Epilepsy & Behavior 24 (2012) 493–496

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Validation of the Spanish version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

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ARTICLE INFO

Article history:
Received 22 April 2012
Revised 5 June 2012
Accepted 7 June 2012
Available online 10 July 2012

Keywords:
Psychiatric comorbidity
Major depressive episode
Patients with epilepsy
NDDI-E
Screening tool

ABSTRACT

Introduction: To translate and validate into Spanish (Spain) the screening instrument of major depressive episodes (MDEs), Neurological Disorders Depression Inventory in Epilepsy (NDDI-E), in patients with epilepsy.
Methods: A total of 121 outpatients, aged 18 years and older, with a diagnosis of epilepsy were included. The diagnosis of a current major depressive episode (MDE) was established with the Mini International Neuropsychiatric Interview (MINI).
Results: A diagnosis of current MDE was established in 20% of the patients with the MINI. Receiver operator characteristics (ROC) analysis showed an area under the curve of 0.89, with an internal consistency of 0.78. At a cutoff score >13, 22% of patients were considered to suffer from MDE with the NDDI-E (sensitivity: 84%; specificity: 78%; positive predictive value: 64.7%; and negative predictive value: 92.2%).
Discussion: The Spanish-Spain version of the NDDI-E appears to be a good screening instrument to identify MDE.

1. Introduction

Affective disorders, especially depression, are the most frequent psychiatric comorbidity in patients with epilepsy (PWE). Compared to the general population, PWE have a 5- to10-fold higher risk of experiencing a depressive disorder with lifetime prevalence rates estimated to range between 30 and 35% [1,2]. Depression is more frequent in patients with focal epilepsy and in those patients with uncontrolled seizures [3,4].

Despite the relatively high prevalence of depression in epilepsy, it is under-recognized and under-treated. And yet, early recognition of depressive disorders is of the essence as they have a negative impact in the quality of life of these patients, even after controlling for seizure frequency, severity, and other psychosocial variables [5–8]; it has been found to increase health care costs (not necessarily related to the mood disorder) [9,10] and of greater concern, it has been associated with a 32-fold increased risk of completed suicide [11]. Furthermore, depressive disorders have also been associated with a worse response to pharmacotherapy of the seizure disorder [12].

Major depressive episodes (MDEs) are the most severe expression of depression. To help identify MDE in PWE, Gilliam and colleges developed a brief, simple, self-rating screening instrument, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [13]. The NDDI-E includes six items rated in a Likert scale (1 = absent, 4 = all the time) (Table 1). A diagnosis of current MDE is suspected with a cutoff score >15; for this diagnosis, the NDDI-E has a specificity of 90%, a sensitivity of 81%, a positive predictive value (PPV) of 62% and a negative predictive value (NPV) of 96%. Its internal consistency is 0.85 and test–retest reliability is 0.78. This instrument takes 3 min to complete and has the advantage of not including any somatic or cognitive symptoms that can also result from toxicity of the antiepileptic drugs (AEDs) or cognitive deficits associated with the underlying neurologic disorder [14,15].

The objective of our study was to translate and validate into Spanish of Spain the English version of the NDDI-E in patients with epilepsy.

2. Methods

2.1. Participants

A total of 121 consecutive adult outpatients suffering from epilepsy and 18 years old and older treated in the Epilepsy Service of the

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doi:10.1016/j.yebeh.2012.06.005

Table 1
English version/Spanish version and frequency of response for each of the items of the NDDI-E.

	Always/often/Siempre o casi siempre	Sometimes/A veces	Rarely/Rara vez	Never/Nunca
Everything is a struggle/Todo me supone un esfuerzo	25 (21%)	40 (33%)	30 (25%)	26 (21%)
Nothing I do is right/Nada de lo que hago me sale bien	10 (8%)	42 (35%)	23 (19%)	46 (38%)
Feel guilty/Me siento culpable	11 (9%)	31 (26%)	27 (22%)	52 (43%)
I'd be better off dead/Siento que estaría mejor muerto	8 (7%)	11 (9%)	8 (7%)	94 (78%)
Frustrated/Me siento frustrado	21 (17%)	32 (26%)	25 (21%)	43 (36%)
Difficulty finding pleasure/Tengo dificultad para sentir placer	18 (15%)	17 (14%)	21 (17%)	65 (54%)

Hospital Universitario Clinico San Carlos, a tertiary care public center in Madrid, were included in this study. The diagnosis of epilepsy was documented clinically and confirmed with EEG studies. All patients had also undergone a brain MRI. Patients' epileptic seizure type(s) and syndrome were established according to the classification of the International League Against Epilepsy [16]. Patients with psychogenic non epileptic seizures, or with other neurological or psychiatric disorders that prevented them from understanding the questionnaires were excluded.

The study protocol and informed consent were approved by the local ethics committees. All patients signed a written informed consent.

2.2. Procedures

The diagnosis of MDE was established with the Spanish version of the Mini International Neuropsychiatric Interview (MINI), which also identified other types of mood disorders (e.g., dysthymia) and suicide risk. Only the mood disorder module of the MINI was administered. The questionnaire was administered by the same neurologist (DD) who has expertise in the field of epilepsy.

The MINI is the most widely used and validated short structured questionnaire to identify DSM-IV-TR Axis 1 diagnosis [17,18] and was used as the gold standard for the diagnosis of current MDE.

The translation from English to the Spanish version of the NNDI-E was carried out with the Brislin technique [19] for the translation of questionnaires into other languages. It was achieved through two translations from English to Spanish, followed by two back translations from Spanish to English, with the participation of independent bilingual translators who were not familiar with the NDDI-E. The first Spanish version was tested in 20 patients to identify any item that may not be well understood or may cause confusion. The final version was reviewed and approved by one of the authors (A.M.K.) of the NDDI-E (Table 1).

The procedure and design of this study followed the instructions provided by one of the original authors of the NDDI-E (A.M.K.). In principle, our method is close to the one used by Oliviera et al. to validate the Brazilian version of the NDDI-E [14]. By utilizing the same procedure, all the validations of NDDI-E in different languages can be compared.

Additional data were collected and included socio-demographic (age, gender) and epilepsy-related information, such as age of onset of epilepsy, epileptic syndrome, type and frequency of seizures, etiology and currently prescribed AEDs.

3. Statistical analysis

Variables are presented with their frequency distribution. Quantitative variables are summarized by their mean and standard deviation (±SD). Quantitative variables that show asymmetrical distribution are summarized by their median interquartile range (IQR). The association between qualitative variables was evaluated by the χ^2 test or Fisher's exact test, in the event that more than 25% of the expected would be lower than 5. For quantitative variables, measures were compared through Student's *t*-test or the non-parametric U Mann–Whitney test if the quantitative variables would not adjust to a normal distribution. Internal consistency was determined with Cronbach's alpha coefficient and was recalculated after items were removed. The Pearson correlation coefficient was calculated for the relationship between each of the items and the total corrected score.

Receiver operator characteristics (ROC) analysis was calculated to assess the utility of the NDDI-E global score to distinguish the diagnosis of major depression defined by the MINI. Area under the curve (AUC) and its 95% confidence intervals (CI) for the ROC curve were calculated.

For all of these tests, the accepted significance level was 5%. Data processing and analysis were carried out using SPSS 15.0 (SPSS, Chicago, IL, USA).

4. Results

Among the 121 patients, the median age was 42 years old (IQR 34–62), 80 (66%) of whom were women. A diagnosis of current MDE

Table 2
Demographic and clinical characteristics of the study sample.

N = 121	Non-depressed (n = 96, 79%)	Depressed (n = 25, 20%)	p-Value
Sex			
Male	34 (35%)	7 (28%)	0.48[a]
Female	62 (64%)	18 (72%)	
Median age	39 (IQR 33–61)	50.03 (IQR 41–66)	0.09[c]
Etiology			
Mesial temporal sclerosis	17 (17%)	8 (32%)	0.11[a]
Vascular	3 (3%)	3 (12%)	0.10[b]
Idiopathic	11 (11%)	0 (0%)	0.11[b]
Undetermined	38 (39%)	9 (36%)	0.74[a]
Others	4 (4%)	4 (16%)	0.05[b]
Cortical development malformation	6 (6%)	1 (4%)	1.00[b]
Vascular malformation	7 (7%)	0 (0%)	0.34[b]
Neurocysticercosis	3 (3%)	0 (0%)	1.00[b]
Tumors	7 (7%)	0 (0%)	0.34[b]
Type of epilepsy			
FPS	34 (35%)	8 (32%)	0.13[a]
FS	50 (52%)	17 (68%)	
GI	12 (12%)	0 (0%)	
Type of seizures			
Partial simple	4 (4%)	0 (0%)	0.06[a]
Partial complex	6 (6%)	1 (4%)	
Simple/complex	8 (8%)	4 (16%)	
Partial with secondary generalization	58 (60%)	20 (80%)	
Generalized seizures	0 (0%)	20 (20%)	
Schedule of seizures			
Awakening	6 (6%)	2 (8%)	0.83[a]
Wake	52 (54%)	12 (48%)	
Sleep	16 (16%)	5 (20%)	
Wake/sleep	21 (21%)	5 (20%)	
Antiepileptic therapy			
Monotherapy	58 (60%)	10 (40%)	0.067[a]
Polytherapy	38 (39%)	15 (60%)	
Median time since onset of non-febrile seizures (years)	19 (IQR 7–38)	39 (IQR 18–48)	0.008[c]
Antidepressive treatment			
Yes	13 (13%)	12 (48%)	0.001[a]
No	83 (86%)	13 (52%)	

FPS = Functional Performance System; FS = Febrile Seizures; GI = Glycemic Index.
Note. Values are expressed as numbers (%) or median (interquantile range IQR).
[a] χ^2.
[b] Fisher's exact test.
[c] U Mann–Whitney.

Table 3
ROC analysis of NDDI-E.

Cutoff point	S	E	PPV	NPV
>12	96.0	70.8	46.2	98.6
>13	84.0	78.1	50.0	94.9
>15	64.0	88.5	59.3	90.4
>18	44.0	97.9	84.6	87.0

was established in 25 (20%) patients with the MINI and dysthymia in seven (5%). Twenty-nine patients (24%) endorsed suicidal ideation and/or behavior, which was classified as low risk in 18 (15%), moderate risk in 7 (6%), and high in 4 (3%).

Demographic and clinical characteristics of patients are detailed in Table 2. As shown in Table 2, there were no significant differences between depressed and non-depressed groups, and number of antiepileptic drugs. Median evolution time in depressed patients was 39 years (IQ 18–48) and in non-depressed patients was 19 years (IQR7-38), with a p value of 0.008. In the depressed group, 12 (48%) were taking antidepressants, and in the non-depressed group, 13 (13%) were receiving treatment for depression.

4.1. Neurological Disorders Depression Inventory for Epilepsy

Receiver operator characteristics analysis of the NDDI-E showed an area under the curve of 0.89 (95% CI 0.84–0.95), ($p = 0.0001$). A cutoff point of 13 was identified as potentially the more accurate value with the best balance between sensitivity (84%) and specificity (78%) and yielded a PPV of 64.7% and NPV of 92.2%. Table 3 summarizes the sensitivity, specificity, NPV, and PPV for each of the cutoff points, while frequency of response for each of the items is detailed in Table 1. The results of the ROC analysis of the NDDI-E are presented in Fig. 1.

Using a cutoff score >13, the NDDI-E identified possible MDE in 27 patients (22%). The mean score in depressed patients was 17 (±3.5; min 11, max 23) and in non-depressed patients was 10 (±3.4; min 6, max 22).

Reliability of the NDDI-E was measured in terms of internal consistency using Cronbach's alpha coefficient. The internal consistency was 0.78. All NDDI-E items were significantly and positively associated with the total NDDI-E score, and none of them would increase α if deleted (Table 4).

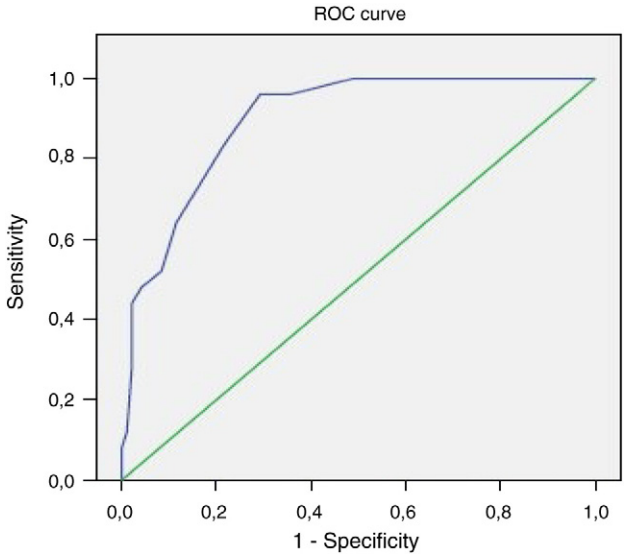

Fig. 1. ROC analysis of the NDDI-E.

Table 4
Corrected item-total correlations and Cronbach's α if item is deleted from the NDDI-E.

	Corrected item-total correlation	Cronbach's alpha if item eliminated
Item 1	0.58	0.74
Item 2	0.50	0.76
Item 3	0.54	0.75
Item 4	0.51	0.76
Item 5	0.55	0.75
Item 6	0.53	0.75

5. Discussion

Our study has demonstrated that the Spanish version of NDDI-E is a useful tool for detecting MDE in epilepsy. It showed a very good internal consistency, with values of Cronbach's alpha higher than the required psychometric standard (0.7), indicating that it has a good internal homogeneity.

The Spanish version had a lower cutoff score (>13). One possible explanation for this finding can be found in the limited variability of item 4 (I'd be better off dead), as three quarters of the patients answered 1 ("never") (Table 1). This effect can lower the total scores. This item was not scored in a different way, and our hypothesis for this result is that, perhaps, there are cultural reasons in a society in which suicide has a negative connotation for religious reasons. The other items evaluated had a more homogeneous variability among the different responses.

We have also observed that the sensitivity and specificity did not change when adjusted for treatment with antidepressant medication or age. The NDDI-E is a questionnaire that was specifically designed to identify MDE in PWE. In addition to the fact that it is a self-reported instrument and it takes only 3 min to complete, has the advantage of not including symptoms that could result from side effects of AEDs or from the underlying neurologic disorder (e.g., memory problems in temporal lobe epilepsy) [13]. These symptoms could act like confounders that alter in most of the cases the sensitivity and specificity of a screening tool and the potential of false positives that do not reflect genuine depression [20].

The presence of MDE was comparable to other population-based studies [1,2]. Indeed in the study conducted in Canada, Tellez-Zenteno et al. found a current prevalence of MDE in 17% of PWE.

In our study, only 48% [12] of the depressed patients were being treated with antidepressant drugs, which confirms the findings of other studies in which one third of the patients with mood symptoms were treated [5]. This observation shows that more than half of the patients suffering from MDE are not being treated.

The concern that antidepressant medications decrease the seizure threshold and have a pro-convulsive effect is a frequent cause for under-treatment of depressed PWE [21]. This concern has been found to be based on erroneous premises. In fact, when used at therapeutic doses, selective serotonin re-uptake inhibitors (SSRIs) have been found to be safe in these patients [22–25] and even more, some of them have been reported to have a potential effect in the reduction of seizure frequency [26,27]. Seizures associated with the use of antidepressant medications have been observed in overdoses and with the use of only four antidepressant drugs at therapeutic doses, which include maprotiline, amoxapine, clomipramine, and bupropion. Selective serotonin re-uptake inhibitors and serotonin–norepinephrine re-uptake inhibitors, which have become the first-line drugs to treat MDE, are safe [28,29].

The main limitation of our work is that the patient sample was drawn from epilepsy clinics at a tertiary care academic hospital and might give a bias toward more severely affected subjects. Furthermore, when using these instruments, clinicians must be certain that the patient's IQ is >80, as this instrument was only validated in such of patients.

To conclude, we have demonstrated that the Spanish version of the NDDI-E can identify MDE in a satisfactory way and could lead to better recognition of this disorder in epilepsy. This study encourages clinicians from Spain to routinely use the NDDI-E as a screening tool, and in this way have the opportunity to improve the quality of care of people with epilepsy.

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