Predictors of non-adherence in children and adolescents with epilepsy: A multi-method study investigating influence of beliefs about treatment

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Abstract

Background: There is a lack of a standardised tool for adherence measurement in patients with epilepsy. Studies In children with epilepsy have reported adherence in 50-96.5%. The primary objective of this study was to identify predictors of non-adherence to Anti-Epileptic Drugs (AEDs) using two different methods in Jordanian children and adolescents with epilepsy.

Methods: Participants included 63 children and adolescents with epilepsy and their primary caregivers. Adherence measures included a subjective approach (using parent and child self-reports via Medication Adherence Report Scale (MARS) and an objective method (measuring plasma levels of AEDs coupled with the application of population pharmacokinetic models to predict AED concentrations in the children). The Beliefs about Medicines Questionnaire (BMQ) was used to examine the association beliefs about medicines with non-adherence in the participating patients.

Results: Measuring AEDs in plasma samples captured the highest percentage of nonadherence (36.2%).The overall non-adherence (combined methods) to AED therapy in children with epilepsy was 44.4%. Logistic regression analysis indicated that children with longer duration of disease were more likely (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.16–2.04) to be classified as non-adherent as were children whose parents have lower AED Necessity scores (OR 0.68, 95% CI 0.53–0.87) and higher AED Concerns (OR 1.6, 95% CI 1.26–2.04) as measured by the BMQ.

Conclusion:

The use of a mutli-method approach for assessing adherence increases sensitivity for detection of non-adherence to AEDs. Disease duration and parental Necessity beliefs and Concerns assessed by the BMQ-Specific questionnaire were significant predictors of non-adherence to the AED therapy. The need for the development and implementation of interventions that can be employed to improve adherence within this paediatric population has been highlighted by the high levels of non-adherence identified.

Keywords: Anti-Epileptic Drugs, adherence, Medication Adherence Report Scale (MARS), Children, BMQ, Necessity Concerns Framework

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Introduction

Worldwide, 50 million people have epilepsy [1] and 10.5 million of them are children under 15 years old [2]. Adherence assessment and factors that affect adherence in children with epilepsy are not widely researched [3]. The term of medication adherence can be defined as ‘‘the extent to which patients take medication as prescribed by their health care providers” [4].Successful therapy using anti-epileptic drugs (AEDs) can eliminate or reduce symptoms; adherence to AEDs is subsequently a key to treatment success [5].

Reports on the extent of non-adherence to (AEDs) in children and adults with epilepsy vary considerably, ranging from 3.5% to 74.8% depending on the population studied and method used to assess adherence ([6-10].

Generally there are three types of factors that can influence medication adherence to AEDs in particular: 1) disease-related factors including disease severity and duration of illness; 2) patient-related factors such as forgetfulness and stigmatization; 3) medication-related factors such as cost, side effects, and complexity of dosing regimen [11]. Poor adherence to prescribed AEDs is associated with negative consequences such as reduced seizure control [12-14], higher incidence of hospital admissions [14-16] and increased health care costs [5, 17, 18]

There is no standardised tool for adherence measurement in patients with epilepsy [19]. Several studies have used the Morisky scale [20] or the Medication Adherence Report Scale (MARS) scale[3, 21] as self-report measures to assess adherence in patients with epilepsy[13, 22]. Other researchers have assessed adherence using ‘pill’ counts [23] electronic monitors [6, 24] and medication refills [5, 17, 25, 26].

Adherence assessment using objective methods such as blood level determination of AEDs has also been utilised in various studies [3, 27-31]. However, variability in the pharmacokinetics of the AEDs due to variable absorption, drug interactions with

medications taken concomitantly and differences in rates of drug metabolism may influence the results obtained [29].

Adherence is best determined by using different assessment approaches and triangulating the results obtained to provide an overall assessment [29]. The aim of the present study was to use subjective and objective approaches to assess the level of adherence to prescribed AEDs in children with epilepsy, and to identify factors that influence adherence.

Methods

Study design

This cross sectional study was carried out at the child neurology clinic at Jordan University Hospital (JUH), a tertiary care hospital in Amman, the capital of Jordan. The study was approved by the Research Ethics Committee of the University of Jordan Hospital. The study was carried out between October 2015 and November 2016. Subjective adherence to AEDs was assessed in children with epilepsy using a validated Arabic version of the Medication Adherence Report Scale (MARS) [32] and by measuring AED plasma levels (objective method).

Factors affecting adherence to antiepileptic drugs were determined by using Parent necessity and concern subscales of the validated Arabic version of the Beliefs about Medicines Questionnaire (BMQ)-specific [32].

The overall seizure severity of each participating child was assessed by their physician, using the Global Assessment of Severity of Epilepsy (GASE) Scale [33].

Study patients and data collection

Children with epilepsy aged $\leq$18 years and who were receiving AEDs [including one or more of the following: carbamazepine (CBZ), levetiracetam (LVT), sodium valproate (VPA)] for at least one month were included. Parents were asked to sign a consent form after receiving a full explanation of the study and only children whose parents provided written informed consent were included. Assent was also obtained from children who were considered capable of providing this by their physician.

The medical files were reviewed to collect data on patients ' demographics, current medications and medical history.

Study measures and adherence assessment

The MARS and BMQ-Specific questionnaires were self-completed by parents and their children (if ≥11 years old, during the clinic visit). Capability of children to complete the questionnaire was determined by his/her physician.

Medication Adherence Report Scale (MARS)

The validated Arabic translations of the MARS questionnaires (parent and child version) were used [32] to assess adherence to medication in the past month. The child's version consists of five items; mean scores were summed to give a scale score ranging from 1 to 5.; The parent's version consists of six questions mean scores were summed to give a scale score ranging from 1 to 5. Higher scores indicate higher levels of self-reported adherence. In the present study, a 90% cut-off point for adherence was used, i.e. a participant was considered to be adherent, if the parental/child MARS score was at least 4.5 out of 5.

Beliefs about Medicines Questionnaire (BMQ-Specific)

The validated Arabic translation of the BMQ-Specific questionnaires (parent and child versions) were used [32]. The BMQ-Specific involves assessment of patients' beliefs about medication prescribed for a specific illness, in this case AED. It comprises two scales: the AED-Necessity scale comprises 5 items assessing perceptions of personal need for AED to maintain or improve health now and in the future. The AED-Concerns scale comprises 6 items assessing concerns about AED. For each scale, Adjusted Scale Mean Scores were computed by summing the individual item scores and dividing by the number of items in the scale (range 1-5). Higher scores indicate stronger perceptions of the constructs represented by the scales.

AED concentration in plasma samples

Blood samples (2 ml) were collected from each participating child at a clinic visit. All samples were labelled with patient study number, the date and time of collection. Plasma was obtained for each sample after blood centrifugation and stored at –80°C until AED analysis was performed. For VPA and CBZ measurement was performed

using (chemiluminescent microparticle immunoassay (CIMA). For measurement of LVT, a validated micro-analytical method using high-performance liquid chromatography (HPLC) with UV detection (210 nm) was utilized [34]. The concentrations of AEDs were expressed in μg/ml.

To determine whether a child was adherent, a pharmacokinetic simulation method was utilized to estimate the 0.95 interval of predicted plasma concentrations for each AED at the time of sampling in individual patients (n = 1,000 sets of simulations using the non-linear mixed effect modeling software package, NONMEM, Icon Development Solutions, Ellicott City, MD, U.S.A.). In this methodology, literature values of population pharmacokinetics (PopPK) parameters for each drug were employed [35-37]. In addition, significant covariates reported to influence PK parameters for each drug (e.g. age, dose, body weight) were incorporated into the simulation models.

Patients were considered adherent if their measured AED concentrations were within the calculated 95% prediction intervals. Patients taking more than one drug of interest were categorized as non-adherent if the measured concentration was lower or higher than the simulated concentration for at least one of the AEDs prescribed.

Data analysis

All analyses were carried out using SPSS version 22 (SPSS Inc., Chicago, IL, U.S.A.). Group differences (adherent vs. non-adherent) were explored using Mann-Whitney *U* analysis for continuous variables and using the chi-square or Fisher's exact test for categorical variables. The significance level was set at 0.05 throughout analyses. The magnitude of agreement between different adherence assessment methods was determined using the Kappa (κ) coefficient [38].

Factors which were shown to have significant effect on adherence ($p<0.05$) were subjected to multivariate analysis using binary logistic regression to evaluate the potential predictors of adherence categorization.

Results

Patients demographic Characteristics

The parents of eighty seven eligible patients were approached and sixty three agreed to take part in this cross sectional study. Four participating children refused to give blood. About half of the patients received LVT. The demographics and disease characteristics of the study subjects are described in Table 1. The number of medications received by patients ranged between 1-6 medications (median= 1).

Table 1. Demographic and disease characteristics of the study sample (n= 63)

Parameters	
Children age (years), mean (SD)	8.36 (4.22)
Children weight (kg), mean (SD)	29.09 (14.30)
Children gender, n (%)	
▪ Males	38 (60.3)
▪ Females	25 (39.7)
Type of seizure n (%)	
▪ Generalized seizures	39 (61.90)

▪ Partial/focal seizures	24 (38.10)
***Overall epilepsy severity using GASE scale n (%)**	
▪ Not at all severe	11 (17.46)
▪ A little severe	38 (60.32)
▪ Somewhat severe	13 (20.63)
▪ Moderately severe	1 (1.59)
Disease duration (years), mean (SD)	4.20 (3.63)
Number of medications, mean (SD)	1.60 (1.01)
Number of AED prescribed	
▪ 1	47 (74.60)
▪ 2	12 (19.05)
▪ 3	3 (4.76)
▪ 4	1 (1.59)
Type of AED of interest prescribed, n (%)	
▪ Sodium valproate	30 (47.62)
▪ Levetiracetam	31 (49.21)
▪ Carbamazepine	7 (11.1)
Measured AED concentrations (median [range], µg/ml)	
▪ Sodium valproate	61.64 (2.00-136.80)
▪ Levetiracetam	11.61 (0.01-42.30)
▪ Carbamazepine	5.91 (1.10-12.56)
Parent education, n (%)	
▪ No formal education	2 (3.17)
▪ Primary School	4 (6.35)
▪ Secondary School	35 (55.56)
▪ Bachelor degree	8 (12.70)
▪ Master degree or PhD	14 (22.22)

SD: Standard deviation.
(GASE) Scale: Global Assessment of Severity of Epilepsy

Beliefs about medicines

Sixty three parents and twenty one children completed the BMQ-specific questionnaire. The majority of parents (88.9%) and children (76.2%) had a strong belief about the necessity of AEDs (BMQ-specific scores above scale midpoint), whereas approximately 76.2% (parents) and 61.9% (children) had concerns about AED harmful effects. The median total scores for the necessity and concern subscales were 3.8 (range 2–5) and 3.2 (2–5) for parents and 3.8 (1.0–4.6) and 3.0 (2.2–4.2)

for children, respectively. Reliability coefficients (Chronbach's alpha) for the necessity and concern subscales were 0.707 and 0.769 for parents and 0.802 and 0.747 for children respectively, indicating reliability of the methodology.

Adherence assessment

Adherence using MARS specific (parent and child versions)

Score distribution for the MARS questionnaires is presented in Table 2. Children were classified as being adherent if they recorded a total score ≥ the 90th percentile of the maximum score [i.e ≥ 4.5 for MARS (parents and child)]. Accordingly, using the parental MARS questionnaire scores, a total of 50 children (79.4%) were classified as being adherent. On the other hand, among the 21 children who answered the MARS (child) questionnaire (those aged 11 years or above), fourteen children (66.7%) were classified as being adherent.

The mean MARS score for parents [4.67, SD (0.5)] was higher than mean MARS score for children [4.34, SD (0.17); p=0.042].

Table 2. Distribution of the total scores for the MARS questionnaires reported by participating parents and children

Measure	n	Total score mean	Total score range	Score indicating non-adherence	Number (%) of non-adherent patients
MARS (Parent)	63	4.65	3.5-5	< 4.5	13 (20.63%)
MARS (Child)	21	4.34	1.8-5	< 4.5	7 (33.33%)

AED concentrations in plasma samples

A total of 58 plasma samples were obtained from the 63 patients recruited in the study i.e. four patients refused to give a blood sample for analysis and one blood sample was of insufficient volume for analysis. Sixteen patients (27.6%) had AED plasma concentrations lower than the 95th percentile of the predicted concentrations according to the PopPK modeling while five patients were found to be over adherent (8.6%). Twenty one patients were therefore deemed non-adherent using this measure (36.2%). Measured AED concentrations (median and range) are shown in Table 1.

Assessment of different measures of adherence

Measuring AEDs in plasma samples captured the highest percentage of nonadherence (36.2%) followed by the MARS (child) questionnaire (33.3%). The lowest percentage of nonadherence (20.6%) was observed using the MARS (parent) questionnaire, Figure. 1. When all the three methods were taken into consideration 44.4% of children were classified as non-adherent.

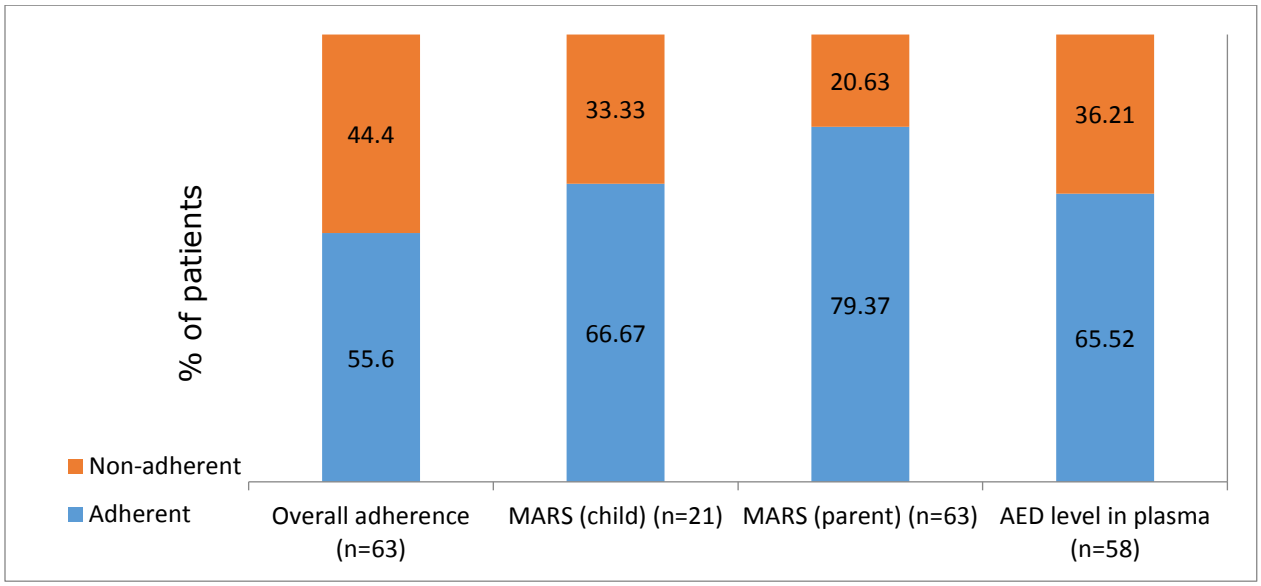

Figure 1.Comparison of different methods of adherence assessment (percentage of adherent patients vs non adherent patients).

The interrater reliability agreements across the different adherence assessment methods are presented in Table 3. The interrater reliability for the MARS (parent) and MARS (child) was found to be significant (Kappa = 0.64, *p*-value= 0.002) indicating a significant agreement between the two assessment methods. On the other hand, no significant agreement was found between the AED plasma level method and both the MARS (parent) and MARS (child).

Table 3. Assessment of agreements between the three methods of measuring adherence using Cohen's Kappa analysis

Method	**Cohen's Kappa Coefficient**	***p*-value**
AED plasma level vs MARS* (Parent)	0.187	0.133
AED plasma level vs MARS (Child)	0.131	0.585
MARS (Parent) vs MARS (Child)	0.640	0.002**

*MARS: Medication Adherence Report Scale
**Significant at 0.05 level

Factors affecting adherence to antiepileptic drugs

Univariate analysis showed that parental beliefs about their child's AED (BMQ-Necessity and BMQ-Concerns) and disease duration were associated with overall adherence to AEDs. These variables were subjected to logistic regression analysis (backward LR). The analysis indicated that increased disease duration and higher scores for the BMQ-Concerns (parent) scale and lower scores for the parental BMQ-Necessity scale were significantly and independently associated with nonadherence Table 4. The mean disease duration in adherent patients [3.10, SD (0.54) was shorter than in those who were deemed non-adherent [5.56, SD (0.71)], *p*-value=0.002.

The mean BMQ Necessity score (parent) in adherent patients [19.63, SD (3.08) was higher than in those who were deemed non-adherent [17.17, SD (3.50)], *p*-value=0.004. The mean BMQ-Concern score (parent) in adherent patients [17.29, SD (4.27] was lower than those who were deemed non-adherent [21.36, SD (3.75)], *p*-value<0.001.

Table 4 Predictors of non-adherence to AEDs using binary logistic regression

Independent variable	**B**	**SE**	**Odds ratio**	**95% CI**	***p*-value**
Disease duration	0.43	0.144	1.54	1.16-2.04	0.003*
Parent BMQ-Necessity score	-0.39	0.13	0.68	0.53-0.87	0.002*
Parent BMQ-Concern score	0.47	0.12	1.60	1.26-2.04	<0.001*

*p-value < 0.05. Adherence coded 0, nonadherence coded 1.
B, regression coefficient; SE, standard error associated with the coefficient B; CI, confidence interval.

Discussion

This is the first study in Jordan that investigated the adherence to AEDs in children and adolescents utilizing a combined subjective method (self-reported questionnaires) and an objective method (measuring AEDs in plasma samples) to better describe non-adherence to anti-epileptic treatment.

Adherence to AED therapy is crucial for effective disease management, yet non-adherence rates are high due to several barriers [39]. The adherence rate varies depending on the unique characteristics of the population being studied (e.g. differences in the patients' attitude toward adherence due to cultural or educational influences, or their clinicians' approach and method being used to assess adherence[22, 40].

In the present study, there was a significant agreement between child-reported and parent-reported adherence rates (Kappa = 0.64, p-value= 0.002), and this follows the trend of good parent-child agreement from prior studies [3, 41]. Parent-reported adherence rates (79.4%) were, however, greater than child-reported adherence rates (66.7%) highlighting the subjectivity of the self-reported approach, i.e. 100% honesty in answers provided is not guaranteed. Children are perhaps more likely to answer the questions honestly due to their naïve nature, while parents are more likely to present their child as adhering to prescribed regimens and not admit to going against doctors' advice.

The highest percentage of non-adherence was observed with plasma AED concentrations (36.2%). This reflects the known overestimation of adherence using subjective methods[6, 42].

The application of PopPK models, to predict AED concentrations in individual children according to the relevant covariates present (i.e. time of sampling, age, dose, body weight) minimizes the intra- and inter-individual variability associated with the measured concentrations and this approach has been shown to be useful for estimating levels of adherence in children with epilepsy [3].
The overall non-adherence rate to the AEDs when the results of different methods were combined was 44.4%, which was considered high, however, it is within the reported range in published literature on the non-adherence to treatment in children with epilepsy of 3.5–58% [3, 6, 22, 24]. The use of a multi-method approach increases the sensitivity of detecting non-adherence to treatment in patients [3, 43].

It was possible that non-adherence was overestimated in the present study, as patients were classified as being non-adherent if one of the assessment methods employed was indicative of non-adherence, despite other measures implying adherence. Furthermore, five patients were classified as over-adherent using the plasma analysis. The small sample size and the diversity within the study population may have influenced the findings. The current research could be considered as a preparatory work for a national study in this field, with a larger population of children.

Patients' characteristics (i.e. age, gender and number of prescribed medicines) were not found to be predictors of non-adherence in the present study. This was consistent with previous studies in the literature [24, 44, 45].

Longer disease duration was significantly and independently associated with non-adherence. This finding is similar to the results reported by Mbubaetal, who found patients with epilepsy who had seizures for less than 10 years might be more likely to seek treatment compared with people with disease of longer duration because they had learnt to cope with their disorder[46].

In the present study, children of parents with negative beliefs about their child's medicine were more likely to be classified as non-adherent to AEDs. Our findings confirm the applicability of the Necessity–Concerns Framework ([47]) and results are consistent with previous adult studies linking non-adherence to AEDs to patients' beliefs about AEDs[48-50]. The present results have implications for the provision of adherence support to parents and children. They suggest the need to apply a Perceptions and Practicalities Approach to supporting informed adherence (ref) as recommended by the NICE Medicines Adherence Guidelines (ref) This emphaisises the need to address not just the practicalities of adherence (eg ability to use the medication as advised) but also the perceptions that influence motivations to adhere. Consistent with NICE our findings suggest the importance of the Necessity Concerns Framework in identifying salient adherence-related perceptions of AED. Adherence support should be tailored to communicate a common-sense rationale for the necessity of regular AED and to elicit and address specific concerns about AED. Epilepsy nurses or clinical pharmacists, may be suitable as delivery channel for this type of adherence to parents and children but further studies are needed to demonstrate the efficacy of this approach.

Further evaluation of reasons for non-adherence to AEDs in children in Jordan using prospective longitudinal designs should also be undertaken to support the development of appropriate adherence interventions for implementation into routine paediatric clinical practice.

Limitations

The findings of this study should be considered within the context of a few limitations. Firstly, a modest sample size was used, within which there was a narrow range of demographic characteristics. Future work should include a larger sample size consisting of a more even proportion of patients within gender, diagnosis, disease severity and medication type categories. Secondly, the study design was observational, cross-sectional and therefore could not assess cause–effect relationship between parental beliefs and adherence. This can be further assessed using prospective longitudinal designs.

Conclusions

The overall adherence to AED therapy in children in Jordan with epilepsy was 55.6%, which was within the range reported in the literature. Measurement of the AED concentrations using plasma sampling, coupled with the use of published PopPK models for predicting AED plasma concentrations, was shown to be a valuable approach for estimating levels of adherence. Logistic regression analyses identified the disease duration and parental AED Necessity and AED concern beliefs assessed by the BMQ-specific questionnaire as significant predictors of non-adherence to the AED therapy. There is a need for the development and implementation of clinical interventions aimed at overcoming the high level of non-adherence in children with epilepsy i.e. strives to increase adherence to more acceptable levels.

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