HHS Public Access

Author manuscript

Epilepsy Behav. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Epilepsy Behav. 2015 April ; 45: 101–104. doi:10.1016/j.yebeh.2015.03.014.

The Pediatric Epilepsy Side Effects Questionnaire: Establishing clinically meaningful change

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Abstract

The present study extends the utility of the Pediatric Epilepsy Side Effects Questionnaire (PESQ) by determining distribution-based minimally clinically important difference (MCID) scores. Participants (N=682) were youth (ages 2–25) with newly diagnosed and chronic epilepsy pooled from research and clinical data in the Comprehensive Epilepsy Center. Caregivers completed the PESQ. Demographic and medical data were extracted from medical chart reviews or via a questionnaire. The MCIDs, which are the standard errors of measurement for each scale, for the entire sample were: Cognitive = 4.66; Motor = 4.67; Behavior = 8.05; General Neurological = 7.41; Weight = 9.58; Total PESQ = 3.25. Additionally, MCIDs for patients with new-onset (<12 months) epilepsy on monotherapy, new-onset epilepsy on polytherapy, chronic epilepsy on monotherapy (>12 months), and chronic epilepsy on polytherapy were calculated. Results from the present study extend the utility of the PESQ by providing clinicians and researchers an enhanced understanding about clinically meaningful changes in side effect profiles across the pediatric epilepsy spectrum. These data can inform clinical decision making for clinicians and researchers.

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Disclosures, Conflicts of Interests

Financial Disclosures: Drs. Avani Modi, Katherine Junger, and Diego Morita report no disclosures.

Additional contributions: We would like to extend our deepest appreciation to children, adolescents and their families who participated in this study. We would like to especially thank the research assistants, undergraduate and graduate students, pre-doctoral interns, and postdoctoral fellows (Cincinnati Children's Hospital Medical Center) for recruiting study patients and data collection. We would also like to thank the New Onset Seizure and Advanced Therapies Teams at Cincinnati Children's Hospital for their support of the study.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Keywords

children; seizures; antiepileptic drugs; side effects; MCID; patient-reported outcome

1. Introduction

1.1

Antiepileptic drugs (AEDs) are the first line of treatment in pediatric epilepsy to control seizures. They are associated with a wide range of side effects that negatively impact health-related quality of life[1, 2]. The Pediatric Epilepsy Side Effects Questionnaire (PESQ)[3] was developed as a patient-reported outcome (PRO) to systematically assess for perceived side effects. The PESQ has demonstrated excellent psychometrics[3] and has been used in clinical and research applications[1, 2, 4]. The PESQ can be used to inform clinical decisions; however, it is unclear what level of change is significant and meaningful for a patient. Thus, establishing a minimally clinically important difference (MCID) for the PESQ is a critical next step to refine the usability of this instrument. While MCIDs have been well-established for PRO quality of life instruments[5, 6], they have seldom been used with other PROs.

1.2

There are several methodologies to determine minimal clinically important difference (MCID) including anchor-based and distribution-based approaches. The standard error of measurement (SEM) is a commonly used distribution-based approach that uses the error variability of the scales to determine whether differences in scores are more likely attributable to measurement error or meaningful change. Changes in scores less than the SEM are thought to be errors in measurement while changes exceeding the SEM are presumed to reflect actual change. Advantages of this approach are that MCID is sample-independent and is expressed in the same units as the instrument. The latter allows for rapid determination of whether differences in scores over time constitute meaningful change[7], which is ideal in busy medical clinics. The SEM approach converges with anchor-based methods[8] and has been shown to correspond to minimally important intra-individual changes. The aim of the current study was to establish the MCIDs for the PESQ using a distribution-based method.

2. Materials and Methods

2.1

Participants included 682 patients with epilepsy (2–25 years of age and their caregivers) recruited from Cincinnati Children's Hospital Medical Center (CCHMC). Participants were pooled from two research studies and clinical data: 1) a consecutive cohort of patients being clinically treated for pediatric epilepsy (N=380; M_{childage}=10.99±4.85; 43.9% female); 2) a longitudinal research study examining adherence over time in children with newly diagnosed epilepsy (N=115; M_{childage}=7.28±2.94; 37.4% female); and 3) a retrospective chart review of patients seen in complex care clinics within the Comprehensive Epilepsy

Center (N=188; $M_{childage}$=12.11±5.39; 45.7% female). Methodological details for the research studies have been published elsewhere[3]. Across all cohorts, inclusion/exclusion criteria were as follows: diagnosis of epilepsy, treatment with at least 1 anti-epileptic drug (AED), and patient age between 2–25 years.. The decision to include patients up to age 25 was made to capture the transitional adolescent/young adult developmental period and mirrors the age at which offspring can no longer be covered by parents' insurance. Race/ethnicity data were not collected for Study 1. The Institutional Review Board (IRB) approved all of the studies.

All patients in the current study were seen through the Division of Neurology and Comprehensive Epilepsy Center at CCHMC which includes several different clinics: General Neurology, New Onset Seizure Clinic, Advanced Therapies Clinic, and Neurosurgery Clinic. The New Onset Seizure Clinic evaluates children with newly diagnosed epilepsy and follows these children for the course of their treatment. These children are followed by advanced nurse practitioners and are typically developing with no major medical comorbidities. The Advanced Therapies Clinic serves patients who have medically refractory seizures or are seeking second opinions. In addition to AEDs, these patients may also be treated with therapeutic diets or be post-neurosurgery. The Surgery clinic includes children being evaluated for and followed for neurosurgical treatment of epilepsy and requires that children have failed at least 2 AEDs. Children within the complex care clinics often have medical and developmental comorbidities.

2.2

All caregivers completed the Pediatric Epilepsy Side Effects Questionnaire© (PESQ)[3]. The PESQ is a 19-item validated measure assessing side-effects of AEDs for youth with epilepsy. Items cover a broad range of cognitive, motor, behavioral, neurological, and weight related side-effects. Items are rated on a 6-point Likert scale from 1 (not present) to 6 (high severity). Scaled scores are calculated for several subscales (Cognitive, Motor, Behavior, General Neurological, Weight), as well as a Total Side Effects score. Scores range from 0 (no side effects) to 100 (highest level of side effects). The measure has demonstrated excellent reliability and validity[3] . Medical and demographic data were collected from medical chart reviews and background information forms.

Means, standard deviations, and frequencies were calculated for demographic and medical variables as well as PESQ scales. MCID scores were calculated for each scale and the total score using the SEM with the following equation: SEM=SD$\sqrt{}$[1-α], SD=standard deviation of mean PESQ score; α=scale reliability[8].

3. Results

3.1 Participants

Participants included 682 patients with epilepsy and their caregivers ($M_{childage}$=10.7±5.0; 43.3% female) Demographic and disease characteristics by subpopulation are presented in Table 1. Overall, 63% percent of patients had focal seizures, 27% had generalized seizures, 8% had unclassified seizures, and 2% had both types. Twenty-six percent of patients were

newly diagnosed with epilepsy (<12 months) and 74% of patients had chronic epilepsy (>12 months). The mean number of AEDs per patient was 1.4±0.70 (range 1–6). Seventy percent of patients were on monotherapy. The following AEDs were prescribed: carbamazepine = 26.3%; valproic acid = 27.1%; oxcarbazepine = 13.6%; topiramate = 12.1%; lamotrigine = 13.0%; levetiracetam = 14.2%; clonazepam = 6.1%; gabapentin = 1.9%; phenytoin = 3.3%; zonisamide = 4.6%; ethosuximide = 1.3%; felbamate = 2.3%; lorazepam = 4.2%; lacosamide = 4.3%; other = 4.3%.

3.2 MCID

SEMs, which represent the MCID for each scale for the entire sample, ranged from 3.25 -9.58 units (Table 2). SEMs were also calculated for patients with new-onset (<12 months) epilepsy on monotherapy, new-onset epilepsy on polytherapy, chronic epilepsy on monotherapy (>12 months), and chronic epilepsy on polytherapy.

4. Discussion

4.1

AED therapy is the most effective intervention to control seizures in pediatric epilepsy but can be associated with a range of side effects. The PESQ allows for the systematic assessment of AED side effects at the point of clinical care and can guide clinical decision making.

The current study extends the clinical utility of the PESQ by providing information about the MCID, the minimal amount of change that is perceived as meaningful by a patient/caregiver. In turn, MCIDs can help clinicians determine whether the AED should be adjusted or other remediating interventions introduced (e.g., behavior management training, school accommodations) to reduce the impact of side effects on patients' quality of life. Consistent clinical assessment of side effects is an essential aspect of pediatric epilepsy treatment in light of data that identifies side effects as a more powerful predictor of quality of life in patients with epilepsy than seizure control [2].

MCIDs were calculated for an overall score, by subscales, and in different patient subgroups (e.g., new onset monotherapy/polytherapy; chronic monotherapy/polytherapy) to increase the measure's utility in clinical and research applications. Overall, the MCID for the Total PESQ Score was 3.25, indicating that this level of change is perceived as meaningful to patients/caregivers; however, there was variability in MCIDs across the PESQ subscales. Specifically, families perceive even a 4.7 point change in the cognitive scale as meaningful whereas changes have to exceed 9.5 points for weight to be perceived as important by patients. Clinically, this may mean that children and families are more tolerant of weight gain but may be less tolerant of an AED if it results in cognitive side effects. In cases of reported change, a variety of interventions to mitigate the side effect could be initiated, including medication changes, adjunctive therapy (e.g., Vitamin B-6), cognitive or cognitive-behavioral therapies, and provision of school-based accommodations.

When examining MCID scores by different patient subgroups (e.g., those on mono versus polytherapy, new-onset versus chronic), there was some variability in MCIDs by PESQ

subscale. After the first year of treatment, MCIDs are generally smaller for patients on monotherapy compared to those on polytherapy. There was much more variability in the range and intensity of side effects reported for children on polytherapy, resulting in a larger MCID for that subgroup. This finding likely reflects that each AED is associated with its own side effects, and that the interactions between AEDs may introduce additional risks. Given the variability, families with children on polytherapy need to endorse a greater magnitude of change in order for those changes to exceed the MCIDs. In practice, this means that children on monotherapy after the first year of treatment may perceive smaller changes in side effects as clinically meaningful and requiring intervention (e.g., adjusting dose or medicine, behavioral or school-based interventions to manage side effects) as compared to children on polytherapy who may be more tolerant of changes in the side effect profile. If the MCIDs are being used in a mixed sample of new-onset and chronic patients, it would make sense to use the MCIDs derived across the overall sample.

4.2

The primary limitation of the current study was the use of only one approach to calculating MCIDs. The distribution based-method could vary from anchor-based methods. Additionally, the sample size of newly-diagnosed children on polytherapy was small (N=13), as would be expected, and so MCIDs calculated for that subgroup should be interpreted with caution. Finally, understanding the cost-benefit ratio of seizure control compared to side effect burden is an important next step and is likely to be variable based on disease characteristics.

4.3

Overall, the PESQ is a reliable and valid measure that now has established MCIDs that can be used in clinical practice and research to assess for clinically meaningful changes in reported side effects. In the future, MCIDs can also be used to identify predictors of clinically meaningful change in side effects and evaluate the effectiveness of intervention strategies (e.g., using vitamin B6 to address mood changes on levetiracetam)[9]. Furthermore, research could study whether clinically meaningful changes in side effects correspond to other significant treatment indices (e.g., quality of life, seizure control, adherence).

Acknowledgement

Sources of funding and support: This research was funded by a grant from the National Institutes of Health (NIH) awarded to the first author (K23HD057333: *Novel Adherence Measurement and Intervention in Children with New-Onset Epilepsy)*.

Role of the Sponsors: The study sponsors had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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Table 1

Demographic and disease characteristics by subpopulations

	New-Onset Monotherapy (N=163)	New-Onset Polytherapy (N=13)	Chronic Monotherapy (N=318)	Chronic Polytherapy (N=189)
Female Sex	42.3%	46.2%	40.6%	48.7%
Child Age (years; M(SD))	8.38 (3.97)	8.83 (4.62)	10.67 (4.75)	12.77 (5.35)
Child race				
White	46.0%	46.2%	21.4%	48.1%
African American	8.0%	69.2%	5.3%	5.3%
Asian	0.6%	0.0%	0.3%	2.1%
American Indian	0.0%	0.0%	0.0%	0.5%
Other	0.6%	0.0%	0.9%	1.1%
Bi-racial	3.6%	0.0%	0.0%	0.5%
Missing	41.1%	30.8%	72.0%	42.3%
Child Ethnicity				
Hispanic	1.8%	69.2%	0.3%	1.6%
Non-Hispanic	56.4%	0.0%	27.7%	56.1%
Missing	58.3%	30.8%	28.0%	42.3%
Seizure Type				
Focal	58.3%	61.5%	67.9%	59.8%
Generalized	29.4%	30.8%	25.8%	25.9%
Both	0.0%	0.0%	1.3%	4.2%
Unclassified	12.3%	7.7%	4.4%	9.5%
Time since seizure onset (years; M(SD))	0.42 (.24)	0.48 (.25)	10.67 (4.75)	7.82 (5.19)
Number of AEDs M(SD)	1 (0)	2.3 (.63)	1 (0)	2.35 (.62)
AED initiated or changed in past month	26.4%	15.4%	5.0%	4.2%

Table 2

PESQ: Means (SD), Reliability Coefficients and MCID for Total Sample and by subgroup

Total Sample (n=682)						
PESQ Scales	**Mean(SD)**	**Alpha**	**MCID**			
Cognitive	13.32 (20.8)	0.95	4.66			
Motor	8.01 (15.6)	0.91	4.67			
Behavioral	14.11 (21.51)	0.86	8.05			
General Neurological	13.92 (17.5)	0.82	7.41			
Weight	12.48 (21.98)	0.81	9.58			
Total Side Effects	12.36 (14.5)	0.95	3.25			
	New Onset (< 12 months) Monotherapy (n=163)			**New Onset (< 12 months) Polytherapy (n=13)**		
PESQ Scales	**Mean(SD)**	**Alpha**	**MCID**	**Mean(SD)**	**Alpha**	**MCID**
Cognitive	9.03 (17.2)	0.93	4.55	17.18(29.2)	0.98	4.14
Motor	4.17 (9.1)	0.83	3.76	13.45 (19.1)	0.73	9.91
Behavioral	12.68 (19.7)	0.81	8.57	24.61 (32.6)	0.98	4.61
General Neurological	13.31 (15.7)	0.71	8.45	13.08 (11.8)	0.72	6.25
Weight	13.19 (22.4)	0.76	10.99	27.69 (30.6)	0.67	17.57
Total Side Effects	9.93 (11.4)	0.91	3.43	17.81 (19.5)	0.92	5.52
	Chronic (>12 months) Monotherapy (n=318)			**Chronic (> 12 months) Polytherapy (n=188)**		
PESQ Scales	**Mean(SD)**	**Alpha**	**MCID**	**Mean(SD)**	**Alpha**	**MCID**
Cognitive	11.04 (19.2)	0.95	4.29	20.61 (23.8)	0.95	5.32
Motor	5.20 (10.9)	0.87	3.91	15.72 (22.3)	0.91	6.70
Behavioral	11.66 (19.7)	0.84	7.89	18.76 (24.1)	0.86	9.02
General Neurological	11.86 (16.4)	0.79	7.53	17.98 (20.1)	0.86	7.54
Weight	9.97 (19.1)	0.77	9.17	15.05 (24.7)	0.86	9.23
Total Side Effects	9.97 (12.6)	0.94	3.08	18.16 (17.6)	0.95	3.94