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Brief report

# Ultra-short screening instruments for major depressive episode and generalized anxiety disorder in epilepsy: The NDDIE-2 and the GAD-SI

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ABSTRACT

*Background:* Systematic screening is recommended for major depressive episode (MDE) with the Neurological Disorders Depression Inventory for Epilepsy NDDI-E, 6 items and generalized anxiety disorder (GAD) with the GAD 7 items in patients with epilepsy (PWE). Shorter versions of the NDDI-E and the GAD-7 could facilitate increased screening by busy clinicians and be more accessible to patients with mild cognitive and/or language impairments.

*Methods:* The effectiveness of ultra-short versions of the NDDI-E (2 items) and the GAD-7 (the GAD-2, 2 items, and the GAD-SI with a single item) in comparison with the original versions were statistically tested using ROC analysis.

*Results:* ROC analysis of the NDDIE-2 showed an AUC of 0.926 ($p < 0.001$), a sensitivity of 81.82% and a specificity of 89.16%, without significant difference with the NDDI-E ($z=1.582$, $p=0.11$). ROC analysis of the GAD-SI showed an AUC of 0.872 ($p < 0.001$), a sensitivity of 83.67% and a specificity of 82.29%, without significant difference with the GAD-7 ($z=1.281$, $p=0.2$). The GAD-2 showed poorer psychometric properties.

*Limitations:* The limitation is the use of data from previously reported subjects in a single language version, the NDDIE-2 that lacks detection of dysphoric symptoms in comparison with the NDDIE-6 and the GAD-SI that exhibited a more than 10% lower sensitivity than the GAD-7.

*Conclusions:* This study highlights the potential utility of the NDDIE-2 and the GAD-SI as ultra-short screening tools for MDE and GAD respectively in PWE. Further studies in a larger population, including multi-lingual versions, could be a valuable next step. However, the brevity and simplicity of this tool could be an advantage in PWE who present cognitive difficulties, especially attentional or language deficits.

## 1. Introduction

Major depressive episode (MDE) and generalized anxiety disorder (GAD) are the two most prevalent psychiatric disorders in persons with epilepsy (Kwon and Park, 2014). Given effects on epilepsy prognosis, quality of life and mortality, systematic screening is recommended for MDE and GAD in this population. To this aim 2 short self-rated questionnaires, validated in multiple languages, are promoted by the International League Against Epilepsy (ILAE) Commission on Neuropsychiatry (Gilliam et al., 2006; Micoulaud-Franchi et al., 2015). The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a 6-item self-rated questionnaire on a balanced four point Likert scale ranging from 1 to 4 (Gilliam et al., 2006; Micoulaud-Franchi et al., 2015). For clarity, we will refer to the original NDDI-E as the "NDDIE-6". The Generalized Anxiety Disorder 7 (GAD-7) is a 7-item self-rated questionnaire on a balanced four point Likert scale ranging from 0 to 3 (Micoulaud-Franchi et al., 2016; Ruiz et al., 2011). Within the spectrum of screening instruments, the NDDIE-6 and the GAD-7 are considered "short screening tools" (i.e. 5–14 items, taking between 2 and 5 min to complete) as opposed to "standard screening

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tools" (i.e. 15 or more items, > 5 min to complete) (Mitchell and Coyne, 2007).

Though short, these tools may still seem too lengthy and under-utilized in busy clinical practice (Kroenke et al., 2003, 2007). Epilepsy patients may have cognitive deficits making even relatively short questionnaires challenging to complete. Diverse ethnic case-mix in epilepsy care giving rise to variable language abilities has also been highlighted (Rampling et al., 2012).

So-called "ultra-short screening instruments" (1–4 items, < 2 min to complete) have been validated in the general population (Kroenke et al., 2003, 2007) and some specific clinical conditions (Seo and Park, 2015a, 2015b). The best known is the PHQ-2 (Kroenke et al., 2003; Mitchell and Coyne, 2007; Whooley, 2016), a self-reported screening questionnaire for depression based on only two questions, promoted in national guidelines for widespread use by both the National Institute of Health in the United States and the National Institute for Clinical Excellence in the United Kingdom. A community-based study of persons with epilepsy comparing the NDDIE-6 and the PHQ-2 found good positive and negative predictive values for both scales, and good patient acceptability (Margrove et al., 2011). However, a large tertiary hospital study found poor sensitivity with the PHQ-2, suggesting that it should not be recommended for routine screening use in persons with epilepsy (Fiest et al., 2014). A 2 item screening tool (GAD-2) and a single item screening tool (GAD-SI) have also been validated for screening for GAD (Donker et al., 2011; Kroenke et al., 2007), but not to date studied in persons with epilepsy.

The present study aims to analyze the potential effectiveness of ultra-short versions of the NDDIE-6 and the GAD-7 in screening for MDE and GAD respectively, in a sample of persons with epilepsy in a tertiary specialist epilepsy service.

## 2. Methods and materials

### 2.1. Study design

This study was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices. Persons with epilepsy were invited to participate in the study during routine neurological evaluation, usually in the outpatient clinic setting and more rarely during inpatient stay in the videotelemetry unit. After receiving a detailed description of the study, participants gave their informed consent. During the same session, specific modules of the Mini International Neuropsychiatric Interview (MINI) were administered and the screening instruments performed.

### 2.2. Participants

Persons with epilepsy were consecutively recruited from the Clinical Neurophysiology Department of the Marseille University Hospital and the Hôpital Henri Gastaut, Marseille, (these 2 centers forming part of an integrated specialist tertiary epilepsy service), over a 6-month period (January 2014-Jun 2014) for the NDDIE-6 and over an 11-month period (November 2014-September 2015) for the GAD-7.

Inclusion criteria were: native French-speaking adult patients ( > 18 years) with any type of active epilepsy according to the ILAE criteria [46], treated or not by antiepileptic drugs. The diagnosis of epilepsy was documented clinically and confirmed where necessary with video-EEG investigations. Exclusion criteria were: insufficient capacity to consent and to understand and answer the self-report questionnaires, and presence of other severe chronic medical, neurological, and psychiatric conditions (other than epilepsy).

The study sample included 116 persons with epilepsy for the NDDIE-6 and 145 different persons with epilepsy for the GAD-7. The samples were the same as used in previous studies to validate the NDDIE-6 and the GAD-7 (Micoulaud-Franchi et al., 2015, 2016).

For the NDDIE-6 population, mean age was 40.39 years (SD=13.83); 58.6% were women; 87.1% had focal epilepsy. Current MDE was diagnosed in 28.4%. For the GAD-7 sample, mean age was 39.38 years old (SD=14.01); 63.4% were women; 75.9% had focal epilepsy. GAD was diagnosed in 33.8%.

### 2.3. Test methods

#### 2.3.1. The reference standard

The mood disorder module of the (MINI) was the reference standard for the diagnosis of MDE. The Generalized Anxiety Disorder module was the reference standard for the diagnosis of GAD. The French validated version of the MINI was used (Sheehan et al., 1998). The MINI module was administered by physicians with expertise in the field of epilepsy and psychiatry and for whom an explanation and a training session with the MINI module was performed by an experienced psychiatrist. The physician diagnosed MDD or GAD based on the interview, without information on the result of the screening instrument.

#### 2.3.2. The screening instruments

*2.3.2.1. The NDDIE.* Using the MINI as a reference standard for the diagnosis of current MDE, receiver operator characteristics (ROC) analysis of the NDDIE (6 items) showed AUC of 0.958 (Micoulaud-Franchi et al., 2015). The NDDIE-6 showed sensitivity 87.88% [71.8; 96.6], specificity 87.95% [79.0; 94.1], positive predictive value (PPV) 74.4% [57.9; 87] and negative predictive value (NPV) 94.8% [87.2; 98.6].

The item reduction process of the NDDIE took into account both the expertise of a steering committee and the results of statistical analyses. The choice of the two screening items of the NDDIE was discussed with regard to impact on the final instrument's content, taking into account the items' meanings, which was based on the PHQ-2 (Kroenke et al., 2003). The NDDIE-6 does not have a specific item on the feeling of being depressed and we thus did not have a readily equivalent question to that used in the PHQ-2. We chose the items "I'd be better off dead" and "Difficulty finding pleasure".

*2.3.2.2. The GAD-7.* Using the MINI as a reference standard for the diagnosis of GAD, ROC analysis of the GAD-7 showed an AUC of 0.899 (Micoulaud-Franchi et al., 2016). The GAD-7 showed sensitivity 95.9% [86.0; 99.5], specificity 76% [66.3; 84.2], PPV 67.1% [54.9; 77.9], and NPV 97.3% [90.7; 99.7].

The choice of the two screening items of the GAD-7 was based on the GAD-2 (Kroenke et al., 2007). The GAD-2 consists of the following two items: "Feeling nervous, anxious or on edge" and "Not being able to stop or control worrying". The GAD single item (GAD-SI) has also been validated with the following item: "Trouble relaxing" (Donker et al., 2011).

### 2.4. Statistical analyses

Data analysis was performed using MedCalc software (Version 14.8 for Windows). ROC analyses were calculated to assess the utility of two items scores of the NDDIE-2 or the GAD-2 and the single item of the GAD-SI to distinguish the diagnosis of MDE and GAD respectively (as defined by the MINI). Area under the curve (AUC) and its 95% confidence intervals for the ROC curve were calculated. Sensitivity, specificity, PPV and NPV and their confidence intervals were computed. Cut-off point was obtained by selecting the point on the ROC curve that maximized both sensitivity and specificity. ROC analyses for the NDDIE-6 and the NDDIE-2, for the GAD-7 and the GAD-2 scores, and for the GAD-7 and the GAD-SI items were compared using a