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Original Research Article

The Stability and Influence of Barriers to Medication Adherence on Seizure Outcomes and Adherence in Children With Epilepsy Over 2 Years

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Abstract

Objective To determine the stability and influence of adherence barriers on medication adherence and seizure control in pediatric epilepsy. **Methods** Caregivers of 118 children aged 2–12 years old with epilepsy completed the Pediatric Epilepsy Medication Self-Management Questionnaire at nine time points over 2 years post diagnosis. Electronically monitored antiepileptic drug adherence and seizure outcome data were collected. **Results** Hierarchical linear modeling results for overall barriers remained stable over 2 years. Specific item-level barriers were also generally stable over time, with the exception of running out of medication becoming more of a barrier over time. No specific barriers were related to seizure control; however, difficulties swallowing medication, forgetting, and medication refusal were related to electronically monitored adherence over time. **Conclusions** Assessing for specific adherence barriers over time may lead to identification of interventions that result in improved adherence and care.

Key words: barriers; epilepsy; medication adherence; pediatric.

Epilepsy is a neurological disorder characterized by recurrent unprovoked seizures that affects ~1% of youth (Russ, Larson, & Halfon, 2012). Antiepileptic drugs (AEDs) are the primary treatment modality for most patients with epilepsy, and the overall goal of treatment is no seizures, no side effects and best quality of life (Glauser, 2002). Although multiple efficacious AEDs are available to treat children with epilepsy, one-third of children with newly diagnosed epilepsy continue to have seizures despite the use of an AED (Geerts et al., 2010; Holland & Glauser, 2007; Holland, Monahan, Morita, Vartzelis, & Glauser, 2010; Kwan & Brodie, 2000). The precise reason for experiencing continued seizures despite the use of medications is often unknown, but may be because of seizure type, disease etiology, genetics, medication selection/combination, underlying brain abnormalities, or AED nonadherence (Berg, Testa, & Levy, 2011; Geerts et al., 2012; Glauser et al., 2006; Modi, Ingerski, Rausch, & Glauser, 2011; Modi, Rausch, & Glauser, 2014).

AED nonadherence is both a common and modifiable factor contributing to continued seizures. Prior studies have shown that 58% of young children with epilepsy exhibit nonadherence to AEDs in the first 6 months of treatment (Modi, Rausch, & Glauser, 2011). Although patterns of nonadherence vary in course and level (Modi, Rausch, et al., 2011), children with nonadherence in the first 6 months of therapy are 3.24 times more likely to have continued seizures 4 years post diagnosis (Modi, Rausch, et al., 2014).

Variable adherence patterns over the first 2 years of AED therapy have also been shown to result in a higher likelihood of having seizures over the same time course (Modi, Wu, Rausch, Peugh, & Glauser, 2014). AED nonadherence also contributes to other significant health and economic ramifications, such as uninformed clinical decision-making (Modi, Wu, Guilfoyle, & Glauser, 2012), increased health-care costs (Faught, Duh, Weiner, Guerin, & Cunnington, 2008; Faught, Weiner, Guerin, Cunnington, & Duh, 2009), and higher incidence of emergency room visits, hospitalization admissions, motor vehicle injuries, and fractures (Faught et al., 2009).

Given the modifiable nature and significant medical and economic ramifications of nonadherence to AEDs, adherence and barriers to adherence are ideal target areas for interventions aimed to improve the health outcomes of children with epilepsy. Following a prescribed medication treatment of daily oral AED medications can be difficult for families for a variety of reasons and understanding the family's perceptions of their own adherence barriers can aid in intervention selection and development. A recent systematic review indicated that adherence barriers generalize across chronic conditions and are often categorized as follows: relational barriers (peers, parents, health professionals), developmental barriers (strive for normality, freedom vs. control), health and illness barriers (mental well-being, physical well-being including ingestion difficulty, treatment perceptions), forgetfulness, poor organization, medicine complexity, and financial costs (Hanghoj & Boisen, 2014). The quantity and types of barriers endorsed have been found to be associated with nonadherence in children with epilepsy (Modi, Monahan, Daniels, & Glauser, 2010) as well as children with other chronic conditions (Bond, Aiken, & Somerville, 1992; Modi et al., 2010; Simons, McCormick, Devine, & Blount, 2010; Zelikovsky, Schast, Palmer, & Meyers, 2008).

Although lacking in epilepsy, several studies have examined the presence, stability, and influence of barriers in adolescents following a solid organ transplant (Lee et al., 2014; Simons & Blount, 2007; Simons et al., 2010). Specifically, these studies demonstrated temporal stability in the total number of barriers over 18 months and that increased barriers related to Regimen Adaptation and Cognitive Issues (Parent Medication Barriers Scale) were related to poorer adherence for teens following transplant (Simons et al., 2010). In addition, perceived barriers related to child ingestion difficulties were associated with clinical outcomes such as medical complications and mortality (Simons et al., 2010). The stability of barriers to medication adherence at the specific barrier (or item) level over 18 months has also been documented for children taking immunosuppressant medication following a transplant (Lee et al., 2014). In other words, once a child or family endorses a specific barrier, it is likely to be a continued barrier without targeted intervention (Lee et al., 2014). Little evidence is available regarding the presence, stability, and influence of barriers in children with epilepsy.

The purpose of this study was to understand the stability of treatment barriers and the influence of these barriers on adherence and seizure control over time. The current study is modeled after the transplant literature examining the relationship between barriers and distal health outcomes to address these important gaps in the literature by examining specific parent-reported barriers to medication adherence every 3 months over a 2-year period. Our overarching goal was to identify "critical barriers" most associated with health outcomes and adherence that can be targeted for future adherence promotion interventions. It is hypothesized that, similar to barriers experienced by children posttransplant, the overall level of barriers and individual barriers will remain stable over a 2-year period and that barriers will negatively impact adherence and seizure control. Specifically, based on the work Lee and colleagues (2014) and Simons and colleagues (2010), we hypothesized that the following specific barriers would be stable and related to adherence and seizure control: forgetting to give medications, medications are difficult to swallow, activities interfere with taking medications, and child refused to take medication. Although we hypothesized that a linear model would demonstrate the best fit, we will also examine cubic and quadratic models because the stability barriers and the relationship of barriers with adherence and seizure control have not been specifically examined in children with epilepsy.

Method

Participants and Procedures

Participants were recruited from the New Onset Seizure Disorder Clinic on the day of their epilepsy diagnosis and were prescribed an AED. Children were eligible to participate if they: (1) received an epilepsy diagnosis and were prescribed an AED, (2) were between 2 and 12 years of age, (3) had no comorbid medical conditions requiring a daily medication, (4) had no significant developmental disorders reported by their caregiver, and (5) the family was fluent in English. This study received approval by the hospital institutional review board before families being approached, recruited, and enrolled in clinic. Caregivers provided informed consent for each patient and completed a demographics form on enrollment. Families were given an electronic monitoring bottle to measure AED adherence. Subsequent study visits were completed at the time of routine clinic appointments ~1,

4, 7, 10, 13, 16, 19, 22, and 25 months post diagnosis. Electronic monitoring adherence data were downloaded and caregivers completed a battery of questionnaires at each of these visits.

In total, 130 eligible children with epilepsy and their caregivers were approached for participation in the larger study. Five families declined participation because of lack of time or interest and one family who provided consent was deemed ineligible because of a pervasive developmental disorder. Of the families that provided consent, three families did not return to the multidisciplinary New Onset Seizure Disorder Clinic for medical follow-up, two families did not return baseline measures, and one patient was disenrolled from the study because of a complex differential cardiological diagnosis. This resulted in 118 participants in this study cohort (91% of those initially eligible). In total, 67% of those initially eligible completed the final 25 month follow-up assessment. Of the 33% who did not complete a final 25 month follow-up assessment, seven patients withdrew from the study, while the rest were removed because of routine clinical care recommendations. Retention rates at intermediate time points ranged from 42% to 95%. These rates are lower because of the observational, longitudinal nature of the current study, and reasons for missing data points included being weaned from AEDs, family moved, missed clinic visit, or left clinic because of clinical care recommendations. Participants were not required to complete every time point and instead were considered to be completing the time point within the closest 1.5 months even if they had not completed the previous visit time point.

Measures

Demographics and Medical Characteristics

Background information such as child age and sex was collected from the primary caregiver using a demographics form. Socioeconomic status (SES) was measured using an occupation-based measure of SES, the Duncan scoring system (Stevens & Featherman, 1981). Scores were calculated for each family and range from 15 to 99, with lower scores indicating poorer socioeconomic status. For households with two caregivers, the higher Duncan score was used. Disease information such as seizure type and etiology was obtained through medical chart review. Seizures were classified using the International League Against Epilepsy standard classification (i.e., partial, generalized, or unclassified seizures) (Berg et al., 2010).

Barriers

The barriers to Medication Adherence scale of the Pediatric Epilepsy Medication Self-Management Questionnaire (PEMSQ) (Modi et al., 2010) was used to assess parent perceptions of things that make it difficult (e.g., barriers) for their child to take AEDs as prescribed. The PEMSQ was developed and validated for caregivers of children newly diagnosed with epilepsy between 2 and 14 years of age (Modi et al., 2010). The barriers to Medication Adherence scale includes 8 items (forget to give medications, medications are difficult to swallow, ran out of medication, embarrassed to take medications in front of others, difficult to get medication from pharmacy, dislikes taste of medicine, activities interfere with taking medications, and child refused to take medication) and the five-choice response set ranged from "never" to "always." Endorsement of an item included all responses with the exception of "never." Unlike previous studies, items were not reverse scored for ease of interpretation. Scores range from 8 to 40 with lower scores indicating fewer barriers or that barriers are less of a problem. The internal consistency coefficient was 0.76 for the barriers to Medication Adherence scale (Modi et al., 2010) and was 0.68 for the current study.

Adherence

The Medication Event Monitoring System (MEMS) TrackCap (Aardex Group, Sion, Switzerland) was used to assess adherence. This electronic monitoring system measures the dosing histories of patients prescribed oral medications by using a cap with a microelectronic circuit to register the dates and times the bottle is opened and closed. Data from electronic monitors were downloaded at all follow-up clinic visits. Electronic data were assumed to be an accurate proxy for patients taking the correct medication dose. Families were told that the provided bottles were MEMS TrackCaps that would monitor their adherence. Caregivers were also given the opportunity to reveal days the electronic monitor was not used (e.g., vacation) to ensure that the most accurate representation of adherence behaviors was collected. Nonmonitored periods were not used in analyses. Daily adherence rates of 0%, 50%, or 100% based on a twice-daily doings schedule were used and were capped at 100% per day. Daily adherence was averaged between visits. In the rare instance of malfunctioning MEMS, families were immediately provided with a replacement bottle, and the malfunctioning bottle was sent to manufacturer for data retrieval.

Seizure Occurrence

Seizure frequency was assessed throughout the study beginning at the time of treatment initiation. Similar to other studies (Mitchell, Scheier, & Baker, 2000; Modi, Ingerski, et al., 2011), seizure occurrence was dichotomized into the low "no seizures" or high "one or more seizures" trajectory group based on the presence of seizures for the duration of the study. Seizures were dichotomized because of the heterogeneity of seizures that were included in our sample. Tonic–clonic seizures, for example, tend to occur rarely, while

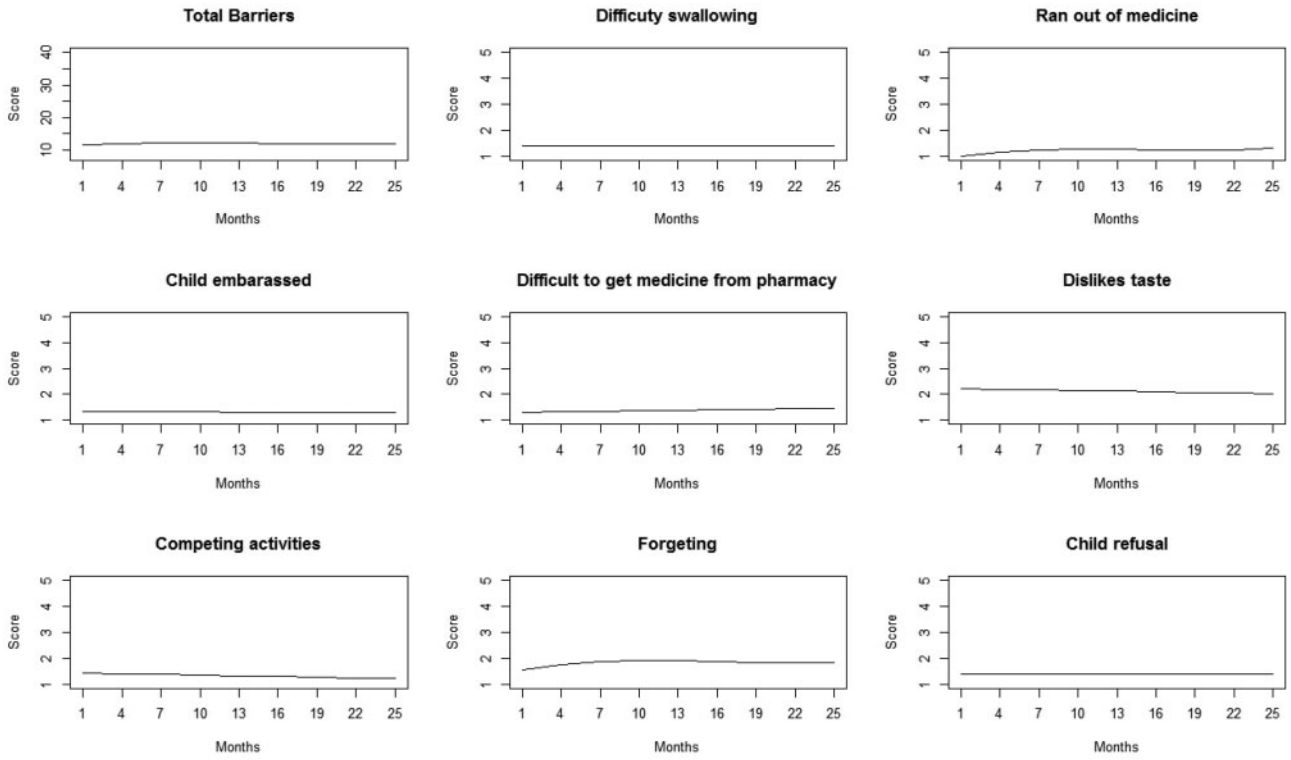

Figure 1. Total and individual barriers over 2 years for children with epilepsy.

absence seizure may occur hundreds of times per day. Overall, 28% of the participants experienced a seizure during the course of the study, which is consistent with the literature demonstrating that 30% of patients with epilepsy continue to have seizures once an AED is initiated (Laxer et al., 2014).

Statistical Analyses

Mixed-effect models were used to assess adherence barriers over time. For each outcome, linear, quadratic, and cubic terms of time were tested using separate models, and the *p*-values of the highest order term for each outcome were used to choose the best fit. Mixed-effect models were also used to examine the impact of time, barriers, and the interaction of barriers and time on adherence; generalized linear mixed-effect models were used to model dichotomous seizure outcome on time, barriers, and barriers × time interaction; all models adjusted for child age. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). Mixed-effect models have the advantage of retaining the participants in the model who have missing data for some assessment time points, and is thus less affected by attrition assuming a missing at random missing data mechanism.

Results

Children with epilepsy were 7.24 ± 2.93 years of age at baseline and 63% were male. 75% of the children identified as White, 18% as Black, 5.1% as biracial, and 2.5% as other. Localization-related epilepsy was the most common diagnosis (59.4% overall; 45.8% idiopathic, 8.5% cryptogenic, and 5.1% symptomatic), and the remainder were diagnosed with generalized (25.4% overall; 19.5% idiopathic, 5.1% cryptogenic, and 1% symptomatic) or unclassified (overall 15.3%; all idiopathic) epilepsy. Initial AED prescriptions were either carbamazepine (59.3%) or valproic acid (40.7%). Primary caregivers participating in the study were primarily mothers (84.7%) and were married (64.4%). Family SES based on the Duncan scale was 52.97 ± 20.34, which is associated with occupations such as property managers, law enforcement, mail carriers, physician's assistants, and fire prevention. Descriptive statistics for adherence and seizure frequency can be found in previous published studies (Modi, Rausch, et al., 2011, 2014; Modi, Wu, et al., 2014). Group comparisons between completers and noncompleters revealed no significant differences on the aforementioned or outcome variables ($p > .05$), with the exception of family SES. Families who completed the study had higher SES (56.1 ± 20.1) than noncompleters (44.7 ± 19.0; $t(121) = -3.0$, $p < .05$).

Caregiver report of overall and individual treatment barriers over time can be found in Figure 1. Mixed-effect modeling results for overall barriers as reported by caregivers revealed a nonsignificant cubic trend over 2 years, suggesting that overall barriers were stable over time ($t(95) = -1.79$, $p = .07$).

Table I. *Percentage of Families' Endorsement of Barriers Over Time*

Barrier	Months								
	1	4	7	10	13	16	19	22	25
Medication is difficult to swallow	24.3	18.2	18.6	25.3	21.2	26.4	20.0	25.0	23.5
We have run out of medication	10.4	17.2	22.7	14.4	21.2	12.5	17.1	13.5	25.9
Child is embarrassed to take medication in front of others	18.3	22.2	13.4	20.0	16.5	29.2	18.6	15.4	17.6
It is difficult to get the medication from pharmacy	25.2	26.3	23.7	23.3	29.4	19.4	22.9	25.0	32.9
Child dislikes taste of medication	50.9	51.5	50.5	49.5	51.8	50.0	40.0	46.2	51.8
Child has other activities that interfere with taking medication	24.6	30.3	29.9	21.1	17.6	22.2	18.6	23.1	22.4
I forgot to give my child medications	47.0	67.7	61.9	61.1	58.8	65.3	60.0	73.1	64.7
Child refuses to take medication	25.2	27.3	27.8	25.6	22.4	22.2	27.5	28.8	22.6
Total barriers	80.9	87.8	86.6	90.0	84.7	80.6	84.1	86.5	86.9

Note. Percentage endorsement of a specific barrier at each time point includes all responses with the exception of "never" indicating that the family experiences the barrier on at least some occasions. Percentage endorsement of total barriers for each time point indicates families that endorsed at least one barrier at that time point.

Average overall scores on the barriers assessment were as follows: $M_{1month\ post\ diagnosis} = 10.77$, $SD = 3.07$; $M_{4months\ post\ diagnosis} = 11.34$, $SD = 3.52$; $M_{7months\ post\ diagnosis} = 10.67$, $SD = 3.94$; $M_{10months\ post\ diagnosis} = 10.45$, $SD = 3.32$; $M_{13\ months\ post\ diagnosis} = 10.90$, $SD = 33.04$; $M_{16months\ post\ diagnosis} = 10.24$, $SD = 2.75$; $M_{19months\ post\ diagnosis} = 10.29$, $SD = 3.62$; $M_{22\ months\ post\ diagnosis} = 10.46$, $SD = 3.12$; and $M_{25months\ post\ diagnosis} = 10.36$, $SD = 2.97$. Specific item-level barriers were also generally stable over time (Figure 1). The specific barriers "Ran out of medicine" and "Forgetting" exhibited curvilinear change over time with significant cubic time terms in the models, while all other item-level barriers indicated linear increase over time. The one exception was the specific barrier "We have run out of the medication" demonstrating a significant positive slope, which suggests that running out of medication becomes more of a problem as children move further from diagnosis ($p < .001$). The most commonly endorsed barriers across all time points were "child dislikes the taste" and "forgetting to give medication," with 40–52% and 47–73% (respectively) of parents endorsing each adherence barrier (Table I).

In the mixed-effect model predicting electronically monitored adherence, several of the individual barrier-by-time interactions (linear) were significant indicating differences in adherence over time based on the presence of a specific barrier. Specifically, the time-by-barrier interaction for "medications are difficult to swallow," "forget to give medication," and "child refused to take medication" were significantly related to adherence (Table II). The relationship between each of these specific barriers with adherence changed over time. For example, adherence did not vary based on the reported level of difficulty swallowing AEDs at 1 month post diagnosis; however, difficulty swallowing the AED resulted in lower adherence at 25 months post diagnosis (Figure 2). The child refusing to take the AED was also related to adherence, such that increased refusal was associated with increased adherence at 1 month post diagnosis and decreased adherence at 25 months post diagnosis (Figure 3).The third barrier, forgetting to give medication, was associated with adherence such that increased forgetting was related to decreased adherence at 1 month post diagnosis, but with increased adherence at 25 months post diagnosis (Figure 4). As noted in Table II, each of the models with a significant barrier-by-time interaction and several of the models with nonsignificant interactions demonstrate a significant time and/or barrier main effect on adherence. Finally, none of the time-by-barrier interactions nor the main effect of time or barriers were significant in the generalized linear mixed-effect models predicting seizure control (Table II).

Discussion

The current study highlights the importance of assessing treatment adherence barriers in children with epilepsy to promote AED adherence and optimal seizure treatment. For families of children with epilepsy, the overall number of barriers and nearly all of the specific barriers (e.g., forgetting, disliking taste) remain stable during the initial 2 years of a child's epilepsy diagnosis. One barrier, running out of medication, became more of a barrier to AED adherence over time. From a clinical standpoint, this suggests that barriers experienced by patients and caregivers following diagnosis are likely to persist or worsen over the initial 24 month period following diagnosis. It seems reasonable to believe that these barriers would remain stable or worsen without appropriate identification of these barriers and interventions to mitigate these barriers. If barriers remain consistent, AED adherence will likely not improve. These findings are similar to studies of adherence barriers in children taking immunosuppressant drugs following transplant (Lee et al., 2014; Simons et al., 2010). Obtaining information about the specific barriers that are present for children with

Table II. *Effect of Time and Barriers on Adherence and Seizures Controlling for Age*

Variable	Adherence			Seizure control		
	t	*SE*	*p*	*T*	*SE*	*p*
Intercept	7.10	16.77	<.0001	−0.52	2.22	.60
Age	−0.21	0.72	.83	−1.32	0.05	.19
Time	−3.01	2.74	.003	0.49	0.36	.62
Overall barriers	−1.71	0.44	.09	0.67	0.06	.50
Time × overall barriers	1.85	0.08	.07	−0.91	0.01	.36
Intercept	10.97	9.72	<.0001	.59	1.24	.56
Age	−0.19	0.71	.85	−1.38	0.05	.17
Time	−5.18	1.43	<.0001	−1.24	0.20	.21
Difficulty swallowing	−1.80	1.73	.07	−0.36	0.25	.72
Time × difficulty swallowing	2.96	0.30	.01	0.53	0.04	.60
Intercept	8.34	9.30	<.0001	−0.85	1.10	.40
Age	−0.19	0.71	.85	−1.32	0.05	.19
Time	−0.20	1.33	.85	0.51	0.18	.61
Forget to give medication	2.01	1.74	.04	1.23	0.24	.22
Time × forget to give medication	−2.20	0.33	.03	−1.34	0.04	.18
Intercept	10.47	10.72	<.0001	−0.85	1.10	.40
Age	0.11	.73	.92	−1.32	0.05	.19
Time	−3.94	1.73	<.0001	0.51	0.18	.61
Child refuses medication	−2.22	2.12	.03	1.23	0.24	.22
Time × child refuses medication	2.12	0.37	.04	−1.34	0.04	.18
Intercept	7.53	14.23	<.0001	−0.89	1.88	.38
Age	−0.22	0.71	.83	−1.37	0.05	.17
Time	−3.31	2.19	.01	1.00	0.28	.32
Ran out of medication	−1.18	2.71	.24	1.10	0.38	.27
Time × ran out of medication	1.88	0.46	.07	−1.54	0.06	.12
Intercept	7.32	12.19	<.0001	0.73	1.51	.47
Age	−0.08	0.72	.94	−1.40	0.05	.16
Time	−2.38	1.88	.02	−0.82	0.25	.41
Embarrassed to take medications in front of others	0.24	2.20	.81	−0.55	0.30	.58
Time × embarrassed to take medication in front of others	0.66	0.39	.51	0.24	0.05	.81
Intercept	9.64	11.62	<.0001	0.34	1.50	.73
Age	−0.31	0.71	.76	−1.37	0.05	.17
Time	−3.45	1.51	<.001	−0.47	0.21	.64
Difficult to get to pharmacy	−1.95	2.13	.05	−0.14	0.31	.89
Time × difficult to get to pharmacy	1.33	0.32	.19	−0.23	0.05	.81
Intercept	14.13	6.96	<.0001	0.15	0.74	.88
Age	−0.10	0.72	.92	−1.34	0.05	.18
Time	−5.26	0.87	<.0001	−0.95	0.11	.34
Child dislikes taste of medication	−1.51	1.11	.13	0.29	0.16	.77
Time × child dislikes taste of medication	1.57	0.20	.12	−0.36	0.03	.72
Intercept	7.62	12.10	<.0001	−0.70	1.46	.48
Age	−0.09	0.73	.93	−1.27	0.05	.21
Time	−0.30	2.01	.76	0.13	0.03	.90
Activities interfere with taking medication	−0.07	2.21	.94	0.95	−.30	.34
Time × activities interfere with taking medication	−1.28	0.43	.20	−0.68	0.06	.50

epilepsy and their families will help clinicians to identify children in need of interventions aimed at improving adherence select appropriate interventions, and provide resources that will be helpful to the family. Similar to studies of adherence barriers in other illness groups, forgetting to give medication and disliking the taste of the medication were the most common adherence barriers reported during the initial 25 months following an epilepsy diagnosis (Hommel & Baldassano, 2010; Modi et al., 2009; Simons & Blount, 2007).

One major strength of the current study is that we were able to examine the interaction between time and adherence barriers on two different outcome variables: electronically monitored adherence and seizure control. Although none of the time-by-barrier interactions predicted seizure control, several of the time-by-barrier interactions were related to electronically monitored adherence over time: child difficulty swallowing medication, forgetting to give medications, and child refusing to take the medication. These barriers appear to be critical agents for change in adherence promotion efforts in the future. It should be noted that although barriers remained stable over time, adherence decreased substantially over time.

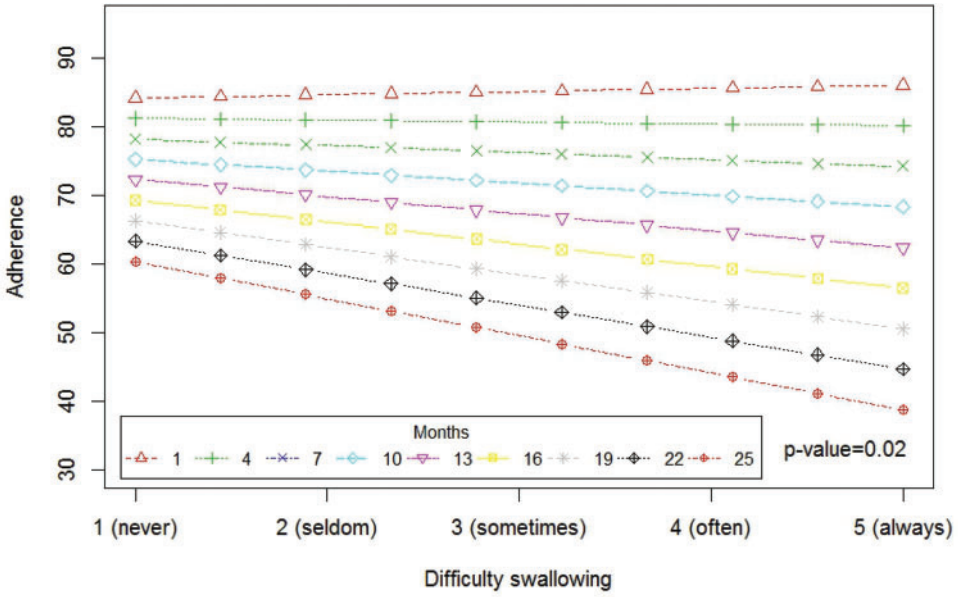

Figure 2. The relationship between swallowing difficulties and adherence by visit.

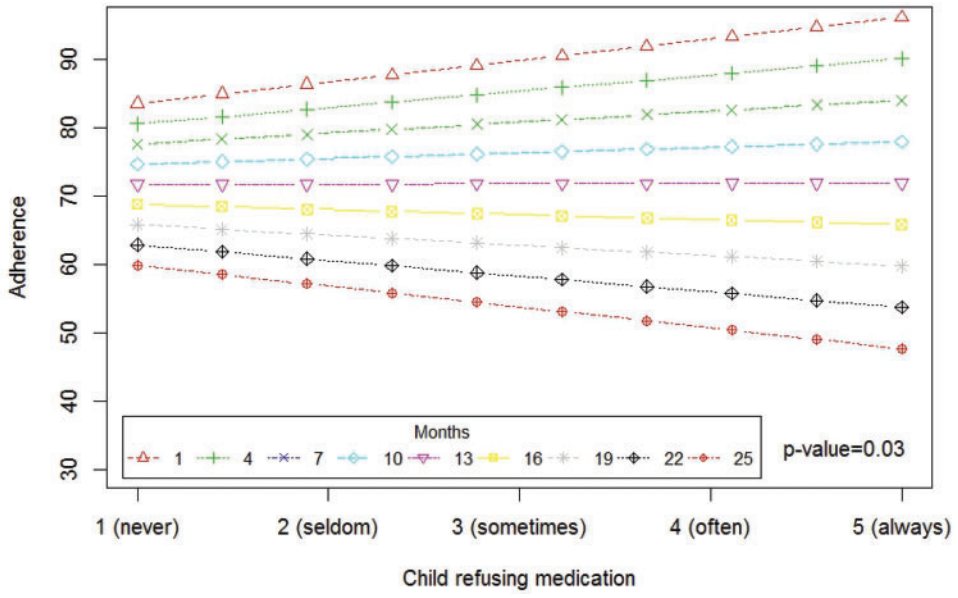

Figure 3. The relationship between child refusing to take medications and adherence by visit.

Declining adherence over time is consistent with the larger adherence literature (Modi, Rausch, et al., 2011); however, our study findings suggest that other factors, such as SES, family involvement, and child behavioral/emotional disorders, may contribute to nonadherence above and beyond adherence barriers measured in this study (Loiselle, Rausch, & Modi, 2015). The lack of seizure control findings may also be because of other salient factors that contribute to seizure control beyond adherence and adherence barriers, including biology (e.g., type of seizure, medication, and seizure combination), SES, or a host of other factors (Berg et al., 2011; Geerts et al., 2012; Modi, Wu, et al., 2014).

Results demonstrate that shortly following diagnosis, adherence did not vary based on the reported level of difficulty swallowing medication; however, increased difficulty swallowing the medication and adherence were related at 25 months post diagnosis, such that more difficulty swallowing the medication was related to lower adherence. It should be noted that at 1 month post diagnosis adherence was high

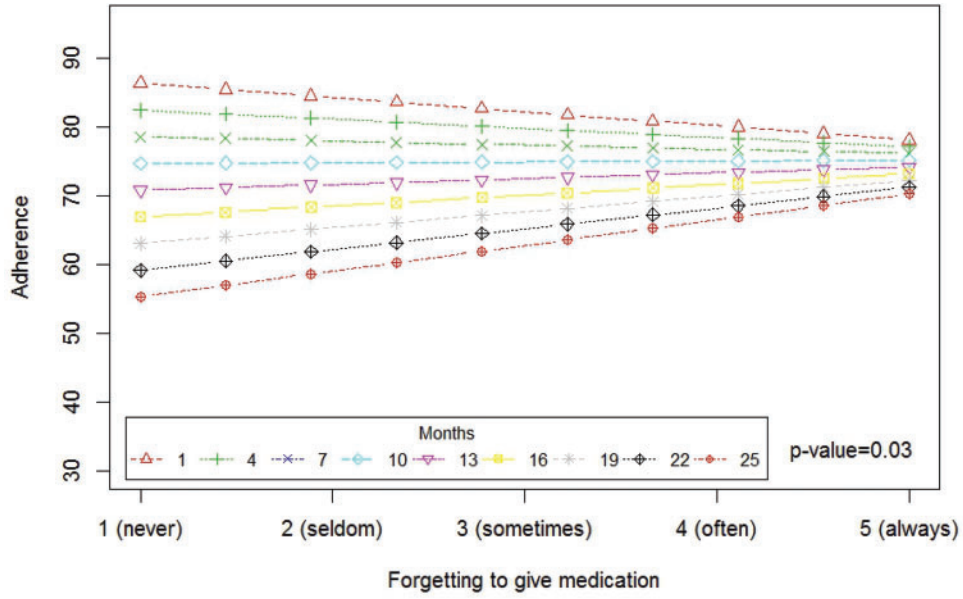

Figure 4. The relationship between forgetting to give medication and adherence by visit.

across all levels of reported barriers with regard to difficulty swallowing. In other words, although some children with epilepsy reported having difficulty swallowing their AED medication, children with all levels of swallowing difficulty maintained, on average, a high level of adherence (>84.17%) during the first month of a child's epilepsy. The relationship between higher levels of difficulty swallowing and poorer adherence, however, becomes more exaggerated over time such that by the end of 25 months, children who report the more difficulty swallowing had, on average, 38.81% adherence, while children with no difficulty swallowing difficulties had 60.36% adherence. Although speculative, perhaps early in the child's diagnosis, parents are more vigilant about ensuring that the child is adherent to the AED despite swallowing barriers or they quickly identify and implement solutions that are beneficial (e.g., pill glide or coating the capsules or switching to liquid AEDs). With time, however, this vigilance may decrease, previously used solutions may be less effective or less frequently used, and simultaneously a new normal related to seizure activity (seizure free vs. continued seizures) is developing. The combination of these factors, along with the frustration and conflict that may arise from swallowing problems and medication refusal, may lead to AED nonadherence as an avoidance coping strategy. Alternatively, parents may attempt to give AEDs (despite swallowing difficulties) more consistently following diagnosis and may open the bottle less often months into the diagnosis because of frustration of trying to make the child swallow their AEDs. In this case, the barrier of swallowing is still present; however, attempting to overcome the barrier may be absent. Given the relationship between difficulty swallowing medication and rates of adherence over time, providers should assess and provide interventions for this particular barrier at diagnosis and throughout treatment. In fact, pill swallowing can be effectively taught to even young children (Patel, Jacobsen, Jhaveri, & Bradford, 2015).

The adherence barrier "child refusal to take AEDs" by time interaction was significant in predicting adherence resulting in a positive relationship at 1 month post diagnosis and a negative relationship at 25 months post diagnosis. The relationship between increased refusal of taking AEDs and poorer adherence at 25 months was expected; however, the relationship between increased refusal and increased adherence at 1 month post diagnosis was surprising. Both difficulty swallowing and child refusing medication are ingestion barriers that fall under the broad category of Health and Illness barriers (Hanghoj & Boisen, 2014). As such, they are categorically different from the typical barriers of forgetting, organizational, or financial cost types of adherence barriers. In the case of ingestion-related barriers, families are often hyperaware of the barriers, eager to discuss these difficulties, and actively working to fix these barriers to improve adherence. For example, it may be that early in treatment, parents are acknowledging barriers, such as medication refusal and difficulty swallowing, even if the child eventually winds up taking the AED, and therefore AED adherence is high. This may be in direct contrast to other barriers such as forgetting or financial barriers, which often results in a missed AED dose. As mentioned, the identification of ingestion-related barriers are amenable to intervention with the use of pill swallowing (Patel et al., 2015) or

behavior management techniques (Pai & McGrady, 2014). Given our results, it is important that providers continue to assess barriers over time and understand that barriers may impact adherence differentially over the disease course.

Finally, regarding the barrier of forgetting to give medication, the main effect of time indicated that overall adherence is higher at 1 month post diagnosis compared with 25 months post diagnosis across the range of forgetting difficulties. For the interaction of time and forgetting, increased AED forgetting was related to poorer adherence 1 month following diagnosis and improved adherence 25 months later. This time by barrier interaction was in the expected direction at 1 month post diagnosis as increased forgetting to give/take AEDs resulted in poorer electronically monitored adherence. However, the finding at 25 months post diagnosis is unexpected. Specifically, results revealed higher adherence for those individuals endorsing forgetting as a barrier. There are several plausible explanations. First, social desirability may play a large role in whether parents endorse forgetting as an adherence barrier. Acknowledging that you sometimes or often forget to give your child his/her AED for epilepsy places the responsibility for the child's adherence and condition status on the parent. Perhaps when adherence is high across the board (shortly following AED initiation and early in treatment), the influence of social desirability reporting is less evident, but as adherence decreases, it becomes clearer. Alternatively, it may be that parents become less aware of how often they forget to give AEDs because forgetting has become more routinized. It is also important for clinicians to consider whether it is likely that any child "never" forgets to take their AEDs. One additional consideration regarding forgetting, which was not assessed in this study, is purposeful forgetting or volitional nonadherence. It is possible that "purposefully forgetting" is because of side effects or beliefs regarding the efficacy of the medication. Barriers such as forgetting are amenable to organization-focused strategies, including reminders via technology (e.g., cell phone reminders and text messaging services) (Militello, Kelly, & Melnyk, 2012) or incorporating AEDs into daily routines (e.g., pairing with brushing teeth and use of pillbox) (Rapoff, 2010).

The findings from the current study should be considered in the context of several limitations. First, children age 2–12 years participated in this study, and results are not generalizable to adolescents with epilepsy. In addition, parents provided information regarding adherence barriers because of the young age of the participants. A larger developmental range and child assessment of adherence barriers should be included in future studies given that adolescents with epilepsy may have their own unique perspective on how adherence barriers interfere with their treatment regimen. Second, there was attrition across the course of this 2-year longitudinal study, which further limits the generalizability of the results. Third, adherence was assessed by MEMS Caps and nonmonitored periods, as reported by families, were not included in the adherence calculation. Although use of the MEMS TrackCaps can only confirm when the bottle was opened and not actual ingestion, this method is still considered the gold standard of adherence assessment (Quittner, Modi, Lemanek, Ievers-Landis, & Rapoff, 2008). Also, it is possible that medication refills were not always placed in the MEMS bottle and that nonmonitored periods occurred during times of nonadherence, artificially inflating the adherence rate. It should be noted, however, the exact dates of the nonmonitored periods were reported to study staff during the study visit, with no information regarding their actual adherence data. Finally, data collection occurred at one site, and future studies should include a larger sample size across multiple sites to further examine the stability of overall barriers over time.

Overall, this study contributes to the literature by addressing the important question of the stability and influence of adherence barriers on AED medication adherence and seizure control for children with epilepsy over the 25-month disease course. The overall barriers experienced by families of children with epilepsy were stable, while the specific barriers were stable or worsened over time. The specific barriers including difficulties swallowing medication, medication refusal, and forgetting, were related to adherence over time; however, the relationship between these barriers and AED adherence changed over time. Assessing patients' specific barriers at diagnosis and throughout epilepsy treatment will allow for the selection of the most appropriate interventions to improve clinical care and outcomes.

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References

Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., van Emde Boas, W. . . . Scheffer, I. E. (2010).

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, *51*, 676–685. doi:10.1111/j.1528-1167.2010.02522.x

Berg, A. T., Testa, F. M., & Levy, S. R. (2011). Complete remission in nonsyndromic childhood-onset epilepsy. *Annals of Neurology*, *70*, 566–573. doi:10.1002/ana.22461

Bond, G. G., Aiken, L. S., & Somerville, S. C. (1992). The health belief model and adolescents with insulin-dependent diabetes mellitus. *Health Psychology*, *11*, 190–198. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1618173

Faught, R. E., Duh, M. S., Weiner, J. R., Guerin, A., & Cunnington, M. C. (2008). Nonadherence to antiepileptic drugs and increased mortality: Findings from the RANSOM study. *Neurology*, *71*, 1572–1578. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18565827

Faught, R. E., Weiner, J. R., Guerin, A., Cunnington, M. C., & Duh, M. S. (2009). Impact of nonadherence to antiepileptic drugs on health care utilization and costs: Findings from the RANSOM study. *Epilepsia*, *50*, 501–509. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19183224

Geerts, A., Arts, W. F., Stroink, H., Peeters, E., Brouwer, O., Peters, B. ... van Donselaar, C. (2010). Course and outcome of childhood epilepsy: A 15-year follow-up of the Dutch Study of Epilepsy in Childhood. *Epilepsia*, *51*, 1189–1197. doi:10.1111/j.1528-1167.2010.02546.x

Geerts, A., Brouwer, O., Stroink, H., van Donselaar, C., Peters, B., Peeters, E., & Arts, W. F. (2012). Onset of intractability and its course over time: The Dutch study of epilepsy in childhood. *Epilepsia*, *53*, 741–751. doi:10.1111/j.1528-1167.2012.03429.x

Glauser, T. (2002). Advancing the medical management of epilepsy: Disease modification and pharmacogenetics. *Journal of Child Neurology*, *17* (Suppl 1), S85–S93.

Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Chadwick, D., Guerreiro, C. ... Tomson, T. (2006). ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*, *47*, 1094–1120.

Hanghoj, S., & Boisen, K. A. (2014). Self-reported barriers to medication adherence among chronically ill adolescents: A systematic review. *Journal of Adolescent Health*, *54*, 121–138. doi:10.1016/j.jadohealth.2013.08.009

Holland, K. D., & Glauser, T. A. (2007). Response to carbamazepine in children with newly diagnosed partial onset epilepsy. *Neurology*, *69*, 596–599. doi:10.1212/01.wnl.0000267274.69619.f3

Holland, K. D., Monahan, S., Morita, D., Vartzelis, G., & Glauser, T. A. (2010). Valproate in children with newly diagnosed idiopathic generalized epilepsy. *Acta Neurologica Scandinavica*, *121*, 149–153. doi:10.1111/j.1600-0404.2009.01308.x

Hommel, K. A., & Baldassano, R. N. (2010). Brief report: Barriers to treatment adherence in pediatric inflammatory bowel disease. *Journal of Pediatric Psychology*, *35*, 1005–1010. doi:jsp126 [pii] 10.1093/jpepsy/jsp126

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *New England Journal of Medicine*, *342*, 314–319.

Laxer, K. D., Trinka, E., Hirsch, L. J., Cendes, F., Langfitt, J., Delanty, N. ... Benbadis, S. R. (2014). The consequences of refractory epilepsy and its treatment. *Epilepsy and Behavior*, *37*, 59–70. doi:http://dx.doi.org/10.1016/j.yebeh.2014.05.031

Lee, J. L., Eaton, C., Gutierrez-Colina, A. M., Devine, K., Simons, L. E., Mee, L., & Blount, R. L. (2014). Longitudinal stability of specific barriers to medication adherence. *Journal of Pediatric Psychology*, *39*, 667–676. doi:10.1093/jpepsy/jsu026

Loiselle, K., Rausch, J. R., & Modi, A. C. (2015). Behavioral predictors of medication adherence trajectories among youth with newly diagnosed epilepsy. *Epilepsy and Behavior*, *50*, 103–107. doi:10.1016/j.yebeh.2015.06.040

Militello, L. K., Kelly, S. A., & Melnyk, B. M. (2012). Systematic review of text-messaging interventions to promote healthy behaviors in pediatric and adolescent populations: Implications for clinical practice and research. *Worldviews on Evidence-Based Nursing*, *9*, 66–77. doi:10.1111/j.1741-6787.2011.00239.x

Mitchell, W. G., Scheier, L. M., & Baker, S. A. (2000). Adherence to treatment in children with epilepsy: who follows "doctor's orders"? *Epilepsia*, *41*, 1616–1625. doi:10.1111/j.1499-1654.2000.001616.x

Modi, A. C., Crosby, L. E., Guilfoyle, S. M., Lemanek, K. L., Witherspoon, D., & Mitchell, M. J. (2009). Barriers to treatment adherence for pediatric patients with sickle cell disease and their families. *Children's Health Care*, 107–122.

Modi, A. C., Ingerski, L. M., Rausch, J. R., & Glauser, T. A. (2011). Treatment factors affecting longitudinal quality of life in new onset pediatric epilepsy. *Journal of Pediatric Psychology*, *36*, 466–475. doi:10.1093/jpepsy/jsq114

Modi, A. C., Monahan, S., Daniels, D., & Glauser, T. A. (2010). Development and validation of the pediatric epilepsy medication self-management questionnaire. *Epilepsy and Behavior*, *18*, 94–99. doi:10.1016/j.yebeh.2010.03.009

Modi, A. C., Rausch, J. R., & Glauser, T. A. (2011). Patterns of non-adherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA*, *305*, 1669–1676. doi:10.1001/jama.2011.506

Modi, A. C., Rausch, J. R., & Glauser, T. A. (2014). Early pediatric antiepileptic drug nonadherence is related to lower long-term seizure freedom. *Neurology*, *82*, 671–673. doi:10.1212/WNL.0000000000000147

Modi, A. C., Wu, Y. P., Guilfoyle, S. M., & Glauser, T. A. (2012). Uninformed clinical decisions resulting from lack of adherence assessment in children with new onset. *Epilepsy and Behavior*, *25*, 481–484. doi:10.1016/j.yebeh.2012.09.008

Modi, A. C., Wu, Y. P., Rausch, J. R., Peugh, J. L., & Glauser, T. A. (2014). Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes. *Neurology*, *83*, 2085–2090. doi:10.1212/WNL.0000000000001023

Pai, A. L., & McGrady, M. (2014). Systematic review and meta-analysis of psychological interventions to promote treatment adherence in children, adolescents, and young adults with chronic illness. *Journal of Pediatric Psychology*, *39*, 918–931. doi:10.1093/jpepsy/jsu038

Patel, A., Jacobsen, L., Jhaveri, R., & Bradford, K. K. (2015). Effectiveness of pediatric pill swallowing interventions: A systematic review. *Pediatrics*, *135*. doi:10.1542/peds.2014-2114

Quittner, A. L., Modi, A. C., Lemanek, K. L., Ievers-Landis, C. E., & Rapoff, M. A. (2008). Evidence-based assessment of adherence to medical treatments in pediatric psychology. *Journal of Pediatric Psychology*, *33*, 916–936. discussion 937-918. doi:10.1093/jpepsy/jsm064

Rapoff, M. (Ed.) (2010). *Adherence to pediatric medical regimens* (2nd ed.). New York, NY: Springer Science+Business Media.

Russ, S. A., Larson, K., & Halfon, N. (2012). A national profile of childhood epilepsy and seizure disorder. *Pediatrics*, *129*, 256–264. doi:10.1542/peds.2010-1371

Simons, L. E., & Blount, R. L. (2007). Identifying barriers to medication adherence in adolescent transplant recipients. *Journal of Pediatric Psychology*, *32*, 831–844. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17522111

Simons, L. E., McCormick, M. L., Devine, K., & Blount, R. L. (2010). Medication barriers predict adolescent transplant recipients' adherence and clinical outcomes at 18-month follow-up. *Journal of Pediatric Psychology*, *35*, 1038–1048. doi:10.1093/jpepsy/jsq025

Stevens, G., & Featherman, D. L. (1981). A revised socioeconomic index of occupational status. *Social Science Research*, *10*, 364–395. doi:http://dx.doi.org/10.1016/0049-089X(81)90011-9

Zelikovsky, N., Schast, A. P., Palmer, J., & Meyers, K. E. (2008). Perceived barriers to adherence among adolescent renal transplant candidates. *Pediatric Transplantation*, *12*, 300–308. doi:10.1111/j.1399-3046.2007.00886.x