Antiepileptic Drug Adherence and Psychosocial Factors in Children: Is There a Connection?

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Abstract
Pediatric epilepsy is a neurological disorder characterized by recurrent seizures, globally affecting 15 million children. Antiepileptic drug therapy is commonly used in the treatment and control of epilepsy. Previous research has analyzed children’s antiepileptic drug adherence from the perspective of parents and/or caregivers. This analysis examined the child’s perspective (N = 34) regarding level of adherence to antiepileptic drug adherence and focused on psychosocial factors (e.g., child knowledge and worry) in children aged 6 to 12 years at 13 months after being diagnosed with epilepsy. The results suggested that socioeconomic status based on income may be a predictor of adherence (p = 0.00004) along with the positive correlation between child’s knowledge about the disease and parent’s disease-specific knowledge (p = 0.040). The findings indicate that further research on parent–child relationships is needed to improve medication adherence.

Keywords
► epilepsy
► psychosocial factors
► medication adherence

Background
Epilepsy is a disease marked by repeated seizures, affecting millions of adults and children worldwide.1,2 In the United States, 2.2 million individuals have epilepsy, including more than 300,000 children under the age of 15 years.2 The first method of treatment for epilepsy typically includes antiepileptic drug (AED) therapy.3 The proper use of AEDs can lead to the management and control of the symptoms of epilepsy. Often, it is a daunting task to determine which AED is the most appropriate therapy to use in the treatment and control of pediatric epilepsy.4

Children experience unique challenges to AED adherence, including problems with swallowing medications, disliking the taste, nausea, and weight gain.5 Also, medication side effects, disease severity, and seizure frequency within the first year after diagnosis are issues that may lead to decreased AED adherence. The research found that children with general neurological side effects had more disease-specific knowledge (p = 0.002), whereas children with weight gain side effects had less disease-specific knowledge (p = 0.033). Modi et al6 reported higher general neurological and weight gain side effects to AEDs in females compared with males possibly due to hormonal differences between the sexes. Clinicians have used a variety of methods to promote and encourage AED adherence treatment in children diagnosed with epilepsy and their parent/caregivers. For example, prescribing medications that can be given once or twice daily, regular phone contact with the physician, information counseling, and a written action plan are among a few of the methods used to decrease AED nonadherence.7 Lack of adherence to prescribed AEDs is a major and costly healthcare problem.8

A potential key to reducing healthcare costs associated with improving seizure control and medication adherence is to better understand information of the suboptimal factors that predict poor AED adherence, such as the parent’s and the child’s knowledge of epilepsy and their worry related to the treatment. An earlier study linked poor adherence to AEDs in females compared with males possibly due to hormonal differences between the sexes. Clinicians have used a variety of methods to promote and encourage AED adherence treatment in children diagnosed with epilepsy and their parent/caregivers. For example, prescribing medications that can be given once or twice daily, regular phone contact with the physician, information counseling, and a written action plan are among a few of the methods used to decrease AED nonadherence.7 Lack of adherence to prescribed AEDs is a major and costly healthcare problem.8
States in 1995 to range from US $1,071 to US $1,490 per patient.\textsuperscript{11,12} Not even a decade later, the cost per child nearly tripled, ranging from approximately US $3,100 to US $4,350 per patient, with expected future annual increases of nearly US $2,000 per patient.\textsuperscript{13,14}

Previous studies related to epilepsy and other chronic diseases such as hemophilia and depression suggest that patients' direct perception of their disorder acts as a decisive factor in their level of adherence to treatment and maintaining health.\textsuperscript{11,15} A study by Shoreel al reported that a child's need for information and concerns about support remained high, even 24 months postdiagnosis.\textsuperscript{13,16} Research suggests that less knowledge by both the parent and the child may be linked to worry about the diagnosis of illness and its ramifications. Knowledge is a psychosocial factor because the level of knowledge about the chronic disease complemented by knowledge on the importance of adherence may determine the level of seizure control and wellness.\textsuperscript{17,18}

Virtually, no research focuses on a child's perspective of epilepsy diagnosis, disease-specific knowledge, and magnitude of postdiagnosis worry. The objective of this study was to explore possible relationships between child knowledge, worry, and AED nonadherence defined as doses not taken or taken incorrectly and the important role parents play. Research conducted by Modi et al indicated AED nonadherence in 58% of young children recently diagnosed with epilepsy.\textsuperscript{19} Aylward et al reported AED nonadherence in 50% of study participants 1 year after initial epilepsy diagnosis.\textsuperscript{20} This study was designed to examine the correlations between child knowledge, worry, and AED adherence.

**Methods**

A cross-sectional quantitative secondary analysis was used to determine associations between child knowledge and worry/fear, and adherence based on self-reported surveys and data from the MEMS 6 TrackCaps (Aardex Group) download at the 13-month clinic visit at a large Children's Hospital in the Midwestern United States.\textsuperscript{21} The use of the cross-sectional design was an appropriate approach for data evaluation at a specific time point (e.g. 13 months). At 13 months postdiagnosis, one would expect that caregivers and children alike have overcome the initial stress of diagnosis and are more likely to have developed a routine treatment plan.\textsuperscript{22} Importantly, study investigators have previously examined the effects of parental/caregivers' knowledge and worry/fear in new-onset pediatric epilepsy patients and found that both are significantly associated with AED nonadherence.\textsuperscript{19} AED adherence was also found to account for 13% of variance in predicting seizure outcomes.\textsuperscript{23}

Children with psychological conditions, including attention deficit hyperactivity disorder and learning disorder, were included because of their high levels of comorbidity with epilepsy, which more accurately reflects the pediatric epilepsy population. Children and their families were excluded if they had any other developmental disorders (e.g., autism, Down's syndrome) or any other parent-reported comorbid chronic illnesses (e.g., asthma, diabetes) that required medications. Their exclusion allowed investigators to avoid the impact of these illnesses and their medications on the psychosocial factors that predict adherence. During the prospective parent study, one of the study investigators or trained research assistants/personnel made clear the project and acquired consent forms from caregivers and verbal/written assent from children (aged 11 years and older). During the consent process, questions were answered and signatures were obtained.

The research staff members provided instructions on the use of the MEMS6 TrackCap and completion of a demographics and seizure history survey. Understanding the child’s perspective may help identify factors contributing to AED nonadherence and interventions to improve medication adherence.\textsuperscript{9,24} MEMS 6 TrackCaps are electronic monitoring devices that measure the number of times medications are opened by study participants (Aardex,\textsuperscript{21} Cramer et al\textsuperscript{25} ( Appendix A)). Children used the MEMS 6 TrackCaps system for the full 13-month period. Analysis of 13-month postdiagnosis archival data refers to the de-identified data from the previously conducted prospective study, which includes, the Pediatric Epilepsy Side Effects Questionnaire. Parent Report of Psychosocial Care, Child Report of Psychosocial Care ( Appendix A), the Epilepsy Knowledge Questionnaire ( Appendix A). Limitations of secondary data included missing details, conflicting information, lack of access to subjects, and inability to recruit additional participants.

Analysis included 34 children aged 6 to 12 years old and their parent/caregivers. Only participants surveyed regarding their child knowledge and worry and its effect on their level of AED adherence were included. The surveys were evaluated for test–retest reliability and validity. After evaluating the dataset for missing information and ensuring correctness of the data to be used, tests for normality were performed along with frequency analysis to determine if variables were normally distributed and to assess the variables’ central tendencies. Histograms were first examined using the Kolmogorov–Smirnov Shapiro–Wilk tests. Since each was significant (p < 0.05), it was concluded that variable distribution was not typical; attempts to transform (log, inverse, square root) the variables were unsuccessful. Therefore, Spearman’s correlations were used in the analysis to assess associations between the selected demographic/psychosocial factors and adherence. Parents were responsible for ensuring that the children were taking their AED medications and were educated on the appropriate use of the MEMS 6 TrackCaps system. While this number is relatively small, there is no similar dataset that addresses AED nonadherence of children 13 months postdiagnosis.

The child’s perspective along with their parent’s/caregiver’s perspective are important for gaining an understanding of the child’s level of knowledge and worry and its impact on AED nonadherence. Children in this age group are developing autonomy and possible evolution of beliefs and values that may differ from their parents. Postepilepsy diagnosis, the relationship between the parent and child should be explored to understand the relationship dynamic as it relates to the responsible and accurate taking of AED medications as prescribed. Likewise, as the child assumes more responsibility, the trajectory of the high rate of AED nonadherence...
Correlation with Adherence Results

The study found that only 50.9% of the children were adherent (took their medication as prescribed) to their AEDs 1 year post-diagnosis. The average child knowledge score was 73.8% (SD = 13.4%); only 38.2% correctly answered 80% or more of the questions (Table 1).

Child–Parent Correlation Results

Child knowledge was significantly and positively correlated with parent knowledge \((r = 0.36; p = 0.040)\) (Table 2). This positive association might be an important first step in formulating strategies to reduce the high AED nonadherence rate.

Correlation with Demographic and Socioeconomic Factors Results

Duncan score based on family income was the single factor that was moderately and significantly correlated with adherence \((r = 0.523; p = 0.00004)\) (Table 3). Those with higher socioeconomic scores had far better adherence. Caucasian parents and those with higher Duncan Scores had greater knowledge. Those parents with more income also had more worry.

Socioeconomic status (SES) contains many subfactors (e.g., cost of food, cost of healthcare, access to healthcare, and beliefs related to health), which can be examined under the SES umbrella. A significant but weak positive correlation was also observed between age and child knowledge \((r = 0.388; p = 0.024)\), but age was not correlated with child worry, parent knowledge, or parent worry. Parents of non-Caucasian children had significantly lower knowledge \((r = -0.291; p = 0.045)\), and those with greater annual incomes had greater worry \((r = 0.334, p = 0.022)\). Those with higher Duncan Scores also had more knowledge \((r = 0.433; p = 0.002)\) (Table 3).

Results of Correlation with AED Side Effect

Common side effects of AED medications were not correlated with adherence, parent knowledge, or parent worry. However, children with general neurological side effects had more knowledge \((r = 0.507; p = 0.002)\) but children with weight gain side effects had significantly less knowledge \((r = -0.367; p = 0.033)\) (Table 4).

<table>
<thead>
<tr>
<th>Spearman’s correlation</th>
<th>Child knowledge (N = 32)</th>
<th>Child worry (N = 32)</th>
<th>Parent knowledge (N = 32)</th>
<th>Parent worry (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(p)-Value</td>
<td>(r)</td>
<td>(p)-Value</td>
</tr>
<tr>
<td>Adherence</td>
<td>-0.177</td>
<td>0.332</td>
<td>0.058</td>
<td>0.754</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant.

<table>
<thead>
<tr>
<th>Table 1 Correlations with adherence</th>
</tr>
</thead>
</table>

| Table 2 Child–parent correlations |

<table>
<thead>
<tr>
<th>Spearman’s correlation</th>
<th>Child worry (N = 32)</th>
<th>Parent knowledge (N = 32)</th>
<th>Parent worry (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(p)-Value</td>
<td>(r)</td>
</tr>
<tr>
<td>Child knowledge</td>
<td>(r)</td>
<td>0.164</td>
<td>0.354</td>
</tr>
<tr>
<td>Child worry</td>
<td>(r)</td>
<td>-0.101</td>
<td>0.575</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant.

| Table 3 Correlations with demographic and socioeconomic factors \(N = 34\) |

<table>
<thead>
<tr>
<th>Child age (years)</th>
<th>Adherence (N = 34)</th>
<th>Child knowledge (N = 34)</th>
<th>Child worry (N = 34)</th>
<th>Parent knowledge (N = 34)</th>
<th>Parent worry (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(r)</td>
<td>(p)-Value</td>
<td>(r)</td>
<td>(p)-Value</td>
<td>(r)</td>
<td>(p)-Value</td>
</tr>
<tr>
<td>-0.049</td>
<td>0.723</td>
<td>0.388</td>
<td>0.024</td>
<td>0.066</td>
<td>0.712</td>
</tr>
<tr>
<td>-0.077</td>
<td>0.577</td>
<td>0.033</td>
<td>0.852</td>
<td>0.054</td>
<td>0.760</td>
</tr>
<tr>
<td>-0.216</td>
<td>0.113</td>
<td>0.059</td>
<td>0.739</td>
<td>-0.194</td>
<td>0.271</td>
</tr>
<tr>
<td>0.249</td>
<td>0.069</td>
<td>0.321</td>
<td>0.068</td>
<td>-0.165</td>
<td>0.359</td>
</tr>
<tr>
<td>0.523</td>
<td>0.00004</td>
<td>0.248</td>
<td>0.157</td>
<td>-0.150</td>
<td>0.397</td>
</tr>
</tbody>
</table>

\(^a\)An additional child is missing a value for this variable. Values in bold are statistically significant.
**Table 4 Correlations with AED side effects**

<table>
<thead>
<tr>
<th>Spearman’s correlation</th>
<th>Adherence (N = 34)</th>
<th>Child knowledge (N = 34)</th>
<th>Child worry (N = 34)</th>
<th>Parent knowledge (N = 34)</th>
<th>Parent worry (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-Value</td>
<td>r</td>
<td>p-Value</td>
<td>r</td>
</tr>
<tr>
<td>Cognitive</td>
<td>−0.195</td>
<td>0.190</td>
<td>0.125</td>
<td>0.483</td>
<td>0.001</td>
</tr>
<tr>
<td>Motor</td>
<td>−0.044</td>
<td>0.769</td>
<td>−0.021</td>
<td>0.905</td>
<td>0.060</td>
</tr>
<tr>
<td>General neurologic</td>
<td>0.027</td>
<td>0.859</td>
<td>0.507</td>
<td>0.002</td>
<td>0.239</td>
</tr>
<tr>
<td>Behavioral</td>
<td>−0.213</td>
<td>0.151</td>
<td>−0.105</td>
<td>0.555</td>
<td>0.047</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.070</td>
<td>0.640</td>
<td>−0.367</td>
<td>0.033</td>
<td>0.239</td>
</tr>
</tbody>
</table>

Abbreviation: AED, antiepileptic drug. Values in bold are statistically significant.

**Discussion**

The participants were newly diagnosed with epilepsy and their adherence behavior was assessed from the parent/caregivers’ perspective over a 2-year period. The data were evaluated for missing information. The primary focus of the evaluation was the dependent variable (adherence) and independent variables (child knowledge and worry). Also, the data evaluation examined child’s age. The research study examined data such as central tendency, test of normality, and participant characteristics. Children included in the analysis were on average 8.74 ± 1.87 years of age (range: 6.02–12.96 years); 47.1% were male and 17.6% were non-Caucasian (Table 5).

**Child Knowledge and Worry, and AED Adherence**

These data demonstrated that lower household income and minority status along with other factors are commonly associated with diminishing AED adherence but do not completely explain the high rate of nonadherence. This study found that only 50.9% of the children were adherent (took their medication as prescribed) to their AEDs 1 year postdiagnosis. Previous studies of epilepsy and other chronic diseases have found significant decreases in adherence within the first 6 to 12 months following diagnosis. A study by Staniszewska et al found that 54% of the study participants feared they might become addicted to AEDs over time and modified their prescribed treatment regimen, thus negatively impacting adherence. To date, this was the first known study to have examined knowledge of epilepsy in children age group and objectively measured AED adherence.

A previous study of both self-reported and parent-reported adherence among teenagers with epilepsy revealed a significant correlation with greater epilepsy knowledge/expectations, suggesting that adherence to AEDs might be improved by ensuring that teens have a good grasp of their condition and its treatment. Some studies suggest that disease knowledge, while necessary, had no major bearing on adherence to medication regimen. In addition to child knowledge, the correlation between child worry and AED adherence was also assessed. The data suggested a low degree of worry among both the parents and their children 1 year postdiagnosis.

**Correlations with Demographic and Socioeconomic Factors**

Socioeconomic status index is a family’s social position based on their access and command over wealth, prestige, and power. Socioeconomic indices are usually measured using parental education, occupation, and wealth. Family income was used to assess SES in this study. Pew research defines low-income range as US $0 to US $37,866 per year in the United States. Families earning more than US $25,000 annually were measured in the high SES and those earning less than US $25,000 annually were measured as low SES.

Child knowledge was weakly and positively correlated with age. It seems that older children are likely to have a greater capacity for higher knowledge. A moderate positive correlation was observed between Duncan Score based on income and adherence. SES was the only significant predictor of nonadherence. Berg et al identified other family barriers (e.g. split families, increased family criticism) and social barriers (e.g., inner city residence, decreased social support from family and friends, and emotional and behavioral problems) that increased the likelihood of nonadherence. Likewise, a significant correlation was also observed between child’s race and child knowledge. Non-Caucasians were less knowledgeable...
compared with Caucasians. Furthermore, studies should be undertaken to examine the depth and breadth of the impact of SES based on income along with the potential significance as to the role of race in the level of adherence.

**Correlations with Medication Side Effects**

Correlations between AED side effects were assessed because of their potential to make taking AEDs more challenging. The analysis suggested that these common side effects of AED medications were not correlated with adherence, parent knowledge, or parent or child worry. Surprisingly, no significant correlational relationship was found between child worry, parent knowledge, parent worry, and AED medication side effects. A marginally significant correlation was found between child knowledge and parent knowledge. Similarly, child worry was not correlated with adherence 1 year post-diagnosis, particularly as worry levels were low overall. Only a single factor, Duncan Score, was correlated with AED adherence 1 year post-diagnosis.

**Implications and Future Recommendations**

Poor adherence is one of leading reasons for pharmacological treatment failure. Future studies examining the combined effect of parent and child adherence are needed. Furthermore, an effort to better educate the parent will increase the child’s knowledge as well and provide a common goal to achieve seizure control. Children in the age group under investigation are still young and thus parental influence will be a strong driver of adherence behavior. It is likely that improving one or the other alone will not significantly improve adherence. Rather, other factors must be evaluated simultaneously, particularly race and socioeconomic factors.

**Strengths and Limitations**

There are several strengths associated with this research study. First, the study objectively measured adherence using the MEMS6 TrackCap. Most studies use a self-report or parental report of adherence. Self- and parental report are often biased (they over report adherence). Furthermore, adherence was measured over a 60-day period: 30 days before the 13-month study visit and 30 days after making the findings much more robust than self-report. Next, the study looked at younger children in addition to parents and assessed both knowledge and worry. While other studies have found them to be associated early on, this study showed that they were not correlated 1 year post-diagnosis. This finding as well as the lower reported levels of worry suggest a greater perception of comfort 1 year post-diagnosis. Analysis of these associations over the year following diagnosis might provide greater insights into this relationship. Also, future studies might examine the changes in child knowledge and child worry from baseline to 13 months.

There were also several limitations to this study. The participant sample was taken from a single well-equipped distinguished hospital in the Midwestern United States that cares for many epilepsy patients, reducing generalizability to smaller and less resourced hospitals. The analyses were also based on a smaller sample size (N = 34). A larger sample size would increase the power to evaluate the effect of child knowledge and child worry/fear on adherence while considering other important factors simultaneously.

**Conclusion**

Nonadherence to AED medication has been identified as a major barrier to seizure control. A highly important component to improving AED adherence is to identify psychosocial and other barriers that hinder good adherence. This study examined two potential psychosocial barriers (child knowledge and child worry) and several potential confounders that may affect adherence behavior. Modifiable (SES) and non-modifiable (race) confounders alike were evaluated. Seizure control is difficult to achieve because of disease variability (type of seizure, types of AED medication, disease severity, SES, level of knowledge, etc.). Based on the data, most children and parents are worrying less at 1 year post-diagnosis, likely making worry less of an influence on adherence to AEDs. Duncan scores and adherence were significantly positively correlated, which validates the need for further research on this important association. Interventions that target both children and parents/caregivers are recommended to optimize AED adherence.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

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**References**

Appendix A Hyperlinks to Study Surveys

https://www.aardexgroup.com/solution/mems_caps/22

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440448/

https://www.seizure-journal.com/article/S1059-1311(05)80125-6/pdf