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Efficacy of phenobarbital and sodium valproate in treating convulsive epilepsy in rural northeast China

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ABSTRACT

Purpose: Phenobarbital and sodium valproate are broad spectrum and inexpensive antiepileptic drugs that are used to treat convulsive epilepsy. We examined the therapeutic effects of phenobarbital and sodium valproate in patients with convulsive epilepsy in the rural northeast China, and discuss our efforts to ensure patients' compliance.

Methods: Patients with convulsive epilepsy were screened by trained township health center doctors. Patients in the phenobarbital group were enrolled between January 2011 and December 2012, and followed up until December 2017. Patients in the sodium valproate group were enrolled between January 2011 and December 2017, and followed up for 1 year. Efficacy of phenobarbital or sodium valproate was assessed by the reduction in seizure frequency.

Results: A total of 1200 patients were diagnosed by screening and rechecking, of which 925 patients received phenobarbital and 275 received sodium valproate. In the phenobarbital group, 528 patients were followed up for ≥60 months, and the efficacy rates of reduction of seizure frequency by at least 75% was in the fifth year. In the sodium valproate treatment group, 228 patients were followed up for 12 months, and the reduction of seizure frequency by at least 75% was 60.4%. 444 patients (37%) did not complete the study. Dizziness (27%) was a common adverse event in phenobarbital group. In the sodium valproate group, gastrointestinal complaints (27.3%) was a common adverse event.

Conclusion: Phenobarbital and sodium valproate were proven to be efficacious in treating convulsive epilepsy in rural northeast China. The patients' compliance still needs to be improved.

1. Introduction

Epilepsy is a commonly encountered disease of the nervous system. Epidemiological data from the International League Against Epilepsy (ILAE) showed that the prevalence of epilepsy is 5.8‰ in developed countries and 15.4‰ in developing countries. The prevalence of active epilepsy is 4.9‰in developed countries and 12.7‰ in developing countries [1]. More than 85% of epilepsy cases occur in 49% of the world's population that resides in low and middle income countries (LMIC) [1,2]. In China, the lifetime prevalence is 7.0 cases per 1000 people. For active epilepsy, the lifetime prevalence is 4.6 per 1000 people [3]. The economic and medical service conditions in rural areas of China are relatively insufficient when compared to those in urban areas, and doctors and patients in rural areas often lack extensive knowledge of the disease. As a result, many epilepsy patients in rural areas do not receive effective treatment in a timely manner. The mortality rate among epileptic patients in LMIC is always higher than that in high income countries (HIC), and this difference is associated with the higher incidence of untreated epilepsy in LMIC, as well as other risk factors that have not been fully identified [4].

In 1997, the Global Campaign Against Epilepsy (GCAE) was started by the World Health Organization (WHO), the International League Against Epilepsy (ILAE), and the International Bureau for Epilepsy (IBE) [5]. In 2000, with support from the Mental Health Division, WHO and the Bureau of Disease Prevention and Control, National Health Commission of China, a project which included an epidemiological survey, intervention trial, and educational program was initiated to study epilepsy in China [6].

In recent years, many types of antiepileptic drugs (AEDs) have been tested and used in the clinic, and about 70% of epileptic patients are now taking AEDs [7]. However, despite the apparent 'benign' prognosis of epilepsy, 73.3% of active epilepsy patients in LMIC remain untreated

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or are improperly treated [8]. Phenobarbital and sodium valproate are two traditional broad-spectrum AEDs that are inexpensive, efficacious, and usually taken with good compliance. These traits make them suitable for low income patients. In recent years, the progress of the GCAE Demonstration Project in China has been reported continuously. However, there are few reports of long-term follow-up of people with epilepsy (PWE) who enrolled in the study in rural areas of northeast China. In this study, we evaluated the efficacy of phenobarbital and sodium valproate, respectively, as monotherapy for convulsive epilepsy, and discuss our efforts to ensure patients' compliance.

2. Materials and methods

2.1. Patient recruitment

The protocol for this study was approved by the Ethics Committee of the First Hospital of Jilin University, and each enrolled patient provided their or their parents' (patient under the age of 16) signed written Informed Consent for participation.

From January 2011 to December 2017, seven counties (Huadian, Fuyu, Tonghua, Dunhua, Taonan, Panshi, and Huinan counties) were the sites of a demonstration project for Epilepsy Prevention and Treatment in the rural areas of Jilin province, China (Fig. 1). Patients who displayed two of the first three following symptoms and any one of symptoms 4–7 were diagnosed as convulsive epilepsy [9] and were eligible to be recruited in the study: ①loss of consciousness; ②rigidity; ③generalized convulsive movements; ④urinary incontinence; ⑤bitten tongue or an injury sustained in a fall; ⑥post-seizure fatigue; ⑦headache or muscle aches after seizure.

Patients who met the following criteria were eligible for treatment with phenobarbital or sodium valproate [9,10]: at least 2 seizures within one year before investigation or at least two unprovoked (or reflex) seizures occurring > 24 h apart; convulsive seizures in addition to other types of seizures; never or irregular treatment with phenobarbital or sodium valproate.

Patients with any of the following characteristics were not eligible for the phenobarbital treatment: seizures during pregnancy only; seizures only associated with alcohol or drug reduction; age < 2 years or weight < 10 kg; history of ADHD; phenobarbital allergy; progressive neurological diseases; history of epileptic status; patients receiving regular effective treatment with an AED [11].

Patients with any of the following characteristics were not eligible for the treatment of sodium valproate: history or family history of drug-induced jaundice; liver disease or significant liver damage; blood diseases; renal impairment; hypertension; active mental illness; history of allergies to valproic acid-based AEDs; age < 4 years old; progressive neurological disorders; undergoing treatment with other antiepileptic drugs; history of poor compliance [10].

We selected the patients who enrolled in the phenobarbital group between January 2011 and December 2012, and these patients were followed up until December 2017. Patients who enrolled in the sodium valproate group from January 2011 to December 2017 were evaluated in the first year. All patients in both groups were treated with monotherapy.

2.2. Study procedure

All public health workers (PHW) and many local medical staff members involved in the study received basic training in the diagnosis and management of epilepsy. They were responsible for the management of PWE, including drug delivery and filling out follow-up forms. The project's processes included patient screening, review, management, follow-up, and data entry (Fig. 2).

Screening meant that all PWE were screened by PHW in village level and then registered according to criteria on a convulsive epilepsy screening form. The form included basic patient information, a brief history of the patient's epilepsy, a treatment history, and a description of treatment status and seizure attacks during the previous 12 months. Re-examinations were performed by trained physicians or neurologists in the county hospital, and were designed to confirm whether PWE satisfied criteria for enrollment in the phenobarbital group or valproic acid group. During this re-examination, the neurologist also filled out a "neurologist re-examination form" which included the rationale for diagnosis, status of treatment, actual diagnosis, type of epileptic seizure, and the patient's or patient family's opinion about participating in this therapeutic investigation.

Our study used a door-to-door survey technique. Also, because rural areas have many migrant workers, some of the patients were surveyed by telephone, and their family members helped them to get the drug. Follow-up surveys were conducted every two weeks at the beginning of the study, and then conducted once each month after the fourth follow-up. Patients who had no seizures during the preceding 6 months were subsequently followed up every two months. However, patients who continued to have seizures were urged to immediately go to the hospital and have their dose of drugs adjusted. During each follow-up, the PHW at village level filled out a follow-up form, which including the last follow-up time, the dose of drugs prescribed (the dose prescribed at the last follow-up), the number of seizures between two follow-ups, any new adverse reactions, compliance, the patient's subjective feelings, and the reason for and date of withdrawal from treatment. Any patient with an accident or death was recorded in detail. The patient's compliance was judged by checking the number of tablets remaining in the patient's prescription bottle during the follow-up visit.

Patients with one or more of the following conditions were required

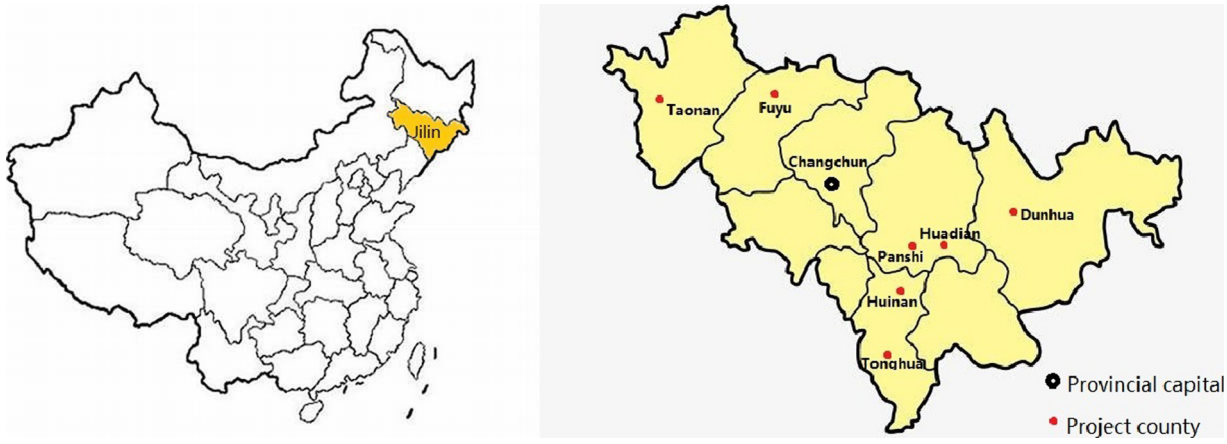

Fig. 1. The counties included in the study.

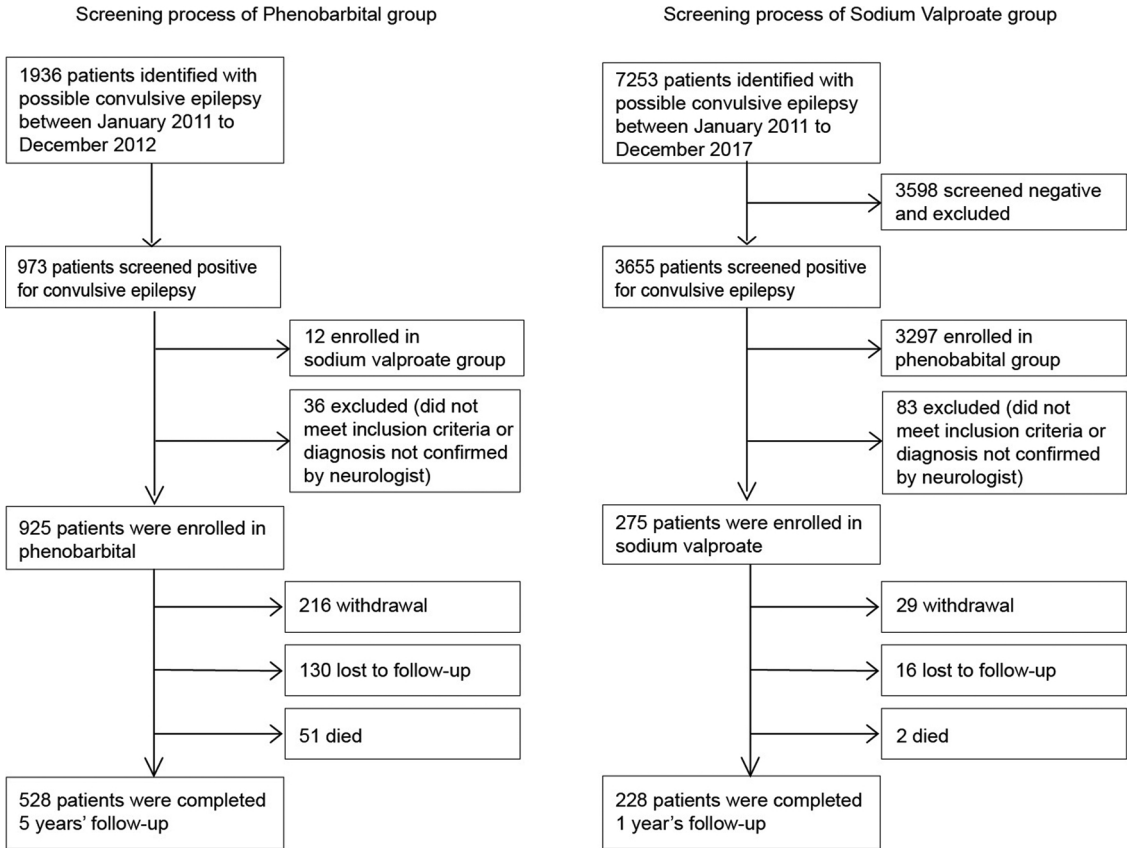

Fig. 2. Study implementation flow chart.

to withdraw from treatment: ①an allergic reaction (rash) that occurred after taking the medicine; ②the physicians in township hospital believed that the treatment had no effect; ③the seizure frequency increased by > 50%; ④the patient or guardian opposed continued treatment; ⑤three consecutive non-compliances with medical advice or three times without follow-up and medication; ⑥a progressive disorder of nervous system, heart, liver or kidney; ⑦the physicians in the township hospital determined that the patient could not tolerate treatment with phenobarbital.

2.3. Phenobarbital and sodium valproate therapy

The initial dose of phenobarbital given to adults (≥15 years old or a body weight > 30 kg) was 60 mg per day before sleep. This initial dose was maintained for 2 weeks to achieve a stable blood concentration, and then increased to 90 mg after 2 weeks if the patient experienced more than one seizure. After 2 months of dosing, the patients were followed up at 1 month intervals. The maximum dose for adults did not exceed 210 mg/day. If the attacks remained uncontrolled, the patient was advised to consult the senior physician and add additional antiepileptic drugs. The initial dose given to children (< 14 years old, body weight < 30 kg) was 2 mg/kg/day, and could be increased to 3 mg/kg/day if the number of attacks increased. The maximum dose usually did not exceed 5 mg/kg/day [12].

The initial dose of sodium valproate given to adults was 600 mg per day and was divided into 2–3 doses. Liver function and other blood tests were performed before and 1, 3, 12 months after sodium valproate treatment. The initial dose given to children was 20 mg/kg/day, 2–3 times daily. This was maintained if no seizures occurred at that dose, but if seizures continued to occur, the dose was increased to 5–10 mg/kg/week until the seizures were controlled. The maximum daily dose given to children did not exceed 30 mg/kg [10].

Efficacy was assessed using the percentage reduction in seizure frequency from baseline at observation time points. Efficacy was classified as follows: ①seizure free for at least one year; ② > 75% but < 100% reduction in the seizure frequency; ③ > 50% but ≤75% reduction in the seizure frequency; ④ > 25% but ≤50% reduction in the seizure frequency; ⑤less than 25% reduction or increase in the seizure frequency [9].

2.4. Statistical analysis

Values for continuous variables are expressed as the mean ± standard deviation (SD), and values for categorical variables are expressed as frequencies (%). Student's t-test, analysis of variance (ANOVA), Pearson's Chi-squared test, the rank sum test, the Kruskal-wallis test and Fisher's exact test were used to compare the continuous variables and categorical variables. Survival (Kaplan—Meier) analysis was used to estimate the long-term retention rate, which was a composite measure of efficacy and tolerability and was used as a measure of overall effectiveness of the protocol [9].

All p-values were estimated in a two-tailed manner. Differences with a p-value < 0.05 were considered to be statistically significant. The data were input into EpiData software (The EpiData Association, Odense, Denmark), and then analyzed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 1200 patients were enrolled in this study between January 2011 and December 2017, of whom 688 (57.3%) were male and 512 (42.7%) were female. According to the admission criteria, 925 patients were treated by phenobarbital and 275 were treated by sodium valproate. Demographic information for the study participants is provided in Table 1. It shows that the mean disease onset age was 21.2 ± 16.3 years and the mean disease duration was 19.1 ± 13.3

Table 1
Demographic and clinical characteristics of the patients.

Characteristic	N (%) or mean (SD)		
	Phenobarbital	Sodium valproate	Total
Number of patients	925	275	1200
Sex			
Male	526 (56.9%)	162 (58.9%)	688 (57.3%)
Female	399 (43.1%)	113 (41.1%)	512 (42.7%)
Onset age (years)	20.1 (15.1)	27.4 (20.6)	21.2 (16.3)
Duration of disease (years)	19.9 (13.2)	16.2 (13.6)	19.1 (13.3)
Median number of seizures per year (range)	8 (1-365)	10 (1-200)	10 (1-365)
Seizure type			
Generalized tonic-clonic	757 (81.8%)	227 (82.5%)	984 (82.0%)
Absence	24 (2.6%)	7 (2.5%)	31 (2.6%)
Focal aware seizures	6 (0.7%)	3 (1.1%)	9 (0.8%)
Focal impaired awareness seizures	2 (0.2%)	2 (0.7%)	4 (0.3%)
Focal to bilateral tonic–clonic seizure	18 (1.9%)	8 (2.9%)	26 (2.2%)
Other types	85 (9.2%)	16 (5.8%)	101 (8.4%)
Unclassified	33 (3.6%)	12 (4.4%)	45 (3.7%)

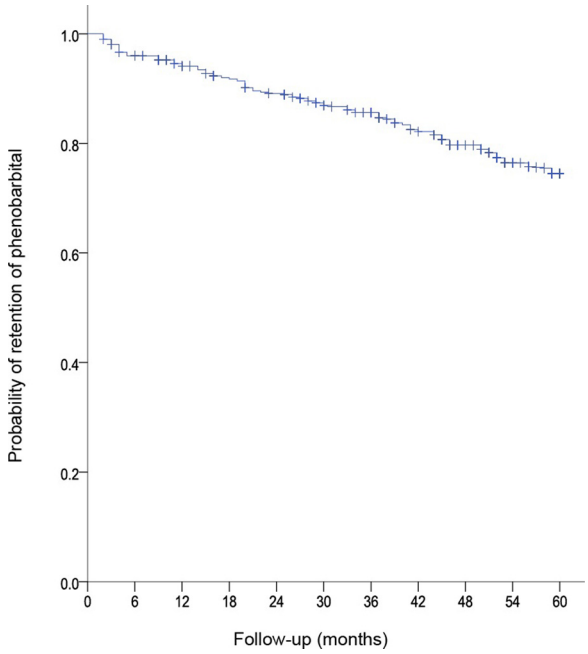

Fig. 3. Probability of retention of phenobarbital.

years. There were 7 types of seizures included in this study, of which 82% were generalized tonic-clonic seizures. There were 1099 activity epilepsy [13] patients (1200 cases of total screening and review), and these accounted for 91.6% of the screened patients. Of them, 435 cases had not received formal treatment, and 192 cases had never been treated; the treatment gap rate was 57.1%. Fig. 3 shows the estimated probability of retention of two treatments. Probability of retention of phenobarbital was 94.1% at 1 year, 85.6% at 3 years, and 74.5% at 5 years. Probability of retention of sodium valproate was 86.8% at 1 year (Fig. 4).

3.1. Efficacy of phenobarbital treatment

A total of 925 patients were enrolled in the phenobarbital group and followed up for 5 years. Table 2 shows the changes in seizure frequency of phenobarbital given as monotherapy at the first year (n = 802), the

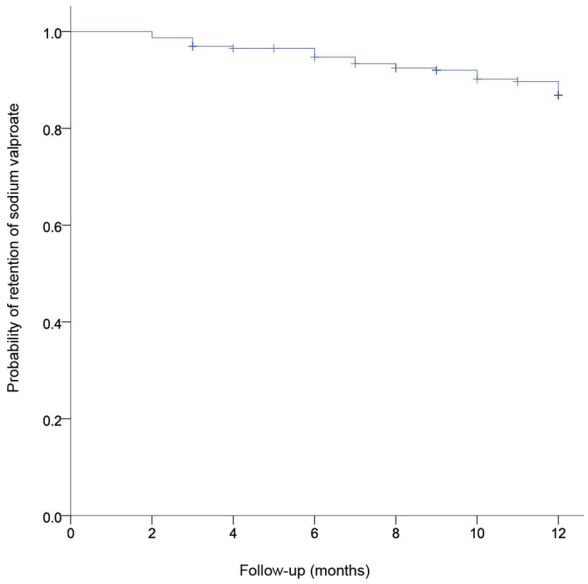

Fig. 4. Probability of retention of sodium valproate.

third year (n = 693) and the fifth year (n = 528). A half of patients who completed 3 years' treatment had a reduction in seizure frequency of at least 75% and forty-one percent of patients remained seizure free. Forty-six percent of patients who completed 5 years' treatment had reduction in seizure frequency of at least 75% and 36.1% of patients remained seizure free.

Based on the seizure frequency before enrollment, the patients were divided into group A (1–3 times / year), B (4–10 times/year), C (11–20 times /year) and D (≥21 times/ year) (Table 4). The Pearson's Chi-squared test showed that there was significant difference of phenobarbital treatment among these 4 groups in the first year ($\chi 2 = 30.819$, $P < 0.001$), the third year ($\chi 2 = 19.458$, $P < 0.001$) and the fifth year ($\chi 2 = 27.503$, $P < 0.001$). With the prolongation of the treatment time, the efficacy of the drug in four groups all decreased.

As the study progressed, the number of patients under treatment gradually decreased, and some patients withdrew from the study. 397 (42.9%) patients failed to complete the study in the phenobarbital group (Table 3). Lost-to-follow up was the main cause of withdrawal (32.8% of all withdrawals), followed by the non-adherence to regimen (22.9% of all withdrawals), the withdrawals due to adverse events (9.0% of all withdrawals, including 3.5% withdrew for allergy) and finally the patients who migrated from the study area (6.8% of all withdrawals). No difference in withdrawal was observed between the different reasons.

3.2. Efficacy of sodium valproate treatment

A total of 275 patients in the sodium valproate group were followed up for 12 months. Table 2 shows the changes in seizure frequency of sodium valproate given as monotherapy at 1 year (n = 228). In the 12th month, 60.4% of patients had reduction of seizure frequency of at least 75% and 34.9% of patients were seizure free. There was no significant difference between the two groups in terms of reduction of seizure frequency of at least 75% during one year of follow-up ($\chi 2 = 0.167$, $P > 0.05$).

In one-year's follow-up in this group, 47 (17.1%) patients withdrew from the study (Table 3). It was similar to the phenobarbital group that lost-to-follow up was the main cause of withdrawal (34.0% of all withdrawals), followed by the non-adherence to regimen (31.9% of all withdrawals) and lastly the patients who migrated from study area (14.9% of all withdrawals). There was no withdrawal due to adverse events. No difference in withdrawal was observed between the different

Table 2
The changes in convulsive seizure frequency of Phenobarbital or Sodium valproate monotherapy.

	Phenobarbital n (%)			Sodium valproate n (%)
	The 1st year (n = 802)	The 3rd year (n = 693)	The fifth year (n = 528)	The 1st year (n = 228)
Seizure free	413 (44.6%)	385 (41.6%)	334 (36.1%)	96 (34.9%)
Reduced by > 75%	158 (17.1%)	139 (15%)	95 (10.3%)	70 (25.5%)
Reduced by 51–75%	81 (8.8%)	73 (7.9%)	67 (7.2%)	15 (5.5%)
Reduced by 26–50%	77 (8.3%)	58 (6.3%)	24 (2.6%)	36 (13.1%)
Less than 25% change	73 (7.9%)	38 (4.1%)	8 (0.9%)	11 (4%)

Table 3
Reasons for withdrawal.

	Phenobarbital n (%)	Sodium valproate n (%)	P value
Non-adherence to regimen	91 (22.9%)	15 (31.9%)	0.075
Migrated from study area	27 (6.8%)	7 (14.9%)	
Pregnancy or planned pregnancy	8 (2.0%)	0 (0.0%)	
Adverse events	36 (9.0%)	0 (0.0%)	
Lost to follow up	130 (32.8%)	16 (34.0%)	
Death	51 (12.9%)	2 (4.3%)	
Other	54 (13.6%)	7 (14.9%)	
Total	397 (100.0%)	47 (100.0%)	

reasons.

3.3. Adverse events

Dizziness (27%) was a common adverse event in the phenobarbital group during the first six months of medication, followed by drowsiness (22.8%) and ataxia (16.1%). Skin rash (6.4%) was the least adverse event. In the first six months for the sodium valproate group, gastrointestinal complaint (27.3%, including nausea, vomiting, diarrhea and so on) was the most common adverse event, followed by the drowsiness (19.6%), and headache (10.9%). The least adverse event was the ataxia (5.5%) and dizziness (5.5%). Most adverse events were mild. Thirty-six patients withdrew the study because of adverse events. With the extension of follow-up time, the number and extent of adverse events gradually decreased (Table 5).

4. Discussion

In this study, 46.4% of patients who completed 5 years' phenobarbital treatment had reduction of seizure frequency by at least 75% and 36.1% of patients were seizure free. In the first year of sodium valproate follow-up, 60.4% of patients had reduction of seizure frequency by at least 75% and 34.9% of patients were seizure free. Probability of retention of phenobarbital was 74.5% at 5 years. Probability of retention of sodium valproate was 86.8% at 1 year.

In 1977, the WHO adopted the concept of the Essential Drug List in response to a request submitted by the World Health Assembly (1975) for a plan to select and procure essential, effective and inexpensive medications that meet the needs of low-income countries [14,15]. Phenobarbital was listed as an antiepileptic drug for its few side effects, exact curative effect, low price, easy availability, and long half-life *in vivo* [16,17]. Phenobarbital is currently recommended as a first-line treatment for partial and tonic-clonic seizures in resource-poor countries, and is often selected as the initial treatment for this type of intervention [18]. Taking this medicine once before going to sleep each night is easy to remember, and it can also reduce adverse reactions during the day while improving the night's sleep; these traits serve to support patient compliance with a phenobarbital dosing regimen. With the development of the Epilepsy Management Project in rural areas of China, the curative effect of phenobarbital has been further confirmed. However, most of the therapeutic effects of phenobarbital have been evaluated within the first 1 to 12 months of dosing, and few studies have evaluated the efficacy of long-term use of phenobarbital. Notable papers from Tanzania [19], India [20], Nigeria [21], Mali [22] and China [9] all showed relatively similar efficacy rates of seizure control around 50–55%. In our study at 12 months, the rate of reduction of seizure frequency of at least 75% was 61.7%, which was higher than that in those previous studies. Furthermore, our results showed that by the fifth year, 36.1% of patients in the phenobarbital group were seizure free, and 46.4% of patients had reduction of seizure frequency by at least 75%. Further, our probability of retention was higher [9]. This may reflect that the patients in rural northeast China have better response and tolerability to phenobarbital. We further analyzed the efficacy of patients with different seizure frequencies. Our results showed that the patients taking phenobarbital with low seizure frequency had poorer efficacy at early treatment but better efficacy at later treatment. However, patients with high seizure frequency performed poorly during all courses of treatment. With the prolongation of the treatment time, the efficacy of the drug in four groups all decreased. This may have resulted from the decrease in the drug responsiveness.

Sodium valproate is a broad-spectrum antiepileptic drug [23]. Previous studies showed that sodium valproate is better tolerated than topiramate, and more effective than lamotrigine [24]. It can be used in patients with seizures that cannot be classified, and its main side effect is hepatic injury. We analyzed 275 patients in the sodium valproate group who had been followed up for 12 months. In our study, the PWE

Table 4
Efficacy of Phenobarbital and Sodium valproate in different groups with seizure frequency at baseline.

	Group A (1-3 times/year)		Group B (4-10 times/year)		Group C (11-20 times/year)		Group D (≥21 times/year)		P
	Efficacy*	Inefficacy*	Efficacy	Inefficacy	Efficacy	Inefficacy	Efficacy	Inefficacy	
Phenobarbital, n (%)	n = 247		n = 217		n = 253		n = 208		
1st year	155 (62.8%)	92 (37.2%)	177 (81.6%)	40 (18.4%)	201 (79.4%)	52 (20.6%)	138 (66.3%)	70 (33.7%)	< 0.001
3rd year	167 (67.6%)	21 (32.4%)	124 (57.1%)	93 (42.9%)	131 (51.8%)	122 (48.2%)	102 (49.0%)	106 (51.0%)	< 0.001
5th year	112 (45.3%)	135 (54.7%)	114 (52.5%)	103 (47.5%)	137 (54.2%)	116 (45.8%)	66 (31.7%)	142 (68.3%)	< 0.001
VPA, n (%)	n = 56		n = 85		n = 59		n = 75		
1st year	32 (57.1%)	24 (42.9%)	55 (64.7%)	30 (35.3%)	33 (55.9%)	26 (44.1%)	46 (61.3%)	29 (38.7%)	0.699

* Efficacy = seizure free + > 75% reduction in seizure frequency, Inefficacy = 1-Efficacy.

Table 5
Adverse events of treatment with Phenobarbital and Sodium valproate.

	Phenobarbital n (%)				Sodium valproate n (%)	
	1-6 months (n = 925)	7–12 months (n = 877)	3rd year (n = 693)	5th years (n = 528)	1–6 months (n = 275)	7–12 months (n = 263)
Drowsiness	211 (22.8%)	209 (23.9%)	131 (18.8%)	68 (12.9%)	54 (19.6%)	33 (12.5%)
Ataxia	149 (16.1%)	149 (17%)	86 (12.4%)	32 (6.1%)	15 (5.5%)	14 (5.3%)
Dizziness	250 (27%)	252 (28.7%)	138 (19.9%)	61 (11.6%)	15 (5.5%)	16 (6.1%)
Headache	161 (17.4%)	136 (15.5%)	82 (11.8%)	37 (7%)	30 (10.9%)	22 (8.4%)
Hyperactivity	85 (9.2%)	97 (11.1%)	41 (5.9%)	24 (4.5%)	–	–
Skin rash	59 (6.4%)	64 (7.3%)	31 (4.5%)	3 (0.6%)	–	–
Gastrointestinal complaints	92 (9.9%)	92 (10.5%)	42 (6.1%)	4 (0.8%)	75 (27.3%)	64 (24.3%)
Others	102 (11%)	96 (10.9%)	43 (6.2%)	11 (2.1%)	–	–

experienced at least a 50% reduction in seizure frequency in the 12th month (65.9%) which was lower than the previous study of Wang et al. (84%, n = 431) [10]. The difference may be due to the small sample size. Some studies indicated no significant difference in efficacy between treatment with phenobarbital and with carbamazepine, phenytoin, or valproate [25–27]. And our result shows no significant difference between phenobarbital and sodium valproate in terms of reduction of seizure frequency by at least 75% at one-year's follow-up ($\chi 2 = 0.167$, $P > 0.05$). Thus, it is feasible to use phenobarbital as the first choice in the current therapeutic regimen.

According to previous studies [9,28–30] and our clinical experiences, we found some factors may influence the compliance of rural PWE, such as low income, migration, limited education, misunderstanding of AEDs, *etc.* In order to ensure patients' compliance, we have been focusing our attention on three aspects: Firstly, from the aspect of professional support, medical professors in provincial and county institutions provided professional support for the project. With the help of provincial epilepsy experts, the correct diagnosis and prescriptions could be ensured, increasing the control rate of epilepsy. Secondly, from the aspect of administration, the multilevel divisions for Disease Prevention and Control coordinated local resources and managed them systematically. The screening, review, management and follow-up were supervised to reduce the loss of follow-up due to poor personal compliance. Finally, from the aspect of publicity and education, we took advantage of every possible channel of publicity to inform people in rural areas of the national free treatment policy for convulsive epilepsy, such as local broadcasting and leaflets. We tried to ensure that PWE fully understood the need for treating epilepsy with drugs available and the possible side effects to reduce the financial concerns of patients and the fear of antiepileptic drugs which made for better adherence to regimen.

In our study, 37% patients (444/1200) did not complete the study. The result is higher than other studies [9,28]. Except for patients lost to follow up, non-adherence to regimen was the main cause of withdrawal. Compared with the rural areas in south China, the economy in rural northeast China is more challenged which may lead to lower level of education and a worse understanding of disease.

Studies have shown that the adverse effects of phenobarbital [9,20,22] and sodium valproate [10] were mild and not common. In our study, most adverse effects were mild, but the incidences were higher than other studies. A higher incidence of adverse events in two groups may be associated with the carefulness of PHWs at the village level, and if PHWs could ask about possible adverse events one by one, there might be more feedback than asking patients to report them on their own. Another possible reason is the gradually increasing attention attached to individual health; our patients reported adverse events in a timely manner instead of ignoring them.

5. Conclusion

In this study, PWE in rural areas received a standardized, free treatment for their disease and we managed to increase the compliance. The results showed that phenobarbital and sodium valproate were both effective for treating epilepsy. However, many more patients in rural areas remain untreated, thus additional reasonable and effective intervention is needed. We are still a long way from complete success.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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