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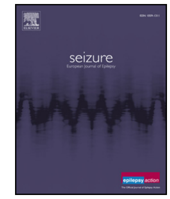

Comparison between the Neurological Disorders Depression Inventory for Epilepsy and the Patient Health Questionnaire-9 in patients with epilepsy according to antiepileptic drug load

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ABSTRACT

Purpose: We compared the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) with the Patient Health Questionnaire-9 (PHQ-9) according to different antiepileptic drug (AED) loads in people with epilepsy (PWE).

Methods: Depression and suicidality were assessed with the Mini International Neuropsychiatric Interview (MINI), the NDDI-E, and the PHQ-9. A receiver operating characteristic (ROC) curve analysis was used. Sensitivity and specificity of the NDDI-E and PHQ-9 were compared between an AED load < 2 and ≥ 2.

Results: Of 213 participants included, 22.5 % were diagnosed with current depression by the MINI, and 9 % had a moderate to severe risk of suicide. Using the cutoff of 9.5 and 13.5 for the PHQ-9 and NDDI-E, respectively, in the total group, the PHQ had a higher sensitivity (91.7 %) but lower specificity (75.8 %) than the NDDI-E (66.7 % and 87.3 %, respectively) ($p < 0.001$). In a group with an AED load < 2, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E. In a group with an AED load ≥ 2, however, the PHQ-9 had a higher sensitivity (90.9 %, $p < 0.063$) but lower specificity (65.2 %, $p < 0.001$) than the NDDI-E (68.2 % and 81.2 %, respectively). For screening of suicide risk, the sensitivity and specificity were not different between the PHQ-9 and NDDI-E in all tested groups. The negative predictive values of both instruments were above 95 % for suicide risk.

Conclusion: In patients with a low AED load, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E. In contrast, in patients with a high AED load, the PHQ-9 had a poor specificity whereas the NDDI-E had a poor sensitivity.

1. Introduction

Depression is common in patients with epilepsy (PWE): the prevalence of depression in PWE is about five times higher than in the general population [1,2]. The pathophysiological and psychosocial features of epilepsy put individuals at greater risk of depression, and conversely, depression has an adverse effect on epilepsy [3]. Depression is significantly associated with drug-resistant epilepsy and poor quality of life [4,5]. Together with depression, suicide is also a serious problem in PWE. The suicide rate in PWE is about three times higher than in the general population, and is higher when accompanied by depression [6].

Although depression is a serious factor in PWE, it remains underdiagnosed in this patient population [7]. Thus, proper screening should be implemented in the clinical field. Various diagnostic and screening tools have been used, but the gold standard for identifying depression in PWE is still unclear [8]. To date, 16 screening tools for depression have been validated in PWE [9]. Of these, most were designed for use with the general population. However, various factors related to epilepsy could adversely affect the accuracy of a screening tool for depression. For example, adverse effects of antiepileptic drugs (AEDs), such as decreased concentration, fatigue, and sleep problem, could overlap with somatic symptoms of depression [10]. Cognitive problems commonly reported in PWE such as memory difficulties could affect the accuracy of a screening tool for depression. Also, patterns of symptoms can be atypical in some mood disorders common to epilepsy. After taking these confounders into consideration, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was specifically developed to diagnose depression in PWE [10]. The NDDI-E is the most-studied

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screening tool for PWE.

There is international consensus that the NDDI-E should be used to screen for depression in all PWE [11]. However, it is unclear whether the NDDI-E is actually superior to other tools in screening for depression in PWE. One study compared the NDDI-E with the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) and described the NDDI-E as a superior screening tool because of its higher sensitivity with an acceptable specificity [12]. However, in another study comparing the NDDI-E and the HADS-D, the sensitivity and specificity of the two tools did not differ [13]. Furthermore, in a study comparing the NDDI-E and the Patient Health Questionnaire-9 (PHQ-9), the two tools did not differ in accuracy [14]. However, since the NDDI-E was developed to take into account the somatic side effects of AEDs, a proper comparison needs to compare each tool with respect to the dosage and number of AEDs used, yet no previous studies have done this. For PWE taking high doses of AEDs, the NDDI-E may be superior to general screening tools for depression, especially in terms of specificity since somatic symptoms due to AED usage can be confused with symptoms of depression. We designed this study to test this hypothesis specifically. The purpose of this study was therefore to compare the efficacy of the NDDI-E with that of the PHQ-9 according to AED load when evaluating depression and suicidality in PWE.

2. Material and methods

2.1. Subjects

Patients who visited the outpatient epilepsy clinic of the Asan Medical Center, Korea between February 8 and March 31, 2017 were surveyed. The inclusion criteria were as follows: (1) 18 years of age or older; (2) after diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) diagnostic criteria [15], one or more AEDs were taken continuously for more than 1 month; (3) patients could read and write in Korean and had sufficient intellectual ability and judgment to complete the Mini International Neuropsychiatric Interview (MINI). Patients with non-epileptic seizures, confusion due to psychosis, delirium, amnestic disorder, intoxication, or postictal state, and/or an unstable somatic disorder were excluded from the study. Demographic, clinical seizure-related, and social data (such as education, employment, and marital status) were collected. This basic information was obtained from the patients' medical charts. Written informed consent was obtained from all study participants. The study was reviewed and approved by the Institutional Review Board of the Asan Medical Center.

2.2. Diagnostic tool for depression and suicidality

Depression and suicidality in the study population were assessed with the MINI, which served as a reference diagnostic tool. This interview is a simple yet effective tool that is used in many countries, and there are many studies on its use in PWE [9,16]. The Korean version of MINI Plus 5.0.0 was used in this study [17]. The MINI is used to assess patients for depression, and associated psychiatric disorders, and suicidality. The risk of suicide was low for scores of 1–5, moderate for scores of 6–9, and high for scores of 10 or more. In this study, a presence of suicidality was defined as suicidality score ≥ 6 in the MINI. The MINI interview was conducted by two epileptologists (Jeon JY and Kim HW) with patients who visited the outpatient clinic.

2.3. Screening tools

The NDDI-E and PHQ-9 were used as screening tools for depression and suicidality. The NDDI-E is a self-administered questionnaire consisting of six symptom items assessed over the last 2 weeks [10]. Each item is rated on a 4-point scale, with the sum of the scores ranging from 6 to 24. The PHQ-9 is a self-administered questionnaire consisting of nine items [18]. Each item is rated on a 4-point scale for frequency during the last 2 weeks, with the overall score ranging from 0 to 27. Validated Korean versions of the NDDI-E and PHQ-9 were used [19,20].

2.4. Measuring AED load

AED loads for each individual patient were calculated as the sum of the prescribed daily dose/defined daily dose ratios for each AED included in the treatment regimen [21], where defined daily dose corresponds to the assumed average maintenance daily dose of a drug used for its main indication [22]. AED load was categorized into two groups: low (drug load < 2) and high (drug load ≥ 2).

2.5. Statistical analysis

We compared demographic and epilepsy-related variables between PWE with and without a MINI-defined depression diagnosis. The normality of the continuous variables was assessed with the Kolmogorov-Smirnov test, and these variables are expressed in terms of the mean, median, standard deviation, and range. For comparisons between groups, Student's *t*-test was used when the continuous variables were normally distributed and the Mann-Whitney *U* test was used when the variables were not normally distributed. When we compare differences in categorical variables such as gender, seizure frequency, and epilepsy types between depression and non-depression groups, chi-square and Fisher's exact tests were used.

A receiver operating characteristic (ROC) curve analysis was used to identify the area under the ROC curve (AUC) and the optimal balance of sensitivity and specificity of the NDDI-E and the PHQ-9 for detecting the presence of depression or suicidality in PWE. The ROC curve is a graphical plot displaying true positives versus false-positives across a range of cut-off values for clinical use. The AUC is a measure of the overall accuracy of a diagnostic test. It can be any value between 0 and 1, since both the x and y axes have values ranging from 0 to 1. The closer AUC is to 1, the better the overall diagnostic accuracy of the test. The Youden Index was used as a metric to identify the optimal cutoff score. The Youden Index is defined as $J = \max_c$ {Sensitivity(c) + Specificity(c)-1} and ranges from 0 to 1 [23]. Sensitivity of a test is defined as the probability of being test positive when disease present whereas specificity of a test is the probability of being test negative when disease absent. Differences in sensitivity and specificity between the NDDI-E and the PHQ-9 were analyzed using McNemar test. The following scale is commonly used for classifying accuracy using AUC, sensitivity, and specificity: 0.90–1, excellent accuracy; 0.80 to 0.90, good accuracy; 0.70 to 0.80, acceptable accuracy; 0.60 to 0.70, poor accuracy [24]. All statistical tests were two tailed, and a p-value of < 0.05 was considered significant. Data were analyzed using the Statistical Package for the Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Clinical and demographic features

A total of 213 PWE were recruited (47.9 % female), with a mean age of 41.0 years (standard deviation [SD] = 12.0). The basic characteristics of participants with or without depression, as determined from the MINI interview, are shown in Table 1. Forty-eight patients (22.5 %) had depression, and 20 patients (9 %) had a moderate or high risk of suicide. There were statistically significant differences in sex, occupation, etiology of epilepsy, seizure frequency, and AED polytherapy (defined as taking two or more AEDs) between the patients with and without depression. The proportion of women (66.7 % vs 42.4 %) and the unemployment rate (46.8 % vs 28.8 %) were higher in the patients with depression. The proportion of patients with structural epilepsy was higher among the patients with depression. Furthermore, the seizure-

Table 1
Demographic and clinical characteristics of the study participants (n = 213).

	With depression (n = 48)	Without depression (n = 165)	p value
Age, year, mean (SD)	40.6 (10.5)	41.1 (12.4)	0.689
Sex, female, n (%)	32 (66.7)	70 (42.4)	0.003
Education, high school or above, n (%)	42 (89.5)	142 (86.6)	0.615
Unemployed, n (%)	22 (46.8)	47 (28.8)	0.021
Married, n (%)	16 (33.4)	71 (43.0)	0.150
Age at seizure onset, year, mean (SD)	19.5 (13.1)	22.0 (12.8)	0.231
Epilepsy duration, year (SD)	22.0 (13.0)	20.1 (12.2)	0.605
Epilepsy classification, n (%)			0.308
Focal	40 (83.3)	127 (77.0)	
Generalized	7 (14.6)	24 (14.5)	
Unknown	1 (2.1)	14 (8.5)	
Etiology of epilepsy, n (%)			0.038
Structural	23 (47.9)	47 (28.5)	
Genetic	7 (14.6)	19 (11.5)	
Infectious	4 (8.3)	15 (9.1)	
Unknown	14 (29.2)	84 (50.9)	
Seizure type, n (%)			0.440
Focal aware	6 (12.5)	25 (15.2)	
Focal impaired awareness	20 (41.7)	69 (41.8)	
Focal to bilateral tonic-clonic	14 (29.2)	33 (20.0)	
Generalized tonic-clonic	7 (14.6)	24 (14.5)	
Unknown	1 (2.1)	14 (8.5)	
Presence of generalized or focal to bilateral TCS, n (%)	17 (35.4)	44 (26.7)	0.277
Seizure frequency, n (%)			0.003
Seizure-freedom in the last year	4 (8.3)	40 (24.2)	
1–11 per year	20 (41.7)	81 (49.1)	
≥ 1 per month	24 (50.0)	44 (26.7)	
AED load ≥ 2, n (%)	22 (45.8)	69 (41.8)	0.623
AED polytherapy, n (%)	40 (83.3)	107 (64.8)	0.015
Previous epilepsy surgery, n (%)	8 (16.7)	18 (10.9)	0.284
Past history of psychiatric illness, n (%)	18 (37.5)	11 (6.7)	< 0.001
Taking antidepressants, n (%)	10 (21.3)	2 (1.2)	< 0.001
Family history of psychiatric illness, n (%)	6 (12.8)	7 (4.2)	0.032
PHQ-9 score, median (IQR)	17.0 (12.0, 21.0)	4.0 (2.0, 9.0)	< 0.001
NDDI-E score, median (IQR)	16.0 (12.0, 19.0)	9.0 (7.0, 12.0)	< 0.001

AEDs, Antiepileptic drugs; IQR, interquartile range; n, number; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation; TCS, tonic-clonic seizure.

freedom rate for the previous year was lower in the group of patients with depression and a greater proportion of patients in this group received AED polytherapy.

3.2. Depression analyses

In a ROC curve analysis, the optimal cutoff was 9.5 (sensitivity 91.7 %, specificity 75.8 %, and AUC 0.890) and 13.5 (sensitivity 66.7 %, specificity 87.3 %, and AUC 0.838) for the PHQ-9 and NDDI-E, respectively, in the total patient group (Table 2, Fig. 1). The sensitivity was significantly higher in the PHQ-9 than NDDI-E ($p < 0.001$) whereas the specificity was significantly higher in the NDDI-E than the PHQ-9 ($p < 0.001$). In a group with AED load < 2, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E. In contrast, in a group with AED load ≥ 2, the PHQ-9 tended to have higher sensitivity than the NDDI-E (90.9 % vs. 68.2 %, $p < 0.063$), but had lower specificity than the NDDI-E (65.2 % vs. 81.2 %, $p < 0.001$).

3.3. Suicidality analyses

In a ROC curve analysis, the optimal cutoff was 12.5 for both PHQ-9 (sensitivity 80.0 %, specificity 77.2 %, and AUC 0.817) and NDDI-E (sensitivity 85.0 %, specificity 74.1 %, and AUC 0.830) in the total patient group (Table 3, Fig. 2). The optimal cutoff was also 12.5 for the PHQ-9 and NDDI-E in a group with AED load < 2, but was increased to 16.5 for the PHQ-9 and NDDI-E in a group with AED load ≥ 2. The sensitivity and specificity were not statistically different between the PHQ-9 and NDDI-E in the total group, a group with AED load < 2, and a group with AED load ≥ 2. Regardless of AED load, the negative predictive values of both instruments were above 95 % for moderate to severe suicide risk.

4. Discussion

The aim of this study was to compare the efficacy of the NDDI-E with that of the PHQ-9 according to AED load when screening depression and suicidality in PWE. The optimal cutoff scores for depression were identified as 9.5 and 13.5 for the PHQ-9 and NDDI-E, respectively. Using these cutoff points, in a total patient group, the PHQ-9 had notably better sensitivity than the NDDI-E, but had lower specificity than the NDDI-E. In patients with a high AED load, the NDDI-E had higher specificity than the PHQ-9, but had poor sensitivity. In patients with a low AED load, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E. With regard to moderate to high suicidality, the sensitivity and specificity were not statistically different between the PHQ-9 and NDDI-E in the total group and the subgroups. Regardless of an AED load, the negative predictive values of both instruments were above 95 % for moderate to high suicide risk, which confers utility as practical screening approach to suicide prevention in PWE.

NDDI-E is the most validated tool for PWE: it has been tested in 26 studies in a variety of languages [9]. Twelve studies validated the cutoff point of 15.5 same to the original study, and ten studies validated the cutoff point of 13.5 same to our study. Although the NDDI-E cutoff point of 15.5 has been recommended, when plotting the median sensitivity and specificity for the NDDI-E, it appears that the cutoff point of 13.5 may also be optimal for detecting depression in PWE because the sensitivity and specificity curves converge at this point, indicating the best balance of sensitivity and specificity [9]. In the present study, the sensitivity of the NDDI-E was somewhat lower than that of the previous studies. The sensitivity in the entire patient population was 66.7 % at a cutoff point of 13.5, which was lower than the median sensitivity (83.7 % at a cutoff point of 12.5; range: 65.4–92.3 %) produced by other studies [9].

As we hypothesized, the specificity of the NDDI-E was significantly higher than that of the PHQ-9 for screening of depression in patients with a high AED load (81.2 % vs 65.2 %). The specificity of the NDDI-E and the PHQ-9 was similar in patients with a low AED load (85.4 % vs 83.3 %), but the specificity of the PHQ-9 decreased sharply in patients with a high AED load. This suggests that AED dosage has less effect on the screening of depression by the NDDI-E than on screening by the PHQ-9. However, the sensitivity of the NDDI-E in patients with a high AED load was 68.2 %, which is not acceptable. On the other hand, in patients with a low AED load, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E for screening of depression.

Various aspects of epilepsy can act as confounders in screening tools for depression, including somatic symptoms, a side effect of AEDs. The NDDI-E is a depression screening tool designed for PWE that takes these confounders into account [10]. The NDDI-E questionnaire lacks the factors “trouble sleeping”, “fatigue”, and “trouble concentrating”, which are included in the PHQ-9 [14]. Because these items may be affected by the side effects of AEDs, this difference between the two questionnaires may result in differences in specificity in patients with a high AED load. One study compared the efficacy of the PHQ-9 after

Table 2
Receiver operating characteristic analysis of the PHQ-9 and NDDI-E for the diagnosis of current major depression as determined by the MINI.

	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %	ROC AUC (95 % Cl)	p-value
Total (n = 213)							
PHQ-9	9.5	91.7***	75.8***	52.4	96.9	0.890 (0.845–0.934)	< 0.001
NDDI-E	13.5	66.7	87.3	60.4	90.0	0.838 (0.774–0.902)	< 0.001
AED load < 2 (n = 122)							
PHQ-9	9.5	92.3	83.3	60.0	97.6	0.930 (0.884–0.975)	< 0.001
NDDI-E	12.5	76.9	85.4	58.8	93.2	0.872 (0.795–0.949)	< 0.001
AED load ≥ 2 (n = 91)							
PHQ-9	9.5	90.9*	65.2***	45.5	95.7	0.832 (0.744–0.920)	< 0.001
NDDI-E	13.5	68.2	81.2	53.6	88.9	0.787 (0.676–0.898)	< 0.001

AED, antiepileptic drug; AUC, area under the receiver operating characteristic curve; Cl, confidence interval; MINI, Mini International Neuropsychiatric Interview; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; NPV, negative predictive value; PHQ-9, Patient Health Questionnaire-9; PPV, positive predictive value; ROC, receiver operating characteristic.
* $p < 0.1$ between the PHQ-9 and NDDI-E.
*** $p < 0.001$ between the PHQ-9 and NDDI-E.

dividing it into items related to somatic symptoms and items not related to somatic symptoms: screening with the PHQ-9 somatic items was less accurate than screening with the remaining PHQ-9 items [14]. This supports the hypothesis that the items associated with somatic symptoms in the PHQ-9 contribute to the reduced specificity in patients with a high AED load.

It should also be noted that the PHQ-9 showed much better sensitivity than the NDDI-E and acceptable specificity in screening for depression in total patients. The PHQ-9 is one of the most commonly used tools in primary care settings because it has been validated in more than 11,000 general patients [25,26]. In addition, the PHQ-9 has been studied in the context of other neurological disorders such as stroke and traumatic brain injury, and has proven usefulness as a screening tool [27,28]. As discussed above, the PHQ-9 has not been found to be inferior to the NDDI-E in other studies of PWE [14]. Therefore, PHQ-9 may be a good screening tool in PWE, especially taking only one or two AEDs.

Limitations should be noted when interpreting the results of the present study. Firstly, we considered the overall AED load but did not consider the effect of the type of AED. It is well known that psychiatric and behavioral adverse effects occur more frequently in PWE taking some AEDs, especially topiramate, levetiracetam, and perampanel [29–31]. However, it would be difficult to design a study that takes the types of AED into account. Secondly, a patient assessment of drug side effects was not included in this study. Given that the NDDI-E was developed bearing in mind the overlap between AED side effects and some symptoms of depression, it would be better to compare the performance of the NDDI-E and PHQ-9 in the presence or absence of AED side effects assessed by patients rather than depending on the level of AED load. Thirdly, intellectual ability to complete the MINI was assessed subjectively by the interviewer, but not objectively assessed using the neuropsychological tests. Participants in our study were, however, a highly functioning group - as indicated by the fact that more that 85 % of participants had at least 12 years of education. Finally, the MINI interview was conducted by two epileptologists, but not conducted by professionals trained in the evaluation of mental health disorders.

In conclusions, the sensitivity and specificity did not differ between the PHQ-9 and NDDI-E in patients with a low AED load. In contrast, in patients with a high AED load, the PHQ-9 had a poor specificity whereas the NDDI-E had a poor sensitivity. For screening of moderate to high suicidality, there are no differences in sensitivity and specificity between the PHQ-9 and NDDI-E. Given the paucity of information about usefulness of the screening tools depending on an AED load, our findings provide a better understanding of usefulness of the PHQ-9 and NDDI-E for screening of depression, and may be helpful to choose an appropriate screening tool for patients with high or low amount of AED.

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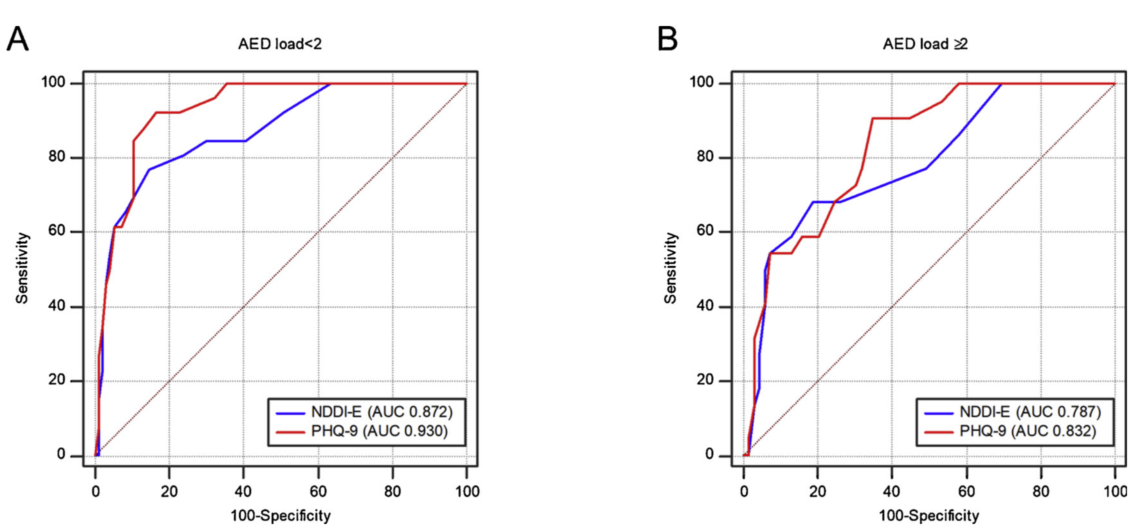

Fig. 1. Comparison of area under the ROC curve (AUC) of NDDI-E and PHQ-9 for depression according to antiepileptic drug (AED) load.

Table 3
Receiver operating characteristic analysis of the PHQ-9 and NDDI-E for the diagnosis of moderate to severe suicidality as determined by the MINI.

	Cutoff	Sensitivity, %	Specificity, %	PPV, %	NPV, %	ROC AUC (95 % Cl)	p-value
Total (n = 213)							
PHQ-9	12.5	80.0	77.2	26.7	97.4	0.817 (0.722–0.913)	0.000
NDDI-E	12.5	85.0	74.1	25.3	97.9	0.830 (0.736–0.924)	0.000
AED load < 2 (n = 122)							
PHQ-9	12.5	80.0	82.1	28.6	97.9	0.847 (0.742–0.951)	0.000
NDDI-E	12.5	90.0	77.7	26.5	98.9	0.856 (0.778–0.934)	0.000
AED load ≥ 2 (n = 91)							
PHQ-9	16.5	70.0	87.7	41.2	97.4	0.791 (0.625–0.958)	0.003
NDDI-E	16.5	80.0	91.4	53.3	95.9	0.807 (0.617–0.996)	0.002

AED, antiepileptic drug; AUC, area under the receiver operating characteristic curve; Cl, confidence interval; MINI, Mini International Neuropsychiatric Interview; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; NPV, negative predictive value; PHQ-9, Patient Health Questionnaire-9; PPV, positive predictive value; ROC, receiver operating characteristic.

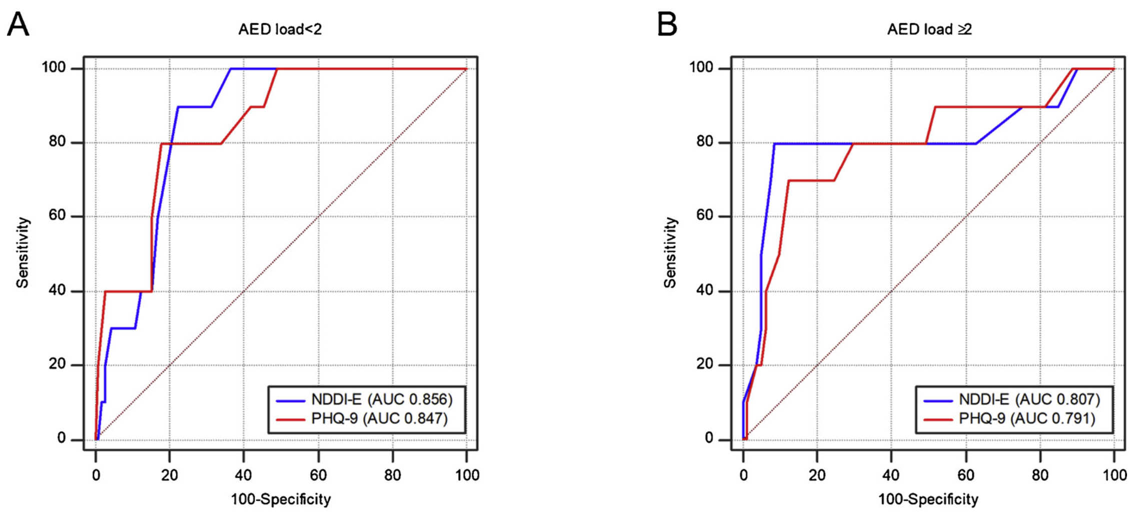

Fig. 2. Comparison of area under the ROC curve (AUC) of NDDI-E and PHQ-9 for moderate to severe suicidality according to antiepileptic drug (AED) load.

Declaration of Competing Interest

The authors declare no conflicts of interest in relation to this study.

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