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Original Article

# Effectiveness analysis of three-drug combination therapies for refractory focal epilepsy

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ABSTRACT

Selecting appropriate antiseizure medications (ASMs) for combination therapy in patients with drug-resistant epilepsy (DRE) is a complex task that requires an empirical approach, especially in patients receiving polytherapy. We aimed to analyze the effectiveness of various three-drug combinations in a group of patients with DRE under real-world conditions. This single-center, longitudinal observational study investigated patients with drug-resistant focal epilepsy who received three-drug regimens in the outpatient clinic of Tongji Hospital from September 2019 to December 2022. The effectiveness of each triple regimen was evaluated by the seizure-free rate and within-patient ratio of the seizure frequency (a seizure frequency ratio [SFR]<1 indicated superior efficacy). The independent *t*-test or Mann–Whitney *U* test was used for effectiveness analysis, and *P* values were adjusted by the Benjamini–Hochberg method for multiple comparisons. A total of 511 triple trials comprising 76 different regimens were conducted among 323 enrolled patients. Among these triple regimens, lamotrigine (LTG)/valproic acid (VPA)/topiramate (TPM) was the most frequently prescribed (29.4%, $n = 95$). At the last clinical visit, 14.9% ($n = 48$) of patients achieved seizure freedom after receiving triple therapy. LTG/VPA/TPM and LTG/VPA/levetiracetam (LEV) exhibited the highest seizure-free rates at 17.9% and 12.8%, respectively. These two regimens also had significantly lower median SFRs of 0.48 (interquartile range [IQR], 0.17–0.85; adjusted $P < 0.001$) and 0.63 (IQR, 0.21–1.04; adjusted $P < 0.01$), respectively. LTG/VPA/perampanel (PER) was another promising regimen that showed marginal effectiveness (median SFR = 0.67; adjusted P = 0.053). LTG/VPA/phenobarbital had the highest incidence of regimen-specific side effects (40.0%, 4/10), while the incidence of side effects from LTG/VPA/LEV was minimal (5.1%, 2/39). In conclusion, LTG/VPA/TPM and LTG/VPA/LEV exhibited superior efficacy and good tolerability in treating patients with DRE. Our results provide preliminary insights into the selection of ASMs for three-drug combination therapies in this clinically challenging population.

## Introduction

Although the overall treatment outcomes of epilepsy have not improved with the emergence of new antiseizure medications (ASMs) [1], some patients with drug-resistant epilepsy (DRE) can still achieve seizure freedom (SF) through continuous adjustment of drug regimens [2,3]. Patients with epilepsy (PWEs) who fail to respond to monotherapy often receive combination therapy comprising two or more ASMs [4]. Stephen et al. [5,6] evaluated 1617 and 2379 PWEs who were seizure free for at least one year in 2000 and 2010 and found that 20.5% and 20.4% of them received polytherapy (two, three, or even four ASMs), respectively. However, the evidence for guiding drug selection in polytherapy is insufficient, making the process of choosing suitable ASMs for combination therapy a complex task that requires an empirical approach. The dual-combination regimens of valproic acid (VPA) with lamotrigine (LTG) and levetiracetam (LEV) with carbamazepine (CBZ), among others, have been proven to have promising synergistic effects [7–9]. Among the adult outpatients at the Kork Epilepsy Centre, nearly 20% of PWEs achieved SF under dual therapies [10]. Nevertheless, a proportion of patients with ultrarefractory epilepsy, who often experience greater disease severity and worse quality of life, still have the opportunity to benefit from three-drug combination therapies when they do not obtain satisfactory outcomes with dual therapies [11,12]. Some experts believe that patients with “severe” DRE are more likely to achieve SF through three-drug schedules and that add-on therapy is preferred [13]. Indeed, approximately 20% of PWEs using three or more ASMs simultaneously achieve better seizure control [10]. In cases of focal DRE, this proportion reaches 30% [12]. However, unlike for dual-ASM treatment, even fewer

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formal recommendations exist for guiding drug selection via triple combinations.

For rational selection of ASMs in polytherapy, physicians need to consider not only factors such as patient age, sex, seizure type, comorbidities, tolerability, and social factors that must be accounted for in monotherapy but also pharmacokinetic and pharmacodynamic interactions [14]. This poses an immense challenge in selecting suitable ASMs for combination therapy, especially for triple or higher therapies. To address these challenges, researchers are dedicated to developing novel medications with different mechanisms of action and minimal drug–drug interactions. In recent years, pharmacotherapy for epilepsy has developed rapidly, and several new third-generation ASMs have been released into the market [15]. However, the efficacy of three-drug combination therapies has not been updated through research. Very few studies have demonstrated that specific triple regimens, such as VPA/LTG/LEV, CBZ/LTG/LEV and clobazam/LEV/LTG, are effective at achieving SF in certain patients [6,12]. Nevertheless, these studies were either cross-sectional or involved a limited number of patients receiving triple therapies. Moreover, none of them were specifically designed to investigate the efficacy of three-drug combinations. Therefore, we conducted this study to update and fill the gap in real-world pharmacotherapy research on the efficacy of triple therapies for epilepsy.

The present study aimed to (1) identify the clinical characteristics of patients with drug-resistant focal epilepsy who were treated with three-drug regimens; (2) explore the optimal three-drug regimens; (3) investigate potential factors related to the therapeutic efficacy of the optimal regimens; and (4) analyze the overall drug loads and side effects of various regimens.

## Methods

### *Study design and participants*

This was a single-center, longitudinal observational study involving consecutive individuals who were diagnosed with drug-resistant focal epilepsy and regularly visited the outpatient Department of Neurology, Tongji Hospital, from September 1, 2019, to December 31, 2022. Patients' complete medical records from epilepsy onset to the last clinical visit before December 31, 2022 were retrospectively extracted. The institutional ethics board of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology (ID: TJ-IRB20211229), approved this study and waived the requirement for written informed consent.

The inclusion criteria for patients were as follows: (1) patients diagnosed with DRE according to the 2010 International League Against Epilepsy (ILAE) criteria [16] supported by evidence of focal epilepsy; (2) patients who had received at least one three-drug combination regimen; (3) based on the previous study [11], we included only regimens that had been used for at least four months to avoid the variability inherent in short-term trials where ASMs were likely discontinued for tolerability issues; and (4) patients who had detailed medical records or seizure diaries available to provide recorded information about medications and seizure activity. The exclusion criteria for patients were as follows: (1) patients with epilepsy of unknown or generalized onset; (2) patients with a transient course of triple therapy as part of a crossover schedule (as determined by clinicians); (3) patients who received triple therapy for the first time after epilepsy surgery or vagal nerve stimulator implantation, as well as the triple regimens used after these treatments; (4) patients with an unclear frequency or number of seizures during medication; (5) patients with psychogenic nonepileptic seizures; (6) patients with persistent poor drug adherence, defined as those having two or more documented instances of “skipped/forgot/missed doses (for any reason)” in their medical records; and (7) patients with incomplete medical records.

### *Epilepsy treatment and clinical visits*

In clinical practice, clinicians select suitable ASMs depending on the seizure type, side effects, mechanism of action, drug interactions and patient willingness, starting with a small dose and gradually titrating up to the best-tolerated dose. Initial treatment is usually monotherapy, and if the initial ASM causes intolerable adverse effects at a low daily dose or fails to improve seizure control with the maximum tolerable dose, it is replaced. If the first ASM is tolerated well at an appropriate dosage and can partly control seizures, combination therapy is considered. If two monotherapies fail, combination therapy may be considered. If dual therapy is tolerable and partially effective or if multiple dual-therapy attempts fail, triple therapy might be considered. Side effects are monitored, and drug dosages are adjusted based on clinical indications during treatment. After a determined and sufficient period of SF, gradual reduction of medication can be considered.

Patients were required to visit the outpatient clinic for follow-up once a month during the first three months after drug adjustment. Thereafter, follow-up visits were usually conducted every three to six months. If outpatient clinic visits were not feasible, telephone interviews were conducted by healthcare personnel. Patients were instructed to record the seizure descriptions and the number of seizures between two visits and report this information to the attending physician at the follow-up visit.

### *Data collection*

The demographic details, epilepsy history, seizure characteristics, the existing auxiliary examination results and previous ASMs usage were documented in the initial medical records of patients at the Epilepsy Center of the Neurology Department at Tongji Hospital. At each subsequent clinical visit, any modifications to ASMs regimens, drug dosages, presence of side-effects, the seizure types and their corresponding frequencies or occurrences between two visits, comorbidities, and auxiliary examination results were recorded. In this study, we categorized side effects of a specific drug regimen into the regimen-specific side effects and the total side effects. The regimen-specific side effects of the index regimen were defined as any new-onset or worsened side effects that arose during treatment. The total side effects included residual side effects from previous medications and the regimen-specific side effects. A detailed description of the collected data is presented in the Supplementary Table 1. All these data were retrospectively extracted from the well-documented longitudinal medical records.

### *Assessing the effectiveness of triple regimens*

Two methods were used to assess the efficacy of the drug regimens. One was the seizure-free rate, and the other was the within-patient seizure frequency ratio (SFR). Seizure freedom (SF) was defined as the absence of seizures for 12 months or longer without relapse before the last clinic visit [1]. The seizure-free rate referred to the number of patients who achieved SF with a specific regimen divided by the total number of patients using that regimen. The calculation of the within-patient SFR was performed according to the previous methods [11]. In brief, the seizure frequency associated with each ASM regimen was calculated as the seizure count divided by the number of usage months. The within-patient SFR for each three-drug combination was calculated as the seizure frequency with the index triple regimen divided by the aggregate seizure frequency with all the other ASM regimens to which the patient had been exposed (i.e., the seizure frequency with regimen "A"/the seizure frequency with regimen "B + C+ … +X". In head-to-head comparisons, the SFR of each triple regimen and every other triple regimen that the patient ever used was calculated sequentially. An SFR<1 indicated that the index regimen was more effective

than the other regimens, while an SFR>1 indicated a less effective regimen. This method normalized the differences in the average seizure frequency between patients. For patients with multiple seizure types, we calculated the SFR for the seizure type that had the greatest impact on the patient. For ASM regimens where no seizures were recorded, the seizure frequency was calculated as 1/(the treatment months of that regimen). To further explore factors related to the efficacy of a particular triple regimen, group comparisons were conducted based on an SFR<0.5 and an SFR≥0.5. An SFR = 0.5 indicated that the seizure frequency of the index regimen was 50% of the seizure frequency of all other regimens used by the patient, similar to the 50% reduction in seizure frequency in previous studies [17,18]. The overall drug loads were calculated as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD) ratios for each ASM at a relatively stable dose, i.e., the sum of the PDD/DDD [19]. According to previous studies [19,20], drug load was predominantly assessed in adult patients. Therefore, we analyzed only the drug dosage and drug load for the triple regimens in patients aged 18 years and older at the beginning of usage.

### *Statistical analysis*

Numerical data are shown as counts and percentages, while continuous variables are presented as the means ± standard deviations (SDs) or medians (interquartile ranges, IQRs), depending on the normality of the data. Categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test, and continuous variables were analyzed by the independent *t*-test or Mann–Whitney *U* test. The median or average SFR of each three-drug regimen was compared with "1" (assuming the efficacy of the index regimen was equal to that of other regimens) using the one-sample Wilcoxon test or the one-sample *t*-test. In the analysis of drug efficacy, multiple comparisons may increase Type I errors; therefore, we used the Benjamini–Hochberg method to adjust the P value. Kaplan-Meier survival curves with log-rank tests were used to evaluate differences in the time needed for each triple regimen to achieve SF and to demonstrate the retention of the triple regimens over time. A two-sided $P < 0.05$ was considered to indicate statistical significance, and statistical analyses were performed using IBM SPSS 24 software (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, Inc.).

## Results

### *Demographic and epilepsy-related characteristics*

Between September 1, 2019, and December 31, 2022, a total of 503 patients with DRE who had been treated with triple therapy for at least four months attended the outpatient clinic of the neurology department, Tongji Hospital. After 180 patients were excluded, a total of 323 individuals were ultimately included. The demographic and clinical characteristics of the patients at the last clinical visit are summarized in Table 1. Among the included patients, 55.7% were male and 74.6% were adults. The median ages at the last clinical visit and at epilepsy onset were 25 years and 12 years, respectively. The median duration of traceability for the available ASM regimens and corresponding epilepsy frequency records was 95 months (IQR, 48–159 months). One hundred sixty-six (51.4%) patients were considered to have a structural etiology. The most common seizure type was focal impaired awareness seizures (62.2%). Additionally, 136 patients (42.1%) had multiple seizure types, and eight (2.5%) patients were diagnosed with epileptic encephalopathy. Up to the last clinical visit, patients had tried a median of five ASM regimens (IQR, 4–7; range, 3–15), and 56 (17.3%) patients achieved SF. One hundred seventy-five (54.2%) patients were categorized as refractory de novo [21] because they had never achieved one year of SF

**Table 1**
Demographic and clinical characteristics of study patients.

| Characteristics | No. (%)/Median (IQR, Range) |
|---|---|
| Sex, male | 180 (55.7%) |
| Age, years | |
| At epilepsy onset | 12 (IQR 7–20, range 0–74) |
| At the first use of triple regimen | 22 (IQR 14–31, range 1–75) |
| At the last clinical visit | 25 (IQR 17–34, range 2–77) |
| Traceability months of ASM records | 95 (IQR 48–159, range 15–236) |
| First-degree family history of epilepsy | 9 (2.8%) |
| History of febrile convulsions | 41 (12.7%) |
| History of status epilepticus | 62 (19.2%) |
| Etiology | |
| Structural | 166 (51.4%) |
| Non-structural | 157 (48.6%) |
| Seizure types | |
| Focal aware seizures | 68 (21.1%) |
| with motor features | 64 (19.8%) |
| with nonmotor features | 26 (8.0%) |
| Focal impaired awareness seizures | 201 (62.2%) |
| with motor features | 179 (55.4%) |
| with nonmotor features | 88 (27.2%) |
| Focal to bilateral tonic–clonic seizures | 164 (50.8%) |
| Multiple seizure types | 136 (42.1%) |
| Epileptic encephalopathy | 8 (2.5%) |
| Total number of ASM regimens | 5 (IQR, 4–7; range, 3–15) |
| Number of ASM regimens tried before three-drug combination therapy | 2 (IQR, 2–3; range, 1–7) |
| Total number of ASMs | 4 (IQR, 4–5; range, 3–9) |
| Seizure frequency at the last clinical visit, seizure/mo | |
| ≥1 | 161 (49.8%) |
| <1 | 106 (32.8%) |
| Seizure freedom | 56 (17.3%) |
| Seizure frequency before treatment, seizure/mo | |
| ≥1 | 187 (57.9%) |
| <1 | 64 (19.8%) |
| Start treatment after one seizure | 37 (11.5%) |
| Unknown | 35 (10.8%) |
| Patterns of drug resistance[a] | |
| Refractory de novo | 175 (54.2%) |
| Progressive refractoriness | 51 (15.8%) |
| Wax-and-wane pattern | 64 (19.8%) |
| Gradual remission | 33 (10.2%) |
| Comorbidities | |
| Any | 96 (29.7%) |
| Psychiatric comorbidities | 33 (10.2%) |
| Cognitive impairment | 62 (19.2%) |
| Others | 11 (3.4%) |
| EEG before three-drug combination therapy | |
| Epileptiform discharge | 237 (73.4%) |
| Slow wave | 25 (7.7%) |
| Normal | 61 (18.9%) |
| EEG at the last clinical visit | |
| Epileptiform discharge | 165 (51.1%) |
| Slow wave | 23 (7.1%) |
| Normal | 135 (41.8%) |
| Head MRI | |
| Normal | 117 (36.2%) |
| Abnormal | 180 (55.7%) |
| Unknown | 26 (8.0%) |

Abbreviations: ASM, antiseizure medication; IQR, interquartile range; EEG, electroencephalography; MRI, magnetic resonance imaging.

[a] Clinical prognostic patterns for refractory epilepsy [21]: Refractory de novo: No remission had been achieved from the onset of epilepsy ("remission" was defined as no seizures for at least 1 year); Progressive refractoriness: Initially seizure-free, but seizures recurred and became uncontrollable; Wax-and-wane pattern: Epilepsy alternated between controlled and uncontrolled; Gradual remission: Epilepsy was refractory initially but with time became drug responsive.

since the onset of epilepsy. There were 61 (18.9%) patients with normal EEG results before triple therapy, and this number doubled (135, 41.8%) at the last clinical visit.

*ASM usage pattern*

VPA and LTG were the most frequently prescribed ASMs, both in triple regimens (88.2% and 73.1%, respectively) and in all regimens (90.1% and 79.3%, respectively). VPA and oxcarbazepine (OXC) were the most common first-line ASMs, accounting for 28.5% (92/323) and 23.2% (75/323), respectively (Supplementary Fig. 1). The maximum number of triple regimens administered to a single patient was five. Specifically, 192 patients received only one triple regimen, 89 patients received two regimens, 28 patients received three regimens, 13 patients received four regimens, and only one patient received five regimens (not shown). In the first and second triple regimens, LTG/VPA/TPM had the greatest proportion, accounting for 15.5% (50/323) and 26.0% (34/131), respectively. Among the third triple regimens, LTG/VPA/perampanel (PER) and LTG/VPA/lacosamide (LCM) were the two most frequently prescribed combinations, each accounting for 21.4% (9/42). In the fourth triple regimen, LTG/VPA/PER emerged as the predominant combination (42.9%, 6/14). Notably, the probability of achieving a seizure-free period of 12 months with the first and second three-drug regimens was similar (16.4% vs. 15.3%), while the likelihood of achieving SF with more than two triple regimens was negligible (Fig. 1). Among all the triple regimens, LTG/VPA/OXC was the most commonly used in children (14%), and LTG/VPA/TPM exhibited the highest proportion in adults (23%) (Supplementary Fig. 2).

*Comparisons of the therapeutic effects of each triple regimen*

Among the 323 patients included in this study, a total of 511 triple therapy trials were conducted involving 76 unique combinations of three drugs. Across all the trials, the combination of LTG, VPA, and another ASM accounted for the majority (65.2%, 333/511), with LTG/VPA/TPM being the most frequently prescribed (95 patients), followed by LTG/VPA/OXC (54 patients), LTG/VPA/PER (48 patients), LTG/VPA/CBZ (41 patients), LTG/VPA/LEV (39 patients), LTG/VPA/LCM (37 patients), and LTG/VPA/phenobarbital (PB) (10 patients), among others. LTG/VPA/CBZ had the longest median duration of usage, 22.0 months (IQR, 9.5–49.0 months), while LTG/VPA/TPM had the highest proportion of patients who used it for more than 12 months (74.7%) (Table 2).

Up to the last clinical visit, a total of 48 patients (14.9%) achieved SF by triple therapy, and 22.6% of patients (73/323) had ever experienced a seizure-free period of 12 months during triple therapy usage. LTG/VPA/TPM and LTG/VPA/LEV demonstrated the highest rates of SF achievement, accounting for 17.9% and 12.8%, respectively, in the whole population. LTG/VPA/LEV exhibited the highest seizure-free rate in children (14.3%), and LTG/VPA/TPM showed the highest seizure-free rate in adults (19.0%). Regarding the SFR, LTG/VPA/TPM and LTG/VPA/LEV still had good therapeutic effects, with median SFRs of 0.48 (IQR, 0.17–0.85; adjusted $P < 0.001$) and 0.63 (IQR, 0.21–1.04; adjusted $P < 0.01$), respectively, in the whole population. Additionally, LTG/VPA/TPM showed excellent efficacy in both children (median SFR = 0.39, $p = 0.036$) and adults (median SFR = 0.49, adjusted $p < 0.001$). LTG/VPA/LEV also performed well in adults (SFR = 0.69, adjusted $p < 0.05$). LTG/VPA/PER was another regimen that showed marginal effectiveness in the whole population, with a median SFR of 0.67 (IQR, 0.26–1.07; adjusted $P = 0.053$ (not shown)) (Table 2). According to head-to-head comparisons, the efficacy of LTG/VPA/TPM was significantly superior to that of VPA/OXC/TPM (average SFR = 0.34; adjusted $P = 0.016$) in the whole population, while there was no significant difference in efficacy between the other pairs of combinations after correcting for P values (Supplementary Table 2).

In the whole population, we further compared the cumulative probability of SF by treatment duration and the overall retention rate of LTG/

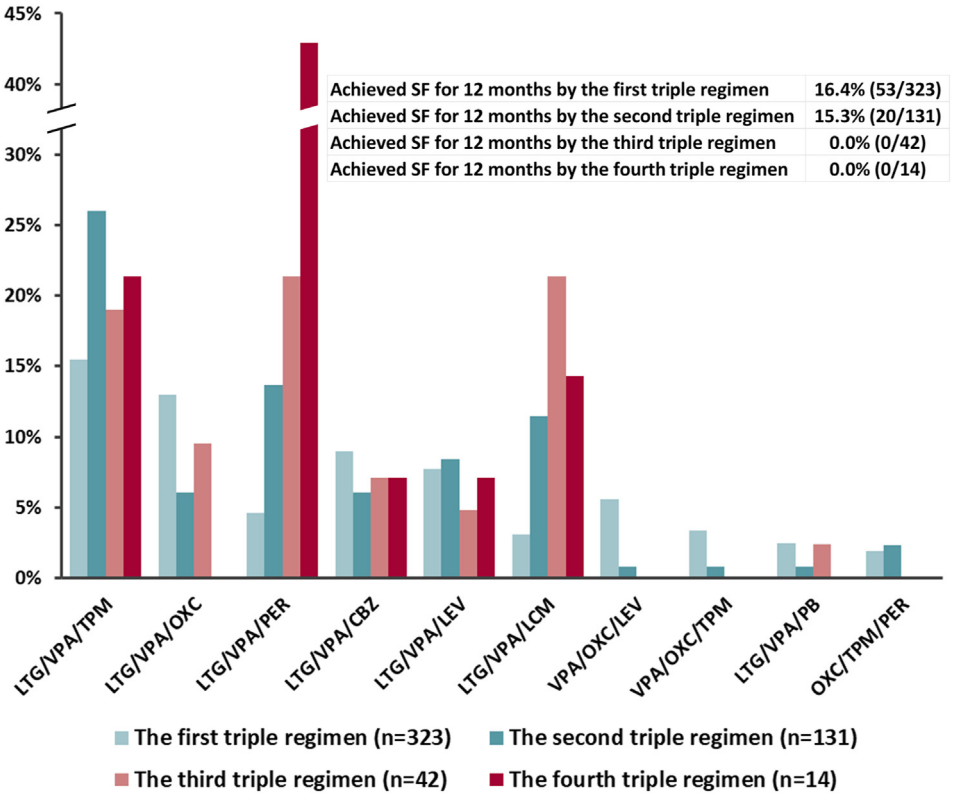


**Fig. 1.** Proportions of the top 10 commonly used three-drug combination regimens depending on prescription order. Abbreviations: SF, seizure freedom; LTG, Lamotrigine; VPA, Valproic acid; TPM, Topiramate; OXC, Oxcarbazepine; PER, Perampanel; CBZ, Carbamazepine; LEV, Levetiracetam; LCM, Lacosamide; PB, Phenobarbital.

**Table 2**
Comparative efficacy of individual three-drug ASM combination regimen to the aggregate average of other regimens to which each patient had been exposed.

| Three-drug combination | No. | Month of usage, Median (IQR) | Retention ≥12 months, n (%) | Seizure-free period ≥12 months, n (%) | SF, n (%) | SFR, Median (IQR) | P value for SFR | SF in children, n (%) | SFR in children, Median (IQR) | P-value for SFR in children | SF in adults, n (%) | SFR in adults, Median (IQR) | P-value for SFR in adults |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LTG/VPA/TPM | 95 | 18 (11.0–34.0) | 71 (74.7%) | 22 (23.2%) | 17 (17.9%) | 0.48 (0.17–0.85) | *<0.001*** | 1 (9.1%) | 0.39 (0.14–1.00) | *0.036* | 16 (19.0%) | 0.49 (0.18–0.80) | *<0.001*** |
| LTG/VPA/OXC | 54 | 12.5 (7.8–24.3) | 31 (57.4%) | 6 (11.1%) | 6 (11.1%) | 0.82 (0.38–1.49) | 0.743 | 1 (4.8%) | 0.76 (0.46–1.11) | 0.244 | 5 (15.2%) | 1 (0.31–1.56) | 0.769 |
| LTG/VPA/PER | 48 | 12.5 (8.3–23.3) | 26 (54.2%) | 7 (14.6%) | 3 (6.3%) | 0.67 (0.26–1.07) | *0.016* | 0 (0.0%) | 0.67 (0.25–1.22) | 0.17 | 3 (10%) | 0.61 (0.22–1.01) | *0.045* |
| LTG/VPA/CBZ | 41 | 22 (9.5–49.0) | 30 (73.2%) | 4 (9.8%) | 2 (4.9%) | 0.78 (0.47–1.08) | 0.069 | 0 (0.0%) | 0.5 (0.25–1.44) | 0.345 | 2 (5.7%) | 0.79 (0.54–1.13) | 0.126 |
| LTG/VPA/LEV | 39 | 12 (8.0–22.0) | 23 (59.0%) | 8 (20.5%) | 5 (12.8%) | 0.63 (0.21–1.04) | *0.001*** | 2 (14.3%) | 0.36 (0.19–1.22) | 0.096 | 3 (12.0%) | 0.69 (0.19–1.00) | *0.004** |
| LTG/VPA/LCM | 37 | 12 (6.0–22.5) | 19 (51.4%) | 4 (10.8%) | 0 (0.0%) | 0.91 (0.31–1.31) | 0.371 | 0 (0.0%) | 1.07 (0.83–1.24) | 0.612 | 0 (0.0%) | 0.95 (0.38–1.63) | 0.922 |
| VPA/OXC/LEV | 19 | 13 (6.0–24.0) | 11 (57.9%) | 2 (10.5%) | 1 (5.3%) | 1.00 (0.79–1.75) | 0.492 | 0 (0.0%) | 1.04 (0.89–1.84) | 0.285 | 1 (11.1) | 1.00 (0.23–1.63) | 0.866 |
| VPA/OXC/TPM | 12 | 8.5 (6.0–18.0) | 4 (33.3%) | 0 (0.0%) | 0 (0.0%) | 1.16 (0.96–1.64) | 0.117 | 0 (0.0%) | 1.14 (0.52–2.65) | 0.465 | 0 (0.0%) | 1.16 (1.01–1.44) | *0.036* |
| LTG/VPA/PB | 10 | 11.5 (7.8–36.3) | 5 (50.0%) | 1 (10.0%) | 0 (0.0%) | 0.92 (0.65–1.29) | 0.441 | 0 (0.0%) | 0.76 (0.51–1.00) | 0.317 | 0 (0.0%) | 0.92 (0.70–1.39) | 0.779 |
| OXC/TPM/PER | 9 | 8 (5.0–19.5) | 3 (33.3%) | 1 (11.1%) | 0 (0.0%) | 1.48 (0.84–3.47) | 0.139 | 0 (0.0%) | 2.91 (1.48–3.53) | 0.109 | 0 (0.0%) | 0.96 (0.66–3.67) | 0.753 |
| Others# | 147 | 11 (6.0–19.0) | 66 (44.9%) | 18 (12.2%) | 14 (9.5%) | / | / | 6 (13.3%) | / | / | 8 (8.2%) | / | / |
| Total | 511 | 12 (7.0–24.0) | 290 (56.8%) | 73 (14.3%) | 48 (9.4%) | / | / | 10 (6.9%) | / | / | 38 (10.4%) | / | / |

Abbreviations: SF, seizure freedom; SFR, seizure frequency ratio; LTG, Lamotrigine; VPA, Valproic acid; TPM, Topiramate; OXC, Oxcarbazepine; PER, Perampanel; CBZ, Carbamazepine; LEV, Levetiracetam; LCM, Lacosamide; PB, Phenobarbital. Children were patients aged under 18 years old at the last clinical visit, and adults were patients aged 18 years and older. #The remaining 66 different three-drug combination regimens. ***P < 0.001 after adjusted by Benjamini-Hochberg method (BH method); **P < 0.01 after adjusted by BH method; *P < 0.05 after adjusted by BH method.

VPA/TPM and LTG/VPA/LEV using survival analysis with the log-rank test. From the cumulative incidence curves, we found no difference in the cumulative probability of SF between the two regimens (P = 0.452). However, the retention of LTG/VPA/TPM was significantly longer than that of LTG/VPA/LEV (P = 0.031), as shown in the Kaplan-Meier curves (Supplementary Fig. 3).

*Factors related to treatment effectiveness*

Table 3 shows the factors related to the efficacy of LTG/VPA/TPM and LTG/VPA/LEV. An SFR<0.5 represented the group with superior efficacy, while an SFR≥0.5 represented the group with inferior efficacy. In the LTG/VPA/TPM group, an SFR<0.5 was associated with no history of status epilepticus (P = 0.030) or a single type of seizure (P = 0.002). Focal impaired awareness seizures were associated with an SFR≥0.5 (P = 0.012). In the LTG/VPA/LEV group, fewer ASM regimens were used before triple therapy (P = 0.046), and the absence of comorbidities (P = 0.049) was associated with an SFR<0.5. Variables associated with the use of LTG/VPA/TPM and LTG/VPA/LEV are shown in Supplementary Table 3. Patients with a history of febrile seizures (P = 0.042), multiple seizure types (P = 0.019), or a greater number of ASM regimens before triple therapy (P = 0.014) were more likely to use LTG/VPA/TPM. Patients with a structural etiology (P = 0.010) and abnormal head MRI (P = 0.012) were more likely to receive LTG/VPA/LEV.

*Prescription dosage and side effects of various triple combination therapies*

As presented in Table 4, among the top 10 most frequently prescribed triple combinations, the highest overall drug load was observed for VPA/OXC/LEV (2.47 ± 0.55), and the lowest was observed for LTG/VPA/TPM (1.42 ± 0.30). For LTG/VPA/TPM, the median prescribed dose was 200 mg/day for LTG, 500 mg/day for VPA, and 100 mg/day for TPM. The overall drug load for LTG/VPA/LEV was 1.81 ± 0.39, with a median prescribed dose of 150 mg/day for LTG, 750 mg/day for VPA, and 1000 mg/day for LEV. The triple regimens that had the highest total side effects were LTG/VPA/PB (60.0%, 6/10), followed by LTG/VPA/TPM (53.7%, 51/95). The highest incidence of regimen-specific side effects was observed in LTG/VPA/PB (40.0%, 4/10), followed by LTG/VPA/PER (31.3%, 15/48). The side effects of LTG/VPA/LEV were relatively minimal, with only 5.1% (2/39) of patients experiencing regimen-specific side effects during the period of usage (Fig. 2). Supplementary Fig. 4 displays the detailed proportions of various regimen-specific side effects associated with triple therapies, where at least four patients reported such side effects. The figure shows that the most common side effect of LTG/VPA/TPM was poor appetite (36.8%, 7/19). Shaky hands was the most common side effect for LTG/VPA/OXC (57.1%, 4/7). Dizziness (33.3%, 5/15) and weight gain (33.3%, 5/15) were the most prevalent side effects of LTG/VPA/PER. The average overall drug load of all triple therapies was 1.6 ± 0.4 (not shown) in adult patients, and there was no difference in the average overall drug load between patients who experienced regimen-specific side effects during the usage of triple regimens and those who did not (1.69 vs. 1.61, P = 0.221; not shown).

## Discussion

With over 20 approved ASMs available on the market [13], there are more than 10,000 potential combinations of three drugs. Conducting rigorous drug trials to assess the efficacy of all these combination regimens is impractical. In this context, real-world studies provide a viable approach to comprehensively evaluate the drug regimens used by patients. In this study, a total of 511 three-drug trials involving 76 different drug combinations were conducted among 323 enrolled patients with DRE. Forty-eight patients (14.9%) achieved SF in these three-drug trials. After analyzing the seizure-free rate and within-patient SFR, we found that LTG/VPA/TPM and LTG/VPA/LEV showed significantly superior efficacy in patients with refractory focal epilepsy, especially in adult patients. In addition, LTG/VPA/PER displayed promising trends toward good efficacy in terms of the SFR.

ASMs affect fundamental brain excitability mechanisms to suppress abnormal hyperexcitability and hypersynchronized discharge in brain circuits [22]. The main mechanisms of action of ASMs include regulating voltage-gated ion channels (e.g., CBZ and LTG), antagonizing excitatory receptors (e.g., PER), enhancing inhibitory neurotransmission (e.g., PB), and modulating synaptic release (e.g., LEV). Some ASMs, such as VPA

**Table 3**
Variables associated with the efficacy of LTG/VPA/TPM and LTG/VPA/LEV.

| Variables | LTG/VPA/TPM | | | P | LTG/VPA/LEV | | | P |
|---|---|---|---|---|---|---|---|---|
| | Total (95) | SFR≥0.5 (42) | SFR<0.5 (53) | | Total (39) | SFR≥0.5 (21) | SFR<0.5 (18) | |
| Sex | | | | 1.000 | | | | 0.742 |
| Male | 49 (51.6%) | 22 (52.4%) | 27 (50.9%) | | 24 (61.5%) | 12 (57.1%) | 12 (66.7%) | |
| Female | 46 (48.4%) | 20 (47.6%) | 26 (49.1%) | | 15 (38.5%) | 9 (42.9%) | 6 (33.3%) | |
| Age at epilepsy onset, ≥18 years old | 23 (24.2%) | 13 (31.0%) | 10 (18.9%) | 0.229 | 15 (38.5%) | 8 (38.1%) | 7 (38.9%) | 1.000 |
| Age at the last follow-up, ≥18 years old | 84 (88.4%) | 37 (88.1%) | 47 (88.7%) | 1.000 | 25 (64.1%) | 15 (71.4%) | 10 (55.6%) | 0.337 |
| Epilepsy related history before the index regimen | | | | | | | | |
| First-degree family history of epilepsy | 2 (2.1%) | 1 (2.4%) | 1 (1.9%) | 1.000 | 1 (2.6%) | 0 (0.0%) | 1 (5.6%) | 0.462 |
| History of febrile convulsions | 18 (18.9%) | 9 (21.4%) | 9 (17.0%) | 0.608 | 4 (10.3%) | 1 (4.8%) | 3 (16.7%) | 0.318 |
| History of status epilepticus | 12 (12.6%) | 9 (21.4%) | 3 (5.7%) | *0.030* | 11 (28.2%) | 8 (38.1%) | 3 (16.7%) | 0.171 |
| Etiology | | | | 0.408 | | | | 1.000 |
| Non-structural | 44 (46.3%) | 17 (40.5%) | 27 (50.9%) | | 11 (28.2%) | 6 (28.6%) | 5 (27.8%) | |
| Structural | 51 (53.7%) | 25 (59.5%) | 26 (49.1%) | | 28 (71.8%) | 15 (71.4%) | 13 (72.2%) | |
| Seizure types during the index regimen | | | | | | | | |
| Focal aware seizures | 15 (15.8%) | 3 (7.1%) | 12 (22.6%) | 0.049 | 9 (23.1%) | 7 (33.3%) | 2 (11.1%) | 0.207 |
| Focal impaired awareness seizures | 74 (77.9%) | 38 (90.5%) | 36 (67.9%) | 0.012 | 22 (56.4%) | 12 (57.1%) | 10 (55.6%) | 1.000 |
| Focal to bilateral tonic–clonic seizures | 46 (48.4%) | 23 (54.8%) | 23 (43.4%) | 0.306 | 24 (61.5%) | 11 (52.4%) | 13 (72.2%) | 0.323 |
| Multiple seizure types | 50 (52.6%) | 30 (71.4%) | 20 (37.7%) | *0.002* | 17 (43.6%) | 10 (47.6%) | 7 (38.9%) | 0.748 |
| Number of ASMs regimens tried before triple therapy | 3 (2–4) | 3 (2–4) | 3 (2–3) | 0.514 | 2 (2–3) | 3 (2–3) | 2 (2–2.3) | *0.046* |
| At least one seizure per month before treatment | 56 (58.9%) | 25 (59.5%) | 31 (58.5%) | 1.000 | 20 (51.3%) | 10 (47.6%) | 10 (55.6%) | 0.751 |
| Comorbidities existed before the index regimen | 26 (27.4%) | 11 (26.2%) | 15 (28.3%) | 1.000 | 16 (41.0%) | 12 (57.1%) | 4 (22.2%) | *0.049* |
| Epileptiform discharges of EEG before the index regimen | 65 (68.4%) | 28 (66.7%) | 37 (69.8%) | 0.825 | 29 (74.4%) | 15 (71.4%) | 14 (77.8%) | 0.726 |
| The most recent result of Head MRI before the last clinical visit | | | | 0.348 | | | | 0.464 |
| Normal | 30 (31.6%) | 10 (23.8%) | 20 (37.7%) | | 9 (23.1%) | 6 (28.6%) | 3 (16.7%) | |
| Abnormal | 57 (60.0%) | 28 (66.7%) | 29 (54.7%) | | 30 (76.9%) | 15 (71.4%) | 15 (83.3%) | |
| Unknown | 8 (8.4%) | 4 (9.5%) | 4 (7.5%) | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |

**Table 4**
Prescription dosages and the overall drug load of the 10 most frequently prescribed three-drug combination regimens.

| Combination | No. | ≥18 years[a] | The prescribed dose of the first ASM[a], M (IQR) | The prescribed dose of the second ASM[a], M (IQR) | The prescribed dose of the third ASM[a], M (IQR) | Overall drug load[a], Mean ± SD | Patients with side effects# | Patients with side effects[a]# |
|---|---|---|---|---|---|---|---|---|
| LTG/VPA/TPM | 95 | 73 (76.8%) | 200 (175–200) | 500 (500–1000) | 100 (100–100) | 1.42 ± 0.30 | 51 (53.7%) | 41 (56.2%) |
| LTG/VPA/OXC | 54 | 29 (53.7%) | 100 (100–150) | 750 (500–750) | 600 (450–900) | 1.55 ± 0.33 | 24 (44.4%) | 15 (51.7%) |
| LTG/VPA/PER | 48 | 28 (58.3%) | 200 (150–225) | 750 (563–1000) | 6 (6–6) | 1.89 ± 0.41 | 24 (50.0%) | 17 (60.7%) |
| LTG/VPA/CBZ | 41 | 32 (78.0%) | 200 (100–200) | 775 (500–1000) | 325 (200–500) | 1.44 ± 0.31 | 16 (39.0%) | 15 (46.9%) |
| LTG/VPA/LEV | 39 | 24 (61.5%) | 150 (100–200) | 750 (500–1000) | 1000 (1000–1500) | 1.81 ± 0.39 | 11 (28.2%) | 7 (29.2%) |
| LTG/VPA/LCM | 37 | 27 (73.0%) | 200 (200–200) | 750 (500–1000) | 200 (150–200) | 1.69 ± 0.33 | 19 (51.4%) | 15 (55.6%) |
| VPA/OXC/LEV | 19 | 9 (47.4%) | 1000 (750–1000) | 1050 (750–1200) | 1500 (1000–1500) | 2.47 ± 0.55 | 5 (26.3%) | 4 (44.4%) |
| VPA/OXC/TPM | 12 | 6 (50.0%) | 500 (500–625) | 900 (563–975) | 100 (69–131) | 1.55 ± 0.26 | 5 (41.7%) | 3 (50.0%) |
| LTG/VPA/PB | 10 | 8 (80.0%) | 225 (150–250) | 875 (563–1000) | 60 (34–98) | 1.88 ± 0.35 | 6 (60.0%) | 5 (62.5%) |
| OXC/TPM/PER | 9 | 6 (66.7%) | 600 (563–900) | 113 (63–131) | 6 (6–7) | 1.80 ± 0.36 | 3 (33.3%) | 2 (33.3%) |

[a] Patients aged ≥18 years at the beginning usage of the index regimen, and the subsequent data on ASMs dosages and overall drug loads were derived from this population. The terms "first," "second," and "third" ASM in the table correspond to the ASM listed in sequential order in the "Combination" column. For example, in "LTG/VPA/TPM", LTG is the first ASM, VPA is the second ASM, and TPM is the third ASM. In "VPA/OXC/LEV", VPA is the first ASM, OXC is the second ASM, and LEV is the third ASM. [#]The total side effects that existed during the usage of the index regimen.

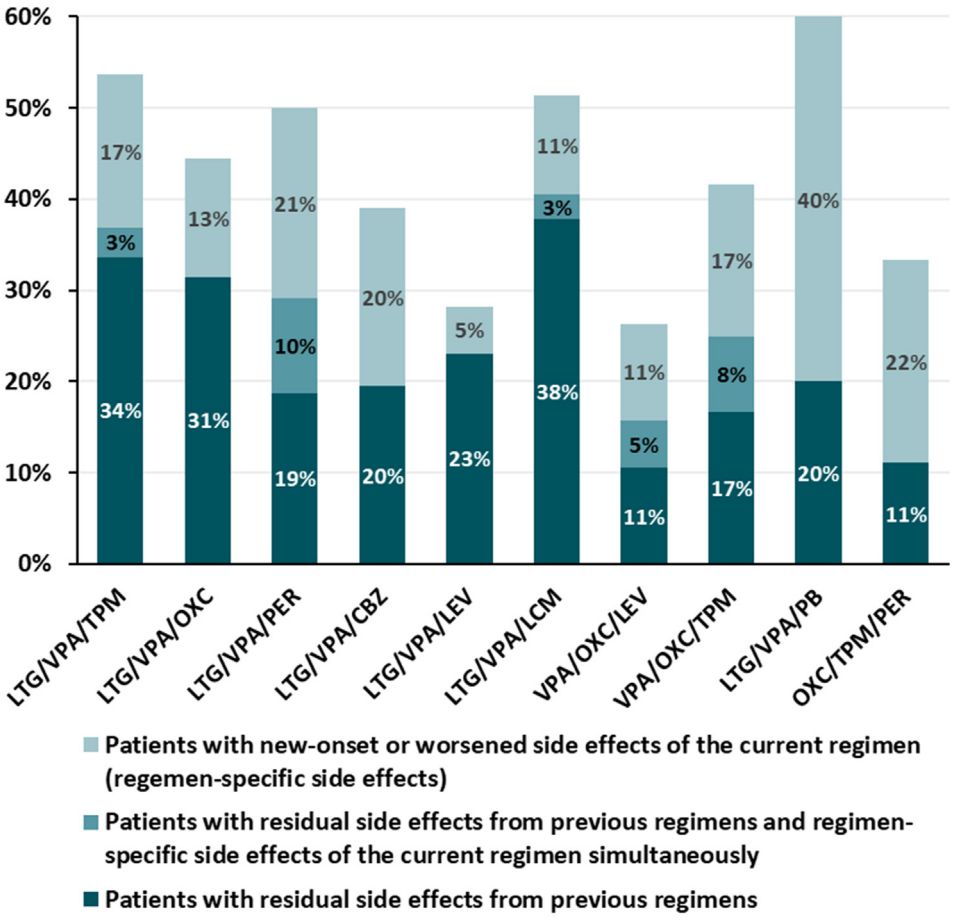


**Fig. 2.** Patient-reported side effects of the top 10 commonly used three-drug combination regimens.

and TPM, act via mixed or unknown mechanisms [22]. Researchers have suggested the use of ASMs with diverse mechanisms of action in polytherapy to enhance seizure management, and broad-spectrum ASMs are particularly well suited for combination therapy [23]. This concept bears similarities to the "target" hypothesis, which is one of the hypotheses concerning the mechanism of DRE [24]. The hypothesis suggests that acquired or genetic alterations in ASM target proteins contribute to decreased treatment sensitivity [25]. Combining ASMs with different mechanisms of action may have a greater likelihood of covering different "targets". Clearly, the optimal regimens identified in our study, including LTG/VPA/TPM, LTG/VPA/LEV, and LTG/VPA/PER, are combinations of drugs with distinct mechanisms of action. Many large-scale clinical studies have confirmed the efficacy of LTG/VPA [7,11,26]. The efficacy of these two drugs was partially explained by the pharmacokinetic effect of VPA on LTG through a reduction in hepatic clearance and, more importantly, by the synergistic action of the mechanisms of the two drugs [11,26]. In addition to LTG/VPA, LTG/TPM [8] and LEV/VPA [27,28] exhibited synergistic effects. Therefore, considering our research findings, we speculate that the combinations of TPM or LEV with LTG/VPA may also exhibit undisclosed synergistic effects. Another deeply explored theory of DRE is the "transporter" hypothesis, which suggests that increased expression or modification of efflux transporters such as P-glycoprotein (P-gp) at the blood–brain barrier decreases the effective concentrations of ASMs at their targets [25]. VPA and LTG appear to inhibit P-gp [29,30], whereas TPM and LEV have been proven to be substrates of P-gp [31,32]. Interestingly, the use of LTG and TPM does not increase the expression of P-gp [33]. Therefore, combining TPM or LEV with VPA and LTG may increase the bioavailability of TPM and LEV, which could also partially explain the improved efficacy observed in LTG/VPA/TPM and LTG/VPA/LEV. From another perspective, the combination of LTG/VPA/TPM may indirectly aid in the control of epilepsy by managing comorbidities, such as migraines [34]. Given the intricate and incompletely understood mechanisms of refractory epilepsy and ASMs, further investigations are warranted.

Side effects and dosage are other concerning aspects in polytherapy. The rate of regimen-specific adverse effects in LTG/VPA/TPM was 20%, that in LTG/VPA/PER was 31%, and that in LTG/VPA/LEV was 5%. In a previous study, the incidence of side effects after the addition of LTG to VPA-containing regimens was 38% [35]. These findings indicate that the coadministration of TPM, LEV, or PER with LTG/VPA might not yield a significant additive effect of side effects, possibly due to the distinct mechanisms of action associated with these medications. The relationship between drug load and side effects remains controversial. A review by Deckers et al. [20] suggested that ASM toxicity might be more related to the overall drug load than to the number of prescribed ASMs. While Canevini et al. [19] reported no correlation between patient-reported adverse effects or adverse event profile (AEP) questionnaire scores and the total load of ASMs. Consistent with the findings of Canevini et al., in our study, no relationship was observed between regimen-specific side effects during triple therapy and overall drug load in adult patients. However, the drug load of triple therapy was lower in our study ($1.6 \pm 0.4$) than in that of Canevini ($3.7 \pm 1.1$) [19]. This difference may be attributed to the inherent variations among patients and discrepancies in prescribing habits among physicians.

Our study has several limitations. First, this was a single-center retrospective study. The classic perspective on the synergistic therapeutic effect of LTG/VPA, along with the limited availability of ASMs, may restrict the adoption of new, potentially effective drug combinations (e.g., clobazam/LTG/LEV [12]) in real-world single-center clinical practice. The retrospective design of this study may have led to bias in the data collection and difficulty in controlling for potential confounding variables. However, our data were extracted from well-documented longitudinal medical records of patients, which may have reduced recall bias for important information such as seizure frequency, seizure type, and drug dose. In addition, the comparison of within-patient SFRs eliminated the variability in seizure frequency among patients [11], increasing the reliability of the results. And the description of epilepsy-related details and age group analysis might have partially controlled for confounding factors. Second, epilepsy is a complex disorder that can cause neurobiological, cognitive, psychological, and social consequences [36]. We focused solely on seizure frequency and did not conduct a comprehensive evaluation of quality of life, cognition, or other aspects, which may not provide a complete representation of the overall condition of these patients. However, seizure frequency is a major concern for PWEs and has a major impact on their quality of life [37,38]. In previous studies, a 50% reduction in seizure frequency or the achievement of SF was often used as the primary outcome measure [39,40]. Third, we did not measure blood drug concentrations, and the assessment of side effects relied mainly on patient self-reports without the use of structured questionnaires. This may have led to inaccuracies in the estimation of the actual drug load and patient adherence. The assessment of side effects based on doctor inquiries and patient self-reports may have underestimated the incidence rate of certain short-term and mild side effects. Finally, in the subgroup analysis evaluating the efficacy and side effects of different triple regimens, the sample sizes in some individual subgroups were relatively small, possibly compromising the statistical power. To establish a robust foundation for the application of diverse combinations, multicenter prospective clinical studies with larger sample sizes and extensive pharmacological research are needed.

In conclusion, approximately 15% of patients with refractory focal epilepsy achieved seizure freedom under three-drug combination therapies, with LTG/VPA/TPM and LTG/VPA/LEV showing notable efficacy. For patients with DRE who have not responded to dual therapy, rational selection of triple therapy may improve their prognosis. However, importantly, personalized factors should still be accounted for when considering the utilization of these treatment plans.

## Author contributions

Chunmei Wu designed the study, acquired data, performed the analysis and drafted the manuscript; Huiting Wu and Yingying Zhou undertook data collection and interpreted of the data; Xiaoyan Liu designed and conceptualized study; Shanshan Huang and Suiqiang Zhu led the study, provided critical intellectual input in the study's conceptualization, and critically reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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## Availability of data and material

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2024.e00345.

## References


[1] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018 Mar 1;75:279–86. https://doi.org/10.1001/jamaneurol.2017.3949.

[2] Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007 Oct;62:375–81. https://doi.org/10.1002/ana.21064.

[3] Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. J Neurol Neurosurg Psychiatry 2012 Aug;83:810–3. https://doi.org/10.1136/jnnp-2011-302085.

[4] Moeller JJ, Rahey SR, Sadler RM. Lamotrigine-valproic acid combination therapy for medically refractory epilepsy. Epilepsia 2009 Mar;50:475–9. https://doi.org/10.1111/j.1528-1167.2008.01866.x.

[5] Stephen LJ, Brodie MJ. Seizure freedom with more than one antiepileptic drug. Seizure 2002 Sep;11:349–51. https://doi.org/10.1053/seiz.2002.0711.

[6] Stephen LJ, Forsyth M, Kelly K, Brodie MJ. Antiepileptic drug combinations–have newer agents altered clinical outcomes? Epilepsy Res 2012 Feb;98:194–8. https://doi.org/10.1016/j.eplepsyres.2011.09.008.

[7] Pisani F, Oteri G, Russo MF, Di Perri R, Perucca E, Richens A. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. Epilepsia 1999 Aug;40:1141–6. https://doi.org/10.1111/j.1528-1157.1999.tb00832.x.

[8] Stephen LJ, Sills GJ, Brodie MJ. Lamotrigine and topiramate may be a useful combination. Lancet 1998 Mar 28;351:958–9. https://doi.org/10.1016/S0140-6736(05)60613-7.

[9] Florek-Luszczki M, Wlaz A, Luszczki JJ. Interactions of levetiracetam with carbamazepine, phenytoin, topiramate and vigabatrin in the mouse 6Hz psychomotor seizure model - a type II isobolographic analysis. Eur J Pharmacol 2014 Jan 15;723:410–8. https://doi.org/10.1016/j.ejphar.2013.10.063.

[10] Steinhoff BJ, Maren Staack A, Wisniewski I. Seizure control with antiepileptic drug therapy in 517 consecutive adult outpatients at the Kork Epilepsy Centre. Epileptic Disord 2012 Dec;14:379–87. https://doi.org/10.1684/epd.2012.0544.

[11] Poolos NP, Warner LN, Humphreys SZ, Williams S. Comparative efficacy of combination drug therapy in refractory epilepsy. Neurology 2012 Jan 3;78:62–8. https://doi.org/10.1212/WNL.0b013e31823ed0dd.

[12] Legge AW, Detyniecki K, Javed A, Hirsch LJ, Kato K, Buchsbaum R, et al. Comparative efficacy of unique antiepileptic drug regimens in focal epilepsy: an exploratory study. Epilepsy Res 2018 May;142:73–80. https://doi.org/10.1016/j.eplepsyres.2018.03.011.

[13] Verrotti A, Tambucci R, Di Francesco L, Pavone P, Iapadre G, Altobelli E, et al. The role of polytherapy in the management of epilepsy: suggestions for rational antiepileptic drug selection. Expert Rev Neurother 2020 Feb;20:167–73. https://doi.org/10.1080/14737175.2020.1707668.

[14] Abou-Khalil B. Selecting rational drug combinations in epilepsy. CNS Drugs 2017 Oct;31:835–44. https://doi.org/10.1007/s40263-017-0471-7.

[15] Lattanzi S, Trinka E, Zaccara G, Striano P, Russo E, Del Giovane C, et al. Third-generation antiseizure medications for adjunctive treatment of focal-onset seizures in adults: a systematic review and network meta-analysis. Drugs 2022 Feb;82:199–218. https://doi.org/10.1007/s40265-021-01661-4.

[16] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010 Jun;51:1069–77. https://doi.org/10.1111/j.1528-1167.2009.02397.x.

[17] Klein P, Aboumatar S, Brandt C, Dong F, Krauss GL, Mizne S, et al. Long-term efficacy and safety from an open-label extension of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology 2022 Jun 15;99:e989–98. https://doi.org/10.1212/WNL.0000000000200792.

[18] Labate A, Fortunato F, Giugno A, Martino I, Caligiuri ME, Gambardella A. Perampanel as first add-on choice on the treatment of mesial temporal lobe epilepsy: an observational real-life study. Neurol Sci 2021 Apr;42:1389–94. https://doi.org/10.1007/s10072-020-04636-7.

[19] Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, et al. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia 2010 May;51:797–804. https://doi.org/10.1111/j.1528-1167.2010.02520.x.

[20] Deckers CL, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia 1997 May;38:570–5. https://doi.org/10.1111/j.1528-1157.1997.tb01142.x.

[21] Kwan P, Brodie MJ. Refractory epilepsy: mechanisms and solutions. Expert Rev Neurother 2006 Mar;6:397–406. https://doi.org/10.1586/14737175.6.3.397.

[22] Sills GJ, Rogawski MA. Mechanisms of action of currently used antiseizure drugs. Neuropharmacology 2020 May 15;168:107966. https://doi.org/10.1016/j.neuropharm.2020.107966.

[23] Kwan P, Brodie MJ. Combination therapy in epilepsy: when and what to use. Drugs 2006;66:1817–29. https://doi.org/10.2165/00003495-200666140-00004.

[24] Perucca E, Perucca P, White HS, Wirrell EC. Drug resistance in epilepsy. Lancet Neurol 2023 Aug;22:723–34. https://doi.org/10.1016/S1474-4422(23)00151-5.

[25] Remy S, Beck H. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. Brain 2006 Jan;129:18–35. https://doi.org/10.1093/brain/awh682.

[26] Brodie MJ, Yuen AW. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. Epilepsy Res 1997 Mar;26:423–32. https://doi.org/10.1016/s0920-1211(96)01007-8.

[27] Dudra-Jastrzebska M, Andres-Mach MM, Ratnaraj N, Patsalos PN, Czuczwar SJ, Luszczki JJ. Isobolographic characterization of the anticonvulsant interaction profiles of levetiracetam in combination with clonazepam, ethosuximide, phenobarbital and valproate in the mouse pentylenetetrazole-induced seizure model. Seizure 2009 Nov;18:607–14. https://doi.org/10.1016/j.seizure.2009.06.009.

[28] Wojda E, Wlaz A, Patsalos PN, Luszczki JJ. Isobolographic characterization of interactions of levetiracetam with the various antiepileptic drugs in the mouse 6 Hz psychomotor seizure model. Epilepsy Res 2009 Oct;86:163–74. https://doi.org/10.1016/j.eplepsyres.2009.06.003.

[29] Patel KA, Bhatt MH, Hirani RV, Patel VA, Patel VN, Shah GB, et al. Assessment of potential drug-drug interactions among outpatients in a tertiary care hospital: focusing on the role of P-glycoprotein and CYP3A4 (retrospective observational study). Heliyon 2022 Nov;8:e11278. https://doi.org/10.1016/j.heliyon.2022.e11278.

[30] Weiss J, Kerpen CJ, Lindenmaier H, Dormann SM, Haefeli WE. Interaction of antiepileptic drugs with human P-glycoprotein in vitro. J Pharmacol Exp Therapeut 2003 Oct;307:262–7. https://doi.org/10.1124/jpet.103.054197.

[31] Luna-Tortós C, Rambeck B, Jürgens UH, Löscher W. The antiepileptic drug topiramate is a substrate for human P-glycoprotein but not multidrug resistance proteins. Pharm Res (N Y) 2009 Nov;26:2464–70. https://doi.org/10.1007/s11095-009-9961-8.

[32] Behmard E, Barzegari E, Najafipour S, Kouhpayeh A, Ghasemi Y, Asadi-Pooya AA. Efflux dynamics of the antiseizure drug, levetiracetam, through the P-glycoprotein channel revealed by advanced comparative molecular simulations. Sci Rep 2022 Aug 11;12:13674. https://doi.org/10.1038/s41598-022-17994-3.

[33] Wang-Tilz Y, Tilz C, Wang B, Tilz GP, Stefan H. Influence of lamotrigine and topiramate on MDR1 expression in difficult-to-treat temporal lobe epilepsy. Epilepsia 2006 Feb;47:233–9. https://doi.org/10.1111/j.1528-1167.2006.00414.x.

[34] Romoli M, Costa C, Siliquini S, Corbelli I, Eusebi P, Bedetti C, et al. Antiepileptic drugs in migraine and epilepsy: who is at increased risk of adverse events? Cephalalgia 2018 Feb;38:274–82. https://doi.org/10.1177/0333102416683925.

[35] Faught E, Morris G, Jacobson M, French J, Harden C, Montouris G, et al. Adding lamotrigine to valproate: incidence of rash and other adverse effects. Postmarketing Antiepileptic Drug Survey (PADS) Group. Epilepsia 1999 Aug;40:1135–40. https://doi.org/10.1111/j.1528-1157.1999.tb00831.x.

[36] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the international League against epilepsy (ILAE) and the international bureau for epilepsy (IBE). Epilepsia 2005 Apr;46:470–2. https://doi.org/10.1111/j.0013-9580.2005.66104.x.

[37] Baranowski CJ. The quality of life of older adults with epilepsy: a systematic review. Seizure 2018 Aug;60:190–7. https://doi.org/10.1016/j.seizure.2018.06.002.

[38] Guekht AB, Mitrokhina TV, Lebedeva AV, Dzugaeva FK, Milchakova LE, Lokshina OB, et al. Factors influencing on quality of life in people with epilepsy. Seizure 2007 Mar;16:128–33. https://doi.org/10.1016/j.seizure.2006.10.011.

[39] Bresnahan R, Hill RA, Wang J. Perampanel add-on for drug-resistant focal epilepsy. Cochrane Database Syst Rev 2023 Apr 14;4:Cd010961. https://doi.org/10.1002/14651858.CD010961.pub2.

[40] Manral M, Dwivedi R, Gulati S, Kaur K, Nehra A, Pandey RM, et al. Safety, efficacy, and tolerability of modified atkins diet in persons with drug-resistant epilepsy: a randomized controlled trial. Neurology 2023 Mar 28;100:e1376–85. https://doi.org/10.1212/WNL.0000000000206776.