Epilepsy & Behavior xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Liverpool Adverse Events Profile: Italian validation and predictive value for dropout from antiepileptic treatment in people with epilepsy

Michele Romoli [a], Paolo Eusebi [a], Sabrina Siliquini [a], Chiara Bedetti [a], Paolo Calabresi [a,b], Cinzia Costa [a,*]

[a] Neurology Clinic, University Hospital of Perugia, Perugia, Italy
[b] IRCCS "Santa Lucia", Rome, Italy

ARTICLE INFO

Article history:
Received 3 December 2017
Revised 21 January 2018
Accepted 24 January 2018
Available online xxxx

Keywords:
Liverpool Adverse Events Profile
Epilepsy
Adverse events
Patient compliance

ABSTRACT

Introduction: Adverse events (AEs) of antiepileptic drugs (AEDs) affect patient compliance and dropout. No questionnaire measuring AEs of AEDs is available for Italian-speaking people with epilepsy. Moreover, no questionnaire has been shown to predict patient dropout.
Objective: The aim of this study was to provide a validated Italian version of the Liverpool Adverse Events Profile (iLAEP) and to define iLAEP reliability in AE monitoring and dropout risk prediction.
Methods: The original LAEP was translated and tested for internal consistency and reliability. Patients with epilepsy who are on stable AED regimen completed the questionnaire as well as a 3-month follow-up to assess dropouts.
Results: Overall, 204 patients with epilepsy were enrolled (mean age: 47.1 ± 21.5). High internal consistency (Cronbach's $\alpha = 0.88$) was demonstrated, and very quick completion time was registered (mean = 9 min). A 3-month follow-up was performed to assess treatment discontinuation and potential predictive value of the iLAEP score. Treatment was discontinued in 33.3% of the cohort. Moreover, iLAEP scores (mean = 30.71) significantly differed between patients interrupting (39.15 ± 5.66) and those prosecuting treatment (29.4 ± 6.54, $p < .001$). A cutoff of 36.5 had an 85% accuracy in predicting treatment discontinuation (85% sensitivity, 79% specificity). Scores >36.5 were associated with a 20.27-fold increase in dropout relative risk (RR), with a 66% positive predictive value.
Conclusions: The iLAEP represents a reliable, quick, and inexpensive assessment tool for patient-reported AEs of AEDs. An iLAEP cutoff of 36.5 differentiates patients unlikely to interrupt treatment from those more prone to stop AEDs in the following 3 months. The iLAEP might help clinicians in weighting the risk of dropout and better tailor treatment to patients.

1. Introduction

Epilepsy is a common neurological disorder, with a prevalence of 0.8% in the general population [1] and a detrimental impact on quality of life [2,3]. Despite being paramount for seizure control, antiepileptic drugs (AEDs) are associated with adverse events (AEs) in up to 80% of patients [4]. In particular, AEs of AEDs may be more disabling than epilepsy itself and negatively impact on patients' quality of life and treatment compliance [5,6]. The Liverpool Adverse Events Profile (LAEP) was developed to detect AEs of AEDs [7–9]. The LAEP is a standardized, quick, and reliable instrument of AE patient-reporting and allows clinicians to measure the side effects of a medication and quantify patient distress [7–9]. Validated versions of LAEP exist in several languages [10–12], but no Italian version is available to date. The aim of this study was to validate the LAEP in the Italian language (iLAEP) to provide a reliable tool for AE assessment. Moreover, since AEs are known to limit patients' compliance [4], we assessed the predictive value of LAEP scores for dropouts, which might help clinicians in AED management.

2. Material and methods

The iLAEP was developed following a standard procedure including translation, cultural adaptation, and testing for content validity, concurrent validity, construct validity, and internal consistency. The LAEP was specifically designed for AE reporting in persons with epilepsy [9]. The original scale has 19 items measuring the prevalence and severity of AEs in the previous 4 weeks. Both physical and psychological disturbances are listed in the LAEP. Patients rate each item on a 4-point Likert scale (1 = never a problem; 2 = rarely a problem; 3 = sometimes a problem; 4 = always a problem). The overall score, ranging from 19 to 76, directly relates to the prevalence and severity of adverse effects [9].

* Corresponding author at: University Hospital of Perugia, Sant'Andrea delle Fratte, Perugia 06132, Italy.
E-mail address: cinzia.costa@unipg.it (C. Costa).

https://doi.org/10.1016/j.yebeh.2018.01.028
1525-5050/

2.1. Translation

Translation and cultural adaptation of the LAEP into the Italian version (iLAEP) were performed as follows. The scale was translated from English to Italian by the authors. Two language experts, unaware of the original LAEP version, backtranslated the scale into English and compared it to the original one to assess consistency. No significant differences were found between the versions. After that, 20 patients with epilepsy were asked to fill the iLAEP for relevance, representativeness, and comprehension of its language. All questions were well-accepted, and patients found no issue in answering them appropriately. Content and relevance of the scale were rechecked by the authors at the end of the translation process.

2.2. Adaptation

The original version of the LAEP scale contains "any other problem" as the last item. During the pilot trial, we noticed 6 recurrent AEs reported in this last item box. Considering the intrinsic shortcomings of patient self-compiled questionnaires, we welcomed the opportunity to provide more specific items to help patients in self-reporting. Thus, as reported for LAEP validation in other languages [11], to ease AE assessment, we added the following items: paresthesia, hematological abnormalities, sexual disorders, kidney stones, weight loss, and language disorders. Overall, iLAEP encompassed 25 items, each to be rated on a 4-point scale, with overall scores ranging from 25 to 100, directly increasing with severity and prevalence of AEs.

2.3. Data collection

After pilot testing, the iLAEP was administered to 204 persons with epilepsy during a standard follow-up visit at the Epilepsy Center of the Neurology Clinic of Perugia (Italy). Informed consent was obtained for all patients; the study was carried out in accordance with the Declaration of Helsinki. The entire cohort has already been reported for AE prevalence comparison between migraineurs and patients with epilepsy taking valproate (VPA), topiramate (TPM), and lamotrigine (LTG) [13]. For the purpose of this study, all patients with epilepsy were taken into consideration (n = 204) to validate the iLAEP. Briefly, we enrolled patients with (i) an established diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria [14]; (ii) at least 6 weeks of AED monotherapy; (iii) an age > 18 years; and (iv) a Mini Mental State Examination (MMSE) score > 24. Demographic, clinical, and pharmacological data were collected, and dropouts were verified within the following 3 months. The study was approved by the Internal Advisory Board and was conducted according to the ethical standards of the Declaration of Helsinki. All subjects gave informed consent; none dropped from the study or withdrew consent after compiling LAEP. Patients compiled LAEP unassisted, and then two neurologists (CC, SS) ensured accurate completion of all items.

2.4. Data analysis

Statistical analysis was performed with R software using stats and psych packages. Descriptive statistics are presented for continuous variables as means, standard deviations, medians, and interquartile ranges. Categorical variables are presented as counts and percentages. Chi-square and Student's t tests were used for univariate inference as appropriate. Construct validity was assessed by estimating the association between iLAEP and dropout probability. The instrument's internal consistency reliability was assessed by estimating Cronbach's α coefficient and item–test correlations. The 2-week test–retest reliability was assessed repeating iLAEP scale in a smaller sample of 20 patients. Significance level was set to be 0.05.

3. Results

All recruited patients (n = 204) completed the LAEP questionnaire. Demographic, clinical, and pharmacological characteristics of the studied cohort are reported in Table 1. Patients were relatively young (mean age: 47.1, SD = 21.5; 58.3% women). Epilepsy diagnosis dated back to a mean of 17.3 months from LAEP completion, while iLAEP scale was administered 13.1 ± 6.1 weeks after starting AED. All reported AEs referred to the previous 4 weeks of treatment; no AED modification in AED regimen was performed. Genetic and structural etiology accounted for 8.8% and 29.4% of the cohort, respectively, with unknown etiology highly prevailing (61.8%). Regarding seizure type, focal seizures were more common (44.6%) than generalized (32.4%) and focal to bilateral seizures (22.5%). Antiepileptic drug treatment duration mirrored disease duration. Prescription for AEDs resembled the specific population selected [13], with VPA, LTG, and TPM used as monotherapy in the cohort in 40.7%, 32.4%, and 27% of patients, respectively. Overall, 33.3% of patients (68/204) interrupted treatment, while 66.67% (136/204) continued AED therapy (Table 1).

The iLAEP scale demonstrated good internal consistency (Cronbach's α = 0.88), and 2-week test–retest, performed in a subpopulation of 20 patients, showed identical overall and single-item scores. Total scores, theoretically ranging from 25 to 100, were confined in this study in a finer range (25–50), with a mean of 30.71 ± 7.2 (Table 2). The iLAEP scores <26, corresponding to the lack of AEs, were reported in 54.9% of the population, while scores ≥45 were reported by only 9.9% of the cohort. Overall iLAEP scores significantly differed between patients with dropouts and those prosecuting treatment (39.15 ± 5.66 versus 29.48 ± 6.54, p < .001). Indeed, iLAEP scores showed a predictive value on future dropouts. A cutoff iLAEP overall score of 36.5 demonstrated an 85% sensitivity, 79% specificity, and 85% accuracy (CI: 0.79–0.91) in predicting treatment interruption in the following 3 months (Table 2). Scores <36.5 had a negative predictive value of 91% on future dropouts. Moreover, iLAEP scores >36.5 had a positive predictive value of 66% on future dropouts, with a 20-fold increase in the risk of AED discontinuation (relative risk (RR): 20.27). Among all iLAEP items, sleepiness and tiredness were the most frequently reported AEs (in 34%, and 37% of patients, respectively) as well as the most severe (Likert score = 4 in 5% and 7% of patients, respectively) (Fig. 1, Supporting information). Multivariate analysis demonstrated the correlation between some AEs and future dropout risk. In particular, tiredness, sleepiness, and disturbed sleep proved again to be highly

Table 1
Demographic and clinical data of the cohort (n = 204).

Age (mean ± SD)	47.1 ± 21.5
Sex	
M	85 (41.7%)
F	119 (58.3%)
Epilepsy	
GE	18 (8.8%)
SE	60 (29.4%)
UE	126 (61.8%)
Epilepsy (seizure type)	
Generalized	66 (32.4%)
Focal	91 (44.6%)
Focal to bilateral	46 (22.5%)
Undetermined	1 (0.5%)
AED prescription	
LTG	66 (32.4%)
TPM	55 (27.0%)
VPA	83 (40.7%)
Disease duration (weeks)	17.3 ± 3.1
AED duration (weeks)	13.1 ± 6.1
Dropouts	
Yes	68 (33.33%)
No	136 (66.67%)

AED: antiepileptic drug; GE: genetic epilepsy; SE: structural epilepsy; UE: unknown epilepsy.

Please cite this article as: Romoli M, et al, Liverpool Adverse Events Profile: Italian validation and predictive value for dropout from antiepileptic treatment in people with epilepsy, Epilepsy Behav (2018), https://doi.org/10.1016/j.yebeh.2018.01.028