

**DEPRESSION, DISEASE KNOWLEDGE, AND EPILEPSY:
MEASURING THE IMPACT ON ADHERENCE**

By

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To all those who have taught me what it means to be ill, and what it means to become well. To my mother and father. To my partners in crime, Calvin, Wei, and Chris, you are always there for me.

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LIST OF ABBREVIATIONS

AED	Anti-epileptic drug
AES	Apathy Evaluation Scale
AUC	Area under the curve
BMQ	Beliefs About Medicine Questionnaire
CBT	Cognitive-behavioral therapy
CES-D	Center for Epidemiological Studies Scale for Depression
EKS	Epilepsy Knowledge Scale
EPKQ	Epilepsy Patient Knowledge Questionnaire
FSIQ	Full scale intelligence quotient
GABA	Gamma-aminobutyric acid
HAART	Highly active anti-retroviral therapy
IPQ	Illness Perception Questionnaire
MDD	Major depressive disorder
MDE	Major depressive episode
MHLC	Multidimensional Health Locus of Control Questionnaire
MINI	Mini International Neuropsychiatric Interview
MPR	Medication possession ratio
RAM	Retrospective adherence measurement
RAVLT	Rey Auditory Verbal Learning Test
ROC	Receiver operating characteristic
SD	Standard Deviation
SEK	Standard error of kurtosis
SES	Standard error of skewness
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition

WAIS-R

Wechsler Adult Intelligence Scale – Revised

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DEPRESSION, DISEASE KNOWLEDGE, AND EPILEPSY:
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Adherence to medication is crucial to the success of treatment for chronic illness.

Research investigating adherence behaviors in individuals with chronic illnesses has identified comorbid depression as a major factor decreasing the likelihood of adherence. While this research has shown that depressed individuals are less likely to adhere successfully to their medication regimens, the mechanisms for this effect remain unclear. Research has also examined a limited set of factors predicting adherence behaviors for people with epilepsy, a chronic illness in which depression is a known, common comorbidity, but has not evaluated the relationship between depression and adherence in people with epilepsy. The present study proposes several candidate mechanisms through which depression may affect complex healthcare behaviors such as medication adherence: difficulty acquiring and using disease knowledge, increased perception of illness severity, difficulty maintaining positive attitudes towards medical care, lack of an internal locus of control with respect to achieving healthcare outcomes, and lack of general motivation to engage in complex behaviors.

The effects of depression and the possible roles of these mechanisms on adherence were investigated in a sample of 56 participants recruited from outpatient epilepsy clinics. Surprisingly, no association between depression and adherence was found. Using several

different self-report measures of adherence, different healthcare behaviors as well as other variables were found to predict adherence, with Caucasian race and epilepsy knowledge predicting one measure of adherence, a Chance locus of control predicting a second measure of adherence, and total learning on the Rey Auditory Verbal Learning Test, a measure of word list learning, predicting a third measure of adherence. No differences in predictor patterns were seen between depressed and non-depressed individuals; it was found, however, that the measures of adherence were not significantly correlated in non-depressed individuals but became strongly correlated in depressed individuals. Finally, no evidence of an impact on self-report adherence on seizure control was observed. The study suggests that healthcare knowledge and attitudes play a complex role in reported adherence. Better understanding the role of various aspects of knowledge and attitudes about epilepsy and epilepsy care may allow clinicians to improve medication adherence in the future.

CHAPTER 1

INTRODUCTION

Epilepsy is a chronic illness that affects a significant portion of the population and contributes substantially to impairment in many domains of life (Duncan et al., 2006). Advances in medical management of epilepsy have allowed many individuals with epilepsy to return to important occupational, social, and recreational activities (Sander, 2004). Nonetheless, a number of individuals do not become seizure-free with pharmacotherapy for epilepsy (French, 2007). Some of these cases may represent forms of epilepsy that do not respond for reasons related to pathology at the neurochemical or neuroanatomical level (Winawer, 2006). Others may represent cases of refusal or inability to make use of anti-epileptic drugs, or complete non-compliance with the pharmacotherapy regimen (Cramer, Glassman, & Rienzi, 2002).

Based on knowledge of health behaviors in other chronic illness populations, it is likely that there also exist cases of people with epilepsy who do not achieve adequate seizure control because of marginal adherence. Relatively little is known about the effects of marginal adherence on seizure control, or about psychological or health education factors that represent barriers between marginal and adequate adherence. The present study aims to identify factors such as comorbid depression, poor disease knowledge or negative attitudes towards epilepsy and epilepsy management, and overall motivation levels that may affect adherence to anti-epileptic drug regimens in this population. Understanding these issues may assist in the development of targeted, brief psychoeducational interventions designed to increase disease knowledge, modify attitudes toward self-management, or address specific motivation issues that affect AED adherence in this population. Such interventions may have the potential to add to the number of people who achieve adequate seizure control via pharmacotherapy.

CHAPTER 2

REVIEW OF LITERATURE

Diagnosis, Treatment and Outcomes for Epilepsy

Epilepsy is a disorder of the brain in which abnormalities in neural activity and abnormal propagation of neuroelectrical signals predispose the individual to occurrence of seizures. Unusual neuronal discharge patterns during a seizure impair normal neurocognitive functioning. Epilepsy affects children and adults of all ages, although some forms of epilepsy occur predominantly during certain neurodevelopmental periods (Duncan, 2006). Initial care for 80% of individuals experiencing seizures is delivered via a primary care physician, although ultimately, most people with ongoing treatment for epilepsy see a neurologist as well (Trost et al., 2005). As apparent seizure events occur in a variety of neurologic conditions (strokes, tumors, substance intoxication and withdrawal, and neuropsychiatric conditions), characterization of the seizure disorder is a primary goal of initial care (Trost et al., 2005; Beghi et al., 2006). Standards for this vary widely, with varying recommendations regarding the interpretation of patient historical information and the use of diagnostic techniques such as structural brain imaging, electroencephalography, and neuropsychological examinations, which all identify some causes of seizures but not others and have imperfect concordance (Trost et al., 2005).

Once an epilepsy diagnosis is made, recommendations on continuing management by a primary care physician or specialty care by a neurologist also vary depending upon the underlying nature of the condition (Payakachat, Summers, & Barbuto, 2006). However, for the majority of adolescent and adult epilepsies, first line treatment with anti-epileptic drugs (AEDs) is indicated, with alternatives such as neurosurgical interventions considered if AED treatment does not succeed and in some cases where surgery has particular efficacy (Trost et al., 2005).

Role of Anti-Epileptic Drugs and Efficacy

At least fifteen different medications are currently approved in the United States for treatment of epilepsy (Trost et al., 2005). The four “old” AEDs (phenytoin, phenobarbital, carbamazepine, and valproic acid) are often distinguished from “new” AEDs (lamotrigine, oxcarbazepine, tiagabine, gabapentin, and a number of others) (Brunbech & Sabers, 2004). Phenytoin and phenobarbital are less commonly used at present due to serious side effects, but carbamazepine and valproic acid are still commonly used as effective first line medications (Brunbech & Sabers, 2004). The “new” AEDs generally have a beneficial side effect profile, although not all are approved as monotherapy in the United States (Brunbech & Sabers, 2004; Loring & Meador, 2001; Meador et al., 2003). AEDs are often categorized based on primary site of pharmacological action – glutamate antagonists are differentiated from GABA agonists (Chengappa, Gershon, & Levine, 2001). This categorization can be beneficial in terms of primary and secondary symptom management: GABA agonists are generally anxiolytic but increase fatigue and sedation and cause weight gain, while glutamatergic drugs typically are activating and cause weight loss, but can be anxiogenic (Chengappa, Gershon, & Levine, 2001).

Overall, treatment with AEDs achieves adequate seizure control in 60-70% of people with epilepsy (Duncan, 2006). Approximately 50% of patients achieve adequate seizure control on their first medication trial (French, 2007). When the initial therapy does not work, physicians have the option of trying an additional monotherapy or using “add-on” therapy, in which an additional medication is added with the intention of being complementary to the initial therapy (Sander, 2004). In particular, a number of newer AEDs are often used in this way, including lamotrigine, levetiracetam, and oxcarbazepine (Sander, 2004). Interestingly, while 10-20% of the remainder eventually achieve adequate control via pharmacotherapy, those who tolerate their first anti-epileptic drug but do not achieve seizure control are unlikely to achieve adequate

seizure control on subsequent trials, in comparison to those for whom failure occurs in the first trial due to side effects (French, 2007).

Treatment Resistance

There are many possible causes of failure to achieve seizure control with AEDs. One possible cause is that certain epilepsy pathophysiolgies are less effectively controlled by the presently existing anti-epileptic drugs. Certain neuropathological characteristics, such as mesial temporal sclerosis, in the case of temporal lobe epilepsy, appear to increase risk of treatment resistance (French, 2007). Another possible cause is that techniques of matching patients to medications are insufficient to allow for adequate testing of all potentially efficacious combinations of available AEDs. Because of this, treatment success in all individual patient cases may actually be possible, but is not reached for logistical reasons. A third possibility is an inability to balance response and iatrogenesis; AEDs may be partially efficacious but achieve toxicity or excessive adverse effects at doses sufficient for adequate seizure control. The most common side effects reported by patients include fatigue, tremors, weight gain, memory and attentional problems, agitation and irritability, although certain AEDs also carry small risks for serious, acute adverse reactions (Carpay, Aldenkamp, & van Donselaar, 2005). An additional possibility is that suboptimal adherence to AEDs appears to reflect treatment resistance when in fact the medications being taken are capable of achieving success. Notably, pharmacoresistance does not occur only during the initial process of diagnosing epilepsy or during initial attempts to achieve seizure control. A large proportion of the epilepsy population becomes medically intractable many years after diagnosis, following years of adequate management; and a subset of these individuals actually again achieve adequate control at a later time, suggesting that some dynamic physiological or behavioral aspect of the patient's presentation is at least partly

responsible for changing efficacy (Berg, 2006). While many processes may play a role in this, adherence to medications is certainly one.

The Role of Adherence

Healthcare professionals prescribe medications and other therapies with the expectation and belief that these therapies have the potential to reduce symptoms, improve functioning, or otherwise support, heal, or cure their patients. Medications in particular are rigorously tested before they can be prescribed, to insure that they deliver benefits to patients without doing excessive harm. All of this assumes that patients use medications in the way in which they were designed and prescribed to be used. However, this is often not the case. Broad research has shown that as many as 50% of individuals across disease populations do not take their medications as prescribed; and one in five does not even get their prescription filled at all (Marinker, 1997). In addition, this research suggests that healthcare providers may not consistently screen for adherence in a valid way or even inquire about their patients' medication taking practices.

Maladherence has been shown to impact a number of healthcare outcomes. In the context of epilepsy, Manjunath et al. (2009) demonstrated that individuals who were identified as maladherent have a higher near-term likelihood of having seizures. Faught et al. (2009) demonstrated that individuals who showed evidence of non-adherence to anti-epileptic drugs had a 1.4x rate of hospitalization for seizure-related complications. While this study could not demonstrate that maladherence *caused* these excess hospitalizations, the individuals who were found to be non-adherence had longer hospital stays, and also had a higher number of emergency department visits. In terms of healthcare utilization, non-adherence in the Faught et al. (2009) study was associated with more than \$4000 per quarter in additional emergency and inpatient

healthcare costs. Ettinger et al. (2008) in a sample of only older adults with seizure disorders, also found a total increase in healthcare utilization costs of more than \$2600 per annum.

Jones et al. (2006) demonstrated that adherence may be related to seizure control; the rates of poor seizure control in this study were significantly higher for those identified as maladherent. Hovinga et al. (2008) likewise demonstrated that individuals identified as maladherent had poorer seizure control, were more likely to have experienced a past loss of seizure control, and were more likely to have had seizures in the past year. Faught et al. (2008) also demonstrated that maladherence to anti-epileptic drugs was associated with an all-cause mortality risk increase of nearly five times as well as increased risks of motor vehicle accidents and fractures. In summary, maladherence to anti-epileptic drugs has been shown to have a wide range of effects ranging from increase seizure risk, increased but less efficient healthcare utilization, and increased risk of morbidity and mortality.

It should also be noted that two choices of nomenclature are made here. First, the extent to which a patient is faithful to a prescribed medication regimen has been variously referred to as “compliance”, “adherence”, and “concordance” (Vermeire et al., 2001; Bissonnette, 2008; Lehane & McCarthy, 2009). Each of these terms denotes a different notion of the responsibilities of patient and prescribing healthcare provider in management of the medication regimen (Horne, 2006). Compliance is sometimes used to connote a relatively authoritarian relationship in which doctors prescribe medication without significant input from patients. In contrast, adherence and concordance are viewed as recognizing the significant role of patients in this process, such as indicating to their doctors that their medications are unacceptable because of any one of a number of reasons including side-effect profile, complexity of administration, or cost (Vermeire et al., 2001). While these terms are sometimes taken to have subtle distinctions in meaning, they

are often used interchangeably, particularly in the context of empirical research into medication-taking behavior (e.g., Bissonnette, 2008). The term “adherence” has been presently chosen as being reflective largely of the current *practice* of healthcare on the side of both professionals and patients. While patients provide feedback and guidance on their preferred medication prescriptions, the prescription ultimately serves as a form of “contract” between patient and doctor, explicitly denoting a set of behaviors to which both have committed.

A second choice of notation is made to use the term “maladherent” to refer to behavior that is inconsistent with, or violates, this contract between practitioner and patient. This term is not chosen here to invoke blame or intentionality, but merely to encompass the entire theoretical range of imperfect adherence behaviors; while a person who never fills a prescription could accurately be called non-adherent, likewise calling a person who misses a medication dose once every two weeks or once every month “non-adherent” has the potential to be confusing due to the significant fraction of the time in which they *are* adherent. Therefore, maladherence will be used throughout to refer to behaviors that deviate from the prescription plan created by a patient and their doctor.

Measuring Adherence

Studies inside and outside of the epilepsy literature have used a variety of techniques to assess adherence to medication regimens. The methods most commonly used can be loosely categorized into self-report questionnaires, methods that make use of drug level measurements (e.g. via a blood assay), and methods that track dispensation or use rates of medications. Each of these methods is generally considered to have advantages and disadvantages, with no method providing a perfect assessment of adherence behaviors (Dunbar, 1984; Vitolins et al., 2000; Berg, 2006). In this section, a brief review of the most common techniques for assessing adherence will be provided.

Self-report questionnaires have a long history in adherence assessment, with published studies using self-reported adherence as a measurement as early as 1984 (Mattson, 1984). They have the advantages of being low-cost and having extremely short administration times, allowing for wider use (Morisky, Green, & Levine, 1986). One of the most widely used assessments in this category is a four-item questionnaire developed by Morisky and colleagues (1986). The questionnaire uses four yes / no questions to assess the likelihood of adherence, with more than one affirmative response being considered an indicator of likely maladherence. Although this method is very simple, it has been shown in a variety of studies to have predictive validity in the form of effective prediction of future overall health status related to an illness as well as specific clinical variables being targeted by a medication, such as blood pressure control (Morisky, Green, & Levine, 1986; Morisky et al., 2008; Jerant et al., 2008). One major limitation of this method is its subjectivity – no specific definitions of adherence behaviors are utilized, and little is done to differentiate or quantify maladherence. To address this concern, most other self-report methods make use of some kind of process to assist a participant or patient in identifying the number of deviations from their medication schedule over a given time period. These methods commonly involve cueing them to guide recollection of medication-taking over different set intervals such as the past 48 hours, past week, or past month. These methods have the advantage of quantifying the type (i.e., missed or extra doses, or deviations from dosing quantity or time) and frequency of maladherence events. Although such methods may not reflect a long-term or trait characteristic of maladherence, they appear to predict near-term adherence reasonably well (Jerant et al., 2008). Nonetheless, even these adaptations do not remove the issue of subjectivity entirely. In addition to the question of subjectivity in the form of *defining* maladherence, patients may be understandably inclined to respond to perceived consequences of endorsing

maladherence. For instance, patients may fear the disapproval of their physician, offending or insulting their physicians by admitting lapses in adherence, or even a refusal to continue treating them if they admit to adherence issues. Patients may also be disinclined to report lapses in their adherence based on a perception that their physician may be less likely to trust them in the future, because the maladherence may be perceived as “telling a lie.” Research participants may also respond differently to self-report questionnaires in a research study based on the way in which the researcher’s relationship to the clinician is presented, including how research confidentiality is explained, whether the study takes place in or near the epilepsy clinic setting, and so on.

Drug level measurements became popular in adherence assessment because of their appeal as “objective” measures of adherence, which do not rely on patient reports that may be limited by recollection, demand characteristics of the clinical interview, willingness to disclose maladherence behavior, or other factors (Vitolins et al., 2000). Indeed, this technique has demonstrated that many patients do present for clinical visits with either insufficient or toxic levels of their epilepsy medications (Shakya et al., 2008). One complexity of this method is that drug levels are unique to each medication, with different anti-epileptic drugs having different half-lives, different therapeutic windows, and many other characteristics that are different (Gomes Mda, Maia Filho Hde, & Noe, 1998; Trost et al., 2005). Also, such measurements are not applicable as measurements for adherence in all anti-epileptic drugs (Walters et al., 2004). Further complicating the picture is that blood levels of medications are not singly determined by adherence. Interactions with other medications or even other substances can attenuate or potentiate metabolic consumption of a medication. For instance, besides other medications, grapefruit juice is a well-known example of a common consumable that affects the blood levels

of some epilepsy medications (Garg et al., 1998). Blood levels can also be affected by factors such as renal or hepatic compromise, and even in the absence of specific interactions with other consumed substances or renal or hepatic malfunction, can vary merely by phenotypic variability in body metabolism of medications (Goldstein et al., 2007; Johannessen & Landmark, 2008). Finally, drug level measurements are highly time-dependent – not only do they depend heavily on short-term adherence to recent medication dosages, but they also vary over the course of the day based on the time between the last dosage and the blood assay, particularly in short half-life medications (Glauser & Pippenger, 2000).

A second category of “objective” measures of adherence includes various methods to assess the rate at which medications are dispensed or used (Karve et al., 2008; Cooper et al., 2009). The logic of these measurements is that medications are prescribed at the rate at which they are intended to be used (e.g., if a person is to use sixty pills of a medication that is taken twice daily over the course of a month, they are prescribed sixty pills every month). Therefore, if an individual is found, perhaps, to refill this prescription only once every 40 days instead of once a month, or alternatively is found to have more of the given pill in their possession than they should at a given point in time, they are presumed to be under-using the medication (missing doses). Similarly, if they refill the prescription more frequently than indicated or have less remaining supply than expected, they are presumed to be over-using the medication.

There are several ways this kind of assessment can be made. Reviews of pharmacy or insurance data are often able to reveal the refill dates and quantities of medications, which can then be used to compute a medication possession ratio (MPR), a measure of the actual prescription rate in comparison to the expected rate (Cooper et al., 2009). This method has strength in that it is typically able to access a large cross-section of patients. It may create

problems during medication transitions – for instance, in handling tapering of doses or mid-refill changes in prescription that may cause a patient to have more or less medication than expected (for instance, patients are sometimes allowed to use multiple pills from a smaller dose to complete already prescribed medications before filling a prescription for a new, higher dose). Another method of monitoring pill consumption is to conduct a “pill audit” by having patients present for a research study or clinical visit with all of the medications they have in their possession, including the bottles in which they were originally dispensed. Based on the time that has passed since the prescription was filled, the expected number of remaining pills can be computed and compared to the actual number of pills the patient possesses. Both this method and the MPR method potentially are vulnerable to error in situations when patients engage in *both* over- and under-dosing or who take the correct dosage overall but do not follow the dosing schedule correctly. For instance, a patient who stops taking their medication for a week and then “doubles up” to compensate for this would appear adherent according to these methods. One more recent development in medication use rate monitoring of adherence that addresses this limitation is the advent of electronic monitoring techniques (Vaur et al., 1999). In these methods, patients are dispensed medications in special containers that electronically record pill dispensation and the data from these dispensers is used to compute adherence. This method still supposes that pills, once dispensed, are actually *consumed*, but it does have the potential to address variability in adherence that is masked by MPR calculations or pill audits. One major strength of electronic monitoring is that it can be used to essentially continuously sample adherence behaviors over a longer period of time, rather than estimating adherence based on a snapshot obtained at the time of the clinical or research assessment. This can be very important – one study determined that adherence measured in this way peaks around the time of a clinical

assessment and then drops significantly in the month following the assessment (Cramer, Scheyer, and Mattson, 1990). Another study established that electronic monitoring identified adherence lapses that were missed by other techniques, in particular demonstrating that adherence measured in this way had a non-significant correlation with blood level monitoring (Cramer et al., 1989).

Thus, while there are many established methods of assessing adherence both clinically and in research, it has become generally accepted that no measurement of adherence can take the place of a “gold standard,” either in the sense of providing a completely reliable snapshot of actual adherence behaviors or of providing a measurement that is demonstrably *more accurate* than most other measurements. Dunbar (1984) advocated this position, for instance, noting, “Each measurement procedure offers somewhat different information and has unique advantages and disadvantages.”

Why Do People Adhere or Not Adhere?

Given that adherence is necessary, at least at some level, for medications to be beneficial to patients, and given that adherence can be measured, it is reasonable to then ask whether a patient’s ongoing adherence behaviors might be predicted. This would allow for identification of patients who might be at higher risk for adherence problems and for whom additional interventions could be used to maximize the likelihood of their benefit from medications for their disease.

There are a number of reasons, both intentional and unintentional, why patients do not adhere to prescribed medication. In the framework of adherence proposed here, intentional maladherence consists of situations in which patients *choose* to deviate from adherence, whereas unintentional maladherence involves situations in which patients have chosen to follow the medication regimen devised with their provider but may not do so due to other barriers. In the area of intentional maladherence, research indicates that the formation of subjective theories is

very important for patients (Wagner, 2003). These subjective theories are “rational” and “sophisticated” in the same sense that scientific theories are, but are “naïve” in the sense that they benefit only from personal experience and not from available scientific and clinical evidence. However, patients take them very seriously, and they can have very important consequences. For example, Remien et al. (2003) found that individuals taking highly active anti-retroviral therapy (HAART) for HIV formed sophisticated theories about medication effects. One such theory was that an individual could train their body to resist HIV by reducing or skipping HAART doses. This has some surface validity without medical education – individuals are often encouraged to wean themselves off painkillers, cigarettes, or alcohol in exactly this way. However, it may not be true in the case of managing other kinds of chronic illness such as HIV. Other aspects of intentional non-adherence include independent response to and management of side effects by the patient (Remien et al., 2003). Again, patients engage in problem solving using locally available information (their own experiences and those of influential others). This problem solving often occurs in a complex social ecology; and research has indicated that significant variance in medication adherence is accounted for by interactions with important others as well as internal cognitive modeling of disease (Naar-King et al., 2006; Remien et al., 2003; Johnson et al., 2006). This suggests the importance of assessing the roles of “important others” in making medical decisions as well as assessing disease knowledge in the context of understanding the motivation or process which underlies maladherence.

In the area of unintentional maladherence, factors cited include such concerns as motivational level and regimen complexity. Depression is often examined in this context. A meta-analysis conducted by DiMatteo et al. (2000) found that individuals with chronic health problems including cancer, cardiovascular disease, and renal disease had substantially lower

rates of adherence to medications if they suffered from comorbid depression. Aggregating the results of 12 studies with more than 650 participants, these researchers found that clinically significant depression, was highly predictive of adherence across disease groups, with an overall odds ratio of 3.03 (individuals with comorbid depression are three times more likely to be non-adherent than their non-depressed peers). Interestingly, this study found that, while depression predicted adherence, anxiety disorders and/or symptoms of anxiety did not. Apathy, which Marin defined simply as “the lack of motivation seen in many neuropsychiatric disorders,” and which can occur in the absence or presence of depression (Marin, Biedrzycki, & Firinciogullari, 1991), has also been independently examined to some extent. Rabkin et al. (2000) investigated the symptoms of apathy as a predictor of adherence to HIV regimens. These researchers found that apathy did not remain predictive once control for the highly correlated symptoms of depression was added to the model. However, as the relationship between apathy and depression can vary greatly based on the neuropathology of a disorder, more work is necessary to understand the independent role of apathy (Litvan, Cummings, & Mega, 1996). As might be expected, regimen complexity has also been investigated as a contributor to adherence. The majority of studies indicate that adherence decreases with increases in regimen complexity, although this is not found in all instances (Yeager et al., 2005).

Several researchers have noted that informational, emotional, motivational, and logistical aspects of adherence can interact with each other dynamically, changing based on other contributions to emotional functioning, new information and experience, and so on (Remien et al., 2003; Fisher et al., 2006). In fact, this dynamic process underscores the notion that demographically identifying the likely maladherent patient in some general way is not particularly likely to meet with success. Thus, we are not yet at a stage where adherence behavior

can be accurately predicted based on knowledge of the informational, emotional, motivational, and logistical context in which the individual patient exists.

Depression in the Context of Epilepsy

Comorbidity of Major Depressive Disorder is high in many different symptomatic chronic illnesses, although rates vary from illness to illness for reasons that are not yet fully known (Evans et al., 2005). In a review of the literature on depression in epilepsy, Kanner (2003) notes that reported rates of depression vary between 3-9% in patients whose epilepsy is considered well-controlled and between 20-55% in patients experiencing recurrent seizures, making seizure control a major predictor of depression in this population. Psychosocial explanations appear to be very important in understanding depression in the context of chronic illnesses, including epilepsy. In particular, coping style and self-efficacy (belief that one is capable of planning and executing actions that can lead to desired outcomes) appear to have a substantial relationship to the formation and/or maintenance of depression (Goldstein et al., 2005; DiIorio et al., 2006). Some factors suggest general biological disease process mechanisms for comorbid depression as well. For instance, there are differential gender distributions in primary and comorbid depression, with men at greater risk for secondary, or comorbid depression, and women at greater risk for primary depression, in spite of similar characteristics of depression as a disease process in both cases (Harden, 2002). This suggests a potential role for biological factors in the comorbid depression disease process. .

While depression occurs at elevated rates in a variety of chronic illnesses, rates of depression in people with epilepsy are particularly high, with some studies suggesting higher rates of comorbidity with epilepsy than with other chronic illnesses (Torta & Keller, 1999; Ettinger et al., 2004). Some studies have indicated that rates are particularly high in intractable temporal lobe epilepsy, a common refractory epilepsy syndrome, with studies reporting rates as

high as 88% (Edeh & Toone, 1987; Gaitatzis, Trimble, & Sander, 2004). There are many possible explanations for this. It is conceivable that the differences may be related to different forms in which impacts on quality of life occur in refractory epilepsy such as the disruption of work, driving, and other basic life activities. On the other hand, since limbic system structures commonly involved in refractory epilepsy syndromes are also important in the pathogenesis of depression (Kennedy, Javanmard, & Vaccarino, 1997; Drevets, 2001), it might be inferred that particularly high rates of depression in people with refractory epilepsy may be due to a common pathway whereby an epilepsy disease process temporal lobe pathology leads to seizures, cognitive problems, *and* depression. Supporting this are several studies that identified higher rates of depression in temporal lobe epilepsy than in other epilepsy syndromes (Rodin, 1976; Gurege, 1991). On the other hand, at least two larger studies examined depression rates and failed to find this pattern. Although rates were elevated in patients with refractory epilepsy, they were not higher in patients with temporal lobe epilepsy in particular (Swinkels et al., 2006; Adams et al., 2008).

Comorbid depression is not only common but serious. It negatively affects health-related quality of life (HRQoL) not just within areas such as emotional functioning but broadly across all areas (Cramer et al., 2003; Cramer, Brandenburg, & Xu, 2005; Johnson et al., 2004). Zeber et al. (2007) showed that individuals with epilepsy and comorbid psychiatric disorders had significantly lower health-related quality of life, with depression having the second greatest impact on quality of life after posttraumatic stress disorder (PTSD). Indeed, comorbid depression has been shown to be a better predictor of HRQoL than clinical severity variables such as seizure type or frequency; this has itself been interpreted as evidence that depression is not just a reaction to the psychosocial experience of having seizures (Kanner & Balabanov, 2002). A

‘vicious cycle’ has been proposed in epilepsy, in which comorbid depression and poorly regulated stress responses might contribute to negative outcomes such as higher seizure frequencies. Thapar, Roland, & Harold (2005) demonstrated not only that individuals with high seizure frequency are at greater risk for experiencing depression but also that individuals who experience depression are likely to experience higher seizure frequencies in the future than non-depressed peers. However, studies that have investigated the efficacy of empirically supported psychotherapeutic techniques for stress management have thus far had poor methodological quality and have not been able to demonstrate an ability to reduce seizure frequency by controlling stress responses (Ramaratnam, Baker, & Goldstein, 2005). Finally, it may also be that other symptoms of depression such as insomnia (and resulting sleep deprivation) are indirect contributors to seizure frequency. One more aspect of the serious nature of comorbid depression is that it may be less amenable to resolution than primary depression. On the one hand, depression comorbid with epilepsy has been shown in a number of studies to be amenable to a variety of pharmacological interventions and psychotherapeutic interventions, although, of note, randomized, controlled trials of antidepressants specifically in the population of individuals with epilepsy and comorbid depression have not been published, nor have efficacy studies for psychotherapeutic treatments such as cognitive behavioral therapy in this population (Krishnamoorthy, 2003; Garcia-Morales, de la Pena Mayor, & Kanner, 2008; Mula, Schmitz, & Sander, 2008). On the other hand, seizure control has been found, even in large, community studies, to be among the largest determinants of point prevalence of depression in individuals with epilepsy, with dramatically lower rates of depression in individuals who have fully controlled seizures when compared to those who have incomplete seizure control (Evans et al., 2005). This suggests that depression is not only common but likely persistent in many

individuals who have active seizures, even given the broad availability and accessibility of treatments.

Comorbid depression negatively and seriously impacts other aspects of epilepsy management including healthcare utilization and hospitalization. Individuals with comorbid depression indicate greater severity of seizures and describe their seizures as more bothersome than people with epilepsy who do not have comorbid depression (Cramer et al., 2003). Cramer et al. (2004) indicated that individuals with epilepsy and comorbid depression had higher healthcare utilization costs whether or not their depression was being treated with antidepressants. In a review of the impacts of comorbid illnesses on management of refractory epilepsy, Lee et al. (2005) found that, while comorbidity in general increased healthcare utilization, depression particularly had the strongest effect on both the likelihood for hospitalization and increase in healthcare costs (costs were 83% greater in refractory epilepsy patients who were also depressed).

Mechanisms Behind the Impact of Depression on Adherence

Depression has a strong relationship with adherence and is frequently comorbid with chronic illness. Not only do individuals with chronic illnesses broadly have a rate of depression on the order of 25-40%, but 60-70% of individuals who are depressed suffer from one or more chronic illness (Cassano & Fava, 2002). Individuals who have comorbid depression have frequently been observed to have both poorer adherence and poorer health outcomes, and yet few studies have explicitly shown adherence to be a mediator of this process or have addressed why depression impacts adherence (Wing, Phelan, & Tate, 2002). For this reason, understanding the mechanisms behind the large effect of depression on adherence has begun to receive considerable attention. Researchers investigating the comorbidity of depression with asthma have shown that this combination of illnesses is associated both with poorer knowledge and

attitudes regarding asthma and with poorer disease-monitoring ability (Baiardini et al., 2006).

Motivational or perseverative aspects of health behavior have also been implicated – some researchers have demonstrated that sensitivity to treatment side-effects, leading to higher rates of apparent treatment resistance due to adverse effects of medication, is a mechanism by which depression affects adherence (Magai et al., 2007).

Attitudes underlying coping styles may vary qualitatively between individuals who do and do not experience comorbid depression (Barton et al., 2003). Sacco et al. (2005) demonstrated that, in the context of Type II Diabetes, the relationship between adherence and depression is fully mediated by an attitudinal variable – perceived self-efficacy (in this model, adherence was a predictor of depression, the effect of which was completely mediated when self-efficacy was taken into account). Based on existing research outside of epilepsy, it does therefore appear that depression exacerbates many of the major causes of maladherence already identified. Safren et al. (2001), in comparing interventions to improve adherence, noted that, when HIV positive patients had comorbid depression, they could improve adherence when administered a cognitive-behavioral therapy (CBT) intervention that worked not only on adherence barriers but also addressed depression. In this study, the CBT intervention was compared to a purely adherence-skills-oriented intervention that was approximately equally effective in non-depressed participants. Treating depression by other means such as the use of antidepressants has also been shown to improve adherence rates for treatment of comorbid illness (Dalessandro et al., 2007). On the other hand, Wang & Li (2003) examined the role of health education in individuals with comorbid depression and hypertension. Health education was found to be specifically effective in modifying hypertension health behavior in this study, improving both hypertension medication adherence and physiological outcomes without requiring the need for successful treatment of

depression. In fact, although individuals in this intervention who had comorbid depression did not show any decrease in depressive symptoms, they showed a larger magnitude of intervention-related improvement compared to controls than did non-depressed participants. This suggests that identifying specific health behavior and health education interventions for chronically ill populations may possibly be an avenue through which health status can be improved for these patients independently of success in treating secondary depression.

Identifying and Addressing Adherence Behavior in Epilepsy

A literature search was performed in order to identify existing studies that have attempted to determine predictors of adherence to anti-epileptic drugs. Using keyword-driven searches of the Pubmed database as well as individual review of cited articles within these and other publications¹, 19 studies were identified. These studies are summarized in Table 2-1. Studies were included if they employed any specific measure of adherence to medications and examined one or more possible predictor variables quantitatively. Studies were included if they used either cross-sectional or longitudinal techniques, and case-control studies in which adherence was a group characteristic rather than an outcome measure were included if study dependent variables contained one or more variable that could be construed as a predictor of adherence. Studies were not included if adherence was used primarily as a predictor or dependent variable, such as when adherence was used to predict seizure control or healthcare utilization costs. Studies that reported relationships between predictors of adherence and adherence but did not appear to make use of statistical tests of significance were not included.

Twelve of these studies focused on adults (with one also including adolescents), while

¹ Keywords used in this search for adherence were: adherence, compliance, maladherence, non-adherence, and non-compliance; epilepsy and depression were also added as search terms. Each article was individually screened to ensure that it met the criteria described above.

seven studies focused exclusively on children. Twelve studies used a variety of self-reported adherence measures, administered primarily in questionnaire format, and one more study used a clinician rating system. Four used an assay method such as a phenobarbitol challenge or a serum level check (including one of the previously mentioned studies which used both self-report and assay methods). Three studies used consumption monitoring – two of these studies used the medication prescription ratio and the third used electronic monitoring of pill dispensation. The studies found somewhat conflicting results with respect to epilepsy clinical variables but fairly consistent results with respect to psychosocial variables. Variables that fell into the category of disease attitudes were the most frequently significant predictors. These variables included any variable that measured beliefs, attitudes, or other affective labeling of medical treatment, symptoms, diagnosis, or prognosis in the context of epilepsy. Variables in this category were found to be significant in eight of the studies and only found to be non-significant in one study.

On the other hand, clinical variables such as duration of epilepsy and treatment complexity were strong but inconsistent predictors in some studies and non-significant in others. For instance, two studies examined duration of epilepsy or epilepsy treatment and found this to be significant in predicting adherence, while three more found this to be non-significant. Demographics were supported as predictors only occasionally, with conflicting results in different studies. For instance, Faught et al. (2009) found higher rates of adherence based on medication prescription ratio in Caucasian participants and McAuley et al. (2008) found *lower* rates of adherence based on the Morisky measure in Caucasian participants. Finally, of note, no study examined the *presence* of depression as a predictor of adherence, although one study (McAuley et al., 2008) did examine a past history of depression *treatment* as a predictor of adherence. These studies are summarized in Table 2-1.

Rationale for the Present Study

While it seems generally true that patients with epilepsy have adherence characteristics similar to those seen in other chronic illnesses, the literature in this area has not addressed some major concerns. First, the literature does not provide an adequate answer as to why some people with epilepsy do not maintain adequate adherence. This is a barrier to the development of specific, streamlined interventions that target actual factors related to adherence issues in this population. Second, depression, a condition that is frequently comorbid with symptomatic epilepsy, has rarely been specifically considered as a contributor to adherence. In fact, only one study was identified that assessed any relationship between adherence and depression in people with epilepsy, and that study (McAuley et al., 2008) only examined the relationship between adherence and a reported history of *being treated* for depression. As depression is likely to exacerbate many processes implicated in poor adherence, understanding its specific contribution to adherence in epilepsy is important for two reasons. First, such an understanding may assist in identifying a subset of epilepsy patients who are at increased risk for recurrent seizures. As well, it may help in targeting a subset of patients in whom direct treatment of depression would have secondary benefits on adherence and subsequent seizure control.

Statement of the Problem

The present study seeks to determine, in an epilepsy sample, how disease knowledge, attitudes, and motivation contribute to adherence to anti-epileptic drugs, and to determine whether comorbid depression plays a specific role in adherence and seizure control. Specifically, the aims of this study are:

1. To determine whether comorbid depression reduces the likelihood that people with epilepsy will maintain adequate adherence to epilepsy medications
2. To determine whether epilepsy knowledge and attitudes towards medical care affect rates of adherence to antiepileptic medications

3. To ascertain whether knowledge and attitudes have differential contributions to adherence rates in depressed individuals
4. To determine whether depression may negatively affect seizure control (e.g., through the mechanism of poorer adherence)

Table 2-1. Studies of adherence in epilepsy

Publication	Method	Sample	Measure of Adherence	Supported Predictors of Adherence*	Predictors of Adherence Not Supported**
Asadi-Pooya et al. (2005)	Cross sectional design, interview	Children with epilepsy (n = 181)	Self-report via interview	Younger mother, family history of epilepsy	Therapy complexity, parental education
Buck et al. (1997)	Cross sectional design, postal questionnaires	Adolescents and adults with epilepsy (n = 696)	Self-report (frequency of missed doses)	Disease attitudes, treatment complexity, side effects, practitioner quality, age	Duration of epilepsy, seizure severity
Briesacher et al. (2008)	Longitudinal design, retrospective claims data analysis	Adults with epilepsy (n = 4984) and other chronic illnesses	Medication prescription ratio	Higher comorbidity, polytherapy, previous familiarity with epilepsy medications	Demographics
Cramer et al. (2002)	Cross sectional design, postal questionnaires	Adults with epilepsy (n = 661)	Self-report (frequency of missed doses)	Duration of epilepsy treatment, some treatment complexity variables (trend level)	Total number of capsules taken for either epilepsy medication or all medication
Dilorio et al. (2003)	Mixed longitudinal / cross sectional design, questionnaires	Adults with epilepsy (n = 314)	Self-report via questionnaire (Morisky)	Disease attitudes (stigma)	
Enriquez-Caceres et al. (2006)	Cross sectional design, retrospective chart review	Adults with epilepsy (n = 114)	Clinician-report adherence	Disease knowledge and attitudes, access to treatment, clinician relationship	Side-effects
Faught et al. (2009)	Longitudinal design, retrospective claims data analysis	Adults with epilepsy (n = 33,658)	Medication prescription ratio	Younger age, male sex, Caucasian race, higher comorbidity	
Gomes et al. (1998)	Cross sectional design, questionnaire	Adults with epilepsy (n = 45)	Self-report via questionnaire (missed doses in last week)	Disease knowledge and attitudes	Demographics, SES, treatment complexity
Hazzard et al. (1990)	Cross sectional design	Children with epilepsy (n = 35)	Serum level	Disease attitudes, psychosocial risk factors	
Hovinga et al. (2008)	Cross sectional design, online study	Adults with epilepsy (n = 408)	Self-report (frequency of missed doses)	Several measures of illness / disability severity, past history of loss of seizure control	
Jones et al. (2006)	Cross sectional design, questionnaire	Adults with epilepsy (n = 54)	Self report via questionnaire (Morisky)	Disease knowledge and attitudes	

Publication	Method	Sample	Measure of Adherence	Supported Predictors of Adherence*	Predictors of Adherence Not Supported**
Kemp et al. (2007)	Cross sectional design, questionnaire	Adults with epilepsy (n = 37)	Phenobarbitol challenge	Time since last seizure	Age at onset and duration of epilepsy diagnosis, disease attitudes
Kyngäs et al. (2001)	Cross sectional design, postal questionnaire	Adolescents with epilepsy (n = 232)	Self-report via questionnaire	Psychosocial risk factors, disease attitudes	
Lugo Gonzalez et al. (2001)	Cross sectional design, questionnaire	Children and adolescents with epilepsy (n = 54)	Self-report via questionnaire	Subjective memory complaints, time between clinical follow-up visits	
Lusic et al. (2005)	Cross sectional design, questionnaire	Adults with epilepsy (n = 146)	Self report via questionnaire	Substance abuse, duration of treatment, treatment complexity	
McAuley et al. (2008)	Cross sectional design, questionnaire	Adults with epilepsy (n = 50)	Self report (Morisky)	Non-Caucasian race	Other demographics, history of seizure freedom, treatment for depression
Mitchell et al. (2000)	Longitudinal design, questionnaire	Children with epilepsy (n = 119)	Adherence to follow-up schedule, self-reported via questionnaire, serum level	Psychosocial risk factors	Seizure severity, disease knowledge
Modi et al. (2008)	Longitudinal design, prospective	Children with epilepsy (n = 35)	Electronic monitoring system	Married parents, higher socioeconomic status	Other demographics, type of epilepsy, specific medications, seizure frequency, duration
Snodgrass et al. (2001)	Cross sectional case-control design	Children with epilepsy (n = 200) selected for serum-level-determined adherence or non-adherence	Serum level	Race, insurance status	Treatment complexity

Notes: (*) A predictor was considered “supported” if it was a statistically significant predictor of adherence based on the study’s chosen criteria or if it was statistically significantly predicted by epilepsy in the model of choice but represented a pre-standing risk factor theoretically. (**) A predictor was considered “not supported” if it was entered into a model in the study and was statistically non-significant or failed to enter / was dropped from a model in a stepwise process. Again, the original author’s criterion for significance was used in all cases.

CHAPTER 3

METHODS

Population

Although epilepsy represents a complex constellation of syndromes with different etiologies, prognoses, and neurocognitive impacts, individuals with different seizure disorder variations generally receive similar care and neurologists who work with epilepsy patients similarly provide their array of services to patients with a broad range of seizure disorder characteristics. Therefore, the present study sought to recruit a sample that is generally representative of the broad adult clinical epilepsy population. A focus on adult patients only was selected due to the relatively substantial differences in clinical care, family involvement, and established research instruments between pediatric adult patient populations. As such, epilepsy patients age 20 years or older were recruited for the current study. Two key inclusion criteria were (a) stable diagnosis of epilepsy for at least two years, and (b) at least one seizure in the past 6 months. These inclusion criteria were imposed in order to derive a sample of individuals with epilepsy for whom medication adherence may be a relevant issue.

Recruitment Procedure

Two recruitment sites were used in order to produce a demographically representative sample comprised of individuals living in an urban / suburban environment and individuals living in a rural environment. Individuals were recruited during their visits to outpatient neurology clinics at Shands at the University of Florida (Gainesville, FL) and Shands Jacksonville (Jacksonville, FL), two tertiary-care, academic medical centers in Florida. Patients who arrived for appointments at epilepsy clinics at these two sites were screened to identify individuals who met the recruitment criteria. Eligible individuals were then approached and were given information about the study and obtain informed consent. Participants received a nominal

financial compensation (\$20) for their participation. Institutional Review Board approval was obtained for all procedures.

Assessment Procedure

Participants were asked to complete self-report questionnaires after consent was obtained and prior to being seen by their physician. They were then given a brief neurocognitive and diagnostic assessment by a Masters' level graduate student in clinical psychology and completed additional self-report questionnaires after their appointment with their neurologist. Participants were also asked to participate in a follow-up session, consisting of a brief telephone interview in which knowledge and adherence was re-assessed along with seizure frequency over the month following the initial assessment.

Assessment Instruments

Epilepsy Knowledge Instruments

Two instruments were used to assess patient-centered knowledge of epilepsy as a disorder, appropriate management of epilepsy, and the relationship between epilepsy and daily activities such as driving and employment. The *Epilepsy Patient Knowledge Questionnaire (EPKQ)* is a brief, 13-item instrument consisting of a mixture of true/false, multiple choice, and free response items addressing each of these areas (Long et al., 2000). This instrument can be scored and interpreted on the basis of the total percent of items answered correctly. In a validation study (Long et al., 2000) with 175 adult patients with epilepsy, the authors found moderate mean response accuracy (58%). The items on this instrument range in difficulty from items answered correctly by only 14% of the validation sample to items answered correctly by 92% of the validation sample. Resulting scores are relatively free of effects of age, education, or length of diagnosis but unfortunately has not been formally assessed for validity or reliability to our knowledge. *The Epilepsy Knowledge Scale (EKS)* is an additional brief instrument

consisting of either 10 or 19 yes/no items (see below) assessing the major domains of epilepsy knowledge discussed above (Ried et al., 2001). It was originally developed as a component of an intervention, Modular Service Package Epilepsy (MOSES), designed to improve health education for patients with epilepsy in Germany. This instrument is designed so that 10 items can be given at a baseline assessment, with an additional nine items delivered at follow-up to control for practice effects. The dependent measure is the percentage of items answered correctly. As this is a brief instrument assessing multiple domains of knowledge, the reliability of each sub-segment is moderate, although it improved when all 19 items were considered (Cronbach alpha for the initial 10 items, $\alpha_{CR} = 0.45$, for the additional nine items, $\alpha_{CR} = 0.0.57$, and for the entire 19 item scale, $\alpha_{CR} = 0.72$). This instrument was also shown to be sensitive to increases in epilepsy knowledge as delivered by the MOSES intervention (May et al., 2002). The 19 item version of this scale was used in this study.

Epilepsy Attitudes Instruments

Three different, but overlapping, aspects of attitudes towards epilepsy were measured with three different instruments. The first instrument, the *Illness Perception Questionnaire (Brief IPQ)*, assesses a patient's attitudes about having the diagnosis of epilepsy and the impact of epilepsy on their life. This instrument consists of nine items rated by the participant on a 0-10 Likert scale with anchors relevant to each individual item (e.g. "How much does your illness affect your life?" where 0 = "no affect at all" and 10 = "severely affects my life"). This instrument has been broadly used in many illness groups and was found to have good test-retest reliability (item reliability between $r = 0.6-0.7$ for most items) (Broadbent et al., 2006). It also has good concurrent validity (both with respect to the original long-form Illness Perception Questionnaire – Revised and to some other measures of disease-specific self-efficacy, with

which it had correlations ranging from $r = 0.26-0.61$ (2006). The Brief IPQ can also reliably discriminate between individuals who experience chronic illness and those who experience truly episodic illnesses (Broadbent et al., 2006).

The second instrument, the ***Beliefs About Medicine Questionnaire (BMQ)***, assesses an individual's attitudes towards the use of medical techniques, including pharmacotherapy, to manage or improve their health functioning. It consists of ten items assessing attitudes about the medications used to treat their illness (e.g., "Having to take medicine for epilepsy worries me") and beliefs about medications in general (e.g., "Doctors use too many medicines"). BMQ items appear to cluster on four factors, consisting of beliefs about the need for medication to treat the patient's illness, concerns over dependency and other adverse impacts of medication, general belief that medications are harmful or dangerous, and general beliefs that they are over-prescribed (Horne & Weinman, 1999). These four dimensions have good internal reliability ($\alpha_{CR} = 0.51-0.86$) when tested in several different populations, justifying the use of subscale total scores computed by summation of items associated with each dimension, and the instrument also shows good measurement stability in the form of two-week test-retest reliability ($\alpha_{CR} = 0.60-0.78$).

The final instrument, the ***Multidimensional Health Locus of Control (MHLC)***, assesses a patient's beliefs about the extent to which their health functioning is under their own control, is controlled by healthcare providers, or is not amenable to control by either themselves or their care providers (Wallston, Wallston, & DeVellis, 1978). These three dimensions of locus of control are commonly referred to as Internal, Powerful Others, and Chance loci of control, respectively, and these abbreviations will be used throughout. It consists of 18 Likert scale items (values of 1-6 corresponding to strongly disagree, moderately disagree, slightly disagree, slightly

agree, etc.), with six items falling in each of these three areas. Scores are summed within each area to determine the strength of each aspect of locus of control. For example, an item indicative of Internal locus is, “I am directly responsible for my condition getting better or worse.” An example of an item indicative of Chance locus is, “If my condition worsens, it’s a matter of fate.” Scores on these dimensions have been specifically related to adjustment and health functioning in people with epilepsy (Gramstad, Iversen, & Englesen, 2001; Spector, Cull, & Goldstein, 2001).

Apathy Instrument

The *Apathy Evaluation Scale (AES)* was used to measure symptoms of clinical apathy as a proxy for general patient motivational level (Marin, Biedrzycki, & Firinciogullaari, 1991). This instrument is also sometimes referred to as the “Marin Apathy Inventory.” Apathy has been shown to be at least somewhat related to depression in clinical studies of neurological populations, with some populations presenting relatively low correlations and apathy and depression as two relatively distinguishable syndromes, and others showing moderately strong correlations between the two. It is generally thought that apathy presents to varying degrees a component of depression but can also occur independently of depression in certain neurological disorders (Hama et al., 2006). At least one study has previously used this measure to assess the concept of general motivational level (Resnick et al., 1998). It has been shown to have good internal consistency and test-retest reliability and good validity when compared to a structured interview assessing Marin’s research criteria for syndromal apathy (Marin, Biedrzycki, & Firinciogullaari, 1991).

Adherence Instruments

Adherence to AED’s was determined using two alternative self-report methods that have been validated in various patient populations. The measure developed by Morisky, Green, &

Levine consists of four questions (e.g., “Sometimes if you feel worse when you take the medicine, do you stop taking it?”), to which a participant responds with either a “yes” or a “no.” (1986). More than one “yes” response is considered a sensitive indicator of poor to marginal adherence. This measure has previously been used successfully with epilepsy patients (Jones et al., 2006). Gao and Nau (2000) examined this scale in comparison to self-reports of the number of missed doses (a direct , retrospective adherence measurement, or RAM) over the past two days and the past two weeks; they found that the latter measures produced consistently higher apparent adherence than the Morisky scale. As it is not yet clear how this difference arises, and few studies have compared these two commonly used methods, the present study will use the methods of both Morisky et al. and Gao & Nau. These measures of adherence will be referred to simply as the Morisky measurement and the RAM.

Clinical Variables

As part of the questionnaire packet administered to participants, a number of clinical history variables were elucidated. Participants were asked to provide the age at which they first experienced seizures (age at onset), the duration of time that they have had epilepsy, if they have ever experienced a period of seizure remission of six months or longer, and their seizure frequency in the last 30 days. Medication regimen complexity was also estimated by determining the daily frequency of epilepsy medication dosages (i.e., whether a participant took AEDs at one, two, three, four, etc., different times per day). Several basic healthcare behaviors were also assessed, including whether the participants use a pillbox to organize their medications, whether they have family members or other loved ones take part in their healthcare by participating in clinic visits, and whether they receive assistance at home with their medication-taking. Finally, a list of AEDs was also collected.

Depression Instruments

Participants were administered the 20-item version of the *Center for Epidemiological Studies Scale for Depression (CES-D)* prior to their clinical appointment and the *Mini International Neuropsychiatric Interview* after their clinical appointment. Both measures have been validated for use with people with epilepsy (Jones et al., 2005). The CES-D scale allows for investigation of depression as a multidimensional construct with quantitative measurement of severity (Radloff, 1977). The Mini International Neuropsychiatric Interview is a structured clinical interview that identifies 17 major Axis I psychiatric diagnoses; it has comparable validity to the DSM-IV Structured Clinical Interview Diagnostic (Sheehan et al., 1998).

Cognitive Screening

Cognitive screening consisted of a brief battery of neuropsychological tests. The Shipley Institute of Living Scale (SILS) was administered to gauge overall intellectual functioning; this brief measure consists of a Vocabulary subtest in which a participant must chose one of four words that most closely matches the meaning of a target word, and an Abstraction subtest, which involves tests of inductive reasoning (Shipley, 1940). This test is able to provide an estimation of the likely Full Scale Intelligence Quotient that would be obtained using the Wechsler Adult Intelligence Scale (WAIS-R). The Stroop Test was used to measure both cognitive processing speed and freedom from interference, an aspect of executive functioning (Golden, 1978). The Digit Symbol subtest of the WAIS-III was also used to measure cognitive processing speed (Wechsler, 1997). Finally, the Rey Auditory Verbal Learning Test (RAVLT), a test of word list learning, was used to assess memory (Rey, 1964).

Table 3-1 briefly summarizes the instruments listed above.

Power Analysis and Statistical Methods

Chi-squared tests were selected for use to determine if depression is associated with adherence. For this analysis, sample size was estimated using the method of Fleiss, Tytan, & Ury (1980). In order to do this, the Morisky et al. (1986) questionnaire was used. The measured adherence rate in epilepsy (41% indicating good adherence and 59% indicating poor adherence, using the Morisky questionnaire) in Jones et al. (2006) was taken to be the population base rate of adherence in epilepsy. The widely reported approximation of the depression base rate in epilepsy as 30% was used as an estimate of the prevalence of depression (Jones et al., 2005). Finally, the meta-analysis by DiMatteo et al. indicated an odds ratio of 3.0 for the increased likelihood of poor adherence in individuals with depression comorbid with a chronic illness (2000). Using these figures, the expected rate of good adherence in non-depressed individuals is 51% and in depressed individuals is 17%. Given these figures, the sample size required for a power of 0.80 is 72 (50 non-depressed, 22 depressed) and the sample size required for a power of 0.90 is 93 (65 non-depressed, 28 depressed). A projected sample size of 100 was therefore likely to recruit both sufficient depressed and non-depressed participants to be adequately powered without the need for over-sampling either of the two groups.

In order to determine best predictors in the domains of epilepsy knowledge and attitudes, initial analysis were planned to be completed by examining distributional properties to select the most psychometrically sound instruments and then using bivariate correlations between these potential predictors and adherence. Distributional properties could then be assessed by investigating skewness and kurtosis. Skewness was considered “acceptable” if the absolute magnitude of skewness was less than the standard error of skewness (SES), mildly problematic if it was between 1-2x the SES, and problematic if it was >2x the SES. The magnitude of kurtosis was compared to the standard error of kurtosis (SEK) according to the same criteria, again with

acceptable kurtosis being smaller than the SEK, mild kurtosis problems being 1-2x the SEK, and problematic kurtosis >2x the SEK. For cognitive variables, the decision was also made to make use of raw scores rather than demographically corrected scores. This decision was based on the rationale that adherence is a specific behavior that does or does not occur, and is not itself adjusted in interpretation based on the demographics of patients. Raw scores, as they reflect actual ability in various cognitive areas, are therefore preferable on the presumption that adherence may require a certain level of cognitive ability, rather than a certain degree of superiority or inferiority compared to other individuals with the same age, sex, race, or education of the participant.

Logistic regression was chosen to determine the impact of factors such as knowledge and attitudes on adherence rates, as well as the differential importance of these factors with comorbid depression. Linear regression was chosen to predict the impact of adherence on subsequent seizure frequency. A regression model was chosen to determine if comorbid depression reduces seizure control through the mechanism of poorer adherence to epilepsy medications or through some other mechanism. These analyses were estimated to have between three and six predictors; with an estimate of 15 participants per predictor variable, the study would also be adequately sized to allow for evaluation of these models at the desired sample size.

Participants

Recruitment for the study began in the Summer of 2007 and ended in the Summer of 2008. Although a significant number of pre-screened clinic patients met criteria for the study, many declined or were unable (e.g. because of transportation issues) to participate, and the study recruited participants in smaller numbers than expected. A total of 56 participants were successfully recruited and participated in the study, although some of these individuals were unable to complete significant portions of the study successfully ($n = 7$), generally because they

were found to have excessive difficulty answering questionnaire items. This lead to a smaller sample of 49, who completed the assessment without substantial missing components.

Modifications to Methods

Due to the smaller than anticipated enrollment in the study, analyses were simplified to be appropriate for the obtained sample size. In addition to addressing multicollinearity, the numbers of predictors used in multiple variable models such as the regressions were reduced by considering only those variables that had significant univariate associations. As the number of individuals who were successfully contacted for follow-up was also very small, longitudinal analyses were deferred. Finally, rather than determining the impact of depression on seizure control via linear regression, separate chi-square analyses were completed for the depressed and non-depressed groups.

Table 3-1. Summary of Study Measures

Measure	Domain	Format
Epilepsy Patient Knowledge Questionnaire (EPKQ)	Disease Knowledge	Questionnaire
Epilepsy Knowledge Scale (EKS)	Disease Knowledge	Questionnaire
Illness Perception Questionnaire (Brief IPQ)	Disease Attitudes	Questionnaire
Beliefs about Medicine Questionnaire (BMQ)	Disease Attitudes	Questionnaire
Multidimensional Health Locus of Control (MHLC)	Disease Attitudes	Questionnaire
Apathy Evaluation Scale (AES)	Emotional Functioning	Questionnaire
Morisky Questionnaire	Adherence	Questionnaire
Reported Adherence Measure (RAM)	Adherence	Questionnaire
Questionnaire Items to Assess Clinical History	Clinical History	Questionnaire
Center for Epidemiological Studies Depression Scale (CES-D)	Emotional Functioning	Questionnaire
Mini International Neuropsychiatric Interview (MINI)	Emotional Functioning	Interview
Shipley Institute of Living Scale (SILS)	Cognitive Functioning	Individual Testing
Stroop Test	Cognitive Functioning	Individual Testing
Digit Symbol subtest (WAIS-III)	Cognitive Functioning	Individual Testing
Rey Auditory Verbal Learning Test (RAVLT)	Cognitive Functioning	Individual Testing

CHAPTER 4 RESULTS

Characterization of Sample

Demographics

Of the enrolled participants, 79% were female, and the average age of study participants was 43 years ($SD = 12.5$ years), with a range of 20-78 years. The most commonly represented racial group was Caucasian (63%), followed by African Americans (29%). Two participants identified themselves as Hispanic (4%) and one each as Native American and multi-racial. The most commonly reported level of education was completion of high school (29%). 28% of the sample did not complete 12 years of education, however, and almost 44% had some college education or more. Almost half of the participants (49%) identified themselves as currently married or in another kind of committed relationship, while the remainder were approximately evenly split between those who were divorced or separated (28%) and those never married (24%). Only 10% reported living alone; 8% reported only children living with them, while the remainder reported having other adults in the home.

Clinical Characteristics

With respect to seizure disorder onset, slightly more than half of the participants had onset after the age of 21 years (51%), with another 33% having onset between 7-21 years and the remainder having onset earlier than 7 years of age. The majority of the sample had duration of illness of longer than five years (71%). Approximately half the population (53%) reported having a period of at least six months of seizure freedom at some point since their first seizure, while the remainder had never been seizure free for such a period of time. 28% had been seizure free in the past 30 days, 50% reported one or less seizures in the past month, and the remainder reported a larger number of seizures, with 7 individuals reporting 10 or more seizures in the past thirty days

(14%). In terms of medication regimen complexity, participants on average took seizure medications twice daily ($M = 2.0$, $SD = 0.6$, Range = 1-4 times per day). Most participants received polytherapy, with 49% of participants for whom medication information was available receiving two medications and 22% receiving three or more. The most commonly prescribed AEDs were levetiracetam (Keppra; 19 participants), lamotrigine (Lamictal; 13), phenytoin (Dilantin; 12), and topiramate (Topamax; 11).

In terms of basic healthcare behaviors, 31% reported that they attend doctors visits unaccompanied. 43% indicated that they are accompanied by someone to their appointments who communicates with their doctors for purposes of their care, while the remainder indicated that they are accompanied by someone who does not take part in their clinic visits (e.g. for assistance with transportation). 45% of respondents indicated that they use a pillbox with separate spaces for different days and/or times of day for their medication, while 51% keep their medication in the containers received from the pharmacy and the remainder indicate keeping their medications in some other way. In this sample, most participants (77%) indicated that they manage their own medications, while the remainder indicated that they receive help in of some kind. Demographic and clinical characteristics of participants are summarized in Table 4-1.

Psychiatric Characteristics

Psychiatric characteristics of participants were determined using the Mini International Neuropsychiatric Interview (MINI). Table 4-2 below summarizes the rates of various psychiatric co-morbidities observed in the sample population. Based on responses to the MINI, the most common psychiatric co-morbidity was a current major depressive episode (MDE; 19 of 48 participants who were able to complete the MINI, or 40%). Four of the participants with a current major depressive episode also met criteria for a past manic episode, and one more for a past hypomanic episode, however, indicating that these individuals meet criteria for Bipolar

Disorder rather than Major Depressive Disorder. Fourteen participants met the additional criteria for *recurrent* major depressive episodes (29%), and three met criteria for psychotic features of depression. An additional four individuals who did not meet criteria for a major depressive episode met criteria for current dysthymia. The second most common current co-morbidity was generalized anxiety disorder (21%).

In comparison to the structured clinical interview, self-reported rates of depression on the CES-D were somewhat higher. The range of respondent scores on the CES-D was from 0 to 49 out of a possible 60 points, with a mean score of 21.7 ($SD = 11.7$). In terms of distributional properties, the skewness and kurtosis of the CES-D were both acceptable. If the traditional clinical cut-off of 16 points is used, 70% of participants endorsed depressive symptoms at the level of Major Depressive Disorder on the CES-D. A receiver operating characteristics (ROC) analysis of the CES-D scale, using the MINI diagnosis of current major depressive episode as the referent standard, indicated only fair detectability ($AUC = 0.736$), with no cut-off achieving simultaneously strong sensitivity and specificity. The non-parametric association between the CES-D and the MINI MDE criteria was likewise modest (Spearman's $\rho = 0.40$, $p = 0.005$).

Cognitive Characteristics

Cognitive characteristics are summarized in Table 4-3. The mean raw score on the Shipley Institute of Living Scale Vocabulary subtest, with blank items imputed at chance level, was 23.2 ($SD = 5.9$, Range = 11-36). The mean Abstraction subtest raw score was 15.2 ($SD = 8.4$, Range = 2-36), and the mean Total Raw Score was 38.4 ($SD = 11.5$, Range = 18-60). All three scores had acceptable skewness and kurtosis. These scores were also age corrected to provide a basic estimation of participants' general intellectual functioning. When age-corrected, the mean Vocabulary T-score was 37.7 ($SD = 10.2$, Range = 15-60). In particular, it was notable that only two participants obtained a Vocabulary T-score above 50 (that is, above the 50th %ile compared

to age peers). The mean Abstraction T-score was 44.4 (SD = 7.6, Range = 31-62). Interestingly, participants' Abstraction T-scores were significantly higher than their Vocabulary T-scores ($t(46) = -4.50$, $p < 0.001$). Finally, the Shipley Institute of Living Total Raw Score can also be used to estimate the likely WAIS-R Full Scale IQ (FSIQ); when this was computed, the average estimated FSIQ was 96.6 (SD = 9.3, Range = 76-112), suggesting overall average intellectual functioning. All individuals in the study are likely to fall into the Borderline Intellectual Functioning classification or higher.

On the Stroop Test, participants completed on average 76.1 responses on the Word condition (SD = 17.3) and 59.4 on the Color condition (SD = 15.0). Their Color-Word Interference was on average -2.1 (SD = 9.2, Range = -17.6 to +20.6). When these scores were age-corrected, the mean Interference T score (where T scores have a mean of 50 and standard deviation of 10) was 49.1 (SD = 8.7). Using a 5th percentile cutoff for impairment (i.e. a T score of 34 or less), two participants were impaired on this measure.

On the Digit Symbol subtest from the WAIS-III, their mean raw score was 53.5 (SD = 21.2, Range = 14-89). When Digit Symbol raw scores were age-corrected, participants had a mean scaled score (where scaled scores have a mean of 10 and standard deviation of 3) of 7.1 (SD = 3.0). Using a 5th percentile cutoff for impairment (i.e., a scaled score of 5 or lower), 18 participants were impaired on this measure.

On the RAVLT, average Total Learning was 36.7 (SD = 10.2) with a range of 14-58. Delayed Recall (Trial VII) was 6.3 (SD = 3.4) with a range of 0-12. When RAVLT Delayed Recall was corrected for age and sex (Savage & Gouvier, 1992), the mean T score was 39.8 (SD = 13.3). Using a 5th %ile cutoff, 16 participants were impaired on this measure.

Overall, the distributional properties of cognitive variables were acceptable except that the Digit Symbol raw score showed mild problems with kurtosis (kurtosis = -1.2, 1.8x SEK).

Healthcare Attitudes and Beliefs

Illness Perception

On the Illness Perceptions Questionnaire, participants endorsed relatively high levels of perceived illness related to their epilepsy, with scores ranging from 10-64, out of a possible theoretical range of 0-80 (Mean = 46.1, SD = 10.4). The highest average levels of severity were reported for items related to how long the condition is likely to persist and the level of concern over the condition ($M = 8.3$ and 8.4 , respectively). In contrast, patients reported feeling fairly strongly that treatment *can* help them with their illness ($M = 2.2$, SD = 2.0) and that they understand their illness fairly well ($M = 2.4$, SD = 2.9). This instrument had significant negative skew (skewness = -1.1, 3.3x SES) and was highly leptokurtic (kurtosis = 2.7, 3.9x SEK).

Medications

On the Beliefs About Medicines Questionnaire, the average reported Specific Necessity was 2.1 (SD = 0.8) and the average reported Specific Concerns was 3.0 (SD = 0.8). The average reported General Harm was 3.3 (SD = 0.8) and General Overuse was 3.8 (SD = 0.7). The Specific Necessity scale had significant positive skew (skewness = 1.0, 3.0x SES) as well as some issues with kurtosis (kurtosis = 0.9, 1.4x SEK). The General scales both had mild problems with skew, with the General Harm scale having a slight, positive skew and the General Overuse scale having a slight, negative skew (Both <2x SES).

Locus of Control

On the Multidimensional Health Locus of Control instrument, the mean Internal scale was 25.4 (SD = 4.2), the mean Chance scale was 18.6 (SD = 6.1), and the mean Powerful Others

scale was 23.5 (SD = 5.2). The Powerful Others scale had mild negative skew but the distributional properties of the three subscales were otherwise acceptable.

Apathy

On the AES, respondent scores ranged from 18 to 57 out of a theoretically possible range of 18-72. The mean response was 32.8 (SD = 10.0), and both the skewness and kurtosis of this measure were acceptable.

Epilepsy Knowledge

On the 19-item Epilepsy Knowledge Scale, scores ranged from 6-16 correct, with an average of 11.1 correct responses (SD = 2.4). The most frequently correct responses were an item asking whether blood samples could determine the level of anti-epileptic drugs in the body and an item asking whether doctors can achieve seizure control through medication in most cases (both 94% correct). The least frequently correct question was one asking if a person with epilepsy who drives is legally required to inform authorities about their condition (8% correct). This measure showed acceptable distributional properties.

On the 13-item Epilepsy Patient Knowledge Questionnaire (EPKQ), participant scores ranged from 4-12 correct, with an average of 8.2 correct answers (SD = 2.3). The most frequently correct answers were the item related to appropriate actions to take when one stops having seizures while taking seizure medications (88% correct), situations under which a car can be driven by a person who still has seizures (84%), and ability to name seizure medications (84%). The least commonly correct response was for an item probing for the ability of people with epilepsy to do various activities such as swimming under supervision, exercising, and consuming a limited amount of alcohol with dinner (only 18% answered correctly). The skewness of the EPKQ was acceptable; it was slightly platykurtotic (kurtosis = -1.0, or 1.5x the SEK).

Adherence Characteristics

Morisky

On the 4-item Morisky measure of adherence, 33% endorsed none of the four items, and 43% endorsed one item, for a total of 76% of participants indicating good adherence. Of the remainder, most (20% of sample) endorsed 2/4 items, while only one participant each endorsed 3/4 or 4/4 items. The most frequently endorsed item was the first item (“Do you ever forget to take your medicine?”), which was endorsed by 49% of participants.

RAM

Using the Gao & Nau (2000) measure of adherence, 33% of participants endorsed maladherence on the two day retrospective and 53% on the 14-day retrospective. The association between 2-day and 14-day RAM was strong (Spearman’s $\rho = 0.66$, $p < 0.001$). If any reported maladherence during either time period is taken as a sign of likely maladherence, then only 47% of participants reported good adherence using this measure. However, it was noted that many participants endorsed taking their medications either early or late. As no guideline was given to participants regarding what constitutes a significant deviation from the prescribed time schedule for medication, reports of early or late doses were recorded as maladherence events whenever participants mentioned them. When the retrospective adherence measure was recalculated using only recollections of missed doses, extra doses, or taking medications at a different dosage than prescribed, then the adherence rates using this measure improved. With the alternate methodology, 69% reported likely adherence, more in line with the results obtained with the Morisky technique. These two alternate calculations of RAM will be described herein as the Inclusive RAM (including reports of early or late dosing) and the Exclusive RAM (not including early or late dosing).

Associations among Morisky and RAM Measures of Adherence

Surprisingly, the association between the Morisky measurement and the RAM measurement was not significant either with the inclusion of early / late doses (Spearman's $\rho = 0.23$, $p = 0.12$) or without them (Spearman's $\rho = 0.17$, $p = 0.26$). The association between the RAM measure of adherence including and excluding time deviations from the dosing schedule was strong (Spearman's $\rho = 0.63$, $p < 0.001$).

Adherence and Depression

The association between depression and reported adherence was calculated in several different ways using depression as assessed by the MINI and the CES-D separately, since the concordance between these measures was poor in the sample. Individuals meeting current criteria for a Major Depressive Episode on the MINI were not found to be more likely to report maladherence than individuals using the Morisky measure, the Inclusive RAM, or the Exclusive RAM (Morisky: $\chi^2[1] = 0.15$, $p = 0.70$; RAM inclusive: $\chi^2[1] = 0.03$, $p = 0.86$; RAM exclusive: $\chi^2[1] = 0.36$; $p = 0.55$). When individuals with a history of mania or hypomania were excluded to consider only individuals who meet criteria on the MINI for Major Depressive Disorder, the results were unchanged.

Symptoms of depression as assessed by the CES-D Total Score were likewise unrelated to any of the three measures of adherence, either when used as continuous variables (i.e., Spearman correlations with the dichotomous adherence variables) or when used to classify individuals as depressed or non-depressed using the established cut-off score of 16. Correlations among the CES-D Total Score and the measures of adherence are provided in Table 4-4, and dichotomous tests of association among depression and the measures of adherence, with unadjusted odds ratios, are provided in Table 4-5.

In summary, no evidence was found in support of an association between depression and self-reported maladherence in this sample of epilepsy patients.

Bivariate Relationships among Predictors of Adherence

Bivariate relationships among the remaining proposed predictors of adherence behavior and the adherence measurements were considered next. Since most of these variables take on wide ranges and have interval or ratio-level data properties, and assessment of issues such as multicollinearity for a regression model rely on Pearson correlations, Pearson correlations were used for this analysis, excepting for a few variables which did not lend themselves well to use as continuous variables, in which case data was reduced into dichotomous form and chi-squared tests of association were used. These results are summarized in Table 4-6.

Demographics

No sex differences were observed in reported rates of adherence using any of the three measures (RAM Inclusive: $\chi^2[1] = 0.18$; $p = 0.67$; RAM Exclusive: $\chi^2[1] = 0.24$; $p = 0.63$; Morisky: $\chi^2[1] = 1.28$; $p = 0.26$). Age was not correlated with any of the three adherence measures. (all $p > 0.50$). The effects of race were considered using the two largest racial groups in the sample, Caucasians and African Americans. Using the inclusive RAM measure, Caucasian participants were more likely to endorse maladherence than African Americans (65% vs. 23%; RAM Inclusive: $\chi^2[1] = 6.30$; $p = 0.01$). This effect was non-significant for the other measures of adherence (RAM Exclusive: $\chi^2[1] = 2.30$; $p = 0.13$; Morisky: $\chi^2[1] = 0.14$; $p = 0.71$). When Caucasians were compared to *all* other racial groups in the sample, the same results were obtained. Those who had completed high school were not more or less likely to report maladherence using any of the measures than those who had not completed this much schooling (RAM Inclusive: $\chi^2[1] = 2.10$; $p = 0.15$; RAM Exclusive: $\chi^2[1] = 0.00$; $p = 0.97$; Morisky: $\chi^2[1] = 0.27$; $p = 0.60$). In summary, among demographic variables, only race was significantly

associated with any of the measures of adherence, with Caucasians reporting higher rates of maladherence on one measure.

Clinical Characteristics

With respect to basic healthcare behaviors and clinical variables, individuals who had partners, family members, or friends participate in their doctor's appointments were not more or less likely to report maladherence than those who did not receive this kind of assistance, according to any measure (RAM Inclusive: $\chi^2[1] = 0.41$; $p = 0.52$; RAM Exclusive: $\chi^2[1] = 1.58$; $p = 0.21$; Morisky: $\chi^2[1] = 0.41$; $p = 0.52$). The number of AEDs an individual was prescribed was not correlated with any measure of adherence, and when those who were prescribed monotherapy were compared to all individuals receiving polytherapy, there was also no association between monotherapy and adherence with any measure. Individuals who used a pillbox were likewise not more or less likely to report adherence than those who did not (RAM Inclusive: $\chi^2[1] = 0.07$; $p = 0.79$; RAM Exclusive: $\chi^2[1] = 1.37$; $p = 0.24$; Morisky: $\chi^2[1] = 0.88$; $p = 0.35$). Age of onset for the seizure disorder achieved trend-level significance in its association with adherence for the inclusive RAM only ($\chi^2[1] = 2.97$; $p = 0.09$), with a trend towards higher maladherence with those who had onset in childhood (64% reporting maladherence vs. 39% in those with adult onset). The same pattern was seen for the exclusive RAM, but the effect was not significant ($\chi^2[1] = 1.86$; $p = 0.17$); no difference was seen using the Morisky measure ($\chi^2[1] = 0.01$; $p = 0.94$). Those who had seizures for at least five years were more likely to report maladherence according to the inclusive RAM than those with shorter illness durations (62% vs. 29%; $\chi^2[1] = 4.38$; $p = 0.04$), but this effect lost significance for the exclusive RAM ($\chi^2[1] = 0.89$; $p = 0.35$) and for the Morisky measure ($\chi^2[1] = 0.12$; $p = 0.73$). As an approximation of quality of seizure control, those who reported no seizures in the past 30 days were compared to those who had reported one or more seizure in that time period. Those who

reported no seizures in the last 30 days were not significantly more or less likely to report adherence according to any of the measures (RAM Inclusive: $\chi^2[1] = 2.12$; $p = 0.15$; RAM Exclusive: $\chi^2[1] = 2.65$, $p = 0.10$; Morisky: $\chi^2[1] = 0.05$; $p = 0.83$). In summary, among clinical variables, earlier age at onset and longer duration of seizures were associated with maladherence.

Cognitive Characteristics

The Shipley Verbal subtest raw score was positively associated with reported maladherence (i.e., higher measured verbal intellectual abilities were associated with a lower likelihood of adherence) using the inclusive RAM ($r = 0.29$, $p = 0.048$), but not to either other measure. The relationship with the inclusive RAM dropped to trend significance when demographically corrected ($r = 0.26$, $p = 0.86$) and the relationships with the other measures remained non-significant. The Abstraction subtest raw score was not associated with any measure of adherence, nor was the corresponding demographically corrected T score. The SILS WAIS-R IQ estimate was also not significantly associated with any measure of adherence. The Stroop Word raw score was associated at the trend level, again, positively, to the exclusive RAM ($r = 0.28$, $p = 0.054$) but not to the other adherence measures. The Stroop Color raw score was positively associated with reported maladherence by the exclusive RAM ($r = 0.32$, $p = 0.03$) only. The Stroop Color-Word raw score was positively associated with the exclusive RAM ($r = 0.32$, $p = 0.03$) and at the trend level with the inclusive RAM ($r = 0.28$, $p = 0.06$). The calculated interference was not associated with any of the measures, but when the interference score was demographically adjusted, the T score was associated at a trend level with the inclusive RAM only ($r = 0.25$, $p = 0.09$). Neither raw score on the Digit Symbol subtest of the WAIS-III nor the age-corrected scaled score were significantly associated with any measure of adherence. RAVLT Total Learning was negatively associated with maladherence measured by the Morisky measure ($r = -0.32$, $p = 0.03$) only; similarly, the RAVLT Delayed Recall was negatively associated with

Morisky maladherence at the trend level ($r = -0.29$, $p = 0.052$) only; the latter relationship was likewise trend significant only with the Morisky measure ($r = -0.28$, $p = 0.059$). In summary, among cognitive variables, higher Shipley Verbal raw scores, higher Stroop Word, Color, and Color-Word raw scores, and lower RAVLT Total Learning and Delayed Recall were associated with maladherence using one or more measure.

Healthcare Attitudes and Beliefs

Scores on the IPQ were not associated with reported adherence using any of the measures. On the MHLC, Internal scale scores were unrelated to reported adherence. In contrast, higher Chance scale scores were associated with lower reported adherence on both the inclusive and exclusive RAMs ($r = -0.34$, $p = 0.02$; $r = -0.48$, $p = 0.001$, respectively). The Powerful Others scale score (i.e., the extent to which locus of control is attributed to healthcare providers) was negatively associated with the exclusive RAM maladherence ($r = -0.37$, $p = 0.01$) and at the trend level also with the inclusive RAM ($r = -0.24$, $p = 0.10$) but not with the Morisky measure. The BMQ Specific Necessity subscale was not significantly associated with any of the measures, but the Specific Concerns scale was negatively associated with inclusive RAM ($r = -0.28$, $p = 0.05$) only. Neither the General Harm nor the General Overuse subscales were associated with any of the measures of maladherence. Epilepsy knowledge as measured with the EKS was positively associated with inclusive RAM ($r = 0.37$, $p = 0.01$) but not with the other measures. The EPKQ was not significantly associated with any of the measures. Finally, the AES was associated at the trend level with both the inclusive and exclusive RAMs ($r = 0.26$, $p = 0.08$; $r = 0.26$, $p = 0.08$, respectively). In summary, higher Chance and Powerful Others locus of control, higher levels of Specific Concerns with respect to epilepsy medications, and greater epilepsy knowledge were associated with reduced adherence.

The Effect of Depression on Relationships among Adherence and Health Behaviors

To assess whether any of the health behaviors, clinical, or cognitive characteristics that predicted adherence had different effects in depressed individuals than in non-depressed individuals, correlations for the significant variables mentioned above were repeated separately for those individuals who met MINI criteria for current Major Depressive Disorder and those who did not. In those who did not meet current criteria for MDD, the MHLC Chance scale continued to be negatively associated with exclusive RAM ($r = -0.51, p = 0.003$) and at a trend level with the inclusive RAM as well ($r = -0.33, p = 0.07$). The BMQ Specific Necessity scale was significantly positively associated with inclusive RAM ($r = 0.36, p = 0.04$) and at a trend level with the exclusive RAM ($r = 0.35, p = 0.052$). The EKS was positively correlated with inclusive RAM only ($r = 0.38, p = 0.04$). The RAVLT Total Learning was negatively associated with Morisky maladherence at the trend level only ($r = -0.33, p = 0.07$). Caucasian race continued to be associated with the inclusive RAM ($r = 0.47, p = 0.01$). Duration of seizures was no longer a significant predictor.

When these correlations were repeated in the *depressed* group (it should be noted that this group was very small, leading to a very large requirement for the magnitude of correlations in order for them to reach statistical significance), the MHLC Chance scale was no longer significantly associated with the exclusive RAM but continued at the trend level of association with the inclusive RAM ($r = -0.51, p = 0.06$). Neither the BMQ Specific Necessity subscale nor the EKS continued to have significant correlation with any measure of adherence. The RAVLT Total Learning score likewise was no longer significant as a predictor, even at the trend level. Likewise, Caucasian race was also non-significant. Duration of seizures continued to be non-significant. As well, while the Morisky measure of adherence was not significantly correlated with either the inclusive or exclusive RAM in the non-depressed subgroup, it was moderately to

strongly correlated with both RAM measures in the depressed group (with the inclusive RAM: $r = 0.60$, $p = 0.02$; with the exclusive RAM: $r = 0.83$, $p < 0.001$). The correlation between the Morisky measure and the inclusive RAM was significantly greater in the depressed group than in the non-depressed group ($Z' = -1.7$, $p = 0.049$), as was the correlation between the Morisky measure and the exclusive RAM ($Z' = -3.6$, $p < 0.001$). Finally, these associations were also tested with the Kappa statistic, an assessment of association between dichotomous variables, with similar results. In the non-depressed group, the inclusive RAM was likewise not significantly associated with the Morisky measure ($\kappa = 0.09$, $p = 0.54$) but this association became significant in the depressed group ($\kappa = 0.53$, $p = 0.02$). The exclusive RAM was similarly not significantly associated with the Morisky measure in the non-depressed group $\kappa = -0.11$, $p = 0.52$) but this association again became significant in the depressed group $\kappa = 0.81$, $p = 0.002$). In the non-depressed group, only 53% of participants showed concordance on the exclusive RAM and the Morisky measure of adherence. In contrast, the concordance rate was 93% in the depressed group. Results of the separate analyses for the depressed and non-depressed groups of participants are summarized in Table 4-7.

Adherence and Health Behaviors

Because of the small sample size, variables with larger bivariate associations with at least one of the adherence measures as well as good distributional properties were chosen for the regression analysis. The set of predictors was fixed for regressions against both the Morisky and RAM assessments of adherence, in order to allow for comparison between models.

First considering variables significant for any measure of adherence, race, duration, Shipley Verbal raw score, Stroop task scores, RAVLT Total Learning, Chance and Powerful Others loci of control, Specific Concerns from the BMQ, and knowledge as measured by the EKS were all significantly associated with at least one measure of adherence at the $p < 0.05$.

level. Since a number of intercorrelated cognitive and healthcare attitude variables met this criteria, further rationalization in these areas was undertaken. Numerous strong correlations among the cognitive variables existed; to avoid multicollinearity, the cognitive variable with the most robust univariate relationship (by magnitude of both the correlation itself and of the significance, or p value), the RAVLT Total Learning Score, was chosen. Among the healthcare attitude variables, since the Chance and Powerful Others scales of the MHLC were similar and positively associated, the Chance scale was chosen, as it likewise had the most robust univariate relationship with one of the adherence measures (again, by both magnitude of the correlation and by significance). This left a total of six predictors: race, duration, RAVLT Total Learning, MHLC Chance, BMQ Specific Concerns, and the EKS. When bivariate correlations among this remaining group were considered, no strong correlations (all $r < 0.6$) remained. This set of predictors was then used for regression models against each of the three measures of adherence – the inclusive and exclusive RAMs and the Morisky measure.

The model assessing the six predictors' ability to predict maladherence with the inclusive RAM was significant ($\chi^2[6] = 23.13$; $p = 0.001$) and correctly classified 78% of participants (compared to a correct classification of 52% of participants with a constant model). Caucasian race and the EKS were significant predictors and the MHLC Chance subscale and the BMQ Specific Concerns subscale were significant at the trend levels. The results of this regression are provided in Table 4-8.

When the same model was applied to the exclusive RAM, it was also significant ($\chi^2[6] = 13.78$; $p = 0.03$) and correctly classified 74% of participants (compared to 67% for this null model). Only the MHLC Chance subscale was significant as a predictor. The results of this regression are provided in Table 4-9.

Next, the model was applied to the Morisky adherence measure. This model was not significant ($\chi^2[6] = 8.41$; $p = 0.21$); while it correctly classified 80% of participants, the null model classified 76% of participant correctly due to the lower base rate of maladherence reported by this measure. Since the individual significance of the RAVLT Total Learning score was still significant, this model was re-attempted with all other predictors removed. The model predicting the Morisky adherence using only the RAVLT Total Learning was significant ($\chi^2[1] = 5.10$; $p = 0.024$) and correctly classified 81% of participants. The odds ratio associated with each point change in the RAVLT Total Learning was 0.921 (95% CI = 0.853 – 0.995).

Adherence, Depression, and Seizure Control

Finally, to assess the relationships among reported adherence, seizure control, and depression, chi-square tests for the association between seizure control and adherence were repeated separately for the participants who did and did not meet criteria for current Major Depressive Disorder on the MINI. For these tests, seizure control was approximated by comparing participants with no reported seizures in the past 30 days with those who had one or more reported seizures in the last 30 days. On the inclusive RAM measure, the association between seizure control and adherence was not significant for either the depressed ($\chi^2[1] = 1.75$; $p = 0.19$) or non-depressed group ($\chi^2[1] = 1.01$, $p = 0.31$). Similarly, on the exclusive RAM, no significant association was found for either the depressed ($\chi^2[1] = 1.75$; $p = 0.19$) or the non-depressed ($\chi^2[1] = 0.93$; $p = 0.33$) group. Finally, for the Morisky measure as well, no significant association was found for either the depressed ($\chi^2[1] = 0.01$; $p = 0.94$) or the non-depressed group ($\chi^2[1] = 0.64$; $p = 0.43$). To evaluate the possibility that depression might have an association to seizure control without taking adherence into account, the association between current Major Depressive Disorder and seizure control was also considered. Those who met

criteria for current MDD were not significantly more or less likely to report being seizure free over the past 30 days ($\chi^2 [1] = 2.29$; $p = 0.13$).

Table 4-1. Demographic and clinical characteristics of participants

<i>Characteristic</i>	<i>Frequency (%) or Mean (SD in parenthesis)</i>
Female	79%
Age	42 y (12.5 y)
Race: Caucasian	63%
African American	29%
Education: <12 y	28%
12 y	28%
>12 y	44%
Married	49%
Seizure onset at 21 y old or older	51%
Illness duration > 5 y	71%
Period of seizure freedom >6 months (lifetime since seizure onset)	53%
Seizure freedom in the last 30 days	28%
Number of medication doses per day	2.0 (0.6)
Receiving monotherapy	19%

Table 4-2. Psychiatric comorbidities observed in the study sample

<i>Comorbidity*</i>	<i>Number Meeting Criteria</i>	<i>Percentage</i>
Major Depressive Episode	19	40
Dysthymia	4	8
Mania	1	2
Hypomania	1	2
Panic Disorder	6	13
Agoraphobia without Panic Disorder (AWOPD)	2	4
Social Phobia	4	8
Obsessive-Compulsive Disorder	2	4
Posttraumatic Stress Disorder	7	15
Alcohol Dependence	3	6
Substance Dependence	2	4
Anorexia Nervosa	0	0
Bulimia Nervosa	2	4
Generalized Anxiety Disorder	10	21

Notes: * All comorbidities listed were assessed for *current* fulfillment of criteria.

Table 4-3. Cognitive characteristics of study participants

<i>Test</i>	<i>Average Score*</i>	<i>Minimum</i>	<i>Maximum</i>	<i>SD</i>
SILS Vocabulary Raw Score	23.2	11	36	5.9
SILS Vocabulary T score	37.7	15	60	10.2
SILS Abstraction Raw Score	15.2	2	36	8.4
SILS Abstraction T score	44.4	31	62	7.6
SILS Estimated FSIQ (StS)	96.6	76	112	9.3
Stroop Word Raw	76.1	38	113	17.3
Stroop Color Raw	59.4	29	89	15.0
Stroop Color-Word Raw	30.9	0	64	13.7
Stroop Color-Word Interference	-2.1	-17.6	20.6	9.2
RAVLT Total Learning	36.7	14	58	10.2
RAVLT Delayed Recall	6.3	0	12	3.4
Digit Symbol Raw Score	53.5	14	89	21.2

Notes: * Scores are listed as raw scores unless otherwise indicated. T scores and Standard Scores represent demographically corrected performance in comparison to published population norms. Where T scores are indicated, these scores have a mean of 50 and a standard deviation of 10 in the normative sample. Where Standard Scores (StS) are listed, these have a mean of 100 and a standard deviation of 15 in the normative sample.

Table 4-4. Correlations among CES-D Total Score and measures of adherence

	<i>Correlation with CES-D Total Score</i>	<i>sig</i>
Inclusive RAM	0.04	0.77
Exclusive RAM	0.00	0.99
Morisky	0.12	0.40

Table 4-5. Associations among measures of depression and measures of adherence

<i>Measure of Depression</i>	<i>Measure of Adherence</i>	<i>Percentage of depressed individuals reporting maladherence</i>	<i>Percentage of non-depressed individuals reporting maladherence</i>	<i>Risk Ratio</i>	<i>Test Statistic</i>	<i>sig</i>
CES-D	Inclusive RAM	59%	38%	1.6	$\chi^2 [1] = 2.05$	0.15
	Exclusive RAM	34%	25%	1.4	$\chi^2 [1] = 0.44$	0.51
	Morisky	24%	19%	1.3	$\chi^2 [1] = 0.15$	0.70
	Inclusive RAM	53%	50%	1.1	$\chi^2 [1] = 0.03$	0.86
	Exclusive RAM	37%	29%	1.3	$\chi^2 [1] = 0.36$	0.55
	Morisky	26%	21%	1.2	$\chi^2 [1] = 0.15$	0.70

Table 4-6. Relationships among health knowledge, attitudes, and adherence

	<i>Inclusive RAM</i>	<i>Exclusive RAM</i>	<i>Morisky</i>	<i>IPQ</i>	<i>MHLC Internal</i>	<i>MHLC Chance</i>	<i>MHLC Others</i>	<i>BMQ Specific Necessity</i>	<i>BMQ Specific Concerns</i>	<i>BMQ General Harm</i>	<i>BMQ General Overuse</i>	<i>EKS</i>	<i>EPKQ</i>	<i>AES</i>
Inclusive RAM	1.00	0.62**	0.23	0.13	0.01	-0.34*	-0.24†	0.16	-0.28*	0.08	0.09	0.37*	0.20	0.26†
Exclusive RAM		1.00	0.17	0.04	0.09	-0.48**	-0.37*	0.13	-0.04	0.03	0.13	0.14	0.05	0.26†
Morisky			1.00	0.12	0.15	-0.01	0.03	-0.03	0.14	-0.04	0.09	0.02	-0.13	0.01
IPQ				1.00	0.01	-0.05	-0.14	-0.14	-0.46**	-0.22	-0.19	-0.14	0.02	0.29*
MHLC Internal					1.00	0.04	0.12	-0.20	0.22	0.39**	0.10	0.08	0.03	-0.21
MHLC Chance						1.00	0.35*	-0.06	-0.06	-0.16	-0.38**	-	-0.15	0.00
MHLC Others							1.00	-0.21	-0.03	0.29*	0.02	-0.15	-0.08	0.10
BMQ Specific Necessity								1.00	-0.01	-0.11	-0.11	0.33*	-0.11	-0.34*
BMQ Specific Concerns									1.00	0.37*	0.40**	0.09	-0.04	-0.21
BMQ General Harm										1.00	0.64**	-0.02	0.15	-0.02
BMQ General Overuse											1.00	0.17	0.25†	0.11
EKS												1.00	0.32*	-0.10
EPKQ													1.00	0.06
AES														1.00

Note: Correlations marked with (†) are trend-significant at the $p < 0.10$ level; (*) are significant at the $p < 0.05$ level, and (**) at the $p < 0.01$ level.

Table 4-7. Effects of attitudes and knowledge on depressed and non-depressed participants

	Inclusive RAM		Exclusive RAM		Morisky	
	Not Depressed	Depressed	Not Depressed	Depressed	Not Depressed	Depressed
Inclusive RAM	1.00	1.00	0.65**	0.73**	0.11	0.60*
Exclusive RAM	0.65**	0.73**	1.00	1.00	-0.11	0.83**
Morisky	0.11	0.60**	-0.11	0.83**	1.00	1.00
MHLC Chance	-0.33†	-0.51†	-0.51**	-0.36	0.11	-0.20
BMQ Specific	0.36*	-0.30	0.35†	-0.27	0.04	-0.20
Necessity						
EKS	0.38*	0.39	0.20	0.00	0.04	-0.07

Note: Correlations marked with (†) are trend-significant at the $p < 0.10$ level; (*) are significant at the $p < 0.05$ level, and (**) at the $p < 0.01$ level.

Table 4-8. Logistic regression model predicting inclusive RAM

Predictor	B	SE	Wald	Df	Sig	Risk Ratio	95% CI
Constant	0.52	3.44	0.02	1.00	0.88	1.69	
Caucasian race	2.02	0.99	4.21	1.00	0.04	7.57	(1.10, 52.32)
Duration of epilepsy >5 yrs	1.21	0.90	1.83	1.00	0.18	3.36	(0.58, 19.47)
RAVLT Total Learning Score	-0.05	0.05	1.21	1.00	0.27	0.95	(0.87, 1.04)
MHLC Total Chance Scale	-0.13	0.08	2.75	1.00	0.10	0.87	(0.75, 1.02)
BMQ Specific Concerns	-1.09	0.61	3.22	1.00	0.07	0.34	(0.10, 1.11)
EKS Total Score	0.43	0.21	4.18	1.00	0.04	1.54	(1.02, 2.34)

Table 4-9. Logistic regression model predicting exclusive RAM

Predictor	B	SE	Wald	df	sig	Risk Ratio	95% CI
Constant	2.93	3.45	0.72	1.00	0.40		
Caucasian race	0.83	0.87	0.91	1.00	0.34	2.30	(0.41, 12.77)
Duration of epilepsy >5 yrs	0.66	0.90	0.54	1.00	0.46	1.94	(0.33, 11.32)
RAVLT Total Learning Score	-0.02	0.04	0.31	1.00	0.58	0.98	(0.90, 1.06)
MHLC Total Chance Scale	-0.23	0.08	7.18	1.00	0.01	0.80	(0.68, 0.94)
BMQ Specific Concerns	-0.11	0.50	0.05	1.00	0.83	0.90	(0.33, 2.39)
EKS Total Score	0.03	0.18	0.02	1.00	0.89	1.03	(0.71, 1.47)

CHAPTER 5 DISCUSSION

Review of study findings

Aim 1: Relationship between Depression and Adherence

It was hypothesized that, consistent with findings in studies of adherence in other diseases, co-morbid depression would be significantly associated with decreased adherence. Despite the use of two independent measures of self-reported adherence as well as two measures of depression, no relationship between depression and adherence was observed, nor even a trend towards such a relationship. This was quite unexpected, since this finding has been widely reported and replicated in other disease populations. On the one hand, the present study had an insufficiently large sample size to conclusively rule out the possibility of a relationship between depression and adherence in epilepsy patients. On the other hand, the lack of even a trend towards such a pattern is surprising.

Adding to the surprising nature of this finding are the observations that the base rates of reported maladherence and depression are both generally consistent with expectations from other studies, limiting the possibility that this finding arose from an atypical sample. The rates of maladherence, ranging from 24% for the Morisky measure to 31% for the exclusive RAM and 53% for the inclusive RAM, were generally consistent with reports of maladherence rates both across chronic illness groups and specifically when comparing the obtained Morisky rate of adherence in comparison to with studies of epilepsy patients using this same measure (Jones et al., 2006; McAuley et al., 2008). For instance, Jones et al. (2006) reported that 59% of their sample endorsed one or more Morisky items, which is comparable to the 67% observed in the present study (this study classified all individuals who endorsed at least *one* Morisky item as maladherent). McAuley et al. (2008) reported that 69% of participants endorsed 0-1 Morisky

items, which compares favorably with a rate of 76% observed in the present study. Likewise, while the rate of reported depression according to a traditional cut-off score for the CES-D was higher than expected (70%), the percentage of individuals meeting criteria for a current Major Depressive Episode on the MINI (40%) was very comparable to the observed rates of depression of 20-55% in people with incompletely controlled epilepsy (Kanner, 2003).

Aim 2: Relationships among Health Knowledge, Attitudes, and Adherence

It was hypothesized that health knowledge, beliefs, and attitudes would predict rates of adherence, and this hypothesis was partially validated. Measures of healthcare knowledge and attitudes in several different areas were assessed: perception of the impact of illness, beliefs about medications, beliefs about locus of control in the context of health management, knowledge about epilepsy, and apathy as a measure of ability to engage in motivated behavior. *None* of these measures was found to be significantly associated with Morisky reports of adherence. In contrast, several of them were found to be associated with RAM reports of adherence. Higher levels of Chance or Powerful Others locus of control on the MHLC instrument were found to be associated with more reported maladherence on the RAMs. Higher levels of endorsed concerns about epilepsy medications on the BMQ Specific Concerns subscale were also found to be associated with more reported maladherence on the RAMs. Finally, higher knowledge as measured by one of two knowledge instruments had the same association. While the first two findings are generally consistent with expectations, the finding that greater levels of epilepsy knowledge predicted lower adherence was surprising.

Additionally, several other variables were found to significantly predict reported adherence. Among demographic variables, Caucasian race was found to be a significant predictor of lower adherence rates. This finding has been replicated by at least one other study in epilepsy (McAuley, 2008). The relatively weak importance of demographic factors in predicting

adherence is consistent with studies outside of epilepsy that examine adherence to medications in chronic illnesses have generally suggested that demographic variables are not very strong predictors of adherence (e.g., Curtis et al., 2009). Among basic clinical variables, only the related characteristics of age at onset and duration of the seizure disorder were predictors of adherence. Finally, among cognitive variables, two separate patterns were observed. A number of cognitive variables – performance on the Shipley Institute of Living Scale's Verbal subtest, a measure of verbal reasoning ability, as well as speed of performance (but not level of interference) on the Stroop Test – were *positively* associated with the RAM measures of adherence. That is, individuals who performed better on these instruments were *more* likely to report maladherence. The second pattern observed was that performance on the RAVLT was *negatively* associated with the Morisky measure – that is, that individuals with poorer verbal memory performance were more likely to report maladherence. Thus, interestingly, individuals with stronger cognitive performance were likely to report maladherence on one instrument, and individuals with weaker cognitive functioning (albeit, in different domains) were likely to report maladherence on another.

Aim 3: Effects of Knowledge and Attitudes in Depressed Individuals

It was hypothesized that knowledge, belief, and attitude measures would be more strongly associated with adherence reports in depressed individuals because of the effect of depression on these cognitive and emotional processes. Surprisingly, while different relationships were found between these variables and adherence in depressed and non-depressed individuals, the *opposite* pattern was largely found, with these variables having generally more predictive power in non-depressed individuals, falling mostly to non-significance in depressed individuals.

The effect of depression on the relationships between other predictors of adherence took a somewhat complex form. In non-depressed individuals, the relationships tended to be similar to

the relationships in the whole sample, with different health behavioral and cognitive variables predicting the RAM and Morisky measures of adherence, which were themselves not strongly associated. In contrast, in the depressed group, many of these predictors became non-significant, but the relationship between the Morisky and RAM measures of adherence became quite strong. In fact, in the depressed group, only a single person had different assessments of adherence by the Morisky and exclusive RAM methods.

Aim 4: Depression, Adherence, and Seizure Control

Surprisingly, no significant relationships were found between seizure control and adherence using any of the adherence measures, either in the full sample or in either the depressed or non-depressed groups. This is in contrast to the findings of Jones (2006) who found an association between the Morisky measure and seizure control, using a similar measure of seizure control (patient report of less than one seizure per month). Likewise, no relationship was found between depression and seizure control even without considering adherence.

Implications of the Study

Depression's Role in Epilepsy Adherence

The surprising lack of an association between adherence and depression in this study, using two different measures of adherence as well as two different measures of depression has several possible explanations. First, the study *was* nonetheless under-powered to detect adherence differences between populations at the average rate observed in other disease populations. Given this and the absence of other published studies assessing the relationship between adherence and depression in epilepsy patients, interpreting the findings as indicative that there truly is *not* the strong relationship between these variables in epilepsy that exists outside of epilepsy is not yet justified. Although this may be the case, more work would be necessary to confirm this hypothesis. As adherence studies do not exist in every chronic or

serious illness, however, it has not fully been established whether there *are* significant differences in medication adherence rates from disease to disease. One notable issue is that much of the research on adherence and depression has been done with populations that have non-neurological diseases. While results associating adherence and depression have been reported in neurological diseases, including multiple sclerosis (Mohr et al., 1996) and Parkinson's disease (Grosset, Bone, & Grosset, 2005), these studies did not report data that could readily be converted into an odds or risk ratio as has typically been done in other studies of adherence and depression, and it is difficult to determine, based on these studies, whether the expectation for the risk for maladherence conferred by co-morbid depression should be of the same size observed in other studies or not. Should the risk be smaller for some reason in patients with neurological conditions, then a substantially larger sample might be needed to detect it.

One aspect that differentiates neurological and psychiatric diseases from diseases of other systems of the body is that many of them have a direct effect on cognition and/or emotion, by virtue of disrupting brain function, in addition to the indirect effects on these areas through biological (e.g. stress response) and/or other psychosocial processes (e.g. stigma, loss of roles, etc.). In some neurological disorders, depression is less a co-morbid feature and nearly a part of the typical disease process – in the case of Parkinson's disease, emotional disturbances associated with depression can even *precede* clearly identifiable motor symptoms (Müller et al., 2006; Reisberg et al., 2008). In this way, depression may possibly be thought of as a marker of the underlying neural disruption of epilepsy itself, rather than as a secondary and separate disease process. Indeed, some authors have suggested that, as in Parkinson's disease, depression may sometimes be a prodromal feature of epilepsy (Kanner, 2008). This would argue that epilepsy-related depression is in some way a different disorder than observed in other chronic

illness populations not involving brain dysfunction. Arguing against this, however, are the observations that depression happens at a similar base rate in epilepsy as in other symptomatic chronic illnesses, and that the clinical presentation of depression in epilepsy is by and large very similar to that in other chronic illness populations as well as in depressed individuals without other medical co-morbidities (Evans et al., 2005). The neurological basis of epilepsy may also make health behaviors different in epilepsy in other ways, perhaps by eliciting different kinds of supportive services from family members and other loved ones. The effects of epilepsy on memory might also distort either adherence or ability to report adherence. Arguing against these last two hypotheses is the finding that reported rates of adherence and adherence measurement tools generally appear similar in people with epilepsy and other individuals, as well, in the latter case, as the finding that at least one of the adherence measures in this study was *not* associated with an objective measure of memory. Nonetheless, given the strong body of literature finding adherence issues across diseases to be related to depression, and the similarities observed in adherence behaviors themselves in people with epilepsy and people with other chronic illnesses, multiple replications or very large samples would be necessary before we can conclude that depression does not affect adherence in people with epilepsy.

Additionally, while DiMatteo et al. (2000) demonstrated effects on adherence that were isolated to depression, it is notable that the population in the present study had significant psychiatric comorbidity outside of depression, including substantial rates of panic disorder, generalized anxiety disorder, and posttraumatic stress disorder. Even if these disorders do not directly affect adherence, this study included individuals as “depressed” participants who often had other psychiatric comorbidities, and individuals as “not depressed” who may likewise have had psychiatric comorbidities other than depression. While this increases generalizability to the

clinical setting, where psychiatric disorders are often *not* seen in isolation, unmeasured effects of these comorbidities may also confound attempts to detect the effect of depression on adherence.

Possible Roles of Knowledge and Attitudes in Adherence

It was hypothesized that healthcare knowledge and attitudes might be mechanisms through which the cognitive and emotional sequelae of depression affect adherence behaviors.

Surprisingly, it was instead found that, not only did adherence not depend on depression in this sample, but that adherence in depressed individuals was more uniformly described by different adherence measurements and had few associations with healthcare knowledge and attitudes, whereas, in contrast, these aspects of thought and belief *were* modestly strong predictors of adherence in *non-depressed* individuals. Although healthcare beliefs, attitudes, and knowledge are certainly acknowledged to vary in non-depressed individuals, there is no theoretical basis to expect problems in these areas in the non-depressed individuals instead of the depressed individuals. There are a number of possible interpretations of this. One possibility is that depression either reduces the range or reliability of report on these other instruments, artificially making them less capable as predictors of adherence. Another possibility is that depression acts on adherence through completely different mechanisms that were not examined in this study. It is also possible that depression truly does not have a significant impact on adherence rates in people with epilepsy, but that the proposed model might describe its mechanism of impact in other populations where it does have the generally established impact of reducing adherence rates. Finally, it is possible that, while the two adherence measures more closely measure the *same* thing in people with epilepsy and co-morbid depression, they do not actually measure *adherence* effectively, thus leading to a spurious lack of association. However, if this were the case, it would seem quite odd that these measures would produce such comparable rates of “adherence” in depressed and non-depressed participants.

In terms of the independent impact of knowledge and attitudes on adherence, some of this study's findings were consistent with the idea that maladherence is, in part, the by-product of subjective theories developed by patients through which they attempt to understand their relationship with their illness and their ability to take actions to maintain their health and wellbeing (Wagner, 2003; Remien et al., 2003). For instance, it was found that individuals who had specific concerns about their epilepsy medications were less likely to be adherent. One possible explanation for this is that when patients identify concerns about their medications, they may develop subjective models for how their medications may negatively impact them, and based upon these models, either more frequently choose to engage in maladherence or else be more passively tolerant of their maladherence and less motivated to change it. Supporting this is the finding in another study that both adherence and the BMQ Specific Concerns and Specific Necessity subscales were associated with seizure control (Jones et al., 2006). Similarly, it was found that individuals who had higher Chance and Powerful Others loci of control were less likely to be adherent. It seems reasonable that individuals who perceive that their health is determined by forces outside their control are unlikely to see their own actions as being strong determinants on their health status. Therefore, these individuals may place a low importance on the consistency of their actions, for instance being relatively indifferent to missing medication doses. At least one other study of adherence behaviors outside of epilepsy has found that adherence was associated with higher internal locus of control and lower chance and powerful other loci of control (Ubbiali et al., 2008).

The findings that stronger levels of epilepsy knowledge on at least one measure of this construct led to lower reported rates of adherence is more surprising, especially considering that it was found in the same measures (the RAMs) in which better cognitive performance was also

found to be associated with lower reported adherence. One possible explanation is that the adage that “a little bit of knowledge can be dangerous” holds true in this case, and that certain levels or kinds of knowledge about seizure disorders or about health and medicine in general may fuel the “subjective theories” described by Remien et al. (2003) and cause individuals to engage in “intentional” maladherence. Another possibility is that both the higher levels of epilepsy knowledge and higher cognitive functioning suggest that individuals reported more events of maladherence on the RAM not because they actually *were* more maladherent, but because they either better remembered these events or were more sensitive to reports of *subtle* maladherence, raising their internal standard for good adherence to their medication regimen or more conscientiously reporting their adherence behaviors. Arguing in favor of this is the finding that the relationship between epilepsy knowledge and adherence was found only in the inclusive RAM and not in the exclusive RAM, as the inclusion in the former measure of early or late dosing by the participants’ own definition allowed more room for report of “subtle” maladherence. On the other hand, the relationships between health attitude or belief measures on instruments such as the MHLC and BMQ and these same RAM measures of adherence seem harder to explain if the adherence reports are primarily driven by this conscientiousness, and if both mechanisms are at play, disentangling them will be challenging.

Implications for Seizure Control

The surprising failure to find a relationship between seizure control and adherence may be attributable to a number of causes. Some non-significant associations did approach significance, and it is possible these might become significant in a larger sample. In addition to the effects of sample size, this result may reflect choices made in the selection of the sample. While the sample of individuals who have a stable diagnosis but continue to have had recent seizures was intended to generate a sample in which the question of adherence would be particularly relevant, it is

possible that the opposite result was obtained by excluding a large number of adherent and seizure free individuals who had not had a seizure in the past six months, as in the study by Jones et al. (2006). Although this is possible, the fact that observed adherence rates are generally in keeping with those reported elsewhere does make this seem somewhat less likely. Finally, there are inherent limitations in considering only the last 30 days as a measure of the quality of seizure control – an individual who typically has one seizure in six months would be classified, quite arbitrarily, by this system into the good seizure control category if the most recent seizure occurred more than 30 days ago, and into the poor seizure control category if it happened to occur in the last 30 days, even if this did not represent a deviation from the historical seizure frequency.

As for the relationship between *depression* and seizure control, the failure to find this relationship was also surprising. On the one hand, this study selected only individuals with relatively recent seizures. As a result of this inclusion criteria, the effect of individuals who do not have recent seizures, who in other studies (as discussed by Kanner, 2003) have been found much less likely to be depressed, were not considered. It is possible that depression *may not* have an impact on short-term seizure frequency. For instance, Haut, Shinnar, & Moshé (2005) found that there was no significant relationship between seizure clustering and depression. On the other hand, since the majority of participants in this study (50%) had 0-1 seizures in the past month, with a small number having a much larger number of seizures, it is also certainly possible that this effect is due primarily to the difficulty in measuring changes in seizure frequency in a group that has a relatively low base seizure frequency. Also not considered in the present study is that many of the participants who were depressed were actively being treated with antidepressants. While those classified as depressed for study purposes still met full criteria for Major Depressive

Disorder, it is also possible that any partial antidepressant response obtained by participants had a confounding impact on seizure frequency.

The Challenge in Measuring Adherence

Of the three chief constructs under study in this dissertation, epilepsy, depression, and adherence, adherence is unique in that there is no established reference measurement or assessment of adherence that is considered essentially fully accurate (Dunbar, 1984). Each technique (self-report, pill counting, electronic monitoring of adherence, and blood assay monitoring of medication levels) has significant limitations. In addition, there is no consensually-agreed upon definition of a maladherence event, particularly in the case of a deviation from the time at which a dose is prescribed to be taken. While researchers have attempted to define this construct (e.g., Cramer, Vachon, Desforges, & Sussman, 1995), these definitions have not been universally adopted.

One might imagine a continuous video monitoring of a patient in their natural environment (although even this might result in measurement reactivity). Were this referential standard to exist, then all other, more economical measures of adherence could be assessed for efficacy against it. Unfortunately, in the absence of such a circumstance, no existing measure of adherence is able to play this role – just as the self-report measure of adherence is susceptible to the possibility of forgetting or intentionally distorting the recollection of adherence behaviors, so too the blood level is susceptible to mechanisms other than adherence that alter observed levels of a medication.

Thus, significant work still needs to be done to establish more acceptable operational definitions of adherence and maladherence through the process of convergent and discriminant validation. Work by the International Society of Pharmacoeconomics and Outcomes Research Economics of Medication Compliance Working Group is encouraging in this regard, as this body

may have the ability to standardize practice within research as well as clinical settings (Hughes et al., 2007). Even if an eventual standard lacks complete reliability, the use of common protocols is likely to extend the interpretability and comparability of adherence research.

While the two measures of adherence used in this study were both within the self-report domain, they had relatively poor concordance, except when considered in depressed individuals separately. The finding of poor concordance between the Morisky measure and the RAMs is consistent with results reported outside of epilepsy (Gao & Nau, 2000). However, in the absence of a referential standard, it is hard to *interpret* the discordant results of the instruments. In judging the two measures of adherence used in the present study, then, it becomes necessary to attempt to understand their behavior in terms of their relationships with other study variables. One striking finding is that only one of the two measures, the Morisky measure, correlated with a test of memory and learning, the Rey Auditory Verbal Learning Test. In fact, where the retrospective adherence measure (RAM) correlated with cognitive variables, it had the unexpected pattern of generally indicating *more* reported maladherence in cognitively stronger participants. There are many possible interpretations of this. Certainly, one possibility is that the relationship between the RAVLT and the Morisky measure is an indicator that memory functioning plays a role in adherence and the Morisky measure, since it is correlated with memory functioning, is more likely to concord with the true adherence behaviors. At the same time, it might be argued that the task in the RAM is not truly a retrospective memory task (as the RAVLT is) but is actually a test of an aspect of *prospective* memory (i.e., memory that a task that was to be done, was in fact done; Gould, McDonald-Midczak, & King, 1997). The body of literature investigating prospective memory is much smaller than the body of literature investigating retrospective memory, with some studies in other illnesses suggesting that they

may be incompletely correlated (e.g., Martins & Damasceno, 2008). Only two studies were found investigating prospective memory in people with epilepsy (López-Góngora et al., 2008; Adda et al., 2008). One of these studies (Adda et al., 2008) did suggest, however, that prospective memory may be impaired via pathology of the same mesial temporal structures through which retrospective memory is impaired in individuals with temporal lobe epilepsy. Nonetheless, this research is still limited, and one might not *expect* the RAM, if it measures an aspect of prospective memory, to correlate strongly with a test of retrospective memory. Still another possibility is that individuals with weak memory performance may be less *aware* of their adherence behaviors, and that their report might represent a systematic bias to endorsing maladherence in the absence of memories that contradict it, although there does not seem to be an obvious reason to expect a systematic bias towards reporting *maladherence* instead of adherence.

Another striking finding was that, while the measures of adherence were poorly correlated in the non-depressed portion of the sample, they became very highly concordant in the depressed portion of the sample. While studies have looked at the effect of depression on assessed adherence, we are not aware of other studies that have looked at the *performance* of self-report adherence measurements in depressed and non-depressed individuals. One possibility for explaining this finding is that individuals who are not depressed use disparate processes for responding to the two types of questionnaires. Supporting this is the observation that only the Morisky measurement was strongly associated with measures of memory. As discussed above, memory may play a different role in the Morisky measure, which does not require identification of specific instances of maladherence, and the RAM, which does. In qualitative analysis of the concordance of the Morisky and RAM measures in the non-depressed and depressed groups, it

was noted that numerous individuals who were discordant were present both in the category of those endorsing maladherence by the Morisky measure but not by the RAM and in the category of those endorsing maladherence by the RAM and not the Morisky measure, so if an effect based on memory does occur, it does not appear to be a biasing effect. It is also possible that the difference in performance of the instruments across groups was due not to difference in utilization of a cognitive ability, such as memory, but to an attitudinal or motivational difference, such as a bias towards self-negativity in individuals who are depressed, although again, reconciling this with the lack of a directionality of the effect of depression seems difficult. Certainly, given the extremely small sample sizes considered in the separate depressed and non-depressed populations as well as the number of bivariate tests of association conducted, the possibility that this effect is a form of Type I error, cannot be ruled out.

While this study cannot draw a strong conclusion about the relative efficacy of the two different types of measures, one strength of the study is that it demonstrates how they behave differently in this sample of people with epilepsy. More studies that compare different adherence measures “head to head” in the same sample would be beneficial in better characterizing the strengths and weaknesses of adherence measures.

Characteristics of the Study Sample

Epilepsy studies are often faced with the challenge of balancing the desire for representativeness of clinical seizure disorder patients and with adequate control for the confounding effects of the heterogeneity of populations of seizure disorder patients. At the extreme of generalizability, very heterogeneous samples of patients can be problematic. For instance, adherence behaviors may be very different in patients who have been seizure free for many years on stable medication management as compared to patients with newly diagnosed seizure disorders. Studies outside of epilepsy have suggested that individuals behaviors and

cognitions related to adherence differ when diseases are seen as acute or episodic and when they are seen as chronic (Halm, Mora, & Leventhal, 2006). Patients who have been seizure free for many years may even be taking their medications for a minimal benefit of prophylaxis in some cases – that is, they may not be likely to *have* seizures if they are maladherent or discontinue their medications. At the other extreme, while very specific populations such as intractable temporal lobe epilepsy patients are fairly well characterized and homogenous, their medication-resistant disorder variants may be different than that seen in the 80% of epilepsy patients whose seizures can be controlled via medications. The present study attempted a compromise between these extremes by considering adult patients with a variety of seizure disorder characteristics, but limiting the sample to individuals who have a stable diagnosis as well as recent seizures. The former limitation was chosen to exclude individuals who have isolated seizures that might not evolve into epilepsy and whose prognosis might depend primarily on diagnosis and / or management of another primary disorder (e.g. diabetic seizures), as well as to remove the added complexity that newly diagnosed patients may be on complex titration schedules or otherwise experience a relatively large number of medication changes in a short period of time. The latter limitation was chosen to exclude seizure-free patients who may have relatively fewer risks associated with any deviations from medication adherence. This group may include at least some individuals whose seizures are, or will be, considered intractable. It also likely includes at least some people who will achieve satisfactory seizure management through medications. While this still certainly represents a subpopulation of people with seizures, it is likely to represent a subpopulation in which adherence problems, could they be identified and intervened upon, might hold potential for clinical benefit.

Beyond the above restriction, no explicit restrictions were placed on recruitment, such as cognitive exclusionary criteria. At the same time, the study's relatively intensive dependence on multiple choice and Likert scale questionnaires did require a fair amount of reading ability, and patients were not enrolled who would not be able to complete these questionnaires with minimal assistance. This issue was surprisingly common during study recruitment. In part as a result of the reading requirements of the study, while the participants had a range of cognitive functioning, the lowest estimated FSIQ in the sample was 76, and previous studies have indicated that a number of epilepsy patients who have had seizures for an extended period of time have cognitive compromise beyond this level (Hermann et al., 2006; Dodrill, 2004). Limiting recruitment to individuals able to individually complete questionnaires is the likely reason for this. On the one hand, this was a necessary limitation for pragmatic reasons. On the other, this study cannot speak to adherence challenges with more cognitively impaired subgroups.

With respect to presence of depression, individuals with depression were not specifically recruited. Although, as previously noted, the point prevalence of depression in the study population was well within expectations, it was also observed anecdotally that individuals who, per their clinical records, were more severely depressed, frequently declined to participate in the study. While no formal record of this could be kept, it is possible that the depressed individuals in the study represent a selective subset of all depressed individuals with seizure disorders. It is possible that severely depressed individuals were under-recruited. To the extent that difficulty in engaging in motivated behaviors is a component of the pathology of depression, it is also notable that individuals who are depressed and particularly lacking in motivation may be underrepresented in voluntary studies of this kind in general. This issue might even raise the

need for stratified sampling of depressed individuals in studies of adherence and depression, for instance by placing additional emphasis on duration and severity of depression, and whether treatment is being received for depression. Additional research is also needed to determine whether participants who are experiencing a depressive episode that may be in the context of underlying bipolar disorder should be considered or excluded from analysis.

Study Limitations

This study has a number of limitations. Most prominently, the smaller-than-anticipated sample size limits the interpretability of negative results, such as the lack of relationship between adherence and depression, as well as limiting the ability to assess more complex mediational models such as the hypothesis that changes in healthcare knowledge utilization, beliefs, and attitudes may mediate the relationship between depression and adherence. In spite of designing a relatively brief study protocol, providing financial compensation, attempting to make the study convenient for patients by conducting recruitment at outpatient epilepsy clinics, and recruiting at multiple epilepsy clinics in different locations, the rate of participant recruitment was significantly lower than expected. Several factors may contribute to this. As mentioned previously, a number of individuals who were identified as potential candidates during pre-screening were found to have substantial cognitive impairments such as extreme psychomotor retardation or extremely poor reading ability, and these participants were frequently unable to participate in the study because they were unable to complete the questionnaire packet or complete the interview independently. Considering those patients who met eligibility criteria and were able to participate in the study at a basic level, successful recruitment rates were still low. Most patients who elected to enroll in the study expressed their pleasure in doing so, frequently noting that they enjoyed opportunities to support scientific progress in understanding epilepsy and that they enjoyed “giving back” to the epilepsy community. Informally, participants who did

not enroll indicated concerns over time pressure or lack of transportation as barriers to enrolling in the study. While attempts were made to make alternative arrangements to enroll participants outside of their clinic visit, this proved time consuming and also resulted frequently in prospective participants failing to attend their scheduled study session. Prospective participants also informally cited the length of the study as a concern. Finally, the total volume of patients in outpatient epilepsy clinics at the recruitment sites was affected adversely during the course of the study by the departure of two epileptologists from the University, reducing the number of individuals who could be recruited for the study. In addition to logistical barriers, the recruitment technique may also entail systematic biases related to individuals who did or did not agree to participate, such as individuals who see themselves as epilepsy advocates being more likely to participate and individuals who experience stigma being less likely to participate. Future studies of this kind may be more likely to succeed in recruitment if a fixed protocol is maintained for a relatively long period of time (e.g., several years) as part of a broader research initiative within an epilepsy clinic. Combining epidemiological techniques such as brief mail-in or internet-based surveys with targeted recruitment of a subset of participants for more detailed in-person assessments may also allow for both large sample sizes for basic analyses and the ability to more thoroughly assess possible aspects of healthcare knowledge and attitudes that impact adherence.

While the study recruited both urban and rural participants, it did so only in a single geographic region of the United States, possibly limiting interpretation to other regional or international groups of patients. Likewise, the choice to include a broad sample of epilepsy patients has the potential to obscure any subgroup-specific mechanisms of adherence. Similarly, as all participants were recruited from neurology clinics in academic medical centers that primarily fulfill a tertiary medical care role, participants may possibly not be representative of

patients who receive care from community neurologists, for instance. This larger population may also enable recruitment of larger study samples.

As discussed previously, this study, like all adherence studies, is also limited by the lack of a fully reliable measure of adherence. While the use of multiple measures of adherence is a strength of this study, the use of only self-report measures and no measures of “objective” adherence such as pill counts (through manual medication audits or electronic monitoring) or blood levels is a potential weakness, as using multiple classes of adherence measurements may provide the ability to provide a more comprehensive assessment of adherence. Future studies may therefore benefit from combining self-report and “objective” adherence measurements in a single study protocol.

Conclusion

The objective of this study was, first, to adapt the finding in a fairly large body of literature that co-morbid depression reduces the rate of adherence to medication regimens for chronic or serious illnesses substantially. As an extension of this, the study also sought to demonstrate possible mechanisms whereby depression might affect the relatively complex behavior of medication-taking, and how this might lead to observable differences in epilepsy management. While some of the proposed mechanisms were indeed found to be associated with self-reported adherence, particularly the presence of a chance locus of control with respect to medical health and the presence of specific concerns about epilepsy medications, others, such as epilepsy knowledge, had effects contrary to expectations, and others, such as illness severity perception and apathy, had non-significant relationships with adherence. However, surprisingly, depression itself was *not* found to play a role in this process. Indeed, many of the effects seemed to be blunted in their effect in the depressed individuals in the study sample. It was hypothesized that people with epilepsy and co-morbid depression might make up a high-risk group for which

future interventions might be planned targeting the areas of healthcare beliefs and attitudes represented in the study measures in order to help them achieve better adherence and thereby possibly even better seizure management. However, there is no evidence to support this approach in the present study.

Nonetheless, while the relationship with depression was not found in this study, interventions to address epilepsy patients' locus of control as well as psychoeducation to address concerns they have over their epilepsy medications appear, based on the present findings, might be promising areas of intervention for epilepsy patients. If further research verifies that the findings related to cognition and adherence are generally true for people with epilepsy, these findings also argue for an increased role of assessing cognitive functions, and memory in particular, for people with epilepsy. These assessments, in addition to the traditional role of neuropsychological assessment in assessing epilepsy's impact on the brain and also in assisting in localizing seizure foci, might be important even for patients who are not necessarily current surgical candidates for the purpose of identifying individuals who need increased healthcare support, particularly in the area of medication management and psychoeducation.

Future studies should continue to assess the relationship between adherence and depression in people with epilepsy, ideally using a larger sample and measures of adherence from multiple classes, such as the combination of a self-report measure with electronic monitoring of medication usage. Such studies may not only have greater ability to shed light on adherence behaviors but would also provide guidance on the clinical and research use of these different measurements of adherence. More research should also be done to determine how difficulties in health locus of control and medication concerns arise in people with epilepsy, in order to better understand how to work with patients to overcome these problems in the clinic.

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BIOGRAPHICAL SKETCH

Mohan Krishnan graduated from the University of Michigan with a Bachelor of Science in engineering physics, in 1997, and a Master of Science in nuclear engineering and radiological sciences, in 1999. He then spent approximately 5 years working in various engineering and business roles within the automotive industry. During this time, he pursued coursework in psychology at Wayne State University, and participated in research studying the relationship between cardiovascular disease and depression in the elderly at the Wayne State University Institute of Gerontology. He obtained a Master of Science in clinical psychology from the University of Florida in 2006. His master's thesis, submitted in partial fulfillment of requirements for that degree, was entitled "Relationships Between Medication Levels And Depressive Symptoms In Older Individuals." Mr. Krishnan completed clinical training at Shands at the University of Florida, Shands Jacksonville, and with the Veterans Administration. Currently, Mr. Krishnan is in the process of completing his internship in clinical neuropsychology at the University of Chicago Medical Center. Mr. Krishnan is working toward a doctorate in clinical and health psychology, with a specialization in clinical neuropsychology, at the University of Florida.