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Screening for epilepsy-specific anxiety symptoms: French validation of the EASI

^{1,2}Jean-Arthur Micoulaud, ³Iliana Kotwas, ³Marie Arthuis, ³Lisa Soncin, ³Pauline Rontani,
³Geraldine Daquin, ⁴Michel Cermolacce, ^{3,5}Fabrice Bartolomei, ^{3,5}Aileen McGonigal*

- 1- Sleep Medicine Unit, University Hospital of Bordeaux, Place Amélie Raba-Leon, 33 076 Bordeaux, France
- 2- USR CNRS 3413 SANPSY, University Hospital of Bordeaux, 33 076 Bordeaux, France
- 3- APHM, Timone Hospital, Clinical Neurophysiology, Marseille, France
- 4- University department of psychiatry, APHM, Sainte Marguerite Hospital, Marseille, France
- 5- Aix Marseille Univ, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France

Corresponding author :

Dr Aileen McGonigal

APHM, Timone Hospital, Clinical Neurophysiology, Marseille, France

aileen.mcgonigal@univ-amu.fr

Tel +33 491 38 49 95

Fax +33 491 38 58 26

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Abstract

Objectives

(1) To translate and validate the Epilepsy Anxiety Survey Instrument (EASI) in French people with epilepsy (PWE); (2) to further investigate the screening properties of each dimension of the EASI in terms of Diagnostic and Statistical Manual of Mental Disorders (DSM) anxiety disorders and of epilepsy-specific anxiety disorders, namely, anticipatory anxiety of seizures (AAS) and epileptic social phobia.

Methods

Following back-translation, the French EASI was tested in PWE >18 years using the Mini-International Neuropsychiatric Interview (MINI) as gold standard for DSM anxiety disorders. We added 3 original questions to explore epilepsy-specific anxiety symptoms. The Generalized Anxiety Disorders-7 (GAD-7), Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and Adverse Events Profile were performed for external validity. Receiver operator characteristics (ROC) were analyzed.

Results

149 native French speakers with epilepsy were included. Concerning DSM disorders, around 25% had GAD, 18% Agoraphobia and <10% Social Phobia or Panic Disorder. Concerning possible epilepsy-specific anxiety disorder, 35% had AAS and 38% had epileptic social phobia. Bi-dimensional structure of the EASI was confirmed. Internal and external validity was satisfactory. ROC analysis showed AUC of 0.83 for detection of GAD and AUC 0.79 for other DSM anxiety disorders. ROC analysis of the 8-item French brEASI showed good performance for detection of GAD (AUC 0.83) and other DSM anxiety disorders (AUC 0.76) but not for epilepsy-specific anxiety symptoms (AUC 0.63). Conversely, dimension 2 of the French EASI (=10 items) allowed good detection of epilepsy-specific anxiety symptoms (AUC 0.78); cut-off >4, sensitivity 82.4, specificity 66.7.

Conclusion

Epilepsy-specific anxiety symptoms were prevalent, in around 60%. The French version of the EASI showed robust performance. The French 8-item brEASI allows screening for all DSM

anxiety disorders with superior performance than the GAD-7 but is less suited to screening for epilepsy-specific anxiety. We propose the “Epilepsy-Specific Anxiety” (ESA) 10-item screening instrument, based on dimension 2 of the EASI, as a complementary clinical and research tool.

Keywords

Anxiety, EASI, GAD-7, seizure phobia, screening

1. Introduction

Anxiety disorders in people with epilepsy (PWE) seem at least as prevalent as depressive disorders, but are relatively neglected [1] and have been described as the “forgotten” psychiatric comorbidity [2]. Anxiety symptoms have an independent, adverse effect on quality of life in PWE [3]. Screening for anxiety symptoms and disorders forms part of recommended psychological assessment of PWE, according to the International League Against Epilepsy (ILAE) [4]. Anxiety symptom and disorders screening has also been included in the American Academy of Neurology (AAN) epilepsy management guidelines as a key component of delivery of care, favoring short auto-questionnaires for their ease of use [5].

While a dedicated screening tool for depressive disorder screening in epilepsy has been developed (Neurological Disorders Depression Inventory for Epilepsy, NDDI-E) [6] and validated in numerous languages and geographic regions [7], until recently only non-dedicated screening tools for anxiety disorders had been validated in PWE, notably the Generalized Anxiety Disorder 7 (GAD-7) [8], including multi-language versions validated in PWE [9-13] and other clinical populations [14]. Psychometric performance of the GAD-7 is overall satisfactory in PWE and correlates with other psychological and quality of life measures in this clinical population [15], but it is designed only to detect presence of generalized anxiety disorder (GAD). Amongst anxiety disorders, those characterized in the Diagnostic and Statistical Manual of Mental Disorders (DSM; IV edition and latest), are Generalized Anxiety Disorder (GAD), Panic Disorder, Agoraphobia, and Social Phobia. These typical anxiety disorders can be reliably diagnosed with the Mini International Neuropsychiatric Interview (MINI) [16]. Any of these may be present in association with epilepsy.

Recently, a welcome initiative by Australian colleagues led to the development of a new 18-item anxiety disorders screening tool for epilepsy, the Epilepsy Anxiety Survey Instrument (EASI) [17]. This carefully constructed tool was developed and validated in PWE. A brief 8-item scale (brEASI) derived from this study has been proposed, which showed slightly superior performance to the GAD-7 for detecting GAD, and superior performance to the GAD-7 for detecting other typical DSM anxiety disorders that are may occur in association with epilepsy but that are not specific to PWE (i.e., Panic Disorder, Agoraphobia, and Social

Phobia) [17]. The authors considered the EASI and the brEASI to be the first valid and reliable screening instruments for epilepsy-specific anxiety disorders [17].

Epilepsy-specific anxiety disorders are new nosological entities that have received some attention but remain to be fully characterized and assessed in large epilepsy populations. The most studied form of epilepsy-specific anxiety has recently been termed “Anticipatory Anxiety of Seizures” (AAS) [18, 19]. This interictal manifestation is characterized by “a daily persistent fear, dread, or excessive worry of having a seizure” [19], or more simply “fear of seizures” [20, 21], a kind of specific phobia related to epilepsy and seizures. AAS has been reported in over half of patients with focal drug-resistant epilepsy in a recent study [19]. The ILAE has recognized seizure phobia as part of the spectrum of interictal neuropsychiatric phenomena specific to epilepsy [21], but there is not yet a consensus about how best to screen for and diagnose this; notably there is no gold standard equivalent to the MINI for diagnosing this category. Other epilepsy-specific anxiety entities may relate to “epileptic social phobia” [18] (fear of being observed by others during seizures), but this remains even less well characterized than AAS.

Our objective in the present study was twofold: (1) to translate and validate the EASI in French PWE; (2) to further investigate the screening properties of each dimension of the EASI, particularly in terms of typical DSM anxiety disorders and of epilepsy-specific anxiety disorders, in terms of AAS and epileptic social phobia.

2. Methods

2.1. Participants

PWE were recruited from the Clinical Neurophysiology Department of the Marseille University Hospital, Marseille, from May 2020 until May 2021. Inclusion criteria were native French-speaking adult PWE (>18 years) with any type of epilepsy according to ILAE criteria. Exclusion criteria were insufficient capacity to consent and to understand and answer the self-report questionnaires. Patients were invited to participate in the study during their routine neurological evaluation. After receiving a detailed description of the study, participants gave their informed consent. This study was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices.

2.2. Procedure

2.2.1. Translation of the EASI

Authorization for the translation was obtained from the authors of the original version of the EASI. A forward-backward translation was performed. The original version was translated into French independently by two French native speakers, a psychiatrist (JAMF) and a neuropsychologist (IK) with a high level of fluency in both English and French. The back-translation into English was undertaken by an English native speaker and neurologist (AMcG) independently of the forward-translation. Divergences between the back-translation and the original English version were identified and discussed. For items where cross-language agreement could not be reached, French sentences were reworded. The translated version of the EASI was administered to 5 PWE and showed good clarity and cultural acceptability of the instrument. No further adaptations were required. The final version of the French EASI is shown in **Table 2**. Scores of the EASI can range between 0 and 54.

2.2.2. Clinical assessment

Sex, age, type and frequency of seizures, age of onset of epilepsy, number and name of antiepileptic drugs currently being taken, presence of vagal nerve stimulation and use of antidepressant drugs were noted. Demographic information about employment and marital

status was also collected. Diagnosis of epilepsy was documented clinically and confirmed where necessary with video-EEG investigations.

The General Anxiety Disorder, Panic Disorder, Agoraphobia and Social Phobia modules of the French version of the Mini International Neuropsychiatric Interview (MINI) were completed as part of the psychiatric assessment. These are 4 short, structured questionnaires to identify most frequent specific anxiety disorders according to the criteria of the DSM-IV-TR.

As well as the classical MINI questionnaire, and since there are currently no diagnostic criteria for epilepsy-specific anxiety disorders (defined here as the entities that have been termed “anticipatory anxiety of seizures (AAS)” and “epileptic social phobia”[18]), we added 3 additional questions, aimed at exploring epilepsy-specific anxiety symptoms. The wording of these was based on the MINI and the Epilepsy Addendum for Psychiatric Assessment (EAPA), a brief instrument which was designed to assist in making Axis I psychiatric diagnoses in patients with epilepsy [22]. The questions about excessive worry of having a seizure or fear of seizures, related to the AAS construct, were: “*Are you excessively concerned, worried or anxious about having a seizure?*” and “*Do you have marked and persistent fear related to the expression or the consequences of your seizures?*”. The question about epileptic social phobia was: “*Do you have marked and persistent fear or are excessively embarrassed by the way others view your seizures?*” A “yes/no” response was given for each, based on the patient’s responses to the questions and the epilepsy specialist’s judgment of clinical significance of symptoms. The neurologist was blinded with regards to the response to the patient’s self-rated assessments (see below). Thus, the diagnostic standard for possible epilepsy-specific anxiety disorders in the present study can be considered as expert opinion, as has been applied in previous screening tool validation studies[23].

The structured questionnaire (MINI + additional questions) was administered by a neurologist with expertise in the field of epilepsy and its psychiatric aspects. Diagnoses obtained with the MINI and the interview based on the 3 additional questions were used as a gold standard for the presence of current anxiety disorders.

2.2.3. Self-rated assessments

French versions of the EASI, the NDDI-E[7], the GAD-7[10], and the Adverse Events Profile (AEP)[15] were completed. The NDDI-E is constituted of 6 items to evaluate depressive symptoms. The GAD-7 is constituted of 7 items to evaluate general anxiety symptoms. The AEP is constituted of 19 items to evaluate adverse effects related to antiepileptic drugs.

2.3. Statistical analyses and hypotheses

Descriptive statistics of the obtained data included frequencies and percentages of categorical variables together with means and standard deviations of continuous variables. Demographical and clinical data were compared between PWE with and without epilepsy-specific anxiety disorders using Chi2 test for categorical variables and Student's t-test for continuous variables. Based on expert opinion and the answers to the 3 additional questions, a possible epilepsy-specific anxiety disorder was considered to be present in any subject with either AAS or epileptic social phobia, or both.

For the validation process, we analyzed the psychometric properties of the French EASI version including internal structural validity, external validity, and receiver operator characteristics. Data analysis was performed using SPSS software (Version 18 for Mac, PASW Statistics) and MedCalc software (Version 14.8 for Windows). For all tests, the accepted significance level was 5%.

2.3.1. Computation of the EASI scores

The score was obtained by computing the sum of the scores obtained by items associated with it, from 0, "not at all", to 3, "nearly every day". The possible total score ranges from 0 to 54.

2.3.2. Internal structural validity

Floor and ceiling effects were reported to assess the response distribution. The rate of floor and ceiling effects were calculated as the proportion of individuals who obtained the lowest ("not at all") and the highest ("nearly every day") scores for any of the items.

Internal consistency reliability was assessed by Cronbach's alpha coefficient and recalculated after items were removed. To confirm consistency, a coefficient of at least 0.7 was expected for each item removed.

Construct validity was assessed using principal components factor analyses with Varimax rotation to obtain the dimensions of the EASI. Items were included in a factor if they revealed a loading greater than 0.4. Major dimensions of the EASI were determined based on this factor analysis.

Item-internal consistency (IIC) was assessed by correlating each item with its related dimension using Pearson's coefficient; correlations of at least 0.4 are recommended for supporting item-internal consistency. Item discriminant validity (IDV) was assessed by determining whether items correlated better with the dimension they were hypothesized to represent compared with the other dimensions. IIC are correlations between items and the dimension that they were hypothesized to represent, and IDV are correlations between items and the other dimensions that they were not hypothesized to represent. Therefore, the IIC and IDV ranges should not largely overlap to be considered as satisfactory.

2.3.3.External validity

External validity was tested by studying convergent and discriminant validity. To explore external convergent validity, relation between the EASI and the GAD-7 was investigated. To explore external divergent validity, relation between the EASI and the NDDIE, AEP scores, age and duration of epilepsy were investigated. Pearson's coefficients were computed.

2.3.4.Receiver operator characteristics

Receiver operator characteristics (ROC) analysis was calculated to assess the utility of the EASI total score, and of the EASI score of major dimensions obtained with the principal component factor analyses, to distinguish the diagnosis of typical DSM anxiety disorders as diagnosed by the MINI (General Anxiety Disorder, Panic Disorder, Agoraphobia, Social Phobia) and of epilepsy-specific anxiety disorders (AAS and epileptic social phobia) as diagnosed by the expert neurologist interview based on the additional questions.

Area under the curve (AUC) and its 95% confidence intervals for the ROC curve were calculated. An AUC of 0.5 indicates no predictive power, whereas an AUC of 1 indicates perfect prediction.

Sensitivity, specificity, and positive/negative predictive values, as well as their confidence intervals, were computed. A cut-off point was obtained by selecting the point on the ROC curve that maximized both sensitivity and specificity. The chosen cut-off point correctly

classified the highest number of individuals and incorrectly classified the least number (thus maximizing both sensitivity and specificity).

ROC analyses for the EASI total score, EASI dimension scores, brEASI (using the same items in French as the original brEASI) and the GAD-7 for GAD (defined by the MINI), and ROC analyzed for EASI total score, EASI dimensions scores and GAD-7 for epilepsy-specific anxiety disorders, were compared using a nonparametric approach for paired samples.

3. Results

3.1. Sample characteristics

A total of 149 native French speakers with epilepsy were included. None of the patients reported any difficulties in understanding the items of the EASI.

The mean age was 38.55 years old (SD=13.26, range: [19-70] years old); 57.0% (85) were female; 83.9 % had focal epilepsy (125); 47.0 % had more than one seizure per month (70). The mean duration of epilepsy was 19.48 years (SD=14.62), the mean number of antiepileptic drugs currently being taken was 2.17 (SD=0.97), the number of patients with vagal nerve stimulation was 8 (5.4%) and the number taking antidepressants was 13 (8.7%). The mean EASI score was 15.70 (SD=11.72), brEASI score was 7.36 (SD=5.79), GAD-7 score was 7.74 (SD=5.51), NDDI-E score was 11.56 (SD=4.91) and AEP score was 42.22 (SD=11.31). Using the MINI, a diagnosis of current General Anxiety Disorder was established in 38 (25.5%) PWE, Panic Disorder in 6 (4%), Agoraphobia in 27 (18.1%) and Social Phobia in 13 (8.7%). Using the additional questions, 61.7 % of PWE had a possible epilepsy-specific anxiety disorder (92): AAS was present in 53 (35.6%) PWE and epileptic social phobia in 58 (38.9%). **Figure 1.** Of subjects with possible epilepsy-specific anxiety disorder, 34.8 % (32) also had GAD and 20.7 % (19) Agoraphobia diagnosed with the MINI.

Demographic and clinical characteristics of PWE with and without specific anxiety disorders are detailed in **Table 1**. There were some significant differences between PWE with and without epilepsy-specific anxiety disorders in terms of employment status, frequency of seizures and number of antiepileptic drugs taken.

3.2. Validity

3.2.1. Internal structural validity

Floor effects ranged from 41.6% to 75.8 % and ceiling effects ranged from 4% to 20.1 %.

Table 2.

The Cronbach's alpha coefficient was 0.902 and ranged from 0.895 to 0.900 after items were removed. None of the items would increase the Cronbach's alpha if deleted.

The structure of the EASI was confirmed by principal components factor analysis, accounting for 62.2% of the total variance. **Table 3.** The content of each dimension was considered relevant and meaningful by the group of experts: GAD for factor 1 (six items), panic disorder for factor 4 (two items), AAS for factor 2 (seven items) and epileptic social phobia for factor 3 (three items). Thus factor 1 and 4 can be considered as constituting dimension 1 of the EASI for typical DSM anxiety disorders screening, and the factors 2 and 3 as dimension 2 of the EASI for epilepsy-specific anxiety disorder.

As expected, IIC were all higher than 0.40 and the correlation of each item with its contributive dimension was globally higher than that with the other dimension (IIC > IDV) (see **Supplementary material 1**).

3.2.2.External validity

The correlation between the EASI and the GAD-7 scores was ($r(149) = 0.70, P < 0.0001$). The correlation between the EASI and the NDDIE scores was ($r(149) = 0.58, P < 0.0001$) and AEP scores was ($r(149) = 0.56, P < 0.0001$). The correlation between the EASI and age was non-significant ($r(149) = -0.15, P = 0.072$) and with epilepsy duration also non-significant ($r(149) = -0.026, P = 0.75$).

3.2.3.Receiver operating characteristics (ROC)

The different ROC analysis of the EASI are shown in **table 4** and **Supplementary material 2**. Pairwise comparisons of ROC curves for EASI, brEASI, French EASI dimension 1 (=EASI1, 8 items) and GAD-7 for GAD screening were not statistically significant: EASI-EASI1 ($p = 0.622, z = 0.494$), EASI-GAD-7 ($p = 0.730, z = 0.345$), EASI1-GAD7 ($p = 0.487, z = 0.694$), brEASI-EASI1 ($p = 0.197, z = 0.266$), brEASI-GAD-7 ($p = 0.791, z = 0.266$), brEASI-EASI ($p = 0.826, z = 0.219$). The ROC is shown in **Figure 2**.

Pairwise comparisons of ROC curves for French EASI dimension 2 (=EASI2, 10 items) with EASI, EASI1 (8 items) and GAD-7 for epilepsy-specific anxiety disorders screening were statistically significant: EASI2-EASI ($p = 0.006, z = 2.744$), EASI2-EASI1 ($p < 0.001, z = 4.140$),

EASI2-GAD-7 ($p=0.009$, $z=2.604$), EASI2-brEASI ($p=0.0001$, $z=4.030$). The ROC is shown in **Figure 3**.

4. Discussion

The present work has 3 main contributions: (1) translating and validating the French version of the EASI screening tool for anxiety disorders in PWE; (2) exploring epilepsy-specific anxiety symptoms (anticipatory anxiety of seizures (AAS) and epileptic social phobia), and proposing a short (10-item) screening tool for these, based on a subdimension of the EASI and validated by diagnostic questions assessed by expert opinion; (3) highlighting the high prevalence of possible epilepsy-specific anxiety disorder in a large, heterogeneous group of PWE, with around 60% of our patients reporting symptoms of either AAS, epileptic social phobia or both.

4.1. Validation of the EASI in French

The French version of the EASI showed robust statistical performance in screening for GAD and other DSM anxiety disorders, validated using the MINI (**Table 4**). Comparison of the screening properties of the French EASI (18 items) with the original version cannot be done because the ROC curve analysis was not described by Scott et al. [17]. Concerning the shortened screening instruments, the French 8-item brEASI for detection of GAD was similar to the original brEASI, and was superior in terms of both sensitivity and specificity to the GAD-7 for detecting GAD (**Supplementary material 2**) [17]. However, the French brEASI proved to have less good performance than the original brEASI in detecting Agoraphobia, Social Phobia and Panic Disorder (AUC 0.76 for French brEASI, compared to the AUC of 0.89 for the equivalent analysis in the original study).

4.2. Epilepsy-specific anxiety: anticipatory anxiety of seizures (AAS) and epileptic seizure phobia

The present results highlight the importance of epilepsy-specific anxiety symptoms, namely anticipatory anxiety of seizures (AAS) and epileptic social phobia, and the need to systematically screen for these in PWE, given their high prevalence here and in previous works [19, 24]. These were detected in our study using original questions designed to assess

presence of these, the clinical significance of symptoms being interpreted by expert clinicians. In our cohort, 60% reported at least one epilepsy-specific anxiety symptom, and prevalence of possible epilepsy-specific anxiety disorder was higher than any DSM-confirmed anxiety disorder, since GAD was diagnosed in 25.5% followed by Agoraphobia in 18.1%, with the other DSM diagnoses of Panic Disorder and Social Phobia being less common (both <10%) (see **Figure 1**). Epileptic social phobia was slightly more prevalent (38.9%) than AAS (35.6%) in our series. Presence of any epilepsy-specific anxiety symptom in our population was significantly associated with higher seizure frequency and higher number of antiepileptic drugs being taken (Table 1). A recent study of 84 patients with pharmacoresistant focal epilepsy reported AAS in just over half of patients [19], thus somewhat higher than prevalence of around one third of those included in the present series who had AAS, possibly reflecting case-mix since our series included patients with pharmacoresistant and relatively well-controlled epilepsy.

The observation of anticipatory fear in epilepsy (“seizure phobia”) is not new, and was described at least several decades ago [20, 25]. In the 1980s, a dedicated screening questionnaire, the “Fear of Seizures Scale” was proposed [26] and subsequently revised by different authors [25]. However, this psychological entity has remained rather poorly characterized and probably under-recognized by clinicians, likely due in part to lack of inclusion of items related to anticipatory anxiety of seizures in currently available screening or diagnostic tools [19]. The most widely used screening tools for anxiety in epilepsy include the GAD-7 [9, 10] and the Hospital Anxiety and Depression Scale (HADS) [27]. Neither of these include any epilepsy-specific item, both having been developed in general populations; of the two, the GAD-7 appears to have better specificity than the HADS for anxiety symptoms [28, 29] including in PWE [10], but is only suitable for detecting presence of symptoms of generalized anxiety disorder and does not screen for the other DSM-5 recognized entities of panic disorder, agoraphobia and social phobia. The MINI is a structured diagnostic interview that ascertains presence or absence of these aforementioned DSM-5 diagnoses [16], but does not include any questions addressing symptoms specific to epilepsy. Even the “Epilepsy Addendum for Psychiatric Assessment (EAPA)”, proposed in conjunction with the MINI [22], aims at distinguishing psychiatric symptoms from epileptic seizure semiology (e.g. separating panic disorder from ictal fear), but does not test for epilepsy-specific psychiatric symptoms. Thus, the most commonly used

screening tools and diagnostic questionnaires fail to detect epilepsy-specific symptoms, including AAS and epileptic social phobia, that nevertheless appear to be highly prevalent and may be disabling for patients.

4.3. Structure of the EASI

Taking into account these aforementioned limitations, the need to improve both scope and specificity of anxiety screening in PWE was indeed the motivation for developing the Epilepsy Anxiety Screening Instrument (EASI), which was carefully constructed and validated by an expert group [17], using methodology similar to that used for developing the NDDI-E in PWE[6]. The authors demonstrated 2 main dimensions making up the structure of the full-length 18-item EASI: dimension 1 reflecting more typical anxiety symptoms, and dimension 2 reflecting epilepsy-specific anxiety symptoms [17]. However, while questions reflecting symptoms of AAS or epileptic social phobia are included within the 18-item EASI, no proposed cut-off score of the EASI is given with regards to screening for these epilepsy-specific symptoms and no brief screening tool is currently available for this, since the items of the 8-item brEASI were largely derived from the non-epilepsy-specific dimension.

4.4. Dimensional analysis of the EASI

Because of the pressing clinical need to better detect and measure epilepsy-specific anxiety symptoms [30], namely, anticipatory anxiety of seizures (AAS) and epileptic social phobia, we wished to explore a means of screening for these, based on the EASI and an investigation of the screening properties of each dimension of the EASI. The French version of the EASI showed the same structure as the original EASI, with two major dimensions. Dimension 1 of the original EASI, which reflects typical DSM anxiety disorders (GAD, Agoraphobia, Panic Disorder, Social Phobia), was composed of items 1, 2, 3, 4, 6, 10, 14, 15, and 17 (**Table 2**); based on Varimax rotation analysis, the French version of dimension 1 of the EASI included the same items, except item 14. Dimension 2 of the original EASI, which reflects epilepsy-specific anxiety symptoms, was constituted of items 5, 7, 8, 9, 11, 12, 13, 16, and 18 (Table 2), with item 14 added in the French version of dimension 2. Thus, the 2-dimensional structure of the EASI was confirmed to be robust in the French version with only item 14 (*"I worried about situations where I might make a fool of myself"*) changing

dimension (i.e., becoming included in the epilepsy-specific rather than the non-specific dimension). This item, which reflects social phobia, was indeed correlated in our study with responses to our additional question relating to epileptic social phobia (*“Do you have marked and persistent fear or are excessively embarrassed by the way others view your seizures?”*), and it seems clinically relevant that item 14 be grouped with the epilepsy-specific symptoms.

4.5. Screening for epilepsy-specific anxiety symptoms

Given our objective of ideally finding a way to screen for epilepsy-specific symptoms, we were particularly interested in the 10 items that made up the epilepsy-specific dimension 2 of the EASI. We recall that the brief 8-item version of the EASI (brEASI) proposed by Scott and colleagues for routine screening in epilepsy clinics was essentially composed of items from dimension 1 reflecting more typical anxiety symptoms, rather than epilepsy-specific ones. Of the 8 items of the original brEASI (items 1, 2, 3, 4, 6, 8, 14 and 15), which were chosen by Scott et al. based on statistical correlation with the GAD-7 ($r > 0.4$), only item 8 (*“I avoided places where it would be difficult to get help if I had a seizure”*) was from the epilepsy-specific dimension, while all the others were items related to non-epilepsy-specific anxiety symptoms. Thus, while performance of the original brEASI was good for screening for GAD and other DSM anxiety diagnoses, anticipatory anxiety or seizure phobia symptoms are unlikely to be detected using this tool. Note that the screening properties of the French brEASI are significantly similar to dimension 1 of the French EASI for GAD and typical DSM anxiety disorders, both scales exhibiting similar items except for two (items 8 and 14 of the original brEASI being replaced by item 10 and 17 in dimension 1 of the French EASI according to the statistical analysis, see **Table 3**).

According to our validation of the EASI and comparison with the diagnosis of AAS and social phobia (based on expert opinion and 3 structured questions), we found good performance of the 10 items contained within dimension 2 of the French version, which predominantly reflected symptoms specific to epilepsy (see Table 4). Thus, with a cut-off score of 4, the 10-item questionnaire based on dimension 2 of the EASI, which we propose to term here the Epilepsy-Specific Anxiety (ESA) screening tool for epilepsy-specific symptoms, showed a sensitivity of 82.4% and a specificity of 66.7% for detecting AAS and/or epileptic social phobia, with AUC of 0.78 (**Table 4**). These results are overall satisfactory; while specificity is

lower than equivalent results for previous validation studies of the GAD-7 [10] or the brEASI [17], it can be argued that good sensitivity is the more important factor for a screening tool, to reduce the risk of false negatives that could limit management of anxiety, and sensitivity of the ESA is comparable to that of previous studies of the GAD-7 [10] and the brEASI [17]. The 10-item ESA could have a role as a complementary screening tool for screening for epilepsy-specific anxiety symptoms of AAS and epileptic social phobia. Indeed, ESA (i.e., dimension 2 of the French EASI) exhibited significantly higher screening properties than the GAD-7, brEASI and dimension 1 of the EASI for screening for epilepsy-specific disorders in our French sample.

4.6. Limitations and scope for future research

Our study has some limitations, which relate mainly to the challenge of validating the presence or absence of epilepsy-specific symptoms, since, unlike GAD and the other DSM anxiety disorders, no pre-defined gold standard diagnostic instrument exists. While anticipatory anxiety of seizures and epileptic social phobia appear to be clinically pertinent categories, they are diagnostic entities that remain to be fully characterized [18, 19]. In the field of psychiatry, the term “disorder” underlies the delimitation of normal and pathologic features according to supposed dysfunction in processes underlying mental functioning and significant distress or disability [31, 32]. Validation studies are very important to avoid the risk of circularity in the diagnosis of “epilepsy-specific anxiety disorders”. Here, we attempted to overcome methodological difficulties by developing 3 specific questions designed to test for validating presence or absence of anticipatory anxiety of seizures and epileptic social phobia, interpreted by expert clinicians. A certain degree of anxiety with regards to epilepsy can be a normal occurrence given the nature of the disorder, and so expert clinical judgment of when anxiety symptoms are excessive and disabling is very important to try to determine clinical significance. The high prevalence of around 60% of patients in our series reporting symptoms of AAS and/or epileptic social phobia suggests that future studies may benefit from use of a graded response to these questions (rather than a yes/no answer), in order to better judge severity; this could also help refine thresholds for delineating normal and pathological in the field of “epilepsy-specific anxiety disorders”. Yet, a threshold necessarily needs a first quantitative tool, which we propose

here to the clinical and research epilepsy community in the form of the ESA. We encourage future studies to further explore this important topic, in particular its validity with regards to pathophysiology, prognosis and therapeutics.

Another issue to be further explored is the likely association between presence of AAS and prior trauma in PWE, highlighted in a recent study[19]. The same authors also reported an association between AAS and subjective anxiety during seizures (e.g. aura consisting of an anxious feeling), leading them to suggest that an important factor in development of AAS was the patient's painful subjective emotional experience of the seizure rather than objective seizure severity[19]. Seizures may themselves be experienced as psychologically traumatic events, even leading to post-traumatic stress disorder (PTSD) [33]. It has been noted that exposure to trauma and occurrence of PTSD may be higher in at least some PWE than in the general population[34]. The relation between trauma and psychiatric profile in PWE may be conceptualized as a dynamic framework with interactions between anxiety, depression and PTSD[35]. If the patient has perceived one or more of their seizures as a psychologically traumatic experience, this is likely to increase avoidance behaviors and induce hypervigilance with regards to possible seizure occurrence, contributing to AAS[35]. Further work is needed to better evaluate the interactions between trauma and epilepsy-specific anxiety symptoms; this aspect is potentially very important therapeutically since specific therapeutic approaches for trauma exist[36] and may be helpful for some PWE.

4.7. Conclusion

The present work confirms that the EASI and the brEASI showed satisfactory properties when tested in French PWE. While the French version of the brEASI performed somewhat less well than the original brEASi for detecting Agoraphobia, Social Phobia and Panic Disorder, it showed superior performance to the GAD-7 for detecting GAD and all DSM anxiety disorders, and as such can be recommended to replace the French GAD-7 as a screening tool for all DSM anxiety disorders in PWE.

Using specifically-designed questions, we also tested for the presence of epilepsy-specific anxiety symptoms related to anticipatory anxiety of seizures (AAS) and epileptic social phobia and validated the French EASI against these. We thus propose an additional, complementary instrument based on dimension 2 of the EASI, the 10-item Epilepsy Specific

Anxiety screening tool (ESA), which may be useful for screening for AAS and epileptic social phobia with an optimal cut-off of 4 in our study. This could be used in clinical practice and in a research context, to complement screening for GAD and other DSM anxiety disorders. Epilepsy-specific anxiety symptoms appear to be highly prevalent and future studies should aim to further characterize these in different epilepsy populations.

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Conflicts of interest

None to declare

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Legends to Tables and Figures

Table 1: Demographic and clinical characteristics of the study sample

Table 2: English version / French version and frequency of response for each item of the EASI

Table 3: Principal component factor analysis with Varimax rotation for the 18 items of the EASI. Dimension 1 of the EASI comprises factors 1 and 4; dimension 2 of the EASI (ESA) comprises factors 2 and 3.

Table 4: ROC analysis of the EASI total score and dimensional scores for the diagnosis of anxiety disorders in PWE. All the other ROC analyses are shown in **Supplementary material 2**.

Figure 1: Prevalence of the diagnosis of typical DSM anxiety disorders as determined by the MINI, and possible epilepsy-specific anxiety disorder as determined by expert neurologist based on specific additional questions

Figure 2: Comparison of the ROC curve of the EASI, the brEASI (8 items) and the GAD-7 for the diagnosis of current General Anxiety Disorder

Figure 3: Comparison of the ROC curve of the EASI dimension 2 (EASI_2, "ESA") (10 items) with the EASI, the BrEASI (8 Items) and the GAD-7 for the diagnosis of possible specific-epilepsy anxiety disorders

Table 1

Demographic and clinical characteristics of the study sample

	Total (n=149)		P value
	Non-Epilepsy-specific anxiety disorders (n=57) Number (%) or Mean (SD)	Epilepsy-specific anxiety symptoms (n=92) Number (%) or Mean (SD)	
Gender			
Male	37 (64.9)	49 (53.3)	
Female	21 (35.1)	43 (46.7)	.24 ^a
Age (years)	37.25 (12.21)	40.30 (14.58)	.19 ^b
Employment status			
Employed	37 (64.9)	55 (59.8)	
Unemployed	11 (19.3)	35 (38.0)	
Retired	9 (15.8)	2 (2.2)	.002^a
Marital status			
Single	22 (38.6)	38 (41.3)	
Married	31 (54.4)	46 (50)	
Divorced	4 (7.0)	8 (8.7)	.85 ^a
Seizure type			
Generalized	12 (21.1)	11 (12.0)	
Partial	45 (48.9)	81 (88.0)	.14 ^a
Partial epilepsy syndrome			
Temporal	29 (64.4)	51 (63.0)	
Extratemporal	16 (35.6)	30 (37.0)	.87 ^a
Onset of seizures (years)	19.26 (16.02)	19.25 (13.41)	.99 ^b
Frequency of seizure (per month)			
Less than 1/year	21 (36.8)	18 (19.6)	
Less than 1/month	19 (33.3)	21 (22.8)	
Less than 1/week	11 (19.2)	25 (27.2)	
Less than 1/day	6 (10.5)	16 (17.4)	
More than 1/day	0 (0)	12 (13.0)	.005^a
Number of Antiepileptic drugs	1.89 (0.88)	2.35 (0.98)	.005^b
Currently taking antidepressants	4 (7.0)	9 (9.8)	.56 ^a
Currently vagal nerve stimulation	3 (5.3)	5 (5.4)	.96 ^a
EASI	9.92 (9.67)	19.05 (11.51)	P<0.001
BrEASI	5.57 (4.88)	8.32 (6.07)	P=0.005
EASI Dimension 1	5.72 (4.90)	8.09 (6.49)	P=0.022
EASI Dimension 2	4.41 (5.67)	10.84 (6.66)	P<0.001

(“ESA”)			
GAD-7	5.80 (4.75)	9.89 (5.66)	P=0.001
NDDI-E	10.05 (4.37)	12.43 (5.03)	P=0.004

^a Chi-square test

^b Student’s t-test

GAD-7: Generalized Anxiety Disorder – 7, PSWQ: Penn State Worry Questionnaire, NDDI-

E: Neurological Disorders Depression Inventory for Epilepsy

ESA: Epilepsy Specific Anxiety screening instrument

Table 2

English version / French version and frequency of response for each item of the EASI

BrEASI	Dimension 1 of the EASI	Dimension 2 of the EASI (ESA)		0: Not at all	1: Several days	2: More than half the days	3: Nearly every day
X	X		1. Once I started worrying, I could not stop or control it <i>Quand j'ai commencé à m'inquiéter, je n'ai pas pu m'arrêter ou le contrôler</i>	43%	26.2%	18.1%	12.8%
X	X		2. I found it hard to relax <i>J'ai eu du mal à me détendre</i>	23.5%	33.6%	22.1%	20.1%
X	X		3. Worrying thoughts went through my mind <i>Des pensées préoccupantes m'ont traversé l'esprit</i>	29.5%	32.3%	17.4%	19.5%
X	X		4. I got sudden feelings of panic, unrelated to my seizures <i>J'ai eu des sentiments de panique soudains, sans rapport avec mes crises</i>	64.8%	17.4%	8.7%	8.1%
		X	5. I found it difficult to stop worrying about having a seizure <i>J'ai trouvé difficile de m'arrêter de m'inquiéter à l'idée de faire une crise</i>	57.0%	21.5%	12.1%	9.4%
X	X		6. Fear and anxiety stopped me from doing what was important <i>La peur et l'anxiété m'ont empêché de faire ce qui était important</i>	59.1%	15.5%	12.8%	12.8%
		X	7. If I feared something might trigger a seizure, I avoided it completely <i>Si j'ai eu peur que quelque chose puisse déclencher une crise, je l'ai complètement évité</i>	51.7%	22.8%	12.1%	13.4%
X		X	8. I avoided places where it would be difficult to get help if I had a seizure	61.7%	18.8%	6.7%	12.8%

			<i>J'ai évité des lieux où il aurait été difficile de trouver de l'aide si j'avais eu une crise</i>				
		X	9. I avoided places where people could witness me having a seizure <i>J'ai évité les lieux où les gens pourraient être témoins d'une de mes crises</i>	75.8%	11.4%	4.0%	8.7%
	X		10. I got terrified out of the blue (unrelated to my seizures) <i>J'ai eu des terreurs qui semblaient ne venir de nulle part</i>	75.2%	8.7%	11.4%	4.0%
		X	11. I thought a lot about the possibility of having a seizure <i>J'ai beaucoup pensé à l'éventualité de faire une crise</i>	43.0%	24.8%	15.4%	16.8%
		X	12. I worried about what others would think of me <i>Je me suis demandé ce que les autres penseraient de moi</i>	47.7%	20.8%	12.1%	19.5%
		X	13. I worried about the impact of epilepsy on people around me <i>Je me suis inquiété(e) de l'impact de l'épilepsie sur mon entourage</i>	41.6%	24.8%	17.4%	16.1%
X		X	14. I worried about situations where I might make a fool of myself <i>Je me suis inquiété(e) des situations où je pourrais me ridiculiser</i>	59.1%	20.8%	8.1%	12.1%
X	X		15. I found it hard to enjoy myself because I could not get my mind off my worries <i>J'ai trouvé qu'il était difficile de m'amuser car je n'arrivais pas à libérer mon esprit de ses soucis</i>	50.3%	23.5%	12.8%	13.4%
		X	16. I became frightened when I noticed signs or symptoms related to my epilepsy <i>J'ai eu peur quand j'ai remarqué des signes ou des</i>	43.6%	27.5%	15.4%	13.4%

<i>symptômes liés à mon épilepsie</i>					
X	17. I tended to expect or predict the worst outcome in situations <i>J'ai eu tendance à attendre ou à prédire le pire dans chaque situation</i>	51.0%	21.5%	15.4%	12.1%
X	18. I worried whether I might do something to bring on a seizure <i>Je me suis inquiété(e) de faire quelque chose qui provoquerait une crise</i>	52.3%	22.8%	12.8%	12.1%

ESA: Epilepsy Specific Anxiety screening instrument

Table 3

Principal component factor analysis with Varimax rotation for the 18 items of the EASI.

Dimension 1 of the EASI comprises factors 1 and 4; dimension 2 of the EASI (ESA) comprises factors 2 and 3.

Factors	1 GAD	2 AAS	3 Epileptic social phobia	4 Panic disorder
Item 2 EASI*	.838			
Item 1 EASI*	.727			
Item 15 EASI*	.709			
Item 3 EASI*	.681			
Item 17 EASI	.604			
Item 6 EASI*	.530			
Item 11 EASI		.799		
Item 16 EASI		.664		
Item 8 EASI*		.660		
Item 9 EASI		.608		
Item 5 EASI		.582		
Item 18 EASI		.536		
Item 7 EASI		.515		
Item 12 EASI			.800	
Item 14 EASI*			.770	
Item 13 EASI			.602	
Item 10 EASI				.837
Item 4 EASI*				.739

GAD: Generalized Anxiety Disorder; AAS : Anticipatory Anxiety of Seizures; ESA: Epilepsy Specific Anxiety
* Items of the BrEASI in the original version

Table 4

ROC analysis of the EASI total score and dimensional scores for the diagnosis of anxiety disorders in PWE. All the other ROC analyses are shown in **Supplementary material 2**.

Questionnaire	Anxiety disorders	Cutoff score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	95%CI	SE	P value
GAD 7 (7 items)	GAD	>7	81.6	64.9	44.3	91.1	.818	.747-.877	.036	<0.001
brEASI (8 items)	GAD	>7	84.2	73.9	52.5	93.2	.828	.758-.885	.041	<.001
brEASI (8 items)	Typical DSM Anxiety disorders	>7	72.2	76.8	63.9	83.0	.757	.680-.824	.044	<.001
EASI dimension 2 (10 items) ("ESA")	Epilepsy-specific anxiety disorders	>4	82.4	66.7	79.8	70.4	.781	.705-.844	.041	<.001

PWE: Person with epilepsy; GAD: Generalized Anxiety Disorder; ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; 95%CI: 95% confidence interval; SE: standard error.

Typical DSM anxiety disorders: General Anxiety Disorder, Panic Disorder, Agoraphobia and Social Phobia

Epilepsy-specific anxiety disorders: Anticipatory Anxiety of Seizures (AAS), epileptic social phobia

ESA: Epilepsy Specific Anxiety screening instrument

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Figure 1

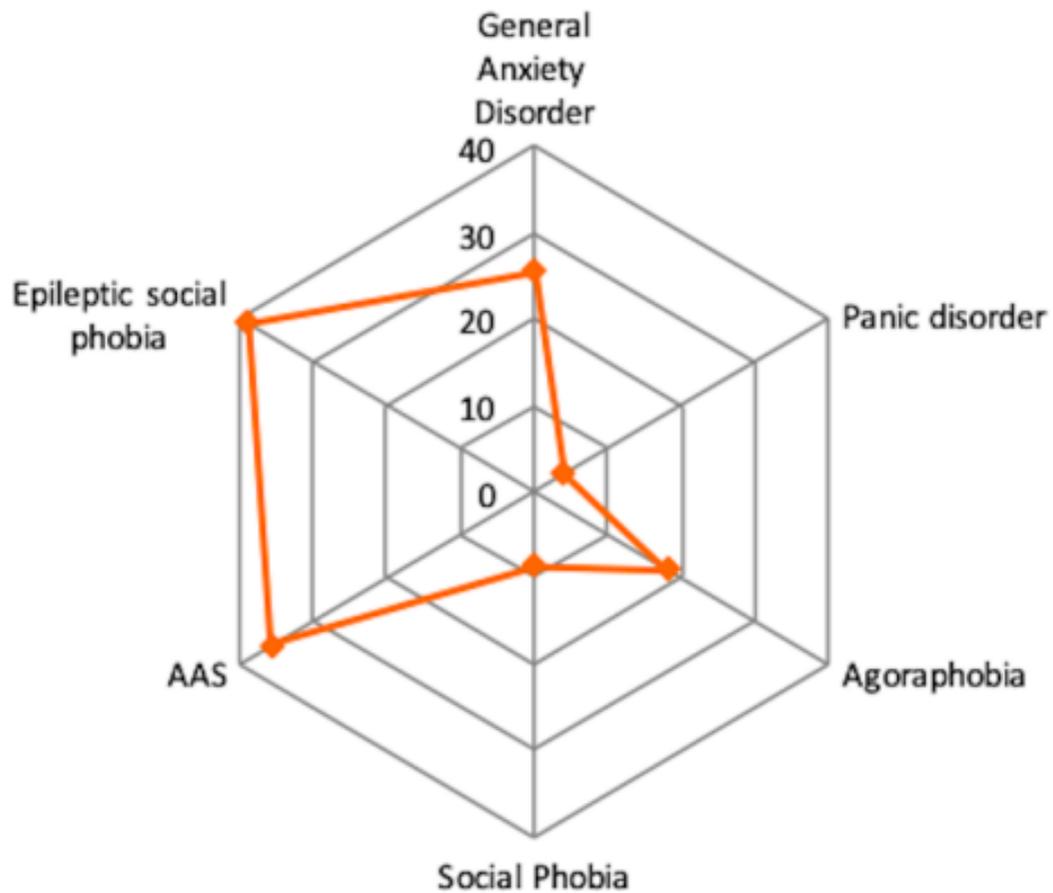


Figure 2

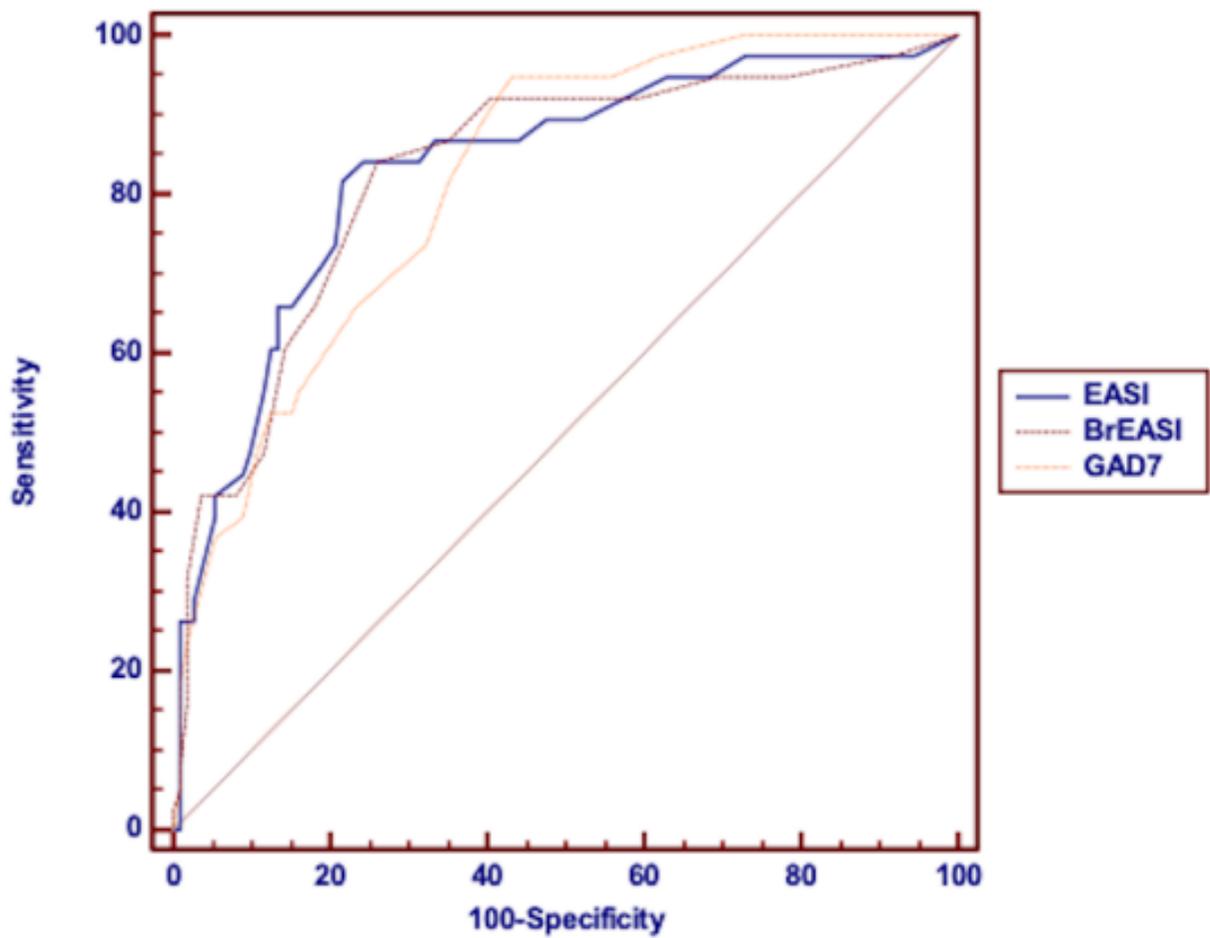


Figure 3

