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Depression in people with epilepsy in West China: Status, risk factors and treatment gap

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ABSTRACT

Purpose: To evaluate the prevalence, suicidality and treatment gap (TG) of depression in people with epilepsy (PWE) in West China, and to explore the related risk factors.

Methods: A consecutive cohort of PWE from West China Hospital was recruited. The Chinese version of the Neurological Disorders Depression Inventory for Epilepsy scale was used to assess depression and suicidality. Prevalence and TG of depression were calculated. Logistic regression analysis was used to assess risk factors of depression and suicidality.

Results: Among a total of 461 participants, there were 29.9% with depression and 15.8% had suicidality. Being female, an unmarried status, disease course, seizure frequency, seizure occurrence in the last 6 months, and focal impaired awareness seizure were risk factors for depression. Depression was an independent risk factor for suicidality. The TG of depression was 72.5%. The TG was larger in the 30–40 year age group, in rural populations, and among those with a disease course between 5 and 10 years. The TG figures dropped with increasing annual family income.

Conclusions: The prevalence of depression and the rate of suicide risk for PWE in West China are high. A large TG for depression exists in PWE. Clinicians should focus on depression and suicidality for PWE and identify the related risk factors in a timely manner so as to reduce the incidence of depression and suicide. Management including public education as well as professional training of neurologists are necessary to fill the TG.

1. Introduction

There are many comorbidities in people with epilepsy (PWE), with depression being the most frequent comorbidity. The lifetime prevalence for depression is around 10% in the general population [1] but is estimated at 30% in PWE [2]. A bidirectional relationship between depression and epilepsy was described more than 2000 years ago [3]. Depression may lower the seizure threshold [4]. Many recent epidemiological studies have found that the presence of primary depressive disorder was associated with a three to seven fold higher risk of developing epilepsy [5,6]. Findings of an increased risk for seizures in people with depression are consistent with the increased prevalence of depression in epilepsy patients [7].

Comorbid depression is associated with a poorer quality of life [8], worse prognosis [9], greater possibility of side effects due to antiepileptic drugs (AEDs) [10], increased risk of drug resistance [11], poorer post-surgical outcomes [12], and added medical costs [8]. More severely, depression is closely related to an increased risk of suicide for PWE and is the main risk factor for suicide [13,14]. However, 1/3 to 2/3 of PWE with depression are reported to be misdiagnosed [15], and 44% of patients said they would not seek help from professional physicians [15]. Less than one-third of PWE with a diagnosis of comorbid depression are treated for their mood disorder [16]. This shows that clinicians are not paying enough attention to comorbid depression and are inadequately aware of the related risk factors. Meanwhile, many patients with epilepsy are unable to accept a diagnosis of depressive disorder [15]. Therefore, there is a significant need to understand, detect, and manage these comorbidities in PWE.

The screening tools [e.g., the Hamilton Depression Scale (HAMD) and the Beck Depression Inventory (BDI)] used in the previous studies are relatively complex. Moreover, education in West China has been relatively limited, and PWE tend to receive a poor education due to seizures, social discrimination and stigmatization. It can be relatively difficult and time-consuming to complete these scales, restricting the promotion and utilization of these scales. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which is simple and easy

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to understand, has been translated and validated in several languages [17–22] and has been widely used to screen for major depressive disorder (MDD) in PWE, especially in busy clinical settings. The Chinese version of the NDDIE (C-NDDI-E) has been proven to be a reliable and valid clinical instrument for screening for MDD in Chinese PWE with a sensitivity of 0.926 and a specificity of 0.804 [23]. Item 4 of the NDDIE represents an easy and straightforward way to introduce the issue of suicide by simply asking the patient why he or she has answered item 4 in that way, and whether he or she already has a plan. A recent study validated the use of item 4 of the NDDIE as a screening instrument for high risk suicidal ideation, showing effectiveness and good psychometric properties with a sensitivity of 0.842 and a specificity of 0.909 [24].

At present, there are no studies with a large sample size on the status and related risk factors of depression and suicidality in PWE in West China. There is a lack of research on the treatment gap (TG) of comorbid depression in China and abroad. The aim of this study was to evaluate the prevalence, suicidality and TG of depression in PWE in West China, and to explore the related risk factors so as to provide a theoretical basis for targeted intervention measures and the prevention of epilepsy comorbidity in West China.

2. Methods

2.1. Participants

Adult patients with epilepsy treated between January and November 2017 at the epilepsy clinic of West China Hospital, a large tertiary care hospital in western China, were invited to participate in the present study. This study was approved by the Ethics Committee of the West China Hospital of Sichuan University, and all patients provided written informed consent prior to their participation in the study.

Patients had to meet the following inclusion criteria: (1)18 years of age or older, (2) current diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria [25], (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. Every patient had undergone EEG (routine or monitoring) and usually a brain MRI. Patients with psychogenic non-epileptic seizures or other significant neurological/psychiatric disorders, such as cognitive deficits, aphasia or schizophrenia, which might hamper appropriate understanding and completion of the questionnaire, were excluded. In this study, cognitive deficits referred to a score on the Mini-Mental State Examination (MMSE) of less than 20 for individuals with 6 years of education and a score of less than 24 for those with 7 or more years of education [26].

2.2. Data collection

2.2.1. 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 course, age at onset, AED therapy regimen, and number of seizures in the last 6 months) was obtained from the medical records of each patient. Disease course referred to the length of time since onset of seizures.

2.2.2. Measures

Each patient was asked to complete the Chinese version of the NDDI-E (C-NDDI-E), which is a six-item self-rating questionnaire that was developed and validated as a screening instrument for depression in PWE [17,23]. The NDDI-E is not a substitute for clinical interview and Diagnostic and Statistical Manual (4th ed.) diagnosis, but it is a reliable, validated, and widely used self-report measure of depression. The items in this instrument investigate symptoms of depression over the past two weeks excluding items with possible correlation to antiepileptic drug (AED) side effects or the epilepsy itself, such as somnolence or memory problems. The six items are rated on a 4-point scale from 1 to 4, where “Never” scored one, “Rarely” scored two, “Sometimes” scored three, and “Always/often” scored four. The total score ranges from 6 to 24, with a higher score indicating a higher risk for developing major depression. The original study suggests that scores greater than 15 show a sensitivity of 0.81 and a specificity of 0.90 for major depressive episode [17]. This instrument was validated for Chinese PWE with a suggested cutoff point of > 12, with a sensitivity of 0.926 and a specificity of 0.804 [23]. In this study population the C-NDDI-E adopted > 12 as the cutoff score [23]. Subjects with a score greater than 12 were considered to be depressed [23]. Item 4 (“I'd be better off dead”) of the NDDIE was used as a suicidality screening instrument, with a cutoff score of > 2 [24].

2.2.3. Assessment of treatment

Each patient was asked whether they were receiving antidepressant treatment by self-report during the month prior to screening, and the AED therapy regimen of each patient was obtained from their medical records. In the current study antidepressant treatment was defined as regular treatment according to the international consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy, which was developed by ILAE [27], including medicine, psychological consultation and spiritual guidance.

The TG of comorbid depression in PWE refers to the ratio of the number of epilepsy patients with depression who are not receiving antidepressant treatment to the number of all epilepsy patients with depression, expressed as a percentage [28].

2.3. Statistical analysis

Statistical analysis was performed with SPSS Version 20.0 software for Windows. Categorical demographic and clinical variables were analyzed by Chi-square tests or Fisher’s exact tests, and continuous variables were analyzed by Man-Whitney U tests as the data did not show a normal distribution. Multivariable analyses were performed with a binary logistic regression model in which each variable with a p-value of < 0.05 (based on the univariate analysis) was entered into the model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The significance level was set at $p < 0.05$ (two-tailed).

3. Results

A total of 493 adults with epilepsy were invited to participate in this study. Among them, 19 declined to participate. There were no significant differences in demographic or clinical features between patients who declined and patients who agreed to participate ($n = 474$). Among these 474 patients, two had experienced a stroke, four had cognitive deficits, one had schizophrenia and six had fewer than 6 years of educational experience. Following exclusion of these patients, a total of 461 patients completed the study. No major difficulties were reported in the process of answering the questionnaire and no items of the scale were left blank.

3.1. Demographic and clinical characteristics

The mean age was 29.68 ± 11.46 years old. There were 213 (46.2%) men and 248 (53.8%) women, and 138 of 461 (29.9%) screened positive for depression. Of these 138, 86 (62.3%) were women who were more likely to be depressed ($p = 0.016$), and 91 were unmarried who were also more likely to be depressed ($p < 0.001$). There were no statistical differences in age, domicile, education level, occupation or per capita annual family income between the groups with and without depression. There were more patients with focal impaired awareness seizures screened positive for depression ($p < 0.001$), while

Table 1
Demographic and clinical characteristics of all participants and comparison between groups with and without depression.

	Mean ± SD (range) or number (%)			
	Total (n = 461)	Group without depression (n = 323)	Group with depression(n = 138)	P-Value
Age (years)	29.68 ± 11.46	30.38 ± 11.92	28.06 ± 10.16	0.061[b]
Sex				**0.016**[a]
Male	213 (46.2)	161 (49.8)	52 (37.7)	
Female	248 (53.8)	162 (50.2)	86(62.3)	
Domicile				0.064[a]
Urban area	277 (60.1)	203 (62.8)	74 (53.6)	
Rural area	184 (39.9)	120 (37.2)	64 (46.4)	
Marital status				< **0.001**[a]
Unmarried	240 (52.1)	149 (46.1)	91 (65.9)	
Married	221 (47.9)	174 (53.9)	47 (34.1)	
Education level				0.084[a]
Junior high school	193 (41.9)	134 (41.5)	59 (42.8)	
High school	145 (31.5)	94 (29.1)	51 (37.0)	
University and above	123 (26.6)	95 (29.4)	28 (20.3)	
Per capita annual family income (yuan)				0.708[a]
< 10,000	112 (24.3)	75 (23.2)	37 (26.8)	
10,000-50,000	296 (64.2)	210 (65.0)	86 (62.3)	
> 50,000	53 (11.5)	38 (11.8)	15 (10.9)	
Occupation				0.065[a]
Student	61 (13.2)	44 (13.6)	17 (12.3)	
Unemployed	225 (48.8)	145 (44.9)	80 (58.0)	
Employed	161 (34.9)	124 (38.4)	37 (26.8)	
Retired	14 (3.1)	10 (3.1)	4 (2.9)	
Number of seizure in the last 6 months				< **0.001**[a]
Seizure free	171 (37.1)	137 (42.4)	34 (24.6)	
Seizure occurrence	290 (62.9)	186 (57.6)	104 (75.4)	
Disease course (years)	7.00 (3.00, 12.00)	5.00 (3.00, 11.17)	9.13 (3.75, 13.33)	**0.017**[b]
Age at onset (years)	20.84 ± 12.80	21.97 ± 13.19	18.20 ± 11.46	**0.001**[b]
Seizure frequency (per month)	0.25 (0.08, 1.00)	0.21 (0.04, 1.00)	0.67 (0.17, 2.25)	< **0.001**[b]
Seizure type				
Focal onset aware	69 (15.0)	55 (17.0)	14 (10.1)	0.058[a]
Focal onset impaired awareness	138 (29.9)	81 (25.1)	57 (41.3)	< **0.001**[a]
Focal to bilateral tonic-clonic	192 (41.6)	143 (44.3)	49 (35.5)	0.080[a]
Generalized Onset	133 (28.9)	85 (26.3)	48 (34.8)	0.066[a]
Unknown Onset	11 (2.4)	10 (3.1)	1 (0.7)	0.232[a]
AED therapy regimen				
None	31 (6.7)	24 (7.4)	7 (5.1)	0.355[a]
Mono-therapy	240 (52.1)	177 (54.8)	63 (45.7)	0.072[a]
Poly-therapy (≥2 AEDs)	190 (41.2)	122 (37.8)	68 (49.2)	**0.022**[a]

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

no such difference was found for other seizure types. Patients who were seizure-free in the last 6 months had less depression (p < 0.001). For the group with depression, their seizures occurred more frequently (p < 0.001), and they were also more likely to be taking multiple AEDs (p = 0.022). Compared to the group without depression, age at onset was younger (P = 0.001) and the disease course was longer (P = 0.017) in the group with depression. For details see Table 1.

There were 73 (15.8%) patients with suicide risk, and among these, 52 of 73 (71.2%) had a depressive disorder, while 51 (69.9%) of the patients with suicide risk were not receiving any psychiatric treatment. For the group with suicide risk, their seizures occurred more frequently (P = 0.013) and their disease course was longer (P = 0.036). The prevalence of suicide risk for PWE with depression was higher (P < 0.001). There was no statistical difference in sex, age, domicile, marital status, education level, occupation, per capita annual income of the family, age at onset, number of seizure in the last 6 months, seizure type or AED therapy regimen between the groups with and without suicide risk. For details see Table 2.

3.2. Risk factors

3.2.1. Risk factors for depression in PWE

Being female (OR = 1.960, 95% CI: 1.241–3.094, P = 0.004), an unmarried status (OR = 4.023, 95% CI: 2.116–7.648, P < 0.001), disease course (OR = 1.045, 95% CI: 1.007–1.083, P = 0.019), seizure frequency (OR = 1.029, 95% CI: 1.012–1.047, P = 0.001), seizure occurrence in the last 6 months (OR = 2.428, 95% CI: 1.490–3.957, P < 0.001), and focal impaired awareness seizure (OR = 1.602, 95% CI:1.003–2.559, P = 0.049) were risk factors for depression in PWE. For details see Table 3.

3.2.2. Risk factors for suicide risk in PWE

Depression (OR = 8.441, 95% CI: 4.791–14.874, P < 0.001) was an independent risk factor for suicide risk in PWE. For details see Table 4.

3.3. Treatment gap

Of 138 patients with depression, 100 had never received any antidepressant treatment, including 79 who were never diagnosed and 21 who were diagnosed but untreated. The treatment gap of comorbid depression was 72.5% (100/138). The TG of comorbid depression in PWE was larger in rural populations than in urban populations (P = 0.032). The TG figures dropped with increasing per capita annual income of the family. Patients in the 30–40 year age group had the largest TG of comorbid depression with a significant difference

Table 2
Comparison of demographic and clinical characteristics in those with and without suicide risk.

	Mean ± SD (range) or number (%)		
	Group without suicide risk (n = 388)	Group with suicide risk (n = 73)	P-Value
Age (years)	29.53 ± 11.47	30.51 ± 11.44	0.311[b]
Sex			0.561[a]
Male	177 (45.6)	36 (49.3)	
Female	211 (54.4)	37(50.7)	
Domicile			0.822[a]
Urban area	234 (60.3)	43 (58.9)	
Rural area	154 (39.7)	30 (41.1)	
Marital status			0.444[a]
Unmarried	199 (51.3)	41 (56.2)	
Married	189 (48.7)	32 (43.8)	
Education level			0.148[a]
Junior high school	155 (39.9)	38 (52.1)	
High school	125 (32.2)	20 (27.4)	
University and above	108 (27.9)	15 (20.5)	
Per capita annual family income (yuan)			0.580[a]
< 10,000	92 (23.7)	20 (27.4)	
10,000-50,000	253 (65.2)	43 (58.9)	
> 50,000	43 (11.1)	10 (13.7)	
Occupation			0.139[a]
Student	54 (13.9)	7 (9.6)	
Unemployed	187 (48.2)	38 (52.1)	
Employed	138 (35.6)	23 (31.5)	
Retired	9 (2.3)	5 (6.8)	
Number of seizure in the last 6 months			0.281[a]
Seizure free	148 (38.1)	23 (31.5)	
Seizure occurrence	240 (61.9)	50 (68.5)	
Disease course (years)	6.00 (3.00, 12.00)	10.00 (4.00, 15.42)	**0.036**[b]
Age at onset (years)	21.00 ± 12.93	20.03 ± 12.13	0.545[b]
Seizure frequency (per month)	0.25 (0.08, 1.00)	0.50 (0.105, 3.00)	**0.013**[b]
Seizure type			
Focal onset aware	61 (15.7)	8 (11.0)	0.295[a]
Focal onset impaired awareness	114 (29.4)	24 (32.9)	0.550[a]
Focal to bilateral tonic-clonic	159 (41.0)	33 (45.2)	0.502[a]
Generalized Onset	113 (29.1)	20 (27.4)	0.765[a]
Unknown Onset	9 (2.3)	2 (2.7)	0.829[a]
AED therapy regimen			
None	24 (6.2)	7 (9.6)	0.287[a]
Mono-therapy	202 (52.1)	38 (52.1)	0.999[a]
Poly-therapy (≥2 AEDs)	162 (41.7)	28 (38.3)	0.589[a]
Depression			< **0.001**[a]
Group without depression	302 (77.8)	21 (28.8)	
Group with depression	86 (22.2)	52 (71.2)	

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

compared with the other age groups. Those with a disease course between 5 and 10 years showed a significantly larger TG. There were no significant differences in TG of comorbid depression related to sex, marital status, educational level, occupation, number of seizure in the last 6 months, age at onset, seizure frequency, seizure type, or AED therapy regimen (P > 0.05). For details see Table 5.

4. Discussion

Comorbidities in PWE have been a hot topic in recent years in the field of epilepsy. In the new classification of seizure types published by the ILAE in 2017, it is particularly emphasized that the comorbidities of epilepsy should run through three levels of epileptic diagnosis (seizure types, epilepsy types, epilepsy syndromes) for early detection and early intervention [29]. The overall prevalence of depression in adult PWE is variable in the literature, ranging from 20% to 55% depending on the population investigated and the screening instrument used [30,31]; however, 30% is estimated to be the average [32]. In the current study, 29.9% suffered from depression, which is very close to the average. In the past ten years, there have been a number of hospital-based studies regarding the prevalence of depression in PWE in different regions of China. A study in Shanghai, China [33], showed a prevalence of 25.7%, using the Hamilton Depression Rating Scale-17(HAMD–17). Studies from Beijing [34] and Sichuan [23] utilizing the Mini International Neuropsychiatric Interview (MINI) showed a prevalence of 30.2% and 26.7%, respectively. Research from Hong Kong [35] showed a prevalence of 30.0% according to the Beck Depression Inventory–II (BDI–II). Although the screening instruments for depression varied among trials, the prevalence rates were not obviously different between eastern and western China.

Table 3
Risk factors of depression in PWE.

	OR	95%CI	P-Value
Sex (Female)	1.960	1.241-3.094	**0.004**
Marital status (Unmarried)	4.023	2.116-7.648	< **0.001**
Disease course	1.045	1.007-1.083	**0.019**
Age at onset	1.011	0.984-1.039	0.436
Seizure frequency	1.029	1.012-1.047	**0.001**
Seizure occurrence in the last 6 months	2.428	1.490-3.957	< **0.001**
Focal onset impaired awareness	1.602	1.003-2.559	**0.049**
Poly-therapy (≥2 AEDs)	1.299	0.814-2.071	0.272

Bold data show statistical significance < 0.05.

Table 4
Risk factors of suicide risk in PWE.

	OR	95%CI	P-value
Disease course	1.027	0.992-1.063	0.131
Seizure frequency	1.002	0.984-1.020	0.825
Depression	8.441	4.791-14.874	< **0.001**

Bold data show statistical significance < 0.05.

This study found that being female, an unmarried status, disease course, seizure frequency, seizure occurrence in the last 6 months and focal onset impaired awareness seizure were risk factors for depression in PWE. Nevertheless, the effect of gender on comorbid depression in PWE has been controversial. There were studies that suggested that men were less likely than women to seek help from professionals [36,37]. The percentage of male patients with epilepsy suffering from depression might be underestimated [36,37]. Therefore, further studies with a larger sample size are necessary to verify this. Seizure frequency has a positive association with depression in PWE [38]. We observed that patients who had clinical episodes within the last 6 months were more likely to have a depressive disorder. Effective seizure control is crucial to protect PWE from depression [39]. It is well acknowledged that depression is more frequent in people with temporal lobe epilepsy and complex partial seizures [40]. This study found that focal impaired awareness seizure, corresponding to the prior term "complex partial seizures" [29], was a risk factor for depression, and this is in agreement with the literature. It has also been observed in some studies that use of multiple AEDs was more significantly associated with depression. Of course, use of multiple AEDs may also produce more side effects, which also contributes to depression [41]. Surprisingly, in this study, no correlation between polytherapy and depression was found. Because of the initial research design, information about the number and type of antiepileptic drugs prescribed in both groups (depressed and

Table 5
TG(%) comparison in different groups.

	Untreatment group (n = 100)	Treatment group (n = 38)	TG (%)	P-Value
Age group (years)				**0.012**[a]
< 30[d]	48	22	68.6	
30–40[e]	40	6	87.0	
> 40[f]	12	10	54.5	
Sex				0.509[a]
Male	36	16	69.2	
Female	64	22	74.4	
Domicile				**0.032**[a]
Urban area	48	26	64.9	
Rural area	52	12	81.2	
Marital status				0.408[a]
Unmarried	68	23	74.7	
Married	32	15	68.1	
Education level				0.555[a]
Junior high school	44	15	74.6	
High school	38	13	74.5	
University and above	18	10	64.3	
Per capita annual family income (yuan)				< **0.001**[a]
< 10,000[g]	33	4	89.2	
10,000-50,000[h]	62	24	72.1	
> 50,000[i]	5	10	33.3	
Occupation				0.091[a]
Student	12	5	70.6	
Unemployed	64	16	80.0	
Employed	22	15	59.5	
Retired	2	2	50.0	
Number of seizure in the last 6 months				0.547[a]
Seizure free	26	8	76.5	
Seizure occurrence	74	30	71.2	
Disease course (years)				**0.001**[a]
≤5[j]	35	11	76.1	
> 5-≤10[k]	36	3	92.3	
> 10-≤15[l]	15	10	60.0	
> 15-≤20[m]	9	5	64.3	
> 20[n]	5	9	35.7	
Age at onset (years)	17.82 ± 9.47	19.19 ± 15.63	—	0.523[b]
Seizure frequency (per month)	0.46 (0.14, 2.00)	0.84 (0.25, 6.00)	—	0.086[b]
Seizure type				
Focal aware	11	3	78.6	0.823[a]
Focal impaired awareness	40	17	70.2	0.614[a]
Focal to bilateral tonic-clonic	31	18	63.3	0.073[a]
Generalized Onset	37	11	77.1	0.375[a]
Unknown Onset	1	0	100.0	1.000[c]
AED therapy regimen				
None	4	3	57.1	0.619[a]
Mono-therapy	46	17	73.0	0.894[a]
Poly-therapy (≥2 AEDs)	50	18	73.5	0.782[a]

Bold data show statistical significance < 0.05.
Comparison between subgroups of age: $P^{de} = 0.024$, $P^{ef} = 0.003$.
Comparison between subgroups of per-capita annual income of family: $P^{gh} = 0.038$, $P^{gi} < 0.001$, $P^{hi} = 0.003$.
Comparison between subgroups of disease course: $P^{jk} = 0.045$, $P^{jn} = 0.013$, $P^{kl} = 0.002$, $P^{km} = 0.038$, $P^{kn} < 0.001$.
Only those with P < 0.05 were listed.
[a] Chi-square test.
[b] Mann–Whitney U test.
[c] Fisher's exact test.

nondepressed) was not collected; therefore, the effect of the drugs on mood in both groups was not very clear-cut. In addition, the current study failed to demonstrate that age, domicile, education level, occupation, per capita annual income of the family and age at onset were associated with depression. Ethnic or cultural differences, different populations investigated and different instruments used for assessing depression might affect the results.

Suicide is considered to be an important contributor to the increased mortality of PWE [42]. The rate of suicide risk for PWE has been reported to be 12%, up to ten times higher than in the general population [13,42], and even higher in PWE with comorbid depression [39,43]. Although suicide accounted for 3.6% of all deaths in China [44] and was among the top 15 causes of death [45], there is limited epidemiological data on suicide risk among Chinese epilepsy patients. In this study we evaluated the prevalence of suicidal ideation in a tertiary epilepsy clinic in West China. It showed that the rate of suicide risk was 15.8% for PWE in West China but higher (37.7%) for PWE with depression, and 71.2% of the patients with suicide risk had depression. Surprisingly, we observed that 28.8% of the patients with suicide risk did not have depression. One advice given is that PWE, both with and without comorbid 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 [46]. While high suicide risk for PWE has been reported in many studies, a significant proportion of patients have not been appropriately diagnosed or treated by clinicians. A UK study found that 30% of PWE with suicide attempts did not undergo psychiatric treatment [47]. A Korean study found that 65.4% of PWE with suicidality had never received psychiatric treatment [48]. The present study found that 69.9% of PWE with suicidality did not receive any psychiatric intervention. This means that suicidality is much more likely to be underrecognized in Asian PWE, such as in China and Korea, than among PWE in some Western countries.

In many studies, the major predictor of suicide risk for PWE was found to be depression rather than seizure-related variables and other demographic variables [14,42,49]. This is the first study to our knowledge to determine predictive factors for suicide risk in epilepsy patients in West China. We found that depression was an independent risk factor for suicide risk in PWE. Although seizure frequency, disease course and depression were each associated with suicide risk in an univariate analysis, only depression remained significant in the logistic regression analysis. This is in line with previous studies [42,49]. Sex and age appear to be important factors in predicting suicide. According to the previous studies, the rate of suicide in China was 25% higher among women than among men [44] and was highest in the elderly [50]. However, we could not confirm these findings in our PWE cohort; moreover, these factors were not found to be predictors of suicidality. In addition, some basic studies also suggested that there exist common pathogenic mechanisms between epilepsy, depression and suicide [51,52].

The diagnosis and treatment of comorbid depression in PWE is often neglected. A study in the USA showed that 29.3% of PWE were associated with depressive disorders, but up to 52% did not receive any antidepressant treatment [53]. Our study showed that the TG (72.5%) was larger in West China. Reasons for such a huge TG may be multiple, including the patients' fear of a psychiatric diagnosis because of potential additional discrimination [15], a paucity of professionals trained to recognize the psychological disorders of PWE, a lack of sufficient time to screen for them in busy epileptic clinics, and a misconception that the depressive disorder was a result of adverse effects of AEDs [54]. What is worse, some physicians are worried that antidepressants may trigger seizures and this may lead them to resist prescribing these drugs even when a patient with epilepsy has been diagnosed with depression [55]. However, the appropriate doses of selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenalin reuptake inhibitors (SNRIs) can effectively improve depressive symptoms in PWE, and their safety has been confirmed [27,55]. Therefore, the management of comorbid depression including public education as well as professional training of neurologists are necessary to fill that gap.

The ILAE concluded that the determinants of TG are diagnostic and therapeutic deficits, economic conditions, cultural beliefs, and distance

from health facilities [28]. In our research, the differences in the TG in different demographics and epileptic clinical characteristics were compared. The results suggested that the TG in rural populations was larger than in urban populations. One possible reason for this is the lack of public education, inadequate understanding of epilepsy comorbidity and weak awareness of medical treatment in rural areas. In addition, relatively poor medical facilities, distance from large comprehensive medical institutions and lack of antidepressant supplies add to the inconvenience of seeking medical treatment for PWE in rural areas. Moreover, the coverage rate and reimbursement rate of medical insurance in rural areas are relatively low, which increases medical costs, so patients are reluctant to seek medical treatment. The TG figures dropped with increasing per capita annual family income. In poor families, inability to afford extra medical costs for a comorbidity leads to a larger TG. Patients in the 30–40 year age group had the largest TG of comorbid depression. On the one hand, this may be because these patients do not pay enough attention to their physical and psychological health due to enormous pressures from life, work and their financial conditions. On the other hand, we have found that the TG for low-income families was wider. In our sample, the proportion of low-income people (per capita annual family income < 10,000) in the 30–40 age group was 32.6%, which was higher than that in other age groups (24.3% in those under the age of 30 years and 22.7% in those older than 40 years of age). This may also be the reason for the increased TG in the 30–40 age group. Because of the small sample size, further studies are necessary to verify this. We observed that patients with a disease course between 5 and 10 years showed the largest TG with a significant difference compared to others. Ten years appeared to be a watershed period that was lower than the period where TG remained low and vice versa. Patients with a disease course longer than 20 years showed a smaller TG. The reasons for these findings are unclear. Possible explanations may reside in the small sample size as only 14 patients with a disease course longer than 20 years were recruited.

There were several limitations to this study. First, it is a cross-sectional study. We therefore cannot comment on the prevalence rates of lifetime depression in PWE. Second, we did not consider cognitive impairment as a risk factor for depression. It has been reported that cognitive impairment is strongly associated with depressive symptoms among patients with epilepsy [56]. In the present study, patients with cognitive deficits were excluded, and so the prevalence of depression might be underestimated in PWE. However, in spite of this limitation, only four of the participants were excluded because of cognitive deficits, which should have little impact on the overall results. Third, all of the participants were recruited from a single center, the epilepsy outpatient clinic of West China Hospital, and thus there may be a selection bias. Therefore, our findings may not be relevant for all patient groups.

In conclusion, depression is a common comorbidity of epilepsy. Clinicians should pay more attention to comorbid depression of PWE, identify the related risk factors in a timely manner and provide effective interventions in order to reduce the incidence of depression and suicide as well as improve the quality of life of the patients. Meanwhile, education for PWE and the public and professional training of neurologists are needed to reduce the TG of comorbid depression in PWE.

Disclosures of conflicts of interest

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

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