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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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1 **TITLE PAGE**

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4 **Rapid detection of Generalized Anxiety Disorder and Major Depression in epilepsy:**

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6

7

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4

1 ABSTRACT

2 **Objective**

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

9 **Methods**

10 This study was performed under the auspices of the ILAE Commission on Neuropsychiatry.
11 PWE >18 years were recruited from the specialist epilepsy unit in Marseille, France. The
12 Mini International Neuropsychiatric Interview (MINI) was performed as gold standard and
13 the Penn State Worry Questionnaire (PSWQ) and the NDDI-E performed for external
14 validity. Data were compared between PWE with/without GAD using Chi2 test and Student's
15 t-test. Internal structural validity, external validity and receiver operator characteristics were
16 analyzed. A principal component factor analysis with Varimax rotation was performed on the
17 13 items of the GAD-7 (7 items) plus the NDDI-E (6 items).

18 **Results**

19 Testing was performed on 145 PWE: mean age 39.38 years old (SD=14.01, range: [18-75]);
20 63.4% (92) women; 75.9 % focal epilepsy. Using the MINI, 49 (33.8%) patients had current
21 GAD. Cronbach's alpha coefficient was 0.898, indicating satisfactory internal consistency.
22 Correlation between GAD-7 and the PSQW scores was high ($r(145) = .549, P < .0001$),
23 indicating good external validity. Factor analysis shows that the anxiety investigated with the
24 GAD-7, and depression investigated with the NDDI-E, reflect distinct factors. Receiver
25 operator characteristics analysis showed area under the curve of 0.899 (95% CI 0.838- 0.943),

1 (p<0.0001) indicating good capacity of the GAD-7 to detect GAD (defined by MINI). Cut-off
2 for maximal sensitivity and specificity was 7. Mean GAD-7 score in PWE with GAD was
3 13.22 (SD= 3.99), without GAD 5.17 (SD= 4.66).

4 **Significance**

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

11

12

1 RUNING TITLE

2 **Validation of the French GAD-7**

3

4 KEY WORDS

5 Epilepsy; Generalized Anxiety Disorder; Psychiatric comorbidity; Screening tool; Validity;

6 Reliability.

7

8 WORD COUNT

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10

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13

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17

18

1 **1 Introduction**

2 Psychiatric disorders are frequent comorbidities in patients with epilepsy (PWE) [1], major
3 depressive episode (MDE) and generalized anxiety disorder (GAD) being the two most
4 prevalent [2-5]. The presence of MDE and/or GAD is associated with higher seizure
5 frequency [6-8], more adverse effects of antiepileptic drugs (AED) [9-11], greater risk of
6 suicidal behaviour [12-14], increased complaints of cognitive deficit and lower quality of life
7 [15, 16], as well as increased health care costs [17]. While various anxiety syndromes may
8 occur in association with epilepsy, generalized anxiety disorder is characterized by disabling
9 and persistent free-floating worry. In particular, GAD occurring in the context of epilepsy is
10 often associated with fear of future seizures, fear of disease progression, or fear of specific
11 complications [18, 19].

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

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

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

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

22

23

1 **2 Methods and Materials**

2 **2.1 Participants**

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

16 Patients were invited to participate in the study during their routine neurological evaluation.
17 After receiving a detailed description of the study, participants gave their informed consent.
18 This study was conducted in accordance with the Declaration of Helsinki and French Good
19 Clinical Practices.

20 **2.2 Procedure**

21 **2.2.2.1 Self-rated assessment**

22 The GAD-7 [38, 47], the Penn State Worry Questionnaire (PSWQ) [48, 49] and the NDDIE
23 [22, 32] were completed as part of the self-rated psychiatric assessment.

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

1 ranging from “not at all” (score=0), “several days” (score=1), “More than half the days”
2 (score=2), to “Nearly every day” (score=3) and takes less than three minutes to complete. The
3 rating was determined according to patients’ experience in the preceding two weeks. The
4 French version of the GAD-7 was developed according to a forward-backward translation by
5 2 independent native French speakers and 2 independent native English speakers [38, 47] and
6 is freely downloadable on the patient Health Questionnaire website (www.phqscreeners.com).
7 We assured the clarity and cultural acceptability of the French version of the GAD-7 in
8 French PWE by administering it to 10 patients. This pre-test showed any difficulties in
9 understanding the items of the French GAD-7 in PWE. No adaptations were required. The
10 version of the French GAD-7 used in this study is shown in Table 1. The score range from 0
11 to 21. Use as a screening tools for GAD, cut-offs were found with values of 6 to 9 [38-40].

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

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

23 **2.2.1 Psychiatric assessment**

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

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

5 **2.3 Statistical analyses and hypotheses**

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

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

11 **2.3.1 Internal structural validity**

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

15 **2.3.2 External validity**

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

1 **2.3.3 Receiver operator characteristics**

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

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

8

9

10

1 **3 Results**

2 **3.1 Sample characteristics**

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

5 The mean age was 39.38 years old (SD=14.01, range: [18-75] years old); 63.4% (92) were
6 women; 75.9 % had focal epilepsy (110) of which 48.3% (70) were temporal lobe epilepsies.

7 Only 4 subjects were untreated by antiepileptic drugs. The mean GAD-7 score was 7.89
8 (SD=5.85), the mean PSWQ was 41.60 (SD=12.23) and the mean NDDI-E score was 11.94
9 (SD=4.81). Using the MINI, a diagnosis of current MDE was established in 49 (33.8%)
10 patients.

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

13 **3.2 Validity**

14 **3.2.1 Internal structural validity**

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

16 The correlation between items with the overall corrected scores was globally higher than 0.4.

17 All GAD-7 items were significantly and positively associated with the corrected overall
18 GAD-7 score. The Cronbach's alpha coefficient was 0.898. Floor effects ranged from 23.4%
19 to 57.2 % and ceiling effects ranged from 11% to 17.9 %.

20 **3.2.2 External validity**

21 The correlation between the GAD-7 and the PSWQ scores was high ($r(145) = .549, P <$
22 $.0001$). The correlation between the GAD-7 and the NDDI-E scores was also high ($r(145)$
23 $= .664, P < .0001$).

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

7 **3.2.3 Receiver operating characteristics (ROC)**

8 ROC analysis of the GAD-7 showed an AUC of 0.899 (95% CI 0.838- 0.943), ($p < 0.001$). The
9 cut-off point that maximized both sensitivity and specificity was 7. The ROC is shown in
10 **Figure 1 and Table 5**. At a cutoff score of 7, the GAD-7 had a sensitivity of 95.9 % [86.0;
11 99.5], a specificity of 76 % [66.3; 84.2], a positive predictive value (PPV) of 67.1 [54.9;
12 77.9], and a negative predictive value (NPV) of 97.3 % [90.7; 99.7]. The mean GAD-7 score
13 in PWE with GAD was 13.22 (SD= 3.99), without GAD 5.17 (SD= 4.66). Among the 49
14 patients who met the criteria of GAD with the MINI, the GAD-7 correctly identified 47 PWE
15 (true positives), while in 2 patients (false negative) the GAD-7 score did not indicate MDE.
16 The 2 false negative patients have a GAD-7 at 6 and 7. On the 47 PWE with GAD, 24
17 (51.1%) had a diagnosis of MDE according to the NDDIE (score > 15). In addition, 23
18 patients had scores > 7 with the GAD-7 whereas the MINI did not indicate GAD (false
19 positives). Eight of these 23 patients (34.8%) had a diagnosis of MDE according to the
20 NDDIE (score > 15).

21

1 **4 Discussion**

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

7 Concerning the psychometric properties of the GAD-7, the present study shows these to be
8 satisfactory. The internal consistency reliability was shown to be high (Cronbach's alpha >
9 0.70 for all) and the Item-internal consistency was globally satisfactory, indicating that the
10 French GAD-7 has a good internal homogeneity in French PWE. The external validity
11 explored with the PSWQ was excellent and confirms the link between the symptoms of GAD
12 explored by the GAD-7 and the symptoms of worry (core symptoms of GAD) explored with
13 the PSWQ. The GAD-7 and the NDDI-E scores were significantly correlated and half of
14 patients with a diagnosis of GAD according to the MINI have a NDDI-E score higher than 15,
15 in favour of a high risk of concurrent diagnosis of MDE. The high comorbidity between GAD
16 and MDE, and the high correlation between anxiety and depressive measures are well
17 described [38, 39, 54]. However, the factor analysis in the present study shows that anxiety as
18 investigated with the GAD-7, and depression as investigated with the NDDI-E, reflect distinct
19 factors. This result is similar to the finding of Spitzer et al. when they developed the GAD-7
20 for use in the general population [38]. Thus, the present result confirms the complementary
21 value of assessing GAD and MDE with two different scales in PWE, as in primary care.

22 In the original version in primary care, a diagnosis of GAD was suspected with a cut-off score
23 > 9, with a sensitivity of 89% and specificity of 82% [38]. In Korea and China, a diagnosis of
24 GAD in PWE was suspected with a cut-off score > 6, respectively with a sensitivity of 92%
25 and specificity of 89% [39] and with a sensitivity of 94% and specificity of 91% [40]. In the

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

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

22 Concerning the sample of this study, around a third of patients tested showed signs of GAD.
23 This prevalence is relatively high but within the range previously described, that is, 11-50%
24 [4]. The fairly high proportion of temporal lobe epilepsy (TLE) in our study (accounting for
25 nearly half of all patients) may partly help to explain this high prevalence [56, 57]. Compared

1 to PWE in general, patient with temporal lobe epilepsy tend to have more worry and anxiety
2 symptoms, and stress is commonly reported to be a particular precipitant factor of seizures
3 [58-60]. On the other hand, there was no difference in our study in terms of the proportion of
4 TLE in the groups with and without GAD.

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

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

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

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

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

11

12

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5 National Research Agency (ANR).

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7 Timone Hospital and Henri Gastaut Hospital.

8

9 **Conflict of interest**

10 We report no conflicts of interest.

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

13

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1 **References**

2

3 [1] Kanner AM. Do psychiatric comorbidities have a negative impact on the course and
4 treatment of seizure disorders? *Curr Opin Neurol* 2013;26: 208-13.

5 [2] Kwon OY, Park SP. Depression and anxiety in people with epilepsy. *J Clin Neurol*
6 2014;10: 175-88.

7 [3] Kwon OY, Park SP. Frequency of affective symptoms and their psychosocial impact
8 in Korean people with epilepsy: a survey at two tertiary care hospitals. *Epilepsy Behav*
9 2012;26: 51-6.

10 [4] Munger Clary H. Anxiety and epilepsy: what neurologists and epileptologists should
11 know. *Curr Neurol Neurosci Rep* 2014;14: 445.

12 [5] Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta*
13 *Neurol Scand* 2004;110: 207-20.

14 [6] Kanner AM, Byrne R, Chicharro A, Wu J, Frey M. A lifetime psychiatric history
15 predicts a worse seizure outcome following temporal lobectomy. *Neurology* 2009;72: 793-9.

16 [7] Petrovski S, Szoeki CE, Jones NC, Salzberg MR, Sheffield LJ, Huggins RM, O'Brien
17 TJ. Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients.
18 *Neurology* 2010;75: 1015-21.

19 [8] Thapar A, Roland M, Harold G. Do depression symptoms predict seizure frequency--
20 or vice versa? *J Psychosom Res* 2005;59: 269-74.

21 [9] Panelli RJ, Kilpatrick C, Moore SM, Matkovic Z, D'Souza WJ, O'Brien TJ. The
22 Liverpool Adverse Events Profile: relation to AED use and mood. *Epilepsia* 2007;48: 456-63.

23 [10] Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. Depressive and anxiety
24 disorders in epilepsy: do they differ in their potential to worsen common antiepileptic drug-
25 related adverse events? *Epilepsia* 2012;53: 1104-8.

26 [11] Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, Gatti G, La
27 Neve A, Muscas G, Specchio LM, Striano S, Perucca E. Determinants of health-related
28 quality of life in pharmacoresistant epilepsy: results from a large multicenter study of
29 consecutively enrolled patients using validated quantitative assessments. *Epilepsia* 2011;52:
30 2181-91.

31 [12] Seo JG, Lee JJ, Cho YW, Lee SJ, Kim JE, Moon HJ, Park SP. Suicidality and Its Risk
32 Factors in Korean People with Epilepsy: A MEPSY Study. *J Clin Neurol* 2015;11: 32-41.

- 1 [13] Gandy M, Sharpe L, Perry KN, Miller L, Thayer Z, Boserio J, Mohamed A. Rates of
2 DSM-IV mood, anxiety disorders, and suicidality in Australian adult epilepsy outpatients: a
3 comparison of well-controlled versus refractory epilepsy. *Epilepsy Behav* 2013;26: 29-35.
- 4 [14] Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk
5 factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy Behav*
6 2003;4 Suppl 3: S31-8.
- 7 [15] Velissaris SL, Wilson SJ, Newton MR, Berkovic SF, Saling MM. Cognitive
8 complaints after a first seizure in adulthood: Influence of psychological adjustment. *Epilepsia*
9 2009;50: 1012-21.
- 10 [16] Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression
11 but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology*
12 2004;62: 258-61.
- 13 [17] Cramer JA, Blum D, Fanning K, Reed M. The impact of comorbid depression on
14 health resource utilization in a community sample of people with epilepsy. *Epilepsy Behav*
15 2004;5: 337-42.
- 16 [18] Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with
17 epilepsy: systematic review and suggestions for clinical management. *Epilepsy Behav* 2005;7:
18 161-71.
- 19 [19] Choi-Kwon S, Chung C, Kim H, Lee S, Yoon S, Kho H, Oh J. Factors affecting the
20 quality of life in patients with epilepsy in Seoul, South Korea. *Acta Neurol Scand* 2003;108:
21 428-34.
- 22 [20] de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. *Epilepsy*
23 *Behav* 2008;12: 540-6.
- 24 [21] Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, Kanner A, Kemp
25 S, Krishnamoorthy E, LaFrance WC, Jr., Mula M, Schmitz B, van Elst LT, Trollor J, Wilson
26 SJ. International consensus clinical practice statements for the treatment of neuropsychiatric
27 conditions associated with epilepsy. *Epilepsia* 2011;52: 2133-8.
- 28 [22] Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. Rapid
29 detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 2006;5: 399-
30 405.
- 31 [23] de Oliveira GN, Kummer A, Salgado JV, Portela EJ, Sousa-Pereira SR, David AS,
32 Kanner AM, Teixeira AL. Brazilian version of the Neurological Disorders Depression
33 Inventory for Epilepsy (NDDI-E). *Epilepsy Behav* 2010;19: 328-31.

- 1 [24] Thomson AE, Calle A, Fontela ME, Yopez L, Munoz Giacomelli F, Jauregui A,
2 Racosta JM, Kanner AM. Screening of major depression in epilepsy: the Neurologic
3 Depression Disorders Inventory in Epilepsy-Spanish version (Argentina). *Epilepsia* 2014;55:
4 331-4.
- 5 [25] Di Capua D, Garcia-Garcia ME, Reig-Ferrer A, Fuentes-Ferrer M, Toledano R, Gil-
6 Nagel A, Garcia-Ptaceck S, Kurtis M, Kanner AM, Garcia-Morales I. Validation of the
7 Spanish version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).
8 *Epilepsy Behav* 2012;24: 493-6.
- 9 [26] Mula M, Iudice A, La Neve A, Mazza M, Bartolini E, De Caro MF, Mazza S, Kanner
10 AM, Cantello R. Validation of the Italian version of the Neurological Disorders Depression
11 Inventory for Epilepsy (NDDI-E). *Epilepsy Behav* 2012;24: 329-31.
- 12 [27] Metternich B, Wagner K, Buschmann F, Anger R, Schulze-Bonhage A. Validation of
13 a German version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-
14 E). *Epilepsy Behav* 2012;25: 485-8.
- 15 [28] Tadokoro Y, Oshima T, Fukuchi T, Kanner AM, Kanemoto K. Screening for major
16 depressive episodes in Japanese patients with epilepsy: validation and translation of the
17 Japanese version of Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).
18 *Epilepsy Behav* 2012;25: 18-22.
- 19 [29] Zis P, Yfanti P, Siatouni A, Tavernarakis A, Gatzonis S. Validation of the Greek
20 version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). *Epilepsy*
21 *Behav* 2013;29: 513-5.
- 22 [30] Alkhamees HA, Selai CE, Shorvon SD, Kanner AM. The use of the NDDI-E in
23 Arabic to identify symptoms of depression of moderate or greater severity in people with
24 epilepsy. *Epilepsy Behav* 2014;32: 55-8.
- 25 [31] Ko PW, Hwang J, Lim HW, Park SP. Reliability and validity of the Korean version of
26 the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E). *Epilepsy Behav*
27 2012;25: 539-42.
- 28 [32] Micoulaud-Franchi JA, Barkate G, Trebuchon-Da Fonseca A, Vaugier L, Gavaret M,
29 Bartolomei F, McGonigal A. One step closer to a global tool for rapid screening of major
30 depression in epilepsy: Validation of the French NDDI-E. *Epilepsy Behav* 2015;44: 11-6.
- 31 [33] ILAE. Commission on Neuropsychiatry, Annual report. In; 2014.
- 32 [34] Gilliam F, Hecimovic H, Sheline Y. Psychiatric comorbidity, health, and function in
33 epilepsy. *Epilepsy Behav* 2003;4 Suppl 4: S26-30.

- 1 [35] Kanner AM, Barry JJ. The impact of mood disorders in neurological diseases: should
2 neurologists be concerned? *Epilepsy Behav* 2003;4 Suppl 3: S3-13.
- 3 [36] Kanner AM. Anxiety disorders in epilepsy: the forgotten psychiatric comorbidity.
4 *Epilepsy Curr* 2011;11: 90-1.
- 5 [37] Ruiz MA, Zamorano E, Garcia-Campayo J, Pardo A, Freire O, Rejas J. Validity of the
6 GAD-7 scale as an outcome measure of disability in patients with generalized anxiety
7 disorders in primary care. *J Affect Disord* 2011;128: 277-86.
- 8 [38] Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing
9 generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166: 1092-7.
- 10 [39] Seo JG, Cho YW, Lee SJ, Lee JJ, Kim JE, Moon HJ, Park SP. Validation of the
11 generalized anxiety disorder-7 in people with epilepsy: a MEPSY study. *Epilepsy Behav*
12 2014;35: 59-63.
- 13 [40] Tong X, An D, McGonigal A, Park S, Zhou D. Validation of the Generalized Anxiety
14 Disorder-7 (GAD-7) among Chinese people with epilepsy. *Epilepsy Res* 2015;120: 31-6.
- 15 [41] Jones JE, Hermann BP, Woodard JL, Barry JJ, Gilliam F, Kanner AM, Meador KJ.
16 Screening for major depression in epilepsy with common self-report depression inventories.
17 *Epilepsia* 2005;46: 731-5.
- 18 [42] Bandelow B, Brassler M. Clinical suitability of GAD-7 scale compared to hospital
19 anxiety and depression scale-A for monitoring treatment effects in generalized anxiety
20 disorder. *European Neuropsychopharmacology* 2009;19.
- 21 [43] Behar E, Alcaine O, Zullig AR, Borkovec TD. Screening for generalized anxiety
22 disorder using the Penn State Worry Questionnaire: a receiver operating characteristic
23 analysis. *J Behav Ther Exp Psychiatry* 2003;34: 25-43.
- 24 [44] Fresco DM, Mennin DS, Heimberg RG, Turk CL. Using the Penn State Worry
25 Questionnaire to identify individuals with generalized anxiety disorder: a receiver operating
26 characteristic analysis. *J Behav Ther Exp Psychiatry* 2003;34: 283-91.
- 27 [45] Callejas R, Rodriguez-Leyva I. Assessment of Anxiety, Depression and Quality of
28 Life in Patients with Epilepsy using three Spanish Validated scores: GAD-7, PHQ-9 and
29 QOLIE-10-P (P3.197). *Neurology* 2015;84: Supplement P3.197.
- 30 [46] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Jr.,
31 Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca
32 E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical
33 definition of epilepsy. *Epilepsia* 2014;55: 475-82.
- 34 [47] Spitzer RL, Williams J, Kroenke K. French version of the GAD-7. In.

- 1 [48] Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the
2 Penn State Worry Questionnaire. *Behav Res Ther* 1990;28: 487-95.
- 3 [49] Gosselin P, Dugas MJ, Ladouceur R, Freeston MH. [Evaluation of worry: validation
4 of a French translation of the Penn State Worry Questionnaire]. *Encephale* 2001;27: 475-84.
- 5 [50] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental*
6 *Disorder, 4th ed, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric
7 Association; 2000.
- 8 [51] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T,
9 Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the
10 development and validation of a structured diagnostic psychiatric interview for DSM-IV and
11 ICD-10. *J Clin Psychiatry* 1998;59 Suppl 20: 22-33;quiz 34-57.
- 12 [52] Carey RG, Seibert JH. A patient survey system to measure quality improvement:
13 questionnaire reliability and validity. *Med Care* 1993;31: 834-45.
- 14 [53] Cronbach LJ, Meehl PE. Construct validity in psychological tests. *Psychol Bull*
15 1955;52: 281-302.
- 16 [54] Kimiskidis VK, Triantafyllou NI, Kararizou E, Gatzonis SS, Fountoulakis KN,
17 Siatouni A, Loucaidis P, Pseftogianni D, Vlaikidis N, Kaprinis GS. Depression and anxiety in
18 epilepsy: the association with demographic and seizure-related variables. *Ann Gen Psychiatry*
19 2007;6: 28.
- 20 [55] Baker GA. People with epilepsy: what do they know and understand, and how does
21 this contribute to their perceived level of stigma? *Epilepsy Behav* 2002;3: 26-32.
- 22 [56] Kimiskidis VK, Valeta T. Epilepsy and anxiety: epidemiology, classification,
23 aetiology, and treatment. *Epileptic Disord* 2012;14: 248-56.
- 24 [57] Mensah SA, Beavis JM, Thapar AK, Kerr MP. A community study of the presence of
25 anxiety disorder in people with epilepsy. *Epilepsy Behav* 2007;11: 118-24.
- 26 [58] Ferlisi M, Shorvon S. Seizure precipitants (triggering factors) in patients with
27 epilepsy. *Epilepsy Behav* 2014;33: 101-5.
- 28 [59] Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants
29 among epilepsy syndromes. *Epilepsia* 2000;41: 1534-9.
- 30 [60] Lanteaume L, Bartolomei F, Bastien-Toniazzo M. How do cognition, emotion, and
31 epileptogenesis meet? A study of emotional cognitive bias in temporal lobe epilepsy. *Epilepsy*
32 *Behav* 2009;15: 218-24.
- 33 [61] Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: investigating
34 the relationship between psychological factors and seizures. *Epilepsy Behav* 2009;14: 134-40.

1 [62] Kotwas I, McGonigal A, Trebuchon A, Bastien-Toniazzo M, Nagai Y, Bartolomei F,
2 Micoulaud-Franchi JA. Self-control of epileptic seizures by nonpharmacological strategies.
3 *Epilepsy Behav* 2016;55: 157-164.

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