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Clinical Research

Multidisciplinary management improves anxiety, depression, medication adherence, and quality of life among patients with epilepsy in eastern China: A prospective study

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ABSTRACT

Objective: The objective of this study was to investigate the effect of a multidisciplinary program on anxiety, depression, medication adherence, and quality of life in patients with epilepsy in eastern China.
Methods: A cohort of 184 patients with epilepsy from the epilepsy clinic of a tertiary hospital in eastern China completed this program, out of which 92 were randomized into the intervention group and 92 the control group. Patients in both groups received standard antiepileptic drugs (AEDs), while those of the intervention group received an additional 12-month multidisciplinary program developed by a group of the epileptologist, pharmacist, psychiatrist, and epilepsy specialist nurse. Patients were assessed both before and after the 12-month period. The Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the eight-item Morisky Medication Adherence Scale (MMAS-8) were used to assess the severity of depression, anxiety, and medication adherence, respectively, along with Quality of life in Epilepsy-31 (QOLIE-31) and self-reported seizure frequency for life quality and seizure severity.
Results: The 12-month multidisciplinary program significantly reduced the number of patients with severe depression ($p = 0.013$) and anxiety ($p = 0.002$), increased the number of patients with moderate-to-high AED adherence ($p = 0.006$) and the overall QOLIE-31 score ($p < 0.001$) in the intervention group. Both groups demonstrated a significant increase in the number of patients with a low seizure frequency after the 12-month period ($p < 0.001$).
Conclusion: The 12-month multidisciplinary program offers an effective management strategy in improving psychiatric comorbidities, medication adherence, and quality of life in patients with epilepsy in eastern China.

1. Introduction

Psychiatric comorbidities are a major concern among patients with epilepsy (PWE), with anxiety and depression most frequently reported [1,2]. In developing countries, the burden of concomitant mood disorders in PWE is even higher. Patients with epilepsy are nearly twice as common to suffer from such psychiatric issues [3]. A study in our center found that nearly 20% of PWE had a moderate-to-severe anxiety or depression [4]. Such psychiatric comorbidities, apart from reducing the quality of life (QOL), even pose a great threat on seizure control [5,6]. Medication adherence is another crucial contributing factor to an optimal seizure control in PWE. Nonadherence to antiepileptic drugs (AEDs) is reported to increase the cost of treatment [7] and increase the mortality risk threefold [8]. However, nonadherence remains a hard-to-tackle problem with its strikingly high prevalence among PWE. More than half of PWE in our epilepsy center had a low-to-moderate medication adherence [4], and from 26% to 79% PWE all over the world suffered from the same issue [9,10]. Making things more complicated, depression and anxiety are associated with reduced AED adherence in PWE in eastern China [4].

Despite the high prevalence and increasingly recognized damage of psychiatric comorbidities and medication nonadherence, a comprehensive strategy for both issues is lacking. Current treatment for depression and anxiety among PWE remains largely limited to psychotropic drugs, which have their own adverse effects and add to the economic burden of PWE as well [11]. Psychological treatments, recently, are emerging as a potential alternative [12]. They encompass a wide range of interventions including psychiatric interventions (cognitive–behavioral therapy, behavioral therapy, motivational interviewing, etc.), self-/

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family-management interventions, adherence interventions, and educational interventions [12,13]. Previous studies implementing education and behavioral interventions among Chinese PWE have seen some beneficial effects in terms of seizure control and AED adherence [14–16]. However, these studies did not assess the psychiatric comorbidities in this group of PWE, and the intervention was only done by the pharmacists or neurologists. Therefore, we developed a 12-month multidisciplinary management program for PWE in a tertiary referral hospital in eastern China, aiming to provide a multidisciplinary team (including the epileptologist, pharmacist, psychiatrist, and epilepsy specialist nurse) to improve their psychological well-being, AED adherence, and QOL.

2. Methods

2.1. Participants and study design

The study was conducted in the Second Affiliated Hospital of Zhejiang University, a tertiary referral hospital in Zhejiang, China. We investigated a cohort of PWE attending the outpatient clinic from June 2014 to January 2016 to assess the role of a multidisciplinary management program on psychological comorbidities, AED adherence, QOL, and seizure control.

Participants enrolled in this study should meet the following criteria: (1) age of ≥18 years, (2) diagnosis of epilepsy according to the 2001 International League Against Epilepsy (ILAE) diagnostic scheme [17,18], (3) AED treatment for at least 3 months, (4) the ability to read and write, and (5) absence of major cognitive impairment. Patients who had intellectual disability or refused to participate were excluded. Enrolled participants were randomly assigned using concealed random allocation to either the intervention group or control group. Randomization was done using a computer-generated table of random numbers (www.randomization.com). A total of 206 PWE met the inclusion criteria, within which 12 refused to join. The remaining 194 PWE were enrolled in our study, out of which 97 were randomized to the intervention group and the other 97 to the control group. Ninety-two of each group completed the program and the final evaluation (Fig. 1). During the 12-month period, the control group received regular AED treatment and routine education. The intervention group, apart from the regular AED treatment, received our multidisciplinary management. Details of the patients' demographic profile, characteristics of seizures, and current treatment regimen were collected at baseline. Psychiatric comorbidities, AED adherence, seizure frequency, and QOL were assessed at baseline and at the last visit. For follow-ups in-between, patients were evaluated at 4 weeks after randomization, and at 3-month intervals thereafter, psychiatric comorbidities and AED adherence were assessed. If patients' condition changes, a visit would be arranged in advance. Assessors were blinded to the group of participants.

The Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University reviewed and approved this study (registration no.: 2013-032). All participants provided written informed consent to participate in this study.

2.2. The multidisciplinary management program

The 12-month multidisciplinary management program was mainly based on an outpatient setting with the cooperation of the research team members, including the epileptologist, pharmacist, psychiatrist, and epilepsy specialist nurse. The contents of our program included epilepsy-related knowledge (the disease itself, its comorbidities, treatments, medication use, pregnancy-related issues), daily self-management skills, and relevant psychosocial information. Specifically, the 12-month multidisciplinary management program included the following items: (1) Face-to-face interviews: When patients visited the epilepsy clinic, they would be arranged to meet with an epileptologist, questions regarding epilepsy knowledge and self-management skills would be answered. The Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI), and the eight-item Morisky Medication Adherence Scale (MMAS-8) were used to evaluate depression, anxiety, and AED adherence, respectively. When the score of BDI ≥ 16 or the score of BAI ≥ 37, patients would be referred to the psychiatrist, the psychiatric interventions would be given if necessary; when the score of MMAS-8 < 6, patients would be referred to the pharmacist, instructed about the medications, and asked to adhere to AEDs, moreover, the epilepsy tracking card for reminder would be provided. (2) Online consultations: We established a group on Wechat, a widely used web-based social media platform in China. The epilepsy specialist nurse would answer patients' questions daily through online messages, monthly release

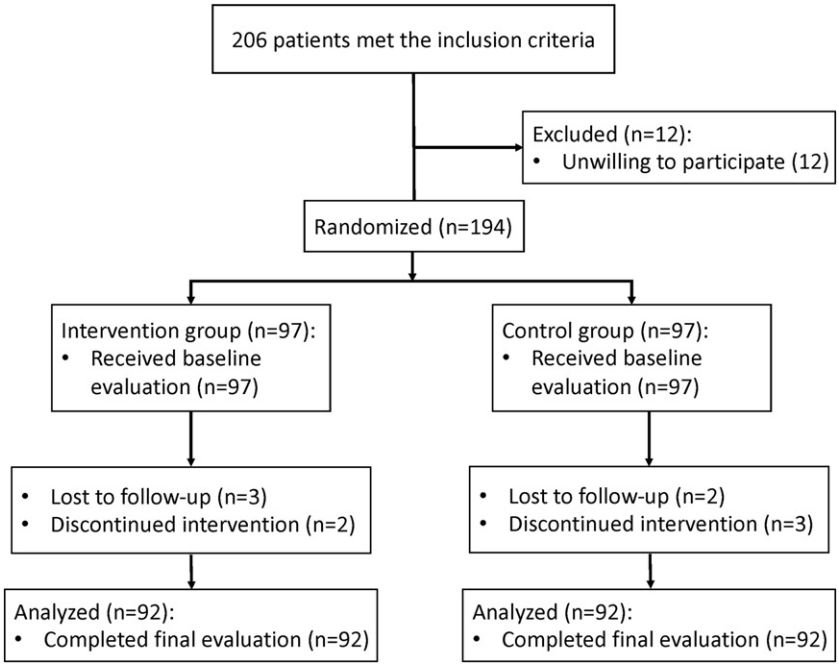

Fig. 1. Flowchart of participants in the study.

the educational information, and remind patients to visit in time. (3) Group education: In the form of group discussion, patients would receive education by the multidisciplinary team twice a year.

2.3. Outcomes

Primary outcomes included proportion of patients with moderate-to-severe depression, moderate-to-severe anxiety, and proportion of patients with low AED adherence. We used the BDI to evaluate depression, BAI for anxiety, and MMAS-8 for AED adherence.

- Beck Depression Inventory is a commonly used self-administered measure of depressive symptoms, consisting of 21 items reflecting subjective and vegetative symptoms of depression [19]. Each item is rated on a 4-point scale ranging from 0 to 3. Total scores range from 0 to 63. A cutoff score is used to classify individuals who have no-to-mild depressive symptoms or moderate-to-severe symptoms. The cutoff score for PWE is higher than that for populations without epilepsy. The cutoff score in our study was 16, as suggested by Devinsky et al. [20].
- Beck Anxiety Inventory is a commonly used self-administered measure of anxious symptoms, consisting of 21 symptoms associated with anxiety [21]. Participants were asked to rate how much each symptom had bothered them over the last week on a 4-point scale ranging from 21 to 84. A cutoff score is used to classify patients who have no-to-mild anxiety (scores < 37) or moderate-to-severe anxiety (scores ≥ 37) [20].
- The validated Chinese version of MMAS-8 is a widely used tool to measure the AED adherence in China [4,22]. To be brief, MMAS-8 is a multi-item questionnaire that includes 8 items. Detailed explanation of MMAS-8 has already been described in the previous validation study [22]. The total score ranges from 0 to 8. Scores of 8, 6–7, and <6 indicate high, moderate, and low adherence, respectively.

Secondary outcomes included QOL and self-reported seizure frequency.

- Seizure frequency was defined as the average number of seizures per month during the preceding six months before the time of assessment. A seizure frequency of less than 1 episode per month was defined low, while that of more than 1 episode per month was deemed high.
- Quality of life was assessed with the Quality of life in Epilepsy-31 (QOLIE-31) [23]. Weighted average values for the seven subscales of the QOLIE-31 were converted to an overall score ranging from 0 to 100, with higher scores reflecting better QOL.

2.4. Statistical analyses

Data were double entered. Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) version 17.0. The normality of distribution of continuous variables was tested by one sample Kolmogorov–Smirnov test. Continuous variables with normal distribution were represented as mean and standard deviation (SD); nonnormal variables were reported as median (interquartile range [IQR]). Categorical variables were described in the form of frequency and percentage. Mean of the continuous variables was compared by independent samples Student's *t*-test. Mann–Whitney *U* test was used to compare means of two groups of variables not normally distributed. The frequencies of categorical variables were compared using Pearson χ^2. A value of $p < 0.05$ was considered significant. All the tests were two-tailed.

3. Results

In total, 194 patients met the study criteria, and 184 completed the program, with a dropout rate of 5.15% in both the intervention and control groups (Fig. 1). The descriptive data for the demographic, characteristics of seizures, and treatment variables are summarized in Table 1. Baseline data regarding the demographic features, treatment regimens, seizure frequency, depression, anxiety, AED adherence, and QOL were no significant difference between the two groups.

We first compared the primary outcomes before and after the 12-month program in each group, respectively (Table 2). There was a significant reduction of number of patients with severe depression (10 [10.9%] vs. 20 [21.7%]; $p = 0.013$) and anxiety (12 [13.0%] vs. 25 [27.2%]; $p = 0.002$), and a significant increase of number of patients with moderate-to-high AED adherence (71 [77.2%] vs. 56 [60.9%]; $p = 0.006$) in the intervention group after 12 months. The control group, by contrast, showed no significant difference in terms of proportion of patients with depression, anxiety, and moderate-to-high medication adherence after 12 months.

Next, we compared the QOL and proportion of patients with a low seizure frequency at baseline and endpoint in each group (Table 3). There was a global improvement in QOL in the intervention group after 12 months' intervention. Significant improvements were observed in five of the seven subscales in QOLIE-31, i.e., overall QOL (74.1 ± 15.0 vs. 63.2 ± 14.6; $p = 0.010$), emotional well-being (81.3 ± 16.2 vs. 69.0 ± 15.5; $p = 0.006$), energy (74.8 ± 18.2 vs. 63.4 ± 17.0; $p = 0.013$), cognitive function (77.7 ± 20.4 vs. 66.5 ± 19.3; $p = 0.011$), and social function (72.0 ± 22.7 vs. 61.8 ± 21.6; $p = 0.015$). By contrast, the control group showed statistically significant improvements in only three aspects including seizure worry (51.0 ± 32.7 vs. 46.1 ± 30.0; $p = 0.038$), emotional well-being (68.7 ± 22.1 vs. 67.8 ± 21.1; $p = 0.007$), and medication effect (52.1 ± 36.3 vs. 47.8 ± 34.4; $p = 0.015$). Proportion of patients with a low seizure frequency increased significantly in both the intervention group (70 [76.1%] vs. 41 [44.6%]; $p < 0.001$) and the control group (74 [80.4%] vs. 50 [54.3%]; $p < 0.001$) after 12 months. When comparing this proportion at the end of the 12-month intervention between the two groups, no significant difference was observed (80.5% vs. 76.1%; $p = 0.475$).

Table 1
Clinical and demographic features at baseline.

	Control group (n = 92)	Intervention group (n = 92)	*p* value
Age (years), median (IQR)	26 (22.3, 33.0)	28(23.3, 38.8)	0.070
M:F, n (%)	48 (52.2): 44 (47.8)	52 (56.5): 40 (43.5)	0.554
Married, n (%)	45 (48.9)	52 (56.2)	0.301
Educational level, n (%)			
High school or less	55 (59.8)	58 (63.0)	0.650
College graduate	37 (40.2)	34 (37.0)	
Occupation, n (%)			
Student	10 (10.9)	12 (13.0)	0.570
Employed	60 (65.2)	53 (57.6)	
Unemployed	22 (23.9)	27 (29.3)	
Living area			
Rural, n (%)	36 (39.1)	43 (46.7)	0.297
Urban, n (%)	56 (60.9)	49 (53.3)	
Age at onset (years), mean ± SD	20.1 ± 9.2	23.0 ± 12.9	0.087
Disease duration (months), median (IQR)	78 (36, 156)	84 (36, 168)	0.806
Seizure type, n (%)			
Generalized seizures	11 (12.0)	14 (15.2)	0.265
Focal seizures	73 (79.3)	75 (81.5)	
Unclassified seizures	8 (8.7)	3 (3.3)	
Seizure frequency, n (%)			
Low	50 (54.3)	41 (44.6)	0.184
High	42 (45.7)	51 (55.4)	
No. of current epileptic drugs, n (%)			
Monotherapy	43 (46.7)	33 (35.9)	0.134
Polytherapy	49 (53.3)	59 (64.1)	
Treatment regimen, n (%)			
≤Twice daily	78 (84.8)	83 (90.2)	0.265
≥Three times daily	14 (15.2)	9 (9.8)	

Table 2
Comparison of primary outcome variables (proportion of patients with severe depression, severe anxiety, and moderate-to-high antiepileptic drug [AED] medication adherence) between baseline and follow-up.

Primary outcomes	Control group (n = 92)		*p* value	Intervention group (n = 92)		*p* value
	Baseline	Follow-up		Baseline	Follow-up	
Depression, n (%)	16 (17.4)	12 (13.0)	0.289	20 (21.7)	10 (10.9)	**0.013**
Anxiety, n (%)	22 (23.9)	19 (20.7)	0.508	25 (27.2)	12 (13.0)	**0.002**
Moderate-to-high AED adherence, n (%)	55 (59.8)	63 (68.5)	0.096	56 (60.9)	71 (77.2)	**0.006**

A *p*-value of less than 0.05 was considered significant and was marked in bold.

4. Discussion

This study demonstrated an effective intervention for PWE in eastern China. The 12-month multidisciplinary management program substantially improved the anxiety, depression, AED adherence as well as QOL among PWE. Our study showed solid evidence to implement multidisciplinary intervention to PWE in eastern China.

Our program focused on an attempt to improve psychological well-being and medication adherence among a general population of PWE. Psychiatric comorbidities are prevalent among PWE, exerting a great impact on various aspects of patients' life. First of all, we found that the 12-month intervention alleviated both depressive and anxiety symptoms. Previous trials have consistently proved a positive impact of psychological interventions on depression [24,25]. Notably, most of the trials targeted only at PWE with a severe depression. In the busy outpatient clinic in China, however, such mental disorders remain underrecognized by clinicians. Because of the limited time for each patient, neurologists are not able to assess the mental status of each PWE and often fail to identify those with insidious depression or anxiety. Therefore, rapid screening psychiatric comorbidities and referral to psychiatry could be both applicable and beneficial for the general PWE in China. Anxiety, another disabling mental disorder for PWE, is yet less investigated [12]. Among all the psychological interventions, only one study, featuring on the efficacy of epilepsy nurses, has investigated the role of educational interventions in anxiety [26]. Our study is the first to prove the efficacy of the multidisciplinary intervention in anxiety among PWE. Though the exact component that reduces anxiety in our trial cannot be determined, we attribute the improvement to a better understanding of the disease and stigma reduction, both of which are major risk factors of anxiety [27,28].

In addition to the psychological well-being, our program increased AED adherence of PWE. Medication adherence is crucial for an optimal seizure control, a lower mortality risk, and economic burden among PWE [10]. Consistent with previous studies, we found education a powerful tool in improving AED adherence [14–16,29]. In 2003, Liu et al. suggested the potential role of educational intervention in Chinese population [16]. Later, Tang et al. further compared educational and behavioral interventions and also advocated the use of educational intervention, including oral and written educative materials as well as regular follow-up [14]. The educational intervention in those studies was only done by pharmacist. In addition, Juan et al. studied the combination of education, consultation services, and reminders in improving phenobarbital adherence in PWE from rural communities in western China and proved its effectiveness [15]. However, these three studies did not assess the psychiatric comorbidities in PWE. Since depression and anxiety are associated with reduced AED adherence in PWE of eastern China, our program including psychological intervention may be more effective for improving AED adherence.

Notably, apart from depression, anxiety, and AED adherence, we found a substantial improvement in QOL. Quality of life is correlated with multiple factors including psychological well-being, seizure control, and socioeconomic status [13,30]. Psychological intervention, with its wide effects, is thereby a potential strategy to improve life quality. A recent meta-analysis on psychological treatments in PWE revealed their efficacy in bettering QOL with different degrees, varying among interventions [13]. Cognitive behavioral therapy was reported to improve QOL to the greatest extent, with psychoeducation the least [13]. Our program, however, led to a global improvement of QOL. Specifically, emotional well-being, energy/fatigue, and overall QOL, the three subscales considered most clinically important in life quality, have profoundly improved after our educational intervention [13,31]. It has been shown that improved knowledge on epilepsy and increased socialization are important determinants of QOL [32–34]. By the same token, we speculate that the two elements contributing greatly to the substantial improvement in our program were the focus on stigma removal and the establishment of an online support group. In addition, the employment of a multidisciplinary delivery further ensures the effective convey of knowledge through our intervention.

Our study failed to reveal a substantial effect on seizure frequency. For both the intervention group and the control group, we found a significant reduction of seizure frequency to a similar extent after 12 months. It may be intriguing that even PWE in the control group had a prominent reduction of seizure frequency after 12 months. We speculate that the improvement in both groups may be due to the relatively poor seizure control at baseline in PWE in our study. Furthermore, our negative results in terms of seizure control were consistent with previous studies with educational interventions [35].

Table 3
Comparison of secondary outcome variables (QOLIE-31 score and proportion of patients with a low seizure frequency) between baseline and follow-up.

Secondary outcomes	Control group (n = 92)		*p* value	Intervention group (n = 92)		*p* value
	Baseline	Follow-up		Baseline	Follow-up	
QOLIE-31 score, mean ± SD						
Worry	46.1 ± 30.0	51.0 ± 32.7	**0.038**	45.4 ± 27.7	53.2 ± 31.1	0.064
Quality of life	64.2 ± 17.4	71.3 ± 18.5	0.465	66.3 ± 16.1	77.9 ± 16.5	**0.008**
Emotion	67.8 ± 21.1	68.7 ± 22.1	**0.007**	69.0 ± 15.5	81.3 ± 16.2	**0.006**
Energy	62.7 ± 20.8	65.8 ± 22.7	0.589	63.4 ± 17.0	74.8 ± 18.2	**0.013**
Cognitive	63.3 ± 22.1	70.0 ± 23.5	0.186	66.5 ± 19.3	77.7 ± 20.4	**0.011**
Medication	47.8 ± 34.4	52.1 ± 36.3	**0.015**	46.9 ± 31.1	54.1 ± 34.0	0.075
Social	61.8 ± 22.6	62.4 ± 24.1	0.089	61.8 ± 21.6	72.0 ± 22.7	**0.015**
Overall score	61.7 ± 17.0	65.8 ± 18.1	0.693	63.2 ± 14.6	74.1 ± 15.0	**0.010**
Low seizure frequency, n (%)	50 (54.3)	74 (80.4)	<**0.001**	41 (44.6)	70 (76.1)	<**0.001**

A *p*-value of less than 0.05 was considered significant and was marked in bold.

Some limitations of our study need to be addressed. Firstly, our study was conducted in a single center in eastern China. It remains to be validated whether our multidisciplinary management program is applicable in other areas of China with different demographic features. Secondly, assessment of psychological well-beings, medication adherence, and seizure frequency were based on self-report measures, which were subject to the recall bias and would thereby impact the accuracy of our results. Thirdly, given the limited information obtained from the outpatient clinic, we did not investigate whether the epilepsy subtypes affect the effectiveness of our program.

In conclusion, our study demonstrated an effective intervention to comprehensively improve the psychological well-being and AED adherence as well as QOL in the general PWE in eastern China. Prospective studies in other areas, with different sample populations and a longer follow-up, are expected to further validate the efficacy and utility of the multidisciplinary management program.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

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