Epilepsy & Behavior 22 (2011) 511–517

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Are adverse effects of antiepileptic drugs different in symptomatic partial and idiopathic generalized epilepsies? The Portuguese–Brazilian validation of the Liverpool Adverse Events Profile

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ARTICLE INFO

Article history:
Received 4 July 2011
Accepted 3 August 2011
Available online 9 September 2011

Keywords:
Liverpool Adverse Events Profile
Antiepileptic drugs
Epilepsy
Adverse effects
Symptomatic partial epilepsy
Idiopathic generalized epilepsy
Validation

ABSTRACT

We report the results of administration of the Portuguese–Brazilian translation of the Liverpool Adverse Events Profile (LAEP) to 100 patients (mean age = 34.5, SD = 12.12; 56 females), 61 with symptomatic partial epilepsy (SPE) and 39 with idiopathic generalized epilepsy (IGE) (ILAE, 1989) who were on a stable antiepileptic drug (AED) regimen and being treated in a Brazilian tertiary epilepsy center. Carbamazepine was the most commonly used AED (43.0%), followed by valproic acid (32.0%). Two or more AEDs were used by 69.0% of patients. The mean LAEP score (19 questions) was 37.6 (SD = 13.35). The most common adverse effects were sleepiness (35.0%), memory problems (35.0%), and difficulty in concentrating (25.0%). Higher LAEP scores were associated with polytherapy with three or more AEDs ($P = 0.005$), female gender ($P < 0.001$), older age ($P < 0.001$), and uncontrolled seizures ($P = 0.045$). The intraclass coefficient (test–retest reliability) for LAEP overall score was 0.848 (95% CI = 0.782–0.895), with a range from 0.370 (unsteadiness) to 0.750 (memory problems). Cronbach's α coefficient (internal consistency) was 0.903. The LAEP was highly correlated with Quality of Life in Epilepsy-31 inventory ($r = -0.804$, $P > 0.001$) and Hospital Anxiety and Depression Scale (Depression: $r = 0.637$, $P < 0.001$; Anxiety: $r = 0.621$, $P < 0.001$) dimensions. LAEP overall scores were similar in people with SPE and IGE and were not helpful in differentiating adverse effects in these two groups. Clinical variables that influenced global LAEP were seizure frequency ($P = 0.050$) and generalized tonic–clonic seizures in the last month ($P = 0.031$) in the IGE group, and polytherapy with three or more AEDs ($P = 0.003$ and $P = 0.003$) in both IGE and SPE groups.

1. Introduction

The use of antiepileptic drugs (AEDs) is frequently associated with adverse effects (AEs) such as idiosyncratic reactions, dose-related neurocognitive effects, and complications of long-term use. Data obtained from cross-sectional studies and randomized controlled trials indicate that up to 80% of people with epilepsy taking AEDs experience an AE [1–3].

The detection and minimization of AEs associated with treatment are very important aspects of epilepsy care [1]. Previous studies have suggested that direct questioning yields higher rates of AEs in patients taking AEDs compared with spontaneous reports [4]. Clinical experience suggests that AEs may be more disabling to the patient than the seizures themselves [5], and this fact contributes to initial treatment failure in up to 40% of the cases, reducing patient compliance [6]. Evidence indicates that AEs negatively impact quality of life (QOL), particularly cognitive and neurological impairment [1]. Interest in the effects of epilepsy on health-related QOL has led to the development of epilepsy-specific QOL instruments, which may be helpful in discriminating between patients treated with different AEDs [7].

The Liverpool Adverse Events Profile (LAEP) was developed in the 1990s by the Liverpool group to evaluate the most common negative AEs reported by patients taking AEDs [8–10]. It is used to quantify patients' perceptions of AEs. The ability of the LAEP to detect and quantify the presence and severity of AEs associated with different AEDs was demonstrated in a large European study that included more than 5000 patients [11]. The LAEP is a relatively simple instrument with strong psychometric properties and can be used for investigational purposes, as well as in daily clinical practice [12]. The LAEP has been validated in Spanish [13] and Chinese [14], but has not yet been validated in Portuguese.

The availability of a questionnaire in different languages is particularly useful for multicenter studies, which require instruments that have been translated and validated with respect to the cultural particulars of the country where they will be used [15]. Comparison of

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1525-5050
doi:10.1016/j.yebeh.2011.08.005

AEs in different epilepsies such as partial and generalized as well as symptomatic and idiopathic forms is important to better characterize the treatment influence on prognosis of such distinct entities. In this study we report the translation and validation of the LAEP in a Portuguese–Brazilian version and the evaluation of its reliability, validity, and ability to differentiate AEs of AEDs in symptomatic partial (SPE) and idiopathic generalized (IGE) epilepsy.

2. Methods

2.1. Translation of the Liverpool Adverse Events Profile

After permission was obtained from the Liverpool group (G. Baker) to translate the original version of the LAEP in April 2010, the process of adaptation to the Portuguese–Brazilian language was initiated and included the following phases: (1) translation into Portuguese by a qualified bilingual translator; (2) backtranslation into English by two independent translators native in the target language; (3) assessment of item comprehension by a multidisciplinary committee review; and (4) pretest of the final version to check for equivalence with the source version following international patterns [16].

This version was administered to a group of consecutive outpatients in the Epilepsy Section of Hospital São Paulo, a tertiary care center of the Universidade Federal de São Paulo, Brazil, with the aim of testing and assessing the adequacy and comprehension of the language used in the translated version. Patients older than 18 with a confirmed diagnosis of epilepsy were included in the study if they were taking AEDs at a stable dose for at least 1 month and if they were able to understand and answer the questions by themselves. Patients with concomitant degenerative or chronic diseases and those with symptomatic epilepsy caused by progressive diseases were excluded. The subjects were recruited after ethics committee approval and gave their written informed consent for the study.

The pretest with the final version was administered to 30 outpatients with epilepsy [17]. For each question, pertinence and comprehensibility were checked.

2.2. Instrument evaluation

The LAEP [4,10,18] is a self-administered, epilepsy-specific, 19-item questionnaire using a scale of 1 to 4, with 4 indicating the most frequent occurrences. Scores ranging from 19 to 76 may be calculated to measure the total AE burden of a medication regimen [4]. The main psychometric properties are considered appropriate if the internal consistency of 0.95 and test–retest reliability of 0.85 are matched [10]. To facilitate the analysis we transformed the range scale 1–4 into 0–100.

2.3. Measures used to assess construct validity

The Hospital Anxiety and Depression Scale (HADS) is a self-report measure of anxiety and depression symptoms developed for use in a hospital outpatient setting [19]. It consists of 14 items rated on a 4-point scale with variable labels. Two subscales of seven items separately measure anxiety and depression symptoms. Total subscale scores range from 0 to 21, with higher scores representing higher levels of anxiety or depression. The scale developers advise that scores of 11 to 21 indicate a possible clinical diagnosis of anxiety or depression, scores of 8 to 10 are considered borderline, and scores from 0 to 7 are considered to indicate noncases [20]. In this study we used the validated Portuguese–Brazilian version of the HADS [21].

Quality of life was measured with the Portuguese–Brazilian version of the disease-specific questionnaire Quality of Life in Epilepsy-31 (QOLIE-31) [22]. It includes 30 items organized into seven subscales—Seizure Worry (5 items), Emotional Well-Being (5 items), Energy/Fatigue (4 items), Social Functioning (5 items), Cognitive Functioning (6 items), Medication Effects (3 items), Overall Quality of Life (2 items)—and an additional item assessing overall health status. The raw scores are rescaled from 0 to 100, with higher values reflecting better QOL [23].

2.4. Data collection

The questionnaire was administered in a face-to-face interview to 100 patients to check the comprehensibility of the measures. The subjects were separated into two groups according to their epilepsy: group 1 comprised patients diagnosed with SPE, and group 2, patients with IGE, based on International League Against Epilepsy classification [24].

Epileptologists documented demographic data, medical history, and clinical characteristics. A pharmacist (H.H.M.) asked the subjects to complete the LAEP, QOLIE-31, and HADS.

2.5. Evaluation of psychometric properties

2.5.1. Reliability

Assessment of reliability involved two steps. First, internal consistency reliability was assessed with Cronbach's α coefficient; the correlation between each item and the global LAEP questionnaire was calculated. Values >0.700 are conventionally considered acceptable [25]. Second, test–retest reliability was determined with the intraclass correlation coefficient (ICC) between the LAEP completed at the initial visit and that completed 2–3 weeks later by the same subject; values >0.600 were considered statistically significant. The medication type and dose were the same as in the initial visit, to maintain the stability of the clinical characteristics that may influence reproducibility.

2.5.2. Validity

Construct validity hypotheses were assessed as the relationships between LAEP score ranges and specific instruments (QOLIE-31 domains and HADS general score) or other external measures (e.g., demographic and clinical variables). We expected to show significant correlations between scales with similar or interdependent content. The LAEP was expected to be sensitive to sociodemographic and clinical characteristics. Pearson's correlation was used to analyze the association of LAEP with QOLIE-31 and HADS.

Assessment of demographic and clinical characteristics consisted of analysis of SPE and IGE groups separately. Variables such as educational level, employment status, epilepsy group, seizure frequency, duration of epilepsy, and treatment were chosen to evaluate construct validity under the hypothesis that they were significantly related to LAEP items. Seizure frequency for SPE was divided into: controlled seizures, 1 or 2, 3 or 4, and ≥5 partial seizures per month. The criteria for classification of seizure control in the IGE group were as follows: controlled seizures; generalized tonic–clonic seizures (GTCS), good (1/year), moderate (1–4/year), or poor (4/year); myoclonic, good (5 single seizures or clusters/month, rare or occasional seizures), moderate (6–14 single seizures or clusters/month, several or frequent seizures) or poor (15 single seizures or clusters/month or daily seizures); and absence, good (5/month, rare or occasional seizures), moderate (6–14/month, several or frequent seizures), or poor (15/month, frequent or daily seizures) [26]. The hypothesis was that higher seizure frequency corresponded to worse QOL and higher LAEP scores.

A cutoff point of 45 on the LAEP was considered "toxicity," as suggested in previous studies [4], to compare the eventual differences in QOL and clinical characteristics reported in the two groups. To analyze the relationship between medication and AE frequency we divided the daily AED doses into the following ranges (lower and higher): carbamazepine (CBZ) ≤800 mg or >800 mg, valproic acid (VPA) <1000 mg or ≥1000 mg, phenobarbital (PB) ≤100 mg or >100 mg, clobazam (CLB) ≤10 mg or >10 mg, lamotrigine (LTG) ≤100 mg or >100 mg, and topiramate (TPM) ≤100 mg or >100 mg. Analysis of variance, Student´s *t* test for independent samples, Fisher´s

Table 1
Etiology, localization, and syndromic classification of the epilepsy groups.

Epilepsy group	*n*
1. Symptomatic partial epilepsy	61
Mesial temporal sclerosis	47 (77.0%)
Neocortical (frontal 4, temporal 1, frontotemporal 1, parietal 4)	10 (16.4%)
Mesial temporal sclerosis + neocortical (frontal 2, occipital 1, multiple 1)	4 (6.6%)
2. Idiopathic generalized epilepsy	39
Juvenile myoclonic epilepsy	29 (74.3%)
Juvenile absence epilepsy	9 (23.1%)
Nonclassified	1 (2.6%)

exact test, and the Mann–Whitney test were used. *P* values less than 0.050 were considered statistically significant [27].

3. Results

3.1. Cultural adaptation

The final Portuguese–Brazilian version of the LAEP was completed by 100 subjects. The translation was adapted and complementary information was needed for some items to clarify their meaning. For example, the item "Unsteadiness" was amended to read "Unsteadiness of the Body." The item "Restlessness" was changed to "Agitation." The item "Feelings of Aggression" required modification in the sequence of the questionnaire, because this term represents more than "Nervousness," and it was replaced after this item, to clarify its meaning. Details are provided in the Supplementary Material (see Appendix).

3.2. Demographic and clinical characteristics

The mean age of the 100 patients was 34.5 years (SD = 12.12); 61 (61.0%) subjects had SPE and 39 (39.0%) IGE (Table 1). As half of the patients had difficult-to-treat epilepsies such as mesial temporal sclerosis and long-duration juvenile myoclonic epilepsy (JME), two or more AEDs were used by 69 (69.0%) patients. CBZ was the most common treatment and was used by 43.0% of the sample, followed by VPA (32.0%), PB (27.0%), CLB (27.0%), LTG (17.0%), and TPM (15.0%). The sociodemographic and clinical characteristics of the two epilepsies are detailed in Table 2.

Twenty-five patients (64.1%) from the IGE group had experienced seizures in the month preceding the study; 8 (20.5%) had good, 4 (10.4%) moderate, and 13 (33.3%) poor control of their seizures. As for seizure type, 16 (41.0%) had absences, 12 (30.8%) myoclonic seizures, and 11 (28.2%) GTCS in the preceding month. Thirty-seven patients (60.7%) in the SPE group had had complex partial seizures in the month preceding the study at the following monthly seizure frequencies: 1 or 2 in 10 (16.4%), 3 or 4 in 20 (32.8%), and >5 in 7 (11.5%).

Table 2
Sociodemographic and clinical characteristics of 100 patients.

Characteristic	Epilepsy type		*P* value	LAEP overall score		*P* value
	SPE (*n* = 61)	IGE (*n* = 39)		<45 (*n* = 69)	≥45 (*n* = 31)	
Gender						
Male	44.3% (27)	43.6% (17)	1.000	56.5% (39)	**16.1% (5)**	**<0.001**
Female	55.7% (34)	56.4% (22)		43.5% (30)	**83.9% (26)**	
Age						
Mean (SD)	37.5 (11.52)	**29.7 (11.60)**	**0.001**	**32.9 (12.59)**	**38.0 (10.36)**	**0.050**
16–34.5	44.3% (27)	**74.4% (29**	**0.004**	65.2% (45)	35.5% (11)	**<0.001**
34.5–70	55.7% (34)	25.6%(10)		34.8% (24)	**64.5% (20)**	
Marital status						
Single	50.8% (31)	71.8% (28)	0.124	62.3% (43)	51.6% (16)	0.261
Married	41.0% (25)	23.1% (9)		29.0% (20)	45.2% (14)	
Other	8.2% (5)	5.1% (2)		8.6% (6)	3.2% (1)	
Educational level						
Elementary school	29.5% (18)	15.4% (6)	0.208	21.8%(15)	29.0%(9)	0.596
High school	52.5% (32)	69.2% (27)		62.3% (43)	51.6% (16)	
University	18.0% (11)	15.4% (6)		15.9% (11)	19.4% (6)	
Employment status						
Employed	44.3% (27)	59.0% (23)	**<0.001**	56.6%(39)	35.5%(11)	0.217
Unemployed	24.6% (15)	7.7% (3)		15.9% (11)	22.6% (7)	
Students/housewives/never worked	3.3% (2)	**25.6% (10)**		11.6% (8)	12.9% (4)	
Retired or with ill-health benefits	27.9% (17)	**7.7% (3)**		15.9% (11)	29.0% (9)	
Epilepsy duration, mean (SD)	20.9 (11.76)	18.4 (13.15)	0.325	19.4 (12.21)	21.2 (12.65)	0.516
Seizure frequency						
Seizure free	39.3% (24)	35.9% (14)	0.834	44.9% (31)	**22.6% (7)**	**0.045**
Uncontrolled seizures	60.7% (37)	64.1% (25)		55.1% (38)	77.4% (24)	
Treatment duration, mean (SD)	19.3 (11.14)	17.5 (13.53)	0.475	18.0 (11.85)	19.9 (12.72)	0.473
AED						
Carbamazepine	**63.9% (39)**	**10.3% (4)**	**<0.001**	37.7% (26)	54.8% (17)	0.129
Valproic acid	**4.9% (3)**	**74.4 % (29)**	**<0.001**	33.3% (23)	29.0% (9)	0.817
Phenobarbital	29.5% (18)	23.1% (9)	0.645	24.6% (17)	32.3% (10)	0.470
Lamotrigine	13.1% (8)	23.1 % (9)	0.275	13.0% (9)	25.8% (8)	0.151
Topiramate	11.5 % (7)	20.5% (8)	0.257	10.1% (7)	25.8% (8)	0.067
Phenytoin	**16.4% (9)**	**0.0% (0)**	**0.006**	13.0% (9)	3.2% (1)	0.167
Clobazam	**42.6% (26)**	**2.6% (1)**	**<0.001**	26.1% (18)	29.0% (9)	0.810
Other[a]	27.9% (17)	20.5% (8)	0.482	21.7% (15)	32.3% (10)	0.320
Number of AEDs						
1	12.9% (11)	**46.2% (18)**	**0.012**	36.2% (25)	**12.9% (4)**	**0.005**
2	45.2% (34)	35.9% (14)		49.3% (34)	45.2% (14)	
≥3	26.2% (16)	18.0% (7)		14.4%(10)	**41.9%(13)**	

Note. Statistically significant values are in boldface. P values determined with Student's *t* test or Fisher's test. IGE, idiopathic generalized epilepsy; SPE, symptomatic partial epilepsy.
[a] Ethosuximide, clonazepam, diazepam, oxcarbazepine.

In this study, LAEP Overall mean score was 37.6 (SD = 13.35), and the most common AEs reported as occurring "frequently" were Somnolence (35.0%), Memory Problems (35.0%), and Difficulty in Concentrating (25.0%). Comparison between LAEP scores <45 or ≥45 and QOLIE-31 domain scores showed association of more AEs with worse QOLIE-31 and HADS ($P<0.001$) scores.

Correlations of LAEP scores with sociodemographic characteristics were studied using a cutoff point of 45 (<45 and ≥45) (Table 2). The questionnaire correlated well with the number of AEDs taken. Patients who used polytherapy (two or more drugs) experienced more AEs than those in monotherapy ($P = 0.018$). In the group of patients with LAEP scores >45 there were more women (26: 17 with SPE and 13 of these receiving CBZ) than men (5: 4 with SPE using CBZ) ($P<0.001$). As compared with younger age (16–34.5 years), older age (34.5–70 years) was associated with the presence of AEs ($P<0.001$). Higher seizure frequency was associated with LAEP scores ≥45 ($P = 0.045$). Level of education, employment status, duration of epilepsy, and epilepsy group did not affect LAEP results.

3.3. Internal consistency and reliability

Internal consistency of the overall score as measured with Cronbach's α coefficient was 0.903 (95% CI: 0.872–0.928). Test–retest reliability of the Portuguese–Brazilian version of the LAEP as determined with the ICC was 0.848 (95% CI: 0.782–0.895), ranging from 0.370 (Unsteadiness) to 0.750 (Memory Problems), as demonstrated in Table 3.

3.4. Construct validity

A strong negative correlation of LAEP Overall score with QOLIE-31 was observed ($r = -0.804$, $P<0.001$), ranging from $r = -0.491$, $P<0.001$ for the QOLIE-31 scale Overall Quality of Life to $r = -0.752$, $P<0.001$ for Cognitive Function. There was a strong positive correlation between LAEP scores and the two HADS dimensions Depression ($r = 0.637$, $P<0.001$) and Anxiety ($r = 0.621$, $P<0.001$) (Figs. 1 and 2).

3.5. Comparison between epilepsy types

Patients with SPE obtained higher mean (SD) scores on the LAEP items Sleepiness, 60.1 (41.19), and Memory Problems, 56.3 (43.69); 63.9% (39) of the patients in this group were taking CBZ (mean daily dose = 1062 mg, SD = 358.8). In the IGE group higher scores on the LAEP items Sleepiness, 47.0 (42.38), and Memory Problems, 41.9 (43.07) were also observed; 74.4% (29) of these patients were taking VPA (mean daily dose = 964 mg, SD = 434) (Fig. 3).

Uncontrolled seizures influenced the increase in LAEP scores in both groups, especially in patients with IGE and poor seizure control ($P = 0.015$); in SPE there was a tendency in the subgroup with 3 or 4 seizures/month ($P = 0.07$).

Liverpool Adverse Event Profile total scores were similar for the two groups and no statistical significance was demonstrated (Fig. 3). Analysis of variance (ANOVA) revealed the clinical variables that influenced global LAEP: seizure frequency ($P = 0.050$) and GTCS (P = 0.031) in the IGE group, and polytherapy with three or more AEDs (P = 0.003) in both the IGE and SPE groups. The IGE group scored higher on the QOLIE-31 (mean = 69.2, SD = 18.38) and lower on the HADS Depression dimension (20.8, SD = 16.76) when compared with patients in the SPE group (59.6, SD = 19.44, $P = 0.016$, and 28.0, SD = 18.32, $P = 0.048$, respectively). The IGE group scored higher ($P = 0.022$) on the QOLIE-31 scale Medication Effects (65.5, SD = 31.33) than those with SPE (50.8, SD = 30.61).

3.6. Antiepileptic drug findings

Twenty-seven of 43 patients taking higher doses of CBZ (>800 mg/day) scored lower on the Nervousness and/or Agitation ($P = 0.006$), Hair Loss ($P = 0.045$), Difficulty in Concentrating (P = 0.003), Problems with Mouth and Gums (P = 0.001), and Depression (P = 0.042) items of the LAEP, as well as Overall score ($P = 0.025$).

Table 3
Reliability, score distribution, and LAEP item mean scores at visit 1 for 100 patients.

Reliability	
Internal consistency, Cronbach´s α	0.903
Mean (SD) [95% CI] (scale 19-76)	
Visit 1	37.6 (13.35) [34.9–40.2]
Visit 2	35.9 (13.29) [33.2–38.5]
Intraclass correlation coefficient	0.783
Score distribution	
Theoretical range	19–76
Observed range	19–67
Floor	7.0% (7)
Ceiling	0.0% (0)
LAEP item, visit 1, mean[a] (SD) [ICC]	
Unsteadiness	19.3 (31.13) **[0.370]**[b]
Tiredness	37.0 (40.17) [0.668]
Restlessness	36.7 (40.06) [0.668]
Nervousness and/or Agitation	43.3 (38.92) [0.560]
Feelings of Aggression	19.7 (33.87) [0.649]
Headache	38.7 (39.56) [0.586]
Hair Loss	29.0 (42.55) [0.621]
Problems with Skin, e.g., acne, rash	23.0 (38.10) [0.608]
Double or Blurred Vision	27.3 (37.72) [0.562]
Upset Stomach	33.7 (42.51) [0.717]
Difficulty in Concentrating	44.7 (40.82) [0.718]
Trouble with Mouth and Gums	13.3 (31.43) **[0.495]**[b]
Shaky Hands	38.3 (39.46) [0.651]
Weight Gain	16.3 (34.33) **[0.394]**[b]
Dizziness	33.7 (38.34) [0.737]
Sleepiness	55.0 (41.94) [0.718]
Depression	31.7 (39.46) [0.695]
Memory Problems	50.7 (43.80) [0.750]
Disturbed Sleep	27.3 (41.13) **[0.509]**[b]
Overall	**37.6 (13.35) [0.783]**

[a] Scores converted to a scale of 0 to 100.
[b] Indicates low reliability.

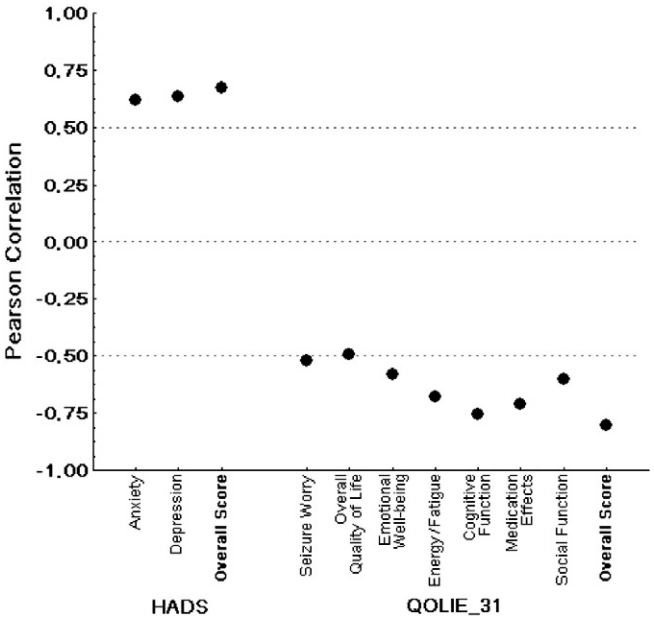


Fig. 1. Correlation of Liverpool Adverse Events Profile scores with Hospital Anxiety and Depression Scale (HADS) and Quality of Life in Epilepsy-31 inventory (QOLIE-31) scores.

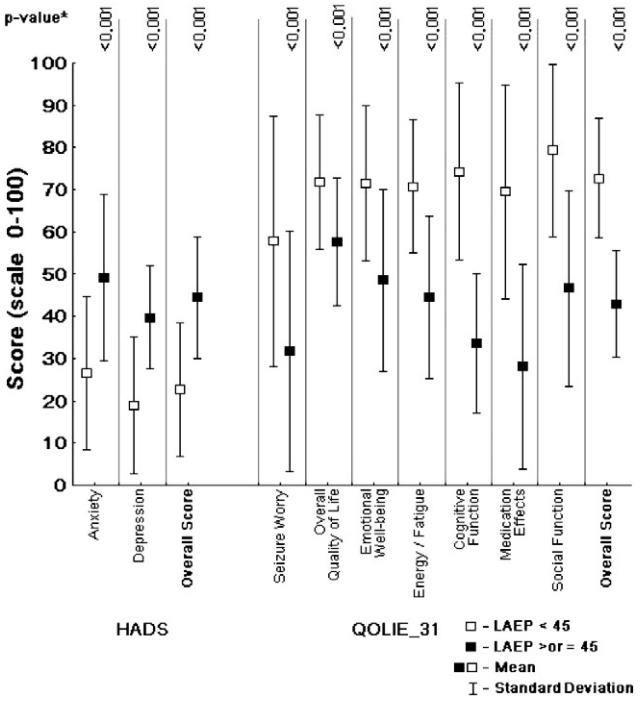


Fig. 2. Comparison of LAEP scores <45 or ≥45 with HADS and QOLIE-31 domain scores.

Seventeen of 32 patients taking VPA at higher doses (>1000 mg/day) had higher scores on the items Unsteadiness ($P=0.005$) and Feelings of Aggression ($P=0.037$). The only item that differed with respect to dose in 10 of 27 subjects taking PB (≤100 and >100 mg/day) was Weight Gain ($P=0.038$). Ten of 27 subjects taking CLB differed on the items Tiredness ($P=0.048$) and Headache ($P=0.044$) in different dose ranges (≤10 and >10 mg/day). There were no differences with respect to dose in those taking LTG and TPM. Range findings for the main AEDs are summarized in Table 4.

4. Discussion

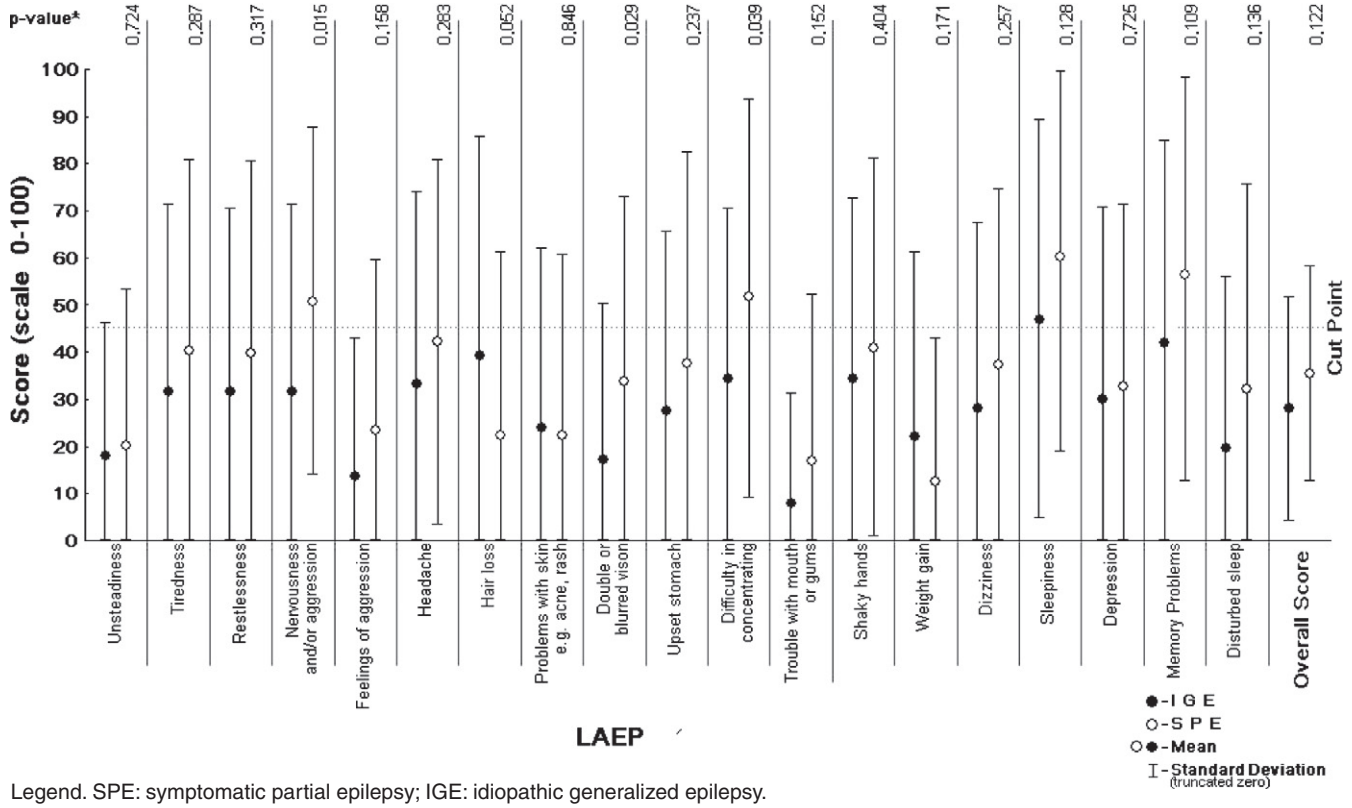
The Brazilian–Portuguese version of the LAEP was culturally validated in a sample of 100 outpatients with two different types of epilepsy (SPE/IGE), and the total score was found to be similar to those previously reported [13,14]. In this study 69% of patients had scores <45 in the first interview, demonstrating the low toxicity of AEDs in the majority of the sample.

4.1. Psychometric properties of the Liverpool Adverse Events Profile

This version of the LAEP demonstrated satisfactory psychometric properties. Internal consistency (Cronbach`s $\alpha=0.90$) was good on all items. This finding is similar to that reported for the original scale [10] as well as the Spanish [13] and Chinese [14] versions, as summarized in Table 5.

Test–retest reliability was satisfactory (ICC = 0.78), which supports the temporal stability of the instrument. The lower ICCs for the items Unsteadiness, Problems with Mouth and Gums, and Weight Gain can be explained by the lack of a physical examination, which may have led to underrepresentation of certain AEs, such as nystagmus, gait disturbances, tremor, hair loss, and weight changes [28]. This discrepancy was also observed in a large multicenter study of 509 patients in which at least 36% of AEs were not self-reported despite being found on physical and neurological examination [29].

Most of the construct validity hypotheses were reached, and all QOLIE-31 domains were strongly correlated with the LAEP items. In this group higher LAEP scores were correlated with lower QOLIE-31 scores, which confirms the negative impact of AEs on QOL [4].



Legend. SPE: symptomatic partial epilepsy; IGE: idiopathic generalized epilepsy.

Fig. 3. Comparison of the LAEP scores of the symptomatic partial epilepsy and idiopathic generalized epilepsy groups.

Table 4
Antiepileptic drug ranges and significant differences in LAEP items between drugs [a].

	Carbamazepine	Valproic acid	Phenobarbital	Clobazam
Number of patients	43	32	27	27
Dose range	≤800 mg/>800 mg	<1000 mg/≥1000 mg	≤100 mg/>100 mg	≤10 mg/>10 mg
Number of patients per group	16/27	15/17	17/10	17/10
LAEP item				
Unsteadiness	31.3/14.8 (0.192)[a]	**2.2/31.4 (0.005)**[b]	33.3/13.3 (0.080)	23.5/20.0 (0.575)
Tiredness	54.2/33.3 (0.097)	22.2/39.2 (0.357)	47.1/30.0 (0.402)	**45.1/13.3 (0.048)**[b]
Nervousness and/or Agitation	**77.1/46.9 (0.006)**[b]	35.6/33.3 (0.934)	62.7/40.0 (0.145)	52.9/63.3 (0.398)
Feelings of Aggression	20.8/25.9 (0.805)	**6.7/27.5 (0.037)**[b]	25.5/23.3 (0.705)	25.5/26.7 (0.884)
Headache	39.6/44.4 (0.661)	33.3/33.3 (0.853)	52.9/43.3 (0.533)	**51.0/20.0 (0.044)**[b]
Hair loss	**35.4/12.3 (0.045)**[b]	31.1/51.0 (0.264)	33.3/20.0 (0.366)	29.4/23.3 (0.787)
Difficulty in Concentrating	**79.2/39.5 (0.003)**[b]	26.7/37.3 (0.432)	64.7/30.0 (0.059)	58.8/53.3 (0.731)
Trouble with Mouth and Gums	**35.4/3.7 (0.001)**[b]	15.6/5.9 (0.135)	3.9/10.0 (0.963)	21.6/10.0 (0.414)
Weight Gain	12.5/17.3 (0.737)	15.6/31.4 (0.282)	**27.5/0.0 (0.038)**[b]	7.8/10.0 (0.927)
Depression	**50.0/24.7 (0.042)**[b]	22.2/29.4 (0.754)	37.3/10.0 (0.076)	41.2/36.7 (0.763)
Overall score	**47.6/32.2 (0.025)**[b]	21.8/33.6 (0.226)	41.5/24.9 (0.063)	42.0/31.6 (0.258)

[a] LAEP scores converted to scale of 0 to 100. Mean at low dose/high dose (*P* value, Mann–Whitney's test).
[b] In boldface are values for which $P<0.050$.

Hospital Anxiety and Depression Scale scores also were strongly correlated with LAEP scores. Many of the symptoms listed on the LAEP as possible effects of AEDs are also symptoms of anxiety and depression. Comorbid psychiatric symptoms are well known to occur in patients with epilepsy. These results agree with the previously reported association between AEs of antiepileptic medication and mood [12,30]. In the present study 44% of patients reported depression on the LAEP, and on the related anxiety symptoms, 53% reported Restlessness and 63% Nervousness/Agitation. It has been reported that depression symptoms may be secondary to the use of AEDs [31] and may be a strong predictor of QOL in epilepsy [32].

4.2. Sociodemographic and clinical analysis of the Liverpool Adverse Events Profile

There was a strong and consistent association of gender, age, seizure frequency, and polytherapy with LAEP scores. There were more women in the group with higher toxicity. Although previous studies have attributed this association to the endocrine effects of AEDs, especially VPA, in women, such as weight gain, skin problems, and teratogenicity [33], most of the women in our study with LAEP scores indicating toxicity had SPE and were taking CBZ. LAEP scores were found to be influenced by age, especially in the range 34.5–70 years, reflecting an increase in AEs with time. This confirms previous findings that the rates of AEs can be influenced by age, gender, comorbidity, duration of treatment, personality traits, and mood state, including anxiety and depression [34].

Seizure frequency and seizure type were strongly related to LAEP scores. Higher seizure frequency was associated with higher LAEP scores. This finding was not in accordance with other studies that found no relationship between seizure frequency and the LAEP or other measures of AEs [13,35]. There has been some controversy regarding the role of QOL, AEs, and seizure frequency. Some authors consider QOL more important than the AEs themselves, but other groups believe that the AEs of AEDs may be more disabling to the patient than the seizures [5,18,36]. Our findings may have also been influenced by the subjective character of the LAEP and the possibility that patients with higher seizure frequency paid more attention to AEs.

With respect to epilepsy groups, the only association found was the presence of GTCS in the preceding month in patients with IGE and higher LAEP scores. This may reflect the fact that the majority of patients diagnosed with JME were in this group and that polytherapy is used in these cases. Although an impact on QOL has been demonstrated for patients with JME [22,37] and was confirmed in the present study, other factors such as the pathophysiological implications of frequent uncontrolled GTCS may lead to worse prognosis and higher burden for these patients.

Overall, the LAEP results for patients with two distinct entities such as difficult-to-treat SPE and IGE did not differ. This fact is not explained by sociodemographic data or types and number of AEDs which differed between the groups. Measurements of QOL in this and other studies were reported to be worse in patients with SPE than in those with IGE [22,37]. HADS Depression scores also differed between the two groups. Nevertheless, in our study the LAEP was strongly correlated with QOLIE-31 and HADS. We hypothesize that although the LAEP is appropriate for diverse epilepsies, it does not differentiate the overall burden of AEs in SPE and IGE, not only because of the subjective nature of QOL, but also because of the specific AEs of drugs indicated for a particular epilepsy seizure type. The LAEP has been described as an instrument for quantification of patients' perceptions of the AEs of AEDs [10], and to our knowledge, this is the first study to evaluate the relationship of different epilepsies to the LAEP. Other instruments that take into account seizure types and frequency as well as systemic, neurological, and behavioral modifications after the initiation of a specific AED are necessary [38].

4.3. Type of antiepileptic drug treatment and Liverpool Adverse Events Profile

The most commonly reported AEs in the sample of patients were Sleepiness, Difficulty in Concentrating, and Memory Problems. These can be associated with the most frequently used AEDs, CBZ and VPA, which may cause these common AEs. Similar results were obtained in a large European study with more than 5000 patients that showed that the most common AEs of CBZ and VPA are tiredness, memory problems, difficulty in concentration, and sleepiness [1].

Polytherapy was associated with higher LAEP scores in the IGE and SPE groups. In recent decades, the availability of new compounds with potentially fewer AEs and drug interactions has led to the use of high doses of AEDs in polytherapy with the goal of better seizure control. This strategy, in turn, may have impaired QOL and resulted in more AEs [39].

Table 5
Comparison of mean score, Cronbach´s α, and test–retest reliability in different versions of the LAEP.

Version	Mean (SD)	Cronbach´s α	Test–retest reliability
Portuguese–Brazilian	37.6 (13.3)	0.90	0.78
Spanish	36.4 (9.7)	0.84	0.81
Chinese	30.7 (11.0)	0.90	0.80

Higher LAEP scores were obtained by patients in different dose range groups of CBZ (5 items), VPA and CLB (2 items each), and PB (1 item). Some of these items are well known to have dose-related neurocognitive AEs such as nervousness/agitation, difficulty in concentration, and depression for CBZ; unsteadiness and feelings of aggression for VPA [40]; and tiredness and headache for CLB [41]. Nevertheless, these AEs were found to be associated with lower doses of CBZ and CLB, which may be due to the difficulty patients have in recognizing these problems among central nervous system-related AEs of other AEDS at higher doses. The same was observed in 10 patients taking more than 100 mg of PB per day who did not report weight gain on the LAEP although all 17 subjects in the low-dose group (<100 mg) did. Surprisingly weight gain in a relatively young population differed neither in distinct epilepsies nor in the two subgroups of VPA and TPM doses.

We acknowledge some restrictions of this study such as the tertiary care character of our institution, as well as the large number of patients with drug-resistant seizures in the sample. Potential limitations of the LAEP may be its subjectivity; the lack of a physical examination to medically confirm some AEs such as weight changes, nystagmus, ataxia, coordination and speech abnormalities; and the lack of objective measures of systemic involvement like hepatic and hematological AEs. Other concerns with the LAEP are the possibility of overreporting as a result of the direct approach of the questionnaire [12] and the absence of a median point in its 4-point rating scale [42].

5. Conclusion

The Portuguese–Brazilian version of the LAEP was confirmed to be a reliable and valid instrument for assessing AEs in patients with epilepsy with important limitations in physical symptoms. This study demonstrated that LAEP items were associated with specific AEs of drugs without a clear dose-dependent pattern. Although LAEP Overall score was not helpful in differentiating epilepsies, this scale may be useful for continued screening of patients in clinical trials of AEDs that affect the items covered by this subjective questionnaire.

Acknowledgments

We are grateful for the assistance of Patricia G.A. Ramos in statistical analysis and of English teachers Thaisa Pinheiro, Gus Schoorlemmer, and Kenny Aguilar in translation of the LAEP.

We acknowledge support from CAPES and FAPESP (Brazil).

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.yebeh.2011.08.005.

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