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Validation of the Neurological Disorders Depression Inventory for Epilepsy (NDDIE) as a rapid suicidality screening tool in Chinese people with epilepsy

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ABSTRACT

Objective: The objective of this study was to validate the Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (NDDIE) as a suicidality screening tool in Chinese people with epilepsy (PWE).
Methods: A consecutive cohort of PWE was recruited from West China Hospital and 363 Hospital. Each patient received a psychiatric evaluation with the Mini International Neuropsychiatric Interview (MINI) and the Chinese version of the NDDIE (C-NDDIE). Demographic and clinical characteristics were collected. Receiver operating characteristic (ROC) curve analysis was conducted. The best possible cutoff was identified with the highest Youden index. Specificity, sensitivity, positive, and negative predictive values were calculated.
Results: Among a total of 355 participants, 41 (11.5%) had a moderate to high suicide risk according to the Suicidality Module (SM) of the MINI. Receiver operating characteristic (ROC) curve analysis showed that item 4 ("I'd be better off dead") of the NDDIE had an area under the curve (AUC) of 0.930 (95% confidence interval [CI] = 0.884–0.977), a sensitivity of 80.5%, a specificity of 94.9%, a positive predictive value (PPV) of 68.0%, a negative predictive value (NPV) of 97.7%, and the largest Youden index of 0.754 for a cutoff score of >2.
Conclusion: Item 4 of the NDDIE is a valuable tool for screening suicidality in Chinese PWE.

1. Introduction

People with epilepsy (PWE) have a higher suicide rate (12%) compared with the general population (1.1 to 1.2%) [1]. Suicide is a major cause of increased mortality among patients with epilepsy [2]. It has been reported that 11.5% of all deaths in patients with epilepsy are a result of suicide, which is a rate much higher than the 1.4% of deaths attributed to suicide in the general population [1].

Several studies have attempted to identify reasons for such an increased risk of suicide in PWE. Some results suggested that temporal lobe epilepsy [3,4], a lack of aura [4], early age of epilepsy onset, high seizure frequency, antiepileptic drug (AED) polytherapy [5], socioeconomic status [6], and female gender [7] were associated with a higher probability of suicide among patients with epilepsy [3]. The use of AEDs has been highlighted as a potential risk factor. In 2008, the U.S. Food and Drug Administration (FDA) issued an alert about an increased risk of suicide ideation and behavior in PWE treated with AEDs [8]. Even though, the FDA alert has been questioned by clinicians and professional associations because of a number of methodological limitations [9], the document has finally highlighted the issue of suicide in epilepsy. While additional risk factors should be considered in PWE because of the impact of seizure-related factors on suicide, more findings showed that depression is the strongest predictor for suicide in PWE [5,6,10–12]. Depression is the most frequent comorbidity in PWE. The prevalence of depression was higher in PWE than in the general population [13]. Meanwhile, depression may lower the seizure threshold [14]. Some basic studies have also suggested that there are common pathogenic mechanisms between epilepsy, depression, and suicide [15,16]. Therefore, there is a significant need to understand, detect, and manage both depression and suicidality in PWE.

Prevention is the only effective treatment for suicide, which depends on accurate identification of at-risk patients. Suicidal ideation is a common medical term for thoughts about suicide, which may be as detailed as a formulated plan but without the suicidal act itself [17]. While there is a big difference between thinking about suicide and acting it out, suicidal ideation appears to be an important marker for identifying patients at risk of suicide [18]. It is reported that patients with a lifetime history of suicidal ideation with intent have a five times increased risk of developing suicidal behaviors [19]. The most reliable predictor of future risk for suicidal behavior is a past history of suicidal behavior and the

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severity of lifetime suicidal ideation [20,21]. Therefore, the development of valid methods for identifying patients at greater risk for suicidal ideation has important implications for research and suicide prevention.

Suicidal ideation is common in patients with epilepsy. A Canadian population-based study found that the lifetime prevalence of suicidal ideation is 25% in PWE, which is almost two times higher than that for people without epilepsy [22]. Similar figures have been reported by another two studies respectively from England and Korea [23,24]. However, the research on screening for suicide risk in epilepsy is still at an early stage, especially the lack of rapid and effective screening tools for suicidality. The Columbia Suicide Severity Rating Scale (CSSRS) [25] is currently recommended to identify and monitor patients at a high risk for suicide in clinical trials of AEDs [26]. It is available in several languages, and a validity study in epilepsy was published [27]. The Suicidality Module (SM) of the Mini International Neuropsychiatric Interview (MINI) is an efficient diagnostic interview designed to detect suicidal ideation, suicidal plans, and suicide attempts [28], and it can be applied to PWE [1]. It has a practical scoring system that helps quantify current suicide risk and may prove helpful in determining the intervention required [1]. However, both the CSSRS and the MINI are time consuming and have to be administered by a trained health professional, which restrict the promotion and utilization of the scales. Other authors suggested the use of item 9 of the Beck Depression Inventory (BDI) [10] but the validity and psychometric properties of this method have never been investigated. The Neurological Disorders Depression Inventory for Epilepsy (NDDIE) [29], including its Chinese version (C-NDDIE) [30], is simple and easy to understand and has been developed and proven to be a reliable and valid clinical instrument to screen for a major depressive disorder in PWE, especially in busy clinical settings. A recent study validated the use of item 4 ("I'd be better off dead") of the NDDIE as a suicidality screening instrument in Western European PWE, showing effectiveness and good psychometric properties [31]. The aim of this study was to validate item 4 of the NDDIE as a suicidality screening tool in Chinese PWE.

2. Methods

2.1. Participants

Adult patients with epilepsy treated between December 2017 and March 2018 at the epilepsy outpatient clinics of West China Hospital and 363 Hospital, two tertiary care hospitals in western China, were invited to participate in the present study. This study was respectively approved by the Ethics Committee of the West China Hospital of Sichuan University and 363 Hospital, and all patients provided written informed consent prior to their participation in the study.

Patients had to meet the following inclusion criteria: (1) age ≥ 18 years;, (2) diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria [32];, (3) having received at least 6 years of education so that they could properly understand the questionnaire;, and (4) willingness to participate and provide written informed consent. Patients with psychogenic nonepileptic seizures or other significant neurological/psychiatric disorders, such as stroke, dementia, aphasia, or schizophrenia, which might hamper appropriate understanding and completion of the questionnaire, were excluded. Eligible patients were then invited to a quiet room for an interview.

2.2. Demographic and clinical information

Demographic data including age, sex, domicile, marital status, education level, occupation, and per capita annual family income were gathered during the structured interview. Clinical information (e.g., frequency and type of seizures, disease duration, age at onset, AED therapy regimen, and number of seizures in the last 6 months) was obtained from the medical records of each patient.

2.3. Psychiatric and suicide risk evaluation

Each patient received a psychiatric evaluation conducted by a well-trained neurologist using the following instruments:

2.3.1. Mini International Neuropsychiatric Interview (MINI)

The MINI is a simple, effective, reliable, and internationally validated structured psychiatric diagnostic interview following Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases (DSM/ICD) criteria. It is mainly used for screening and diagnosis of axis I psychiatric disorders and one personality disorder in DSM-IV and ICD-10 [28]. The modularity is the main advantage of the MINI. Only the SM of the MINI (Chinese version 5.0.0) was administered. The SM of the MINI contains six questions, with scores ranging from 0 to 33. The SM allows a grading of the suicide risk ranging from low, to moderate, to high risk. Low risk is 1–5, moderate risk 6–9, and high risk ≥10. Moderate to high suicide risk (scores ≥ 6 points in the SM) were considered the gold standard in this study. Serious suicide risk was defined as those with moderate to high risk (scores ≥ 6), and low suicide risk was defined as those with a score less than 6.

2.3.2. Chinese version of the Neurological Disorders Depression Inventory for Epilepsy (C-NDDIE)

The NDDIE, including the C-NDDIE, which is a six-item self-rating questionnaire, has been developed and validated as a screening instrument for depression in PWE [29,30]. The sum of the scores obtained on each item results in a total score ranging from 6 to 24. Item 4 ("I'd be better off dead") is rated on a 4-point scale from 1 to 4, with "Never" scored 1, "Rarely" scored 2, "Sometimes" scored 3, and "Always/often" scored 4. In this study population, the C-NDDIE adopted >12 as the cut-off score [30].

2.4. Statistical analysis

Statistical analysis was performed with SPSS Version 20.0 and MedCalc 18.9 for Windows. Categorical demographic and clinical variables were analyzed by chi-square tests or Fisher's exact tests, and continuous variables were analyzed by Mann–Whitney *U* tests as the data did not show a normal distribution. A significance level was set at $P < 0.05$ (two-tailed). Receiver operating characteristic (ROC) curve analysis was carried out to assess the validity, including sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV), of item 4 of the C-NDDIE at different cutoff scores. Additionally, the best possible cutoff was identified with the highest Youden index.

3. Results

A total of 383 adults with epilepsy were invited to participate in this study. Among them, 16 declined to participate. There were no significant differences in demographic or clinical features between patients who declined and patients who agreed to participate ($n = 367$). Among these 367 patients, two had experienced a stroke, three had dementia, two had schizophrenia, and five had fewer than 6 years of educational experience. Following exclusion of these patients, a total of 355 patients completed the study.

3.1. Demographic and clinical characteristics

A total of 355 participants were enrolled: 48.7% were male; mean age ± standard deviation (SD) was 30.74 ± 12.26. According to the SM of the MINI, 41 (11.5%) presented a moderate to high suicide risk. Compared with the group with low suicide risk, the scores of the C-NDDIE and item 4 were higher in the group with serious suicide risk ($P < 0.001$). There were no statistical differences in age, sex, domicile, marital status, education level, annual income of the family, occupation,

Table 1
Demographic and clinical characteristics of the participants.

	Mean ± SD (range) or number (%)			
	Total (N = 355)	Low suicide risk (n = 314)	Serious suicide risk (n = 41)	P-value
Age (years)	30.74 ± 12.26	31.08 ± 12.40	28.12 ± 10.92	0.098[b]
Sex				0.995[a]
Female	182 (51.3)	161 (51.3)	21 (51.2)	
Male	173 (48.7)	153 (48.7)	20 (48.8)	
Domicile				0.234[a]
Urban area	221 (62.3)	192 (61.1)	29 (70.7)	
Rural area	134 (37.7)	122 (38.9)	12 (29.3)	
Marital status				0.112[a]
Unmarried	175 (49.3)	150 (47.8)	25 (61.0)	
Married	180 (50.7)	164 (52.2)	16 (39.0)	
Education level				0.143[a]
Junior high school and below	147 (41.4)	128 (40.8)	19 (46.3)	
High school	111 (31.3)	95 (30.2)	16 (39.1)	
University and above	97 (27.3)	91 (29.0)	6 (14.6)	
Per capita annual family income (yuan)				0.310[a]
<10,000	76 (21.4)	71 (22.6)	5 (12.2)	
10,000–50,000	232 (65.4)	202 (64.3)	30 (73.2)	
>50,000	47 (13.2)	41 (13.1)	6 (14.6)	
Occupation				0.327[a]
Student	46 (13.0)	41 (13.1)	5 (12.2)	
Unemployed	163 (45.9)	139 (44.3)	24 (58.5)	
Employed	129 (36.3)	119 (37.9)	10 (24.4)	
Retired	17 (4.8)	15 (4.8)	2 (4.9)	
Number of seizures in the last 6 months				0.218[a]
Seizure-free	126 (35.5)	115 (36.6)	11 (26.8)	
Seizure occurrence	229 (64.5)	199 (63.4)	30 (73.2)	
Disease duration (years)	6.00 (3.00,11.00)	6.00 (3.00,11.00)	8.00 (4.50,14.00)	0.167[b]
Age at onset (years)	22.16 ± 13.29	22.62 ± 13.36	18.68 ± 12.40	0.053[b]
Seizure frequency (per month)	0.25 (0.08,1.5)	0.25 (0.08,1.00)	1.00 (0.08,3.00)	0.102[b]
Seizure type				
Focal onset aware	39 (11.0)	32 (10.2)	7 (17.1)	0.289[a]
Focal onset impaired awareness	112 (31.5)	98 (31.2)	14 (34.1)	0.704[a]
Focal to bilateral tonic–clonic	166 (46.8)	150 (47.8)	16 (39.0)	0.291[a]
Generalized onset	92 (25.9)	81 (25.8)	11 (26.8)	0.887[a]
Unknown onset	8 (2.3)	6 (1.9)	2 (4.9)	0.519[a]
AED therapy regimen				0.224[a]
None	22 (6.2)	18 (5.7)	4 (9.8)	
Monotherapy	174 (49.0)	159 (50.6)	15 (36.6)	
Dual therapy	128 (36.1)	112 (35.7)	16 (39.0)	
Polytherapy (≥3 AEDs)	31 (8.7)	25 (8.0)	6 (14.6)	
Score of the NDDIE	10.90 ± 3.88	10.18 ± 3.30	16.41 ± 3.51	<**0.001**[b]
Score of the NDDIE item 4	1.50 ± 0.83	1.31 ± 0.60	3.02 ± 0.79	<**0.001**[b]

Bold data show statistical significance <0.05.
[a] Chi-square test.
[b] Mann–Whitney *U* test.

age at onset, number of seizures in the last 6 months, disease duration, seizure frequency, seizure type, or AED therapy regimen between the group with low suicide risk and group with serious suicide risk (P > 0.05). For details, see Table 1.

3.2. ROC curve analysis

Receiver operating characteristic curve analyses and Youden index for C-NDDIE total and individual item scores are shown in Table 2 and Fig. 1. Item 4 showed the largest area under the curve (AUC) of 0.930 (95% confidence interval [CI] = 0.884–0.977; P < 0.001) and the largest Youden index of 0.754 at a cutoff score of >2. Pairwise comparison of ROC curves for NDDIE total and individual item scores showed a statistically better validity for item 4 ("I'd be better off dead") as compared to item 1 "Everything is a struggle" (Z = 5.316; P < 0.001), item 2 "Nothing I do is right" (Z = 5.037; P < 0.001), item 3 "Feel guilty" (Z = 4.787; P < 0.001), item 5 "Frustrated" (Z = 3.043; P = 0.002), and item 6 "Difficulty finding pleasure" (Z = 3.700; P < 0.001). Area under

Table 2
ROC analyses of NDDIE total and individual item scores for MINI Suicidality Module moderate to high risk.

	AUC	95%CI	SE	Youden index	Criterion	P-value
Everything is a struggle	0.719	0.641–0.797	0.040	0.384	>2	<0.001
Nothing I do is right	0.742	0.664–0.821	0.040	0.352	>2	<0.001
Feel guilty	0.756	0.681–0.832	0.039	0.426	>1	<0.001
I'd be better off dead	0.930	0.884–0.977	0.024	0.754	>2	<0.001
Frustrated	0.808	0.743–0.873	0.033	0.465	>2	<0.001
Difficulty finding pleasure	0.784	0.711–0.857	0.037	0.413	>2	<0.001
NDDIE total	0.894	0.850–0.938	0.022	0.667	>13	<0.001

AUC: area under the curve, 95%CI: 95% confidence interval, SE: standard error, ROC: receiver operating characteristic, NDDIE: Neurological Disorders Depression Inventory for Epilepsy, and MINI: Mini International Neuropsychiatric Interview.

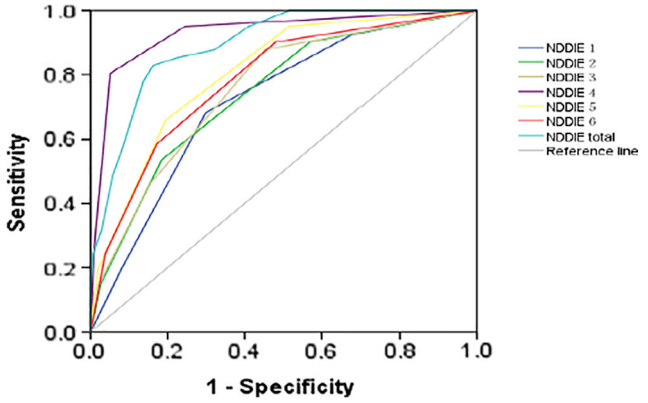

Fig. 1. ROC curves for individual NDDIE items. ROC: receiver operating characteristic; NDDIE: Neurological Disorders Depression Inventory for Epilepsy.

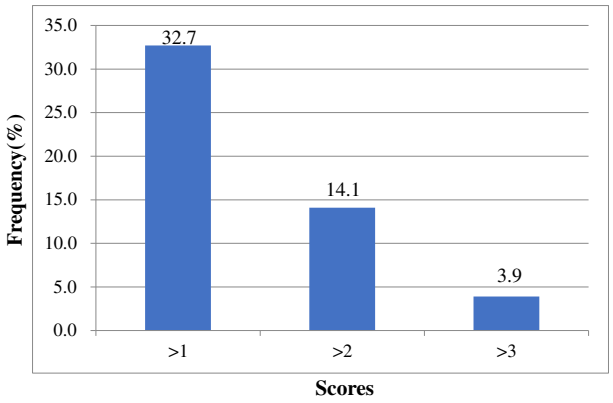

Fig. 2. Estimated frequencies of suicide risk in participants according to different cutoff scores of item 4 of the NDDIE. NDDIE: Neurological Disorders Depression Inventory for Epilepsy.

the curve comparison for the NDDIE total and item 4 scores was not significant ($Z = 1.601$; $P = 0.109$).

As demonstrated in Table 3, item 4 ("I'd be better off dead") had a sensitivity of 80.5%, a specificity of 94.9%, a PPV of 68.0%, a NPV of 97.7%, and the largest Youden index of 0.754 for a cutoff score of >2.

3.3. Frequency of suicide risk in Chinese PWE after applying different cutoff scores

According to the C-NDDIE, 106 participants (29.9%) screened positive for depression. With the cutoff score of >2 for item 4 "I'd be better off dead", 50 (14.1%) patients got positive results for suicidality. Of these 50, 44 (88.0%) had depressive disorder; and 34 (68.0%) presented a moderate to high suicide risk according to the SM of the MINI. Applying other cutoff scores, different frequencies of suicide risk would be screened out in our sample (Fig. 2).

4. Discussion

Patients with epilepsy have a high risk of suicide, especially those patients with comorbid depression [24,33]. It is particularly important to select a screening instrument not only to quickly screen for depression, but also to accurately identify patients at a high risk for suicide. The NDDIE has been translated and validated in several languages [29,34–39], including its Chinese version [30], and has been widely used to screen for depression in PWE. Moreover, there have been studies showing that the NDDIE could be used as a suicidality screening tool [31,40,41]. A previous study showed that the NDDIE for a cutoff score of 15 has a sensitivity of 81% and a specificity of 66% for moderate to high suicide risk [40]. The study by de Oliveira et al. [41] compared the psychometric properties of the NDDIE, Hospital Anxiety and Depression Scale Depression Subscale (HADS-D), and the BDI as screening instruments for suicidality in PWE, indicating that the NDDIE and HADS-D had a good sensitivity (92.9% and 85.7%, respectively), but a low specificity (68%). The BDI was a more robust instrument with a sensitivity of 92.9% and a specificity of 76.8%, but it is difficult to understand and takes longer to apply, which hampers its use by busy clinicians. In fact, there is a suicidality item in the NDDIE questionnaire (item 4 "I'd be better off dead"). The study by Mula et al., which reviewed three studies from three European countries (Italy, Germany, and France), first validated this new application of item 4 of the NDDIE as a suicidality screening instrument, showing better psychometric properties than the NDDIE total score, with a sensitivity of 84.2% and a specificity of 90.9% [31]. The current study validated item 4 ("I'd be better off dead") of the C-NDDIE as a rapid suicidality screening tool in a cohort of PWE in western China. Our results demonstrated that item 4 ("I'd be better off dead") could screen suicidality in PWE with a high sensitivity of 80.5% and a high specificity of 94.9%, and its Youden index could reach a maximum of 0.754 at a cutoff score of >2. Item 4 ("I'd be better off dead") showed a statistically significant better validity and reliability compared to other items on the NDDIE.

We figured out what would happen if other cutoff scores were adopted in our sample. The higher score as >3 would reduce the corresponding frequencies, leading to a decrement of screening power, with a fairly low sensitivity of 26.8%; the lower score as >1 would increase the frequencies, but reduce accuracy, with a specificity of 75.5%. Therefore, a cutoff score of >2 was finally adopted in our research. In addition, the PPVs of the two studies (Mula's and our study) were respectively 32.7% and 68.0%, while the NPVs were higher than 97.0%, indicating that item 4 ("I'd be better off dead") is more of a "rule-out" tool rather than "rule-in" just as the NDDIE for depression has been reported [42].

It could be argued that item 4 ("I'd be better off dead") describes a suicidal ideation rather than a suicidal behavior, some people who experience suicidal ideation do not actually commit suicide. However, predicting suicide is very difficult, it has been reported that nearly half of individuals express their intent prior to suicide [43,44]. Thus, suicidal ideation may be an important warning sign that precedes suicide, especially in high-risk populations such as PWE [1]. The identification of risk factors for suicidal ideation may be critical for preventing PWE from committing or attempting suicide. In our study, the prevalence of moderate to high suicide risk was 11.5%. Reported prevalence in other studies using the MINI varied from 1.6–3.9% [27] to 14.0% [40], which

Table 3
ROC and diagnostic efficiency of the NDDIE item 4 ("I'd be better off dead") for moderate to high suicide risk.

Cutoff score	Sensitivity (%)	95%CI	Specificity (%)	95%CI	PPV (%)	NPV (%)	LR+	LR−	YI
≥1	100.0	91.4–100.0	0.00	0.0–1.2	11.5		1.00		0
>1	95.1	83.5–99.4	75.5	70.3–80.1	33.6	99.2	3.882	0.065	0.706
>2	80.5	65.1–91.2	94.9	91.9–97.1	68.0	97.7	15.784	0.205	0.754
>3	26.8	14.2–42.9	99.0	97.2–99.8	78.6	91.2	28.080	0.739	0.259
>4	0.0	0.0–8.6	100.0	98.8–100.0				1.00	0

PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, YI: Youden index, 95%CI: 95% confidence interval, ROC: receiver operating characteristic, and NDDIE: Neurological Disorders Depression Inventory for Epilepsy.

is significantly higher than in the general population [2]. The major predictor of suicide risk in PWE was found to be depression rather than seizure-related variables or other demographic variables [5,10]. Our data suggested that suicide risk was strongly associated with depression and not by seizure factors (age at onset, number of seizures in the last 6 months, disease duration, seizure frequency, seizure type, and AED therapy regimen), age, gender, domicile, marital status, education level, annual income of the family, or occupation. This is in line with previous studies [5,10]. In addition, the results from Hecimovic et al. [10] indicated that about one-fourth of the suicidal subjects were euthymic or only mildly depressed. We also observed that 12.0% of the patients with suicide risk were without depression. These results suggested that PWE, both with and without depression, should be routinely evaluated for the risk of suicide. If the risk is thought to be increased, then therapeutic interventions should be considered including appropriate treatment, referral to psychiatrist, or even hospitalization [45].

This study has several limitations. First, this analysis was conducted on a restricted sample pool of patients with epilepsy who come from two tertiary referral hospitals, perhaps including more complicated cases; therefore, our results may not be representative of the general population of patients with epilepsy. Second, a cutoff score of >2 for item 4 of the C-NDDIE had a PPV of 68.0%, which may lead to false positive results. The NDDIE assesses symptoms during the preceding two weeks, and suicidality assessed by the MINI takes into account symptoms over the past one month. The difference in the observation period between the two tools may help to explain the low PPV of item 4 of the C-NDDIE for suicidality. However, since the NDDIE was a screening tool rather than a diagnostic tool, we considered this PPV acceptable. Therefore, item 4 of the C-NDDIE provides only probable diagnoses that should be investigated by further evaluation.

In conclusion, item 4 of the NDDIE is proven to be a reliable and valid suicidality screening tool for use in PWE. We recommend >2 as the optimal cutoff score when applying item 4 in Chinese PWE. The new application of the NDDIE could bring earlier detection of suicidality in PWE and promote effective intervention to reduce the incidence of suicide and improve the patients' quality of life.

Disclosures of conflicts of interest

None of the authors have any conflicts of interest to disclose.

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