Rapid detection of Generalized Anxiety Disorder and Major Depression in epilepsy: Validation of the GAD-7 as a complementary tool to the NDDI-E in a French sample

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ABSTRACT

Objective

Generalized Anxiety Disorder (GAD) in people with epilepsy (PWE) is under-diagnosed and under-treated. The GAD-7 is a screening questionnaire to detect GAD. However, the usefulness of the GAD-7 as a screening tool in PWE remains to be validated. Thus, we aimed to: (1) validate the GAD-7 in French PWE; (2) assess its complementarity with regards to the previously validated screening tool for depression, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).

Methods

This study was performed under the auspices of the ILAE Commission on Neuropsychiatry. PWE >18 years were recruited from the specialist epilepsy unit in Marseille, France. The Mini International Neuropsychiatric Interview (MINI) was performed as gold standard and the Penn State Worry Questionnaire (PSWQ) and the NDDI-E performed for external validity. Data were compared between PWE with/without GAD using Chi2 test and Student's t-test. Internal structural validity, external validity and receiver operator characteristics were analyzed. A principal component factor analysis with Varimax rotation was performed on the 13 items of the GAD-7 (7 items) plus the NDDI-E (6 items).

Results

Testing was performed on 145 PWE: mean age 39.38 years old (SD=14.01, range: [18-75]); 63.4% (92) women; 75.9 % focal epilepsy. Using the MINI, 49 (33.8%) patients had current GAD. Cronbach's alpha coefficient was 0.898, indicating satisfactory internal consistency. Correlation between GAD-7 and the PSQW scores was high (r (145) =.549, P< .0001), indicating good external validity. Factor analysis shows that the anxiety investigated with the GAD-7, and depression investigated with the NDDI-E, reflect distinct factors. Receiver operator characteristics analysis showed area under the curve of 0.899 (95% CI 0.838- 0.943),

(p<0.0001) indicating good capacity of the GAD-7 to detect GAD (defined by MINI). Cut-off for maximal sensitivity and specificity was 7. Mean GAD-7 score in PWE with GAD was 13.22 (SD= 3.99), without GAD 5.17 (SD= 4.66).

Significance

This study validates the French language version of the GAD-7 screening tool for generalized anxiety in PWE, with a cut-off score of 7/21 for GAD, and also confirms that the GAD-7 is a short and easily administered test. Factor analysis shows that the GAD-7 (screening for generalized anxiety disorder) and the NDDI-E (screening for major depression) provide complementary information. The routine use of both GAD-7 and NDDI-E should be considered in clinical evaluation of patients with epilepsy.

RUNING TITLE

Validation of the French GAD-7

KEY WORDS

Epilepsy; Generalized Anxiety Disorder; Psychiatric comorbidity; Screening tool; Validity; Reliability.

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1 Introduction

Psychiatric disorders are frequent comorbidities in patients with epilepsy (PWE) [1], major depressive episode (MDE) and generalized anxiety disorder (GAD) being the two most prevalent [2-5]. The presence of MDE and/or GAD is associated with higher seizure frequency [6-8], more adverse effects of antiepileptic drugs (AED) [9-11], greater risk of suicidal behaviour [12-14], increased complaints of cognitive deficit and lower quality of life [15, 16], as well as increased health care costs [17]. While various anxiety syndromes may occur in association with epilepsy, generalized anxiety disorder is characterized by disabling and persistent free-floating worry. In particular, GAD occurring in the context of epilepsy is often associated with fear of future seizures, fear of disease progression, or fear of specific complications [18, 19].

Since psychiatric comorbidities are a worldwide problem in PWE [20], clinicians need diagnostic tools adapted for local language and culture. The ideal tool is a highly sensitive and highly specific self-questionnaire developed for rapid screening of these comorbidities in PWE [21]. These short and easily administered tools, which can readily be incorporated into routine clinical evaluation, i) help to counteract the tendency to under-diagnosis and suboptimal treatment of these psychiatric comorbidities, primarily in order to increase the quality of life of PWE, with the additional benefit of reducing health care costs [20]; and ii) facilitate worldwide epidemiological investigation of the impact of psychiatric comorbidities in PWE once multiple language versions become available.

Concerning major depression in PWE, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) has now been translated into over 10 languages and validated in native speaking populations, under the auspices of the International League Against Epilepsy (ILAE) Commission on Neuropsychiatry [22-32]. Increasing the worldwide availability of reliable screening tools for psychiatric comorbidities is indeed a priority goal of the ILAE

Commission on Neuropsychiatry [33]. While screening for major depression has become easier with the NDDI-E, no such tool is currently widely available for screening for anxiety in epilepsy. As a consequence, GAD in epilepsy has not yet been extensively investigated [34] and clinicians still tend to underestimate its importance [22, 35, 36].

A self-reported symptom scale called the "GAD-7" was recently developed for primary care [37, 38] and is a promising reliable and practicable tool for rapid screening of GAD in PWE [39, 40]. This scale is similar to the NDDI-E as it is a self-reported questionnaire based on only a few items (7 for the GAD-7, and 6 for the NDDI-E), being shorter than classical self-reported screening questionnaires for GAD or MDE [41-44], which helps to optimize its use in a busy clinical practice. In addition it seems particularly well suited as a potential screening tool in PWE since it contains no somatic items that might be confused with symptoms related to epilepsy or AED [36]. Given differences in patient populations with different medical conditions, cultural and demographic factors (reflected in the variable cutoffs of questionnaires in different studies), validation of the GAD-7 specifically in PWE for each language is recommended [39]. The GAD-7 has been translated into multiple languages; the use of the GAD-7 in epilepsy has been so far validated in Korea and China [39, 40] and used in Spain [45], and the need to validate this tool for PWE in other languages has been highlighted by the ILAE [21, 33]. Thus in the present study we analyzed the psychometric properties of the French GAD-7 version in a representative sample of French PWE. In addition, we wished to assess whether different and complementary information was provided by the GAD-7 and the NDDI-E in our patient group.

2 Methods and Materials

2.1 Participants

PWE were recruited from the Clinical Neurophysiology Department of the Marseille University Hospital and the Hôpital Henri Gastaut, Marseille (these 2 centres forming part of an integrated specialist tertiary epilepsy service) over an 11-month period (November 2014-September 2015). Included subjects were different from those in our previous study [32]. Inclusion criteria were: native French-speaking adult patients (>18 years) with any type of active epilepsy according to the ILAE criteria [46], treated or not by antiepileptic drugs. The diagnosis of epilepsy was documented clinically and confirmed where necessary with video-EEG investigations. Both inpatients and outpatients were included. Exclusion criteria were: insufficient capacity to consent and to understand and answer the self-report questionnaires, and presence of other severe chronic medical, neurological, and psychiatric conditions (other than epilepsy). Gender, age, type and frequency of seizures, age of onset of epilepsy, number of antiepileptic drugs currently being taken, presence of vagal nerve stimulation and use of antidepressant drugs were noted.

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

2.2.2.1 Self-rated assessment

The GAD-7 [38, 47], the Penn State Worry Questionnaire (PSWQ) [48, 49] and the NDDIE [22, 32] were completed as part of the self-rated psychiatric assessment.

The GAD-7 consists of 7 items rated by the patients on a balanced four point Likert scale

ranging from “not at all” (score=0), “several days” (score=1), “More than half the days” (score=2), to “Nearly every day” (score=3) and takes less than three minutes to complete. The rating was determined according to patients’ experience in the preceding two weeks. The French version of the GAD-7 was developed according to a forward-backward translation by 2 independent native French speakers and 2 independent native English speakers [38, 47] and is freely downloadable on the patient Health Questionnaire website (www.phqscreeners.com). We assured the clarity and cultural acceptability of the French version of the GAD-7 in French PWE by administering it to 10 patients. This pre-test showed any difficulties in understanding the items of the French GAD-7 in PWE. No adaptations were required. The version of the French GAD-7 used in this study is shown in Table 1. The score range from 0 to 21. Use as a screening tools for GAD, cut-offs were found with values of 6 to 9 [38-40].

The PSWQ consists of 16 items rated by the patients on a balanced five point Likert scale ranging from 1 (“not at all typical of me”) to 5 (“very typical of me”). The PSWQ has previously been translated and validated in French [49]. The PSWQ is a score of severity of worry in the GAD [48]. The score range from 16 to 80. Use as a screening tools for GAD, cut-offs were found with values of 45 to 65 [43, 44, 48].

The NDDI-E consists of 6 items rated by the patients on a balanced four point Likert scale ranging from “never” (score=1), “rarely” (score=2), “sometimes” (score=3), to “always or often” (score=4) [22]. The rating was determined according to patients’ experience in the preceding two weeks. The NDDI-E has previously been translated and validated in French PWE [32]. The score range from 6 to 24. An NDDI-E score that is higher than 15 indicates increased risk of a current episode of major depression in French PWE [32].

2.2.1 Psychiatric assessment

The Generalized Anxiety Disorder module of the Mini International Neuropsychiatric Interview (MINI) was completed as part of the psychiatric assessment before the self-rated

assessment with the GAD-7, the PSWG and the NDDI-E. This is a short structured questionnaire to identify GAD according to the criteria of the DSM-IV TR [50]. The MINI has previously been validated in French [51]. For the purposes of the present study it was used as a gold standard for the diagnosis of current GAD.

2.3 Statistical analyses and hypotheses

Demographical and clinical data were compared between PWE with and without GAD using Chi2 test for categorical variables and Student's t-test for continuous variables.

Data analysis was performed using SPSS software (Version 18 for Mac, PASW Statistics) and MedCalc software (Version 14.8 for Windows). For all the tests, the accepted significance level was 5%.

2.3.1 Internal structural validity

To explore internal structural validity: item-internal consistency [52], internal consistency reliability (Cronbach's alpha coefficient) [52, 53], and floor and ceiling effects were computed.

2.3.2 External validity

To explore external validity, relations between the GAD-7 and the PSWQ and the NDDI-E were investigated by computing Pearson's coefficients. To investigate whether the anxiety investigated with the GAD-7 and depression investigated with the NDDI-E reflect distinct factors, a principal component factor analysis with Varimax rotation was performed on the 13 items of the GAD-7 (7 items) plus the NDDI-E (6 items). Items were included in a factor if they revealed a loading greater than 0.4.

2.3.3 Receiver operator characteristics

Receiver operator characteristics (ROC) analysis was calculated to assess the utility of the GAD-7 overall score to distinguish the diagnosis of GAD as defined by the MINI. Area under the curve (AUC) and its 95% confidence intervals for the ROC curve were calculated. 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.

3 Results

3.1 Sample characteristics

A total of 145 native French speakers with epilepsy were included. None of the patients reported any difficulties in understanding the items of the GAD-7.

The mean age was 39.38 years old (SD=14.01, range: [18-75] years old); 63.4% (92) were women; 75.9 % had focal epilepsy (110) of which 48.3% (70) were temporal lobe epilepsies. Only 4 subjects were untreated by antiepileptic drugs. The mean GAD-7 score was 7.89 (SD=5.85), the mean PSWQ was 41.60 (SD=12.23) and the mean NDDI-E score was 11.94 (SD=4.81). Using the MINI, a diagnosis of current MDE was established in 49 (33.8%) patients.

Demographical and clinical characteristics of PWE are detailed in **Table 2**. There was no significant difference between PWE with and without GAD.

3.2 Validity

3.2.1 Internal structural validity

Results are presented in **Table 1 and 3**.

The correlation between items with the overall corrected scores was globally higher than 0.4. All GAD-7 items were significantly and positively associated with the corrected overall GAD-7 score. The Cronbach's alpha coefficient was 0.898. Floor effects ranged from 23.4% to 57.2 % and ceiling effects ranged from 11% to 17.9 %.

3.2.2 External validity

The correlation between the GAD-7 and the PSWQ scores was high (r (145) =.549, P< .0001). The correlation between the GAD-7 and the NDDI-E scores was also high (r (145) =.664, P< .0001).

The principal component factoring analysis revealed two factors: the first with items of the GAD-7 and the second with the items of the NDDI-E. For each factor the value of item loads was greater than 0.4. The Varimax rotated component matrix clearly confirmed the allocation of the items to the GAD-7, with all anxiety items having the highest factor loading on dimension 1 (0.58-0.79) and all depression items having the highest factor loading on the second dimension (0.64-0.76). Item loads for each factor are indicated in **Table 4**.

3.2.3 Receiver operating characteristics (ROC)

ROC analysis of the GAD-7 showed an AUC of 0.899 (95% CI 0.838- 0.943), ($p<0.001$). The cut-off point that maximized both sensitivity and specificity was 7. The ROC is shown in **Figure 1 and Table 5**. At a cutoff score of 7, the GAD-7 had a sensitivity of 95.9 % [86.0; 99.5], a specificity of 76 % [66.3; 84.2], a positive predictive value (PPV) of 67.1 [54.9; 77.9], and a negative predictive value (NPV) of 97.3 % [90.7; 99.7]. The mean GAD-7 score in PWE with GAD was 13.22 (SD= 3.99), without GAD 5.17 (SD= 4.66). Among the 49 patients who met the criteria of GAD with the MINI, the GAD-7 correctly identified 47 PWE (true positives), while in 2 patients (false negative) the GAD-7 score did not indicate MDE. The 2 false negative patients have a GAD-7 at 6 and 7. On the 47 PWE with GAD, 24 (51.1%) had a diagnosis of MDE according to the NDDIE (score >15). In addition, 23 patients had scores >7 with the GAD-7 whereas the MINI did not indicate GAD (false positives). Eight of these 23 patients (34.8%) had a diagnosis of MDE according to the NDDIE (score >15).

4 Discussion

Our aim was to validate the use of the French version of the GAD-7, in order to make this self-rated questionnaire available for detection of GAD in the French-speaking epilepsy population. We also wished to evaluate whether the GAD-7 provided unique and complementary information in comparison to the NDDI-E or whether significant redundancy between the 2 scales was present.

Concerning the psychometric properties of the GAD-7, the present study shows these to be satisfactory. The internal consistency reliability was shown to be high (Cronbach's alpha > 0.70 for all) and the Item-internal consistency was globally satisfactory, indicating that the French GAD-7 has a good internal homogeneity in French PWE. The external validity explored with the PSWQ was excellent and confirms the link between the symptoms of GAD explored by the GAD-7 and the symptoms of worry (core symptoms of GAD) explored with the PSWQ. The GAD-7 and the NDDI-E scores were significantly correlated and half of patients with a diagnosis of GAD according to the MINI have a NDDI-E score higher than 15, in favour of a high risk of concurrent diagnosis of MDE. The high comorbidity between GAD and MDE, and the high correlation between anxiety and depressive measures are well described [38, 39, 54]. However, the factor analysis in the present study shows that anxiety as investigated with the GAD-7, and depression as investigated with the NDDI-E, reflect distinct factors. This result is similar to the finding of Spitzer et al. when they developed the GAD-7 for use in the general population [38]. Thus, the present result confirms the complementary value of assessing GAD and MDE with two different scales in PWE, as in primary care.

In the original version in primary care, a diagnosis of GAD was suspected with a cut-off score > 9, with a sensitivity of 89% and specificity of 82% [38]. In Korea and China, a diagnosis of GAD in PWE was suspected with a cut-off score > 6, respectively with a sensitivity of 92% and specificity of 89% [39] and with a sensitivity of 94% and specificity of 91% [40]. In the

present study, the GAD-7 in French PWE showed a cut-off score (>7) close to that of the GAD-7 in Korean and Chinese, with sensitivity of 96% and specificity of 76%. The specificity in the present study was therefore slightly lower than in previous studies [39, 40]. Moreover, with a cut-off score of 7, the PPV was 67%. These psychometric properties may lead to false-positive results. These false-positive results can be explained by the fact that the GAD-7 investigates anxiety related problems over the past two weeks, whereas the MINI interview investigates GAD over the past 6 months. However, since the GAD-7 is a screening instrument it can be argued that good sensitivity (as occurred in our study) is the more important indicator in order to limit false negatives. Since false positives are possible, it is recommended that patients with a GAD-7 higher than 7 be evaluated clinically by a psychiatrist.

The reasons for the differences in cutoff in studies of GAD-7 in PWE compared to the use of the GAD-7 in non-PWE primary care remain somewhat unclear. It has been commented that the lower cutoff in PWE (despite high prevalence of anxiety symptoms in this population) could reflect relative under-reporting of symptoms by patients. This could be due to various factors, including a tendency for patients to underestimate their symptoms of worry on the balanced four point Likert scale due to chronic ictal, postictal, and interictal anxiety in line with their epilepsy *per se* [18]; or an unwillingness to disclose their worries because of perceived stigma [55]. However this discrepancy also highlights that the specific characteristics of anxiety disorders in PWE compared with GAD in general patient populations remain rather poorly known and require better characterization [18, 19].

Concerning the sample of this study, around a third of patients tested showed signs of GAD. This prevalence is relatively high but within the range previously described, that is, 11-50% [4]. The fairly high proportion of temporal lobe epilepsy (TLE) in our study (accounting for nearly half of all patients) may partly help to explain this high prevalence [56, 57]. Compared

to PWE in general, patient with temporal lobe epilepsy tend to have more worry and anxiety symptoms, and stress is commonly reported to be a particular precipitant factor of seizures [58-60]. On the other hand, there was no difference in our study in terms of the proportion of TLE in the groups with and without GAD.

One limitation of this study is indeed that patients were recruited from a specialist tertiary care epilepsy centre, thus introducing a likely bias toward patients with more severe epilepsy; these include a number of patients requiring or having undergone epilepsy surgery, this being itself a risk factor for development of anxiety disorders [18]. Thus, further studies should ideally investigate the reliability of the GAD-7 and test the appropriate the cut-off in a larger population of PWE in primary care.

It is of interest that our study suggested the existence of different subgroups of PWE: those with neither GAD nor major depression; those with GAD alone; those with major depression alone; and those with co-existing GAD and major depression. Since we did not design the study primarily to examine these aspects and in particular did not routinely perform both the MINI Major Depression Episode module as well as the other anxiety modules in all patients, no firm conclusions can be drawn from the present data, but these different clinical profiles could be explored in appropriately designed future studies.

Finally, the present study shows a high comorbidity between GAD and MDE, high correlation between anxiety (GAD-7) and depressive (NDDI-E) measures and a lower cut-off of the GAD-7 in PWE than in previous studies in subjects without epilepsy. These observations highlight the likely complex interactions between stress, anxiety and depression with regards to seizure frequency and other factors specific to epilepsy in PWE [18, 61, 62]. These aspects merit exploration in future studies, to explore the directional links between anxiety, depression and seizures [61], and to identify possible risk factors for the different subgroups of PWE according to the presence of GAD and major depression comorbidity, such as

epilepsy type, etiology, seizure frequency, gender and so on. Impact of psychiatric treatment such as drugs (antidepressants, anxiolytics and antipsychotics) and cognitive behavioral therapy (CBT) on these links should be also investigated.

In conclusion, the French version of the GAD-7 is a psychometrically acceptable self-reported questionnaire for detecting GAD in French PWE. The present study shows that the NDDI-E (screening for major depression) and the GAD-7 (screening for generalized anxiety disorder) are two complementary, rapidly and easily administered tests that can and indeed should be incorporated into routine clinical evaluation [21]. As for the NDDI-E, wider multi-language availability of the GAD-7 will also help promote investigation of GAD in a global, epidemiological perspective of epilepsy.

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Conflict of interest

We report no conflicts of interest.

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

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