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Longitudinal Health-Related Quality of Life in Children with Newly-Diagnosed Epilepsy: Identifying Predictors and Assessing Meaningful Change over Time
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Chapter One

Review of the Literature

There are a number of chronic disorders and illnesses that affect children and adolescents across the United States, and one of those is epilepsy. Forty-five thousand children are diagnosed with epilepsy and 120,000 children have a first time seizure every year in the United States (Chen, 2011; Epilepsy Foundation, n.d.; Pellock, 2004; Shinnar & Pellock, 2002). Children diagnosed with pediatric epilepsy may experience psychosocial difficulties in a number of areas including academic (Aguiar, Guerreiro, McBrian, & Montenegro, 2007; Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & van Mil, 2005; Reilly & Neville, 2011), cognitive (Fastenau et al., 2009; Soria et al., 2008), behavioral (Austin, Dunn, Caffrey, Perkins, Harezlak, & Rose, 2002; Dunn, Austin, Caffrey, & Perkins, 2003; Keene et al, 2005), and affective functioning (Jones et al, 2007; Ekinci, Titus, Rodopman, Berkem, & Trevalhan, 2009). Given the high level of comorbidities and impairments experienced by children with epilepsy (Shinnar & Pellock), it is important to study the impact that epilepsy and its treatment have on patient health-related quality of life (HRQOL).

Assessing HRQOL in children with epilepsy gives researchers and clinicians a better understanding of the psychosocial impact of the disorder on children’s functioning in a number of areas including physical, emotional, and social functioning. With the goal of epilepsy treatment being no seizures, no side-effects, and the best quality of life possible (Epilepsy Foundation, 2011), it is important to understand how different factors
may affect this goal, and how these might change over time. Currently there is a paucity of research regarding how HRQOL changes over time in children with newly-diagnosed epilepsy. Research is even more limited when accounting for the role of antiepileptic drug (AED) side-effects and seizure frequency, along with other specific epilepsy characteristics, on HRQOL.

Epilepsy

Epilepsy is a condition marked by recurring seizures that are unprovoked by any immediately identified cause (International League Against Epilepsy [ILAE], 1993). More specifically, epilepsy is a neurological disorder in which clusters of neurons sometimes send abnormal signals in the brain, resulting in a seizure. The ILAE defined epileptic seizures as abnormal and excessive firings of a set of neurons in the brain. As a result of this rapid firing of neurons, sometimes up to 500 times a second, an individual may experience sensations, emotions, behaviors, convulsions, muscle spasms, and/or loss of consciousness. These phenomena can be perceived either by the individual having the seizure or an observer. According to the ILAE guidelines, in order to be diagnosed with epilepsy, an individual must have had at least two seizures that occurred more than 24 hours apart.

Due to the heterogeneity in the presentation of seizures and epilepsy syndromes, there are a number of different classifications used. Recently, a commission of neurologists and other scientists from the ILAE published a report of revised terminology and concepts for classifying seizures and epilepsy syndromes (Berg et al, 2010). Although new definitions have recently been published, they have not been
systematically implemented and thus the old terminology, which is most appropriate to
the current study, will be reviewed.

**Seizure classifications.** The two broad categorizations for seizures, under which
there are more specific categories, are generalized and partial seizures (ILAE, 1993).
When a seizure involves the entire brain, it is categorized as a generalized seizure. That
is, the symptomatology of the seizure and other clinical evidence does not provide an
indication of a specific brain area of onset. Generalized seizures may be further classified
as tonic, clonic, tonic-clonic, absence, or myoclonic. In tonic seizures, the individual’s
muscles tense up or stiffen. Clonic seizures involve rapid alternations between
contraction and relaxation of muscles resulting in a jerking movement. Tonic-clonic
seizures start off with the muscles stiffening, which is then followed by jerking
movements. Absence seizures often present as a staring spell in which awareness and
responsiveness are impaired; the individual, and sometimes those around them, may not
realize a seizure even occurred. Myoclonic seizures involve brief, jerk like movements of
a muscle or group of muscles (Chen, 2011; Epilepsy.com, 2007). According to the ILAE,
if an individual experiences several types of generalized seizures, each type should be
categorized.

Seizures that begin in only part of one brain hemisphere are considered to be
partial or focal seizures; partial seizures may be further categorized as simple or complex.
During simple partial seizures, the individual maintains awareness and responsiveness
and remembers the seizure. Their presentations vary from person to person depending
upon the part of the brain where the seizure starts and they are often categorized by the
symptoms they elicit. These can include motor, sensory, autonomic, and psychological
symptoms (Chen, 2011; Epilepsy.com, 2007). Complex partial seizures typically start in a small area of the temporal or frontal lobes of the brain. The seizure then spreads to parts of the brain that affect awareness and alertness. As a result, during a complex partial seizure, the person is not aware of what is happening and sometimes does not realize anything happened at all when awareness returns (Epilepsy.com). If a seizure begins as a partial seizure, but then spreads to the whole brain, it is considered to be a partial seizure, secondarily generalized (either simple or complex). Similar to generalized seizures, when a person has multiple types of partial seizures, each must be categorized (ILAE, 1993). While there are many categorizations of seizures, there are also many categorizations of epilepsy syndromes.

**Epilepsy etiologies.** The type of epilepsy diagnosed depends on a number of different factors, including the type of seizures, age of onset, cause of seizures, whether seizures have a genetic component, part of the brain involved, what provokes the seizures, how severe/frequent the seizures, and EEG patterns (Chen, 2011; Epilepsy.com, 2007). Due to the combination of factors that go into making a specific epilepsy diagnosis, the conditions are referred to as ‘syndromes.’ These epilepsy etiologies are defined broadly as being symptomatic, idiopathic, or cryptogenic (ILAE, 1993). The first step in categorizing an epilepsy diagnosis is to determine the presence or absence of a precipitating event to the seizures. If a precipitating event can be determined, the epilepsy is considered to be symptomatic.

According to the ILAE (1993), symptomatic epilepsies are those epilepsies considered the result of known or suspected cerebral dysfunctions, such as a structural lesion in the brain and cerebrovascular disease. Idiopathic epilepsies are those epilepsies
that do not have an identified structural brain lesion or other neurological signs or symptoms; they may be considered non-congenital. Finally, cryptogenic epilepsies include partial or generalized unprovoked seizures that have no identified risk factors associated with the presence of seizures; sometimes referred to as “probably symptomatic” as they are often considered to be truly symptomatic with the cause not yet identified. These broader categorizations of symptomatic, idiopathic, cryptogenic, and benign are usually accompanied by more specific diagnoses. However, it is not within the scope of this literature review to describe each possible diagnosis as there are more than 15 possible diagnoses with unique etiologies.

**Updated classification and terminology.** A commission on classification and terminology from the International League Against Epilepsy (ILAE) recently published their revised recommendations regarding epilepsy categorization and terminology (Berg et al., 2010). Some of these recommendations mark change from current practices and guidelines, and are beginning to reshape epilepsy terminology. These recommendations for changes in terminology were brought about due to advances in modern neuroimaging, genomic technologies, and concepts in molecular biology. These changes may not necessarily reflect all previous research with epilepsy, but a brief overview will help describe the current status of epilepsy and seizure terminology, as well as guidelines for future research and clinical practice.

The first recommendations are related to the classifications of seizures. The sub-classification of absence seizures has been simplified, with myoclonic absence seizures and eyelid myoclonia added. Focal seizures are no longer differentiated as being complex partial or simple partial. Finally, myoclonic atonic seizures are recognized. When it
comes to describing epilepsy diagnoses, the terms idiopathic, symptomatic, and
cryptogenic are no longer recommended. Instead the terms genetic, structural/metabolic,
and unknown cause are recommended. To be more consistent among clinicians, the
commission recommends the new groupings when distinguishing among specific
diseases, syndromes, and epilepsies: electroclinical syndromes, constellations,
structural/metabolic epilepsies, and epilepsies of unknown cause. Finally, instead of
using the dichotomy of focal versus generalized, clinicians should characterize each
seizure type and patient according to a number of more salient features such as: age of
onset, cognitive and developmental antecedents, motor and sensory examinations, EEG
features, provoking or triggering factors, and patterns of seizure occurrence with respect
to sleep.

**Treatment.** Epilepsy is commonly treated with antiepileptic drugs (AEDs)
(National Institute of Neurological Disorders and Stroke, 2007). There are a number of
different types of AEDs, but some are more commonly prescribed. The type of AED
prescribed and the dosage depends upon several factors, including the half-life of the
medication (how long it takes to be metabolized), the type of epilepsy, side-effects of the
medication, and number of concurrent AEDs prescribed. According to St. Louis (2009),
monitoring AED side-effects is important, particularly with children, because they may
be closely related to the patient’s overall quality of life. Side effects often associated with
AEDS include (but are not limited to) dizziness, drowsiness, headache, fatigue, blurry or
double vision, impaired concentration or memory, and incoordination. According to the
Epilepsy Foundation (2011), the goal of epilepsy treatment is no seizures, no side-effects,
and the best quality of life possible. Finding a balance between AED benefits and side-
effects is an important aspect of the clinical treatment of children with epilepsy; it can require changes in AED, doses, and/or combinations of AEDs until the optimal balance is achieved.

**Pediatric epilepsy.** Epilepsy is the third most common neurological disorder in children in the United States, after mental retardation and cerebral palsy, and it is the most common, treatable, serious neurological condition in children (Pellock, 2004; Shinnar & Pellock, 2002). Nearly 1.5-3 million individuals in the United States have epilepsy, of which 325,000 are children ages 5-14 (Epilepsy Foundation, n.d.). Every year 300,000 individuals in the United States seek treatment for a first time seizure, with approximately 120,000 of them being children under the age of 18 (Pellock, 2004; Shinnar & Pellock, 2002). Up to 45,000 children under the age of 15 are diagnosed with epilepsy every year, and by the age of 20, one percent of the population in the United States is expected to develop epilepsy. The majority of active epilepsy cases in the United States are childhood onset epilepsies that last into adulthood (Epilepsy Foundation; Pellock, 2004; Shinnar & Pellock, 2002).

Recent epidemiologic studies suggest that most patients with epilepsy, including children, become seizure free with use of AEDs within a few years of diagnosis, and of those, many are eventually able to discontinue their medication. In a recent study of children with newly-diagnosed partial onset epilepsy, who were receiving carbamazepine monotherapy, 65% of the children eventually became seizure free (Holland & Glauser, 2007). Similarly, children with newly-diagnosed idiopathic generalized epilepsy, 57% were found to become seizure free on valproic acid monotherapy (Holland, Monahan, Morita, Vartzelis, & Glauser, 2010). These remission rates are lower than previously
reported rates in the adult population of approximately 70% (Pellock, 2004; Shinnar & Pellock, 2002). The most significant factors that predict whether patients will achieve remission are etiology, the specific epilepsy type and syndrome, childhood onset, seizure frequency, and early response to treatment. Associated findings suggest that 75% of children who are seizure free on AEDs for 2-4 years remain seizure free once medication is discontinued.

Children in their first year of life run the highest risk of developing epilepsy, with the median age of seizure onset being between 5-6 years (Pellock, 2004; Shinnar & Pellock, 2002). Epilepsy is also associated with other conditions, including cerebral palsy and mental retardation, with 15-30% of cases of childhood-onset epilepsy associated with those conditions. That is, children with cerebral palsy often have epilepsy as a comorbidity but the converse is not true. For example, children diagnosed with idiopathic epilepsies tend to have psychosocial comorbidities but not as high a risk for medical comorbidities. Epilepsy is also commonly a comorbid condition in children with developmental disabilities; autism is particularly associated with an increased risk for unprovoked seizures (Shinnar & Pellock, 2002).

**Psychosocial Comorbidities of Pediatric Epilepsy**

Psychosocial difficulties and comorbidities are quite prevalent in children with epilepsy and include problems in school attendance, academic achievement, cognitive functioning, behavioral issues, and affective problems. These areas also comprise some of the areas of HRQOL research, as will be discussed in more detail in later sections. Although several studies have examined the comorbidities of pediatric epilepsy, it remains unclear whether these comorbidities are the result of the AEDs, seizures, typical
individual development, or a mixture of these factors. The answer to this question, which is not within the scope of this literature review, may bring up important implications for treating both the medical and psychosocial aspects of pediatric epilepsy.

**Academic.** Children and adolescents with epilepsy are at increased risk for academic problems (Aguiar, Guerreiro, McBrien, & Montenegro, 2007; Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & Van Mil, 2005; Reilly & Neville, 2011). These problems include increased risk for school absences as a result of epilepsy-related reasons (e.g. seizure before school, medical appointments, hospitalization) (Aguiar, Guerreiro, McBrien, & Montenegro, 2007). Results of studies have also demonstrated that children and adolescents with epilepsy are at risk for performing lower on measures of academic achievement than their healthy peers, with studies finding a relationship between epilepsy-related factors and academic achievement, such as more epilepsy type (localization-related and symptomatic generalization), frequent EEG discharges (seen as spikes on an EEG, and polytherapy (the use of multiple AEDs to treat epilepsy) (Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & van Mil, 2005; Reilly & Neville, 2011). A meta-analytic review of the literature by Reilly and Neville (2011) revealed that there were a number of other factors related to academic achievement, including the home environment, emotional functioning, ADHD, and parental anxiety. These studies highlight that the relationship between epilepsy/seizures and academic achievement is complicated and moderated by a number of factors, but that at times, epilepsy type may play a key role in academic achievement.

**Cognitive.** Studies have also demonstrated cognitive impairments/difficulties in children with epilepsy (Fastenau et al, 2009; Soria et al, 2008). The results of these
studies suggest that children with more severe forms of epilepsy (symptomatic/cryptogenic epilepsy diagnoses) and children with higher seizure frequency experience an increased risk for cognitive problems, which was consistent with caregiver perceptions of cognitive functioning (e.g. reported more attention problems, memory problems, language difficulties, and more overall slowness) (Fastenau et al, 2009; Soria et al, 2008). However, caregivers were found to report cognitive difficulties in children whose forms of epilepsy were not traditionally associated with cognitive difficulties. This highlights the possibility that parents may at times overestimate the impact of their children’s epilepsy has on their functioning. In addition to increased risk for deficits in academic achievement and cognitive functioning, children with epilepsy are at increased risk for externalizing and internalizing disorders.

**Externalizing Disorders.** Behavioral issues are often reported in children with epilepsy and several studies have examined externalizing disorders in this population (Austin, Dunn, Caffre, Perkins, Harezlak, & Rose, 2002; Dun, Austin, Caffrey, & Perkins, 2003; Keene et al, 2005). Results of these studies indicated that children with epilepsy are at increased risk for behavioral problems, particularly children with recurrent seizures (Austin, Dunn, Caffre, Perkins, Harezlak, & Rose, 2002; Dun, Austin, Caffrey, & Perkins, 2003; Keene et al, 2005). Studies have examined the relationship between epilepsy and behavioral problems using parent, teacher, and physician ratings. The overall literature highlights that epilepsy, seizures, and AED treatment have a complicated relationship with externalizing disorders in children. It is likely that the relationship between externalizing disorders and an epilepsy diagnosis is moderated by
the differing neurological underpinnings of certain forms of epilepsy/seizures, as well as possible side effects seen in AED treatment.

**Internalizing Disorders.** In addition to the academic, cognitive, and behavioral problems associated with epilepsy, researchers have also examined the relationship between mood and epilepsy (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009; Jones et al, 2007). Results of these studies indicated that children with epilepsy exhibited significantly higher rates of internalizing disorders, including depressive and anxiety disorders when compared to the general population (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009; Jones et al, 2007). Children with epilepsy and depression often presented with an irritable mood and negative ruminations about themselves, their lives, and their friends and family. They were also at increased risk for suicidal ideation and suicide attempts when compared to the general pediatric population. While children with epilepsy were at greater risk for developing internalizing disorders, affective functioning did not appear to be as related to epilepsy/seizure specific factors. However, other variable, such as parental anxiety/fear/distress and misinformation about the disorder did influence child anxiety. Parental functioning may play a role in both children’s affective functioning as well as possibly affecting parental responses to questions.

Children with more complex forms of epilepsy and more psychosocial comorbidities may be hit harder by the disorder than children with fewer psychosocial comorbidities. As a result, there are multiple areas of a child’s functioning that may be affected by epilepsy and seizures, researchers and clinicians find it important to understand how the disorder affects overall quality of life. Similar to assessment in other
disorders, they assess a multidimensional construct known as health-related quality of life (HRQOL).

**Health-Related Quality of Life**

Health-related quality of life (HRQOL) is a construct with several definitions, but is generally defined as the assessment of an individual’s perception of the impact a disease or condition, or its treatment, has on one’s physical health status, psychological and social functioning, and emotional well-being (Eiser & Morse, 2001). The construct assesses the individual’s perceived ability to participate in different activities, both social and physical, and the level of enjoyment/satisfaction in that involvement given his/her disease/health status (Eiser & Morse, 2001; Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008). The construct of HRQOL was derived, in part, from the definition of health set forth by the World Health Organization (1948), which is a “state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.” Other researchers and clinicians have added other components to the definition of HRQOL, such as spiritual well-being and sexual functioning (Fayers & Hays, 2005). The development of HQROIL as an assessment construct stemmed from the need to not only understand the physical functioning of an individual with a disease/illness, but also the his or her emotional, social, and role functioning (Varni, Burwinkle, Seid, & Sarr, 2003).

The assessment of HRQOL serves several purposes and HRQOL measures have been utilized to estimate the burden of specific diseases and compare the impact of different diseases on patient functioning (Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008). Assessing the multiple domains of functioning in HRQOL assessment
provides the clinician or researcher a broader evaluation of a patient’s functioning, instead of just one domain. Additionally, assessment of HRQOL allows for an examination of the outcomes of medical care or treatments, patient experiences related to physical illness/injury, evaluations of the usefulness of drug therapies, the cost-benefit analyses of medical treatments, and for use in clinical practice (Levi & Drotar, 1998). These assessment tools were first utilized in adult medical populations and have carried over into pediatric populations.

**Assessing HRQOL in pediatric populations.** Assessing HRQOL in pediatric populations is important as it can serve several purposes, similar to those of the adult medical population. These uses can include providing descriptions of the health status of patients, identification of psychological risks or dysfunction, and providing information to treatment providers to potentially improve clinical decision-making (Levi & Drotar, 1998; Quittner, Davis, & Modi, 2003). However, before those purposes can be fully realized, there are several factors that must first be taken into consideration, particularly in pediatric populations. These include the decision of whether to use a proxy- or self-report questionnaire, whether to use disease-specific or general questionnaires, and determining whether changes in HRQOL are actually meaningful to patients and/or their caregivers (Levi & Drotar; Hays & Woolley, 2000; Quittner, Davis, & Modi, 2003).

The first issue that needs to be addressed concerns who completes the HRQOL questionnaire, with the patient, the caregiver, and the physician all being possible choices (Levi & Drotar, 1998). Often times in HRQOL research the parents are the primary respondent as there have been questions about child self-report validity, children may be too young or too ill to respond, and parents tend to know the most about their child’s life.
A review of the literature by Eiser and Morse (2001) suggests that there is generally a moderate to good correlation ($r > .50$) between parent proxy- and child self-reports with the greatest agreement found for observable (i.e. physical HRQOL) versus non-observable factors (i.e. emotional HRQOL). However, there remain some concerns that parental reports of HRQOL may at times be affected by parental anxiety or emotional functioning (Levi & Drotar, 1998). To reduce any potential biases, researchers recommend a multi-informant approach to HRQOL assessment when possible (Quittner, Davis, & Modi, 2003). When a child is younger, it may be better to defer to the parental report of HRQOL and as the child ages to begin giving more weight to the child’s self-report.

**Generic versus disease-specific measures.** The next question is to determine whether to use a general or disease-specific HRQOL questionnaire. Generic measures are generally designed for use with a broad population of patients with varying types of diseases and treatments. Due to the fact that the measures are able to be used across different conditions, researchers and clinicians can compare children diseases and different treatments. However, generic measures may not be as sensitive or as responsive to changes in illness-status as disease-specific questionnaires. Disease-specific questionnaires ask questions uniquely related to an illness, function, population or treatment. While disease-specific measures may not allow for comparison of children across conditions, their potential sensitivity and responsiveness may provide a greater insight into patient functioning (Levi & Drotar, 1998; Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008).
There are several well-established generic HRQOL measures currently used by researchers and clinicians. These include the Child Health Questionnaire (CHQ) (Landgraf, Abetz, & Ware, 1997), the Pediatric Quality of Life Inventory (PedsQL) (Varni, Seid, & Kurtin, 2001), and the Youth Quality of Life (YQOL) (Edwards, Huebner, Connell, & Patrick, 2002; Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008). The CHQ was designed for children 5-18 years old and includes a child-report and parent-report versions (Landgraf, Abetz, & Ware, 1997). The PedsQL was designed for children 2-18 and includes several versions; a young child-report, child-report, adolescent-report, and parent reports for toddler, young child, child, and adolescent. The PedsQL also has disease specific modules for several illnesses (Varni, Seid, & Kurtin, 2001). The YQOL was designed for children 12-18 years old and includes a child-report (Edwards, Huebner, Connell, & Patrick, 2002).

In addition to generic HRQOL measures, there are disease-specific measures that cover a number of chronic diseases including arthritis, cystic fibrosis, diabetes, cancer, epilepsy, etc. For epilepsy, there are a few disease-specific measures that are used regularly (Fayed & Kerr, 2009). These include the Health Related Quality of Life for Children with Epilepsy (HRQL in CWE) (Ronen, Streiner, Rosenbaum, & Canadian Paediatric Epilepsy Network, 2003), Impact of Child Illness (ICI, epilepsy version) (Hoare, Mann, & Dunn, 2000), Quality of Life in Epilepsy – Adolescents (QOLIE-AD) (Cramer, Westbrook, Devinsky, Perrine, Glassman, & Camfield, 1999), Impact of Child Neurological Disability (ICND) (Camfield, Breau, & Camfield, 2001), and the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) (Sabaz et al, 2003). The HRQL CWE was designed for children 6-15 years old. The ICI is a parental report and was
designed for use with school-aged children. The QOLIE-AD was designed for children 11-17 years old and is child-report. The ICND was designed for children 2-18 years old. Finally, the QOLCE was designed for children ages 4-18 years old and is a parent-report measure. There has been limited research that has assessed changes over time in HRQOL in children with newly-diagnosed epilepsy utilizing disease-specific measure (discussed below) and fewer studies have examined the clinical utility and meaningfulness of these measures.

**Minimum clinically important difference.** Finally, to determine whether changes in HRQOL scores are clinically significant and not just statistically significant, researchers utilize the concept of the minimum clinically important difference (MCID). An MCID is defined as the smallest difference in the score of a domain that patients perceive to be beneficial and that would require, barring excessive cost or side-effects, a change in management of their illness (Jaeschke, Singer, & Guyatt, 1989). That is, the smallest change in a score that the patient, or the patient’s caregiver, perceives to be worthwhile or important. For clinicians it may be defined as “the smallest effect size that would lead them to recommend a therapy to their patients” (Hays & Woolley, 2000).

Previous studies have examined changes in HRQOL in comparison to MCIDs with general measures of HRQOL (Modi, Ingerski, Rausch, & Glauser, 2011), but no study has examined change in HRQOL in comparison to MCIDs of an epilepsy-specific instrument.

There are two main ways of establishing MCIDs, anchor-based approaches and distribution-based methods. In the anchor-based method, clinically meaningful changes in HRQOL are obtained by comparing the measures of HRQOL to other relevant
measures or phenomena (Crosby, Kolotkin, & Williams, 2003). Within anchor-based methods there can be either cross-sectional or longitudinal approaches. In the cross-sectional approach, groups that are different in terms of a specific disease-related criterion are compared, with the differences in mean values of their HRQOL scores compared and used to estimate the MCIDs. For example, groups may be compared on the basis of disease severity levels. If the averages of HRQOL scores are calculated for each group, these can then be compared to help determine whether a change in a score is clinically significant for an individual from that population. The differences in the mean scores for the different severity levels serve as the MCIDs in this approach. Another cross-sectional approach involves using non-disease-related factors (i.e. the loss of a job, death of a family member, etc). This is done by comparing the magnitude of the impact for individuals of one of these stressful life events and using that as a comparison to estimate the MCIDs. Longitudinal methods for establishing MCIDs use global ratings of change. With this method, changes in HRQOL scores may be compared to patient ratings of satisfaction over time; MCIDs are established based upon these comparisons. For anchor-based approaches, one advantage is that change in HRQOL is examined in relationship to a clear external anchor and provide the significance of change from the individual perspective. However, limitations to the anchor-based approach include relying on global-ratings which may be susceptible to recall biases, having questionable reliability and validity, and not accounting for all the variance in HRQOL scores. Additionally, using an anchor-based method does not take into account the measurement precision of the HRQOL measure in use.
In the distribution-based approaches, MCIDs are established using statistical characteristics of the sample. There are three main types of distribution-based methods including statistical significance, sample variation, and measurement precision (Crosby, Kolotkin, & Williams, 2003). Distribution-based measures that use statistical significance evaluate change in relation to the probability that change occurred by random variation. This approach utilizes the standard errors of the sampling distribution. The paired t-test and growth curve analysis are both examples of this approach. The second distribution-based approach utilizes change in relation to sample variation, which can look at baseline variations of the sample, variation of change scores, and variation of change scores in a stable group. Finally, the third type of distribution-based measure is based on the measurement precision of an instrument. This approach can use the standard error of the mean and the responsiveness statistic. Distribution-based approaches have several advantages including providing a means of establishing change beyond random variation (a weakness in anchor-based approaches), they provide a common metric across measures and populations, and the computed values are relatively stable across samples. There are also disadvantages to distribution-based approaches, including having few-agreed upon benchmarks for establishing clinically significant change and that the methods used do not, by themselves, provide a clear sense of the clinical relevance of change. However, Crosby, Kolotkin, and Williams (2003) believe that distribution-based approaches that utilize the measurement precision of the questionnaire are promising for establishing clinically meaningful change.

MCIDs calculated using distribution-based methods for total scores for pediatric HRQOL measures are generally around 5 points. The value for subscale scores of
pediatric HRQOL measures is approximately 9 points. This value has been found for scales on the PedsQL (Varri, Burwinkle, Seid, & Skarr, 2003), the TNO-AZL Infant Quality of Life (TAIQOL; Brouwer et al, 2007), and the Cystic Fibrosis Questionnaire-Revised (CFQ-R; Quittner, Modi, Wainwright, Otto, Kirihara, & Montgomery, 2009). There has been a paucity of research in examining whether changes in HRQOL scores for children with newly-diagnosed epilepsy are clinically meaningful, and even fewer studies have done this utilizing a disease-specific measure, such as the QOLCE. Thus, one aim of the current study is to calculate a MCID for the QOLCE using a distribution based method.

**HRQOL and epilepsy.** A theoretical model (see figure 1) has emerged that takes into account a number of variables, or determinants, which may have an effect on a child’s HRQOL (Lach, Ronen, Rosenbaum, Cunningham, Boyle, Bowman, & Streiner, 2006). At one level in this theory is the child’s biomedical status, or level of impairment, which includes epilepsy specific variables (e.g. seizure severity, age of onset, duration of illness, whether or not the epilepsy is active or not active, etc) and comorbidities (e.g. physical disabilities, mental health problems, sleep disorders, etc). At the next level of the theory are intermediate variables/determinants, which include child variables (demographics, social skills, social support, victimization, etc), family variables (demographics, impact of illness on family, parental mood, etc), and community variables (school bonding, health services, social support, etc). These two levels of variables/determinants work together to produce a child’s HRQOL. With this model, researchers can look at both mediating and moderating variables and their effect on the child’s HRQOL, which can have clinical utility for health-care providers. This is
something that researchers have examined in the relationship between HRQOL and epilepsy in children.

Montanaro, Battistella, Boniver, and Galeone (2004) examined the HRQOL in a sample of 285 Italian subjects aged 7-16 years. Of this sample, 140 subjects were diagnosed with idiopathic and cryptogenic epilepsy; there were also 145 healthy-control subjects. Participants were given a measure assessing psychological, social, and scholastic functioning as well as knowledge about epilepsy. Compared to the healthy control group, children with epilepsy reported lower HRQOL in the areas of mood state, optimism, relations with others, and social activities. There was no significant difference on the school subscale. There were negative correlations between HRQOL and higher seizure frequency, longer length of disease, and polytherapy with AEDs. While this study highlights that lower HRQOL scores were associated with a number of different epilepsy/seizure factors, the finding that length of disease was associated with lower scores should be noted. If seizures are being treated with AED therapy and being well controlled after a period of time, length of time may actually be hypothesized to be positively correlated with HRQOL. It may be that the presence or absence of seizures across time may moderate this relationship. Unfortunately, this could not be addressed due to the cross-sectional nature of the study. Additionally, this study was conducted in Italy, which may limit its generalizability to studies conducted in the United States.

Sabaz et al (2003) examined HRQOL among Australian children with epilepsy, aged 4-18 years, differentiated by common epilepsy syndromes. The children were recruited from tertiary pediatric centers in Sydney and Melbourne. Children were differentiated by seizure type into benign rolandic (BRE, characterized by seizures of
different parts of the face), partial, childhood absence (CAE), frontal lobe (FLE),
parietal/occipital lobe (POLE), and temporal lobe (TLE) epilepsy categories. They were
given various measures that assessed HRQOL, including epilepsy specific measures.
When compared to normative data, all six syndrome groups had a significantly higher
percentage of children with social competence scores in the clinically abnormal range.
The TLE, FLE, partial, and CAE syndromes had higher overall behavioral problem
scores. When compared to the normative data, children with all six syndromes had
significantly lower HRQOL scores. In addition, when compared to children with
idiopathic epilepsies (less severe), children with symptomatic epilepsies (more severe),
had significantly lower HRQOL scores.

The current literature (Montanaro, Tattistella, Boniver, & Galeone, 2004; Sabaz et
al, 2003) highlights that children with more severe forms of epilepsy have lower HRQOL
than those with less severe forms of epilepsy, while both groups have lowered HRQOL
compared to healthy controls. Both studies also highlight that the relationship between
epilepsy/seizure variables and HRQOL is complicated, including the use of more than
one AED. However, these studies lacked examination of the relationship between these
variables and HRQOL over time and did not represent children at the time of diagnosis.

Modi et al (2009) examined HRQOL in children with newly diagnosed epilepsy
using the PedsQL. The study assessed the HRQOL of children who had only experienced
one seizure (n = 53), which is not sufficient for a diagnosis of epilepsy, and children with
newly diagnosed, yet to be treated epilepsy (n = 56). Results of the study indicated that
children with newly diagnosed, untreated epilepsy and children with a single seizure both
had significant impairments in HRQOL. There were no significant HRQOL differences
between the single seizure and the untreated epilepsy groups. This suggested that a single seizure was sufficient to negatively impact a child’s HRQOL scores. It may be expected that as AED therapy begins in these children with new-onset seizures/epilepsy, and their seizures start to become better controlled, their HRQOL may actually increase over time.

**Seizure frequency and HRQOL.** Several studies examined the relationship between seizure frequency and the effects of daily functioning in children with epilepsy. Seizure frequency was related to neuropsychological/cognitive deficits in children (Fastenau et al., 2009) and teacher ratings of behavioral problems (Dunn, Austin, Caffrey, & Perkins, 2003). Seizure frequency was also related to lower HRQOL in young Italian patients with epilepsy (Montanaro, Battistella, Boniver, & Galeone, 2004). In a sample of Australian children with epilepsy, seizure frequency was found to be negatively correlated with overall HRQOL (Sabaz et al., 2003).

Camfield, Breau, and Camfield (2001) assessed mothers of children with epilepsy and ratings of their child’s quality of life. Ninety-seven Canadian mothers completed a measure that assessed the child’s academic achievement, participation in activities, health, relationships with family, peers and siblings, social activities, self-esteem, and the caregiver’s hopes for the child’s future. Parents rated children with epilepsy as having lower self-esteem and more emotional problems. Patient HRQOL was significantly related to seizure frequency, the total number of medications taken, the number of visits to a doctor in the previous year, and the number of nights spent in the hospital for neurological reasons.

Although several studies have reinforced the idea that seizure frequency is related to decreased HRQOL scores in children with epilepsy, as well as cognitive and
behavioral problems, to date, few studies have assessed seizure frequency in relation to longitudinal HRQOL in children with newly-diagnosed epilepsy. It may be expected that as the length of time from diagnosis increases and seizures become better controlled with the use of AEDs, therapy is utilized, seizure control there will be improvements in HRQOL. However, AED therapy can also cause significant side effects, which may negatively impact HRQOL and thus should be considered in future studies examining longitudinal HRQOL.

**AED side effects and HRQOL.** In a recent review by St. Louis (2009) the most commonly reported side effects of AEDs in children were dizziness, drowsiness, headache, fatigue, blurry or double vision, impaired concentration or memory, and incoordination. These side effects may be related to other difficulties (i.e. cognitive impairment, behavioral changes, etc) experienced by children on AED therapy. A number of studies already examined emphasized the relationship between AEDs and side effects, and impairments including academic problems/underachievement, cognitive difficulties, and internalizing and externalizing disorders. While the use of a single AED may result in side effects, the relationship between AEDs and side effects is also found to be related to the number of AEDs used in treatment, with more AEDs (polytherapy) correlated with more side effects. Polytherapy was correlated with academic problems and underachievement in a sample of Dutch children with epilepsy (Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & van Mil, 2005). Neuropsychological and cognitive deficits were correlated with the use of AEDs in a sample of children with first time seizures (Fastenau et al., 2009). In a sample of children with new-onset seizures, the use of polytherapy was correlated with poorer teacher ratings of behavior (Dunn, Austin,
Caffrey, & Perkins, 2003). In a review of the literature, affective disorders, particularly depression and anxiety, were also associated with the use of polytherapy (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009).

While the theoretical model set forth by Lach, Ronen, Rosenbaum, Cunningham, Boyle, Bowman, and Streiner (2006) theorizes that the variables in Figure 1 account for HRQOL scores in children with epilepsy, it does not account for all variables that may be expected to account for a significant amount of this variance. A neglected variable may include AED side effect severity. HRQOL scores for children with newly diagnosed epilepsy can be affected by side effect severity, a relationship that has been examined in the literature. In a sample of young Italian patients with epilepsy, there was a negative correlation between polytherapy and HRQOL. The greater the number of AEDs a patient was prescribed, the lower his or her HRQOL (Montanaro, Battistella, Boniver, & Galeone, 2004).

While polytherapy has been associated with greater side effects, both in general impairments and in HRQOL, it begs the question of whether or not it is the side effects associated with a greater number of AEDs used or whether it is the fact that the epilepsy being treated in those cases requires more intense treatment. While the truth may be somewhere in a combination of these two ideas, it is something that has not necessarily been examined well in the HRQOL literature. Benavente-Aguilar, Morales-Blanquez, Rubio, and Rey (2004) studied a sample of 66 Spanish young people, aged 10-19 years, with epilepsy. The patients were assessed for HRQOL, seizure severity, and neurotoxicity. A neurotoxicity measure assessed for side-effects associated with AEDs such as gait, rapid alternating movements, tremor, sedation, mood, cognitive function,
dizziness, and headaches. The results found significant negative correlations between HRQOL and both seizure severity and neurotoxicity. When a partial correlation was conducted between HRQOL and neurotoxicity, controlling for seizure severity, the results were still significant. This suggested that neurotoxicity made a negative contribution over and above the effect of the epilepsy type diagnosed. Again it is unclear whether neurotoxicity levels themselves accounted for differences in HRQOL or if it was because children with higher neurotoxicity levels required higher AED doses to reach a therapeutic effect. Unlike some studies (Modi, Ingerski, Rausch, & Glauser, 2011), there was a small-moderate relationship among gender and socioeconomic status and HRQOL scores, with females describing a greater impact of the disease than males and SES being negatively correlated with HRQOL scores. There were also significant negative correlations between HRQOL and seizure frequency, duration of the illness, and age of onset, with earlier onset correlated with poorer HRQOL.

Jakovljevic, Jankovic, Jankovic, and Todorovic (2008) examined the serum concentration levels of valproic acid (a commonly prescribed AED), in comparison to HRQOL scores, in a sample of 21 Serbian adolescent patients with epilepsy. Serum concentrations and HRQOL scores were measured on two occasions, three months apart. Adverse drug reactions and seizure control were also measured. Serum concentrations were measured as an indicator of intensity of effect for the drug. Serum concentration levels at the time of ingestion were negatively correlated with overall HRQOL scores. For the HRQOL subscales, serum concentration was negatively correlated with memory/concentration scales, and physical functioning scales. Serum concentration levels were also negatively correlated with the number of adverse reactions per patient.
There was no correlation between serum concentration and number of seizures. Similar to the studies that examined children receiving polytherapy, higher serum concentration levels being negatively correlated with HRQOL calls into question whether or not it is the actual serum level contributing to declines in HRQOL scores or whether it is the fact that the child is having seizures that are harder to control. While this study highlighted the role of valproic acid in relation to HRQOL scores, children with epilepsy are prescribed a variety of AED medications depending on the type of epilepsy, age of patient, etc. An assessment of how different AED types affect children diagnosed with epilepsy, specifically their HRQOL, may provide important information for health care providers.

The studies that have examined the relation of HRQOL and AED side effects have some limitations. First, some of the studies do not specifically look at the AEDs prescribed and the side effects associated with each AED (e.g., Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey, 2004). Second, some studies have only focused on one AED (Jakovljevic, Jankovic, Jankovic, & Todorovic, 2008). Additionally, besides the 3-month span in the Jakovljevic et al study, none of the studies cited have looked at the relation between AED side effects and HRQOL over time in children with newly-diagnosed epilepsy. It may be beneficial to look at the AED side effects of the most commonly AEDs prescribed at the beginning of treatment to better understand how they relate to HRQOL and how this relationship changes over time. It may be expected that AED side effects go down over time as doses are adjusted, which would mean an increase in HRQOL over time. Additionally, two of these studies were conducted in countries other than the United States and with non-English speaking participants, this may limit their generalizability (Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey,
2004; Jakovljevic, Jankovic, Jankovic, & Todorovic, 2008). This highlights the need for more research to be conducted in the United States to provide more generalizable results for use with children in U.S. neurology clinics.

**Longitudinal HRQOL in pediatric epilepsy.** There is a paucity of research examining longitudinal trends in HRQOL in children with epilepsy. Of the studies cited thus far, most have been cross-sectional in nature. Furthermore, few studies have examined changes in HRQOL over time and none have focused on a cohort of children with newly diagnosed epilepsy.

Breau, Camfield, Camfield, and Breau (2008) examined the responsiveness of an epilepsy-specific HRQOL measure in a sample of 63 Canadian children, 2-18 years of age. Parents were given the Impact of Pediatric Epilepsy Scale (IPES) during its validation period and then again three years later. Demographic and medical information was collected, as well as seizure severity scores, which were rated by physicians on a scale of 1-3 (with three being the most severe). Lower seizure severity scores were related to higher HRQOL scores at the three year follow-up. Additionally, the authors concluded that the IPES was responsive to changes in seizure severity scores from baseline to three years later. Children who had any decrease in seizure severity showed significantly more improvement in HRQOL scores when compared to those of children whose seizure severity remained stable or worsened. While this study examined changes in HRQOL scores in children with epilepsy, it only looked at baseline and three years later, which did not allow the authors to examine any possible trends in changes in HRQOL scores. Additionally, they utilized a convenience sample of children with a wide age-range and at varying lengths from time of diagnosis. While this provides a snapshot
of changes in HRQOL scores, it does not allow for examination of a complete sample from time of diagnosis, the time when HRQOL may be worst.

A study by Modi, Ingerski, Rausch, and Glausser (2011) examined longitudinal HRQOL in a group of children with newly-diagnosed epilepsy using a generic HRQOL instrument. The study followed 124 patients ages 2-12 over the course of seven months for a total of four visits, including the day of diagnosis. The authors collected demographic information and at each visit patient caregivers filled out the PedsQL, which assessed physical, emotional, social and school functioning. They also completed a pediatric epilepsy specific AED side-effects measure, which covered a wide range of potential side-effects. Information on the patients’ medical history including their seizure type, presence/absence of seizures, and AED type was also obtained. Results indicated that there were no significant changes in HRQOL scores over time. However, there were significant differences in all HRQOL scores in relationship to AED side-effect severity, with children with higher side-effect severity having lower HRQOL scores across the seven months. There was a significant interaction between AED type, side-effects, and time for the emotional functioning HRQOL subscale. Children on carbamazepine who had initial high side-effect severity scores had declining rates of social functioning across the study. Children initially on valproic acid had steady or improving emotional functioning scores over the course of the study. When the authors applied the MCIDs to the HRQOL subscales, these changes were found to be clinically meaningful. There were significantly different physical subscale scores for children when seizures were present versus when they were absent; this was consistent across the course of the study.
The study by Modi, Ingerski, Rausch, and Glauser (2011) is one of few longitudinal studies examining changes in HRQOL for children with newly diagnosed epilepsy. The study used the generic PedsQL to assess HRQOL instead of an epilepsy-specific HRQOL instrument. Additionally, the study did not find significant changes in HRQOL over time, which was not consistent with the hypothesis that scores would improve. As the stated goal of treatment is no seizures, no side-effects, and best overall QOL, one would hope that HRQOL would improve following diagnosis. A lack of change in HRQOL scores may have been a factor of the measure used or the length of time for the study window. In the first seven months following diagnosis, doctors may still be adjusting AEDs to find the optimal balance of no side-effects and no seizures. One novel contribution of this study to the literature was an application of MCIDs to examine the clinical significance of change in HRQOL scores; whether or not parents would notice changes in HRQOL functioning.

Ferro, Avison, Campbell, and Spezchley (2011) examined the role of maternal depressive symptoms on HRQOL in children with newly-diagnosed epilepsy. The authors followed a sample of 339 mothers of children 4-12 years of age, recruited from pediatric neurologists across Canada for a period of 24 months following diagnosis. At four time points across the 24 months, mothers completed a series of measures including a validated, disease-specific HRQOL measure (Quality of Life in Children with Epilepsy Questionnaire [QOLCE]) (Sabaz et al, 2003), a depressive symptoms checklist (Center for Epidemiological Studies Depression Scale [CES-D]), measures of family environment, and a measure assessing perception of patient-centered care. Epilepsy characteristics were also documented by each participant's neurologist. The authors hypothesized that
child HRQOL scores would be mediated by maternal depressive symptoms and family functioning/demands. Results of the study suggested that HRQOL significantly improved over the course of the 24 months. Maternal depressive symptoms were observed to have a negative impact on HRQOL scores at 24 months as well as on the rate of change of scores throughout the follow-ups. Family resources, family functioning, and family demands were all found to have a moderating relationship between depressive symptoms and child HRQOL. Of note, the authors reported that children with better initial HRQOL scores demonstrated greater improvement over time than those with lower initial HRQOL scores. However, the authors did not examine the role of other factors potentially affecting HRQOL scores, such as epilepsy/seizure characteristics. Additionally, the authors did not determine whether or not the change experienced over the two years would be perceived as clinically significant to families.

A separate study by Ferro, Aison, Campbell, and Speechley (2010) examined whether or not depressive symptoms in mothers affected their reports of outcomes for children with new-onset epilepsy. Mothers in the study completed the QOLCE and a depressive symptoms checklist. Neurologists filled out the Global Assessment of Severity of Epilepsy (GASE), as well as answered questions about cognitive, behavioral, physical, and social functioning. To assess whether maternal depression moderated mothers’ reports of the four main HRQOL domains, the authors conducted multiple regressions comparing QOLCE scores and the neurologist-reported measures. The results of the study, which assessed the same 339 Canadian mothers and their children as Ferro, Aison, Campbell, and Speechley (2011), suggested that the mental health status of mothers did not affect how they reported their child’s HRQOL scores on the QOLCE,
with the exception of assessment of their child's energy/fatigue. Mothers who reported more depressive symptoms reported higher scores (better functioning) for their child's energy/fatigue and its impact on their daily functioning.

A study by Speechley, Camfield, Levin, Smith, Wiebe, and Zou (2009) examined change in HRQOL scores over the course of 24 months in a sample of 376 children, ages 4-12, with newly-diagnosed epilepsy. The authors administered both disease-specific and a generic HRQOL measure to caregivers at four time points throughout the 24 month study. Results of the study indicated that the overall scores for the disease-specific measure, the Quality of Life in Children with Epilepsy Questionnaire (QOLCE) improved significantly from diagnosis to 24 months later. This was also true for the two summary scales of the generic HRQOL measure, the Child Health Questionnaire, with mean scores significantly improving on the physical and psychosocial scales. While the authors reported that there was varying amounts of change for the individual domain scores on the two measures, they did not report which scales increased and which remained static. Additionally, the authors did not examine the potential effects of additional variables, such as epilepsy/seizure characteristics, and their relation to changes in HRQOL over time nor did they report if the changes from post-diagnosis to 24 months later were clinically meaningful to families.

One study that did examine the role of predictor variables on HRQOL scores in children with newly-diagnosed epilepsy was done by Harrison, Guilfoyle, Wessendorf and Modi (2012). The study compared HRQOL scores at baseline and one-year post diagnosis. The goal of the study was to examine epilepsy-specific HRQOL scores over the first year of treatment as well as to identify potential predictors of HRQOL. The
authors utilized the QOLCE, a parent-proxy HRQOL measure. They hypothesized that HRQOL would increase from baseline to one year post-diagnosis and that sociodemographic (e.g. age, socioeconomic status) and epilepsy specific factors (e.g. side-effects, epilepsy type) would predict HRQOL one year post-diagnosis. The results of the study indicated that QOLCE scores increased from baseline to one year post-diagnosis, with significant increases in Overall QOL scores as well as on scales of Physical Restrictions, Energy and Fatigue, Control and Helplessness, and General Health. While, as hypothesized, baseline HRQOL scores were expected to be a significant predictor of HRQOL scores one year post-diagnosis, AED side-effects and the presence and absence of seizures also accounted for a significant amount of variance for several HRQOL scales (i.e. depression, memory, social activities, general health, etc).

While Harrison, Guilfoyle, Wessendorf and Modi (2012) examined the role of predictors on HRQOL scores using a disease-specific measure of HRQOL, they looked at the difference between two sets of scores and did not look for trends over time. They examined changes in HRQOL scores one year following diagnosis, which may not capture additional change in HRQOL functioning as time since diagnosis continues to increase. Finally, like the previous studies cited examining longitudinal HRQOL in children with epilepsy, the authors did not examine whether or not the changes in HRQOL scores were meaningful to families.
Chapter Two

Rationale and Hypotheses

Epilepsy is a disorder that affects millions of individuals across the United States every year, with 325,000 of them being children ages 5-14 (Pellock, 2004; Shinnar & Pellock, 2002). Children and adolescents with epilepsy are at risk for a number of impairments including academic (Aguiar, Guerreiro, McBrian, & Montenegro, 2007; Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & van Mil, 2005; Reilly & Neville, 2011), cognitive (Fastenau et al., 2009; Soria et al., 2008), behavioral (Austin, Dunn, Caffrey, Perkins, Harezlak, & Rose, 2002; Dunn, Austin, Caffrey, & Perkins, 2003; Keene et al, 2005), and affective functioning (Jones et al, 2007; Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009). With the number of psychosocial comorbidities and impairments experienced by children with epilepsy (Pellock; Shinnar & Pellock), researchers have studied the impact that epilepsy and its treatment have on patient health-related quality of life, which encompasses a patient’s physical, emotional, role, and social functioning.

Previous research assessing HRQOL in pediatric epilepsy has demonstrated that, in comparison to normative samples, having epilepsy is associated with lower HRQOL (Modi et al., 2009; Montanaro, Battistella, Boniver, & Galeone, 2004; Sabaz et al, 2003). However, the relationship between HRQOL and epilepsy is complicated and there can be several moderating factors. Epilepsy is not a homogeneous disorder, as some patients are diagnosed with more severe forms of epilepsy, which is negatively correlated with HRQOL scores (Montanaro, Battistella, Boniver, & Galeone; Sabaz et al). Additionally, AED side effects (Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey, 2004;
Jakovljevic, Jankovic, Jankovic, & Todorovic, 2008) and seizure frequency (Camfield, Breau, & Camfield, 2001) are also both negatively correlated with HRQOL scores. As clinicians work with patients to reach the ultimate goal of treatment (no seizures, no side-effects, best QOL), the above factors are likely to change over the course of treatment. However, few studies have examined how these factors interact with HRQOL over time.

A study by Breau, Camfield, Camfield, and Breau (2008), found that seizure severity was related to changes in HRQOL over time, but the authors only assessed patients at baseline and three years later, which limited their ability to look at trends in change. Additionally, they used a convenience sample of children with a wide-age range and at varying lengths from diagnosis. While this provides a snapshot of changes in HRQOL scores, it does not allow for examination of a complete sample from time of diagnosis, when HRQOL scores may be lowest. Modi, Ingerski, Rausch, and Glauser (2011) examined HRQOL scores in a newly-diagnosed sample of children and did not find that HRQOL scores improved over time, which may have been a factor of the shorter time period (seven months) and the generic HRQOL instrument (e.g. PedSQL) that was used. However, this was the only study that examined longitudinal HRQOL using MCIDs to see if changes in scores were clinically meaningful. Two studies examined HRQOL in newly-diagnosed children, using a disease-specific measure and found that HRQOL improved over time. However, the authors of both studies did not examine epilepsy characteristics as covariates over time (Ferro, Avison, Campbell, & Speechley, 2011; Speechley, Camfield, Levin, Smith, Wiebe, & Zou, 2009).

With the above considerations, the goals of the present study are to assess changes in HRQOL scores over time, in a sample of children with newly-diagnosed epilepsy,
using a disease-specific measure of HRQOL, and to examine how epilepsy specific and demographic factors, may influence the relationship between a diagnosis of epilepsy and HRQOL scores. A previously proposed model for HRQOL in youth with epilepsy theorized that a number of factors account for variance in HRQOL (Lach, Ronen, Rosenbaum, Cunningham, Boyle, Bowman, & Streiner, 2006). However, this model does not account for all important variables, specifically, the role of AED side effects. The proposed study will examine a subset of the variables in this model, in addition to examining the added role of AED side effects in accounting for variance in HRQOL scores. These variables will also include demographic variables (age, gender, race/ethnicity, socioeconomic status), about which research has demonstrated conflicting findings (Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey, 2004; Modi, Ingerski, Rausch, & Glauser, 2011). Finally, the proposed study will calculate MCIDs, for the QOLCE, using a distribution-based method to assess the level of HRQOL change perceived to be clinically meaningful to patients. The MCIDs calculated for this study will likely be similar to MCIDs calculated for total scores on other pediatric HRQOL measures, which is approximately 5 points, as well as subscale scores, which is approximately 9 points (Brouwer et al., 2007; Quittner, Modi, Wainwright, Otto, Kirihara, & Montgomery, 2009; Varni, Burwinkle, Seid, & Skarr, 2003). Based upon the reviewed research, the proposed study has the following aims and hypotheses:

**Aim One:**

To determine changes in HRQOL scores over time in a sample of children with newly diagnosed epilepsy.
H1: After an initial diagnosis of epilepsy and AED treatment is implemented, overall HRQOL scores will increase over the span of two years.

H2: After an initial diagnosis of epilepsy and AED treatment is implemented, HRQOL subscale scores for Cognitive, Behavior, Depression, Anxiety, Physical Restrictions, Energy and Fatigue, Control and Helplessness, and General Health will increase over the course of two years.

**Aim Two:**

Identify significant predictors of HRQOL over time in children with newly diagnosed epilepsy, including the exploration of demographic variables as significant predictors (age, gender, race/ethnicity, socioeconomic status).

H3: Increases in overall HRQOL scores over the course of two years will be negatively predicted by the total side effects reported at each time point.

H4: Increases in HRQOL over the course of two years will be positively predicted by the absence of seizures at each time point.

H5: Epilepsy type will serve as a predictor for HRQOL over the course of two years, with less severe forms of epilepsy predictive of higher HRQOL scores at the end of two years.

**Aim Three:**

To determine and apply the MCID scores for the QOLCE in a sample of children with newly diagnosed epilepsy.

H6: Consistent with prior research with pediatric HRQOL measures, MCIDs calculated for the total QOLCE score will be approximately 5 points and MCIDs calculated for subscale QOLCE scores will be approximately 9 points.
H7: Changes in overall HRQOL over the course of two years will be clinically meaningful in relation to MCIDs calculated for the QOLCE.
Chapter Three

Methods

Design

The archival data for the proposed study were gathered as part of a larger, IRB approved, longitudinal study that examined antiepileptic drug (AED) adherence in children 2-12 years of age with newly-diagnosed epilepsy. For the larger study, children and their caregivers were recruited from a neurology clinic at a large Midwestern children’s hospital the day of the epilepsy diagnosis.

Procedure

Consent for the study was obtained from primary caregivers and assent was obtained from children who were at least eight years of age. Families who consented to the study were given an electronic monitoring pill bottle and cap (MEMs TrackCap) to assess treatment adherence over the course of two years. The data from the MEMS TrackCaps were downloaded at each follow-up clinic visit, which occurred 1, 4, 7, 10, 13, 16, 19, 21, and 25-months following diagnosis. Additionally, families completed a variety of questionnaires that assessed the following constructs: parenting stress, health-related quality of life, stigma, family stress, AED side-effects, etc. At each follow-up clinic visit, caregivers were asked about current medication(s), changes in medication, number of seizures since their last clinic visit, and about the presence of staring spells since their last clinic visit. These medication and disease-related variables were also
obtained through medical chart reviews. When there were discrepancies between
caregiver-report and the chart review (i.e. family did not remember to report a seizure or
medication change that was captured in the medical chart), the medical chart was used.
The proposed study will examine a subset of these questionnaires assessing HRQOL and
AED side-effects; these will be drawn from the following follow-up clinic visits: 1, 7, 13,
19, and 25 months post-diagnosis.

Participant Data

Overall, 124 participants were recruited for the larger study (96% recruitment
rate). However, for the proposed study, only 113 patients with newly-diagnosed epilepsy
will be examined as 11 participants did not complete the epilepsy specific HRQOL
measure at any time point (see Figure 2 for more information about missing data).
Inclusion criteria for the larger study included being between 2-12 years old, a new
diagnosis of epilepsy (day of recruitment), and being initially prescribed carbamazepine
(e.g. Tegretol) or valproic acid (e.g. Depakote). Exclusion criteria included parent-
reported comorbid chronic illness requiring daily medication (e.g. diabetes), or a
diagnosis of a significant developmental disorder (e.g. Autism, Down Syndrome). For the
proposed study, only the records of those who were 4-12 years old will be examined, as
the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) is only validated for
use in children starting at age four. In summary, there were 113 participants included for
the proposed study (ages 4-12, \( M=7.49 \), Male = 62.8%, White = 75.2%). For a complete
summary, see Table 1 for demographics and epilepsy/seizure information.
Measures

**Demographic information.** A demographics form was completed by the primary caregiver and included age of child, sex, race/ethnicity of child and parents, socio-economic status, marital status of parents, and parents' level of education.

**Chart review.** A chart review was conducted at each study visit to assess for several factors including the number of seizures the child experienced including specific dates. The presence or absence of staring spells the child had since the last clinic visit and the dates they happened or if the child had any staring spells since the last clinic visit were also assessed. The chart review included information about prescribed AED, AED dose, and any AED changes that were made at the clinic visit. These data were confirmed with primary caregivers during the study visit.

**Quality of Life in Childhood Epilepsy Questionnaire (QOLCE).** The QOLCE (see Appendix A) is a 76-item parent-report measure designed to assess epilepsy-specific health-related quality of life in children ages 4-18. It was developed from an original questionnaire created in Australia and subsequently validated for use in America (Sabaz et al, 2003). The QOLCE covers five domains of life functioning including physical functioning, social functioning, cognition, emotional, and behavioral well-being. These five domains cover 16 subscales, including physical restrictions, energy/fatigue, attention/concentration, memory, language, other cognitive, depression, anxiety, control/helplessness, self-esteem, social interactions, social activities, stigma, behavior, general health, and general quality of life. Items on the questionnaire are rated on a five-point Likert scale (very often to never), which is used to calculate the 16 subscale scores and an overall QOL score. The measure also includes several opportunities for parents to
provide additional information via open ended questions (e.g. “Is there anything else you would like to tell us about your child’s activities?”). The internal consistency reliabilities of the multi-item scales ranged from moderate to excellent (range from 0.76-0.97). The internal consistency reliability of the overall QOL scale is 0.92. Construct validity was evaluated by assessing the convergent validity between similar and dissimilar scales on the QOLCE and the Child Health Questionnaire (CHQ). Correlations between theoretically similar scales of the measures were moderate to high (0.61 for physical restrictions and physical functioning, 0.71 for anxiety and mental health, 0.65 for behavior scales). The correlations were weaker for theoretically dissimilar scales. The scale has also demonstrated strong clinical validity, displaying sensitivity to quality of life differences based on epilepsy variables including seizure severity and number of AEDs.

**Pediatric Epilepsy Side Effects Questionnaire (PESQ).** The PESQ Scale (see Appendix B) is a reliable and valid measure developed for clinical care and research to assess AED toxicity, or side effects (Morita, Glauser, & Modi, 2012). It is a 19-item questionnaire that includes five subscales: Cognitive, Motor, Behavioral, General Neurological, and Weight. Items are rated either by the patient or guardian on a 6-point Likert scale ranging from zero (not present) to five (high severity). Individuals are instructed to rate the severity of side-effects or side effects associated with their antiepileptic medication. The side effects examined in the scale include (but are not limited to): slow thinking, headaches, aggression, personality change, hyperactivity, dizziness, fatigue, etc. To score the PESQ Scale, items are summed to obtain a total side-effect severity score; higher scores indicate greater side-effect severity (Morita, Glauser,
Altaye, Fordyce, & Holder, 2003). The total side-effect score will be included in the proposed analyses. The PESQ Scale has demonstrated both strong reliability and validity for working with children with epilepsy. The test-retest reliability was 0.91 for total side-effect severity score, while the Cronbach’s alpha were quite high, $r = 0.90$. In this same study construct validity was assessed. As the number of drugs increased, side-effect severity also increased (Morita, Glauser, & Modi, 2012). Of note, participants who were prescribed valproic acid had significantly higher scores on the Weight scale versus those on carbamazepine (Morita, Glauser, & Modi, 2012).
Chapter IV

Proposed Analyses

Descriptive statistics were calculated to describe demographic characteristics (see Table 1). Additionally, descriptive statistics, including means, standard deviations, and reliability coefficients will be calculated for the QOLCE Total Scale scores and specific subscale scores (Cognitive, Behavior, Depression, Anxiety, Physical Restrictions, Energy and Fatigue, Control and Helplessness, and General Health).

Aim One. To test the proposed hypotheses that HRQOL scores, assessed using the QOLCE, will increase over the course of two years, hierarchical linear modeling (HLM analyses [Singer & Willett, 2003]) will be employed to assess changes over time in Total Scale scores and specific subscale scores of the QOLCE. Scores from the following time points will be included: one month (baseline), seven months, thirteen months, nineteen months, and twenty-five months following diagnosis. HLM analyses will be run using Statistical Analysis Software (SAS 9.3). In this model the HRQOL Total Scale and subscale scores will be entered as the outcome, or dependent variables, while time will be entered into the model as the independent variable.

HLM analysis is a statistical technique that can be used to examine changes over time, it is particularly useful (in comparison to more traditional analyses, such as repeated measures ANOVAs) for examining scores when there is missing longitudinal data and when there are time varying covariates (e.g. seizure frequency, side effect severity, etc)
(Fitzmaurice, Laird, & Ware, 2011). Specifically, HLM analysis creates a curve for each participant in the dataset, utilizing a maximum likelihood estimation, which results in the creation of both intercepts and slopes. These slopes and intercepts can then be used to examine baseline scores and change in scores over time.

**Aim Two.** To test the hypotheses that side effect scores on the PESQ and the presence/absence of seizures, these variables will be entered into a model as predictors to examine if they interact with time and account for a significant amount of change in HRQOL Total Scale scores and subscale scores. Epilepsy type will also be entered into a separate model to test if it is predictive of changes in HRQOL Total Scores and subscale scores over two years. To determine whether sociodemographic variables (age, gender, race/ethnicity, socioeconomic status) account for a significant amount of variance in HRQOL scores, Pearson correlations and independent samples t-tests will be conducted to examine their relation to QOLCE scores at the one month following diagnosis visit. If these variables are significant predictors of HRQOL scores, they will be controlled for in the above model.

**Aim Three.** To test the proposed hypotheses that increases in HRQOL scores are clinically meaningful, MCIDs will be calculated for HRQOL Total Scale and subscale scores of the QOLCE, using a distribution-based, statistical significance approach, which utilizes standard errors of the sampling distribution for calculation. Changes in the HRQOL scores on the QOLCE will then be examined in relation to the calculated MCIDs to estimate if changes are clinically significant. The formula for calculating MCIDs using the standard error of measurement is s.e.m. = s.d. \sqrt{1-\alpha}, s.d. = standard deviation of mean baseline QOLCE scores for each scale; \alpha = scale reliability (Wyrwich, Tierney, &
Wolinsky, 1999). The distribution-based approach has several advantages, including providing a means of establishing change beyond random variation, it provides a common metric across measures/populations, and the computed values are relatively stable across samples (Crosby, Kolotkin, & Williams, 2003).
References


Harrison, J., Guilfoyle, S., Wessendorf, K., & Modi, A. (2012, April). Predictors of HRQOL one year following a pediatric epilepsy diagnosis. Poster presented at the Midwest Regional Conference in Pediatric Psychology, Milwaukee, WI.


<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics and Epilepsy/Seizure Information</th>
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<tr>
<td>Sex</td>
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<td>Age</td>
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<td>Ethnicity</td>
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<td>Initial AED</td>
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<td>Seizure Types</td>
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<tr>
<td>Socioeconomic Status</td>
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Figure 1
Theoretical model of youth with epilepsy

Biomedical status/Level of Impairment

- Epilepsy Variables
  - Severity
  - Age of onset
  - Duration
  - Proportion of life with seizures
  - Active/Not Active
  - Recovery time
  - Hx of injury

- Co-morbidity
  - Physical Disability
  - Intellectual disability
  - Mental health
  - Sleep disorders

Intermediate Variables

- Child Variables
  - Demographic
  - Social Skills
  - Self-worth
  - Participation
  - Victimization
  - Social support
  - Efficacy

- Family Variables
  - Family Demographics
  - Impact of illness on family
  - Parental mood
  - Parenting
  - Economic burden of health-care

- Community Variables
  - School bonding
  - Health services
  - Social support

HRQOL

- Social
- Worries
- Emotional
- Normality
- Secrecy
Figure 2
Explanation of Missing QOLCE Data

Total possible at each time point: n=124
Total across all time points: n=113

One month following diagnosis: n=94
Missing data due to: Did not return to clinic (n=3), parent did not send back measure (n=7), disenrolled due to being seen in different clinic (n=1), child too young for measure (n=19)

Seven months following diagnosis: n=86
Missing data due to: Did not return to clinic (n=8), missed appointment (n=11), parent did not send back measure (n=1), withdrew from study (n=2), disenrolled due to being seen in different clinic (n=1), moved (n=3), missed appointment due to good clinical progress (n=1), child too young for measure (n=11)

Thirteen months following diagnosis: n=82
Missing data due to: Did not return to clinic (n=17), missed appointment (n=4), parent did not send back measure (n=2), withdrew from study (n=5), disenrolled due to being seen in different clinic (n=2), moved (n=3), missed appointment due to good clinical progress (n=4), child too young for measure (n=5)

Nineteen months following diagnosis: n=67
Missing data due to: Did not return to clinic (n=22), missed appointment (n=7), parent did not send back measure (n=3), withdrew from study (n=7), disenrolled due to being seen in different clinic (n=2), moved (n=3), missed appointment due to good clinical progress (n=12), child too young for measure (n=1)

Twenty-five months following diagnosis: n=84
Missing data due to: Did not return to clinic (n=22), parent did not send back measure (n=2), withdrew from study (n=7), disenrolled due to being seen in different clinic (n=2), moved (n=4), weaned medication early (n=3)

No QOLCE data for 11 participants:
Missing data due to: Never returned to clinic after initial visit (n=3), initially too young for measure and then never returned to clinic (n=3), initially too young for measure and then withdrew from study (n=2), initially did not return measure and then never returned to clinic (n=1), disenrolled due to being seen in different clinic (n=1), initially too young to complete measure and then moved (n=1)
Appendix A

The Quality of Life in Childhood Epilepsy Questionnaire is protected by copyright so it is not reproduced in this document. The measure is available by contacting the developing author, Anne M. E. Bye, at a.byce@unsw.edu.au.
Appendix B

The Pediatric Side Effects Questionnaire is protected by copyright so it is not reproduced in this document. The measure is available by contacting the developing author, Diego Morita, at diego.morita@cchmc.org.
Chapter V: Dissertation

Abstract

Compared to healthy peers, children with epilepsy, of which there are approximately 325,000 under the age of 15 in the United States, are at increased risk for lower health-related quality of life (HRQOL) (Epilepsy Foundation, n.d.; Modi et al., 2009; Montanaro, Battistella, Boniver, & Galeone, 2004; Sabaz et al., 2003). A number of variables may affect HRQOL in children with epilepsy, including epilepsy specific variables, comorbidities, and child, family, and community variables (Lach et al., 2006). Few studies have examined how these variables predict changes in HRQOL over time for children with newly-diagnosed epilepsy using a disease specific measure. The aims of the current study were to: 1) examine changes in HRQOL scores of children with newly-diagnosed epilepsy over two years using a disease specific measure (Quality of Life in Childhood Epilepsy Questionnaire [QOLCE][Sabaz et al., 2003]) 2) examine clinical significance of changes in HRQOL scores 3) examine how seizures (dichotomized as present vs. absent) and antiepileptic drug (AED) side effects predict changes in HRQOL scores over the course of two years. One hundred and twelve caregivers of children from 4-12 with epilepsy participated in the study. Hierarchical linear modeling (HLM) revealed statistically significant increases of QOLCE-Overall scores and Physical Restrictions, Energy and Fatigue, Behavior, and General Health subscale scores from baseline to two years post-diagnosis. Calculated minimum clinically important difference (MCID) scores showed only QOLCE-Overall scores had clinically significant
improvements over time. HLM analyses examined the role of seizures and AED side
effects on HRQOL scores. Children who had seizures between visits had significantly
lower Energy and Fatigue scores than children without seizures, although this difference
disappeared by the end of two years. Children with higher side effects had lower
Attention and Concentration, Memory, Language, and Anxiety scores compared to
children with lower side effects. Unexpectedly, at baseline, children with higher side
effects had higher Energy and Fatigue scores compared with children with lower side
effects. However, by the end of two years children with higher side effects had lower
scores compared to children with lower side effects. While, overall HRQOL may
improve overtime for children with newly-diagnosed epilepsy, the results highlight the
role AED side effects play for these children. Health-care providers need to continue to
be sensitive to the potential of side effects and work with families and children to know
what to expect when starting an AED for the first time. This education and guidance may
help patients and families better be able to communicate with their health-care providers
and create a better decision-making process.
Longitudinal Health-Related Quality of Life in Children with Newly-Diagnosed Epilepsy: Identifying Predictors and Assessing Meaningful Change over Time

Children diagnosed with epilepsy may experience psychosocial difficulties in a number of areas including academic (Aguiar, Guerreiro, McBrian, & Montenegro, 2007; Aldenkamp, Weber, Overweg-Plandsoen, Reijs, & van Mil, 2005; Reilly & Neville, 2011), cognitive (Fastenau et al., 2009; Soria et al., 2008), behavioral (Austin, Dunn, Caffrey, Perkins, Harezlak, & Rose, 2002; Dunn, Austin, Caffrey, & Perkins, 2003; Keene et al, 2005), and affective functioning (Jones et al., 2007; Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009). Given the high level of comorbidities and impairments experienced by children with epilepsy, it is important to study the impact that epilepsy and its treatment have on health-related quality of life (HRQOL), which encompasses a patient’s physical, emotional, and social functioning. With the goal of epilepsy treatment being no seizures, no side effects, and the best possible quality of life (Epilepsy Foundation, 2011), it is important to understand how different factors may affect this treatment goal, and how these might change over time. Currently there is a paucity of research regarding how HRQOL changes over time in children with newly-diagnosed epilepsy. Research remains limited when accounting for the role of antiepileptic drug (AED) side effects and seizure frequency on HRQOL.

Epilepsy

Epilepsy is a condition marked by recurring seizures that are unprovoked by any immediately identifiable cause (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 2010). More specifically, epilepsy is a
neurological disorder in which clusters of neurons sometimes send abnormal signals in the brain, resulting in a seizure. The ILAE defined epileptic seizures as abnormal and excessive firings of a set of neurons in the brain. As a result of this rapid firing of neurons, sometimes up to 500 times a second, an individual may experience sensations, emotions, behaviors, convulsions, muscle spasms, and/or loss of consciousness. New guidelines from the ILAE recommend an individual can be diagnosed with epilepsy if he or she has had at least two seizures that occurred at least 24 hours apart, has had one unprovoked seizure but has at least a 60% probability of further seizures, or has been given a diagnosis of an epilepsy syndrome (Fisher et al., 2014).

Due to the heterogeneity in the presentation of seizures and epilepsy syndromes, there are a number of different classifications used. The two broad categorizations for seizures, under which there are more specific categories, are generalized and localization-related, or partial seizures (ILAE, 2010). When a seizure involves the entire brain, it is categorized as a generalized seizure, which includes tonic, clonic, tonic-clonic, absence, or myoclonic seizures. Seizures that begin in only part of one brain hemisphere are considered to be partial or focal seizures; partial seizures may be further categorized as simple or complex. During simple partial seizures, the individual maintains awareness and responsiveness and remembers the seizure. Complex partial seizures typically start in a small area of the temporal or frontal lobes of the brain. The seizure then spreads to parts of the brain that affect awareness and alertness.

The specific type of epilepsy, or syndrome, diagnosed depends on a number of different factors, including the type of seizures, age of onset, cause of seizures, whether seizures have a genetic component, part of the brain involved, what provoked the
seizures, severity/frequency, and EEG patterns (Chen, 2011; Epilepsy.com, 2007). Formerly, the epilepsy types were referred to as symptomatic (cause of seizures known), idiopathic (cause unknown), or cryptogenic (likely symptomatic) (ILAE, 1993), with idiopathic being the most common. In 2010, the ILAE updated its terminology and diagnoses are now more specific and consistent (ILAE, 2010).

**Pediatric epilepsy.** Epilepsy is the third most common neurological disorder in children in the United States, after mental retardation and cerebral palsy, and it is the most common, treatable, serious neurological condition in children (Pellock, 2004; Shinnar & Pellock, 2002). Nearly 1.5-3 million individuals in the United States have epilepsy, of which 325,000 are children ages 5-14 (Epilepsy Foundation, n.d.). Every year 300,000 individuals in the United States seek treatment for a first time seizure, with approximately 120,000 of them being children under the age of 18 (Pellock, 2004; Shinnar & Pellock, 2002). Up to 45,000 children under the age of 15 are diagnosed with epilepsy every year, and by the age of 20, one percent of the population in the United States is expected to develop epilepsy. The majority of active epilepsy cases in the United States are childhood onset epilepsies that last into adulthood. Children in their first year of life run the highest risk of developing epilepsy, with the median age of seizure onset being between 5-6 years (Epilepsy Foundation, n.d.; Pellock, 2004; Shinnar & Pellock, 2002).

**Treatment.** Epilepsy is commonly treated with antiepileptic drugs (AEDs) (National Institute of Neurological Disorders and Stroke, 2007). The type of AED prescribed and the dosage depends upon several factors, including the half-life of the medication (how long it takes to be metabolized), the type of epilepsy, side effects of the
medication, and number of concurrent AEDs prescribed. Monitoring AED side effects is important, particularly for children, because they may be closely related to the patient’s overall quality of life (St. Louis, 2009). Side effects often associated with AEDs include (but are not limited to) dizziness, drowsiness, headache, fatigue, blurry or double vision, impaired concentration or memory, and incoordination (St. Louis, 2009). As the goal of epilepsy treatment is no seizures, no side effects, and the best quality of life possible (Epilepsy Foundation, 2011), finding a balance between best seizure control and least side effects is an important aspect of the clinical treatment of children with epilepsy. This can require changing the AED, doses, and/or prescribing a combination of AEDs until the optimal balance is achieved.

Psychosocial Comorbidities of Pediatric Epilepsy

Psychosocial difficulties and comorbidities are quite prevalent in children with epilepsy, including difficulties with school attendance, academic achievement, cognitive, behavior, and affect. These areas also comprise some of the areas of HRQOL research, as will be discussed in more detail in later sections. Although several studies have examined the comorbidities of pediatric epilepsy, it remains unclear whether these comorbidities are the result of the AEDs, seizures, atypical individual development, or a mixture of these factors. The answer to this question, which is not within the scope of this literature review, may bring up important implications for treating both the medical and psychosocial aspects of pediatric epilepsy.

Children are at increased risk for academic problems, with studies finding a relationship between academic achievement and epilepsy type, frequent EEG discharges, and polytherapy (Aldenkamp, Weber, Overweg-Plundsoen, Reijs, & van Mil, 2005;
Reilly & Neville, 2011). Research has also demonstrated cognitive impairments.difficulties in children with epilepsy; results suggest that children with more severe forms of epilepsy and children with more seizures experience an increased risk for cognitive problems (Fastenau et al., 2009; Soria et al., 2008). Additionally, behavioral issues are often reported in children with epilepsy and several studies have examined externalizing disorders in this population (Austin, Dunn, Caffrey, Perkins, Harezlak, & Rose, 2002; Dun, Austin, Caffrey, & Perkins, 2003; Keene et al., 2005). Results of these studies indicated that children with epilepsy, particularly those with recurrent seizures, are at increased risk for behavioral problems. Finally, researchers have examined the relationship between mood and epilepsy, with results suggesting that children with epilepsy exhibited significantly higher rates of internalizing disorders, including depressive and anxiety disorders, when compared to the general population (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009; Jones et al., 2007).

The psychosocial impact of epilepsy and seizures on children is complicated as children with the disorder are at risk for a number of comorbidities that can affect daily functioning. Thus, one important area of patient reported outcome research for children with chronic conditions is assessing the construct of health-related quality of life.

**Health-Related Quality of Life**

Health-related quality of life (HRQOL) is typically defined as the assessment of an individual’s perception of the impact a disease or condition, and/or its treatment, has on his or her physical, psychological, social functioning, and emotional functioning (Eiser & Morse, 2001). The assessment of HRQOL serves several purposes: HRQOL measures are used to estimate the burden of specific diseases and compare the impact of
different diseases on patient functioning (Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008). Assessing the multiple domains of in HRQOL assessment provides the clinician or researcher a broader evaluation of a patient’s functioning, instead of in just one area. These assessment tools were first utilized in adult medical populations and have been carried over into pediatric populations.

**Assessing HRQOL in pediatric populations.** The assessment of HRQOL in pediatric populations can serve several purposes, including providing descriptions of health status of patients, identification of psychological risks or dysfunction, and providing information to treatment providers potentially to improve clinical decision-making (Levi & Drotar, 1998; Quittner, Davis, & Modi, 2003). There are several factors that must first be taken into consideration, particularly in pediatric populations, including the decision of whether to use a proxy- or self-report questionnaire, whether to use disease-specific or general questionnaires, and determining whether changes in HRQOL are actually meaningful to patients and/or their caregivers (Levi & Drotar, 1998; Hays & Woolley, 2000; Quittner, Davis, & Modi, 2003).

The first issue of concern is who completes the HRQOL questionnaire, with the patient, the caregiver, and the physician all being possible choices (Levi & Drotar, 1998). Often parents are the primary respondents as there have been questions about child self-report validity; children may be too young or too ill to respond, and parents tend to know the most about their children’s lives. A review of the literature by Eiser and Morse (2001) suggests that there is generally a moderate to good correlation ($r > .50$) between parent proxy- and child self-reports with the greatest agreement found for observable (i.e. physical HRQOL) versus non-observable factors (i.e. emotional HRQOL). However,
there remain some concerns that reports of HRQOL may at times be affected by parental anxiety or emotional functioning (Levi & Drotar, 1998).

The next issue is to determine whether to use a general or disease-specific HRQOL questionnaire. Generic measures are generally designed for use with a broad population of patients with varying types of diseases and treatments. Because the measures are able to be used across different conditions, researchers and clinicians can compare children’s diseases and different treatments. However, generic measures may not be as sensitive or as responsive to changes in illness-status as disease-specific questionnaires. Disease-specific questionnaires ask questions uniquely related to an illness, function, population or treatment. While disease-specific measures may not allow for comparison of children across conditions, their potential sensitivity and responsiveness may provide a greater insight into patient functioning (Levi & Drotar, 1998; Palermo, Long, Lewandowski, Drotar, Quittner, & Walker, 2008).

Finally, to determine whether changes in HRQOL scores are clinically significant and not just statistically significant, researchers utilize the concept of the minimum clinically important difference (MCID). An MCID is defined as the smallest difference in the score of a domain that patients perceive and that would require, barring excessive cost or side effects, a change in management of their illness (Jaeschke, Singer, & Guyatt, 1989). That is, the smallest change in a score that the patient, or the patient’s caregiver, perceives to be significant (Hays & Woolley, 2000). Previous studies have examined changes in HRQOL in using MCIDs with general measures of HRQOL (Modi, Ingerski, Rausch, & Glauser, 2011), and few have examined change in HRQOL using MCIDs of an epilepsy-specific instrument (Ferro et al., 2013; Speechley et al., 2012).
Two primary ways of establishing MCIDs are anchor-based and distribution-based approaches. In anchor-based methods, clinically meaningful changes in HRQOL are obtained by comparing measures of HRQOL to other relevant measures or phenomena (Crosby, Kolotkin, & Williams, 2003). An advantage of an anchor-based approach is that change in HRQOL is examined in relationship to a clear external anchor and provides the significance of change from the individual perspective. Limitations to an anchor-based approach include relying on global-ratings which may be susceptible to recall biases, having questionable reliability and validity, and not accounting for all the variance in HRQOL scores.

In distribution-based approaches, MCIDs are established using statistical characteristics of the sample. There are three main types of distribution-based methods including statistical significance, sample variation, and measurement precision (Crosby, Kolotkin, & Williams, 2003). Distribution-based measures that use statistical significance evaluate change in relation to the probability that change occurred by random variation. A second distribution-based approach utilizes change in relation to sample variation. The third distribution-based approach is based on the measurement precision of an instrument and can use the standard error of the mean and the responsiveness statistic. Distribution-based approaches have several advantages including providing a means of establishing change beyond random variation, providing a common metric across measures and populations, and the computed values are relatively stable across samples. Disadvantages to distribution-based approaches include having few agreed upon benchmarks for establishing clinically significant change and that the methods used do not, by themselves, provide a clear sense of the clinical relevance of change. However, Crosby,
Kolotkin, and Williams believe that distribution-based approaches that utilize the measurement precision of the questionnaire are promising for establishing clinically meaningful change.

MCIDs calculated using distribution-based methods for total scores for pediatric HRQOL measures are generally around 5 points. The value for subscale scores of pediatric HRQOL measures is approximately 9 points. This value has been found for scales on the PedsQL (Varni, Burwinkle, Seid, & Skarr, 2003), the TNO-AZL Infant Quality of Life (TAIQOL; Brouwer et al., 2007), and the Cystic Fibrosis Questionnaire-Revised (CFQ-R; Quittner, Modi, Wainwright, Otto, Kirihara, & Montgomery, 2009). Previously published MCIDs, using the standard error of the mean, for the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE [Sabaz, 2003]) were approximately four for the QOLCE-Overall and eight for subscales (Speechley et al., 2012). There has been a paucity of research in examining whether changes in HRQOL scores for children with newly-diagnosed epilepsy are clinically meaningful, and even fewer studies have done this utilizing a disease-specific measure.

**HRQOL and epilepsy.** A theoretical model (see figure 1) has emerged that takes into account a number of variables that may have an effect on a child’s HRQOL (Lach et al., 2006). At level one in this model is the child’s biomedical status, which includes epilepsy specific variables (e.g. seizure severity, age of onset, duration of illness, whether or not the epilepsy is active, etc) and comorbidities (e.g. physical disabilities, mental health problems, sleep disorders, etc). The next level of the model has intermediate variables, which include child variables (demographics, social skills, social support, victimization, etc), family variables (demographics, impact of illness on family, parental
mood, etc), and community variables (school bonding, health services, social support, etc). These two variable levels work together to produce a child’s HRQOL. With this model, researchers can look at both mediating and moderating variables and their effect on the child’s HRQOL, which can have clinical utility for health-care providers.

In one Italian study, when compared to healthy peers, children with epilepsy had significantly lower HRQOL in the areas of mood state, optimism, relations with others, and social activities. There were negative correlations between HRQOL and higher seizure frequency, longer length of disease, and polytherapy with AEDs (Montanaro, Battistella, Boniver, & Galeone, 2004). An Australian study found that, when compared to normative data, children with epilepsy were more likely to have lower HRQOL scores. Children with symptomatic epilepsy had significantly lower HRQOL scores than children with less idiopathic epilepsy (Sabaz et al., 2003). These studies highlight that the relationship between epilepsy and seizure variables, including AED use, and HRQOL is complicated. However, these studies lacked examination of the relationship between these variables and HRQOL over time and did not represent children at the time of diagnosis. Modi et al. (2009) examined HRQOL in children with newly diagnosed epilepsy using the PedsQL. Results revealed that children with newly diagnosed, untreated epilepsy and children with a single seizure both had significant impairments in HRQOL. This suggested that a single seizure was sufficient to negatively impact a child’s HRQOL scores.

Seizure frequency and HRQOL. Several studies examined the relationship between seizure frequency and the effects of daily functioning in children with epilepsy. Seizure frequency was related to neuropsychological/cognitive deficits in children.
(Fastenau et al., 2009) and teacher ratings of behavioral problems (Dunn, Austin, Caffrey, & Perkins, 2003). Seizure frequency was also related to lower HRQOL in young Italian patients with epilepsy (Montanaro, Battistella, Boniver, & Galeone, 2004). In a sample of Australian children with epilepsy, seizure frequency was found to be negatively correlated with overall HRQOL (Sabaz et al., 2003). Additionally, in a Canadian study, parents rated children with epilepsy as having self-esteem and emotional problems. Patient HRQOL was significantly related to seizure frequency, the total number of medications taken, the number of visits to a doctor in the previous year, and the number of nights spent in the hospital for neurological reasons (Camfield, Breau, & Camfield, 2001).

While several studies have reinforced the idea that seizure frequency is related to decreased HRQOL scores in children with epilepsy, to date, few studies have assessed the impact of seizures in relation to longitudinal HRQOL in children with newly-diagnosed epilepsy. It may be expected that as the length of time from diagnosis increases and seizures become better controlled through AED therapy, there will be improvements in HRQOL. However, AED treatment can also cause significant side effects, which may negatively impact HRQOL and should also be considered in studies examining longitudinal HRQOL.

**AED side effects and HRQOL.** A number of studies already examined emphasized the relationship between AEDs and side effects, and impairments including academic problems/underachievement, cognitive difficulties, and internalizing and externalizing disorders. While the theoretical model set forth by Lach et al. (2006) theorizes that the variables in Figure 1 account for HRQOL scores in children with
epilepsy, it does not include all variables that may be expected to account for a significant amount of this variance. A neglected variable may include AED side effects. In fact, the literature has demonstrated a relationship between HRQOL scores and side effects.

In a study of Spanish youth, Benavente-Aguilar, Morales-Blanquez, Rubio, and Rey (2004) found significant negative correlations between HRQOL and both seizure severity and neurotoxicity. When a partial correlation was calculated between HRQOL and neurotoxicity, controlling for seizure severity, the results were still significant. This suggested that neurotoxicity made a negative contribution over and above the effect of seizure severity. It is unclear whether neurotoxicity levels themselves accounted for differences in HRQOL or if it was because children with higher neurotoxicity levels required higher AED doses to reach a therapeutic effect. However, it is notable that there were significant negative correlations between HRQOL and seizure frequency, duration of the illness, and age of onset, with earlier onset correlated with poorer HRQOL.

Jakovljevic, Jankovic, Jankovic, and Todorovic (2008) examined the serum concentration levels of valproic acid in comparison to HRQOL scores in Serbian adolescents over a 3-month period. Serum concentration levels at the time of ingestion were negatively correlated with overall HRQOL scores, as well as memory/concentration and physical functioning subscales. Serum concentration levels were also negatively correlated with the number of adverse reactions per patient. The higher serum concentration levels being negatively correlated with HRQOL begs the question whether it was the actual serum level contributing to declines in HRQOL scores or whether these children were having seizures that were harder to control and thus required higher doses.
While there are some studies that have examined the relation of HRQOL and AED side effects, they have some limitations. Besides the 3-month span in the Jakovljevic et al. (2008) study, none of the studies cited looked at the relation between AED side effects and HRQOL over time in children with newly-diagnosed epilepsy. It may be beneficial to look at the AED side effects at the beginning of treatment to better understand how they relate to HRQOL and how this relationship changes over time. It may be expected that AED side effects go down over time as doses are adjusted, which would mean an increase in HRQOL over time.

**Longitudinal HRQOL in pediatric epilepsy.** There is a paucity of research examining longitudinal trends in HRQOL in children with epilepsy. Of the studies cited thus far, most have been cross-sectional in nature. Furthermore, few studies have examined changes in HRQOL over time and even fewer have focused on a cohort of children with newly diagnosed epilepsy.

A study of Canadian children by Breau, Camfield, Camfield, and Breau (2008) examined the responsiveness of an epilepsy-specific HRQOL measure at two intervals, three years apart. Lower seizure severity scores were related to higher HRQOL scores at the three year follow-up. While this study examined changes in HRQOL scores in children with epilepsy, using two time points three years apart does not allow us to understand the fluctuating nature of HRQOL over time and whether there are critical points in time that require intervention. Modi, Ingerski, Rausch, and Glauser (2011) examined longitudinal HRQOL in a group of children with newly-diagnosed epilepsy using a generic HRQOL instrument over a 7-month period. While there were no significant changes in HRQOL scores over time, there were significant differences in all
HRQOL scores in relation to AED side effects, with children with more side effects having lower HRQOL scores across the seven months. These changes were found to be clinically meaningful. Additionally, there were significantly different physical subscale scores for children when seizures were present versus when they were absent, which was consistent across the course of the study.

Speechley, Camfield, Levin, Smith, Wiebe, and Zou (2009) examined change in HRQOL scores over the course of 24 months in a sample of Canadian children with newly-diagnosed epilepsy. The authors administered both a disease-specific (Quality of Life in Childhood Epilepsy Questionnaire [QOLCE]) and a generic HRQOL measure. Results indicated that the overall scores for the QOLCE improved significantly from diagnosis to 24 months later. For the generic HRQOL measure, mean scores significantly improved on physical and psychosocial scales. Using the same sample, Ferro, Avison, Campbell, and Speechley (2011) found that maternal depressive symptoms were observed to have a negative impact on HRQOL scores at 24 months. The authors of these two studies did not report which subscales of the QOLCE changed over time. Additionally, the authors did not examine the potential effects of additional variables, such as epilepsy/seizure characteristics, and their relation to changes in HRQOL over time nor did they report if the changes from diagnosis to 24 months later were clinically meaningful to families.

Ferro et al. (2013) examined trajectories of HRQOL using the same Canadian sample and described five distinct trajectories: low QOLCE scores at baseline that increased over time; moderate baseline scores that decreased over time; moderate baseline scores that increased somewhat over time; high baseline scores that increased for
six months and then plateaued; and the fifth group had consistently high scores. The authors found clinically meaningful improvements in 50% of the children and clinically meaningful declines in 18% of the children. Children with lower HRQOL scores had more AEDs prescribed, more behavior and cognitive problems, parents with more depressive symptoms, worse family functioning, and more family demands. While the authors examined predictors of HRQOL scores and clinical meaningfulness of change, they only looked at overall HRQOL scores and did not look at specific subscales of the QOLCE. Additionally, they only examined epilepsy/seizure factors as a means to compare trajectory groups; they did not examine how epilepsy/seizure factors predicted change over time.

Speechley et al. (2012) examined the HRQOL of Canadian children with new-onset epilepsy and how child and family risk factors at diagnosis predicted HRQOL two years later; they used both the QOLCE and the general Child Health Questionnaire (CHQ). Results revealed that all subscales of both measures showed improvement, with the most improvement in the first six months after diagnosis; the authors did not state if this improvement was statistically significant. On the QOLCE-Overall scale, 50% experienced a clinically significant improvement while 18% had a clinically significant decline, with similar results for the CHQ. When baseline HRQOL scores were controlled for, absence of cognitive problems, high family functioning, fewer AEDs, and fewer family demands were predictors for higher HRQOL two years later. While this study examined predictors of HRQOL and clinical meaningfulness of change, the authors only examined how baseline characteristics predicted HRQOL two years later. Factors such as
AED side effects and seizure frequency are dynamic and likely to change over time, which will likely affect HRQOL scores differently over time.

Finally, Wu, Follansbee-Junger, Rausch, and Modi (2014) examined how parent and family stress factors predicted HRQOL at three different time points over two years in a sample of children with newly-diagnosed epilepsy, using both generic (PedsQL) and disease-specific (QOLCE) measures of HRQOL. Higher levels of both general and epilepsy-specific parent and family stress, fears/concerns, and perceived stigma had negative effects on HRQOL, particularly in the first year post-diagnosis. More side effects predicted lower HRQOL scores, particularly 1 and 25 months post-diagnosis; side effects were more predictive of HRQOL than seizure occurrence. There was also a significant quadratic effect of AED adherence on HRQOL scores 13 months post-diagnosis, with highest and lowest levels of adherence predicting lower HRQOL scores. While this study examined predictors of HRQOL at various time points, it remained cross-sectional in nature and did not examine changes in HRQOL over time.

Aims and Hypotheses

The goals of the present study were to assess changes in HRQOL scores over time in a sample of children with newly-diagnosed epilepsy using a disease-specific measure of HRQOL and examine how epilepsy-specific and demographic factors influence HRQOL scores. A previously proposed model for HRQOL in youth with epilepsy theorized that a number of factors account for variance in HRQOL (Lach et al., 2006). However, this model does not account for all important variables, particularly, the role of AED side effects. The current study examined a subset of the variables in this model, in addition to examining the added role of AED side effects in accounting for variance in
HRQOL scores. Variables included demographic characteristics (age, gender, race/ethnicity, socioeconomic status), for which there is conflicting research findings (Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey, 2004; Modi, Ingerski, Rausch, & Glauser, 2011). Finally, the study calculated MCIDs, for the QOLCE, using a distribution-based method to assess the level of HRQOL change perceived to be clinically meaningful to patients. The MCIDs calculated for this study were compared to MCIDs previously calculated for the QOLCE (Speechley et al., 2012).

The hypotheses of the present study are as follows: H1: After an initial diagnosis of epilepsy and AED treatment implementation, QOLCE-Overall and subscale scores (Language, Memory, Attention and Concentration, Other Cognitive, Behavior, Depression, Anxiety, Physical Restrictions, Energy and Fatigue, Control and Helplessness, and General Health) would increase over the span of two years. H2: Consistent with research with other pediatric HRQOL measures, MCIDs calculated for the QOLCE-Overall score would be approximately 4 points and MCIDs calculated for subscale QOLCE scores would be approximately 8 points. H3: Changes in HRQOL over the course of two years would be clinically meaningful in relation to MCIDs calculated for the QOLCE. H4: Increases in HRQOL over the course of two years would be predicted by the presence or absence of seizures and total side effects at each time point.

Method

Procedure

Data for this study were gathered as part of a larger, IRB approved, longitudinal study that examined antiepileptic drug (AED) adherence in children 2-12 years of age with newly-diagnosed epilepsy. For the larger study, children and their caregivers were
recruited from a neurology clinic at a large Midwestern children's hospital the day of the epilepsy diagnosis and AED initiation.

Consent for the study was obtained from primary caregivers and assent was obtained from children who were eight years of age and older. Families were met with at subsequent clinic visits, which occurred 1, 4, 7, 10, 13, 16, 19, 21, and 25-months following diagnosis. As part of the larger study, families completed a variety of measures that assessed the following constructs: parenting stress, health-related quality of life, stigma, family stress, AED side effects, etc. At each follow-up clinic visit, caregivers were asked about current medication(s), changes in medication, and number of seizures or presence/absence of seizures since their last clinic visit. Medication and disease-related variables were also obtained through medical chart reviews. The current study focused only on the HRQOL questionnaires and medical (e.g., side effects) and demographic variables from the following follow-up clinic visits: 1, 7, 13, 19, and 25 months post-diagnosis.

Participants

Inclusion criteria for the larger study included: 1) being between 2-12 years old, 2) a new diagnosis of epilepsy (day of recruitment), and 3) being initially prescribed carbamazepine or valproic acid. Exclusion criteria included parent-reported comorbid chronic illness requiring daily medication or a diagnosis of a significant developmental disorder, such as Autism. For the current study, only the data for participants four years and older were examined as the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), the primary measure of interest for this study, was validated only for caregivers of children 4-18 years of age.
Measures

**Demographic information.** A demographics form was completed by the primary caregiver that included age of child, sex, race/ethnicity of child and parents, socioeconomic status (measured as Family Duncan score), caregiver marital status, and caregivers’ level of education. The revised Duncan score is an occupation-based measure of socioeconomic status (Stevens & Featherman, 1981). Scores were calculated for each family and ranged from 15 (representing unemployed) to 99 (representing occupations such as lawyers and physicians). Higher Duncan scores reflect higher SES.

**Chart review.** A chart review was conducted at each study visit to assess several factors, including the number of or presence/absence of seizures. The chart review included information about prescribed AED and any AED changes made at the clinic visit.

**Quality of Life in Childhood Epilepsy Questionnaire (QOLCE).** The QOLCE is a 76-item parent-report measure designed to assess epilepsy-specific health-related quality of life in children ages 4-18. The QOLCE covers five domains of life including physical, functioning, social functioning, cognition, emotional, and behavioral well-being. These five domains cover 16 subscales, including physical restrictions, energy/fatigue, attention/concentration, memory, language, other cognitive, depression, anxiety, control/helplessness, self-esteem, social interactions, social activities, stigma, behavior, general health, and general quality of life. Items on the questionnaire are rated on a five-point Likert scale (very often to never), scores for which are used to calculate the 16 subscale scores and an overall score. The internal consistency reliabilities of the
multi-item scales ranged from moderate to excellent (range from 0.76-0.97). The internal consistency reliability of the QOLCE-Overall scale is 0.92 (Sabaz et al., 2003).

**Pediatric Epilepsy Side Effects Questionnaire (PESQ).** The PESQ Scale is a reliable and valid measure developed for clinical care and research to assess AED side effects (Morita, Glauser, & Modi, 2012). It is a 19-item questionnaire that includes five subscales: Cognitive, Motor, Behavioral, General Neurological, and Weight. Items are rated either by the patient or guardian on a 6-point Likert scale ranging from zero (not present) to five (high severity). Individuals are instructed to rate the severity of side effects or side effects associated with their antiepileptic medication. A total scale is calculated and is the score used in the present study. The total scale ranges from 0-100, with higher scores representing more side effects. The PESQ Scale has demonstrated strong reliability for working with children with epilepsy. The test-retest reliability was 0.91 for total side effect severity score, while the Cronbach’s alpha was quite high, $r = 0.90$ (Morita, Glauser, & Modi, 2012).

**Results**

**Participants**

There were 124 children with newly-diagnosed epilepsy and their caregivers recruited for the larger longitudinal study. For the current study, only those who completed the QOLCE at any time point were included, which resulted in a final sample of 112 participants. Due to missing data, sample sizes varied across time points (see Figure 2 for sample sizes at each time point and an explanation of missing data). Demographic data for youth and their primary caregivers are presented in Table 1.
Change in HRQOL over Two Years

Hierarchical linear modeling analyses (HLM analyses [Singer & Willett, 2003]) were employed to test the hypothesis that HRQOL scores (QOLCE-Overall and subscale scores: Attention and Concentration, Language, Memory, Other Cognitive, Behavior, Depression, Anxiety, Physical Restrictions, Energy and Fatigue, Control and Helplessness, and General Health) would increase over the course of two years (1, 7, 13, 19 and 25 months post-diagnosis). QOLCE-Overall and subscale scores were entered as the dependent variables while time was entered into the model as the independent variable (higher QOLCE scores means better perceived HRQOL). Consistent with Hypothesis 1, results indicated that QOLCE-Overall scores showed a significant increase in scores over time from one month to 25 months post-diagnosis ($t_{1,98} = 2.85, p = .01$).

Results revealed statistically significant increases over time for Physical Restrictions ($t_{1,87} = -3.51, p < .001$), Energy and Fatigue ($t_{1,87} = 6.4075, p = .003$), Behavior ($t_{1,98} = 2.17, p = .03$), and General Health ($t_{1,87} = -2.51, p = .01$). Results indicated that for the Physical Restrictions, Energy and Fatigue, and General Health subscales, the relationship between subscale scores and time was non-linear and quadratic. For the Behavior subscale, the relationship between subscale scores and time was linear.

A distribution-based, statistical significance approach, utilizing standard errors of the mean, was used to calculate MCID scores to test Hypothesis 3 that changes in QOLCE scores would be clinically meaningful for the QOLCE subscale and QOLCE-Overall scores. The formula for calculating MCIDs using the standard error of measurement is $SEM = s.d. \sqrt{1-\alpha}$, s.d. = standard deviation of mean baseline QOLCE scores for each scale; $\alpha =$ scale reliability (Wyrwich, Tierney, & Wolinsky, 1999). A
MCID was not calculated for General Health as it is a one item scale and an alpha coefficient could not be calculated. MCIDs are presented in Table 2 for each scale. Partially consistent with Hypothesis 2, the calculated MCIDs ranged from 4.73-13.50 for the subscales and 2.19 for the QOLCE-Overall scale. Results indicated a clinically significant improvement from one month to 25-months post diagnosis for QOLCE-Overall scores (change score = 4.24 points; calculated MCID = 2.19). However, there were no clinically meaningful changes for any of the subscales; thus Hypothesis 3 was not fully supported.

**Demographic Variables and Baseline HRQOL**

Independent t-tests, Pearson correlations, and one-way ANOVAs were conducted to examine relationships between demographic variables and baseline HRQOL total and subscale scores at the 1-month post-diagnosis clinic visit. Results demonstrated a significant effect for gender on Attention and Concentration ($t(91) = 2.38, p = 0.02$), Language ($t(92) = 2.39, p = .02$), and Behavior scores ($t(92) = 2.24, p = .03$). Males had significantly lower scores on all three subscales. Additionally, there was a significant effect for Race on Language ($F(4, 89) = 3.51, p = 0.01$) and Control and Helplessness scores ($F(4, 89) = 3.025, p = .02$). At baseline, children who were African American or Bi/multiracial had significantly lower scores on the Language and Control and Helplessness subscales. There was a significant positive correlation between Socioeconomic status and Control and Helplessness scores ($r(94) = .241, p = .02$). Finally, there was a significant negative correlation for age of patient on Anxiety scores ($r(94) = -.340, p = .001$). As a result of the relation between these demographic variables
and HRQOL scores, those variables found to be significantly associated with scores were included as covariates in the final predictor models.

**Predictors of HRQOL over Time**

To test Hypothesis 4, HLM analyses were conducted to examine the role of side effects (as measured by the PESQ) and seizures (dichotomized as absence vs. presence) on QOLCE scales over time. Separate models were constructed for QOLCE-Overall scores and specific subscale scores.

**Attention and Concentration.** HLM analyses demonstrated a significant effect for the Time x Side Effects interaction term (see Table 3), as well as significant effects for Side Effects and Gender on baseline scores (see above). The Time x Gender interaction term was not significant ($t_{1,182} = -0.27, p = .79$) and was not retained in the final model. As expected, children with higher side effect scores (one SD above the mean) had lower Attention and Concentration scores across two years compared to children with lower side effect scores (one SD below the mean) (see Figure 3).

**Memory.** Results revealed a significant effect for the Time x Side Effects interaction term, as well as a significant effect for Side Effects on baseline scores. The Time x Seizure interaction term was not significant (see Table 4). As expected, children with higher side effect scores (one SD above the mean) had lower Memory scores across two years compared to children with lower side effect scores (one SD below the mean) (see Figure 4).

**Language.** Results indicated there was a significant effect for the Time x Side Effects interaction term, as well as significant effects for side effects, gender, and race on baseline scores (see Table 5). The following terms were not significant and thus not
retained in the final model: Time x Seizure interaction term, Time x Gender, and Time x Race. As expected, children with higher side effect scores (one SD above the mean) had lower Language scores across two years compared to children with lower side effect scores (one SD below the mean) (see Figure 5).

**Other Cognition.** Results showed a significant effect for Side Effects on baseline scores, however, no significant effects were found for the Time x Side Effects or Time x Seizure interaction terms (see Table 6). Neither seizures nor side effects predicted Other Cognition scores over the course of two years.

**Behavior.** Results demonstrated significant effects for Side Effects and Gender on baseline scores, however, no significant effects were found for the Time x Side Effects or Time x Seizure interaction terms (see Table 7). The interaction term Time x Gender was not significant ($t_{1,184} = 0.95, p = .34$) and was not retained in the final model. Neither seizures nor side effects predicted Behavior scores over the course of two years.

**Depression.** Results revealed a significant effect for Side Effects on baseline scores, however, no significant effects were found for the Time x Side Effects or Time x Seizure interaction terms (see Table 8). Neither seizures nor side effects predicted Depression scores over the course of two years.

**Anxiety.** Results indicated there was a significant effect for the Time x Side Effects interaction term, as well as significant effects for Side Effects and Child Age on baseline scores (see Table 9). Seizures and the Time x Seizure interaction term were not significant. The interaction term Time x Child Age was not significant ($t_{1,183} = 1.20, p = .23$) and was not retained in the final model. As expected, children with higher side effect
scores (one SD above the mean) had lower Anxiety scores across two years compared to children with lower side effect scores (one SD below the mean) (see Figure 6).

Physical Restrictions. Results indicated that no significant effects were found for the Time x Seizure interaction term or the Time x Side Effects interaction term (see Table 10). However, as the Time x Time interaction term was significant ($t_{1,84} = -3.87, p < .001$), it was retained in the final model. While there was a change in scores over time, side effects and seizures did not predict changes in Physical Restrictions scores over the course of two years.

Energy and Fatigue. Results showed a significant effect for the Time x Side Effects interaction term, as well as significant effects for Side Effects and Seizures on baseline scores (see Table 11). Time x Time x Side Effects and Time x Time x Seizures interaction terms were also significant and were thus retained in the final model. Unexpectedly, at baseline, children with higher side effect scores (one SD above the mean) had higher Energy and Fatigue scores compared with children with lower side effect scores (one SD below the mean). However, by the end of two years months the results were as expected; children with higher side effect scores had lower scores compared with children with lower side effect scores (see Figure 7). Additionally, children who had at least one seizure between visits had significantly lower Energy and Fatigue scores than those who did not have seizures. However, by the end of the two years this difference was non-existent (see Figure 8).

Control and Helplessness. Results indicated there were significant effects for side effects and race on baseline scores. Seizures, Family Duncan, and the Time x Seizure and Time x Side Effects interaction terms were not significant (see Table 12).
Neither seizures nor side effects predicted Control and Helplessness scores over the course of two years.

**General Health.** Results revealed a significant effect for Side Effects on baseline scores. No significant effects were found for the Time x Seizure interaction term or the Time x Side Effects interaction term (see Table 13). However, as the Time x Time interaction term was significant ($t_{1,84} = -2.30, p = .02$), it was retained in the final model. Neither seizures nor side effects predicted General Health scores over the course of two years.

**QOLCE-Overall.** Results indicated significant effects for Side Effects and Seizures on baseline scores. However, no significant effects were found for the Time x Seizure or Time x Side Effects interaction terms (see Table 14). Neither seizures nor side effects predicted QOLCE-Overall scores over the course of two years.

Only partial support was found for Hypothesis 4, which stated that AED side effects and the presence/absence of seizures would be predictors of change in HRQOL over time for children with newly-diagnosed epilepsy.

**Discussion**

The current study is one of the first longitudinal studies to use a disease-specific measure to assess the role of AED side effects and the presence/absence of seizures on HRQOL for children with newly-diagnosed epilepsy. The study used well-validated measures of HRQOL and AED side effects in order to assess these predictors of HRQOL over time. Results partially supported our first hypothesis that HRQOL would significantly increase from 1-month post-diagnosis to 25-months later. In the present study the QOLCE-Overall scale, and Physical Restrictions, Energy and Fatigue,
Behavior, and General Health subscales showed statistically significant improvements. While a previous study has shown that QOLCE subscale scores increased over the course of 24 months (Speechley et al., 2012), the authors did not examine statistical significance. Thus, our findings represent a new and important finding in that particular QOLCE subscales improve significantly over time for young children with epilepsy.

Improvements from baseline to two years post-diagnosis on the Physical Restrictions, Behavior, and Energy and Fatigue subscales are not surprising. As children are treated, AED side effects are managed, and better seizure control is attained, parents may gradually feel more comfortable allowing children to engage in different physical activities and report improvements in behavior and energy. Both continued seizures and side effects are related to these three factors (Austin, Dunn, Caffrey, Perkins, Harezlak, & Rose, 2002; Carpay et al., 1997; St. Louis, 2009).

In addition to assessing the statistical significance of change over time, it was hypothesized that changes in HRQOL would be clinically meaningful for children. Calculated MCIDs were generally similar to those previously reported for the QOLCE subscales, but different than those calculated for the QOLCE-Overall scale by Speechley et al. (2012). Specifically, the reliability of the QOLCE-Overall scale in the current study was extremely high, which yielded a lower MCID. Results of the present study only partially supported the hypothesis that changes in HRQOL would be clinically meaningful as only changes in QOLCE-Overall scores were clinically significant. This is consistent with work by Speechley and colleagues, in which 50% of patients with newly-diagnosed epilepsy were found to have clinically significant improvements on the QOLCE-Overall scale (Speechley et al., 2012).
There are different possibilities for why changes were not statistically or clinically significant for subscales of the QOLCE. First, while group means for many of the subscales did not show statistically or clinically meaningful changes, changes in data for individual patients could still reveal significant improvements or declines. Examining individual data may still reveal valuable, clinically relevant information for health-care providers (Ferro et al., 2013; Modi, Ingerski, Rausch, & Glauser, 2011). This is important to understand because if a child has poor HRQOL in one area, particularly at the time of diagnosis, he or she is at risk for lower HRQOL over time (Ferro et al., 2013). Future research with this population should identify and examine individual trajectories of the subscales of the QOLCE to better identify areas of difficulty for children with epilepsy, which can be discussed with healthcare providers. Additionally, epilepsy-related factors such as AED side effects, the presence/absence of seizures (Modi, Ingerski, Rausch, & Glauser, 2011) and psychosocial variables (Wu, Follansbee-Junger, Rausch, & Modi, 2014) may mediate any changes over time; something not captured when simply examining changes in group means.

The current study assessed two potential covariates by examining the possible effects of seizures and AED side effects on changes in HRQOL in children with newly-diagnosed epilepsy. Only minimal support was found for the hypothesis that seizures would predict changes in HRQOL over the course of two years. Children who had seizures between clinic visits had significantly poorer Energy and Fatigue scores than those who did not have seizures, with this difference disappearing by the end of 24 months. Fatigue in the hours (or even days) following a seizure, the post-ictal period, is often marked by fatigue and drowsiness (Hamelin, Kahane, & Vercueil, 2010). For
children with intractable epilepsy, who continue to have uncontrolled seizures, the number one complaint is lack of energy (Elliot, Lach, & Smith, 2005). Thus it is not surprising that children in the present study who continued to have seizures had poorer Energy and Fatigue scores. In addition to the fatigue experienced following a seizure, inadequate sleep can be a trigger for seizures and epileptic discharges, which can disrupt the sleep-wake cycle (Batista & Nunes, 2007; Maganti et al., 2005). It is difficult to determine if the presence of seizures is responsible for the poorer Energy and Fatigue scores, if children who were not sleeping adequately were having more seizures, or if it was a combination of both factors.

No other QOLCE subscales, nor the QOLCE-Overall scale, were predicted by seizures over the course of two years. This is contrary to research that has demonstrated seizures have a significant impact of various domains of functioning (Dunn, Austin, Caffrey, & Perkins, 2003; Fastenau et al., 2009) and HRQOL (Camfield, Breau, & Camfield, 2001; Modi, Ingerski, Rausch, & Glauser, 2011; Montanaro, Battistella, Boniver, & Galeone, 2004; Sabaz et al., 2003). One potential reason for our findings is that both partial and generalized seizures were collapsed and coded as a categorical variable (dichotomized as absent vs. present); thus information regarding the impact of seizure frequencies on HRQOL was not assessed. However, given the difficulties in quantifying seizures (e.g. number of absence seizures or myoclonic jerks), seizure frequency is not easily standardized and measured across a heterogeneous group of children with epilepsy.

In addition to the impact of seizures, the present study used a well-validated measure of AED side effects to examine the impact of AED side effects on HRQOL over
time. Results partially supported this hypothesis; AED side effects had a significant impact on Language, Memory, Attention and Concentration, Energy and Fatigue, and Anxiety. The effect on Energy and Fatigue was not surprising as fatigue, drowsiness, and lack of energy are common complaints in children taking AEDs (St. Louis, 2009). Additionally, the effect on Anxiety was consistent with a previous review of the research showing a relationship between anxiety and AED use, particularly polytherapy (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009). Perhaps the most clinically important finding was that AED side effects had a significant impact on cognitive functioning (Language, Attention, and Memory) over the course of the two years (in epilepsy research, cognitive functioning typically means IQ, but for the purpose of this discussion it is generalized to encompass varying domains of cognitive abilities). It is well documented that side effects of AEDs include cognitive difficulties (Dunn, Austin, Caffrey, & Perkins, 2003; Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009; Fastenau et al., 2009). The impact of side effects on cognitive functioning is particularly important because cognitive issues are associated with a number of other problems. For children with epilepsy, cognitive difficulties can be related to behavioral problems, hyperactivity/inattention, academic difficulty, and even social problems with peers (Turky, Beavis, Thapar, & Kerr, 2008). Additionally, children with epilepsy with cognitive problems at diagnosis are at the most risk for decreased HRQOL, while children without cognitive problems have better HRQOL over time (Speechley et al., 2012).

Based on the results of the present study, a number of recommendations for health-care providers working with children with epilepsy can be made. The results
affirm that it is important for health-care providers to be sensitive to the impact seizures are having on patient’s energy and fatigue, and vice versa, given the impact on HRQOL. At diagnosis, it remains vitally important for health-care providers to provide education about the impact of seizures, particularly in the time immediately following a seizure, so parents and children know what to expect. Having this foundation of knowledge at diagnosis may mitigate the possible effects on HRQOL, particularly as it relates to fatigue, if or when seizures continue. Health-care providers also should place an emphasis on education in regards to the importance of sleep for attaining better seizure control as it may have a meaningful impact on quality of life. Additionally, as AED side effects can have such an impact on cognitive domains of HRQOL, which in turn can affect other areas of functioning, it remains crucial for health-care providers to be watchful for the potential effects of these medicines, particularly at the time of diagnosis. As cognitive problems at baseline can predict poor HRQOL later on, health-care providers may need to consider switching AEDs sooner for children who develop cognitive difficulties after treatment is initiated. For the clinic in the present study it is already standard clinical practice to quickly respond to family input about the impact of AED side effects when formulating a treatment plan. In clinics that may not be as responsive to family input, the impact of AED side effects on HRQOL may be more pronounced.

Limitations and Future Directions

While this study has several clinical implications, it also has limitations. First, the measures used in this study, for both HRQOL and side effects, were parent-reported and may not accurately represent how the children were feeling. While child- and parent
proxy-report HRQOL data is generally correlated (Eiser & Morse, 2001), there remain some concerns that parental reports of HRQOL may at times be affected by parental anxiety or emotional functioning (Levi & Drotar, 1998). To reduce any potential biases, future research should use a multi-informant approach to HRQOL assessment (Quittner, Davis, & Modi, 2003). There remains a need for well-validated disease-specific measures that have parallel child and parent forms. These measures exist for other diseases (e.g., PedsQL disease modules exist for sickle cell disease, diabetes, etc) and are currently being developed for epilepsy. When children are as young as four, as in the current study, it is not feasible to use a self-report measure, but in the future it may be better to defer to the parental report of HRQOL for young children and as children age to begin to give more weight to their self-report. Future research may also examine differences in child- and parent proxy-reports of longitudinal HRQOL.

Second, there are some limitations to the subscales of the QOLCE. One is that the Energy and Fatigue subscale only contains two items and was the subscale with the lowest internal consistency; this likely had an impact on results utilizing the subscale and may explain why the results for the Energy and Fatigue subscale were variable. A second limitation of the QOLCE is possible shared variance with the side effects measure used, the PESQ. A number of items, particularly on the subscales measuring cognitive functioning, are similar to those found on the PESQ, and may partially explain the significant impact AED side effects had on these subscales.

Third, as previously mentioned, seizures were coded and represented as a dichotomous, categorical variable (present vs. absent since last clinic visit). This meant it was not possible to distinguish between children with partial and generalized seizures.
Future studies using the QOLCE may consider recruiting children with specific diagnoses/seizure types (e.g., tonic-clonic seizures) to better quantify seizure frequencies. Additionally, it is possible that the impact of individual seizures were not captured at the time the HRQOL measures were completed as the questionnaire asks parents to think about a recent period of time. As such, the impact of seizures that occurred 2-3 months ago may not be detected on the QOL questionnaires.

Fourth, as the sample in the present study excluded children with co-morbid chronic illnesses that require a daily medication and children with developmental disabilities, there are limits to the generalizability of the results. The impact of an additional diagnosis and treatment regimen on HRQOL for children who have co-morbid chronic illnesses and/or developmental disabilities are likely to be different compared to those who are only managing epilepsy.

Fifth, while the present study has important implications for health-care providers when it comes to monitoring side effects, it was unclear if children were having increased side effects because they were less tolerant of the medication or if they were on higher doses of medication to better achieve seizure control. Future research with this population should use well-validated measures of side effects, but take into account the dose of the medication prescribed and the disease severity. Using a generic HRQOL measure has demonstrated that different AEDs have differing effects on HRQOL over time (Modi, Ingerski, Rausch, & Glauser, 2011). It may provide valuable information for families and health-care providers to examine these differences using a disease-specific measure, such as the QOLCE.
Sixth, it should be noted that missing data is a potential limitation. While Hierarchical Linear Modeling was conducted, which accounts for missing data, other statistical analyses were used that do not (T-tests, correlations, one-way ANOVA). As a result, missing data may have influenced the findings of the study and limited generalizability.

Finally, this study did not aim to provide a comprehensive and exhaustive examination of variables that may affect longitudinal HRQOL. Prior studies have identified a number of factors that may influence child HRQOL, including maternal depression (Ferro, Avison, Campbell, & Speechley, 2011), parent and family stress variables (Wu, Follansbee-Junger, Rausch, & Modi, 2014), epilepsy/seizure severity, and other disease/treatment factors. A more comprehensive research study examining many of these factors together may provide a fuller picture of predictors of HRQOL in children with newly-diagnosed epilepsy.

**Strengths**

This is one of only a few longitudinal studies to examine the impact of seizures and AED side effects on HRQOL using a disease-specific measure on children with newly-diagnosed epilepsy. The present study was able to follow a cohort over time from the time of diagnosis. It is vital to study HRQOL from the beginning in order to provide the best possible care to children and their families. A diagnosis of epilepsy may require children and families to go through a substantial adjustment period and this can be difficult, particularly at the beginning. Recruiting children at the time of diagnosis allowed us to better understand the impact of both seizures and side effects throughout the diagnosis and treatment process. Additionally, the current study adds to the literature
by using well-validated measures, both an epilepsy specific measure of HRQOL and a measure of AED side effects. Of the longitudinal studies that have used a disease-specific measure (Ferro et al., 2013; Speechley et al., 2012; Wu, Follansbee-Junger, Rausch, & Modi, 2014), few have assessed the clinical significance of changes of HRQOL scores over time and none have discussed the clinical meaningfulness of changes of the subscales of a HRQOL measure.

In summary, this study examined the statistical and clinical significance of both overall and subscale scores using a disease-specific HRQOL measure. Results found statistically significant changes for multiple subscales and the QOLCE-Overall scale, as well as clinically significant changes in the QOLCE-Overall scale over the course of two years. It also assessed the impact of seizures and AED side effects over time. Seizures had a significant effect on Energy and Fatigue scores over two years while AED side effects had a significant impact on Memory, Language, Attention and Concentration, Anxiety, and Energy and Fatigue scores. While the goal of epilepsy treatment is no seizures, no side effects, and best possible quality of life, the results of this study highlight the role AED side effects play for children with newly-diagnosed epilepsy. As a result, health-care providers need to continue to be particularly sensitive to the potential of side effects and work with families and children to know what to expect when starting an AED for the first time. This education and guidance may help patients and families better be able to communicate with their health-care providers and create a better decision-making process.
References


Table 1  
Demographics and Epilepsy/Seizure Information

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Table 3
Final Model Statistics for Attention and Concentration

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Figure 1
Theoretical model of youth with epilepsy

Biomedical status/Level of Impairment

- Epilepsy Variables
  - Severity
  - Age of onset
  - Duration
  - Proportion of life with seizures
  - Active/Not Active
  - Recovery time
  - Hx of injury

- Co-morbidity
  - Physical Disability
  - Intellectual disability
  - Mental health
  - Sleep disorders

Intermediate Variables

- Child Variables
  - Demographic
  - Social Skills
  - Self-worth
  - Participation
  - Victimization
  - Social support
  - Efficacy

- Family Variables
  - Family Demographics
  - Impact of illness on family
  - Parental mood
  - Parenting
  - Economic burden of health-care

- Community Variables
  - School bonding
  - Health services
  - Social support

HRQOL

- Social
- Worries
- Emotional
- Normality
- Secrecy
Figure 2
Explanation of Missing QOLCE Data

Total possible at each time point:
  n=124
Total across all time points:
  n=112

One month following diagnosis: n=94
Missing data due to: Did not return to clinic (n=3), parent did not send back measure (n=7), disenrolled due to being seen in different clinic (n=1), child too young for measure (n=19)

Seven months following diagnosis: n=86
Missing data due to: Did not return to clinic (n=8), missed appointment (n=11), parent did not send back measure (n=1), withdrew from study (n=2), disenrolled due to being seen in different clinic (n=1), moved (n=3), missed appointment due to good clinical progress (n=1), child too young for measure (n=11)

Thirteen months following diagnosis: n=82
Missing data due to: Did not return to clinic (n=17), missed appointment (n=4), parent did not send back measure (n=2), withdrew from study (n=5), disenrolled due to being seen in different clinic (n=2), moved (n=3), missed appointment due to good clinical progress (n=4), child too young for measure (n=5)

Nineteen months following diagnosis: n=67
Missing data due to: Did not return to clinic (n=22), missed appointment (n=7), parent did not send back measure (n=3), withdrew from study (n=7), disenrolled due to being seen in different clinic (n=2), moved (n=3), missed appointment due to good clinical progress (n=12), child too young for measure (n=1)

Twenty-five months following diagnosis: n=84
Missing data due to: Did not return to clinic (n=22), parent did not send back measure (n=2), withdrew from study (n=7), disenrolled due to being seen in different clinic (n=2), moved (n=4), weaned medication early (n=3)

No QOLCE data for 12 participants:
Missing data due to:
Never returned to clinic after initial visit (n=4), initially too young for measure and then never returned to clinic (n=3), initially too young for measure and then withdrew from study (n=2), initially did not return measure and then never returned to clinic (n=1), disenrolled due to being seen in different clinic (n=1), initially too young to complete measure and then moved (n=1)
Figure 3
Interaction between QOLCE Attention and Concentration Scores and Side Effects

- ▲ Mean Side Effects
- ▲ Mean+1SD Side Effects
- ▲ Mean-1SD Side Effects

QOL

Time in Months

0 6 12 18 24
Figure 4
Interaction between QOLCE Memory Scores and Side Effects

- ▲ Mean Side Effects
- ▲ Mean+1SD Side Effects
- ▲ Mean-1SD Side Effects
Figure 5
Interaction between QOLCE Language Scores and Side Effects

- ▲ Mean Side Effects
- ■ Mean+1SD Side Effects
- ● Mean-1SD Side Effects

QOL

Time in Months

0 6 12 18 24
Figure 6
Interaction between QOLCE Anxiety Scores and Side Effects

- ▲ Mean Side Effects
- ▼ Mean+1SD Side Effects
- ◇ Mean-1SD Side Effects

QOL
50 60 70 80
90 100
0 6 12 18 24
Time in Months
Figure 7
Interaction between QOLCE Energy and Fatigue Scores and Side Effects
Figure 8
Interaction between QOLCE Energy and Fatigue Scores and Presence/Absence of Seizures

- ▲ Yes-Seizures
- ■ No-Seizures

QOL

Time in Months
0 6 12 18 24
Appendix

IRB Approval Letter

June 11, 2013

Jordan Harrison
274 Senator Place, Apt. 15
Cincinnati, OH 45220

Re: Protocol #1299-5, Longitudinal Health-Related Quality of Life in Children with Newly-Diagnosed Epilepsy: Identifying Predictors and Assessing Meaningful Change over Time

Dear Mr. Harrison:

The IRB has reviewed the materials regarding your study, referenced above, and has determined that it meets the criteria for the Exempt from Review category under Federal Regulation 45CFR46. Your protocol is approved as exempt research, and therefore requires no further oversight by the IRB.

If you wish to modify your study, including the addition of data collection sites, it will be necessary to obtain IRB approval prior to implementing the modification. If any adverse events occur, please notify the IRB immediately.

Please contact our office if you have any questions. We wish you success with your project!

Sincerely,

[Signature]

Merrill E. Mullins, Jr., Ph.D.
Chair, Institutional Review Board
Xavier University

MEM/sh

C: Janet Schultz, Advisor
Longitudinal Health-Related Quality of Life in Children with Newly-Diagnosed Epilepsy: Identifying Predictors and Assessing Meaningful Change over Time

Problem

Compared to healthy peers, children with epilepsy, of which there are approximately 325,000 under the age of 15 in the United States, are at increased risk for lower health-related quality of life (HRQOL) (Epilepsy Foundation, n.d.; Modi et al., 2009; Montanaro, Battistella, Boniver, & Galeone, 2004; Sabaz et al., 2003). A theoretical model has emerged that takes into account a number of variables that may affect HRQOL in children with epilepsy, including epilepsy specific variables, comorbidities, and child, family, and community variables (Lach et al., 2006). With the goal of epilepsy treatment being no seizures, no side effects, and the best possible quality of life (Epilepsy Foundation, 2011), it is important to understand how different variables may affect this treatment goal, and how these might change over time.

Cross-sectional research has demonstrated that antiepileptic drug (AED) side effects (Benavente-Aguilar, Morales-Blanquez, Rubio, & Rey, 2004; Jakovljevic, Jankovic, Jankovic, & Todorovic, 2008) and seizures (Camfield, Breau, & Camfield, 2001; Montanaro, Battistella, Boniver, & Galeone, 2004; Sabaz et al., 2003) affect HRQOL. Longitudinal studies have revealed increases in HRQOL over two years (Modi, Ingerski, Rausch, & Glauser, 2011; Speechley et al., 2012), with HRQOL being predicted by family and stress factors, cognitive problems, number of AEDs, and maternal depressive symptoms (Ferro, Avison, Campbell, & Speechley, 2011; Speechley et al., 2012; Wu, Follansbee-Junger, Rausch, & Modi, 2014). However, these longitudinal
studies have not used a disease-specific measure to assess the role of AED side effects and the presence/absence of seizures on HRQOL for children with newly-diagnosed epilepsy. Additionally, very few studies have examined the clinical meaningfulness of change in HRQOL scores over time in this population.

Methods

Archival data from 112 children with newly-diagnosed epilepsy and their caregivers were used to assess changes in HRQOL scores over two years, the clinical meaningfulness of changes, and the role of seizures (dichotomized as absence vs. presence) and AED side effects in predicting changes. Data were used from clinic visits 1, 7, 13, 19, and 25 months post-diagnosis. Measures included demographic information, a medical chart review, the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), and the Pediatric Epilepsy Side Effects Questionnaire (PESQ).

It was hypothesized that QOLCE-Overall and specific subscale scores would increase after an initial diagnosis of epilepsy and AED treatment implementation. It was hypothesized that minimum clinically important difference (MCID) scores would be consistent with those previously published for the QOLCE and changes in HRQOL would be clinically meaningful. Finally, it was hypothesized that increases in HRQOL over the course of two years would be predicted by the absence of seizures and total side effects at each time point.

Findings

Hierarchical linear modeling (HLM) analyses were employed to test the hypothesis that HRQOL scores (QOLCE-Overall and selected subscale scores) would increase over the course of two years. QOLCE-Overall and subscale scores were entered
as the dependent variables while time was entered as the independent variable. QOLCE-Overall ($t_{1,98} = 2.85, p < .01$), Physical Restrictions ($t_{1,87} = -3.51, p < .01$), Energy and Fatigue ($t_{1,87} = 6.4075, p < .01$), Behavior ($t_{1,98} = 2.17, p = .03$), and General Health scores ($t_{1,87} = -2.51, p = .01$) showed significant increases in scores over time. For the Physical Restrictions, Energy and Fatigue, and General Health subscales the relation between subscale scores and time was non-linear and quadratic.

A distribution-based, statistical significance approach was used to calculate MCID scores to assess if changes in QOLCE scores were clinically meaningful. Calculated MCIDs ranged from 4.73-13.50 for the subscales and 2.19 for the QOLCE-Overall scale. Results indicated a clinically significant improvement for QOLCE-Overall scores (change score = 4.24 points; calculated MCID = 2.19). There were no clinically meaningful changes for any of the subscales.

Independent $t$-tests, Pearson correlations, and one-way ANOVAs were conducted to examine possible relations between demographic variables and baseline HRQOL scores. Results demonstrated a significant effect for gender on Attention and Concentration ($t(91) = 2.38, p = 0.02$), Language ($t(92) = 2.39, p = .019$), and Behavior scores ($t(92) = 2.24, p = .029$). There was a significant effect for Race on Language ($F(4, 89) = 3.51, p = 0.01$) and Control and Helplessness scores ($F(4, 89) = 3.025, p = .022$). Socioeconomic status was positively correlated with Control and Helplessness scores ($r(94) = .241, p = .019$). There was a significant negative correlation for age of patient on Anxiety scores ($r(94) = -.340, p = .001$). Those variables found to be significantly associated with scores were included as covariates in the final predictor models.
HLM analyses were conducted to examine the role of side effects (as measured by the Pediatric Side Effect Questionnaire) and seizures (dichotomized as absence vs. presence) on QOLCE scales over time. Separate models were constructed for QOLCE-Overall scores and specific subscale scores. Children who had seizures between visits had significantly lower Energy and Fatigue scores ($t_{1.96} = 2.01, p = .0469$) than those who did not have seizures. However, by the end of the two years this difference was non-existent. Children with higher side effects (side effect scores one SD above the mean) had lower Attention and Concentration ($t_{1.182} = -0.27, p = .0454$), Memory ($t_{1.183} = -2.97, p = .0033$), Language ($t_{1.183} = -2.95, p = .0036$), Energy and Fatigue ($t_{1.96} = -2.68, p = .0088$), and Anxiety ($t_{1.183} = -2.50, p = .01$) scores.

Implications

The current study is one of the first longitudinal studies to use a disease-specific measure to assess the role of AED side effects and the presence/absence of seizures on HRQOL for children with newly-diagnosed epilepsy. Results demonstrated that QOLCE-Overall, and Physical Restrictions, Energy and Fatigue, Behavior, and General Health subscales showed statistically significant improvements, but only the QOLCE-Overall showed clinically meaningful changes. The data provided by the QOLCE can provide health-care providers useful information about changes in the health-status of patients. This is important to understand because if a child has poor HRQOL in one area, particularly at diagnosis, he or she may be at risk for lower HRQOL over time (Ferro et al., 2013).

Children who had seizures between clinic visits had significantly poorer Energy and Fatigue scores than those who did not have seizures, with this difference
disappearing by the end of 24 months. The present study affirms that it is important for health-care providers to be sensitive to the impact seizures are having on patient’s energy and fatigue, and vice versa, given the impact on HRQOL. At diagnosis, it remains vitally important for health-care providers to provide education about the impact of seizures, particularly in the time immediately following a seizure, so parents and children know what to expect. Having this foundation of knowledge at diagnosis may mitigate the possible effects on HRQOL if or when seizures continue. Additionally, health-care providers place should place an emphasis on education in regards to the importance of sleep for attaining better seizure control as it may have a meaningful impact on quality of life.

In addition to the impact of seizures, the present study used a well-validated measure of AED side effects to examine the impact of AED side effects on HRQOL scores over time. AED side effects had a significant effect on Language, Memory, Attention and Concentration, Energy and Fatigue, and Anxiety subscale scores of the QOLCE. For children with epilepsy, cognitive difficulties can be related to behavioral problems, hyperactivity/ inattention, academic difficulty, and even social problems (Turky, Beavis, Thapar, & Kerr, 2008). As AED side effects can have such an impact on cognitive domains of HRQOL, which in turn can affect other areas of functioning, it remains crucial for health-care providers to be watchful for the potential effects of these medicines, particularly at the time of diagnosis. As cognitive problems at baseline can predict poor HRQOL later on (Speechley et al., 2012), health-care providers may need to consider switching AEDs sooner for children who develop cognitive difficulties after treatment is initiated.