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Uninformed Clinical Decisions Resulting From Lack of Adherence Assessment in Children with New Onset Epilepsy

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Abstract

This study examined the relationship between non-adherence to antiepileptic drug (AED) therapy and clinical decision-making in a cohort of 112 children with newly-diagnosed epilepsy. AED adherence was monitored using electronic monitoring over the first six months of therapy. The primary outcome measure was rate of uninformed clinical decisions as defined by number of participants with AED dosage or drug changes to address continued seizures who demonstrated non-adherence prior to the seizure. Among the 52 (47%) participants who had an AED change for continued seizures, 30 (27% of the overall cohort) had imperfect medication adherence prior to their seizures. A quarter of children with new onset epilepsy had uninformed medication changes because adherence was not rigorously assessed in clinical practice. Results highlight the importance of routinely assessing medication adherence in this population.

Keywords

compliance; antiepileptic drugs; professional practice; errors; pediatric; epilepsy

Adherence is defined as the extent to which a person's behavior coincides with medical or health advice [1]. Fifty-eight percent of young children with epilepsy have demonstrated varying levels of non-adherence, ranging from mild to severe [2]. Non-adherence to antiepileptic drug (AED) therapy impacts the morbidity (e.g., seizures); [3] and mortality [4] of patients with epilepsy and is associated with significant healthcare costs [5]. While non-adherence clearly affects the outcomes of patients and families, what remains unknown is the impact of unrecognized non-adherence on healthcare provider's medical decision-making (e.g., changing medications, doses).

Two studies have demonstrated that adults who were non-adherent were more likely to have an increased number of medications or increased medication doses relative to adults who were adherent [6, 7]. These data highlight that clinicians make changes to treatment

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regimens based on patient-reported symptom presentation without considering medication adherence. This can lead to increased side effects, higher healthcare costs, and poor symptom management. No studies have examined the relationship between adherence and clinical decision-making in pediatric epilepsy. Pediatric epilepsy is the ideal disease for examining the relationship between adherence and clinical-decision making for several reasons. First, clinical decisions are routinely made to change the AED to achieve the goal of “no seizures, no side effects”. Unfortunately, non-adherence may be the cause of continued seizures, leading a clinician to unnecessarily change the treatment regimen instead of addressing non-adherence. Second, although AEDs are the primary treatment for epilepsy, they have known side effects which can impact a patient’s quality of life [8]. If patients become adherent after an AED change, toxicities can result if non-adherence was present prior. Finally, epilepsy is classified as intractable when seizures continue despite adequate trials of two or more AEDs [9]. If non-adherence is the true cause of drug failure, then mislabeling a child’s epilepsy as intractable could result in costly treatments (i.e., surgical evaluation) that place considerable stress on patients and families. Thus, healthcare providers need information about patient adherence so they can make informed clinical treatment decisions.

This study explored the relationship between non-adherence and clinical decision-making using a cohort of children with newly diagnosed epilepsy over the first six months of AED therapy. Based on our prior work [2], we hypothesized that AED dose changes would be made due to side effects or lack of efficacy (i.e., continued seizures), and that imperfect adherence (<100%) preceding seizures would be observed for the majority of patients (>50%) who continued having seizures.

Methods

A consecutive cohort of 130 children and their caregivers were recruited during their initial visit in the New Onset Seizure Clinic. Study eligibility criteria included: new epilepsy diagnosis, AED initiation, age 2-12 years, no comorbid systemic illness requiring daily medications (e.g., diabetes), and no parent-reported developmental disorder (e.g., autism). Informed consent/assent was obtained for 125 families (96% recruitment). The final cohort included 112 children and their caregivers (12 lost to clinic follow-up; 1 undisclosed autism diagnosis). Caregivers completed several questionnaires (i.e. demographics, seizure history) and were provided with a cap and bottle for electronic monitoring of AED adherence (see [9] for methodology). All study procedures were approved by the hospital’s Institutional Review Board and were performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

For the current study, adherence data following the initial titration period (i.e., five weeks post-diagnosis) were used to avoid clinical events during upward titration. For the six months following titration, seizure frequency, AED side effects, and AED changes were gathered from medical chart review (i.e., telephone calls, clinical note). A seizure history form was completed at follow-up clinic visits based on parent interview and medical chart review. Specifically, parents were asked whether any seizures occurred since the last clinic visit. From this information, research staff determined the first AED change for each participant and reason for the change (i.e., seizure, side effect). If dose changes were due to seizures and side effects, the dose change reason was coded as seizures.

Due to a twice-daily dosing schedule, daily possible adherence rates were 0 (e.g., missed 2 of 2 doses), 50% (missed 1 of 2 doses), or 100% (missed no doses). Mean adherence across different intervals (e.g., 1-week, 1-month, or 6-months) was calculated by dividing the number of doses taken across the interval by total doses prescribed over the same interval.

Mean adherence rates could be any value ranging from 0 to 100%. Descriptive statistics were calculated to characterize the type of AED change that occurred (i.e., dosage change vs. change to new AED). A 6-month adherence rate was calculated for all participants, participants with or without an AED change, and participants who had an AED change due to seizures or side effects. For participants with an AED change due to seizures, adherence was calculated one-week before the documented seizure date for convulsive seizures or one-month before a clinic visit for staring spells. Although there is no documented relationship between the proximity of adherence behaviors to seizures, we believed it was reasonable to use one-week adherence rates prior to the documented seizure. One-month adherence rates prior to the clinic visit were used for staring spells given the difficulty quantifying staring spells and identifying specific seizure dates. Data were unavailable for seven participants (e.g., two lost electronic monitors, five had seizures when electronic monitors were not used (i.e., vacation)). Imperfect adherence was defined as less than 100%. Although not the focus of the current study aims, t-tests were conducted to examine differences in adherence rates between: 1) patients who had an AED change versus continued with existing treatment regimens and 2) patients who had an AED change due to side effects compared to those with continued seizures.

Measures

The demographic background questionnaire documented family sociodemographic information. To measure AED adherence, participants were provided with a Medication Event Monitoring Systems (MEMS™) Track-Cap (Aardex Group, Sion, Switzerland), which electronically monitors daily adherence by registering dates/times the bottle is opened. Adherence data were downloaded at clinic visits but not shared with the healthcare team. Caregivers reported when the electronic monitor was not used (e.g., vacation) and these times were excluded from analyses. Uninformed clinical decision making was defined by number of participants who had AED dosage or drug changes due to continued seizures while demonstrating imperfect adherence prior to the seizure.

Results

Participant demographics and adherence descriptive statistics are provided in Table 1. Figure 1 summarizes AED changes, reasons for the changes, group comparisons for adherence, and adherence status for participants who had an AED change due to seizures.

In the 6 months following AED titration, 40% (45/112) of the cohort had no AED change while 60% (67/112) had an AED change occurring between or at clinic visits. Of those 67 participants who had an AED change, 15 were due to intolerable side effects. Ten of these participants had a dose change and five were changed to a new AED.

Of the 67 participants who had an AED change, 52 were due to seizures. Specifically, 44 of these patients had an AED dosage change and 8 were changed to a new AED. Based on electronically-monitored adherence data in the week preceding the first documented seizure or the month before a clinic visit, 30 participants had imperfect adherence ($M_{\text{adherence}}=67\% \pm 34\%$) while 15 had perfect adherence. Of the entire sample, 27% of children with new onset epilepsy had imperfect adherence prior to their seizure and a subsequent, uninformed AED change.

Discussion

The current study demonstrates that healthcare providers made uninformed AED changes by not considering adherence in 27% of children with newly-diagnosed epilepsy. Knowledge of AED non-adherence could play a critical role in clinical decision-making and prevent

uninformed medication changes. Consistent with prior adult literature [6, 7] and study hypotheses, of the children whose healthcare providers changed the AED regimen due to seizures, the majority of these participants (30/44=68%) demonstrated imperfect adherence prior to the seizure. These findings are concerning given that suboptimal AED adherence is largely preventable and contributes to continued seizures. Further, uninformed dose increases place this vulnerable population at a substantially higher risk for toxicities/side effects, especially if patient adherence improves.

Our results highlight the importance of integrating adherence information into clinical decision-making, especially when proximal to seizures. Adherence assessments, including electronic monitoring[10], should be used in routine care to inform accurate treatment decisions. This will enable clinicians to have critical information needed to make informed and accurate treatment decisions. For example, symptoms may continue despite perfect adherence, which was illustrated in our subgroup of 15 patients who had an AED change due to seizures despite demonstrating perfect adherence. For these patients, changing the dose or AED appeared to be the best clinical decision.

In contrast, for patients with continued seizures and suboptimal adherence, an evidence-based adherence intervention [11, 12] may be warranted prior to a medication change. While education alone is likely insufficient for promoting adherence, behavioral and multi-component interventions (i.e., educational plus behavioral) have been shown to be more effective in increasing treatment adherence among pediatric patients and their families [11, 12]. Interventions can be used to address specific barriers experienced by families regarding medication-taking [13]. For example, behavioral pill-swallowing interventions are highly effective [14, 15] and problem-solving approaches can be applied to the common barrier of “forgetting.” In addition to these evidence-based adherence promotion approaches, studies have demonstrated that individual patient adherence data based on electronic monitoring can form the basis for tailored adherence promotion interventions in clinical practice [16, 17].

These current study results should be interpreted within the context of several limitations. While every effort was made to document reported seizures using chart review and directly asking caregivers, it is possible that caregivers did not report seizures which occurred between clinic visits. Also, other factors may have influenced adherence behaviors (e.g., reactivity, reimbursement, electronic monitoring); however, reactivity is typically short-lived [18]. A challenge of investigating medication adherence in the pediatric epilepsy population is that it is yet unknown the extent to which non-adherence affects an individual’s illness course, particularly given variability between patients and seizure types (e.g., missing one AED dose leading to seizures in only a subsample of patients). Further, given the potential reciprocal relationship between AED side effects [19] and medication adherence, future studies should examine the extent to which side effects may help to explain non-adherence. Finally, research should examine how non-adherence affects different seizure types and illness courses, as well as the impact of adherence interventions on health outcomes.

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References

- [1]. Haynes, RB. Introduction. In: Haynes, RB.; Taylor, DW.; Sackett, DL., editors. Compliance in Health Care. Vol. 1979. Johns Hopkins University Press; Baltimore: p. 1-7.
- [2]. Modi AC, Rausch JR, Glauser TA. Patterns of non-adherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA*. 2011; 305:1669–76. [PubMed: 21521848]
- [3]. Modi, AC.; Guilfoyle, SM. Adherence to antiepileptic drug therapy across the developmental life-span. In: Pinikahana, J.; Walker, C., editors. Society, Behaviour and Epilepsy. Nova Science Publishers Inc; New York: 2011. p. 175-205.
- [4]. Faight RE, Weiner JR, Guerin A, Cunningham MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. *Epilepsia*. 2009; 50:501–9. [PubMed: 19183224]
- [5]. Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. *Epilepsy Behav*. 2009; 14:324–29. [PubMed: 19028602]
- [6]. Ho PM, Magid DJ, Shetterly SM, Olson KL, Peterson PN, Masoudi FA, Rumsfeld JS. Importance of therapy intensification and medication nonadherence for blood pressure control in patients with coronary disease. *Arch Intern Med*. 2008; 168:271–76. [PubMed: 18268167]
- [7]. Kogut SJ, Andrade SE, Willey C, Larrat EP. Nonadherence as a predictor of antidiabetic drug therapy intensification (augmentation). *Pharmacoepidemiol Drug Saf*. 2004; 13:591–98. [PubMed: 15362081]
- [8]. Modi AC, Ingerski LM, Rausch JR, Glauser TA. Treatment factors affecting longitudinal quality of life in new onset pediatric epilepsy. *J Pediatr Psychol*. 2011; 36:466–475. [PubMed: 21278379]
- [9]. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010; 51:1069–77. [PubMed: 19889013]
- [10]. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based assessment of adherence to medical treatments in pediatric psychology. *J Pediatr Psychol*. 2008; 33:916–36. [PubMed: 17846042]
- [11]. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. *J Pediatr Psychol*. 2008; 33:590–611. [PubMed: 18192300]
- [12]. Graves MM, Roberts MC, Rapoff M, Boyer A. The efficacy of adherence interventions for chronically ill children: a meta-analytic review. *J Pediatr Psychol*. 2010; 35:368–82. [PubMed: 19710248]
- [13]. Modi AC, Monahan S, Daniels D, Glauser TA. Development and validation of the Pediatric Epilepsy Medication Self-Management Questionnaire. *Epilepsy Behav*. 2010; 18:94–99. [PubMed: 20452831]
- [14]. Beck MH, Cataldo M, Slifer KJ, Pulbrook V, Guhman JK. Teaching children with attention deficit hyperactivity disorder (ADHD) and autistic disorder (AD) how to swallow pills. *Clin Pediatr (Phila)*. 2005; 44:515–26. [PubMed: 16015399]
- [15]. Ghuman JK, Cataldo MD, Beck MH, Slifer KJ. Behavioral training for pill-swallowing difficulties in young children with autistic disorder. *J Child Adolesc Psychopharmacol*. 2004; 14:601–11. [PubMed: 15662153]
- [16]. Herzer M, Ramey C, Rohan J, Cortina S. Incorporating electronic monitoring feedback into clinical care: A novel and promising adherence promotion approach. *Clin Child Psychol Psychiatry*. 2011
- [17]. Hilliard ME, Ramey C, Rohan JM, Drotar D, Cortina S. Electronic monitoring feedback to promote adherence in an adolescent with Fanconi Anemia. *Health Psychol*. 2011; 30:503–9. [PubMed: 21688912]

- [18]. Pai AL, Gray E, Kurivial K, Ross J, Schoborg D, Goebel J. The Allocation of Treatment Responsibility scale: a novel tool for assessing patient and caregiver management of pediatric medical treatment regimens. *Pediatr Transplant*. 2010; 14:993–9. [PubMed: 21108707]
- [19]. Glauser TA. Behavioral and psychiatric adverse events associated with antiepileptic drugs commonly used in pediatric patients. *J Child Neurol*. 2004; 19(Suppl 1):S25–38. [PubMed: 15526968]

Highlights

- Non-adherence and clinical decision-making have been understudied in pediatrics
- 25% of children had uninformed drug changes due to lack of adherence assessment
- Integrating adherence data into clinical decision-making is critical in epilepsy

Figure 1.

Clinical decision-making and AED adherence (With percent of the entire sample at each step). ^aNo significant differences were found in adherence between those that had no AED change ($M_{\text{adherence}} = 84\% \pm 14\%$) versus those who had an AED change ($M_{\text{adherence}} = 81\% \pm 17\%$; $t(110) = 1.02$, $p = 0.31$). ^bNo significant differences were found in adherence between those with side effects ($M_{\text{adherence}} = 79\% \pm 17\%$) versus those with continued seizures ($M_{\text{adherence}} = 82\% \pm 17\%$; $t(65) = .59$, $p = .56$).

Table 1Participant and Epilepsy-Specific Descriptive Statistics ($N = 112$)

Characteristics	
Child Age (mean $\pm$ SD)	7.3 $\pm$ 2.9
Child Male (%)	62.5
Child Race (%)	
Caucasian	75.9
African-American	17.0
Biracial	7.2
Caregiver Relation to Child (%)	
Mothers	82.1
Fathers	13.4
Step-mothers	1.8
Other (e.g., legal guardian)	2.7
Caregiver Marital Status (%)	
Married	63.4
Single	19.6
Divorced	11.6
Separated	4.5
Widowed	0.9
Socioeconomic Status (mean $\pm$ SD) ^a	53.3 $\pm$ 20.5
Epilepsy Diagnosis (%)	
Idiopathic Localization-related	46.4
Idiopathic Generalized	17.9
Unclassified	15.2
Cryptogenic Localization-related	8.9
Cryptogenic Generalized	5.4
Symptomatic Localization-related	5.4
Symptomatic Generalized	0.9
Initial Prescribed Anti-Epileptic Drug (%)	
Carbamazepine	60.7
Valproic Acid	39.3
6-month Adherence (%)	82.5 $\pm$ 15.7

Note.

^aBased on Duncan TSEI2 with occupations equivalent to property managers, physicians' assistants, mail carriers, and sheriffs/law enforcement.