to the audiences who were under 12 years old. I also answered questions from a non-scientific audience in a clear and straightforward manner. Through this event, I have appreciated the value of scientific engagement with the public.

**Wake Forest Baptist Medical Center**, Winston Salem, NC  
*Medical Scribe*, October 2016 – May 2017  
Work as a scribe in the departments of ophthalmology and pediatrics. Accompany provider into patient examination room to accurately and efficiently document the encounter. List all proper diagnoses as well as follow-up care instructions as dictated by provider, and document any procedures performed by provider. Apply medical terminology, and billing & coding knowledge in all documentation. Successfully navigate
the location-specific Electronic Medical Record system to input documentation. Inform provider when diagnostic studies are completed, prepare for review, and document in EMR. Process multi-task efficiently and effectively as required. Work under pressure, within time constraints. Act calmly and effectively in a busy or stressful situation. Concentrate on the needs of the provider throughout entire shift.

Dalian Institute of Chemical Physics – Chinese Academy of Science, Dalian, China
Intern, Summer 2015
Conducted literature searches, prepared equipment and conducted analytical processes of data using Originlab. Assisted the managing director with current exhaled gases research project.

Wake Forest Baptist Medical Center, Winston Salem, NC
Department of Neurology, Fall 2017 – Spring 2018
Shadowed neurologists in clinic. Facilitated the neurologists to interview patients and perform screenings

First Affiliated Hospital of Harbin Medical School, Harbin, China
Department of Anesthesiology, Fall 2011
Shadowed and focused on a variety of pulmonary surgeries. Also facilitated to analyze exhaled gases from the patients of pulmonary surgeries in the authorized lab of hospital.

Volunteer of Children Welfare Association, Harbin, China
Volunteer, Summer 2013 and 2014
Served as a volunteer in Heilongjiang Children Welfare Association, tutored children with mathematics, assisted social workers in housekeeping, played basketball and football with children, and donated stationery and books.

Weilan International Model United Nations, Beijing, China
Representative, Summer 2012
Attended the conference as a representative of Turkey in United Nations Commission on Narcotic Drugs. Discussed Narcotics management and control

RESEARCH

Department of Neuroanatomy - Wake Forest Graduate School, Winston-Salem, USA
Anxiety and Depression in Epilepsy, September 2017 - Current
Investigated whether applying chronic care management and advanced practice provider administered medication is more effective than usual psychiatry referral in alleviating anxiety and depression symptoms in epilepsy patients. Reviewed and selected potential eligible individuals from the medical information charts of all patients in epilepsy clinic of Wake Forest Baptist medical center during the 1-year period.

Dalian Institute of Chemical Physics – Chinese Academy of Science, Dalian, China
Exhaled NO concentration research, Summer 2015
Researched in the laboratory of instrumentation and analytical chemistry of Dalian
institute of chemical physics. Conducted experiments of investigating effects of NO\textsubscript{x} concentration in air on NO concentration in human’s exhaled gases. Analyzed data with researchers and reported the result.

**Hospital of Harbin Medical School, Harbin, China**  
*Department of Anesthesiology*, Fall 2011  
Researched on the possibility that exhaled pentane could predict severity of hepatic ischemia-reperfusion injury. Found out that monitoring of exhaled pentane may be benefit in predicting the outcome, and pentane could be the potential biomarker for survival in hepatic ischemia and reperfusion injury.

**Research on Central Air-Conditioning Receiver Mutual Obstruction**, Harbin, China  
*Self-designed patent*, Fall 2011  
Searched information about remote control from internet. Designed a brief anti-screen equipment. Made a hole on the aluminum foil which was covered on the surface of the receiver. Finally controlled temperature properly.

**SKILLS/INTERESTS**

---

**Laboratory and Computer Skills**

Skilled at Arduino, Epic, R, ArcGIS, Microsoft Excel, Word, PowerPoint

**Piano**

Achieved Level 9 Certificate of Central Conservatory of Music and Level 9 Certificate of China Conservatory in piano.

**Basketball**

Helped the team to achieve the 4\textsuperscript{th} place in Wake Forest University intramural basketball game in Spring, 2015.

**Fluent in Japanese**

Had studied Japanese for 4 semesters in Wake Forest University, and had an average GPA of 3.8.