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Research Paper

Effect of perampanel in reducing depression in patients with focal epilepsy

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A B S T R A C T S

Background: High prevalence of depression is very common in epilepsy. This study aimed to discover the effect of perampanel on depression in patients with focal epilepsy.
Methods: This is a prospective observational study. We included a total of 68 patients with focal EP, which were treated with perampanel. We analyzed data before perampanel treatment and at 6 and 12 months of follow-up of the optimal dose. Using the Beck Depression Inventory-II (BDI-II) scale to evaluate depression, the Mini-Mental State Examination (MMSE) to assess the cognitive function, and the Quality of Life in Epilepsy-31 items (QOLIE-31) to estimate the quality of life of EP patients.
Results: The BDI-II score improved significantly compared to before treatment and at 6 and 12 months of follow-up ($P < 0.001$). The mean total QOLIE-31 score significantly increased from 82.9 ± 20.4 to 88.7 ± 21.2 at the 12-month follow-up ($P < 0.001$). In addition, seizure control was improved significantly at 12 months: 32.1 % of patients were seizure-free, and 73.2 % were responsive. Moreover, there was statistical relationship between improvement in depression and seizure control. The MMSE score was not different before and after treatment ($P > 0.05$). Multiple Regression Analysis was found that annual family income, etiology, the frequency of attacks in recent years, types of ASMs and the age were the influence factors of pirampanel in reducing depression ($P < 0.05$).
Conclusion: Perampanel reduced depression symptoms in patients with focal epilepsy, although the lack of a control group or the relatively small sample size.

Keywords

Epilepsy, Perampanel, Quality of life, Antiepileptic drugs, Depression

Introduction

The occurrence of depression is common in patients with epilepsy (EP), up to 20–55 % (Singh and Goel, 2021; Robertson et al., 1987). Patients with EP are twice as likely to suffer from depression as the general population, and the impact of suicide is 3.6–5 times higher than in the general population (Paredes-Aragón et al., 2023). And then, depression is not only severely deteriorated by suicide, but also damages health in patients with EP (Qin et al., 2022; Rafnsson et al., 2001).

It is well known that the action of anti-seizure medications (ASMs) is essential for the treatment of epilepsy. Various researchers have discovered that certain ASMs can worsen depressive symptoms (Maguire et al., 2021), while others may have antidepressant effects (Tallarico et al., 2023). The reason may be that ASMs have complex mechanisms of effects, with additional effects on mood and behavior. Rodent studies have shown that the antidepressant effects of monoamine antidepressants include increased neurotransmission of α-amino-3--hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptor, and positive allosteric modulators of the AMPA receptor can produce antidepressant effects (Barbon et al., 2011; Tanaka and Vécsei, 2024; Battaglia et al., 2024). In a rat model of absence epilepsy with mild depressive comorbidity, it was found that relief of absence epilepsy treated by perampanel was accompanied by a reduction in depression-like behavior (Citraro et al., 2017). Therefore, AMPA receptors have the potential to be new targets for drugs to treat depression and anxiety.

Perampanel, a noncompetitive antagonist of AMPA receptor, has been verified to significantly improve seizure control in epilepsy patients (Potschka and Trinka, 2019). However, whether perampanel affects depression remains unproven. The objective of this study was to evaluate the effect of perampanel on depression symptoms in EP patients before and after treatment by using the Beck Depression Inventory-II (BDI-II).

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Material and methods

This was a prospective, observational study of patients with focal epilepsy. The research object is the focal epilepsy patients, who turned the perampanel adjuvant therapy. The starting dose of perampanel is 2 mg/day, and the daily dose is increased by 1–2 mg every 1–2 weeks or longer intervals until up to the maintenance dosage. The maximum maintenance dosage should not exceed 8 mg/d. The goal was to identify changes in symptoms of depression. The study follows the principles of the Declaration of Helsinki of 1975 as revised in 2013 and guidelines for good Clinical Practice, and was approved by the Institutional Review Board (IRB) of the first affiliated Hospital of Gannan Medical University, Ganzhou city, Jiangxi province, in China on May 07, 2023 (No. GYYFY 2023-S06). The period of this experiment is from July 1, 2023 to June 30, 2024. All participants provided written informed consent before enrolling in the research. We have de-identified all patients details.

The inclusion criteria were as follows: (i) a diagnosis of focal epilepsy patients over 12 years of age, (ii) of patients with additional treatment indications, and (iii) agreed to participate in the research and signed informed consent of patients or their guardians.

The exclusion criteria were as follows: (i) a diagnosis of patients with major depression or bipolar disorder, (ii) patients at risk of suicide, (iii) use of psychotropic drugs or psychotherapy patients at the same time, (iiii) accept the vagus nerve stimulation or epilepsy surgery patients, (iiiii) cardiac conduction or patients with neurodegenerative diseases, (iiiiii) patients taking antidepressants, antipsychotics, antianxiety drugs, antihistamines, opioids, itraconazole, or rifampicin, and (iiiiiii) patients receiving any study drug in the 3 months before the screening visit.

PASS15.0 software was used to estimate the sample size of single-factor repeated measurement ANOVA. The test efficiency was set to 0.9 and the test level to 0.05. According to the average score of 13.8, standard deviation of 8.1, and correlation coefficient of 0.42 obtained from the BD-II pre-experiment, the maximum sample size was 54. Taking into account the 20 % reduction, the final sample size was determined to be 68.

Seizure control

Seizure control was measured by the number of self-reported seizures by patients. "Seizure freedom rates" was defined as absence of self-reported seizures and the duration was longer than 3 months, "responder rates" was defined as the frequency of seizures is reduced by ≥ 50 % after perampanel compared with the average number of seizures per month in the 3 months before perampanel, and "ineffective" was defined as the frequency of seizures is reduced by less than 50 % after treatment. Retention rate was defined was proportion of patients still taking perampanel at follow-up.

Beck depression inventory-II (Beck et al., 1996)

The Beck Depression Inventory II (BDI-II), a commonly used depression screening tool, consists of 21 items, each scored from 0 to 3 for a 0–63 scale. Divided into mild depression score of 0 ~ 13, 14 ~ 19 were divided into mild depression, 20–28 divided into moderate depression, 29 ~ 63 divided into severe depression.

Quality of Life in Epilepsy-31 items (Cramer et al., 1998)

The Quality of Life in Epilepsy-31 items (QOLIE-31), developed by Cramer et al., is a quality of life scale for people with epilepsy that contains 31 questions. It was divided into seven aspects: seizure anxiety (SE), overall quality of life (QOL), emotional well-being (EW), energy/fatigue (E/F), cognitive function (CF), medication effect (ME) and social function (SF). Each subterm is scored in percentage, multiplied by their respective weights, and then added together to get the total score. By checking the table to get a T score, the higher the T score, the better the quality of life.

Mini-Mental State Examination (MMSE) (Folstein et al., 1975)

The MMSE scale is a comprehensive, accurate and rapid scale to reflect the mental state and the degree of cognitive impairment of the subject, and includes the following seven aspects: time orientation, place orientation, immediate memory, attention and computation, delayed memory, language, and visual space. There are a total of 30 items in the scale, with 1 point for a correct answer and 0 points for a wrong or unknown answer. The total score of the scale ranges from 0 to 30 points. Test scores are strongly correlated with educational attainment, with normal cutoff points being > 17 for illiteracy, > 20 for primary school, and > 24 for junior high school and above. According to the score, the cognitive impairment was classified as mild (> 20 points), moderate (10–20 points), and severe (< 10 points).

Statistical analysis

SPSS 22.0 software was used to analyze all the data. Basic demographic data are reported as mean ± standard deviation (SD). The categorical variables are shown as frequency and percentage. Repeated measure Analysis of variance (ANOVA) was used to compare the differences before and after perampanel treatment. Pearson correlation analysis was used to determine the relationship between depression and seizure control. A p value < 0.05 was considered statistically significant.

Results

A total of 68 patients (35 females, accounting for 51.5 %) were enrolled with an average age of 40.2 years (ranged 14–86 years) and an average duration of epilepsy of 6.4 years. 52.9 % ($n = 36$) of epilepsies were structural. The median number of attacks was 2.5 ± 0.4 per month. The most common site was the temporal lobe (38/68, 55.9 %), followed by the frontal lobe (21/68, 30.9 %). At the start of perampanel treatment, 61.8 % of patients were treated with an ASM. In 27.9 % of patients, 2 or more ASMs were used before starting perampanel. The median previous use of ASMs was 2 drugs (ranged 1–5). Levetiracetam (LEV) was used in 58.8 % of patients (Table 1).

After 6 and 12 months of treatment with perampanel, the freedom rate was 26.5 % and 29.4 %, and the responder rate was 66.2 % and 70.6 %, respectively. Drug retention rate was 92.6 %, 82.4 %, 77.9 %.

At baseline, 26 patients (38.2 %) had depression on the BDI-II scale, of which 8 (11.8 %) had mild depression, 13 (19.1 %) had moderate depression, and 5 (7.4 %) had major depression. In the MMSE scale, 49 cases (72.1 %) had normal cognition, 12 cases (17.6 %) had mild cognitive impairment, and 7 cases (10.3 %) had moderate cognitive impairment. In the QOLIE-31 scale, only 30 patients (44.1 %) had normal quality of life, 19 patients (27.9 %) had mild quality of life decline, 14 patients (20.6 %) had moderate quality of life decline, and 5 patients (7.4 %) had severe quality of life decline.

Of the 68 patients initially enrolled, 2 patients dropped out of the study before 3 months due to adverse events. At 6 months, 2 patients withdrew from treatment due to insufficient efficacy, and 1 patient was lost to follow-up. At 12 months, 4 patients dropped out of the study due to lack of follow-up and 3 patients dropped out due to adverse events. Thus, 56 patients completed 12 months of perampanel treatment (Fig. 1).

Variable variation of depression in an effective population

The mean BDI-II score was 13.3 ± 8.9 at baseline, and 10.4 ± 8.5 at 6 months, 7.8 ± 4.9 at 12 months. The BDI-II score decreased significantly at 6 months ($P = 0.003$), and 12 months ($P < 0.001$) (Fig. 2). In the moderate depression group ($n = 12$), patients improved significantly ($P = 0.003$ at 6 months; $P < 0.001$ at 12 months). Although the

Table 1
Baseline characteristics.

	n (%)
Demographics	
Age, years (mean±SD)	40.2 ± 11.8
Female	35 (51.5)
At seizure onset, years (mean ± SD)	24.4 ± 9.1
Duration of epilepsy, years (mean ± SD)	6.4 ± 2.5
Etiology	
Structural	36 (52.9)
Genetic	6 (8.8)
Infectious	2 (2.9)
Immune	7 (10.4)
Metabolic	3 (4.4)
Unknown	14 (20.6)
Epilepsy localization	
Temporal	38 (55.9)
Frontal	21 (30.9)
Occipital	2 (2.9)
Parietal	2 (2.9)
Multifocal	3 (4.5)
Not classified	2 (2.9)
Seizure frequency, times/month	3 ± 6.3
Concomitant ASMs	
Mean previous ASMs	2 ± 2.1
LEV	40 (58.8)
LCM	12 (17.6)
VPA	28 (41.2)
OXC	8(11.8)
CBZ	5 (7.4)
TPM	4 (5.9)
LTG	6 (8.8)

LEV: Levetiracetam,VPA: Sodium valproate, LCM: Lacosamine, OXC: Ocazepine, TPM: topiramate, LTG:Lamosanqin, CBZ: carbamazepine, AEDs: antiepileptic drugs; SD: standard deviation.

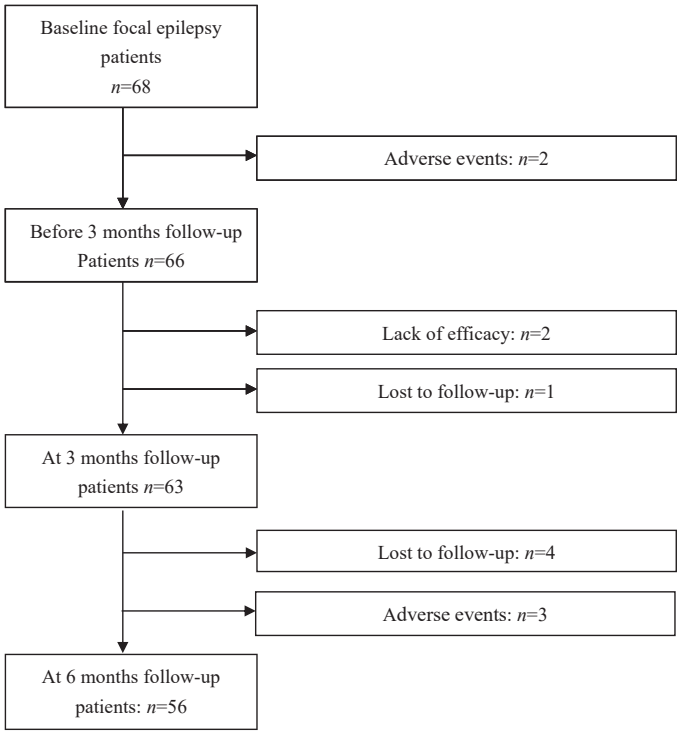

Fig. 1. Flowchart of the study eligible patients.

differences between the normal (n = 32), mild (n = 7), and severe (n = 5) groups were not statistically significant, improvements in the scale were observed at 6 and 12 months. In addition, four patients' scores returned to normal after 12 months (Table 2). No baseline

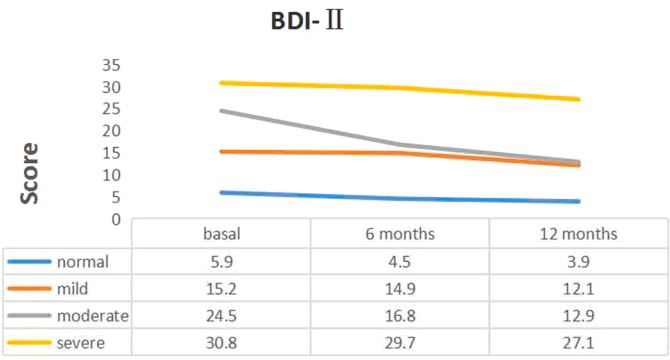

Fig. 2. BDI-II scores change from baseline, at 6 and at 12 months after perampanel treatment ($P = 0.003$ at 6 months; $P < 0.001$ at 12 months).

Table 2
BDI-II changes (categories).

	Baseline	6 months	12 months
Normal	32 (57.2 %)	33 (58.9 %)	36 (64.3 %)
Mild	7 (12.5 %)	8 (14.3 %)	8 (14.3 %)
Moderate	12 (21.4)	10 (17.9 %)	9 (16.1 %)
Severe	5 (8.9 %)	5 (8.9 %)	3 (5.4 %)
Total	56 (100 %)	56 (100 %)	56 (100 %)

The BDI-II score decreased significantly during the assess period (P = 0.001), and $P = 0.003$ at 6 months; $P < 0.001$ at 12 months.

features were associated with improvements in depression.

The mean MMSE score was 22.8 ± 9.1 at baseline, 23.1 ± 8.3 at 6 months, and 23.6 ± 9.0 at 12 months. There was no statistically significant improvement in MMSE scores at 6 months (P = 0.042) or 12 months (P = 0.038). Only two patients improved their scores to normal at 12 months (Table 3, Fig. 3).

The mean total score of the QOLIE-31 was 82.9 ± 12.3 points at baseline and significantly improved to 88.7 ± 10.4 points at 12 months (P < 0.0001). On the QOLIE-31 scale, seizure anxiety (B = 48.1, F = 54.2, P < 0.0001), quality of life (B = 60.1, F = 61.9, P < 0.0001), emotional health (B = 61.3, F = 62.9, P = 0.0298), medication effects (B = 54.9, Average scores of F = 57.6, P = 0.0002) and social function (B = 54.8, F = 57.4, P < 0.0001) showed significant improvement at baseline and at 12 months (Fig. 4).

Clinical efficacy and safety

Adverse events occurred in 21 patients (37.5 %). Dizziness is the most common adverse events (26.8 % of the patients, n = 15), followed by drowsiness (14.3 % of the patients, n = 8), mood changes (10.7 % of the patients, n = 6) and liver function damage (1.8 % of the patients, n = 1).

At the end of the study, 32.1 % of patients have no seizures, 73.2 % of patients have reaction (95 % CI, 13.8–40.9 %). Compared with before treatment, at 6 months (1.8 ± 0.3) (P < 0.001), and 12 months (1.2 ± 0.2) (P < 0.001) significantly reduced.

Seizure control (respondents) was significantly associated with BDI II

Table 3
MMSE changes (categories).

	Baseline	6 months	12 months
Normal	42 (75 %)	43 (76.8 %)	44 (78.5 %)
Mild	8 (14.3 %)	7 (12.5 %)	7 (12.5 %)
Moderate	6 (10.7 %)	6 (10.7 %)	5 (9.0 %)
Total	56 (100 %)	56 (100 %)	56 (100 %)

The MMSE scores were no statistically significant improvement at either 6 months (P = 0.042) or 12 months (P = 0.038).

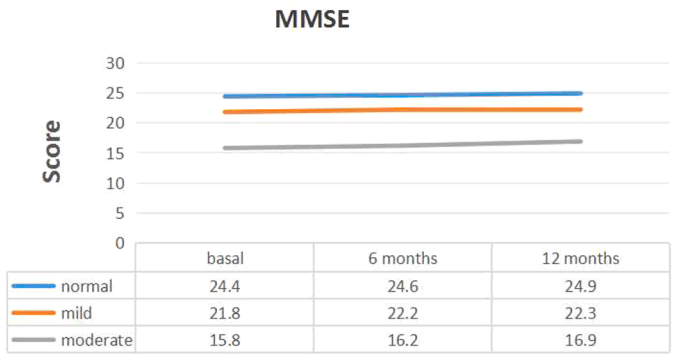

Fig. 3. MMSE scores change from baseline, at 6 and at 12 months after perampanel treatment (P = 0.042 and P = 0.038, respectively).

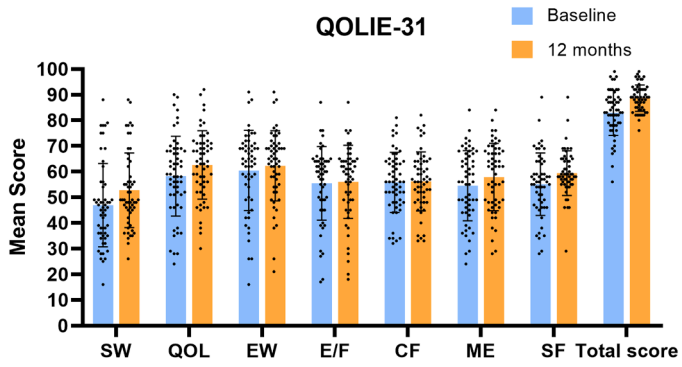

Fig. 4. QOLIE-31 Scale change at 6 months after perampanel treatment. CF, cognitive functioning; E/F, energy/fatigue; EW, emotional well-being; ME, medication effects; OLE, open-label extension; QoL, overall quality of life; QOLIE-31, Quality of Life Epilepsy Inventory-31; SF, social functioning; SW, seizure worry.

(r = 8.56, P = 0.011) or QOLIE (r = 10.28, P = 0.005). In the absence of epilepsy group, quality of life improved significantly over time (P = 0.038), both at 6 months (P = 0.012) and at 12 months (P = 0.008).

Analysis of influencing factors of pirampanel in reducing depression

There are 26 patients with depression based on BDI-II score. At the end of the study, we conducted a subgroup analysis for patients who showed improvement in their depression symptoms after prempanel therapy. Finally, 24 patients were included in the analysis. Among them, 11 patients with depression improved after treatment with pirampanel, 13 cases did not improve. Compared them to patients who did not show improvement, monofactor analysis was found that age, the average family income in the past year, etiology, duration of epilepsy, seizure frequency in the past year, and the types of ASMs were statistically significant ($P < 0.05$) (Table 4). Multiple Regression Analysis was found that annual family income, etiology, the frequency of attacks in recent years, types of ASMs and the age were statistical significance (Table 5).

Discussion

For close relationship between epilepsy and depression, Hippocrates once put forward relevant opinions, epilepsy and depression can be mutual transformation, clinical manifestations depending on the direction of incidence. If the effect to the body, can produce epilepsy, if applied to spirit, can produce depression (Hoppe, 2019). The reasons for the co-occurrence of depression and epilepsy are varied and not fully understood. The scholar thinks, this may be related to nerve inflammation, the hypothalamus - pituitary - adrenal axis (HPAA) highly active, excitatory and inhibitory neurotransmitter glutamate and gamma aminobutyric acid imbalance, tryptophan metabolism and related (17–18).

In addition to the effects of neurochemical transmitters, the use of ASMs also has certain effects on the occurrence of psychiatric symptoms. Studies have shown that Tigabine, Topax, Feamidate, primidone and amino-hexenoic acid have negative effects on mood (Kim et al., 2020), while carbamazepine (CBZ), oxamazepine and valproic acid are mood stabilizers (Mula, 2019). In addition, triazolines have been reported to show potent antidepressant activity and antiepileptic effects in the maximum electric shock seizure (MES) model (Zhao et al., 2023).

Table 4
Monofactor analysis of influencing factors of pirampanel in reducing depression.

Variables	Improvement group (n = 11)	Non-improvement group (n = 13)	P value
Gender (male, %)	6 (54.5)	7 (53.8)	0.335
Age (mean ± SD, years)	43.6 ± 9.8	35.9 ± 6.5	0.038
Age groups			0.012
< 30 years	2	6	
30–50 years	5	4	
> 50 years	4	3	
Education years (mean ±SD)	12.5 ± 4.6	13.1 ± 4.8	0.053
At seizure onset, years (mean ± SD)	22.2 ± 6.2	25.6 ± 8.5	0.227
Duration of epilepsy (mean ± SD, years)	5.8 ± 1.2	6.9 ± 4.1	0.024
Etiology			0.003
Structural	2	5	
Genetic	2	2	
Infectious	1	1	
Immune	2	3	
Metabolic	2	1	
Unknown	2	1	
Epilepsy localization			0.614
Temporal	5	6	
Frontal	2	3	
Occipital	1	0	
Parietal	1	1	
Multifocal	1	2	
Not classified	1	1	
Seizure frequency, times/year	2.1 ± 0.8	4.0 ± 1.1	0.026
Average family income in the past year ($)			< 0.001
< 8 thousands	5	8	
≥ 8 thousands	6	5	
Types of ASMs			0.004
2	7	6	
3	3	5	
≥ 4	1	2	
Adverse drug reaction			0.118
None	8	8	
yes	3	5	

Table 5
Multiple regression analysis of influencing factors of pirampanel in reducing depression.

Variables	B	Wald	*P*	OR (95 % CI)
Etiology	2.439	4.212	0.040	1.465 (0.070,3.044)
Average family income in the past year	8.339	34.390	< 0.001	4.816 (4.475,8.967)
Seizure frequency in the past year	−5.809	21.251	< 0.001	0.003 (−6.499,2.622)
Types of ASMs	−4.004	23.333	< 0.001	0.018(−4.716, 1.993)
Age	1.612	5.788	0.016	0.073 (−3.871,0.395)

Perampanel, a third-generation novel antiepileptic drug, has been used in more than 55 countries for the adjuvant treatment of patients with focal epilepsy, and has achieved good efficacy (Yamamoto et al., 2020). Perampanel is a highly selective AMPA receptor antagonist in postsynaptic membrane neurons (Yang et al., 2020). Perampanel prevents the passage of Na+ and K+ through non-competitive binding to the AMPA receptor, resulting in the failure of postsynaptic membrane depolarization, thus producing anti-epileptic effects (Fukushima et al., 2020). It has been confirmed that perampanel has anti-anxiety effects at low doses by antagonizing AMPA receptors, and AMPA receptors antagonize gamma-amino butyric acid (GABA) and other systems, especially the norepinephrine system, which can increase its anti-anxiety activity (Bektas et al., 2020). Glutamate is an excitatory neurotransmitter of the central nervous system, and its ionic receptors include N-methyl-D-aspartate (NMDA) receptor, alginic acid receptor, and AMPA receptor. AMPA receptor antagonists can selectively inhibit several other neurotransmitter systems, such as cholinergic, gamma-aminobutyric, monoaminergic, and opioid systems. Perampanel, a noncompetitive antagonist of AMPA receptor, which neurophysiological effects involve neurotransmitter systems and cortical limbic circuits, which may underlie its antidepressant and other neurophysiological effects.

Although an observational prospective study evaluating the effect of perampanel adjuvant therapy on anxiety and depression in patients with drug-resistant focal epilepsy showed no significant change in anxiety and depression scores during perampanel treatment (Deleo et al., 2019). Studies have also shown that both anxiety and depression are improved after adding and maintaining perampanel treatment for at least 6 months (Moraes et al., 2020). In our study, the use of perampanel was associated with significant improvements in depressive symptoms and quality of life. On the BDI-II scale, scores decreased at 6 months of treatment ($P = 0.003$) and 12 months of treatment ($P < 0.001$). In the QOLIE-31 scale, the mean total score at the 12-month assessment was also significantly improved ($P < 0.0001$). In terms of anti-epileptic efficacy, 32.1 % of patients had no seizures and 73.2 % had a response at the end of the study. The number of monthly seizures decreased significantly at 6 and 12 months ($P < 0.001$). In addition, we found correlation between efficacy in controlling seizures and depression scores. We think this may mean that the inherently positive psychoactive effects of perampanel are dependent of its effectiveness as an antiepileptic drug.

In terms of adverse reactions, previous studies showed that the incidence of adverse reactions in the perampanel group ranged from 22.6 % to 60.6 %, and the main adverse reactions were irritability, rash, dizziness, drowsiness, anxiety, etc. (Hwang et al., 2020; Piña-Garza et al., 2018; Operto et al., 2020). In this study, the main adverse reactions were dizziness, drowsiness and mood change, with an incidence of 37.5 %, which was similar to the results of previous studies. These adverse effects may have interfered with the results, which explains why the study results did not find a statistical relationship between depression improvement and seizure control. In fact, increasing titration time can reduce adverse reactions. In this study, only 2 patients gave up the use of perampanel due to poor efficacy, and 5 patients gave up the use of perampanel due to adverse reactions. The U.S. Food and Drug Administration issued a black box warning about adverse neurobehavioral events when the perampanel was first introduced. However, most experiments have not found significant effects on cognitive function in patients with epilepsy. In this study, the cognitive function of the patients was preliminarily measured by MMSE, and no significant effect of the perampanel group on cognitive function was found. Some studies have found that perampanel may have an effect on certain subdomains of cognitive function. For example, one study found that the attention of children in the perampanel group decreased significantly ($P = 0.03$) (Piña-Garza et al., 2018). Another study (Operto et al., 2020) evaluated executive function in children treated with perampanel. The results showed that some of the children treated with perampanel had improved executive function. These findings suggest that perampanel may improve cognitive function in certain subdomains. Our study did not find that improvements in depressive symptoms were associated with cognitive function.

There are some limitations to our study. First of all, as this study is a single-center prospective observational analysis, the sample size is not large enough to fully reflect the real situation of the whole population, especially the elderly, children and other special groups. Second, the sample size is small and there is no control group, which may not be meaningful for direct comparison. Third, the use of specific psychiatric assessment scales for epilepsy patients is conducive to the professionalism of future studies. Four, studies showed that perampanel has anti-anxiety effects, but this study lacks data on anxiety assessment. Last but not the last, there are some neuromodulation techniques for treating depression, such as transcranial magnetic stimulation and ECT (Huang and Zheng, 2023; Wen and Zheng, 2023; Yuan et al., 2023). Therefore, patients with epilepsy may benefit from neuromodulation techniques. Future research may benefit from a more detailed assessment of cognitive function and exploring the potential long-term effects of perampanel on depression and quality of life in people with epilepsy.

Conclusion

Perampanel has good efficacy in the treatment of focal epilepsy with or without secondary comprehensive seizures. It can not only effectively and safely control seizures, but also play an antidepressant role and may improve the quality of life of epilepsy patients.

Informed consent

All individuals involved in the research to obtain the informed consent.

Ethical approval

The study adheres to the principles of the Declaration of Helsinki and good clinical practice guidelines and has obtained approval from the Research Ethics Committee (No. GYYFY 2023-S06) of the first affiliated hospital of Gannan Medical University. Prior to participation in the trial, all participants provided written informed consent.

Fundings

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Declaration of Competing Interest

The authors declare that there are no competing interests for this article.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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