SCREENING OF MOOD AND ANXIETY DISORDERS USING SELF-REPORTS IN PATIENTS WITH EPILEPSY: SENSITIVITY AND SPECIFICITY

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DEDICATION

For Clare

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by

ALBERT STEPHEN BANTA, JR.

DISSERTATION

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SCREENING OF MOOD DISORDERS USING SELF-REPORTS IN PATIENTS WITH EPILEPSY: SENSITIVITY AND SPECIFICITY

Albert Stephen Banta, Jr.

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The prevalence of mood and anxiety disorders in outpatients with epilepsy seen at a tertiary care epilepsy center and the impact of these disorders on patient quality of life are not well defined. Also methods designed to assist physicians in the rapid diagnosis of these disorders, such as those used by Jones et al 2005a;b, need further assessment. Eligible outpatients (N = 88) with a diagnosis of epilepsy presenting at a tertiary care center were enrolled in the study during October 2006 to May 2007. After providing consent, patients had undergone the 16 item Quick Inventory of Depressive Symptomatology-Self Rating (QIDS-SR16), Beck Depression Inventory-II (BDI-II), Quality of Life Inventory in Epilepsy-31 (QOLE-31) and

the Mood Disorders Questionnaire (MDQ). Eligible patients were contacted within three days of initial screening via telephone and underwent the Mini International Neuropsychiatric Interview (MINI) and the 16 item Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-C16). A total of 76 patients completed all items and the results indicated a prevalence rate of 32% for current Axis I disorders. The QIDS-SR16, QIDS-C16, and BDI-II appeared to be useful in screening for mood and anxiety disorders when compared to psychiatric disorders detected by the MINI. Anxiety disorders were found to be more common than mood disorders and also had a significant negative effect on patients' QOL. The mood disorder group, mood and anxiety disorder group, and mood disorder plus group in this study experienced a greater negative impact on QOL when compared to the Axis I group and the anxiety alone group. Based on this study and Jones et al. (2005a;b) physicians treating patients with epilepsy in tertiary care settings could expect approximately 16-24% of their patients to experience a comorbid mood disorder. Implementation of screening programs that include self-reports are effective at assisting in the clinical identification of patients with mood and/or anxiety disorders so that treatment can be initiated. These psychiatric conditions are associated with a particularly poor quality of life in patients with epilepsy. Increased attention to the presence of psychiatric conditions in patients with epilepsy is important to patient QOL.

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LIST OF ABBREVIATIONS

AEDs	Anti Epileptic Drugs
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory II
CES-D	Center for Epidemiological Studies – Depression Scale
CIDI	Composite International Diagnostic Interview
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders – III-R
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – IV
EEG	Electroencephalogram
EQ	Epilepsy Questionnaire
GAD	Generalized Anxiety Disorder
HAD	Hospital Anxiety and Depression Scale
HAM-D24	24-item Hamilton Rating Scale for Depression
ICD-9	International Classification of Diseases-9
ICD-10	International Classification of Diseases-10
ICES	International Classification of Epileptic Seizures
IDD	Interictal Dysphoric Disorder
IDS	Inventory of Depressive Symptomatology
IDS-SR30	Self-Report 30-item Inventory of Depressive Symptomology
MDD	Major Depressive Disorder

MDE	Major Depressive Episode
MDQ	Mood Disorders Questionnaire
MINI	Mini International Neuropsychiatric Interview
MTLE	Mesial Temporal Lobe Epilepsy
NCS-R	National Comorbidity Survey Replication
PVN	Negative Predictive Value
PVP	Positive Predictive Value
QIDS	Quick Inventory of Depressive Symptomatology
QIDS-CR16	Quick Inventory of Depressive Symptomatology 16 – Clinician Rated
QIDS-SR16	Quick Inventory of Depressive Symptomatology 16 – Self Rated
QOL	Quality of Life
QOLIE-10	Quality of Life in Epilepsy-10
QOLIE-31	Quality of Life in Epilepsy-31
QOLIE-89	Quality of Life in Epilepsy-89
ROC	Receiver-Operator-Characteristic
SAS	Statistical Analysis Software
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SF-36	36-Item Short-Form Health Survey
SPS	Simple Partial Seizures
SSQ	Seizure Severity Scale

TEG	Texas Epilepsy Group
TLE	Temporal Lobe Epilepsy
TRE	Treatment Resistant Epilepsy
US	United States
VNS	Vagus Nerve Stimulator

LIST OF DEFINITIONS

Antiepilepsy Medications (AEDs) – Medications used to reduce or eliminate seizures.

Aura – The International Classification of Epileptic Seizures (ICES) defines an aura as that portion of the seizure occurring before consciousness is lost, and for which memory is retained when consciousness is regained (http://www.emedicine.com/neuro/topic415.htm, July 4, 2006).

Complex partial seizures - Cause impaired consciousness arising from a single brain region. Complex partial seizures typically originate from the temporal lobe but may also arise from any cortical region (http://www.emedicine.com/neuro/topic415.htm, July 4, 2006).

Current Prevalence Rate – The prevalence rate of the current number of cases of a disease present in a particular population at the time of evaluation.

Generalized seizures - Generalized-onset seizures have an onset recorded simultaneously in both cerebral hemispheres (http://www.emedicine.com/neuro/topic415.htm, July 4, 2006).

Epilepsy - A medical condition with recurrent, unprovoked seizures.

Health Related Quality of Life (HRQOL) – An assessment that evaluates and integrates patients' psychological, social and economic well-being into a global appraisal of overall well-being.

Interictal Dysphoric Disorder (IDD) - The presence of at least three symptoms of the eight affective-somatoform symptoms (anergia, insomnia, atypical pains, irritability, depressive moods, anxiety, fears and euphoric moods) reported in many epilepsy patients (Blumer, 2000). Such symptomotology was labeled as IDD because the symptoms were intermittent and lasted hours or up to one to two days.

Ictal depression - The clinical expression of a simple partial seizure in which the symptoms of depression consist of its sole (or predominant) symptomotology (Kanner, 2003).

Preictal depression - Depressive symptoms typically present as a dysphoric mood that precedes a seizure (Devinskiy & Bear, 1991).

Postictal depression - Depressive symptoms typically present as a dysphoric mood following seizures

Interictal depression - Depressive symptoms are unrelated to seizure activity.

Lifetime Prevalence Rate - The proportion of individuals in a population having had a disease at anytime during their lifespan, or from birth to date.

Mesial Temporal Lobe Epilepsy (MTLE)- A condition characterized by patients with epilepsy seizures originating in or primarily involving mesial temporal limbic structures (Blumer, 2002).

Prevalence - A statistical concept referring to the number of cases of a disease that are present in a particular population at a given time.

Simple partial seizures - A seizure with preserved consciousness. Many patients with complex partial seizures have an aura warning them of their seizure. The many kinds of simple partial seizures include sensory, motor, autonomic, and psychic types. Any discrete experience that involves the cerebral cortex could be a simple-partial seizure. A diagnosis is based on the repeated, stereotypic occurrence of the same experience in association with focal EEG changes or on recurrent auras leading to a complex partial seizure or a secondarily generalized seizure. All partial seizures are characterized by onset in a limited area, or focus, of one cerebral hemisphere. The International Classification of Epileptic Seizures (ICES) classifies simple partial seizures (SPS) as those that are not associated with any impairment of consciousness. Although the ability to respond may be preserved, motor manifestations or anxiety relating to the seizure symptoms may prevent patients from responding appropriately. The lack of availability of trained persons to interact directly with patients during and after the seizure can make distinctions between simple and complex partial seizures difficult, even with high-resolution video-EEG (http://www.emedicine.com/neuro/topic415.htm, July 4, 2006).

Seizure - Paroxysmal manifestations of the electrical properties of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory

and inhibitory forces within the network of cortical neurons in favor of a sudden-onset net excitation. Any structural lesion of the brain that causes an electrical variation in the surrounding tissue can provide an adequate substrate for epileptogenesis. The epileptogenic zone is the area that generates seizures, but it may in fact be clinically silent. The clinical and EEG manifestations may be due to secondary activation of another cortical area. Seizures are the manifestation of abnormal hypersynchronous discharges of cortical neurons. The clinical signs or symptoms of seizures depend on the location and extent of the propagation of the discharging cortical neurons (http://www.emedicine.com/neuro/topic415.htm, July 4, 2006).

Temporal Lobe Epilepsy – TLE has been widely applied in the literature to describe a condition characterized by patients with epilepsy seizures originating in or primarily involving mesial temporal limbic structures (Blumer, 2002).

Treatment resistant epilepsy (TRE) – Despite the fact that reports of clinical trials and review articles regularly use terms such as "intractable," "refractory," or "treatment-resistant" to describe patients for whom one or more treatments have failed, no consensus exists as to precisely what these terms mean (http://www.ahrq.gov/clinic/epcsums/epilsum.htm., April, 10, 2005)

CHAPTER ONE
Introduction

PREVALENCE OF MOOD AND ANXIETY DISORDERS IN EPILEPSY

A Replication Study

The Need for Replication and Study Validation

Clinical experience has clearly established that depression in epilepsy has an additive affect upon the suffering of epilepsy patients. In fact, depression is the most common psychiatric disorder observed in epilepsy centers (Johnson, Jones, Seidenberg, and Hermann, 2004). This proposal will provide an overview of the impact of depression on epilepsy patients, the methods employed to diagnose depression in these patients, and the reported prevalence rates of depression in epilepsy patient populations. In addition to depression, prevalence rates for other mood and anxiety disorders, specifically bipolar disorders, and other cormorbid psychiatric disorders shall be explored.

Typically, epilepsy patients are categorized into three descriptive groups; hospitalized patients or inpatients, and outpatients. Outpatients are further categorized as either living in the community with an epilepsy diagnosis or patients that receive care in tertiary care centers. Tertiary care centers are defined as facilities that treat epilepsy and other neurological conditions. Epilepsy patients

found in tertiary care centers are reported to experience more complications related to their epilepsy and/or other comorbid conditions. For example, tertiary center based epilepsy participants have been shown to suffer from higher rates of mood and anxiety disorders and access health care more frequently than community based epilepsy patients (Kanner, 2003; Grabowska-Grzyb, Jedrzejczak, Naganska, and Fiszer, 2006).

Despite the fact that high incidences of mood-related comorbidity in epilepsy patients are widely reported (see Prevalence Rates Section); mood and anxiety disorders remain underdiagnosed and undertreated in the population. Consequently, current treatments known to be effective for mood and anxiety disorders are underutilized. Several factors contribute to this void in epilepsy patients' care.

A review of the literature demonstrates the course of depression in epilepsy (though consistently high) remains indeterminate. Different research groups have speculated on possible modes of expression for depression in epilepsy; however, there have been no controlled, validated studies. Assessment tools used to identify mood or anxiety disorders in epilepsy patients have varied considerably from one study to another. Due to the various methodologies used for identifying depression: self- reports, structured interviews, clinician diagnosis, or review of patients' records; the ability to generalize findings are limited. Also very few studies have been replicated in order to verify, broaden, or validate findings.

Confounding Diagnostic Factors

The assessment of depression in epilepsy is challenging due to potential confounding factors such as the unknown course of epilepsy and the affect of seizure medications. Many confounding factors are present when attempting to identify mood or anxiety disorders. Anti epileptic drugs (AEDs) are reported to have the potential to cause depression (Kanner 2003). The side effects of AEDs, which can include lethargy among many other central nervous system complaints, lifestyle limitations due to seizure activity, and physiological changes within the brain; all contribute to the manifestation and complexity of mood and anxiety disorders as experienced by this unique patient population.

As with any depressive illness, anxiety is often present as a symptom of depression but some studies have indicated the presence of anxiety disorders independent of depression in epilepsy patients (Cramer, Brandenburg, and Xu; 2005, Jones, Hermann, Barry, Gilliam, Kanner, and Meador, 2005a;b; and Johnson et al., 2004). Several studies (see Comorbidity Section) have reported that anxiety disorders are also frequently diagnosed as comorbid to other psychiatric disorders in epilepsy patients. Some recent studies have reported highly variable rates of bipolar disorder amongst epilepsy patients; however, the methodology varied which again makes it difficult to generalize or compare results.

Often a type of dysthymia seen in patients with epilepsy does not meet the criteria for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) defined dysthymia or major depressive episodes. The atypical dysthymic symptoms found in this subset of patients has generated a discussion in the literature. Some have suggested that depression in epilepsy may actually mimic a chronic dysthymic condition (Blumer 1991, 1995, 2000, Kanner 2003). These suspect, sub-threshold dysthymic disorders in epilepsy patients have been shown to significantly reduce patients' quality of life, and negatively impact the course of epilepsy as demonstrated by reports of poorer reactions to seizure variables and increased utilization of health care resources (Cramer, Blum, Fanning, and Reed, 2004; Barry & Jones, 2005).

Depressed epilepsy patients have also been shown to seek more health care versus other patient populations suffering from depression and more so than non-depressed epilepsy patients (see Health Care Utilization Section). This increased health care utilization by these patients adds up to billions of dollars each year.

Many studies that examined the quality of life (QOL) in depressed epilepsy patients have reported that depression alone caused the greatest decrease in QOL, over any seizure variable (i.e., seizure severity, duration or frequency.)

The majority of these research studies conclude that depression has the greatest impact on patients' QOL (see Quality of Life Section).

Suicide rates relative to patients with epilepsy with depression are an indication of the serious comorbid affect. The rates are reported to be markedly high (see Suicide Rates Section). The high rates of reported suicide completions, suicide attempts, and suicidal thoughts shown in epilepsy patients emphasize the practical importance of this proposed study which will investigate sensitivity and specificity of screening tools for both mood and anxiety disorders.

Further study of anxiety and mood disorders utilizing DSM-IV criteria in order to gain a clearer understanding of the relationship between mood and psychiatric disorders and QOL in tertiary-care populations has previously been recommended by Johnson et al. (2004). The authors encouraged prospective investigations to determine the degree to which treatment of depression or anxiety could improve QOL (Johnson et al., 2004). Trimble and Sander (2004) highlighted one of the aims of this proposed study when the authors stated that participants are characterized by considerable heterogeneity because of differences in methodology used in previous studies that examined this topic. The authors noted that comparisons between studies, was difficult; as was the drawing of definitive conclusions due to the various methodologies used (Trimble & Sander, 2004).

Population-based studies have estimated that the life-long prevalence of depression associated with epilepsy was between 6% and 30%; however, other studies of patients followed in tertiary care centers suggested that the rate was much higher at 50% (Kanner, 2003; Grabowska-Grzyb et al., 2006). The wide ranges evident in these statistics have been partially explained by differences in methodology (Wiegartz, Seidenberg, Woodard, Gidal and Hermann, 1999; Piazzini and Canger, 2001; Kanner and Balabanov, 2002; Cramer, Blum et al., 2003; Attarian, Vahle, Carter, Hykes, and Gilliam, 2003; Jagadheesan, Garg and Nizamie, 2003).

Before treatment of depression or other psychiatric disorders can be addressed, treating physicians must be clear about the prevalence of depression in epilepsy patients and be able to accurately identify the comorbidity of mood and anxiety disorders. Since the literature requires replication to validate research findings regarding depression and anxiety disorders in epilepsy based on similar methodologies; this study will attempt to replicate and extend the recent findings by Jones, Hermann, Barry, Gilliam, Kanner, and Meador, (2005a;b). The study defined the prevalence rate of mood and anxiety disorders amongst epilepsy patients found in five tertiary care centers. Replication and confirmation of previous findings should ensure their accuracy. Replication should also increase the validity of any conclusions repeated in this subsequent study and refute those conclusions not repeated in the results. This proposed study should also clarify

any prior conclusions that may have remained questionable based on the evidence from one study.

In addition to replication, this proposed study intends to further clarify thresholds in the diagnostic screening tools (self-report measures) of mood and anxiety disorders for epilepsy patients. If thresholds of screening tools are established, epileptologists will have valid and reliable tools that can be used in evaluating patients. This is essential in light of the current atmosphere of underidentification and undertreatment of mood and anxiety disorders.

As it is important to distinguish between current (see Definitions) mood and anxiety disorders vs lifetime to date (see definitions) mood or anxiety disorders. This study is designed to facilitate the diagnosis of current anxiety or mood disorders that would enable treating physicians to initiate care. The screening tools to be examined would provide practical information to treating physicians focused on the real time treatment of patients seen in a medical office or tertiary care center. While lifetime to date prevalence rates are important for epidemiological purposes, the focus of this proposed study is the investigation of screening instruments that have the potential to guide or initiate active treatment for patients that present in medical offices or tertiary care centers.

This study, with patients from a local tertiary care center that report symptoms that are consistent with mood and/or anxiety disorders, based on self-report measures and followed by a structured interview, will serve to either extend

and generalize the findings of Jones et al. (2005a;b) and/or Ettinger, Reed, Goldberg, and Hirschfeld, (2005) or question the reported findings. Subsequent research can then explore the treatment of mood and anxiety disorders in epilepsy patients by using the data generated from this study and in future studies with more confidence-based established thresholds.

Rationale

Epilepsy patients appear to have high rates of mood and anxiety disorders. These psychiatric conditions are associated with a particularly poor quality of life (Spencer & Hunt, 1996). Presently, the detection and diagnosis of these symptoms is time consuming. This investigation will attempt to validate use of short diagnostic surveys and establish thresholds with specifications and sensitivity that indicate the prevalence of mood and anxiety disorders.

STUDY OBJECTIVES

Until there is an efficient, valid and reliable screening method for depression and anxiety disorders, physicians who treat epilepsy patients will continue to underdiagnose and undertreat, thereby missing a potential opportunity to improve these patients' overall quality of life. This study is aimed at clarifying the prevalence of mood and anxiety disorders in epilepsy, introducing low cost

and time efficient screening measures for depression and anxiety and further investigating the Mood Disorders Questionnaire (MDQ) and its accuracy in detecting bipolar disorder in epilepsy patients. This study enrolled 88 consecutive epilepsy outpatients from a tertiary care center over an eight-month period of time.

Primary Objective

The primary objective of this study is to better define the prevalence of mood and anxiety disorders in outpatients with epilepsy seen at a tertiary care epilepsy center.

Mood disorders to be screened include:

Major Depression

Dysthymia

and Bipolar Disorders;

and anxiety disorders include:

Panic Disorder,

Agoraphobia,

Social Phobia,

Obsessive-Compulsive Disorder,

Posttraumatic Stress Disorder and

Generalized Anxiety Disorder.

Secondary Objectives

1. To assess the impact of the presence of mood and anxiety disorders on the quality of life of patients with epilepsy.
2. To assess the performance of the total score thresholds on the QIDS-SR16, QIDS-CR16, or BDI-II to screen for the presence of a major depressive episode, dysthymia or anxiety disorder as defined by the MINI International Neuropsychiatric Interview (MINI).
3. To assess the performance of the total score threshold on the Mood Disorders Questionnaire compared to the MINI to establish a diagnosis of bipolar disorder, as defined by the MINI, in epilepsy patients.

CHAPTER TWO
Review of the Literature

EPILEPSY AND DEPRESSION

The Serious Problem of Depression in Epilepsy Patients

Epilepsy patients suffer from the comorbid effects of mood and anxiety disorders, often without proper, if any, treatment. The causes of mood and anxiety disorders in this population will be shown to be multiple and additive. A subjective sense of uncertainty, disease-associated stigma, decreased self-efficacy, decreased self-esteem, genetic predisposition to mood disorders, and stressful life events have all been shown to contribute to the etiology of epilepsy-associated depression (Goldstein, McAlpine, Deale, Toone, and Mellers, 2003; Gaitatzis, Trimble, and Sander, 2004). Results from several studies have reinforced that seizure frequency, seizure severity and/or type of seizure harbor no relation to the occurrence of depression (Kanner, 2003; Beghi, Roncolato and Visona, 2004).

Multiple factors such as seizure variables, AEDs, and ignorance all contribute to a lack of understanding and undertreatment of mood and anxiety disorders in this patient population. The ability to treat depression is well established; however, it appears the manifestation of mood and anxiety symptoms

are often ignored in epilepsy patients and wrongly attributed to the course of epilepsy. The recognition and treatment of depression and anxiety disorders in patients with epilepsy remains unacceptably low or inadequate (Goldstein et al., 2003; Kong, Au, Chan, Li, Leung, Li, and Chan, 2003; Kanner and Barry, 2003). Studies estimate that between 50% and 68% of patients with epilepsy suffering from depression are never treated for depression (Wiegartz et al., 1999; Gaitatzis et al., 2004). Multiple studies have shown that the actual treatment of epilepsy-associated depression and related-research remains under-explored territory despite the prevalence and seriousness of the disorder's occurrence (Davis, Armstrong, Donovan, and Temkin, 1984; Mendez, Cummings, and Benson 1986, Wiegartz et al., 1999; Gaitatzis et al., 2002; Kanner, 2003; and Trimble and Sander, 2004).

Epilepsy and Depression: A Historical Perspective

The historical record of concurrent diagnosis of epilepsy is impressive. Epilepsy and depression have been the subject of discussion for centuries. Hippocrates (circa 400 BC) was first to suggest a direct relationship between epilepsy and depression (Attarian et al., 2003). There is even speculation that Hippocrates believed depression might actually cause epilepsy and that epilepsy might cause depression (Kanner, 2003). Similarly, in 2004, Kanner & Balabanov

suggested that epilepsy and depression might share common pathogenic mechanisms. Despite being reported for centuries, treatment has not changed to reflect the current advances in the fields of mood and anxiety disorders.

In the current day, prejudices associated with epilepsy persist in negatively affecting patients and may be a contributing factor in to epilepsy-associated depression. The persistent social stigma associated with epilepsy is steeped in history. Lombroso, a 19th century historical figure in modern criminology, believed that criminality was genetically tied to epilepsy and this idea became so influential that nearly every person diagnosed with epilepsy was considered a potential criminal (Mikhalov, Wasserman, and Sinyakova, 2005). As recently as the beginning of the twentieth century, worldwide colonies existed for patients with epilepsy (Mikhalov et al., 2005). Doctors were obliged to inform state authorities of each case of epilepsy, as with cases of smallpox and syphilis (Mikhalov et al., 2005). In 1895, nineteen of the United States (US) passed laws prohibiting marriage for people with epilepsy (Mikhalov et al., 2005). These marriage restrictions remained effective for forty-four years (Mikhalov et al., 2005). Sadly, the last act restricting marriage for persons with epilepsy was abolished as recently as 1982 (Mikhalov et al., 2005). As recently as 1907, compulsory sterilization of persons with epilepsy was legally sanctioned in the state of Indiana. The stigma of epilepsy still persists and is reported to extend to the families of epilepsy patients (Mikhalov et al., 2005).

Confounding Factors of Depression in Epilepsy

This section will show the multiple areas that are affected by mood and anxiety disorders in epilepsy patients and common misperceptions or false associations between epilepsy and mood and anxiety disorders.

Trimble and Sander (2004), as well as Barry and Jones (2005), reported that the frequency of major depressive disorders among individuals with epilepsy was higher than expected when compared to the general population. Iatrogenic mechanisms such as patients' particular AED, secondary effects of AEDs or polypharmacy were also associated with increased risk for depression. Prueter & Nora (2005) pointed out that the literature is difficult to interpret because some studies have not distinguished between depressive symptomatology and depressive disorders. Typical signs and symptoms of Major Depressive Disorder (MDD), such as sleep disturbances, loss of appetite and weight gain are reportedly often masked or attributed to being side effects of AEDs. Other depressive symptoms such as loss of energy and activity are often attributed to AEDs without taking into consideration an assessment of possible mood disorders (Kuhn et al., 2003).

Harden (2002) has suggested that psychosocial factors played a role in the etiology of depression; however, the author claimed that other biological mechanisms appeared to be more influential. A family history of depression was reported in over 50% of patients with both epilepsy and depression, which suggested a genetic predisposition (Kanner & Balabanov, 2002). It remained unclear in the article whether nondepressed patients with epilepsy had less than the reported 50% rate of a family history. Mendez et al. (1986) compared 20 depressed inpatients with epilepsy to 20 depressed inpatients without epilepsy in a large psychiatric facility. Only three of the patients with epilepsy (15%) had a first- or second-degree relative with a history of major depression while 11 of the inpatients without epilepsy (55%) gave a positive family history (Mendez et al., 1986, p. 768).

Many studies have found that no consistent relationship exists between depression and seizure frequency, seizure type, etiology, or the presence of an aura. (Attarian, et al., 2003; Cramer et al., 2003; Mendez et al., 1986). Cramer and colleagues (2003) did report that patients experienced better overall seizure recovery, as defined by the Seizure Recovery score, when depression was not present versus epilepsy patients who suffered from severe or moderate depression. The Seizure Recovery score was defined by patient-reported assessment of seizures by both a) categories of seizure frequency based on whether seizures had occurred recently (< 1 week ago, 1-3 weeks ago, 1-3 months ago) or not recently

(4-12 months ago, 1-2 years ago, > 2 years ago); and b) by a patient-rated Seizure Severity Scale (SSQ) (Cramer, Blum et al., 2003). The Overall Score represented the subject's overall impression of severity and levels of bother relative to all seizures (Cramer, Blum et al., 2003).

Furthermore, depression has been reported to affect patients' perception of seizure severity (Cramer, Brandenburg et al., 2005). Patients with moderate to severe symptoms of depression reported in the Quality of Life in Epilepsy-10 (QOLIE-10), as experiencing significantly worse problems than those with no depression with respect to overall seizure recovery, severity and seizure bother, as well as cognitive, emotional and physical aspects of seizure recovery (Cramer, Brandenburg et al., 2005). Cramer and colleagues (2003) found that clinically depressed patients with epilepsy reported higher levels of perceived severity and bother from seizures, as well as greater problems with overall seizure recovery than did non-depressed patients whom experienced similar types of seizures.

Mendez et al. (1986) stressed that depression in epilepsy was more than a nonspecific reaction to a chronic disability. The authors found that significantly fewer hospitalized epilepsy patients had a family history of major depression than nonepilepsy, hospitalized controls (Mendez et al., 1986). With epilepsy, patients' problems can be exacerbated by AEDs which have been shown to contribute to depression. (Grabowska-Grzyb et al., 2006). These complex interactions and lack of similar methodology for measuring depression in epilepsy, all contribute to the

historical difficulty of obtaining an accurate prevalence rate, the implementation of efficient screening, and adequate, if any, treatment.

Manifestations of Depression in Epilepsy

Patients with epilepsy seizures are currently defined as intermittent paroxysmal events that are usually brief and associated with excessive activity of cortical neurons (Blumer, 2002). The lifetime risk of chronic epilepsy has been estimated at close to 5% and up to 10% of the population may experience at least one seizure (Blumer, 2002). The current understanding indicates mood disorders in epilepsy are also episodic in nature (Barry & Jones, 2005). Even though no uniform explanation or model currently defines the pathogenesis of mood disorders in epilepsy patients (Prueter and Nora, 2005), this section will explore the manifestation of depression in epilepsy currently being debated in the literature.

Mendez et al. (1986) found that depression in 20 epilepsy inpatients from a large psychiatric facility involved more abnormal affects and a history of chronic dysthymic states (Mendez et al., 1986) in comparison to 20 depressed controls without epilepsy. The authors described abnormal affects as less depressed and more "detached or distant" (Mendez et al., 1986, p. 768). The authors found that depression in epilepsy exhibited several atypical features

described as chronic dysthymic states, irritability, emotionality, and humorlessness (Mendez et al., 1986). The authors found the presence of chronic dysthmic states accompanied by a history of any agitated peri-ictal psychotic behavior and the relative lack of neurotic traits (e.g., somatization), correctly predicted for 93% of the 20 depressed patients with epilepsy in their sample (Mendez et al., 1986).

Kanner (2000) detailed another manner to describe depression in epilepsy. The author found that symptoms of depression mimicked dysthymic disorders in 69% to 97% of consecutive patients enrolled in one study. The symptoms were disrupted and failed to meet DSM-IV criteria for dysthymic disorder (Kanner, 2000). Kanner (2003) suggested that depressive disorders could be classified according to the temporal relationship between the onset of the psychiatric symptomatology and seizure occurrence. Kanner (2003) divided the onset of the psychiatric symptomatology and seizure occurrence into ictal (the depressive symptoms are a clinical manifestation of the seizure), perictal (symptoms precede and / or follow the seizure occurrence), and interictal (symptoms occur independently of the seizure occurrence). Kanner (2003) defined the classifications as follows:

1. Ictal depression- Clinical expression of a simple partial seizure in which the symptoms of depression comprise its sole (or predominant) symptomotology (Kanner, 2003).

2. Preictal Depression- Depressive symptoms typically present as a dysphoric mood preceding seizures (Blanchet & Frommer, 1986). There are very few reports in the literature according to Kanner (2003) of this type of depression.
3. Postictal Depression- Depressive symptoms follow the seizure. Postictal symptoms were suspected as contributing to the atypical presentation of the symptomotology of depression in patients with epilepsy (Kanner, 2003). Kanner found that this type of depressive presentation was relatively frequent among patients with poorly controlled epilepsy (Kanner, 2003).
4. Interictal Depression- Kanner (2003) suggested that interictal depression was more chronic in nature and more often than not tended to mimic a dysthymic disorder with endogenous features and an intermittent course (Kanner, 2003). This is the most common presentation of depression disorder in epilepsy.

As mentioned, Kanner reported that interictal depression was the most frequently recognized type of mood disorder and could present as major depression, bipolar disorder, dysthymic disorder or minor depression. Kanner defined minor depression as "dysthymic disorders, depressive disorder not otherwise specified, equivalent to Blumer's IDD" (Kanner, 2003, p. 392). Kanner (2003) also noted that a significant proportion of epilepsy patients do not meet

any of the DSM-IV criteria for major depression, bipolar disorder, or dysthymic disorder (Kanner, 2003) This elaboration on the manifestation of depression in epilepsy is quite similar to Blumer's concept of Interictal Dysphoric Disorder (IDD) (Blumer, 1991, 1995).

Blumer, Montouris, and Hermann (1995) found that 33 (34%) of 97 consecutive inpatients admitted for neurodiagnostic monitoring over a seven-month period presented with an "atypical, pleomorphic, and yet surprisingly uniform depressive-irritable (dysphoric) mood disorder, with eight symptoms presenting in an intermittent pattern" which was described as interictal mood disorder (p. 448). The eight key symptoms were defined as depressive mood, anergia, atypical pain, insomnia, irritable-explosive affect, euphoric mood, fear, and anxiety. the Epilepsy Questionnaire (EQ) was used to measure the symptoms (Blumer et al., 1995; and Blumer, 1993).

Blumer (2000) first coined the term Interictal Dysphoric Disorder (IDD). IDD was defined as the presence of at least three symptoms out of the eight affective-somatoform symptoms (i.e., anergia, insomnia, atypical pains, irritability, depressive moods, anxiety, fears and euphoric moods) that were reported in epilepsy patients (Blumer, 2000). Blumer (2000) labeled such symptomotology - IDD because the symptoms tended to be intermittent and lasted from hours to one to two days. Blumer (1991, 1995) suggested that IDD affected almost one-third to one-half of patients with epilepsy that sought medical care and that the sub-

population suffered from sufficiently severe symptoms to require pharmocologic treatment. Paroxysmal affects ranged from irritability and anger through to rage, and Blumer suggest these were the hallmark features of IDD (Blumer, 2002). Blumer found that complex dysphoric episodes occurred without external triggers and without a clouding of consciousness. Additionally, he suggested that symptoms began and ended rapidly and reoccurred fairly regularly in a uniform manner. Blumer reported that these episodes occurred from every few days to every few months and lasted for a few hours and up to two days (Blumer, 2002). Blumer (2000) also reported that symptoms were most commonly reported as phenomena independent of seizures.

Anatomical Correlates

Multiple theories incorporating anatomical correlates into the pathogenesis of depression-associated epilepsy have been discussed in the literature. The following sub-section will examine research that has attempted to understand depression in epilepsy through anatomical correlates.

Piazzini and Canger (2001) indicated that 150 patients with partial epilepsy were more likely to be affected by mood disorders than 70 patients with idiopathic generalized epilepsy. Cramer, Brandenburg et al. (2005) suggested that patients with temporal onset of seizures made up the most depressed and anxious

group. The comorbidity of anxiety and depression in patients with temporal-onset seizures was reported as potentially demonstrating common limbic pathways and effects on neurotransmitters (Cramer, Brandenburg et al., 2005). Mesial temporal lobe structures, particularly the hippocampus and the amygdala are known to affect neuroendocrine function and the hypothalamic-pituitary-adrenal axis (Attarian et al., 2003).

Kanner (2003) in his review of literature, pointed out that seizures that originated in the temporal and frontal lobes and involved the limbic circuit were associated with rates of depression ranging from 19% to 65%. This statistic was referenced as being much higher than in patients with generalized seizure disorder (Kanner, 2003). Manchanda, Schaefer, McLachlan, and Blume (1995) studied a group of patients with chronic epilepsy that consisted of 25 patients with a right temporal seizure focus, 14 with a right nontemporal focus, 25 with a left temporal and four with a left nontemporal seizure focus. They found no statistically significant differences in the prevalence of psychopathology when diagnoses were made based on the Diagnostic and Statistical Manual of Mental Disorders-III-R (DSM-III-R).

Temporal lobe epilepsy (TLE) has been defined as a condition characterized by seizures that originate in or primarily involve mesial temporal limbic structures (Blumer, 2002). Hippocampal sclerosis was found to be the lesion most commonly associated with mesial TLE (Blumer, 2002). Mesial TLE

was reported as the most frequently encountered chronic disorder in patients with epilepsy and was described as simple and complex partial seizures, as well as secondary generalized seizures that were relatively refractory to AEDs (Blumer, 2002). Blumer (2000) stated that the chronic nature of mesial TLE contrasted with the more benign course of primary generalized epilepsy and that mesial TLE was a major factor that contributed to psychiatric comorbidity. Kanner (2003) found that TLE patients had a higher incidence of affective and personality disorders than did patients with juvenile myoclonic epilepsy or diabetic patients (Kanner, 2003). Trimble and Sander (2004) reported that acute psychological disorders appeared more often in patients with complex partial seizures and to a greater extent among patients with TLE (60%) and other focal epilepsy (54%) than among patients with primary generalized epilepsy (37%).

Interestingly, Mendez and colleagues (1996) found that patients with auras of psychic symptoms were likely to have higher rates of depression than patients with partial seizures without auras or whose auras consisted of motor sensory symptoms (Mendez et al., 1996). Gilliam and Kanner (2002) reported that patients with mesial temporal sclerosis (TLE) had significantly higher depression scores and Mendez et al. (1986) reported a greater association of depression in treatment resistant epilepsy (see Definitions Section) and those patients with an electroencephalogram (EEG) focus in the left hemisphere.

Suicide Rates Relative to Epilepsy-Associated Depression

Suicide has been reported as one of the highest standardized mortality ratios of all causes of death among epilepsy patients (Johnson et al., 2004; Gilliam and Kanner, 2002). High suicide rates found in epilepsy-associated depression indicate severe depressive symptomatology as well as the importance of depression management in epilepsy patients (Mendez et al., 1986). This section will show how serious the risk of suicide is reported to be in depressed epilepsy patients.

One sample of patients with epilepsy demonstrated a rate of suicidal ideation as high as 12.2%. In the authors' review of lifetime depression 20.8% of patients had made a suicide attempt (Barry & Jones, 2005). These findings contrast to those within the general population where the expected rate of lifetime suicide attempts ranged from 1.1% to 4.6% (Barry and Jones, 2005).

Suicide risk has been reported to be as much as five times higher for patients with epilepsy versus the general population (Blumer, 2000) Prueter & Nora (2005) reported a nine to ten-fold higher suicide rate in epilepsy patients versus the general population. Other investigators have (Trimble and Sander 2004) described suicide as an important and potentially avoidable cause of death

in epilepsy; however, they were unable to determine the extent of its risk due to the large amount of variation in suicide rates across studies. The range was 0-20% (Trimble & Sander, 2004). By comparison, suicide was recently reported as accounting for 4.2% of premature morbidity in uncomplicated major depression amongst the general population (Coryell and Young, 2005; and McGirr et al., 2007). Suicidal states were also shown to be concurrent with or at times following an increase seizure frequency (Trimble & Sander, 2004). Some reported risk factors for suicide in patients with epilepsy have included a history of self-injuries, a family history of suicide, emotional stress-causing events, and psychiatric diseases such as depression or psychosis and alcoholism (Prueter and Nora, 2005).

Suicide attempts were also shown to be more prevalent in patients with epilepsy than in comparison to chronically handicapped patients (Mendez et al., 1986). Boylan et al. (2004) found that 19% of 122 patients with refractory epilepsy being admitted to an inpatient video-EEG monitoring unit reported suicidal thoughts. In a study comparing patients with epilepsy that presented to vocational service centers for the disabled, with controls, 30% of patients with epilepsy vs. 7% of the controls reported prior suicide attempts (Mendez et al., 1986). The controls that were defined as patients without epilepsy; was reported to be a heterogeneous group consisting of amputees, polio victims, patients with severe pulmonary and cardiovascular disease, and a subgroup of neurological

patients with mild cerebral palsy, from the same aforementioned vocational service centers with similar socioeconomic backgrounds who were employable with training. Employability was a measure used to ensure a relatively equal functional impact of patients' disability (Mendez et al., 1986).

Quality of Life in People Diagnosed with Depression and Epilepsy

Social and psychological problems have consistently been found (more than seizures) to negatively affect QOL in epilepsy patients. Quality of Life (QOL) is a useful measure in epilepsy patients because it can assess the impact of epilepsy on patients' lives and the comorbid impact of depression and other mood disorders. Mikhalov, Wasserman, and Sinyakova, (2005) recommended QOL as the overall standard that should be used to guide treatment of epilepsy with mood and/or anxiety disorders.

Reports have repeatedly indicated that depression and/or comorbid anxiety symptoms accounted for more of the variance in QOL measures than many other epilepsy-related factors such as seizure frequency (Kanner, Wuu et al., 2004; Jones et al., 2005a;b; Hopp, Matausch, Zhu and Krumholz, 2006). Boylan et al. (2004) examined the impact of clinical variables (age, sex, marital status, seizure frequency, duration and type of seizure disorder, seizure location, number of AEDs and depression) on QOL in participants with treatment resistant epilepsy

(TRE). TRE was defined in this study as seizure frequency greater than one per year despite therapy (Boylan et al., 2004). Boylan et al. (2004) found that depression was a powerful predictor of QOL. The authors reported that no other variable except depression, better predicted QOL (Boylan et al., 2004).

Johnson et al. (2004) reported that the general medical literature provided evidence that psychiatric disorders significantly reduced QOL beyond what could be attributed to the effects of the underlying primary medical illness. Studies have also demonstrated that interictal anxiety and/or depression exert independent adverse effects on QOL (Johnson et al., 2004, Hopp et al., 2006). Johnson and colleagues (2004) also reported that current anxiety explained more variance in QOL than did any other demographic or clinical epilepsy variable. The authors showed that current psychiatric comorbidity of depression and / or anxiety was the most powerful predictor of QOL and explained more variance in QOL than the combined impact of clinical seizure variables (e.g. onset of recurrent seizures, duration of epilepsy, monotherapy/polytherapy, frequency of complex partial and secondarily generalized seizures over the past year; Johnson et al., 2004). More recently, Cramer, Brandenburg & Zu (2005) reported that comorbid anxiety and depression had a significant impact across all QOL domains amongst patients with epilepsy.

Cramer, Brandenburg, and Zu (2005) surveyed 201 epilepsy patients from community-based neurology practices across the US. The researchers used the

Quality of Life In Epilpsy-10 (QOLIE-10) as a measure of QOL (Cramer, Brandenburg et al., 2005). The authors reported that the mean scores on the QOLIE-10 decreased significantly with worsening depression, ranging from 70.2 (+/- 16.0) for normal to 50.1 (+/- 16.2) for mild, 44.7 (+/- 16.4) for moderate, and 24.4 (+/- 21.3) for severe levels of depression. All differences in QOLIE-10 scores across the severity groups were reported as significant ($p < 0.0001$) (Cramer, Brandenburg & Zu, 2005). There were no statistically significant differences reported among the anxiety or depression severity groups with respect to age, duration of epilepsy, or number of seizures in the past year (Cramer, Brandenburg, et al., 2005). The authors demonstrated that a regression model of the QOLIE-10 total score; when controlled for age, gender, duration of epilepsy or numbers of seizures, in the past year did not explain much of the variance found (Cramer, Brandenburg, et al., 2005). QOLIE-10 scores were shown to worsen by 29% among participants with symptoms of mild depression, and scores declined further in participants with moderate and severe symptoms of depression (Cramer, Brandenburg, et al., 2005).

Earlier research showed that depression was a key factor in patients' perception of their QOL (Cramer et al., 2003). Additionally, Lehrner et al. (1999) and Gilliam (2002) both reported that depression was the single strongest predictor for each domain of QOL. They observed no correlation between the type and or frequency of seizures and poor QOL scores. Gilliam (2002) noted that

refractory epilepsy with comorbid depression was one of the most important variables to impact QOL. It rated higher than seizure frequency and severity. Major depression in epilepsy has been associated with significant decreases in self-reported QOL, and increases in disability claims, day of missed work, medical utilization and medical costs (Trimble and Sander, 2004).

Society's limited awareness regarding epilepsy causes difficulties for epilepsy patients (Mikhalov, Wasserman, & Sinyakova, 2005). Insufficient public awareness of epilepsy-related problems (e.g. driving limitations) was reported as contributing to the stigmatization of patients (Mikhalov et al., 2005). The stigma has been reinforced by rigid social and labor limitations on top of general social discrimination (Mikhalov et al., 2005). The researchers considered the challenge of destigmatization as one of the most important factors that needed to be addressed in order to improve epilepsy patients' QOL (Mikhalov et al., 2005).

Increased Health Care Utilization

Depression heavily contributes to reduced productivity and absenteeism at work and in the US alone can result in a reported loss of 44 billion dollars per year (Barry and Jones, 2005). This dollar amount does not include disability or medical utilization, which have been estimated in excess of 31 billion dollars (Barry and Jones, 2005).

Epilepsy that is associated with depression has been shown to lead to increased health care utilization as defined by frequency of visits for medical care or psychiatric care – a powerful correlate of overall QOL (Cramer, Blum et al., 2003; and Cramer, Blum Fanning and Reed, 2004). Cramer, Blum, Fanning, and Reed (2004), reported that depressed epilepsy patients (with and without adjustment for seizure type, seizure recency, and days with epilepsy symptoms) visited doctors, emergency departments, and hospitals significantly more than non-depressed epilepsy patients. Cramer, Brandenburg & Xu (2005) further noted that health resource utilization differed only by depression status and not by seizure type or frequency. People with symptoms of mild to moderate and severe depression showed a two- and fourfold increase in visits to medical doctors, respectively when compared with people that were not depressed. It was also shown that people with severe depression made ten-fold more visits annually for psychiatric care than did people with no depression (Cramer Blum, et al., 2003; and Cramer, Blum, Fanning et al., 2004). When compared to people with mild to moderate depression, severely depressed epilepsy patients had a five-fold increase in visits to physicians (Cramer, Blum et al., 2003; and Cramer, Blum, Fanning et al., 2004). When people who were taking an antidepressant medication (considered treated) were separated from those not taking an antidepressant medication (classified as untreated), there was no difference shown in the number of medical visits (Cramer, Blum, Fanning et al., 2004). Patients with current

symptoms of depression who remained untreated reportedly had significantly more medical and psychiatric visits than untreated non-depressed patients (Cramer, Blum, Fanning et al., 2004). Also, there was no significant difference in health care utilization by predominant seizure type. (Cramer, Blum, Fanning et al., 2004).

Kuhn et al. (2003) performed a study that included 75 TLE participants (TLE with partial and/or generalized seizures) and found that only two participants had been treated with antidepressant drugs and received psychotherapy despite an incidence of 20-60% of depressed patients (Kuhn et al., 2003). Patients with epilepsy were four times more likely to have been hospitalized for depression than disabled patients without seizures (disabled patients consisted of amputees, polio victims, patients with severe pulmonary and cardiovascular disease, and a subgroup of neurological patients with mild cerebral palsy with similar socioeconomic backgrounds) (Mendez et al., 1986).

Assessment of Depression, Anxiety and other Mood Disorders in Epilepsy Patients

One goal of this proposed study is to clarify the thresholds of self-report instruments in order to provide treating physicians with valid and reliable tools to facilitate identification of mood and anxiety disorders and initiate appropriate

treatment for epilepsy patients with depression or other disorders. The assessment of mood and anxiety disorders in epilepsy patients is acknowledged as complex but has been proven possible by multiple studies. This section will show that efficient and cost-effective tools exist for screening mood and anxiety disorders as well as outcome measures for assessing QOL.

The studies reviewed have used various instruments amongst different populations, in multiple settings. In an attempt to assess mood and anxiety disorders, researchers have used clinical interviews, chart reviews, self-report instruments, and rarely, structured interviews. Often times, self-report measures of depression were used to determine the severity of depression and/or support the diagnosis of depression obtained by other means.

Anxiety disorders have been assessed much less frequently in this population than depression. There is concern about the seriousness of underdiagnosis and undertreatment of anxiety disorders (Cramer, Brandenburg et al., 2005; Jones et al., 2005a;b; and Johnson et al., 2004). Also, assessments of bipolar disorder in epilepsy patients are still being developed and different instruments have predicted variable rates (Jones et al., 2005a;b; Ettinger et al., 2005).

Evaluation of mood states is as important as treating the underlying mood disorder (Szflarski & Szaflarski, 2003). Kanner (2003) stated that the recognition of depression in patients with epilepsy would become more effective if clinicians

incorporated a few questions aimed at eliciting symptoms of depression in the course of their medical evaluation. Investigators have successfully used self-rating instruments like the Beck Depression Inventory-Second Edition (BDI-II) (Beck, Steer, and Brown, 1996) to screen for and identify depression (Kanner, 2003).

Self-report depression assessments can be used to screen for major depression in clinical settings. Such measures facilitate the clinical identification of patients with mood and/or anxiety disorders so that treatment can be initiated (Jones et al., 2005a;b).

Brookes, G. & Crawford P. (2002) gathered information from questionnaires completed by 65 participants who attended a specialist outpatient clinic during a six month period. The authors defined a history of depressive illness as a past diagnosis of depressive illness documented in the case notes by a psychiatrist or general practitioner (Brookes and Crawford, 2002). The authors reported that 19% of the participants had a history of depression and that 21% were experiencing a current episode of depression as defined as a diagnosis of moderate or severe depressive illness made by the psychiatrist based on International Classification of Diseases-10 (ICD-10) diagnostic criteria. The diagnostic interview by the psychiatrist, based on ICD-10 criteria, was initiated if the self-reported Hospital Anxiety and Depression Scale (HAD) score was greater than eight (Brookes and Crawford, 2002, p. 524). Of the 65 participants, 34 (50 %) reported no depression, 16 (21%) reported current depression, and 15 (19%)

had a history of depression (Brookes and Crawford, 2002). Forty percent of those surveyed declined to take part in the study or were excluded when the questionnaires were not fully completed; this was noted as contributing to a significant loss of power for the study findings (Brookes and Crawford, 2002). An additional weakness was that past diagnosis of depression was defined as evidence in the case notes that a psychiatrist or general practitioner had diagnosed the participant with a depressive illness.

It has been pointed out that self-rating instruments should not replace a psychiatric evaluation (Kanner, 2003). The instruments are not diagnostic by themselves of a major depressive episode or other mood and/or anxiety disorders and a score that suggests a major depressive episode should be followed by a more in-depth evaluation to establish a diagnosis according to DSM-IV criteria (Kanner, 2007). Thus, it is important to perform a structured psychiatric interview to diagnosis participants based on DSM-IV criteria. A comparison between self-report measures and psychological evaluations is known to increase the accuracy and confidence of assessment (Kanner, 2003).

By comparing the sensitivity and specificity of the BDI-II, Quick Inventory of Depressive Symptomatology-16-Self Rated (QIDS-SR16), Quick Inventory of Depressive Symptomatology-16-Clinician Rated (QIDS-C16) and the Mood Disorder Questionnaire (MDQ) with the MINI and the results of Jones et al. (2005a;b), this study will help to clarify the prevalence of depression and

anxiety disorders in epilepsy using similar instruments for assessment. If the study is successful, it will provide neurologists with another, more time-efficient option (i.e., the QIDS-SR16, QOLIE-31, and MDQ) for the diagnosis and management of depression and/or anxiety disorders. One important difference between this current study and Jones et al (2005a;b) will be an attempt to determine the sensitivity and specificity of self-report measures used for the screening of mood and anxiety disorders in epilepsy patients.

One recent study by Ettinger, Reed, Goldberg and colleagues (2005) found that bipolar symptoms, as defined by the MDQ (See Instruments in this Study Section), were reported by 12.2% of epilepsy patients. This reported finding was significantly higher than the 2.8% prevalence rate of bipolar disorders, as defined by the MINI, reported by Jones et al. (2005a); therefore, this study will include the screening instrument used by Ettinger et al. (2005) to determine if the MDQ (Hirschfeld et al., 2000), is accurate in identifying bipolar disorder symptoms among epilepsy patients by comparing the MDQ results to the MINI.

Instruments in this Study

This section will review the rationale of each instrument that will be used in the proposed study and discuss each instruments' psychometric properties. The QIDS-SR16 and the QIDS-C16 will be used to assess for depression. The QIDS

was chosen because it is an accurate, time-efficient measurement of depressive symptom severity and has demonstrated cost-efficient, clinical efficacy, and efficacy in previous trials (Rush et al., 2005). The QIDS-SR16 was developed in order to reduce the time needed to appraise depressive symptom severity. Both the QIDS-C16 (clinician rated) and QIDS-SR16 (self-report) were based on the 16 Inventory of Depressive Symptomatology (IDS) items and obtain ratings (range 0-3) concerning all nine criterion symptom domains. The nine criterion symptoms are sleep disturbance, sad mood, appetite or weight changes, concentration or decision making, self perception, suicidal ideation, interest in activities, energy and psychomotor retardation or agitation. The IDS scales have been subjected to numerous psychometric evaluations and have been administered to patients with major depressive, bipolar and dysthymic disorders (Rush et al., 2005). The evidence to date suggested that both the QIDS-C16 and the QIDS-SR16 have acceptable psychometric properties (Rush et al., 2005).

The questions that make up the QIDS-C16 and the QIDS-SR16 are identical. In each version of the QIDS, four items are used to assess the sleep domain. Two items are used to gauge psychomotor activity and four items assess the appetite/weight domain. For each of these three domains, the highest rating of any one of the relevant items is used to the score the domain. For the remaining six criterion domains (sad mood, concentration, energy, interest, guilt, suicidal ideations/intent), only one item is used for each symptom rating (0-3). The

QIDS16 total score ranges from 0-27 (Rush et al., 2005). The QIDS surveys estimate depression severity as 6-10 mild, 11-15 moderate, 16-20 severe and > 21 very severe depression (Rush et al., 2005).

Kessler et al. (2005) showed that more than 99% of respondents with a 12 month Composite International Diagnostic Interview (CIDI)/DSM-IV classified Major Depressive Disorder (MDD), are independently classified as clinically depressed during the worst month of the year by the QIDS-SR16. The QIDS-SR16 also indicated that 10.4% suffered from mild depression, 38.6% moderate, 38.0% severe, and 12.9% very severe (Kessler et al., 2005). Additionally, the QIDS-SR16 confirmed more than 99% of 12-month CIDI identified MDD cases (Kessler et al., 2005).

In addition to the QIDS, the BDI-II will be used to assess for depression. Investigators have identified optimal cutoff scores for the BDI-II, and diagnostic efficiency statistics have been performed. Using receiver-operator-characteristic statistics (ROC), Jones et al. (2005a;b) examined the ability of the BDI-II (i.e., total scores) to identify current major depression. This procedure was calculated by using the MINI, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), and both MINI and SCID combined diagnoses of major depression with a BDI-II cutoff score of > 11 (Jones et al., 2005a;b). The ROC analyses were all highly statistically significant, with areas under the curve ranging from 0.88 to 0.94 (all $p < 0.001$). Sensitivities consistently ranged

between 0.84 and 0.96, and specificities consistently exceeded 0.78. Though largely similar across both instruments (i.e., SCID and MINI), sensitivities tended to be slightly higher when the MINI was used as the standard (Jones et al., 2005a;b).

Furthermore, positive predictive value was modest for both the BDI-II across both standardized interview procedures (MINI and SCID). In reporting elevated symptoms of depression, the probability of a research standard diagnosis of major depression is ~0.5. It should be noted that, based on these analyses, the cutoff scores are different from the recommended clinical cutoff score (BDI-II >/= 10). When the MINI is used with the BDI-II the clinical cutoff score of > 11 resulted in a 4% increase in sensitivity and a 10% decline in specificity (Jones et al., 2005a;b). The BDI-II has been found to be a valid instrument for screening symptoms of depression in epilepsy patients (Jones et al., 2005a;b).

Surveying Mood Disorders

For the purpose of evaluating bipolar symptoms The Mood Disorder Questionnaire (MDQ) was selected. The MDQ is self-report instrument that screens for the presence of a lifetime history of bipolar disorder (Hirschfeld et al., 2000). The validity of the MDQ is currently being debated in the literature (Ettinger, Reed, Goldberg & Hirschfeld, 2005; and Kanner, 2007). The questionnaire consists of 13 yes/no items derived from both the DSM-IV criteria

and clinical experience. Additional questions ask whether symptoms ever co-occurred during the same period of time (yes/no), and about the degree of functional impairment caused by the symptoms (four point scale from no problem to serious problem). An individual is scored positive for bipolar if seven or more of the 13 symptom items, plus the co-occurrence item, are endorsed and a moderate or serious degree of functional impairment is reported (Hirschfeld et al., 2000). Hirschfeld and colleagues reported that the MDQ was validated in a psychiatric outpatient setting (sensitivity 0.73 and specificity 0.90). and in the general US population (sensitivity 0.28 and specificity 0.97) against a diagnosis of bipolar I and II based on the SCID; however, Kanner (2007) asserted that the MDQ remains unvalidated amongst the epilepsy population. The tool was recently reported to have shown utility in primary care clinics that included patients with diverse medical disorders (Hirschfeld et al, 2000).

Quality of Life

The Quality of Life in Epilepsy-31 Self-Report Questionnaire (QOLIE-31) was developed to provide health-related quality of life instruments that addressed issues pertinent to people with mild, moderate and severe epilepsy (Cramer, Perrine, Devinsky, Bryant-Comstock, Meador, and Hermann, 1998). Designed for both clinical and research purposes, the goal was to use the questionnaire to improve the quality of patient care, differentiate among treatment options, and

evaluate the allocation of health care resources (Cramer et al., 1998). Additionally, the questionnaire was designed to understand the impact of epilepsy on daily life.

First, a test questionnaire of 99 questions was used to develop the initial QOLIE-89, that contained 89 items in 17 scales. It included the seven scales of the RAND 36-Item Health Survey as the generic core (Cramer et al., 1998). The generic core was based on the RAND 36-Item Health Survey which measures physical functioning, role limitations due to physical problems and emotional problems, social functioning, body pain, emotional well-being, energy/fatigue and general health perceptions (Cramer et al., 1998).

Expansion of the generic core (nine items) was based on two 36-Item Short-Form Health Survey (SF-36) role limitations scales which were expanded by three items to make the scales analogous to one another (five items) (Cramer et al., 1998). Two items on health perceptions were added to supplement the general health perceptions scale (Cramer et al., 1998). Additionally, two items that assessed overall QOL using a pictorial QOL chart and an overall QOL item adapted from the Faces Scale (Cramer et al., 1998). The Faces Scale was included twice in the questionnaire to assess reproducibility of a single item in the same administration (Cramer et al., 1998). (See Appendix for samples of all measures used in this study)

Epilepsy-targeted QOL items were added to supplement the generic core and were related to issues commonly reported by epilepsy patients with moderately, well-controlled epilepsy (Cramer et al., 1998). These questions were derived from the experience of six health professionals in epilepsy and from 30 individual outpatient interviews with epilepsy patients regarding QOL issues and a literature review of studies that examined seizure severity and psychosocial aspects of epilepsy (Cramer et al., 1998).

Other items were added specifically for the initial study, regarding attitudes toward seizures and one item on self-esteem (Cramer et al., 1998). Based on field testing, 86 items were selected (multitrait scaling analysis) that showed items distributed in 17 multiitem scales (Cramer et al., 1998). The 86 items were supplemented by three additional items to form the QOLIE-89 (Cramer et al., 1998).

The QOLIE-31 was then derived from the QOLIE-89. In order to determine which items to include on the QOLIE-31, the researchers empirically selected QOLIE-89 subscales that were considered most important based on reports by people with epilepsy instead of using a statistical approach based the highest loadings (Cramer et al., 1998). Generic topics were excluded based on patient reports, for example, pain. The scales were chosen to represent the issues commonly expressed by patients, as determined by an expert panel (QOLIE

Development Group) (Cramer et al., 1998). The result was seven scales and an overall item, totaling 31 questions.

Item to scale correlations were calculated for the 30 items compromising the seven scales. In every instance, individual items correlated more significantly with the scale on which that item loaded that with other scales (Cramer et al., 1998). Item-scale correlations were uniformly very high for all scales, including seizure worry (r = 0.68-0.79), overall QOL (r = 0.90-0.92), emotional well-being (r = 0.71-0.82), energy/fatigue (r = 0.81-0.85), cognitive functioning (r = 0.66-0.81), medication effects (r = 0.75-0.89), and work/driving/social functioning (r = 0.69-0.80) (Cramer et al., 1998). Factor analysis of the 30 items yielded seven factors with eigenvalues > 1.0 (Cramer et al., 1998). The factor analysis produced a structure that paralleled the QOLIE-31 scale structure.

Internal consistency reliability coefficients (Cronbach's alpha) range from .77 for social functioning scale to .85 for the cognitive functioning scale. Test-retest data demonstrated good reliability (range r = 0.64 – 0.85). Correlations between patient self–reports and corresponding proxy reports ranged from 0.29 (role limitations: emotional) to 0.57 (work/social function): all correlations were significant at $p < 0.0001$ (Cramer et al., 1998).

A separate factor analysis of the seven QOLIE-31 scales yielded two factors (Cramer et al., 1998). The first factor, appearing to reflect emotional and psychological issues, comprised high loadings from the seizure worry, overall

QOL, emotional well-being, and energy/fatigue scales. The second factor, appearing to reflect mental efficiency as medical/social effects, comprised high loadings from the medication effects, work/driving /social and cognitive functioning scales. The subscales cover general and epilepsy-specific domains. The subscales are grouped by: Emotional/Psychological Effects (seizure worry, overall QOL, emotional well-being, energy/fatigue subscales) and Medical/Social Effects (medication effects, work-driving-social limits, cognitive function subscales).

Evaluation of the impact of medications and other treatments for epilepsy in QOL is essential because functioning and well-being were suggested as the outcomes that were most important to patients (Cramer et al., 1998).

The QOLIE-31 was designed to serve as an epilepsy-specific instrument for rapid evaluation of the major health-related QOL domains of concern of adults with epilepsy. Health related QOL refers to the way in which individuals function and perceptions of their own well-being in physical, mental and social domains of life (Cramer et al., 1998). Although the instrument assesses fewer domains than the lengthy QOLIE-89, the seven scales selected for the QOLIE-31 approach those areas directly applicable to people with epilepsy, omitting scales with a relatively generic QOL target (e.g. pain, role limitations-physical) (Cramer et al., 1998).

The MINI

The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the US and Europe, for DSM-IV and International Classification of Diseases-10 (ICD-10) psychiatric disorders (Sheehan, Lecrubier, Sheehan, Amorim, Janavs, Weiller, Hergueta, Baker and Dunbar, 1998).

> The MINI is modeled on the clinical interview with priority given to current diagnosis. The MINI was designed for its simplicity and ease of use. Additionally, its brevity allows the MINI to be easily incorporated into a routine psychiatric evaluation or general practitioner consultations (Amorim, Lecrubier, Weiller, Hegueta, and Sheehan, 1998, p. 27).

All questions are answered yes or no. Each diagnostic section has one or two screening questions exploring mandatory criteria. The algorithms are integrated in the structure of the MINI so that diagnoses are established during the interview. The MINI has been compared to the CIDI and the SCID and demonstrated good results (Lecrubier et al., 1997 & Sheehan et al., 1997). The diagnostic concordance between the three diagnostic interviews, specificity and sensitivity were good. The inter-rater and test-retest reliability showed very good results (Lecrubier et al., 1997, Sheehan et al., 1997).

Prevalence Rates

Major Depressive Disorder in the General Population:

This current study will focus on the assessment of mood and anxiety disorders in epilepsy patients therefore a brief review of the literature regarding the prevalence of mood and anxiety disorders found in the general population is necessary to provide a point of comparison. Kessler et al. (2005) provided data on MDD and comorbid psychological disorder trends that were found in the general population. Kessler and others (Kessler et al., 2005) reported the prevalence of lifetime MDD in the general population was 16.2% (95% confidence interval 15.1-17.3) and MDD of 12-month duration was 6.6% (95% CI 5.9-7.3) Kesseler (2005) classified the12 month cases of MDD independently using the QIDS-SR16. Stratification within the group included 10.4% mild cases, 38.6% moderate, 38.0% severe, and 12.9% very severe. The mean episode duration was reportedly 16 weeks (CI 15.1-17.3) (Kessler et al., 2005). Additionally, Kessler reported the ratio of 12 month to lifetime prevalence at approximately 40% (Kessler et al., 2005). Based on these findings, prevalence rates were suggested to be equivalent to national population projections of 32.6 to 35.1 million US adults with lifetime MDD and 13.1 to 14.2 million adults with 12-mos MDD (Kessler et al., 2005).

In 2001-2002, The National Comorbidity Survey Replication (NCS-R) was conducted based on the CIDI /DSM-IV criteria (Kessler, et al., 2005). The response rate was 73% in 48 contiguous states (Kessler et al., 2005). The QIDS-SR16 had been previously shown to have a strong correlation to both the self-report 30-item Inventory of Depressive Symptomology (IDS-SR30) and to the 24-item Hamilton Rating Scale for Depression (HAM-D24) (Rush, Trivedi et al., 2003).

Nearly three fourths (72.1%) of the NCS-R respondents that endorsed lifetime MDD also met the criteria for at least one of the other CIDI/DSM-IV disorders, assessed in the NCS-R, which included 59.2% with an anxiety disorder, 24% with a substance use disorder, and 30% with an impulse control disorder (Kessler et al., 2005). Further, Kessler and colleagues (2005) reported that approximately two thirds (64%) of respondents with 12 month MDD met the criteria for at least one other 12 month disorder, with anxiety disorders (57.5%) again more common that either substance use (8.5%) or impulse control (16.6%) disorders (Kessler et al., 2005).

Data on the prevalence of epilepsy-associated depression varies depending on the patient population studied (Prueter and Nora, 2005). Estimates of depression in epilepsy have been reported to be as high as 50% in tertiary epilepsy centers, and 37% in community-based studies (Ettinger et al., 2005; and Grabowska-Grzyb et al., 2006). Another review of the literature stated that

depression occurred in approximately 30% of epilepsy patients across published studies (Kuhn et al., 2003). Kuhn et al. (2003) estimated the MDD prevalence rate in epilepsy patients in the range of between 20-60%. This sub-section will demonstrate the various methodologies used to access depression in epilepsy.

When examining MDD in the patients with epilepsy population, one study of 175 outpatients with epilepsy and 70 matched controls (matched controls were defined as disabled patients that consisted of amputees, polio victims, patients with severe pulmonary and cardiovascular disease, and a subgroup of neurological patients with mild cerebral palsy with similar socioeconomic backgrounds), indicated that 55% of the 175 outpatients with epilepsy reported depression vs 30% of the 70 matched controls (Mendez, 1986). The lifetime-to-date rate of MDD in patients with epilepsy across several studies ranged from 8 to 48% compared with the general population for whom a rate of 4.9 to 17% was reported (Barry and Jones, 2005).

In one study, Attarian et al. (2003) administered the BDI-II to 143 consecutive epilepsy patients from outpatient clinics, who were treated with one or more AED. The researchers also reviewed participants' monthly seizure rates during the six months prior to their evaluation (Attarian et al., 2003). The investigators found that depression and depressive disorders, defined as a BDI-II score of 16 or higher, were prevalent among patients with epilepsy regardless of the degree of seizure control and that the severity of depression was independent

of the severity of the seizure disorder (Attarian et al., 2003; Prueter and Nora, 2005; and Mendez et al., 1986).

When looking prospectively at patients with treatment-refractory epilepsy who were admitted to a tertiary care center from April 16, 2001, to September 16, 2002, Boylan et al. (2004), disclosed that 65 (54%) of 122 patients reported depression based on the Beck Depression Inventory (BDI) and of these 65 patients, 25 (37%) had never been diagnosed with depression. In Harden's review of the literature, it was reported that interictal depression was common in community-based studies of epilepsy patients, and occurred in 9% to 22% of these patients, however, the author stressed that the exact prevalence remained unknown (Harden, 2002).

Compared with the general population life-to-date estimate of 16% (Johnson et al., 2004) nearly all of the estimates for epilepsy-associated depressions were significantly higher. Kanner (2003) reported that 20% to 55% of patients with recurrent seizures suffered from depression as compared to 3% to 9% in patients with controlled epilepsy (Kanner, 2003).

Interestingly, the literature demonstrated a consistent report of a lack of a gender difference in the prevalence rates of depression among patients with epilepsy (Grabowska-Grzyb et al., 2006; Kanner, 2003; Harden, 2002; and Mendez et al., 1986). Stefansson, Olafsson, and Hauser (1998) studied 103 men and 138 women in Iceland that were receiving disability benefits secondary to

epilepsy. The authors showed that there was no sex difference (40/103 males and 45/138 females) in the prevalence of current psychiatric diagnoses as defined by the Ninth Revision of the International Classification of Diseases (ICD-9).

Depression was reported more frequently amongst patients with epilepsy versus other neurological disorders or other comparable chronically handicapped participants (Mendez et al., 1986; Kanner, 2003; Prueter and Nora, 2005). Kanner (2003) reported that three controlled studies compared the prevalence of depression between patients with epilepsy and patients with other neurologic diseases (traumatic brain injury, neuromuscular diseases, and myasthenia gravis). These studies showed that overall; epilepsy patients had higher rates of depression (Kanner, 2003). In contrast, participants with traumatic brain injury, neuromuscular diseases, and myasthenia gravis when assessed for differences in the rates of depression, failed to demonstrate any difference between groups (Kanner, 2003). Prueter and Nora (2005, p. 21) reported an 'assumed' average incidence of depression in epilepsy of 30-40%.

Trimble and Sander (2004) conducted a non-systematic review of the literature that estimated 6% of patients with epilepsy in the general population appeared to suffer from a psychiatric disorder. The authors went on to report a 10-20% incidence of psychiatric disorders associated with patients diagnosed with TLE or refractory epilepsy (Trimble and Sander, 2004). Mood disorders were reported as most common in epilepsy patients at a rate of 24-74% (Trimble &

Sander, 2004). Trimble & Sanders (2004) reported that depression in epilepsy patients was the most common of all psychiatric disorders found in 30% of patients. However, other findings, namely Jones et al. (2005a), reported a depression rate of 17%. Again, the variance of methodologies likely contributed to the differences found in addition to the differences stemming from sample demographics.

Jones et al. (2005a;b) used the MINI, SCID-I, BDI-II and the Center for Epidemiological Studies-Depression Scale (CES-D) to study 174 outpatients (66.1% women and 33.9% men) from five tertiary medical centers. The MINI produced similar results to the SCID-I (MINI with a .86 concordance rate with the SCID-I). The MINI identified 17.2% of participants meeting criteria for major depressive episode (MDE), while the SCID (an alternative longer structured interview) identified 16.7% of participants as having major depressive disorder (MDD). This was only a difference of one additional patient being identified with a current major depressive episode (MDE) by the MINI (Jones et al., 2005a). A summary of current MINI Axis I disorders reported in Jones et al. (2005a) is presented below.

Table A (Table 2, Jones et al., p. 174, 2005a)

TABLE 2. MINI: Axis I Current Diagnoses (N = 174)

Mood Disorders—Current	24.0%
Depressive Disorders	21.2%
Major Depressive Episode	17.2%
Dysthymia	4.0%
Bipolar Disorders	2.8%
Manic Episode	1.7%
Hypomanic Episode	1.1%
Anxiety Disorders—Current	52.1%
Panic Disorder	3.4%
Agoraphobia	15.5%
Social Phobia	10.9%
Obsessive-Compulsive	3.4%
Posttraumatic Stress Disorder	5.7%
Generalized Anxiety Disorder	13.2%
Schizophrenia & Other Psychotic Disorders—Current Psychotic Disorders	0.6%

A large number of participants had more than one diagnosis (N = 59).

Percentages across the Axis I disorders exceeded 100%, reflecting co-morbidity.

MINI = Mini International Neuropsychiatric Interview

Comorbidity

Various studies estimated that the prevalence of lifetime psychiatric comorbidity in epilepsy patients, from general practices and hospitals, was 20-50%. (Trimble and Saunders, 2004; Blumer, 2002). Psychiatric disorders that accompany epilepsy are comorbid and may precede, co-occur with or follow a diagnosis of epilepsy (Trimble and Sander, 2004). Defined, comorbidity refers to the coexistence of two or more conditions in the same person that is more than coincidental (Trimble and Sander, 2004). Comorbidity can be defined as current or lifetime (see Definitions Section) and will be noted as such for clarification in this proposal. Psychiatric comorbidity in epilepsy patients were reported to occur at higher rates than that of the general population or of other patients with chronic illnesses (Barry & Jones, 2005, Trimble & Sander, 2004). This section will demonstrate the seriousness of psychiatric comorbidity. Trimble and Sander (2004) reported that the percentage of patients with epilepsy that also suffered from a current psychiatric disorder ranged between 19-48%; however, the authors argued that few population-based studies had assessed the prevalence of psychiatric comorbidity in epilepsy.

Stefansson et al. (1998) found that when a psychiatric diagnosis was present, based on the International Classification of Diseases-9 (ICD-9), amongst 85 (35%) out of 241 epilepsy outpatients receiving disability benefits in Iceland,

that 15 (6.2%) out of 85 had a diagnosis of psychotic illness defined as ICD-9 schizophrenia and/or paranoid states. The authors compared the results to 482 control cases made up of chronically handicapped participants that were receiving similar disability benefits secondary to cardiovascular diseases, respiratory diseases, or arthropathies. It was reported that 143 (30%) out of 482 control cases had a current psychiatric diagnosis and out of the 143 patients, 11 had a diagnosis of a psychotic illness, which suggested that there was no difference in the prevalence of non-organic psychiatric disorders among disabled patients as compared with disabled epilepsy patients; however the data indicated that when psychopathology was present disabled epilepsy patients were more likely to have a psychotic illness than other disabled patients.

Jones et al. (2005a;b) reported that major depression was the most common diagnosis found in their 174 participants as referenced earlier in this review (see pages 45 & 46); however, 52% of their sample met criteria for a current DSM-IV anxiety disorder based on the MINI. Repeatedly, it has been demonstrated that these and other psychiatric disorders are under-recognized and undertreated in adults with epilepsy (Johnson et al., 2004; and Kuhn et al., 2003).

One non-systematic review of the literature reported that current anxiety disorders occurred in 10-25% of people with epilepsy in the community (Fiordelli, Beghi, Bogliun, and Crespi, 1993) and rates varied between 7-27% in hospital patients with epilepsy populations and between 11%-44% in patients with

intractable epilepsy (Trimble and Sander, 2004). Additionally, it was reported that psychoses was found in 2-7% of epilepsy patients and personality disorders in 1-2% (Trimble & Sander, 2004). The authors reported that the comorbidity appeared to be related to endogenous and exogenous (including iatrogenic) factors and to the severity and chronicity of epilepsy (Trimble and Sander, 2004). Additionally, in a population-based case controlled study, the authors reported a fourfold increase in risk for lifetime to date psychiatric disorders in the epilepsy participants regardless of whether or not the epilepsy participants were taking AEDs (Jalava and Sillanpaa, 1996).

Bipolar Disorder and Epilepsy

Hilty, Rodriguez, and Hales (2000) indicated that epilepsy and bipolar disorder we both public health problems and had estimated lifetime prevalence rates of 5.0% to 8.0% for epilepsy and 1.0% to 1.6% for bipolar disorder. The authors reported that the prevalence of interictal bipolar disorder had not yet been assessed; however, clinical reports suggested a prevalence of bipolar disorder in epilepsy patients as between 0.1% and 4.3% (Hilty Rodriguez, & Hales, 2000). In Kanner's review, 9.8% of patients reported symptoms of bipolar disorder (Kanner, 2003).

Ettinger et al. (2005) reported that in tertiary care-based populations, psychiatric comorbidity tended to be higher than among community-based patients; therefore, rates of bipolar symptoms were likely to be higher in tertiary care-based populations. The authors stated that many neurologisits and even epilepsy specialists would be surprised by the higher rates of bipolar symptoms in epilepsy patients (Ettinger et al., 2005).

Barry (2003) also reported that in a recent study of 85,358 community sampled participants including 2,282 patients with epilepsy, that used the MDQ, 8.1% of patients met the criteria for likely bipolar spectrum disorder, which was a significantly higher rate than that of people with asthma, diabetes, or the no diagnosis control group (Barry, 2003). Robertson (1992) reported a much lower prevalence rate, between 0.1% and 4.3%, of bipolar disorder in patients with epilepsy.

In contrast, Ettinger et al. (2005) examined the comparative prevalence of bipolar symptoms in respondents with epilepsy versus other chronic medical conditions. The researchers discovered that bipolar symptoms, defined as euphoric mood, irritability, grandiosity, reduced need for sleep, increased talkativeness, racing thoughts, decreased concentration and attention, increased energy, increased activity, much more social or outgoing than usual, and risky behaviors, were evident in 12.2% of epilepsy patients and was 1.6 to 2.2 times more common in participants with epilepsy than in patients with migraines,

asthma, or diabetes mellitus, and 6.6 times more likely to occur than in the healthy comparison group. Ettinger et al. (2005) used the MDQ in conjunction with questions about current health problems. The authors reported that 49.7% (*n* = 85,358 subjects) of patients with epilepsy who screened positive for bipolar symptoms, defined as a MDQ score greater than seven with one or more of the symptoms coocurring, and a moderate or serious degree of functional impairment endorsed, were reported by the epilepsy patients to have a prior formal diagnosis of bipolar disorder by a physician. This rate (49.7%) is nearly twice the rate seen in other disorders (Ettinger et al., 2005). Notably, 26.3% of MDQ positive epilepsy participants also carried a diagnosis of unipolar depression, and 25.8% had neither a uni- nor bipolar depression diagnosis (Ettinger et al., 2005). Bipolar symptoms as defined by the MDQ occurred in 12% of community-based epilepsy patients, and at a rate higher than in other medical disorders (Ettinger et al., 2005). . The MDQ was reported to have an approximate 30% false positive rate for bipolar spectrum disorders or as reported, seven out of ten patients with bipolar spectrum disorders would be correctly identified (Hirschfeld et al., 2000).

In contrast to the 12.2% rate of bipolar disorders reported in Ettinger et al. (2005), Jones et al. (2005a;b) reported a 2.8% rate of bipolar disorders. Jones et al., (2005a;b) utilized the MINI and the SCID-I Research Version for diagnosis purposes. The participants in the Jones et al, (2005a;b) study were from tertiary outpatient epilepsy centers or non-community medical-center-based populations

as referred to by Ettinger et al. (2005). Thus, the results reported in Jones et al. (2005a;b) did not support the prevalence rates of bipolar disorders made by Ettinger et al. (2005), in tertiary care-based epilepsy patients. In the present study, the MINI and the MDQ will be used in order to help clarify this discrepancy by replication in tertiary care based populations.

CHAPTER THREE
Methodology

STUDY DESIGN

Study Scheme

A group of 88 consecutive outpatients from a tertiary epilepsy center were assessed for the presence of current major depressive episode, dysthymia, manic or hypomanic episode, and/or anxiety disorder, as defined by the MINI. While this study attempted to replicate and extend Jones et al. (2005a;b), this study evaluated participants with initial self-report screenings and via a telephone interview rather than using an in-person interview.

Baseline Period

Eligible outpatients had a diagnosis of epilepsy as established by their treating physician. After participants provided written informed consent during a visit to the epilepsy center, they were administered the 16 item Quick Inventory of Depressive Symptomatology-Self Rating (QIDS-SR16), Beck Depression Inventory-II (BDI-II), Quality of Life Inventory in Epilepsy-31 (QOLE-31) and the Mood Disorders Questionnaire (MDQ). In addition, demographic information was obtained. It included seizure history (non-epileptic seizures, age of onset,

seizure within the last year, seizures within the last three months, last seizure, and duration) and concomitant anticonvulsant medication information (monotherapy vs. polytherapy). Following the initial screenings, a telephone interview time was conducted within 3 days. Those who participated in the study earned a financial incentive of $40.00. The enrollment period ran for eight months, beginning in October 2006 and ending in May 2007.

Telephone Assessment

Patients who met study eligibility criteria were contacted within three days of initial screening via telephone for an assessment interview. At that interview, participants were administered the Mini International Neuropsychiatric Interview (MINI) and the 16 item Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-C16). The QIDS-C16 and the MINI were all administered by Clinical Psychology Doctoral Students who were trained in administration and scoring. Group training was held to assure standardization of test administration and scoring. The QIDS-C16 and the MINI were administered to each participant by the same graduate student. Participants were screened for the following disorders from the MINI:

Major Depressive Episode

Dysthymia

Suicidality

(Hypo) Manic Episode

Panic Disorder

Agoraphobia

Social Phobia

Obsessive-Compulsive Disorder

Posttraumtic Stress Disorder

Alcohol Abuse and Dependence

Non-Alcohol Psychoactive Substance Use Disorders

Psychotic Disorders

Bulima Nervosa

Generalized Anxiety Disorder

Instruments of Measure

MINI International Neuropsyciatric Interview (MINI) Copyright 2003 Sheehan D.V. & Lecrubier Y. (Sheehan, Lecrubier, Harnett-Sheehan, Janavs, Weiller, Bonara, Keskinner, Schinka, Knapp, Sheehan, and Dunbar, 1997)

Quick Inventory of Depressive Symptomatology-16-Clinician Rated (QIDS-C16) (Rush, Madhukar, Trivedi, et al., 2003, www.ids-qids.org/tr-english.html, March 8, 2005)

Quick Inventory of Depressive Symptomatology-16-Self Rated (QIDS-SR16) (Trivedi, Madhukar; Rush, et al.2004, www.ids-qids.org/tr-english.html, March 8, 2005)

Quality of Life In Epilepsy-31 (QOLIE) (Devinsky & Penry, 1993, Cramer, Perrine, Devinsky, et al., 1998, www.epilepsy.com/epilepsy/quality_of_life.html, March 8, 2005)

Beck Depression Inventory-II (BDI-II) Beck Depression Inventory and BDI are U.S. registered trademarks of The Psychological Corporation registered in the United States of America and/or other jurisdictions. (Beck, Steer, and Brown, 1996).

Mood Disorder Questionnaire (MDQ) (Hirschfeld, RMA, Williams, J., Spitzer, R, et al., 2000)

Antiepilepsy Medication Record (monotherapy or polytherapy)

Seizure (age of onset, last 3 mos, active/nonactive, last seizure, duration)/Demographic Information

Number of Study Participants

There were 88 consecutive participants that agreed to participate and met the criteria.

Statistical Analysis Plan

This study is aimed at clarifying the prevalence of mood and anxiety disorders in epilepsy. Descriptive analyses will define the prevalence of current major depressive episode, dysthymia, manic or hypomanic episode, and/or anxiety disorder, as defined by the MINI. Comparison of the results of this study will be made with Jones et al. (2005a;b). Additionally, this study will provide information on the relationship of the following variables: type of epilepsy, gender, age, antidepressant medications (none, mono or poly), talk therapy or counseling services, seizure variance (length, onset, number in last 3 months, and

nonepileptic seizures) and any Axis I symptomatology and/or quality of life using independent *t*-tests or Chi-Square tests between groups.

In order to establish the total score on the QIDS-SR16 or BDI-II for the diagnosis of a major depressive episode or dysthymia, Receiver Operator Characteristics (ROC) analyses will be used to identify the optimal total scores on the QIDS-SR16 and BDI-II to identify participants with a major depressive episode, dysthymia and anxiety disorder. Also, in order to assess the Mood Disorders Questionnaire (MDQ) against the results found with the MINI to identify manic episodes and hypomanic episodes in patients with epilepsy, similar diagnostic efficiency analyses will be conducted to assess the sensitivity and specificity of the MDQ to identify the presence of manic or hypomanic episodes.

These groups will be compared in terms of quality of life using the QOLIE-31. Correlation coefficients between groups will be performed using the quality of life (QOLIE-31) and the relationship of depressive symptom severity (using the QIDS-SR16 and BDI-II) and independent t-tests within categories: mood disorder, anxiety disorder, both mood and anxiety disorder, major depressive episode plus (plus refers to participants that met criteria for major depressive episode, recurrent as defined by the MINI), and Axis I disorder, as defined by the MINI.

Study Site

The study site, the Neurological Clinic of Texas – Texas Epilepsy Group (TEG), is one out of the two major outpatient referral centers for epilepsy patients in North Texas (Two centers: Neurological Clinic of Texas - TEG, the private practice of Dr. Harvey and Dr. Leroy and The University of Texas Southwestern James W. Aston Ambulatory Care Center Outpatient Epilepsy Clinic) (R.F. Leroy, personal communication, July 28, 2006).

1. Neurological Clinic of Texas - TEG, the private practice of Dr. Harvey and Dr. Leroy

Study Duration

Study duration was eight months, October 2006 to May 2007.

Patient Selection

Patients selected for participation were chosen from the investigator's patient population after referral by treating neurologist who confirmed the patients' epilepsy diagnosis. The study population was made as widely inclusive as possible to comprise a representative population of tertiary-care-center epilepsy patients. This study is not an epidemiological survey but an examination of current prevalence rates of major depressive episode, dysthymia, manic or hypomanic episode, and/or anxiety disorder, as defined by the MINI. Due to the fact that this is a replication study with financial as well as time constraints, the following inclusion and exclusion criteria determined study eligibility.

Inclusion Criteria

To be eligible for enrollment in the study, patients met all of the following criteria:

1. Patients understood, agreed to and signed the Informed Consent.
2. Patients diagnosed with epilepsy (regardless of seizure type).
3. Able to communicate both verbally and in writing in English. This was due to language constraints of some study instruments.
4. Patients chronological age 18 years and older.
5. To control for possible mood effects or side effects caused by newly initiated AEDs participants were required to be on stable AEDs for the previous 30 days.

Exclusion Criteria

1. Patients with implanted Vagus Nerve Stimulator (VNS). VNS treatment has been shown to treat both treatment resistant epilepsy and depression; therefore, participants that had treated with VNS were excluded to limit confounds.
2. To control for potential confounds as a result of surgical alteration of brain regions that could affect mood states, individuals with a history of surgical treatment of epilepsy were excluded.

CHAPTER FOUR
Results

Description of Subjects

A total of 88 participants completed the QIDS-SR16, BDI-II, and MDQ, and 76 participants completed the MINI and QIDS-CR16. Of the 88 participants enrolled in the study initially, 12 did not complete the follow-up interview. Ten participants were not contacted within three days and two participants provided non-working phone numbers. The enrollment questionnaires and the demographic and seizure history questionnaires contained missing data points, therefore the total number of participants varies according to the individual variable measured [e.g., seizure type (n = 65), seizure medications (n = 87)]. The number of participants analyzed for each variable is noted in the corresponding table or text. The Database Group in the Division of Biostatistics at the University of Texas Southwestern Medical Center at Dallas entered all data twice for the purpose of verification.

Ethnic composition of the sample (n = 87) consisted of the following: 1.2% (1/87) American Indian or Alaska Native, 1.2% (1/87) Asian, 8.0% (7/87) African American, 1.2% (1/87) Native Hawaiian/Other Pacific Islander, 85.1%

(74/87) Caucasian, and 3.5% (3/87) indicated Some Other Race. Participants could also indicate they were a member of the Hispanic group 3.5% (3/86) or Latino group 2.4% (2/85). The majority of participants, 56.8% (50/88), were married and 29.6% (26/88) were never married. There were 5.7% (5/88) participants that were cohabiting with a partner, 6.8% (6/88) were divorced, and 1.1% (1/88) widowed. Regarding years of education, 21.4% (18/84) completed 12 years, 15.5% (13/84) completed 14 years, 15.5% (13/84) completed 15 years, 14.3% (12/84) completed 16 years, 9.5% (8/84) completed 18 years, 5% (5/84) completed 10 years, 5% (5/84) completed 11 years, 3.6% (3/84) completed 13 years, 3.6% (3/84) completed 17 years, 3.6% (3/84) completed 19 years, and 1.2% (1/84) completed 20 years. All participants provided information on their employment status. 51.1% (45/88) were full-time employed for pay, 19.3% (17/88) were unemployed not looking for employment, 9.1% (8/88) were part-time for pay, 8.0% (7/88) were unemployed looking for employment, 8.0% (7/88) were retired, not working, and 4.6% were self-employed for pay.

Results

All statistics were performed using Statistical Analysis Software Institute, Inc. software (SAS). Table 1 lists the actual descriptive statistics obtained for the individual demographic and seizure variables. Age, gender, age of epilepsy onset,

and mono AED or poly AED were compared with Jones et al. (2005a;b) using Chi-Square tests or *t* tests as appropriate. No statistically significant differences were observed (see Table 1). The descriptive statistics on seizure variables from this study are presented in Table 1. Differences in coding methodology prevented comparison of seizure type to participants of Jones et al. (2005a;b).

Table 1. Demographics and Seizure Variable Comparison	Current Study	Jones et al. (2005) (N= 174)	*df*	χ^2 or *t* value	*p*
Age (years) (*n* = 88)	38.82 (*SD*14.04)	39.04 (11.9)	260	0.132	0.895
Gender (*n* = 88)					
women	54 (61.36%)	115 (66.1%)			
men	34 (38.64%)	59 (33.9%)	1	0.571	0.450
Age of epilepsy onset (years) (*n* = 86)	21.34 (*SD*14.70)	21.1 (13.7)	260	0.129	0.897
Seizure duration (years)	----	17.9 (12.7)			
Nonepileptic seizures (*n* = 84)	16/84 (19.05%)	-----			
Seizure within last year (*n* = 87)	52/87 (59.77%)	----			
Seizures within last 3 mos (*n* = 65)	65/87 (74%)	---			
Number of seizures in last 3 mos	6.26 (*SD*12.83)	---			
AED medications (*n* = 87)					
monotherapy	52/87 (59.77%)	94 (54%)			
polytherapy	35/87 (40.23%)	80 (46%)	1	0.778	0.378
Seizure Types (*n* = 65)					
simple partial	7/65 (10.77%)	53 (30.5%)	--	-	-
complex partial	35/65 (53.85%)	96 (55.2%)	--	-	-
secondarily generalized motor	11/65 (16.92%)	55 (31.6%)	--	-	-
generalized motor	9/65 (13.85%)	72 (41.4%)	--	-	-
*Absence	3/65 (4.62%)	---------	--	-	-

Note: Jones et al. (2005) participants were coded with more than one seizure type; therefore, unable to compare for potential differences between studies.
*Absence seizure was not a category in Jones et al. (2005).

A summary of current MINI Axis I disorders among participants is provided in Table 2. Nearly 68% (n = 52/76), of the sample had no current Axis I diagnosis while the remaining 31.58% (n = 24/76) exhibited current disorder symptomatology. Comorbidity across diagnoses was 21.05% (16/76). Jones et al. (2005) reported significantly higher rates of comorbidity, $\chi^2(1, n = 76) = 4.463$, $p < .05$, with 33.9% (59/174; see Table 2); however, the Bonferroni procedure was used to control for potential misleading p-values because there were 16 tests for statistical significance. Based on the Bonferroni procedure a p value of > .003 would not be statistically significant.

Table 2. MINI: Screened Axis I Current Disorders	(*n* = 76) Current Study	Jones et al. (2005) (N = 174)	*df*	χ^2	*p*
Mood Disorders-Current	12 (15.79%)	24%	1	2.177	0.140
Depressive Disorders	9 (11.8%)	21.2%	1	3.128	0.077
Major Depressive Episode	8 (10.5%)	17.2%	1	1.850	0.174
Dysthymia	1 (1.3%)	4%	1	1.252	0.263
Bipolar Disorders	3 (1.3%)	2.8%	1	0.197	0.657
Manic Episode	1 (1.3%)	1.7%	1	0.056	0.813
Hypomanic Episode	2 (2.6%)	1.1%	1	0.738	0.390
Anxiety Disorders-Current	19 (25.0%)	52.1%	1	15.998**	<0.001
Panic Disorder	1 (1.3%)	3.4%	1	0.884	0.347
Agoraphobia	8 (10.5%)	15.5%	1	1.094	0.295
Social Phobia	3 (3.9%)	10.9%	1	3.204	0.074
Obsessive-Compulsive	0 (0%)	3.4%	1	2.685	0.101
Posttraumatic Stress Disorder	5 (6.6%)	5.7%	1	0.065	0.799
Generalized Anxiety Disorder	3 (3.9%)	13.2%	1	4.879*	0.027
Psychotic Disorders	0 (0%)	0.6%	1	0.438	0.508
Comorbid Axis I Disorder	16 (21.05%)	59 (33.9%)	1	4.163*	0.041

Note: **p<.001. *p<.05
(Based on Bonferroni procedure significant only at p < .003)

Major depressive episode was the most common current mood disorder (10.5%), with a considerably smaller proportion meeting criteria for current dysthymia (1.3%) or current manic or current hypomanic episode (1.3%). The rate of mood disorders found in this study was not significantly different when compared to Jones et al. (2005) using Chi-Square tests (See Table 2). Of the 76 participants that completed the MINI seven (9%) met criteria for low, current suicide risk. This study identified an equal rate for bipolar disorder symptoms (1.3%) and dysthymia disorder (1.3%) as defined by the MINI. Jones et al. (2005) reported lower rates of bipolar disorder symptoms (2.8%) compared to dythymia (4%).

Current anxiety disorder symptoms screened for were especially prevalent with 25% of participants meeting criteria for a current anxiety disorder. However, a Chi-Square test demonstrated that this was significantly, $\chi^2(1, n = 76) = 15.998$, $p < .001$, lower than the 52.1% rate of anxiety disorders screened for and reported in Jones et al. (2005).

One other significant difference was observed amongst the anxiety disorder symptoms. Jones et al. (2005) reported that 13.2% of participants met the MINI criteria for generalized anxiety disorder (GAD) compared to 3.9% in the current study, $\chi^2(1, n = 76) = 4.879$, $p < .05$ (see Table 2). However, the Bonferroni procedure was used to control for potential misleading *p*-values

because there were 16 tests performed for statistical significance. Based on the Bonferroni procedure a *p* value of > .003 would not be statistically significant. Further, Chi-square tests demonstrated no other significant differences between participants in the current study and Jones et al. (2005) for anxiety disorders and current Axis I disorders as defined by the MINI (see Table 2).

Participants were divided into five groups; mood disorders, anxiety disorders, mood and anxiety disorders, mde plus (plus refers to participants that met criteria for major depressive episode, recurrent as defined by the MINI), and Axis I disorder, as defined by the MINI. The groups consisted of: mood disorder group15.8% (12/76), anxiety disorder group 25.0% (19/76), mood and anxiety disorders group 10.5% (8/76), mde plus 14.5% (11/76), and Axis I disorder group 31.6% (24/76; see Table 3).

Chi-Square tests were used to determine if there were gender differences between each of the five groups when compared to the remaining participants (see Table 3.2); no significant differences were identified. Also, there were no significant age differences between each of the five groups compared to the remaining participants when examined using independent *t*-tests. For each *t*-test the equality of variances were not significant, therefore, the pooled method was used (see Table 3.3). For analysis, independent *t*-tests were used to assess if there were any differences due to seizure variables such as age of epilepsy onset (Table 4) and seizures within the last three months (Table 4.1). No significant differences

were found between each of the five groups and the remaining participants. Chi-Square tests were used to determine if there were any significant differences between each of the five groups and the remaining population when comparing the type of seizure (Table 4.2) or whether participants had experienced a seizure within the last year (Table 4.3); no significant differences were observed.

Additional analysis examined if there were any significant differences between the 16 (19.0%) participants that reported nonepileptic seizures and the remaining sample. For analysis, *t*-tests were used to assess for differences in age of epilepsy onset, seizures within the last year, seizures within the last three months, number of seizures in the last three months, mono AED or poly AED, or taking an antidepressant or receiving talk therapy or counseling services. No significant differences were found. Also, *t* tests were used to determine if there were any significant differences between each of the five groups and the remaining population when comparing participants that reported nonepileptic seizures; no significant differences were observed.

Quality of Life (see Tables 5 and 5.1)

Using independent *t*-tests, there were significant differences in QOL observed amongst the 5 groups (mde plus, mood, anxiety, mood and anxiety, and Axis I), when compared to the remaining sample (Table 5). The major depressive

episode-plus group reported a significantly lower quality of life with a mean of 38.60 (*SD* = 9.51) on the QOILE-31 compared to a mean of 72.578 (*SD* = 13.72) reported for the remaining participants, $t(72) = 7.52$, $p < .0001$. The mood and anxiety disorders group had a significantly lower reported quality of life with a mean of 39.00 (*SD* = 11.55) on the QOILE-31 compared to the remaining participant mean of 71.50 (*SD* = 14.79), $t(72) = 5.98$, $p < .0001$. The mood disorders group also had a significantly lower reported quality of life with a mean of 40.00 (*SD* = 10.15) on the QOILE-31 compared to the remaining participant mean of 72.87 (*SD* = 13.65), $t(72) = 7.61$, $p < .0001$. The Axis I group had a significantly lower reported quality of life with a mean of 56.04 (*SD* = 18.83) on the QOILE-31 compared to the mean of 73.37 (*SD* = 14.24), $t(72) = 4.37$, $p < .0001$) of the remaining participants. The anxiety disorders group had a significantly lower reported quality of life with a mean of 57.00 (*SD* = 19.28) on the QOILE-31 compared to the remaining participant mean of 71.78 (*SD* = 15.45), $t(72) = 3.37$, $p < .001$.

The severity of symptoms reported on the BDI-II and the QIDS-SR were negatively correlated ($r = -0.5415$ and $r = -0.59323$ respectively) with QOL scores. Correlation coefficients were calculated using the Kendall Tau b Correlation Coefficients. As participants endorsed more symptoms on either the BDI-II or QIDS-SR their scores on the QOLIE-31 decreased significantly ($p < .0001$).

Amongst seizure variables, the number of seizures a participant experienced in the last three months negatively correlated to QOL scores. Correlation coefficients were calculated using the Kendall Tau b Correlation Coefficients. Participants that reported more seizures in the last three months had significantly lower QOL scores (r = -0.35759, p < .0001). There were no significant correlations observed between age of epilepsy onset or length of last seizure in minutes and QOL scores; however, a t-test demonstrated that participants who reported a seizure within the last year had a significantly lower reported quality of life with a mean of 56.60 (SD = 17.45) on the QOILE-31 compared to the remaining participant mean of 72.55 (SD = 13.61), $t(85) = 4.50$, p < .0001.

Treatment with Antidepressant Medication

Chi-Square tests showed that each of the 5 groups, mde plus, mood group, anxiety group, mood and anxiety group, and the Axis I group were all significantly different when compared to the remaining participants when looking at whether participants were currently taking antidepressant medication (Table 6). For example, 50% (5/10) of participants in the mde plus group were taking an antidepressant as compared to only 12.50% (8/64), χ^2 (1, n = 74) = 8.399, p = <

.01, of the remaining participants. No participants reported taking more than 1 antidepressant. Participants in the mood group were much more likely to be taking antidepressant medication versus the remaining participants χ^2 (1, n = 74) = 12.20, $p < .001$. Within the mood group, 54.55% (6/11) were taking an antidepressant and 45.45% (5/11) were not. Similarly, within the anxiety disorder group, less than 37% (7/19) of participants identified as meeting criteria for an anxiety disorder were taking an antidepressant medication; however, Chi-Square tests demonstrated that those participants identified as having an anxiety disorder were significantly more likely to be taking an antidepressant compared to 10.91% (6/55) of participants who were not in the anxiety group and taking an antidepressant, χ^2 (1, n = 74) = 6.558, $p < .01$ (See Table 6). A total of 63.16% (12/19) participants identified as having an anxiety disorder were not receiving antidepressant medication (see Table 6). Seven of the 63 (11.11%) participants who did not meet criteria for a mood disorder were taking antidepressant medications and 10.91% (6/55) who did not meet criteria for an anxiety disorder were taking antidepressant medications.

Treatment with Therapy

It was found that less than 18% (4/23) of participants identified as meeting criteria for an Axis I disorder reported currently receiving any type of talk therapy

or counseling services (See Table 6.1). Between 21% and 38% of participants reported receiving some type of talk therapy or counseling service in the remaining four groups: mde plus, mood group, anxiety group, and mood and anxiety group, (See Table 6.1). Approximately 2% - 3% of participants in the remaining sample were receiving talk therapy or counseling services. There were significant differences amongst participants receiving therapy that met criteria for one of the five groups as defined by the MINI when compared to the remaining sample (See Table 6.1).

Receiver operating characteristic (ROC) analysis

To determine the diagnostic sensitivity of the MINI and the QIDS-SR, BDI-II, and QIDS-CR in identifying a major depressive episode, dysthymia, and anxiety disorders, receiver operating characteristic curve (ROC) analyses were performed. Sensitivity, specificity, and predictive values, both positive and negative were defined (see Table 7, 7.1, and 7.2). When examining major depressive episode, sensitivities and specificities were comparable for both the BDI-II and the QIDS-CR; however, the QIDS-SR was less sensitive (see Table 7). The QIDS-SR, BDI-II, and the QIDS-CR all demonstrated strong negative predictive value, or if participants scored below the respective cut off points there was very low probability that a major depressive episode existed. When

participants scored above the specified cut points, the probability of the presence of a current major depressive episode was 57% for the QIDS-SR, 44% for the BDI-II, and 44% for the QIDS-CR.

When examining dysthymia, sensitivities and specificities were comparable for both the BDI-II and the QIDS-CR; however, the QIDS-SR performed with less specificity (see Table 7.1). The QIDS-SR, BDI-II, and the QIDS-CR all demonstrated strong negative predictive value, or if participants scored below the respective cut off points there was very low probability that dysthymia existed. For participants scoring above the specified cut off points, the probability that a current dysthymic episode was present varied between instruments: 7% for the QIDS-SR, 25% for the BDI-II, and 14% for the QIDS-CR.

When examining anxiety disorders, sensitivities and specificities were comparable between the QIDS-SR, BDI-II, and QIDS-CR (see Table 7.2). The QIDS-SR, BDI-II, and the QIDS-CR all demonstrated strong negative predictive value. If participants scored below the respective cut off points, there was very low probability that an anxiety disorder existed. For participants scoring above the specified cut off points, the probability that a current anxiety disorder was present was 63% for the QIDS-SR, 69% for the BDI-II, and 78% for the QIDS-CR.

Using the MINI and the MDQ (See Table 7.3, 7.4, and 7.5), an additional diagnostic efficiency analysis was performed for participants identified with

manic, hypomanic and/or bipolar disorder symptoms. Overall, the MDQ demonstrated poor sensitivity. The MINI identified three participants with bipolar disorder symptoms. The MDQ identified a total of six as having bipolar symptoms including one of the three participants identified by the MINI and an additional five other participants.

CHAPTER FIVE
Discussion & Conclusions

Introduction

This study examined multiple factors related to mood and anxiety disorders in patients with epilepsy including the current prevalence rates of mood disorders in the tertiary care epilepsy patient population, diagnostic-test efficiency based on use of the QIDS-SR16, BDI-II, QIDS-CR16, and MDQ compared to the MINI, as well as the affects on mood and/or anxiety disorders on QOL. Based on data gathered from 76 participants, the results also enable a comparison to Jones et al. (2005) a study that examined the current prevalence rates of mood disorders in patients with epilepsy. Jones et al. (2005) was among the first research studies to establish the efficacy of using short surveys to screen for mood and/or anxiety disorders in the epilepsy population. In order to reduce differences in prevalence rates that could be attributed to differences in methodology, this study utilized similar screening instruments to those used in Jones et al. (2005). The similarity between results from the current study to Jones et al. (2005) supports and extends the conclusions regarding current prevalence rates of psychiatric disorders found in tertiary care epilepsy centers. This discussion will suggest future directions in

research for this patient population and interventions that have potential to increase diagnosis and treatment of mood and anxiety disorders in patients with epilepsy.

Discussion

This study was designed to replicate Jones et al. (2005) to either extend and generalize the findings or to question the reported findings. In order to test the validity of conclusions put forth in Jones et al. (2005), this current study was designed to closely replicate the study. Prior to this study, no other studies using similar methodology in the patients with epilepsy had been published in the literature.

Jones et al. (2005) reported results based on data collected from 174 participants recruited through five university outpatient epilepsy centers (Medical College of Georgia, Rush Medical Center, Stanford University, Washington University, University of Wisconsin-Madison) compared to 88 participants recruited at the Neurological Clinic of Texas - TEG for this study. Despite these differences in sample size, geographical location, and the number of sites used to recruit participants, the demographic and seizure variable data were similar.

This study found no statistically significant differences in age, gender, age of epilepsy onset or mono or poly AED therapy compared to the patient

demographics and seizure variables in Jones et al. (2005) and the population in the current study appears to be representative of the tertiary care epilepsy patient population. The similarity in demographics and seizure variables found in this study serve to generalize the Jones et al. (2005) findings and provide support for the additional findings observed in the current study.

The distinction between the life-long prevalence of mood and/or anxiety disorders in patients with epilepsy versus current prevalence rates of mood and/or anxiety disorders must remain clear when reviewing the results of this study. Much of the literature reports life-long prevalence rates of mood and anxiety disorders rather than current mood or anxiety disorders. This study was aimed at identifying participants presenting in a tertiary care center with a current mood and/or anxiety disorder(s). Jones et al. (2005) also reported on current patient mood and/or anxiety disorders. These similarities in design allow for comparison of results between the two studies. Most of the literature on patients with epilepsy and major depressive disorder (MDD) defines prevalence rates of MDD of 12-month or lifelong duration in various settings. The current study and Jones et al. (2005) were focused on current prevalence of Axis I disorders in tertiary care clinics in order to provide data to treating physicians and facilitate treatment. This is notably different than obtaining data for epidemiological purposes. This study placed the rate of current major depressive episode at 10.5% compared to Jones et

al. (2005) at 17.2%. Both studies highlight the increased incidence of major depressive episodes as defined by the MINI in the tertiary care patient population.

Data on the prevalence of epilepsy-associated depression varies depending on the patient population studied (Prueter & Nora, 2005). Estimates of depression in epilepsy have been reported to be as high as 50% in tertiary epilepsy centers and 37% in community-based studies. Kuhn et al. (2003) estimated the MDD prevalence rate in epilepsy patients in the range of between 20-60%. This study supports Jones et al. (2005) findings. The difference between 10.5% and 17.2% is small compared to some estimates. Based on the current study and Jones et al. (2005), treating physicians might expect to observe that approximately 17% of patients with epilepsy that will suffer from a major depressive episode. This is lower than the 30-50% prevalence rates suggested in the literature.

Jones et al. (2005a;b) did not report on the current suicide risk for participants. This study observed that 9% (7/76) of participants who completed the MINI met criteria for low, current suicide risk. The treating physician was notified of the low suicide risk for each of the seven participants. No suicide attempts or completions occurred during this study. Barry and Jones (2005) reported on a sample of patients with epilepsy who demonstrated a rate of suicidal ideation as high as 12.2% and Boylan et al. (2004) found that 19% of 122 patients with refractory epilepsy being admitted to an inpatient video-EEG monitoring unit reported suicidal thoughts. The literature on patients with epilepsy and suicide is

limited. Suicidal ideation, attempts, and completions in patients with epilepsy require further study to better define the prevalence and risks for this patient population.

When comparing Axis I disorders as defined by the MINI from this study and the Jones et al. (2005) results, there were only two statistical differences e.g. current prevalence rates of anxiety disorders due to different prevalence rates found in GAD, and current prevalence rates of comorbid Axis I disorders. However, the Bonferroni procedure demonstrated that the difference between prevalence rates in GAD and comorbid Axis I disorders were not statistically significant when examined conservatively. The rates of mood disorders (major depressive episode, dysthymia, manic episode, and hypomanic episode) were not significantly different than the rates observed in Jones et al. (2005). There were no significant differences in the rates of panic disorder, agoraphobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, or psychotic disorders. This supports the current mood and anxiety prevalence rate findings reported in Jones et al. (2005).

There was a significant difference in the rate of anxiety disorders found in the current study (25%) and Jones et al. (2005). This study found only 25% of participants with anxiety disorders, and Jones et al. [(2005) 52%]. A non-systematic review of the literature indicates current anxiety disorders occurred in 10-25% of people with epilepsy living in the community (Fiordelli, Beghi,

Bogliun, and Crespi, 1993) and the rates of 7-27% of hospital patients with epilepsy (Trimble and Sander, 2004). Though they do not concur with the rates determined by Jones et al. (2005), findings on the prevalence of anxiety disorders from the current study are within the range reported in the literature. When examining the data for the source of difference in the rate of anxiety disorders reported in Jones et al. (2005), it was found that the rates of GAD varied in each study. Jones et al. (2005) reported 13.2% of participants with GAD as compared to only 3.9% of participants identified with GAD in this study. This was the sole statistically significant difference found in the current prevalence rates of an Axis I disorder between studies. However, the Bonferroni procedure was used to control for potential misleading *p*-values because there were 16 tests performed for statistical significance. Based on the Bonferroni procedure a *p*-value of $> .003$ would not be statistically significant.

Anxiety disorders were found to be more common than mood disorders and to also have a significant effect on patients' QOL. Within anxiety disorders, both studies indicated that agoraphobia was the most commonly-identified disorder. This study found that 10.5% of participants met the MINI criteria for agoraphobia compared to 15.5% met criteria in Jones et al. (2005).

Much of the literature has focused on rates of mood disorders, specifically major depressive episode and dysthymia amongst this population. It is important to note that only recently has attention been turned toward comorbid anxiety

disorders in this (Cramer, Brandenburg et al., 2005, Jones et al., 2005a;b; and Johnson et al., 2004). Both the current study and Jones et al. (2005) found that anxiety disorders were the most commonly identified Axis I disorders. These findings present an opportunity for further exploration. More research is necessary to develop effective treatments that are aimed at treating comorbid anxiety.

Another statistically significant difference was observed when examining the comorbidity of Axis I disorders between studies. Jones et al. (2005) reported that 33.9% of their participants had comorbid Axis I disorders and this study found 21.05% of participants with comorbid Axis I disorders. The difference in comorbid Axis I disorders was significant at the $p < .05$ level. Again, based on the Bonferroni procedure a p-value of $> .003$ would not be statistically significant. Despite the differences in sample size and number of sites, the current findings were similar to Jones et al. (2005).

When looking at current mood disorders, the prevalence rate based on both studies appears to be between 16% and 24%. Within the category of mood disorders, dysthymia, manic episode, and hypomanic episode all had relatively low prevalence rates (1.3% to 4%) and there were no significant differences found between studies.

The literature contains inconsistent reports of prevalence rates when assessing for bipolar disorder. Hilty et al. (2000) and Robertson (1992) have

suggested the prevalence rate of bipolar disorder in epilepsy patients is between 0.1% and 4.3%. A review of the literature conducted by Kanner (2003) reported that 9.8% of patients reported symptoms of bipolar disorder. Additionally, Barry (2003) reported that 8.1% of patients with epilepsy met criteria for bipolar spectrum disorder as defined by the MDQ. This study assessed for bipolar disorder symptoms in a tertiary care population which possibly explains some of the difference with Kanner's review of literature; however, the 1.3% rate of bipolar disorder symptoms found in this study is more consistent with Hilty et al. (2000) and Robertson's (1992) findings. The fluctuations in the literature highlight the importance and need for replication studies using similar methodology to clarify current prevalence rates.

The literature estimated that the prevalence of lifetime psychiatric comorbidity in patients with epilepsy was 20-50% (Blumer, 2002; Trimble and Saunders, 2004). Another study found that comorbidity of psychiatric disorders in this population ranged from 19-48% (Trimble & Saunder, 2004). The current study found that 32% of participants had a comorbid Axis I psychiatric disorder.

Based on this study and Jones et al. (2005), physicians treating patients with epilepsy in tertiary care settings should expect that approximately 16-24% of their patients to have a comorbid mood disorder. An even higher percentage of patients are likely to suffer from an anxiety disorder. This patient population is particularly at risk for agoraphobia. The social limitations associated with

epilepsy could be a contributing factor. It is possible that the rates of agoraphobia reported in both studies are related to the social stigma and/or social limitations (e.g., driving) reported in the literature. Future research is needed to identify the contributing factors. Additionally, treatment studies are required to explore whether both medication and empirically based talk therapy could offer effective treatment options.

The epilepsy literature has consistently reported a lack of gender difference in the prevalence rates of depression (Grabowska-Grzyb et al., 2006). This study supports those findings. There was no gender difference found in the rates of mood or anxiety disorders or in participants' QOL.

In 2005, Kessler et al. classified cases of MDD over 12 months in the general population using the QIDS-SR16 and found that 10.4% of cases were mild, 38.6% moderate, 38.0% severe, and 12.9% very severe. This study's sample size was too small to stratify cases of major depressive episode by severity; however, there was an interesting finding based on severity. When participants scores on the BDI-II and QIDS-SR16 increased; an indication of symptom severity, their QOL scores decreased significantly ($p<.0001$). The result indicated the importance of gauging the severity of the disorder since severity of the disorder as reflected in participants' self-reports could facilitate effective treatment.

Participants were divided into five groups based on meeting criteria for major depressive episode plus 14.5% (11/76), mood disorder 15.8% (12/76), anxiety disorder 25.0% (19/76), mood and anxiety disorder 10.5% (8/76), and Axis I disorder 31.6% (24/76) as defined by the MINI. Each of the five groups were compared to the remaining participants and there were no differences found to be associated with seizure variables (age of epilepsy onset, number of seizures within the last 3 months, type of epilepsy, or seizure within the last year) , gender, or age (see Tables 3, 3.2, 3.3, 4, 4.1, 4.2, 4.3, and 4.4). These findings replicate the many studies that have found no consistent relationship between depression and seizure frequency, seizure type, or seizure etiology (Attarian, et al., 2003; Cramer et al., 2003; Mendez et al., 1986).

The literature has shown that psychiatric conditions are associated with a particularly poor QOL (Spencer and Hunt, 1996). This investigation measured the impact of different psychiatric disorders as defined by the MINI on QOL. The five groups were used to determine if there were any differences in QOL. Participants in the five groups had significantly lower QOL scores on the QOLIE-31 when compared to the remaining participants. Reports in the literature have repeatedly indicated that depression and/or comorbid anxiety symptoms accounted for more of the variance in QOL measures compared to other epilepsy-related factors such as seizure frequency (Kanner, Wuu, Barry, Herman, Meador and Gilliam, 2004; Jones et al. 2005a;b; and Hopp et al., 2006). This study

confirms and extends these findings. The mood disorder group, mood and anxiety disorder group, and mde-plus group had the most severe impact in QOL when compared to the Axis I group and the anxiety group (see Table 5). Many studies that examined the QOL in depressed epilepsy patients have reported that depression alone caused the greatest decrease in QOL, over any seizure variable (i.e., seizure severity, duration or frequency). The current results confirm these findings as well. The mde plus group score the lowest on the QOL surveys (see Table 5). Despite anxiety disorders occurring at higher rates participants did report higher QOL when only suffering from an anxiety disorder.

There were two notable seizure variables that were associated with decreases in QOL scores. Participants that reported having a seizure within the last year had a significantly lower QOL as reported on the QOLIE-31 (see Table 5.1). By comparison, the mean QOL scores remained lowest in the mde plus, mood, and mood and anxiety groups. Also the more seizures a participant experienced in the last three months the lower their overall reported QOL. As reported previously, the age of epilepsy onset or type of epilepsy did not significantly affect QOL. Past research has demonstrated that the number of seizures in the past year, duration of epilepsy, seizure frequency, or seizure severity did not account for the variance in QOL as did depression and/or comorbid anxiety symptoms (Kanner, Wuu et al., 2004; Jones et al., 2005a;b; Hopp et al., 2006). The current study introduced two additional variables; seizures

within the last year and the number of seizures experienced within the last three months that did account for variance in QOL. This suggestive of a negative effect on QOL related to seizures. Further examination of this relationship of seizures experienced within the last three months and the effects on QOL as measured by the QOLIE-31 is needed to determine whether this seizure variable is consistently found to contribute negatively to QOL.

Receiver operating characteristic statistics were used to clarify the thresholds in screening tools of major depressive episode, dysthymia, and anxiety disorders (see Tables 7, 7.1, 7.2, 7.3). The QIDS-SR16 was examined for sensitivity and specificity in screening for major depressive episode as defined by the MINI. The QIDS-SR16 was found to be less sensitive than the QIDS-CR16 and the BDI-II. The QIDS-SR16 was less likely to detect a participant experiencing a major depressive episode when compared to the sensitivity of using both the QIDS-CR16 and BDI-II. The QIDS-SR16 accurately identified participants with a major depressive episode 50% of the time. Within a small sample 50% is no better than chance.

The QIDS-SR16 was comparable to the use of QIDS-CR16 and the BDI-II when examining specificity or the probability of not identifying a participant with major depressive episode that actually did not have a major depressive episode. The QIDS-SR16 demonstrated a 95% rate of specificity. The QIDS-SR16 had a cutoff score of 14. The results indicated that participants with a QIDS-SR16 score

> 14 should be assessed further for diagnostic assessment. Identifying the QIDS-SR16 cutoff score in this population would assist treating physicians to screen patients and help them to focus only on those likely to be suffering from a major depressive episode.

The BDI-II was also examined for sensitivity and specificity in screening for major depressive episode as defined by the MINI. The BDI-II was found to be both sensitive and specific when assessing for major depressive episode. The BDI-II correctly identified participants with a major depressive episode 88% of the time and correctly ruled out patients without a major depressive episode 86% of the time. The cut off score for the BDI-II was defined as > 14. Participants that score over 14 on the BDI-II require diagnostic clarification and are likely to suffer from a depressive disorder. The cut off score of > 14 coincides with the BDI-II literature that defines a score of > 14 as mild depression. Additionally, Jones et al. (2005) reported a cutoff score for major depressive episode based on the MINI of > 11 and for the SCID as > 15. Based on a review of the literature, one study suggested a score of > 16 on the BDI-II to identify depression and/or depressive episodes (Attarian et al., 2003). The findings of the current study are more conservative but fall closely in line with the literature and assist in clarifying the cutoff score on the BDI-II. Further investigation for diagnostic clarification is necessary.

Additionally, the QIDS-CR16 was examined for sensitivity and specificity in detecting major depressive episode as defined by the MINI. It is important to note that the QIDS-CR16 and the MINI were administered by the same evaluator, and neither is a self-report measure. This may contribute to the higher sensitivity found with the QIDS-CR16. The QIDS-CR16 was found to correctly identify participants with a major depressive episode 100% of the time and correctly rule out participants without major depressive episode 85% of the time. The cut off score for the QIDS-CR16 was determined to be > 7. The score of > 7 fits the QIDS-CR16 scoring literature that defines a score > 6 as mild depression.

The QIDS-SR16, BDI-II, and the QIDS-CR16 were also examined for sensitivity and specificity in detecting participants with dysthymia as defined by the MINI. All three instruments demonstrated excellent sensitivity at 100% and all three had good specificity at 82%, 96%, and 92% respectively. The QIDS-SR16 cutoff was 11 and the QIDS-CR16 cutoff was 12. A QIDS-SR16 and QIDS-CR16 score > 11 indicates moderate depression. The BDI-II was similar in that the cutoff was 27, and a score of 20 to 28 on the BDI-II is considered to be indicative of moderate depression. Interestingly, dysthymia cutoffs all fell within the moderate levels of depression as defined by each instrument.

The QIDS-SR16, BDI-II, and the QIDS-CR16 were further assessed for sensitivity and specificity in screening for anxiety disorders as defined by the MINI. All three instruments demonstrated similar psychometric properties. Each

instrument had high rates of specificity with 89%, 92%, and 96% respectively and all three demonstrated modest results for sensitivity: 52%, 47%, and 36%, respectively. It should be noted that these instruments were not designed to screen for anxiety disorders and may have contributed to the lower sensitivities found. However, the cutoffs were > 10 for the QIDS-SR16, > 18 for the BDI-II, and >11 for the QIDS-CR16.

Cutoff points would be useful to the treating physicians screening for anxiety disorders and/or mood disorders. The ranges for identifying patients with potential mood and/or anxiety disorders were 11 to 14 for the QIDS-SR16 and 11 to 27 for the BDI-II. If physicians were to use the QIDS-SR16 or the BDI-II for screening purposes based on this study, any patient that scored above 11 on the QIDS-SR16 or above 11 on the BDI-II would require further diagnostic clarification. The cut off of > 11 on the BDI-II is consistent with the score identified in Jones et al. (2005) for major depression based on the MINI and the SCID. These efficient screening instruments could provide a useful tool in busy practices and help reduce the number of untreated mood and/or anxiety disorders prevalent in this population.

The findings of this study demonstrate that the QIDS-SR16, QIDS-CR, and BDI-II are screening instruments that are practical and efficient when followed up by further clinical inquiry for diagnostic clarification. These instruments, particularly the QIDS-SR16 and BDI-II offer valid and reliable

screening tools for busy practitioners to identify patients that require additional attention to assess and potentially treat comorbid mood and anxiety disorders; hence, improving their QOL.

The MDQ was assessed for sensitivity and specificity in identifying participants with bipolar disorder symptoms. The MDQ, based on the literature, appears to over estimates bipolar disorder symptoms (Ettinger et al., 2005). The rates of bipolar disorder suggested when the MDQ was used were as high as 12.2% in patients with epilepsy (Ettinger et al., 2005). The results contradict the prevalence rate of bipolar disorder as defined by the MINI reported in Jones et al. (2005) and the current study, rates of 2.8% and 1.3% were indicated, respectively.

This study indicates that the MDQ overestimates and appears to lack validity in identifying patients with bipolar disorder symptoms. The results from the current study must be interpreted with caution due to the small number of patients identified by the MINI as having bipolar disorder symptoms; however, when examined, the MDQ demonstrated 14% sensitivity and 97% specificity. The MINI identified three participants as having bipolar symptoms and the MDQ only identified one of these participants. Furthermore, the MDQ identified five participants as having bipolar disorder symptoms that were not identified by the MINI. The results from this study do not support the use of the MDQ as an accurate screening tool for bipolar disorders in patients with epilepsy being screened in tertiary care centers.

The recognition and treatment of mood and anxiety disorders in patients with epilepsy remains unacceptably low or inadequate (Goldstein, McAlpine, Deale, Toone, & Mellers, 2003; Kong, Au, Chan, Li, Leung, Li, and Chan, 2003; and Kanner and Barry, 2003). Studies estimate that between 50% and 68% of patients with epilepsy suffering from depression are never treated (Wiegartz et al., 1999; and Gaitatzis, Trimble, & Sander, 2004). The actual treatment of epilepsy-associated mood and anxiety disorders remains under-explored despite the prevalence and seriousness of its occurrence (Davis, Armstrong, Donovan, & Temkin, 1984; Mendez et al., 1986; Wiegartz et al., 1999; Gaitatzis et al., 2002; Kanner, 2003; and Trimble and Sander, 2004).

This study found that participants in the five groups were more likely to be currently taking an antidepressant than those participants not within one of the five groups. However, consistent with the literature, only 50% (5/10) of participants within the mde plus group were being treated with an antidepressant. The numbers of participants in the mde plus group was small, but the results fall directly in line with the literature. Of the remaining participants not classified in the mde plus group, 12.50% (8/64) were being treated with an antidepressant. It is possible that the 8/64 participants were being successfully treated with an antidepressant for a mood and/or anxiety disorder; however, further research is required to make such a determination.

Within the anxiety group only 36.84% (7/19) of participants were being treated with an antidepressant. Of the remaining participants not classified in the anxiety group 10.91% (6/65) were being treated by an antidepressant. In the mood group only 54.55% (6/11) participants were being treated with an antidepressant and of the remaining participants not classified in the mood group 11.11% (7/63) were taking an antidepressant.

Overall, within the Axis I group only 39.13% (9/23) of participants were being treated with an antidepressant and of the remaining participants not classified in the Axis I group 7.84% (4/51) were being treated with an antidepressant.

These antidepressant treatment results replicate previous findings and continue to highlight the need for proper screening and treatment of mood and anxiety disorders in patients with epilepsy. It has been speculated in the literature that fears of antidepressants lowering seizure thresholds coupled with potential pharmacokinetic interactions between anticonvulsant and antidepressant medications have strongly contributed to the undertreatment of this population. Finally, the treatment of depressive disorders in epilepsy is understudied, and the few existing research studies have yet to display an effective treatment. Based on the literature and the results of this study, the treatment of mood and anxiety disorders requires focused attention by physicians in addition to epilepsy or as a part of the epilepsy disease process.

This study also examined the treatment of participants by talk therapy or counseling services. When evaluating whether or not participants were engaged in any type of talk therapy or counseling service a significant difference was found between participants in the five groups and the remaining participants. Of the participants meeting criteria for the Axis I group, 18% (4/23) were currently receiving some type of talk therapy or counseling service. Within the mde plus group 30% (3/10) were receiving talk therapy or counseling services and 27% (3/11) within the mood group. Amongst the anxiety disorder group 21% (4/19) were receiving talk therapy or counseling services and 37.5% (3/8) in the mood and anxiety group. The remaining participants that were receiving talk therapy or counseling services ranged between 2-3%. Based on these limited results talk therapy and counseling services seem underutilized in the treatment of mood and/or anxiety disorders. These therapies offer an additional option for treatment that have proven effectiveness and have the added benefit of not introducing additional medications into the treatment regime (Shea et al., 1992).

Limitations

The sample size of this study was relatively small, not ethnically diverse, and participants were obtained from only one tertiary care center and 12 participants that did not complete the study; therefore, any results or conclusions

are made with caution. Despite the small sample size, the findings of this study are well supported in the literature and overall closely replicate the findings of Jones et al. (2005). Extrapolation of these findings is limited outside of the Neurological Clinic of Texas - TEG patient population.

Due to the small number of participants within each of the disorder groups, major depressive episode, dysthymia, and anxiety disorders, the results of the ROC analyses are less robust and must be interpreted with that in mind. Additionally, 74 participants made up the data available for diagnostic efficiency analysis for the QIDS-SR16 and the MDQ which was two less participants than used in the QIDS-CR16 analysis. Finally, despite the strong correlation reported in the literature between the SCID and the MINI, the MINI was not designed to diagnose psychiatric disorders based on DSM-IV criteria.

The QOLIE-31 measures symptoms of depression similar to those measured by the QIDS-SR16, QIDS-CR16, and the BDI-II. As a result, the relationships observed in this study between lower QOL scores and higher scores on the QIDS-SR, QIDS-CR16, and the BDI-II may not be reflective of independent measurements and may actually reflect the overlapping depression symptoms measured in all four instruments. Future research examining the distinction between the QOLIE-31 and the QIDS-SR16, QIDS-CR16, and the BDI-II would be helpful in distinguishing between the overlap of depression symptoms measured in both the QOL instrument and the depression screening

tools.

It is possible that there were participants that did not meet criteria for an Axis I disorder but suffered from an atypical dysthymic disorder – a possibility discussed in the literature. This study did not screen for atypical dysthymic symptoms; therefore, these participants would remain unidentified. Kanner (2003) reported in the literature that a significant proportion of epilepsy patients suffer from atypical dysthymic disorder, but do not meet any of the DSM-IV criteria for major depression, bipolar disorder, or dysthymic disorder; therefore, it is possible that some participants may have not met the MINI criteria for an Axis I disorder but suffered from an atypical type of mood disorder.

There were different methodologies used in Jones et al. (2005) and this study that may have influenced the results. In this study, participants were first administered the QIDS-SR16, BDI-II, MDQ, and the QOLIE-31 during an office visit and subsequently contacted by telephone within three days. During the phone interview, participants were administered the MINI and the QIDS-CR16. Jones et al. (2005) administered the MINI in person and then allowed participants to complete the BDI-II during the same office visit. This variation of methodology may limit the replication results reported in this study.

It is possible that treating physicians at the study site were more aware of mood and anxiety disorders in their patients and treated mood and anxiety disorders more frequently. Their participation in this research has likely made

them more aware, if they were not already. If so, the results of this study could be an overestimate of the treatment of mood and anxiety disorders in other tertiary care centers.

Conclusions

Overall, this study replicated the prevalence rates of current Axis I disorders found in tertiary care epilepsy centers as reported in Jones et al. (2005). Based on this study and Jones et al. (2005) physicians treating patients with epilepsy in tertiary care settings would expect that approximately 16-24% of their patients to experience a comorbid mood disorder.

Psychiatric conditions are associated with a particularly poor quality of life in patients with epilepsy. Increased attention to the presence of psychiatric conditions in patients with epilepsy is important to patient QOL. The screening and diagnosis of these conditions is integral to assisting in the improvement of QOL for patients suffering from mood and/or anxiety disorders.

In particular, the mood disorder group, mood and anxiety disorder group, and mood disorder plus group in this study experienced a greater negative impact on QOL when compared to the Axis I group and the anxiety alone group. Anxiety disorders were found to be more common than mood disorders and also had a

significant negative effect on patients' QOL. This patient population is particularly at risk for agoraphobia.

The current study introduced two different seizure variables, seizures within the last year and the number of seizures experienced within the last three months that accounted for variance in QOL. These results demonstrated a significant difference between participants that reported a seizure within the last year and those who did not, as well as those who reported the number of seizures experienced within the last three months, both had a negative impact on QOL.

This study observed that 9% (7/76) of participants who completed the MINI met criteria for low, current suicide risk. The literature on patients with epilepsy and suicide is limited. Suicidal ideation, attempts, and completions in patients with epilepsy require further study to better define the prevalence and risks for this patient population.

The QIDS-SR16, QIDS-C16, and BDI-II appeared to be useful in the screening of mood and anxiety disorders in patients with epilepsy. Implementation of screening programs that include self reports are effective at assisting in the clinical identification of patients with mood and/or anxiety disorders so that treatment can be initiated.

The MDQ has not been shown to be a valid or reliable screening tool for bipolar disorder symptoms in patients with epilepsy being treated at tertiary care centers. Research to investigate effective alternatives to the MDQ is warranted.

TABLES

Table 3 Comorbid Groups (*n* = 76) Based on MINI	
Mood Disorders	12 (15.79%)
Anxiety Disorders	19 (25.00%)
Mood and Anxiety Disorders	8 (10.53%)
MDE Plus	11 (14.47%)
Axis I Disorder	24 (31.58%)

Table 3.2 Gender Comparison (*n* = 74)	women sample	women group	men sample	men group	*df*	X^2	*p*
MDE Plus Group	46/64 (71.88%)	5/10 (50.00%)	18/64 (28.13%)	5/10 (50.00%)	1	1.9320	0.1645
Mood Group	45/63 (71.43%)	6/11 (54.55%)	18/63 (28.57%)	5/11 (45.45%)	1	1.2462	0.2643
Anxiety Group	38/55 (69.09%)	13/19 (68.42%)	17/55 (30.91%)	6//19 (31.58%)	1	0.0030	0.9566
Mood and Anxiety Group	45/66 (68.18%)	6/8 (75.00%)	21/66 (31.82%)	2/8 (25.00%)	1	0.1548	0.6939
Axis I Group	38/51 (74.51%)	13/23 (56.52%)	13/51 (25.49%)	10/23 (43.48%)	1	2.3944	0.1218

Table 3.3 Age (years) Comparison (*n* = 74)	age sample (*SD*)	age group (*SD*)	*df*	*t* value	*p*
MDE Plus Group	39.016 (14.647)	42.9 (13.228)	72	-0.79	0.4327
Mood Group	38.921 (14.744)	43.091 (12.565)	72	-0.88	0.3805
Anxiety Group	39.909 (15.22)	38.474 (9.2247)	72	0.37	0.7115
Mood and Anxiety Group	39.227 (14.577)	42.125 (13.882)	72	-0.53	0.5954
Axis I Group	39.98 (15.342)	38.565 (12.468)	72	0.39	0.6992

Table 4 Seizure Variables Comparison Sample (*n* = 72)	age of epilepsy onset (*SD*) Sample	age of epilepsy onset (*SD*) Group	*df*	*t* value	*p*
MDE plus group (*n* = 10/72)	21.86 (15.16 *SD*) 62/72 (86.10%)	16.60 (12.65 *SD*) 10/72 (13.90%)	70	1.04	0.3029
Mood group (*n* = 11/72)	22.13 (15.12 *SD*) 61/72 (84.70%)	15.54 (12.50 *SD*) 11/72 (15.30%)	70	1.36	0.1781
Anxiety group (*n* = 19/72)	22.63 (16.21 *SD*) 53/72 (73.60%)	16.95 (9.38 *SD*) 19/72 26.40%)	70	1.44	0.1548
Mood and anxiety group (*n* = 8/72)	26.08 (15.22 *SD*) 64/72 (88.90%)	17.64 (6.90 *SD*) 8/72 (11.10%)	70	1.90	0.0615
Axis I group (*n* = 23/72)	22.61 (16.29 *SD*) 49/72 (68.10%)	17.96 (10.89 *SD*) 23/72 (31.90%)	70	1.24	0.2177

Table 4.1 Seizure Variables Comparison Sample (*n* = 54)	Seizures Within the Last 3 Months Sample	Seizures Within the Last 3 Months Group	*df*	*t* value	*p*
MDE Plus Group (*n* = 9/54)	5.689 (12.87*SD*) 45/54 (83.30%)	11.67 (16.96 *SD*) 9/54 (16.70%)	52	-1.21	0.2333
Mood Group (*n* = 10/54)	5.00 (12.15 *SD*) 44/54 (81.50%)	14.10 (17.74 *SD*) 10/54 (18.5%)	52	-1.96	0.0559
Anxiety Group (*n* = 14/54)	5.68 (12.90 *SD*) 40/54 (74.10%)	9.57 (15.70 *SD*) 14/54 (25.90%)	52	-0.92	0.3623
Mood and Anxiety Group (*n* = 8/54)	8.83 (12.09 *SD*) 46/54 (85.20%)	15.00 (19.35 *SD*) 8/54 (14.80%)	52	-1.92	0.0609
Axis I Group (*n* = 17/54)	5.568 (13.156 *SD*) 37/54 (68.50%)	9.118 (14.735 *SD*) 17/54 (31.50%)	52	-0.89	0.3792

Table 4.2 Seizure Variables Comparison (*n* = 55)	seizure type					*df*	χ^2	*p*
	simple partial	complex partial	secondarily generalized motor	absence	generalized motor			
MDE plus group (N = 8/55) (14.55%)	1/8 (12.50%)	5/8 (62.50%)	1/8 (12.50%)	0/8 (0.00%)	1/8 (12.50%)	4	0.5105	0.9725
mood group (*n* = 9/55) (16.36%)	2/9 (22.22%)	5/9 (55.56%)	1/9 (11.11%)	0/9 (0.00%)	1/9 (11.11%)	4	1.8585	0.7618
anxiety group (*n* = 16/55) (29.09%)	4/16 (25.00%)	7/16 (43.75%)	2/16 (12.50%)	0/16 (0.00%)	3/16 (18.75%)	4	5.6437	0.2274
mood and anxiety group (*n* = 6/55) (10.91%)	1/6 (16.67%)	3/6 (50.00%)	1/6 (16.67%)	0/6 (0.00%)	1/6 (16.67%)	4	0.5804	0.9652
Axis I group (*n* = 20/55) (36.36%)	5/20 (25.00%)	9/20 (45.00%)	2/20 (10.00%)	0/20 (0.00%)	4/20 (20.00%)	4	8.0208	0.0908

Table 4.3 Seizure Within Last Year Comparison (*n* = 73)	Sample	Group	*df*	χ^2	*p*
	Seizure Within Last Year	Seizure Within Last Year			
MDE plus group (*n* = 10/73) (13.70%)	35/63 (55.56%)	8/10 (80.00%)	1	2.1303	0.1444
Mood Group (*n* =11/73) (15.07%)	34/73 (54.84%)	9/11 (81.82%)	1	2.8092	0.0937
Anxiety Group (*n* = 19/73) (26.03%)	31/54 (57.41%)	12/19 (63.16%)	1	0.1920	0.6613
Mood and Anxiety Group (*n* = 8/73) (10.96%)	36/65 (55.38%)	7/8 (87.50%)	1	3.0350	0.0810
Axis I Group (*n* = 23/73) (31.51%)	28/73 (56.00%)	15/23 (65.22%)	1	0.5529	0.4571

Table 5 Group and QOL Comparison (*n* = 74)	Group Mean (*SD*)	Sample Mean (*SD*)	*df*	*t* value
MDE Plus Group	38.60 (9.5126)	72.58 (13.742)	72	7.52**
Mood Group	40.00 (10.149)	72.87 (13.647)	72	7.61**
Anxiety Disorder Group	57.00 (19.284)	71.78 (15.466)	72	3.37*
Mood and Anxiety Disorder Group	39.00 (11.551)	71.50 (14.794)	72	5.98**
Axis I Disorder	56.04 (18.826)	73.37 (14.241)	72	4.37**

Note: Quality of Life based on the QOLIE-31, higher scores reflect a more favorable quality of life.
** $p < .0001$. * $p < .001$

Table 6 Treatment Comparison (*n* = 74)	Sample	Group	*df*	χ^2
Treatment	Mono Antidepressant	Mono Antidepressant		
MDE plus group (*n* = 10/74) (13.51%)	8/64 (12.50%)	5/10 (50.00%)	1	8.3985*
Mood Group (*n* =11/74) (14.86%)	7/63 (11.11%)	6/11 (54.55%)	1	12.2000**
Anxiety Group (*n* = 19/74) (25.68%)	6/55 (10.91%)	7/19 (36.84%)	1	6.5581*
Mood and Anxiety Group (*n* = 8/74) (10.81%)	9/66 (13.64%)	4/8 (50.00%)	1	6.5152*
Axis I Group (*n* = 23/74) (31.08%)	4/51 (7.84%)	9/23 (39.13%)	1	10.715*

Note: *$p < .01$. **$p < .001$

Table 6.1 Therapy Treatment Comparison (*n* = 74)	Sample	Group	*df*	χ^2	*p*
	Therapy	Therapy			
MDE Plus Group (*n* = 10/74) (13.51%)	2/64 (3.13%)	3/10 (30.00%)	1	9.9149*	0.0016
Mood Group (*n* = 11/74) (14.86%)	2/63 (3.17%)	3/11 (27.27%)	1	8.6320*	0.0033
Anxiety Group (*n* = 19/74) (25.68%)	1/54 (1.82%)	4/19 (21.05%)	1	8.2926*	0.0040
Mood and Anxiety Group (*n* = 8/74) (10.81%)	2/66 (2.70%)	3/8 (37.50%)	1	13.4562**	0.0002
Axis I Group (*n* = 23/74) (31.08%)	1/51 (1.96%)	4/23 (17.39%)	1	5.9906*	0.0144

Note: *$p < .01$. **$p < .001$

Table 7. ROC and Diagnostic Efficiency Statistics for MINI Identified Major Depressive Episode	True positive	True negative	False negative	False positive	Percent Correct	Sensitivity	Specificity	PPV	NPV	Cut score
Measure										
QIDS-SR (n = 74)	4	63	4	3	0.90541	0.500	0.95455	0.5714	0.9403	14
BDI-II (n = 74)	7	57	1	9	0.86486	0.875	0.86364	0.4375	0.9828	13
QIDS-CR (n = 76)	8	58	0	10	0.86842	1.00	0.85294	0.4444	1.0000	7

Note: QIDS-SR, Quick Inventory of Depressive Symptomatology (Self-Rated); BDI-II, Beck Depression Inventory-II; QIDS-CR, Quick Inventory of Depressive Symptomatology (Clinician-Rated); PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 7.1. ROC and Diagnostic Efficiency Statistics for MINI Identified Dysthymia	True positive	True negative	False positive	False negative	Percent Correct	Sensitivity	Specificity	PPV	NPV	Cut score
Measure										
QIDS-SR (n = 74)	1	60	0	13	0.82432	1.00	0.82192	0.07142	1.00	11
BDI-II (n = 74)	1	70	0	3	0.95946	1.00	0.95890	0.2500	1.00	27
QIDS-CR (n = 76)	1	69	0	6	0.92105	1.00	0.92000	0.1429	1.00	12

Note: QIDS-SR, Quick Inventory of Depressive Symptomatology (Self-Rated); BDI-II, Beck Depression Inventory-II; QIDS-CR, Quick Inventory of Depressive Symptomatology (Clinician-Rated); PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 7.2. ROC and Diagnostic Efficiency Statistics for MINI Identified Anxiety Disorder	True positive	True negative	False positive	False negative	Percent Correct	Sensitivity	Specificity	PPV	NPV	Cut score
Measure										
QIDS-SR (n = 74)	10	49	9	6	0.79730	0.52632	0.89091	0.6250	0.8448	10
BDI-II (n = 74)	9	51	10	4	0.81081	0.47368	0.92727	0.6923	0.8361	18
QIDS-CR (n = 76)	7	55	12	2	0.81579	0.36842	0.96491	0.7778	0.8209	11

Note: QIDS-SR, Quick Inventory of Depressive Symptomatology (Self-Rated); BDI-II, Beck Depression Inventory-II; QIDS-CR, Quick Inventory of Depressive Symptomatology (Clinician-Rated); PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 7.3. Diagnostic Efficiency Statistics for MINI Identified Bipolar Disorder (*n*= 74)	True Positive	False Positive	True Negative	False Negative	Percent Correct	Sensitivity	Specificity	PPV	NPV
Measure									
MDQ	1	2	65	6	0.89189	0.14286	0.97015	0.3333	0.9155

Note: MDQ, Mood Disorders Questionnaire; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 7.4. Diagnostic Efficiency Statistics for MINI Identified Hypomanic Episode (*n* = 74)	True Positive	False Positive	True Negative	False Negative	Percent Correct	Sensitivity	Specificity	PPV	NPV
Measure									
MDQ	1	1	66	6	0.90541	.14286	0.98507	0.5	0.9167

Note: MDQ, Mood Disorders Questionnaire; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 7.5. Diagnostic Efficiency Statistics for MINI Identified Manic Episode (*n* = 74)	True Positive	False Positive	True Negative	False Negative	Percent Correct	Sensitivity	Specificity	PPV	NPV
Measure									
MDQ	0	1	66	7	0.89189	0	0.98507	0	0.9041

Note: MDQ, Mood Disorders Questionnaire; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

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VITAE

Albert Stephen Banta Jr. was born in Port Sulphur, Louisiana, on February 18, 1969, the son of Lynda Gomez Banta and Albert Stephen Banta. In 1987, he entered Louisiana State University (LSU) in Baton Rouge, Louisiana after completing his work at Buras High School located in Buras, Louisiana. When he completed his prerequisite courses at LSU in 1989, he transferred to Louisiana State University Medical Center in New Orleans. In 1992, he earned the degree of Bachelor of Science in Nursing. During the following three years, he was employed as an intensive care nurse at Doctors Hospital and Baylor Hospital in Dallas, Texas. In September of 1995 he moved to The Netherlands, where he was employed as a Business Development Manager at Excerpta Medica, a division of Elsevier Science. In 2001, he moved to New York City and earned a Post-baccalaureate Certificate in Psychology from Columbia University. While studying at Columbia University, he was employed as a research assistant at the New York State Psychiatric Institute. In August 2003 he entered the Graduate School of Biomedical Sciences at the University of Texas Southwestern Medical Center at Dallas.

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