VALIDATION OF RAPID SUICIDALITY SCREENING IN EPILEPSY USING THE NDDIE

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Running title: Rapid suicidality screening for epilepsy

Key Words: epilepsy, suicide, depression, screening, NDDI-E

Number of words: 3334; Number of references: 38;

Number of figures: 1; Number of tables: 3

SUMMARY

Objective: Standard mortality ratio for suicide in patients with epilepsy is three times higher than in the general population and such a risk remains high even after adjusting for clinical and socioeconomic factors. It is thus important to have suitable screening instruments and to implement care pathways for suicide prevention in every epilepsy centre. The aim of this study is to validate the use of the Neurological Disorder Depression Inventory for Epilepsy (NDDIE) as a suicidality-screening instrument.

Methods: The study sample included adult patients with epilepsy assessed with the MINI International Neuropsychiatric Interview (MINI) and the NDDIE. A high suicidality risk according to the Suicidality Module of the MINI was considered the gold standard. ROC analyses for NDDIE total and individual item scores were computed and subsequently compared using a nonparametric approach. The best possible cut-off was identified with the highest Youden Index (J). Likelihood ratios were then computed and specificity, sensitivity, positive and negative predictive values calculated.

Results: The study sample consisted of 380 adult patients with epilepsy: 46.3% male; mean age was 39.4 +/- 14.6; 76.7% had a diagnosis of focal epilepsy; mean age at onset of the epilepsy was 23.3 +/- 17.5. According to the MINI, 74 (19.5%) patients fulfilled criteria for a major depressive episode and 19 (5%) presented a high suicidality risk. A score > 2 (J=0.751) for item 4 “I’d be better off dead” of the NDDIE displayed excellent psychometric properties with a good to excellent validity (AUC 0.906; 95%CI 0.820-0.992; p<0.001), sensitivity 84.21% (95%CI 60.4-96.6), specificity 90.86% (95%CI 87.4-93.6), likelihood ratio+ 9.21 (95%CI 6.3-13.5), likelihood ratio- 0.17 (95%CI 0.06-0.50).

Significance: Item 4 of the NDDIE has shown to be an excellent suicidality screening instrument allowing the development of further care pathways for suicide prevention in epilepsy centres.

INTRODUCTION

According to The Centers for Disease Control and Prevention (CDC), suicide was the 10th cause of death for all ages, in 2013, with 41,149 suicides in the United States alone, meaning 12.6 per 100,000 and one suicide every 13 minutes[1]. In May 2013, the Sixty-sixth World Health Assembly adopted the first-ever Mental Health Action Plan of the World Health Organization (WHO) of which suicide prevention is an integral part, with the goal of reducing the rate of suicide in countries by 10% by 2020[2].

Over six years ago, the US Food and Drug Administration (FDA) issued an alert to health care professionals about an increased risk of suicide ideation and behaviour in people with epilepsy treated with antiepileptic drugs (AEDs)[3]. It seems now evident that the FDA warning was based on data affected by a number of methodological limitations[4] and the observed increased suicidality rate, reflected basically the increased suicidality risk of patients with epilepsy [5]. In fact, standard mortality ratio for suicide in patients with epilepsy is three times higher compared to the general population[6] and such a risk remains high even after excluding those with a history of psychiatric disorders and adjusting for socioeconomic factors[7]. Several studies have attempted to identify reasons for such an increased risk. Some authors have suggested a link with temporal lobe epilepsy[8], although this has not been replicated by more recent data[9]. Other authors pointed out the role of adverse effects of AEDs and a previous history of febrile convulsions[10]. Severity of the seizure disorder does not seem to be a relevant factor [11] while depression is, at present, the major risk factor [12,13] especially if comorbid with other psychiatric problems (i.e. paranoid ideation or anxiety disorders)[14,15]. However, it is likely that other, still unknown, biological factors contribute to the increased risk of suicide in epilepsy[16] given the bidirectional relationship between epilepsy, depression and suicide [17,18]. Indeed a recent study identified an association between suicide attempts and epilepsy even before epilepsy onset, and independently of psychiatric disorders [19]. It is clear

that screening and prevention strategies represent a priority in clinical research of neuropsychiatry of epilepsy.

It is well known from the psychiatric literature that patients with a lifetime history of suicidal ideation with intent have a five times increased risk of developing suicidal behaviours [20]. A population-based study in England has shown that 25% of patients with epilepsy have a lifetime history of suicidal thoughts and more than 10% have a lifetime history of suicidal attempts[21]. Similar figures have been reported by another population-based study from Canada[22]. Research on screening for suicide in epilepsy is still at a very early stage. The Columbia Suicide Severity Rating Scale (CSSRS)[23] is currently recommended to identify and monitor patients at high suicidality risk in clinical trials of antiepileptic drugs[24]. It is available in several languages, and a validity study in epilepsy has been published [25]. However, it is rather unrealistic to consider the CSSRS as a user-friendly clinical instrument to use in routine clinical practice for screening purposes. The Neurological Disorders Depression Inventory for Epilepsy (NDDIE) was developed for the rapid and objective detection of a major depressive episode in patients with epilepsy [26]. It has shown to be a very practical and user-friendly screening instrument in any outpatient or inpatient setting. The NDDIE is now available in a number of languages and many clinicians are becoming increasingly familiar with this screening tool in their clinical practice. The aim of this study was to investigate the psychometric properties of the NDDIE, with special attention to item 4 "I'd be better off dead", and to validate its use as a suicidality-screening instrument.

METHODS

The study sample includes 380 patients with epilepsy collected in 3 studies in Italy [27], Germany [28] and France [29] (**Table 1**). In all studies, patients were consecutively recruited and assessed with the same clinical instruments, namely the MINI International Neuropsychiatric

Interview (MINI) v. 5.0.0 [30] and the NDDIE [26]. Inclusion criteria were similar as all studies were part of a large project aimed at validating the NDDIE in the local language: (1) diagnosis of epilepsy according to the ILAE criteria; (2) age more than 18 years; (3) no gross cognitive deficits and a sufficient reading ability to manage the questionnaire; (4) absence of severe medical diseases; and (5) willingness to provide written informed consent to undergo the experimental procedures.

The MINIs (MINI, MINI Plus, MINI Screen and MINI Kid) is a family of brief, simple, user-friendly structured psychiatric diagnostic interviews following DSM/ICD criteria available in more than 35 different languages. The modularity is the main advantage of the MINIs. The MINI explores 14 DSM Axis I disorders and it has antisocial personality disorder and suicidality modules. It takes around 15 minutes. The MINI Plus explores 24 DSM Axis I disorders and maintain the same antisocial personality disorder and suicidality modules. It takes around 30 minutes. The MINI Screen consists of 24 dichotomous items and was developed to screen for psychiatric disorders in the general practice setting, while the MINI Kid explores psychiatric diagnoses in children and adolescents. The Suicidality Module (SM) of both the MINI and the MINI Plus, focuses mostly on current suicidal ideation and attempt (last 4 weeks) and allows a grading of the suicidality risk ranging from low, to intermediate, to high risk. Apart from the six questions present in both the MINI and the MINI Plus, the MINI has 3 additional questions that do not contribute to the final risk score. Each item carries a different score which is also slightly different between the MINI and the MINI Plus, leading to a different range for current suicidality risk. In the MINI low risk range is between 1 and 8, intermediate risk between 9 and 16 and high risk >= 17, while in the MINI Plus low risk is 1-5, intermediate 6-9 and high risk >=10. The three categories encompass the same dimensions and high suicidality risk identifies suicide attempt. High suicidality risk was

considered gold standard in this study, as we wanted to focus on the more severe end of the spectrum.

The NDDIE[26] is a six-item, self-report, questionnaire developed for the rapid and objective detection of major depressive episodes in patients with epilepsy. It showed sound psychometric properties and demonstrated to be a very practical and user-friendly screening instrument in an outpatient setting.

As individual validation studies of the NDDIE have identified different cut-off scores (Italy = 13; France = 15; Germany = 16) for a major depressive episode; patients were categorised as positive according to the local cut-off score identified in the original study. In order to demonstrate that the NDDIE presented homogenous psychometric characteristics in the whole sample, data from the three groups was compared for age, gender and NDDIE total scores. In addition, ROC curves for NDDIE for major depressive episode were compared in the three groups using a nonparametric approach for independent samples [31].

In order to investigate the psychometric properties of the NDDIE and Item 4 "I'd better off dead" as suicidality screening instrument, ROC analyses for NDDIE total and individual item scores were computed and subsequently compared using a nonparametric approach for paired samples[32]. The best possible cut-off was identified with the highest Youden Index (J). Likelihood ratios were then computed and specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) calculated. Sensitivity was defined by the proportion of actual positives that are correctly identified as such, while specificity as the proportion of negatives that are correctly identified as such. The PPV and NPV were defined by the proportion of positive and negative results that are true positive or true negative results and describe the performance of a diagnostic test

Frequencies of categorical demographic and clinical variables were analysed using the $\chi 2$ test or Fisher's exact test. Continuous demographic and clinical variables were compared using the Mann-Whitney test. Analyses were carried out using SPSS 22 and MedCalc 16.1 for Windows.

RESULTS

The study sample consisted of 380 adult patients with epilepsy: 46.3% male; mean age +/- SD was 39.4 +/- 14.6, range (18-82); 76.7% had a diagnosis of focal epilepsy; mean age at onset of the epilepsy +/- SD was 23.3 +/- 17.5, 76 (20%) were seizure free; 132 (34.7%) were on antiepileptic drug monotherapy. There was no difference in the three groups in terms of age, gender, NDDIE total scores. ROC curves were not different in the three groups (Italy vs. France z=1.508 p=0.131; France vs. Germany z=-1.499 p=0.103; Italy vs. Germany z=0.142 p=0.887).

According to the MINI, 74 (19.5%) patients fulfilled DSM criteria for a major depressive episode and 19 (5%) presented a high suicidality risk according to the SM. Comparing patients with high suicidality risk to the remaining group, there was no difference in terms of gender, age, age at onset and epilepsy type. In 17 (89.5%) cases with high suicidality risk there was a concomitant major depressive episode diagnosed with the MINI. The remaining two cases presented a positive NDDIE screening for a major depressive episode despite not fulfilling criteria for a major depressive episode according to DSM criteria.

ROC analyses and Youden Index (J) for NDDIE total and individual item scores are shown in Table 2 and Figure 1. Item 4 "I'd be better off dead" showed the highest AUC coefficient (0.906; 95%CI 0.820-0.992; $p<0.001$) and the highest Youden Index (J=0.751) for a cut-off of >2. Pairwise comparison of ROC curves for NDDIE total and individual item scores

showed a statistically significant better validity for item 4 “I’d be better off dead” as compared to item 1 “Everything is a struggle” ($z=3.949$ $p<0.001$), item 3 “Feel guilty” ($z=3.390$ $p<0.001$) and item 6 “Anhedonia” ($z=4.006$ $p<0.001$). Remaining comparisons of ROC curves were not statistically significant.

A score >2 for item 4 “I’d be better off dead” showed the best psychometric properties with a sensitivity of 84.2%, a specificity of 90.9%, a PPV of 32.7% and a NPV of 99.1%. (Table 3). There was no further improvement in psychometric properties, combining item 4 with item 2 or 5 or NDDIE total score.

According to the NDDIE, 103 (27.1%) patients presented a positive screening for a major depressive episode. A positive suicidality screening, defined by a score >2 for item 4 “I’d be better off dead”, was present in 49 (12.9%) patients. In 45 (91.8%) cases there was a concomitant positive NDDIE screening for a major depressive episode. There was no difference in gender, age, age at onset and epilepsy type comparing patients with a positive NDDIE suicidality screening (defined by a score>2 for item 4) with the remaining sample.

DISCUSSION

Our results demonstrate that the NDDIE can be used as screening instrument not only for a major depressive episode, but also to identify patients at high suicidality risk just by looking at the score of the item 4 “I’d be better off dead”. Our results validated this new application of the NDDIE against an internationally accepted gold standard, showing good to excellent psychometric properties especially in terms of specificity and sensitivity. Item 4 “I’d be better off dead” showed a statistically significant better validity compared to other items of the NDDIE, in particular item 1 “Everything is a struggle”, item 3 “Feel guilty” and item 6 “Anhedonia” further confirming the specificity of item 4 for the investigated dimension. The low PPV, 32.7%, is justified by the low prevalence of the phenomenon itself.

In fact, while sensitivity and specificity can be considered fixed properties of a diagnostic test, PPV and NPV vary with the prevalence of the phenomenon. In our sample, there was a 5% prevalence of high suicidality risk. In case of 10% prevalence, PPV would become 50.69% maintaining the same sensitivity and specificity. It is, therefore, obvious that this approach becomes more and more relevant in high-risk settings like patients with high comorbidity rates.

It could be argued that the identification of slightly different cut-off scores in individual validation studies may reflect significant cross-cultural differences. However, there was no difference in NDDIE total scores and AUC ROC curves among the three studies suggesting that the psychometric properties of the NDDIE were similar in the three groups. Further studies investigating item endorsement in individual NDDIE validation studies would be of great interest from an academic point of view. From a clinical perspective, data from a large cross-sectional study based on a stratified multi-stage random sample of 21,425 adult respondents living in non-institutional settings in six European countries (Belgium, France, Germany, Italy, Netherlands and Spain) showed that the endorsement of depressive symptoms is similar rather than different in Western European countries [33]. In addition, a large epidemiological study of depressive disorders in 7934 persons, aimed at testing the pan-European, cross-cultural validity of the Beck Depression Inventory (BDI) [34], showed some minor differences in individual item endorsement but the item-functioning for item 9 (Suicidality) was excellent. All this evidence taken together demonstrates that Western European countries are broadly comparable, especially concerning suicidality, and the similar cultural background explains these similarities. Interestingly enough, no studies have specifically investigated cross-cultural differences in the cut-off score of a well-known screening instrument such as the BDI in Western European countries and it is entirely

possible that different cut-off scores could be identified. While cross-cultural validity does not represent a major issue in Western Europe, studies in countries with non-Western cultural background may yield quite different results. Further studies in this regard are needed.

Someone could also argue that the item "I'd be better off dead" describes a somewhat passive suicide ideation rather than an active one. This is entirely correct from a formal point of view but increasing evidence suggests that active and passive suicide ideations are equally relevant in terms of subsequent risk of suicidal behaviours [35]. Suicidal ideation represents the fertile ground for suicidal plans that represent the major risk factor for suicidal attempts. In fact, 34% of suicidal ideators make a suicidal plan, 72% of subjects with a suicidal plan make a suicidal attempt but, most importantly, 26% of suicidal ideators without a plan commit suicide [36]. In addition, the majority of these transitions occur within the first year after the onset of suicide ideation. For all of these reasons, suicidal ideation represents an important clinical element deserving careful attention.

Previous studies have preliminarily looked at the issue of screening for suicide in epilepsy clinics[13,25]. As already mentioned, the CSSRS was recommended for suicidality screening in clinical trials[24], representing the best way to address the FDA warning about an increased suicidal risk in patients taking antiepileptic drugs[4]. The CSSRS is a well-known clinical instrument and it is already available in several languages. A cross-sectional study compared the CSSRS, administered either in-person or using an Interactive Voice Response System (E-CSSRS) against the MINI, and showed good to excellent psychometric properties[25]. However, the CSSRS, like the MINI itself, is time consuming and has to be administered by a trained health professional, becoming not cost-effective. Other authors

suggested the use of item 9 of the Beck Depression Inventory [37] but the validity and psychometric properties of this method have never been investigated.

Prevalence of high suicidality risk in our sample was 5%. Reported prevalence in other studies using the MINI varied from 1.6-3.9%[25] to 14%[38]. Reasons for different prevalence rates and clinical correlates of suicidality in epilepsy need to be further elucidated as the severity of the seizure disorder hasn't been recognized as a relevant factor by all authors [14,37]. A previous study showed that a cut-off score of 15 at the NDDIE has a sensitivity of 81% and specificity of 66% for intermediate to high suicidality risk[38]. Our results suggest that the Item 4 "I'd be better off dead" has better psychometric properties than NDDIE total score with a sensitivity of 84.2% and a specificity of 90.9%.

It has long been emphasised that psychiatric disorders in epilepsy are frequently ignored because of several reasons: patients' reluctance to spontaneously volunteer information about existing psychiatric symptoms, a paucity (or total lack) of specific training of the treating neurologist to recognize these psychiatric comorbidities and a lack of time in very busy clinics to screen for them. The development of user-friendly and validated screening instruments assists neurologists and epileptologists in becoming familiar with comorbidities and in implementing care pathways. Suicide may be considered an unmentionable issue by many neurologists, as they may feel uncomfortable in asking the patient directly. However, according to the NICE guidelines, suicidal ideation and intent should always be part of the assessment of depression. The NDDIE as a rapid suicidality-screening instrument represents an easy and straightforward way to introduce the issue of suicide in a busy epilepsy clinic, by simply asking the patient why he or she has answered in that way item 4, and whether he or she already has a plan. This will also stimulate epilepsy centres to develop shared care pathways with liaison psychiatric services in order to assess whether the person has adequate

social support and is aware of sources of help; to arrange help appropriate to the level of risk; and to advise the person to seek further help if the situation deteriorates. In fact, it is important to bear in mind that, aside from the already mentioned barriers, reporting suicide ideation or behaviours may be affected by complex and often conflicting cultural attitudes [36]. In 2008, the WHO launched the "Mental Health Gap Action Program" to address the shortage of mental health professionals by broadening the skills of motivated general health care workers under expert supervision. The establishment of a suicide prevention program represents a subsequent step and this has to be individualised depending on local resources and facilities. Referral protocols and clinical pathways should also be individualised according to local resources.

Our results should be considered bearing in mind the following limitations. First, the MINI and the NDDIE cover a slightly different time-frame, namely four weeks for the MINI and two weeks for the NDDIE. However, previous studies also demonstrated that the time-frame does not represent a major issue [25]. Second, as it often happens with any psychometric study, the diagnostic efficiency statistics are likely to decrease with replication as is invariably the case. Third, our results may not be representative of the general population of patients with epilepsy, as subjects included in the present analysis come from tertiary referral centres where more severe and drug-refractory cases are present. However, it remains unknown whether suicidality is over or under-represented in tertiary epilepsy clinics as compared to community services. Fourth, clinicians must remember that the final judgment on suicidality risk depends on clinical assessment and should not be based just on rating scales.

KEY POINT BOX

- Item 4 of the NDDIE “I’d be better off dead” is a valid suicidality screening instrument in epilepsy
- It showed a sensitivity of 84.2%, a specificity of 90.9%, a PPV of 32.7% and a NPV of 99.1%
- Shared care pathways between epilepsy centres and liaison psychiatric services are needed

ACKNOWLEDGMENTS AND DISCLOSURES

MM has received consultancy fees from UCB Pharma, Eisai, Pfizer and Elsevier. He has also received supports from Bial and Special Products Ltd. CB has received personal compensation from Otsuka, Eisai, Desitin, Pfizer, and UCB Pharma for serving on scientific advisory boards, for speaking activities, congress travel, and financial support for research activities from UCB Pharma and Otsuka. TWM has received financial support from Desitin and UCB Pharma for visiting scientific meetings; he served on scientific advisory boards and received honoraria for speaking engagements from Eisai and Desitin. The French part of this study has been carried out within the Federation Hospitalo-Universitaire (FHU) EPINEXT thanks to the support of the A*MIDEX project (ANR-11-IDEX-0001-02) funded by the "Investissements d'Avenir" French Government program managed by the French National Research Agency (ANR). The remaining authors report no conflict of interest. The authors are grateful to the colleagues who took part in data collection in the original studies. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Clinical and demographic characteristics of the study sample (N = 380).

Study	N	Female	Age	Focal	AUC	NDDIE Mean +/- SD (range)	High suicide risk current (%)
France[29]	116	58.6%	40.4 +/- 13.8	87.1%	0.96	12.8 +/-4.8 (6-23)	8 (6.9%)
Germany[28]	144	52.8%	31.1 +/- 13.4	68.1%	0.85	12.7 +/- 4.1 (6-24)	4 (2.7%)
Italy[27]	120	50.0%	44.9 +/- 14.4	75.0%	0.94	11.3 +/- 4.3 (6-22)	7 (5.8%)

Table 2. ROC analyses of NDDIE total and individual item scores for MINI Suicidality module High Risk.

	AUC	95%CI	SE	Youden Index J	Criterion	P value
Everything is a struggle	0.720	0.625-0.815	0.048	0.368	>2	0.001
Nothing I do is right	0.811	0.710-0.912	0.052	0.487	>2	<0.001
Feel guilty	0.710	0.590-0.829	0.060	0.316	>1	0.002
I'd be better off dead	0.906	0.820-0.992	0.044	0.751	>2	<0.001
Frustrated	0.822	0.725-0.920	0.050	0.521	>3	<0.001
Difficulty finding pleasure	0.776	0.702-0.849	0.037	0.485	>2	<0.001
NDDIE Total	0.897	0.862-0.926	0.031	0.712	>15	<0.001

Table 3. Criterion values and coordinates of the ROC curve for the NDDIE item 4 "I'd be better off dead".

Criterion	Sensitivity	95%CI	Specificity	95%CI	LR+	95%CI	LR-	95%CI
>=1	100	82.4-100	0	0-1.0	1	1.0-1.0		
>1	89.5	66.9-98.7	82.5	78.2-86.3	5.1	3.9-6.7	0.1	0.0-0.5
>2	84.2	60.4-96.6	90.9	87.4-93.6	9.2	6.3-13.5	0.2	0.1-0.5
>3	52.6	28.9-75.6	97.5	95.3-98.9	21.1	9.7-45.8	0.5	0.3-0.8
>4	0	0-17.6	100	99.0-100			1.00	1.0-1.0

LR = likelihood ratio

Figure legend
Figure 1. ROC curves for individual NDDIE items.