Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

Name: _____Date: _____

For the statements below, please circle the number that best describes you over the *last two weeks including today.*

	Always or Often	**Sometimes**	**Rarely**	**Never**
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

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Identifying depression in epilepsy in a busy clinical setting is enhanced with systematic screening

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ABSTRACT

Purpose: Depression is a highly prevalent, relatively underdiagnosed and undertreated comorbid condition in epilepsy. The purpose of this study was to determine the effect of using a validated self-reporting depression scale on the ability to detect depression in people with epilepsy receiving care in a busy clinical setting.
Methods: The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a 6-item questionnaire validated to screen for depression in people with epilepsy. We performed a retrospective chart review of 192 consecutive patients who had completed the NDDI-E while receiving care at a seizure clinic in the largest public hospital in Houston, Texas. For comparison, charts of 192 consecutive patients receiving care immediately prior to the implementation of the NDDI-E in the same clinic were assessed.
Results: Fifty-five (28.6%) of patients screened positive for depression with the NDDI-E. They subsequently received a semi-structured psychiatric interview based on the DSM-IV model and 89% ($n = 49$) were confirmed to have major depression. Use of the NDDI-E thus resulted in the detection of active depression in 25.5% ($n = 49$) of the patients, whereas only 2.6% ($n = 5$) of patients in the group not systematically screened were found to have active depression ($p < 0.0001$). Thirty-two of the 49 (65%) patients with depression detected by screening were not previously diagnosed or treated. Multivariate analysis revealed that a history of depression, seizure frequency, and topiramate use were independent predictors of depression. Lamotrigine use was protective against depression.
Discussion: Use of the NDDI-E significantly improved the ability to detect depression in epilepsy patients in a busy clinical practice.

1. Introduction

Depression is a frequent psychiatric complication encountered by patients with chronic epilepsy,[1–4] with prevalence reported to be more than 30% in community-based epilepsy populations[5] and between 20% and 55% in tertiary epilepsy centers.[6,7] It is a comorbid condition that adversely affects patients' health-related quality of life, independent of seizure frequency.[8–12] Depression not only has a substantial negative effect on subjective health, but also is a potentially life-threatening illness, contributing to the significantly higher rates of suicidal behavior when compared to the general population.[13,14] Unfortunately, detecting depression in epilepsy patients is a difficult undertaking in a busy ambulatory setting. The diagnosis is often missed in both adults[15] and children.[16,17] Approaches to promptly identify clinical depression can help to improve not only the recognition, but also treatment of this comorbid disorder. Using self-administered screening tools can assist in dealing with this problem. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a validated screening tool for depression in patients with epilepsy that consists of a 6-item questionnaire (Fig. 1). It can be used to rapidly and reliably detect depression in a busy clinical setting, as well as differentiate symptoms of depression from those of medication toxicity and cognitive effects of epilepsy.[18] The present study aims to determine the effect on recognition of depression by administering the NDDI-E in a busy urban clinic. In addition, we sought to determine the risk factors associated with depression in this patient population.

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Fig. 1. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).

2. Materials and methods

Ben Taub General Hospital is the largest public hospital in Houston, Texas, with more than 184,000 clinic visits a year. The weekly seizure clinic manages a high volume of patients, visited by roughly 25 per 3-h session.

The NDDI-E is a 6-item questionnaire that allows for rapid identification of major depression in epilepsy. NDDI-E scores above 15 are considered positive for depression, with specificity of 90%, sensitivity of 81%, and positive predictive value of 0.62 for a diagnosis of major depression based on the mini international neuropsychiatric interview (MINI).[19] NDDI-E total score, independent of adverse effects of medication, predicted subjective health based on the quality of life in epilepsy inventory-89 (QOLIE-89)[20] total score. Additional construct validity was supported by correlations with previously validated instruments. The Spearman correlation coefficient between the NDDI-E and the Beck Depression Inventory (BDI)[21] was 0.78 and 0.77 between the NDDI-E and the Center for Epidemiological Studies Depression (CES-D) scale.[22,18]

Use of the NDDI-E was approved by the Harris County Hospital District's Patient Education Committee in November 2007. The authors performed a retrospective review of clinic charts of patients who had received the screening tool from December of 2007 to February of 2008. Patients were instructed to complete the questionnaire without the assistance of others. A total of 287 adult patients visited the clinic from December of 2007 to February of 2008. The screening tool was administered to consecutive patients receiving care in the clinic during that period. Fifty-one were excluded because they were unable to understand and complete the NDDI-E without assistance secondary to cognitive limitations such as mental retardation and/or learning disabilities. Another 44 refused to complete the questionnaire. The remaining 192 patients visiting the clinic received and completed the NDDI-E as part of their clinical assessment. NDDI-E scores greater than 15 were considered positive for depression, as this score was previously shown to have a specificity of 90%, sensitivity of 81%, and positive predictive value of 0.62 for a diagnosis of major depression.[18] If a patient was determined to be depressed based on screening, a semi-structured psychiatric interview was conducted by the attending neurologist. The interviews were performed in the clinic by two of the authors (DEF, SL) who were not blinded to the NDDI-E scores. The semi-structured interview followed the DSM-IV criteria for major depression and consisted of questions pertaining to patients' mood, anhedonia, ability to concentrate, fatigue, quality of sleep, changes in appetite, and suicidal ideation and was based on the Structured Clinical Interview (SCID-1 for DSM-IV-TR) for current Major Depressive Episode (MDE).[23] The patient was either treated with antidepressant medication, referred to psychiatry, both, or neither. Treatment decisions were not systematic and were decided by the physician based on individual patient characteristics and clinical impression. For instance, if symptoms of depression were temporally related to initiation or increase in dosage of a particular anti-epileptic drug (AED), stopping or decreasing the AED was considered. For comparing rates of depression detection, the charts of 192 consecutive patients receiving care immediately prior to the implementation of the NDDI-E in the same clinic were assessed. Prior to implementation of the NDDI-E, patients did not undergo a psychiatric interview unless they were complaining of symptoms of depression. Depression was noted if documented in the medical record and was based on patients' complaints and physicians' clinical impression.

Clinical patient variables included age, gender, race/ethnicity, employment status, marital status, depression history, seizure frequency, AEDs used, epilepsy type, brain MRI, and EEG findings. For each variable, descriptive statistics were obtained. Epilepsy diagnosis was categorized into three groups including: (1) generalized epilepsy, (2) localization-related epilepsy, and (3) unknown. EEG findings were categorized into four groups: (1) normal, (2) diffuse slowing, (3) regional slowing, and (4) epileptiform activity. Four groups divided by race or ethnicity: (1) non-Hispanic white, (2) black, (3) Hispanic, and (4) other. Current marital status into four groups: (1) single, (2) married, (3) divorced, and (4) widowed. All other variables were dichotomized including gender (male/female), depression history (yes/no), MRI findings (normal/lesional) and employment (employed/unemployed). Depression at the time of the clinic visit was inferred from the physicians' notes in the medical charts. The strength of association between independent variables and depression was assessed using Fisher's exact test and p values <0.05 were regarded as significant. All significant variables in the univariate test were entered in a multiple logistic regression model to assess potential independent factors and confounders for depression. Odd ratios (OR), adjusted for age and gender, were calculated with 95% confidence intervals (CI).

3. Results

No significant differences in demographic and clinical characteristics were present between the group receiving the NDDI-E and the group not receiving the questionnaire. Table 1 provides the descriptive characteristics of the patients. EEGs were not performed or EEG reports were not available for 79 patients in the pre-NDDI-E group and 65 in the NDDI-E group. MRIs were not performed on 49 in the pre-NDDI-E group or on 29 in the NDDI-E group. Patients were categorized as having localization-related epilepsy (LRE) or primary generalized epilepsy (PGE) based on documentation in clinic charts.

Fifty-five (28.6%) of patients receiving the NDDI-E were screened as positive for depression. Forty-nine (89%) of those that screened positive for depression were confirmed to have depression following the psychiatric interview, representing concurrent validity. Thus, detection of active depression occurred in 25.5% ($n = 49$) of patients with use of the NDDI-E, whereas only 2.6% ($n = 5$) of patients in the group not systematically screened were found to have active depression ($p < 0.0001$). The mean NDDI-E score of the patients with false positive results from screening was 16.7 (median = 16). Thirty-two of the 49 (65%) patients that had evidence on both the NDDE-I and interview of depression were not previously diagnosed or treated. Forty-two percent ($n = 23$) of the 55 patients in the group with scores of 16 or greater had a prior diagnosis of depression, four of which (17%) were not receiving treatment. Sixteen percent ($n = 22$) of patients in the group with scores less than 16 were previously diagnosed with depression, with three (14%) not receiving treatment.

Table 1
Baseline characteristics of patients receiving and not receiving the NDDI-E.

	Pre-NDDI-E ($N = 192$)	NDDI-E ($N = 192$)	p-Value
Age (mean ± S.D.)	41 ± 12	42 ± 13	0.44
Gender n (% male)	91 (48)	85 (44)	0.54
Race/ethnicity n (% Hispanic)	105 (55)	92 (48)	0.18
Depression history n (%)	35 (18)	45 (23)	0.21
Seizure type			
LRE n (%)	136 (71)	136 (71)	1.00
PGE n (%)	14 (7)	20 (10)	0.28
EEG			
Epileptiform n (%)	28 (15)	30 (16)	0.78
Focal slowing n (%)	18 (9)	23 (12)	0.41
Diffuse slowing n (%)	13 (7)	5 (3)	0.05
Seizure frequency (mean ± S.D.)	2 ± 6	3 ± 10	0.24
MRI			
Lesion n (%)	60 (31)	70 (36)	0.28
Normal n (%)	59 (31)	75 (40)	0.09
Number of AEDs (mean ± S.D.)	1.61 ± 0.83	1.77 ± 0.79	0.06
Employed n (%)	44 (23)	50 (26)	0.41
Marital status			
Single n (%)	109 (57)	111 (58)	0.84
Married n (%)	58 (30)	61 (32)	0.74
Divorced n (%)	17 (9)	13 (7)	0.45

S.D., standard deviation; LRE, localization-related epilepsy; PGE, primary generalized epilepsy; AEDs, anti-epileptic drugs.

Risk factors associated with depression diagnosed with the NDDI-E and interview in the univariate analysis included a history of depression ($p < 0.001$), taking three or more AEDs ($p = 0.04$) and current use of topiramate (TPM) ($p = 0.02$). Though seizure frequency was not significantly associated with depression in the univariate model, when adjusting for the number of AEDs on the multivariate analysis, it became significant ($p = 0.04$). Factors independently associated with depression when analyzed with multiple logistic regression included depression history ($p < 0.001$), seizure frequency ($p = 0.04$), and current TPM use ($p = 0.04$). Use of lamotrigine (LTG) was independently protective against depression ($p = 0.03$). Tables 2 and 3 show the univariate and multivariate analyses for patients receiving the NDDI-E.

4. Discussion

This is the first study to demonstrate the effectiveness of using a validated screening tool to identify depression in patients with epilepsy in a busy clinical setting. Use of the NDDI-E resulted in a nearly 10-fold improvement in the detection rate. Utilization of the NDDI-E allowed for an improved recognition of depression, thus enhancing the quality of the outpatient evaluation in our study, as mood disorders have a profound negative effect on patients' subjective health status.[2,3,8,9,11,12,24] Addressing symptoms of depression is an important component of the outpatient evaluation of patients with epilepsy. Though the NDDI-E is not meant to replace definitive means of evaluation such as a structured psychiatric interview, it can assist in identifying those patients that may be at risk. This is particularly relevant in a busy ambulatory setting, where time constraints often restrict the identification of depression.[15,25] Our study is unique for its application of screening for depression in a large urban county hospital system as there is a known association between low income and depression alone[26] and in patients with epilepsy.[5]

In our study we found that 25.5% of the patients had current, major depression, based on the NDDE-I score and confirmation by the interview. This is similar to prior reports, where rates of active depression in patients with epilepsy ranged between 17.2% and 55%.[5,7,13,25,27] Any chronic disorder can predispose a patient to depression. However, depression is more commonly associated with epilepsy when directly compared to other chronic conditions, such as asthma and diabetes mellitus.[5,27] There also appears to be a bidirectional relationship between epilepsy and depression, with depression reported to be a risk factor for epilepsy.[28] A number of neurobiological factors have been implicated in the association between the two disorders.[29] It is possible that epilepsy and depression stem from dysfunction within overlapping neuronal

Table 2
Univariate analysis of patients receiving the NDDI-E.

	NDDI-E < 16 ($N = 137$)	NDDI-E ≥ 16 ($N = 55$)	p-Value
Age (mean ± S.D.)	42 ± 13	43 ± 13	0.63
Gender n (% male)	60 (44%)	25 (45%)	0.83
Race/ethnicity n (% Hispanic)	69 (50%)	23 (42%)	0.28
Depression history n (%)	**22** (**16**%)	**23** (**42**%)	**<0.001**
Past treatment for depression n (%)	3 (2%)	4 (7%)	0.105
Seizure type			
LRE n (%)	95 (69%)	41 (75%)	0.47
PGE n (%)	16 (12%)	4 (7%)	0.44
EEG			
Epileptiform n (%)	19 (14%)	11 (20%)	0.29
Focal slowing n (%)	19 (14%)	4 (7%)	0.23
Diffuse slowing n (%)	3 (2%)	2 (4%)	0.63
Seizure frequency (mean ± S.D.)	2 ± 6	6 ± 16	0.06
MRI			
Lesion n (%)	47 (34%)	23 (42%)	0.33
Normal n (%)	54 (39%)	21 (38%)	0.87
Number of AEDs (mean ± S.D.)	**1.69 ± 0.75**	**1.96 ± 0.88**	**0.05**
≥3 AEDs n (%)	**20** (**15**%)	**15** (**27**%)	**0.04**
AED			
Levetiracetam	55	26	0.37
Topiramate	**15**	**13**	**0.02**
Zonisamide	12	7	0.41
Lamotrigine	27	6	0.14
Carbamazepine	25	15	0.16
Oxcarbazepine	9	6	0.31
Valproic acid	26	11	0.87
Phenobarbital	6	1	0.68
Phenytoin	41	15	0.71
Gabapentin	3	3	0.36
Clonazepam	5	3	0.69
Primidone	2	0	1.00
Employed n (%)	40 (29%)	10 (18%)	0.12
Marital status			
Single n (%)	78 (57%)	33 (60%)	0.70
Married n (%)	46 (34%)	15 (27%)	0.40
Divorced n (%)	10 (7%)	3 (5%)	0.76

S.D., standard deviation; LRE, localization-related epilepsy; PGE, primary generalized epilepsy; AEDs, anti-epileptic drugs. The bolded values represent values that are statistically significant ($p \leq 0.05$).

Table 3
Mutivariate analysis.

	Odds ratios (OR)	95% Confidence interval (CI)	p-Value
Depression history	**4.67**	**2.17–10.02**	**<0.001**
Seizure frequency	**1.04**	1.01–1.09	**0.04**
Number of AEDs ≥ 3 vs. <3	2.13	0.88–5.16	0.09
Topiramate	**2.56**	**1.05–6.28**	**0.04**
Lamotrigine	**0.28**	**0.09–0.85**	**0.03**

AEDs, anti-epileptic drugs. The bolded values represent values that are statistically significant ($p \leq 0.05$).

networks, such as the limbic system. Indeed, patients with temporal lobe epilepsy tend to have higher rates of mood disorders than the other forms of epilepsy.[1,11]

In our cohort, though depression was related to seizure frequency was statistically significant, it was modest, with an odds ratio (OR) of 1.04 [95% confidence interval (CI), 1.01–1.09]. Nevertheless, a relationship between seizure frequency and depression exists. The prevalence of depression in epilepsy is increased in patients with recurrent seizures.[13,30,31] Also, increased relative risk for suicide is associated with a higher seizure frequency.[32] In addition to the possible underlying biological mechanisms responsible for depression in patients with frequent seizures, frequent seizures may correlate with patients' perception of handicap.[33] Consequently, this perceived disadvantage continues to increase the burden and stress of a chronic illness and contributes to symptoms of depression.

A history of depression was related to NDDI-E scores consistent with depression. In our cohort, it was the strongest independent predictor for depression [OR 4.67 (CI, 2.14–10.02)]. This highlights the fact that although patients may carry a diagnosis of comorbid depression and may even be undergoing treatment, it is nevertheless important to screen these patients as well to assess the effectiveness of their treatment. In our study, nearly two thirds (65%) of the patients determined to have depression were not previously diagnosed or treated. Ensuring that patients are receiving proper management for depression is just as important as diagnosing it.

Anti-epileptic drugs alone can contribute to depression. In our cohort TPM use was found to be a risk factor for depression and LTG use protective. Though this data is based on a cross-sectional assessment and not a randomized trial, it is similar to that found in previously published reports. TPM's negative impact on mood in patients with epilepsy is well known.[34–37] Both Kanner et al.[34] and Mula et al.[35] indicated that patients with a past psychiatric history may be at more risk for developing the depressive adverse effects. Though TPM was independently associated with depression, most patients were on AED polytherapy, and thus many symptoms consistent with depression may be attributed to the negative neurocognitive effects associated with AEDs. LTG consistently demonstrates positive psychiatric effects on patients.[38,39] LTG cotherapy reverses the depressive side effects of TPM.[35] LTG monotherapy has been shown to improve depressive symptoms in patients with epilepsy, with a sustained effect for at least 8 months.[40] LTG has also been shown to lead to improvement in mood in patients with primary generalized tonic clonic epilepsy, independent of its effect on seizure reduction.[41]

The limitations of the study must be recognized. Certain risk factors known to be associated with depression in patients with epilepsy could not be assessed for this study. The receiver operating characteristic curve (ROC) analysis revealed an area under the curve of 0.75. This indicates that the variables measured allowed for fair to good predictability. Other factors that may have strengthened our analysis include duration of epilepsy and epilepsy localization. Seizure chronicity is a known risk factor associated with mood disorders.[17,31] Complete data pertaining to duration of epilepsy was not available in many of the charts reviewed and was thus not included in the analyses. Depression is also known to be more common among certain epilepsy disorders, particularly affecting patients with temporal lobe epilepsy.[1,11] Most patients attending our clinic did not undergo video-EEG monitoring, and therefore accurate localization of their epileptogenic region is not known. We cannot account for false negatives, as patients with a score less of than 16 on the NDDI-E did not receive the semi-structured psychiatric interview. However, the results of the NDDI-E and psychiatric interview revealed concurrent validity, for there was a high rate of agreement on the results of the screening and interview. Also, prior to implementing the screening tool, a systematic psychiatric interview was not performed in the clinic. Therefore, the comparison of rates of detecting depression is based on clinical judgment in the pre-NDDI-E group and a combination of the screening tool and the psychiatric interview in the NDDI-E group. In an ideal setting, the psychiatric interview would be performed by a psychiatrist or psychologist. Nevertheless, the aim of this study was to assess the feasibility of detecting depression in a busy neurology clinic with an easily administered validated screening tool.

5. Conclusions

In a busy clinical setting, symptoms of depression are frequently overlooked or mistaken, as evidenced by our study. The use of the NDDI-E allowed us to enhance our outpatient evaluation by improving the identification of depression. Both the prevalence of depression in our study, as well as the risk factors associated with depression, are similar to previous studies, thus further supporting the use of the NDDI-E as an accurate tool for detecting depression in patients with epilepsy. Despite the limitations in our study, we feel the NDDI-E is useful in a busy clinical setting and can supplement a productive clinic visit.

Conflict of interest

The authors have no conflicts to disclose.

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