Adherence to antiepileptic drugs in adolescents with epilepsy

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ABSTRACT

Introduction: The aims of the current study were to identify patterns and predictors of adherence in adolescents with epilepsy over one year, as well as its impact on seizures and health-related quality of life (HRQOL).

Methods: Forty-eight adolescents with epilepsy ($M_{age} = 14.8 + 1.5$, 69% female, 73% White: NonHispanic) and their caregivers completed questionnaires assessing demographics, epilepsy knowledge, side effects, adherence barriers, family functioning, and HRQOL at quarterly clinic visits over one year. Adherence was monitored electronically via MEMS TrackCaps. Seizures were determined via chart review.

Results: Baseline adherence was 86.05% and significantly decreased over 12 months ($b = -2.07$, $p < 0.001$). Higher adherence was predicted by higher socioeconomic status (SES) ($b = 0.04$, $p < 0.05$), more side effects ($b = 0.06$, $p < 0.01$), fewer caregiver-reported adherence barriers ($b = 0.18$, $p < 0.05$), and lower family conflict ($b = -0.19$, $p < 0.05$). Change in adherence over 12 months did not significantly predict HRQOL or seizures.

Conclusions: This is the first longitudinal study of objective adherence in adolescents with epilepsy. Given adolescence is a period of vulnerability during development, including declining adherence, caregivers are encouraged to continue collaborating with their adolescents around epilepsy management. Adherence barriers represent an ideal target for intervention and can be implemented in the clinic by frontline providers. Multidisciplinary care can address low SES (social work, financial advocates) and family conflict (psychologists, therapists) in patients with the ultimate goal of optimizing adherence and health outcomes.

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1. Introduction

Adolescents with epilepsy represent a vulnerable population due to increased autonomy and independence in the context of decreased parental supervision [1], as well as neurobiological underpinnings that increase risky behaviors [2,3]. This often results in decreased adherence to their medical regimen, [4] especially when compared with children [5] and adults [6]. Nonadherence to antiepileptic drugs (AEDs) can cause a variety of negative outcomes for individuals with epilepsy, including continued seizures, higher healthcare costs, and poor health-related quality of life (HRQOL) [7–11]. Unfortunately, continued seizures are associated with negative social, emotional, and behavioral outcomes that can persist into adulthood [12–15]. While much work has been done to examine adherence using evidence-based methods in young children [16,17] and adults with epilepsy [18–20], the prevalence of nonadherence in adolescents with epilepsy using objective electronically-monitored data remains unknown. In addition, the factors that influence nonadherence and its subsequent impact on health and patient-reported outcomes have not been comprehensively and systematically assessed.

Antiepileptic drug adherence in adolescents is likely influenced by individual (age [5,6], family income [10,21,22], disease (time since diagnosis [23], side effects [6], epilepsy knowledge [21,24], individually-identified adherence barriers [8,25,26]), and family factors (e.g., family support [8,16,27]). There is a critical need to identify factors that contribute to nonadherence in adolescents with epilepsy to guide intervention development and prevent poor outcomes in adulthood. Additionally, it is important to examine if longitudinal adherence behaviors impact health outcomes, such as seizures and HRQOL.

The aims of the current study were to identify patterns and predictors of adherence in adolescents with epilepsy over one year, as well as its impact on seizures and HRQOL. Adherence is expected to decline over the course of the year [28]. Younger age [5,6], shorter time since diagnosis [23], higher socioeconomic status (SES) [10,21,22], fewer adherence barriers [8,25,26], fewer side effects [6], greater epilepsy knowledge [21,24], and higher family functioning [8,16,27] are hypothesized predictors of better electronically-monitored AED adherence. Longitudinal adherence will predict better seizure [9,17] and HRQOL [9] outcomes at the end of one year.

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2. Materials and methods

2.1. Participants and procedure

Participants in this longitudinal study were adolescents (aged 13–17 years old) and their caregivers recruited by trained research assistants during epilepsy clinic visits at a Midwestern children's hospital. They attended four study visits across one year, approximately 3–4 months apart. To meet inclusion criteria, participants had a current prescription of only one antiepileptic drug, could not be diagnosed with a significant developmental disorder (e.g., autism), and had the ability to speak and read English. Caregivers completed a background questionnaire at baseline and the Quality of Life in Childhood Epilepsy Questionnaire at all time points. Adolescents completed the Epilepsy Knowledge Questionnaire (EKQ), Parental Environment Questionnaire (PEQ), and Quality of Life in Epilepsy Inventory for Adolescents. Caregivers and adolescents both completed the Pediatric Epilepsy Medication Self-Management Questionnaire (barriers subscale). The Pediatric Epilepsy Side Effects Questionnaire was completed jointly at all visits, and electronically-monitored adherence was obtained via MEMS TrackCaps and downloaded at all visits. Caregivers and adolescents received reimbursement by gift card for study visits. This research was approved by the hospital's Institutional Review Board, and informed consent/assent was obtained from each caregiver and adolescent prior to study initiation.

Seventy families were approached and 10 declined due to lack of interest or time, resulting in a participation rate of 86%. Four participants never returned questionnaires and were lost to follow-up. Two participants withdrew, and adherence data was unavailable for six participants. Thus, the final sample included 48 adolescents with epilepsy and their caregivers.

2.2. Measures

2.2.1. Background information and medical chart review

Caregivers provided information at the baseline visit regarding the adolescent's age, sex, and race. The Revised Duncan score [29], a measure of SES based on caregiver occupation [30,31] was calculated for each family, with higher scores (range 15–97) indicating higher SES. Caregivers also reported on the presence of six potential comorbid disorders, including attention deficit hyperactivity disorder (ADHD), learning disorders, anxiety, depression, behavioral problems, and social difficulties. Time since diagnosis was obtained from medical chart review.

2.2.2. Epilepsy Knowledge Questionnaire (EKQ [32])

The EKQ is a 47-item questionnaire, assessing knowledge about medical and social aspects of epilepsy using a True or False format. This measure was modified from the original [32] to reflect language and medical practice in the United States. The original instrument was evaluated psychometrically and demonstrates adequate reliability and validity for adolescents with epilepsy.

2.2.3. Parental Environment Questionnaire (PEQ [33])

The PEQ is a 42-item adolescent self-report measure assessing parent–child relationship using a four-point scale with answers ranging from "definitely true" to "definitely false". PEQ subscales include Conflict, Parent Involvement, Regard for Parent, Regard for Child, and Structure. The current study used only the Conflict (e.g., "My parent often criticizes me.") and Parent Involvement (e.g., "My parent and I do not do a lot of things together.") subscales, each containing 12 items. Alpha coefficients were 0.82 for Conflict and 0.74 for Involvement in previous research [33]. Higher scores reflect higher conflict and higher parent involvement.

2.2.4. Pediatric Epilepsy Medication Self-Management Questionnaire (PEMSQ [25]) – Barriers subscale

The PEMSQ is a 27-item questionnaire to assess medication self-management in patients with epilepsy via parent proxy report. The PEMSQ has four scales (epilepsy and treatment knowledge and expectations, adherence to medications and clinic appointments, barriers to medication adherence, and beliefs about medication efficacy). The Adolescent Epilepsy Medication Self-Management Questionnaire was adapted from the parent proxy measure [24]. Only the Barriers to Medication Adherence subscale was used in the present study (parent and adolescent report). Higher scores represent fewer barriers or better self-management around adherence barriers. Examples of barriers include difficulty fitting medication into daily routines, forgetting to give/take the medication, and being embarrassed to take the medication in front of friends or family. Cronbach's alpha for the Barriers to Medication Adherence subscale was 0.76 (parent report) [25] and 0.58 (adolescent-report) [24].

2.2.5. Pediatric Epilepsy Side Effects Questionnaire (PESQ [34])

The PESQ is a 19-item measure assessing side effects of AEDs for youth with epilepsy. Items are rated on a 6-point scale from 0 (not present) to 5 (high severity) and cover a range of neurological, behavioral, gastrointestinal, skin, and motor side effects. Items are summed to obtain a total side effects severity score, with higher scores representing higher severity of side effects. The total score has demonstrated excellent reliability in previous research (Cronbach's alpha = 0.92 [34]).

2.2.6. MEMS 6 TrackCap

The Medication Event Monitoring Systems (MEMS© 6 Trackcap; AARDEX Corporation, Union City, CA), was used to measure daily AED adherence. The MEMS cap attaches to the patient's medication bottle and registers the dates and times that the medication was opened. At each study visit, caregivers and adolescents were asked to report any times that the cap was not used (e.g., vacation). Adherence was defined as the number of doses taken/number of expected doses × 100%. Daily adherence data were averaged for each month, yielding a total of 12 adherence data points.

2.2.7. HRQOL

Quality of life was measured via both parent report using the Quality of Life in Childhood Epilepsy Questionnaire (QOLICE [35]) and adolescent self-report using the Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD [36]). The QOLICE is 79-item caregiver report of the child's quality of life for ages 4 to 18. The measure assesses 15 domains of functioning and an overall quality of life score. Raw scores are converted into standardized scores (0–100), with higher scores indicating better quality of life. Internal consistencies coefficients ranged from 0.76–0.97 for all scales in previous research [35]. The QOLIE-AD is a 48-item self-report measure of health-related quality of life for adolescents with epilepsy (11–18 years old). The measure generates eight subscales (epilepsy impact, memory-concentration, attitudes, physical function, stigma, social support, school behavior, and health perceptions), as well as a total score. Scores can be converted to T-scores. The total score has demonstrated acceptable reliability in previous research (Cronbach's alpha = 0.74 [36]).

2.2.8. Seizures

Seizure frequency was dichotomized to seizure absence or presence for each of the three-month intervals given the heterogeneity of seizure types and frequencies. For analyses, seizure outcome for the final three-month period was used. This variable was determined with medical chart review data, as well as parent and adolescent-report of seizures.

2.3. Analytic plan

Descriptive data were examined for participant characteristics and variables of interest using SPSS version 24. Hierarchical linear models in Mplus using robust maximum likelihood estimation were used to: 1) model the change in adherence over 12 months, 2) predict variability in adherence trajectories over the 12 months, 3) assess whether change in adherence predicts HRQOL at the end of 12 months, and 4) assess whether change in adherence over a year predicts presence of seizures over the last 3 months. Predictors of initial adherence included baseline age, time since diagnosis, family SES, and adolescent epilepsy knowledge. Predictors of change in adherence included baseline age, time since diagnosis, family SES, adolescent epilepsy knowledge, parent- and adolescent-reported adherence barriers, side effects, family conflict, and family involvement.

3. Results

3.1. Participants

Participants included 48 adolescents aged 13–17 years with epilepsy and their caregivers (See Table 1).

3.2. Adherence over time

The average adherence at baseline was 86.05% and significantly decreased over 12 months, $b = -2.07$, $p < 0.001$, such that for every month, adherence was decreasing by approximately 2%. Average adherence over one year was 74.57%. There was significant variability in both the average baseline adherence (i.e., variability was significantly different than zero, $p = 0.006$) and significant variability in change in adherence over time ($p < 0.001$), such that significant heterogeneity in the rate of change in adherence was observed. This suggests that while the predominant pattern was decreasing adherence at a rate of 2% per month, there was significant individual variability around this rate (e.g., some individuals may have increased their adherence, some may have decreased more steeply, or some may have remained fairly stable). There was no evidence that the observed changes in adherence were nonlinear over time.

3.3. Adherence predictors

The adherence slope (e.g., change in adherence) was predicted by SES ($b = 0.04$, $p < 0.05$), side effects ($b = 0.06$, $p < 0.01$), caregiver-reported adherence barriers ($b = 0.18$, $p < 0.05$), and family conflict ($b = -0.19$, $p < 0.05$; See Table 2). Specifically, higher SES, higher side effects, fewer caregiver-reported adherence barriers, and lower family conflict predicted better adherence. Age, time since diagnosis, adolescent-reported adherence barriers, adolescent knowledge and parent involvement were not identified as predictors of adherence change. There was still significant variability in the change in adherence over time even after accounting for these predictors.

3.4. Adherence and outcomes

The change in adherence over 12 months did not significantly predict caregiver-reported total HRQOL ($p = 0.22$) nor adolescent-reported total HRQOL ($p = 0.24$) at the end of 12 months. Finally, change in adherence over 12 months did not significantly predict the presence/absence of seizures over the last 3 months ($p = 0.25$).

4. Discussion

To our knowledge, this is the first longitudinal study of objective adherence data in adolescents with epilepsy. Adherence declined significantly over the course of one year, with adolescents missing one in

Table 1
Baseline characteristics (N = 48).

Variable	M (SD) or %
Adolescent age (years)	14.81 (1.45)
Adolescent sex (female)	68.8
Adolescent race	
White (nonHispanic)	72.9
African American	16.7
Other	10.4
Epilepsy etiology, diagnosis, and syndromes	
Idiopathic localization-related epilepsy	16.7
Idiopathic generalized epilepsy	18.8
Idiopathic unclassified epilepsy	22.9
Symptomatic localization-related epilepsy	6.3
Cryptogenic localization-related epilepsy	2.1
Cryptogenic generalized epilepsy	2.1
Juvenile myoclonic epilepsy	16.7
Childhood/juvenile absence epilepsy	12.5
Benign Rolandic epilepsy	2.1
Illness duration (months)	16.60 (22.54)
Comorbid disorders (caregiver report)	
ADHD	10.4
Learning disorders	8.3
Anxiety	10.4
Depression	8.3
Behavioral problems	4.2
Social difficulties	4.2
Caregiver relationship to child	
Mother/stepmother	75.0
Father	22.9
Aunt	2.1
Caregiver marital status	
Married/remarried	68.8
Single	12.5
Divorced/separated	16.7
Widowed	2.1
Average adherence over 1 year	74.57 (25.48)
Family Duncan score[a]	54.63 (19.73)
Side effects	8.62 (11.63)
Barriers – adolescent-report	36.72 (2.58)
Barriers – caregiver-report	37.40 (3.07)
Epilepsy knowledge (% correct)	78.76 (9.35)
Family conflict	23.19 (7.20)
Parent involvement	39.70 (7.38)
HRQOL – adolescent-report	57.87 (6.12)
HRQOL – caregiver-report	80.67 (9.39)
Seizures present	
Seizures present at Time 1 (seizures in past year)	85.4
Seizure present Time 1-Time 2	76.1
Seizures present Time 2-Time 3	72.1
Seizures present at Time 3-Time 4	59.5

[a] Family Duncan scores of 54.63 represent occupations including construction inspectors, property managers, and insurance adjusters. HRQOL = health related quality of life.

four doses of their AED, on average, by the end. This pattern is similar with other chronic illness populations [28] and to younger children with epilepsy [23]. Additionally, the average adherence rate of 75% over one year is similar with previously reported electronically-monitored adherence rates ranging from 79 to 86% in children [37–39] and 63 to 89% in adults [40–43]. Adolescence is a particularly vulnerable developmental period, where adolescents have increased responsibility

Table 2
Predictors of longitudinal adherence.

Variable	Estimate	SE	p-Value
Adolescent age	−0.36	0.26	0.164
Time since diagnosis	−0.01	0.02	0.527
Family SES (Duncan)	0.06	0.02	0.005
Side effects	0.06	0.02	0.012
Adolescent-reported barriers	−0.17	0.13	0.185
Caregiver-reported barriers	0.18	0.07	0.008
Epilepsy knowledge	0.04	0.03	0.134
Family conflict	−0.19	0.08	0.013
Family involvement	−0.03	0.08	0.666

for adherence but poor execution of the necessary tasks due to executive functioning deficits, decreased motivation, lack of parental supervision and monitoring, and increased peer pressure [1–3,44]. For adolescents with epilepsy, this is compounded by higher rates of ADHD, learning disorders, and memory problems due to shared neurobehavioral pathways, as well as cognitive side effects that often occur with AED treatment. Given this vulnerable period, it is recommended that caregivers continue to play a monitoring or supervisory role, similar with when adolescents begin driving (e.g., learner's permit with adult in car, then license). Research suggests that adolescents and parents disagree on who is primarily responsible for medication adherence, but caregiver involvement aids better adherence [45]. Therefore, gaining adequate self-management skills during adolescence, with the safety net of parents, may help prevent poor outcomes as adolescents transition into young adulthood.

Several individual, disease, and family variables contributed to AED nonadherence over time. Disease factors that served as significant predictors of adherence over time included AED side effects. While contrary to the hypothesized finding, this finding is intriguing because adolescents who take their medications (i.e., adherent) are presumably more likely to experience AED side effects compared with nonadherent peers. Although the experience of side effects may hinder some adherence behaviors (e.g., skipping doses to avoid side effects), if the side effects are tolerable, then the adolescent may maintain adherence. In this case, the presence of side effects may serve as a marker of adherence in adolescents and therefore serve as a predictor of adherence over the course of a year. In fact, one study of adults with epilepsy found providers assumed side effects would affect nonadherence more than patients stated it did [9].

In the current study, having fewer adherence barriers was associated with higher adherence over time. This is in line with previous research on adherence barriers in epilepsy [8,25,26], indicating that barriers represent an ideal target to improve adherence. A recent study indicates adherence barriers are stable over two years, with difficulties swallowing medication, forgetting, and medication refusal related to adherence over time [46]. Addressing barriers specific to the individual can improve adherence [47,48] and can be implemented in the clinic setting by frontline healthcare providers [49].

Family factors that predicted higher adherence over time included higher SES and decreased caregiver conflict. Socioeconomic status is a reliable predictor of adherence [10,21,22] such that lower SES is typically associated with financial, transportation, and care access difficulties. Healthcare teams can address low SES in their patients using a multidisciplinary approach that includes social work and financial advocates to reduce barriers to medical care (e.g., difficulty affording prescriptions, lack of transportation to appointments). Relatedly, less family conflict was related to higher adherence over time, which is consistent with the larger literature [50]. Family conflict, particularly during adolescence, may stem from difficulties with communication and the tension between increased desire for autonomy from the adolescent and sustained monitoring from the caregiver. Such miscommunication may result in nonadherence (e.g., missed refills) and lead to miscarried helping (e.g., reminders to take medicine perceived as "nagging" by adolescent). Due to the vital importance of parents remaining involved in epilepsy management, coupled with the negative impact of family conflict, parental support during adolescence requires finesse and good communication strategies. Parents may disengage during adolescence to reduce family conflict with the unintended consequence of decreased epilepsy management support. Clinicians should consider referrals for therapy for families to learn family-based problem solving and communication training around epilepsy management, when needed. Additionally, the use of automated reminders and/or pill boxes may assist families in navigating the balance of codependence and autonomy more effectively.

In the current study, changes in adherence were unrelated to subsequent seizures or HRQOL. It is possible that nonadherence over one year may be an insufficient amount of time to impact HRQOL. Additionally, the heterogeneity of the sample may have resulted in variability in predicting seizure outcomes; separating newly diagnosed from those with chronic epilepsy using a larger sample may clarify this relationship. Despite the lack of association with health outcomes, nonadherence is known to be related to increased healthcare utilization [51] and healthcare costs [52]. Since nonadherence is a costly behavior at the individual and systems level, future research should continue to examine its relationship to health outcomes.

This study's findings should be interpreted within the context of several limitations. First, we had a relatively small number of adolescents, which reduced our ability to examine adherence subgroups that may further shed light on individual variability in adherence over time. The homogenous nature of the sample limits generalizability of the findings to adolescents with more complicated epilepsies or treatments, including higher levels of psychosocial comorbidities. Additionally, adolescents were aware that their adherence behaviors were being monitored and therefore may have experienced reactivity (e.g., temporary increase in adherence due to monitoring); however, reactivity typically only last 2–4 weeks [53–55] and thus, was unlikely to persist across the year of the study. We only examined one year of adherence data; future longitudinal cohort studies should examine adherence and the transition of responsibility for adherence over the course of development (e.g., age 13 through transition to adult care) in order to identify factors that facilitate transition from pediatric to adult settings. Finally, the healthcare setting in which this study was conducted is unique in that pediatric clinical psychologists are integrated into most epilepsy clinic visits. It is possible the psychologists provided intervention that impacted adherence (e.g., use of a home tracking system, recommended increased parental monitoring and problem solving around family conflict), if adherence was of concern. However, if this was the case, current findings are an overestimate of adolescent adherence and still warrant significant concerns.

5. Conclusions

This is the first study to objectively examine adherence in adolescents with epilepsy over one year. Results indicate that adherence significantly declines over time, with, on average, one quarter of AED doses being missed. There are several modifiable targets for intervention, including reducing family conflict and decreasing adherence barriers. Future research should focus on the development and testing of such interventions to prevent poor outcomes.

Conflicts of interest

None.

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