Role of Etifoxine as an Adjunctive Treatment in Patients with Drug-Resistant Epilepsy with Comorbid Anxiety Symptoms

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Abstract

Objective: Drug-resistance epilepsy affects quality of life, researchers aimed to determine the role of etifoxine, a class of Benzoxazines (non-Benzodiazepines) GABA-A receptor agonist, as an adjunctive treatment in patients with drug-resistant epilepsy who had anxiety comorbidity.

Materials and Method: This was a randomized single-blind placebo-controlled study. Patients with drug resistant focal epilepsies treated at Phramongkutklao Hospital were invited to participate. The patients received etifoxine (50 mg) 2 capsules BID or matched placebo and follow up for 12 weeks. Questionnaires including Hamilton Anxiety Rating Scale; (HAM-A), depression (Patient Health Questionaire-9 Thai version; PHQ-9T), and quality of life (Patient Weighted Quality of Life in Epilepsy-10; QOLIE-10) were completed at baseline, and subsequent visits. In addition, seizure diaries were collected in order to determine seizure frequency.

Result: Total of 40 patients met selection criteria: intervention group (n 20), and placebo group (n 20). Mean age of the etifoxine group was 35.06 years old, while the placebo group was 33.94 years old, *p*-value 0.666. Male in the etifoxine group was 9 (52.9 %), and the placebo group was10 (58.8 %), *p*-value 0.730. In etifoxine group, HAM-A score was significantly reduced from 16.0 (baseline) to 12.2 (visit 5), *p*-value 0.009, while the score didn't reach statistically significant reduction in the placebo group, 13.2 (baseline) to 11.8 (visit 5), *p*-value 0.279. The anxiety reduction was significantly reduced in subgroup for fear for the etifoxine group, baseline 1.7 to 0.7, *p*-value 0.035. There was no significant difference for the improvement of

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depression, quality of life and seizure controls between the etifoxine group and the placebo groups. Etifoxine was safe in the epilepsy population.

Conclusion: Etifoxine for patients with drug-resistant epilepsy (DRE) reduced HAM-anxiety score over the study time, which the benefits appeared especially on fear and sleep subtypes of anxiety.

Keywords: drug resistance focal epilepsy, etifoxine, anxiety, HAM-A, PHQ9, QOLIE-10

Introduction

Epilepsy is a high prevalent neurological disorder that affects people of all ages and lives all around the world. Patients with epilepsy are three times more fatality rate than the general population.[1] Furthermore, they are 2-3 times more likely than those without epilepsy to have mental disorders, including anxiety and sadness.[2-4] Their bidirectional effects, such psychological issues might increase seizure frequency or severity. As a result, assessing anxiety or depression is critical in epilepsy and should not be overlooked.[5] According to several previous studies[3,6], anxiety affects 28 percent of people. Drug-resistant epilepsy (DRE) has a higher prevalence than epilepsy that is adequately managed.[7] In two investigations conducted in Thailand, anxiety in epilepsy was shown to be 5.3 percent[8] and 39 percent[9]. Female gender, unemployment, focal onset epilepsy, stigma, extended duration of medication resistant epilepsy, and high seizure frequency are all risk factors for anxiety in Thai epilepsy patients.[10,11]

Treatment-resistance epilepsy affects quality of life. Therefore, further medical studies are needed. Most of the patients experience anxiety symptoms and this can aggravate seizures. Higher anxiety results in the decreased level of various neurotrophic factors and impaired production of proinflammatory cytokines. The anxiolytic etifoxine used to treat anxiety states and adjustment disorder, a class of Benzoxazines (non-Benzodiazepines), acts as a dual-mechanism against GABAergic transmission through activation of GABA-A at β_2/β_3 subunit position (positive allosteric modulation; PAM) and induces the creation of neuroactive steroid (NAS) such as allopregnanolone through activation of translocator protein (TSPO) at the cell membrane in the mitochondria, where the neuroactive steroid is also a positive allosteric modulation at the GABA-A receptor. From such a mechanism it is likely to be synergistic affects the function of the GABAergic neurotransmission system for better. Therefore, researchers aimed to study the role of this drug as the adjunctive treatment in drug-resistant focal epileptic patients with comorbid anxiety symptoms.

Materials and Methods

Primary objectives

1. To study the reduction of anxiety and depression scores using HAM-A

Secondary objectives

1. To study the improvement of depressive symptoms measuring by PHQ-9 and the quality of life of epilepsy patients by QOLIE-10 in Thai version

2. To determine seizure reduction and safety of the treatment

Study design and study period

This study is a randomized single-blind placebo controlled, conducted from July 2021 to December 2022. Patients with drug resistant focal epilepsies treated at Division of Neurology,

Department of Medicine, Phramongkutklao Hospital were invited to participate.

Patient selection

Inclusion criteria

1. Age ≥ 20 years old
2. Diagnosed with medically resistant "focal" epilepsy

- Average seizure frequency ≥ 3 times/ month, determine from the past 3 months
- Taking at least 2 antiepileptic drugs (AEDs) "or" expose to at least 2 sequential monotherapies, with proper dosage and good compliance

3. Comorbid mild-to-severe anxiety symptoms: defined as HAM-A score of 1-30
4. Can maintainable the same concomitant AEDs, other neuropsychiatric medications, and hormonal medications with stable dosage throughout the study from 1 month before the study to entire 3 months after the enrolment
5. In reproductive potential patients, must accept to use at least one method of birth control

Exclusion criteria

1. Any history or presence of hepatic diseases
2. Myasthenia gravis
3. Patients with congenital galactosemia, glucose and galactose malabsorption syndrome or lactase deficit
4. Inability or difficulty swallowing whole capsule
5. History of alcohol abuse
6. Pregnancy, lactation, and plan to conceive
7. Simultaneous participant to a clinical trial or in exclusion period of a previous clinical trial
8. Any conditions or personal circumstances that, in the opinion of investigator, renders the subject unlikely or unable to comply with the full study protocol
9. Currently taking ≥ 2 antidepressants
10. Currently taking "ONLY 1" benzodiazepine but the dosage is very high: alprazolam (10 mg/d), diazepam (40 mg/d), chlordiazepoxide (100 mg/d), clobazam (40 mg/d), clonazepam (40 mg/d), flunitrazepam (2 mg/d), lorazepam (10 mg/d), midazolam (20 mg/d)
11. Currently taking morphine or its derivative, antipsychotic agents, recreational agents: CBD, etc., herbal medicines (Withdrawal period must be at least 3 months before screening.)
12. History of poor medication adherence
13. Advanced cancer or severe medical conditions
14. Severe psychiatric illnesses and history of suicidal ideas or attempts
15. History of status epilepticus within 1 previous year
16. Currently taking etifoxine or progesterone therapy (wash out period of 60 days)
17. Baseline GFR< 30 ml/minute/1.73 m^2)
18. Previous history of allergic to etifoxine or progesterone
19. Unsuitable veins for repeated vein puncture

Sample size

Total 40 patients for whole clinical study: intervention group (n 20), placebo group (n 20), Stratified by 1) gender and 2) taking enzyme inducer AEDs (Figure 1.)

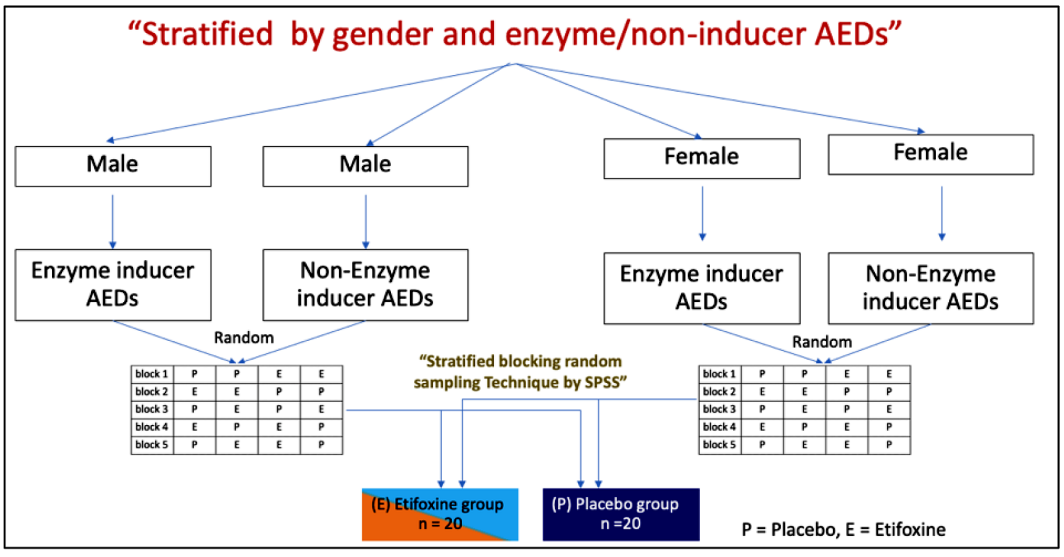

Figure 1 Stratify randomization

Evaluation batteries

1) Hamilton Anxiety Rating Scale; HAM-A for anxiety

2) Patient Health Questionaire-9 Thai version; PHQ-9T for depression

3) Patient Weighted Quality of Life in Epilepsy-10; QOLIE-10 for quality of life.

4) Seizure diary for the 1-month seizure frequency

Study flow

Visit 1 (week -4)

- Patients are informed and sign consent to participate the trial.
- Demographic data including history of epilepsy are collected. Evaluate anxiety level using HAM-A score-Thai
- After screening period, the patients will be appointed in the next 4 weeks for the 2nd visit.

Visit 2 (week 0)

- Review seizure diary (check for eligibility, inclusion criteria if seizure frequency >3 times a month)
- Assess anxiety by HAM-A-Thai, depression by PHQ-9-Thai, Quality of life by QOLIE 10-Thai
- Blood test for renal and liver function, electrolyte, and complete blood count (baseline lab for safety analysis)
- Randomized patients into intervention group or placebo group as stratify and blocked randomizations (using gender and enzyme inducer AEDs)
- Intervention groups will be assigned to take etifoxine (50 mg/cap) 2 capsule q 12 hours (dispensed 140 capsules/month)
- Placebo: identical capsule, container and taking at the same dosage and time as original drugs in intervention groups (dispensed 140 capsules/month)
- Patients note in their seizure diary (monthly basis) for seizure events and adverse events from medications
- Pregnancy test for child baring age female patient is done.
- Appointment for the next visit (4 weeks later)

Visit 3 (week 4)

- After taking medicine for 4 weeks, the patients return medicines for compliance check and seizure diaries are also collected.

- Evaluate anxiety, depression and quality of life using the same batteries (HAM-A-T, PHQ-9-T and QOLIE-10-T)

- Pregnancy test for child baring age female patient

- Intervention groups take etifoxine (50 mg/cap) 2 capsule q 12 hours (dispensed "2" sets of 140 capsules, total "280" capsules)

- Placebo: identical capsule, container and taking at the same dosage and time as original drugs in intervention groups (dispensed "2" sets of 140 capsules, total of "280" capsules)

- Patients note in the seizure diary (x2) for seizure events and also adverse events from medications

Visit 4 (week 8, telephone visit)

- To evaluate adverse events from medication and make sure that the patients have good compliance and note any events on the seizure diary

- Inform the patients to change the package of medicine and seizure diary and keep the old ones for researcher to review

Visit 5 (week 12)

- Return and review seizure diary, and adverse event from medications

- Pill counts for compliance check

- Evaluate anxiety, depression and quality of life using the same batteries (HAM-A-T, PHQ-9-T and QOLIE-10-T)

- Blood test for renal and liver function, electrolyte and complete blood count (baseline lab for safety analysis)

- Pregnancy test for child baring age female patient

Visit 6 (week 16, telephone visit)

- Telephone interview after discontinuing medicine for 2 weeks: review for withdrawal symptoms

Table 1 Study timeline

Visit	1st	2nd	3rd	4th	5th	6th
Week	-4	0	4	8	12	16
Action and Plan	Screening	Baseline	1st month	Telephone visit	3rd month	Telephone visit
Consent	x					
Inclusion/Exclusion		x				
Randomization		x				
Dispend medication E or P --> 2 cap. q 12 h (E; Etifoxine, P; Placebo)		x (for 4 weeks)	x (for 8 weeks)			E or P 1 cap. q 12 h (for 2 weeks)
Dispend seizure diary	x	x	x			
Return and review seizure diary		x	x		x	
HAM-A-T	x	x	x		x	
PHQ-9-T		x	x		x	
QOLIE-10-T		x	x		x	
Adverse event (clinical)		x (for con-Med)	x	x	x	x
Safety test (LFT, CBC, Electrolyte)		x			x	
Patient traveling expense	x	x	x		x	
Urine pregnancy test		x	x		x	
Withdrawal period						x

Statistical analysis and ethical consideration

This study (Q020h/63) was approved by our local IRB on February 25th, 2021. Continuous variables were presented as mean and standard deviation if normally distributed, or by median and interquartile range [IQR] if not. Categorical variables were presented as frequency and percentage. Chi-square or Fisher Exact test were used to determine difference of categorical variable between groups. Independent sample t-test or Mann Whitney U test were determined different of continuous variable between groups. Paired t-test, or Friedman test or Wilcoxon Signed Rank test were used to determine the difference within group. A P-value of less than 0.05 was considered statistically significant. Statistical analyses were performed in SPSS 26.0.

Result

1. Demographic characteristics

Sixty-six patients with drug-resistant epilepsy were invited to participate the study. There were 40 patients met selection criteria. In etifoxine group, initially there were 20 patients, but three patients were drop out before visit 8-week after randomization. Therefore, 17 patients in etifoxine group were finally analyzed for per protocol analysis. In placebo group, initially there were 20 patients, but three patients were drop out before visit 8-week after randomization. Therefore, 17 patients in placebo group were finally analyzed for per protocol analysis.

Mean age of etifoxine group was 35.06 years old, while placebo was 33.94 years old, p-value of 0.666. Male was 9 (52.9 %), 10 (58.8 %), in the etifoxine group and the placebo group, respectively, p-value 0.730. Demographic characteristics and concomitant medications were detailed in Table 2.

Table 2 Baseline characteristics

	Total (34) (mean±sd) Number (%)	Etifoxine (17) (mean±sd) Number (%)	Placebo (17) (mean±sd) Number (%)	*p*-value
Average age (year)	34.5±13.69	35.06±13.22	33.94±14.53	0.666 M
Male gender	19 (55.9)	9 (52.9)	10 (58.8)	0.730 C
Average epilepsy onset (years)	17.82±10.67	17.82±12.21	17.82±9.27	0.769 M
Average epilepsy duration (years)	15.94±11.83	17.29±9.83	14.59±13.72	0.195 M
Epilepsy etiology group				0.419 C
Cryptogenic focal epilepsy	26 (76.5)	12 (70.6)	14 (82.4)	
Symptomatic focal epilepsy	8 (23.5)	5 (29.4)	3 (17.6)	
Hypertension	0	0	0	NA
Dyslipidemia	1 (2.9)	0	1 (5.9)	NA
Diabetes mellitus	0	0	0	NA
Stroke	0	0	0	NA
History of major depressive disorder	3 (8.8)	2 (11.8)	1 (5.9)	NA
Insomnia	1 (2.9)	1	0	NA
History of traumatic brain injury	1 (2.9)	1 (5.9)	0	NA
Mental retardation	0	0	0	NA
Hypothyroid	1 (2.9)	0	1 (5.9)	NA
Alcoholism	1 (2.9)	0	1 (5.9)	NA
Smoking	1 (2.9)	0	1 (5.9)	NA
Drug abuse	1 (2.9)	0	1 (5.9)	NA
Average Seizure frequency/month: at screening time	5.71±12.66	4±2.92	7.41±17.78	0.470 M

Table 2 Baseline characteristics (cont.)

	Total (34) (mean±sd) Number (%)	Etifoxine (17) (mean±sd) Number (%)	Placebo (17) (mean±sd) Number (%)	*p*-value
Report of stress: at screening time	29 (85.3)	14 (82.4)	15 (88.2)	1.000
Average HAM-A score: at screening time	14.91±8.16	16.24±9.05	13.59±7.19	0.448 [M]
Enzyme inducer medication use	22 (64.7)	14 (82.4)	8 (47.1)	0.031 [C]
On Brivaracetam (BRV)	16 (47.1)	10 (58.8)	6 (35.3)	0.169
Average BRV dose (mg)	146.87±46.44	145±43.78	150±54.77	0.048*
On Carbamazepine	9 (26.5)	6 (35.3)	3 (17.6)	0.438
Average Carbamazepine dose (mg)	822.22±438.11	1016.67±402.08	433.33±152.75	0.667
On Topiramate	6 (17.6)	5 (29.4)	1 (5.9)	0.175
Average Topiramate dose (mg)	183.33±116.9	200±122.47	100.0±0	0.690
On Phenytoin	10 (29.4)	5 (29.4)	5 (29.4)	1.000
Average Phenytoin dose (mg)	315±52.97	330±44.72	300±61.24	0.143
On Levetiracetam	9 (26.5)	3 (17.6)	6 (35.3)	0.438
Average Levetiracetam dose (mg)	1875±790.57	2500±866.03	1500±500	0.132
On Valproate	12 (35.3)	5 (29.4)	7 (41.2)	0.473
Average Valproate dose (mg)	1158.42±649.95	1416.83±860.87	900±167.33	0.786
On Clobazam	8 (23.5)	5 (29.4)	3 (17.6)	0.688
Average Clobazam dose (mg)	6.25±3.54	7±4.47	5±0	0.667
On Zonisamide	2 (5.9)	2 (11.8)	0	NA
Average Zonisamide dose (mg)	300±141.42	300±141.42	0	NA
On Perampanel	1 (2.9)	1 (5.9)	0	NA
Average Perampanel dose (mg)	8.0	8.0	0	NA
On Lamotrigine	3 (8.8)	2 (11.8)	1 (5.9)	NA
Average Lamotrigine dose (mg)	150±139.19	212.5±123.74	25.0±0	NA
On Oxcabazepine	1 (2.9)	0	1 (5.9)	NA
Average Oxcarbazepine dose (mg)	450	0	450±0	NA
On Lacosamide	1 (2.9)	1 (5.9)	0	NA
Average Lacosamide dose (mg)	100.0±0	100.0±0	0	NA
On Phenobarbital	2 (5.9)	1 (5.9)	1 (5.9)	NA
Average Phenobarbital dose	90±42.43	60.0±0	120.0	NA
On Diazepam	1 (2.9)	1 (5.9)	0	NA
Average Diazepam dose (mg)	5.0	5.0	0	NA
On Lorazepam	3 (8.8)	3 (17.6)	0	NA
Average Lorazepam dose (mg)	0.83±0.29	0.83±0.29	0	NA
On Clonazepam	2 (5.9)	2 (11.8)	0	NA
Average Clonazepam dose (mg)	1.25±1.06	1.25±1.06	0	NA
On Sertraline	5 (14.7)	4 (23.5)	1 (5.9)	NA
Average Sertraline dose (mg)	50.00±0.00	50.00±0.00	50.0	NA
On Olanzapine	1 (2.9)	1 (5.9)	0	NA
Average Olanzapine dose mg/day	10.0±0	10.0±0	0	NA
On Aripiprazole	0	0	0	NA
On Tricyclic antidepressant	0	0	0	NA
On Quetiapine	0	0	0	NA
On Fluoxetine	0	0	0	NA
On Escitalopram	0	0	0	NA
On Vortioxetine	0	0	0	NA

The reduction of anxiety score using HAM-A

The HAM-A score of the etifoxine group at baseline and each visit were not difference when compared to the placebo group. When compared within group of the etifoxine group, it was found that HAM-A score was significantly reduced from 16.0 (baseline) to 12.2 (at visit 5), p-value 0.009 Friedman Test, while the score didn't reach statistically significant reduction in the placebo group, 13.2 (baseline) to 11.8 (visit 5), p-value 0.279, Table 3.1. The anxiety symptoms reduction was significantly reduced in subgroup for fear for the etifoxine group, baseline 1.7 to 0.7, p-value 0.035 by Wilcoxon Signed Rank test.

Subgroup analysis compared between using concomitant medications as enzyme inducer and no enzyme inducer, the reduction of HAM-A score more than 50% in patients without enzyme inducers was found more in the etifoxine group (33.3%) than the placebo group (22.2%), Table 3.2

Table 3.1 Anxiety assessment using HAM-A score

	Etifoxine			Placebo			*p*-value for *
	n	mean±sd	Median (min-max)	n	mean±sd	Median (min-max)	between group
Visit 2-HAM-A	17	16±7.91	14(6-37)	17	13.24±8.14	9(2-28)	0.178
Visit 3-HAM-A	17	15.29±7.74	13(1-28)	17	12.41±9.47	10(2-34)	0.248
Visit 5-HAM-A	17	12.24±8.18	13(1-29)	16	11.81±6.59	13.5(0-22)	0.957
Visit 2-3-HAM-A	17	0.71±6.56	1(-12-15)	17	0.82±7.15	1(-10-18)	0.972
Visit 2-5-HAM-A	17	3.76±6.69	4(-8-21) Ω	16	1.44±5.27	1(-7-11)	0.295
p-value for within group **			0.009 ** 0.011 Ω			0.729	
V2 HAM fear	17	1.29±1.31	2(0-4)	17	0.53±0.94	0(0-3)	0.064
V3 HAM fear	17	1.12±0.99	1(0-3)	17	0.71±1.1	0(0-3)	0.174
V5 HAM fear	17	0.65±1.22	0(0-4)	16	0.63±0.96	0(0-3)	0.747
V2-3 HAM fear	17	0.18±1.19	0(-2-3)	17	-0.18±0.95	0(-2-2)	0.414
V2-5 HAM fear	17	0.65±1.17	0(-1-3) Ω	16	-0.06±0.85	0(-2-2)	0.084
p-value for within group **			0.120 ** 0.035 Ω			0.687	
V2 HAM sleep	17	1.29±1.31	1(0-4)	17	0.94±1.2	1(0-4)	0.424
V3 HAM sleep	17	1.24±1.25	1(0-4)	17	0.82±0.95	1(0-3)	0.354
V5 HAM sleep	17	1.18±1.13	1(0-3)	16	0.87±0.89	1(0-3)	0.494
V2-3 HAM sleep	17	0.06±1.39	0(-3-3)	17	0.12±1.5	0(-3-3)	0.929
V2-5 HAM sleep	17	0.12±1.32	0(-3-2)	16	-0.06±1.57	0(-3-4)	0.564
p-value for within group **			0.775			0.846	
V2 HAM cognitive	17	2.24±0.97	2(1-4)	17	1.53±1.33	1(0-5)	0.054
V3 HAM cognitive	17	1.59±1.12	2(0-3)	17	1.24±0.9	1(0-3)	0.299
V5 HAM cognitive	17	1.82±0.88	2(0-3)	16	1.25±0.93	1(0-3)	0.092
V2-3 HAM cognitive	17	0.65±1.27	0(-1-3)	17	0.29±1.4	1(-3-3)	0.583
V2-5 HAM cognitive	17	0.41±0.94	0(-1-2)	16	0.25±1.39	0.5(-2-3)	0.822
p-value for within group **			0.255			0.511	
V2 HAM autonomic	17	1.65±1.87	1(0-5)	17	2.65±1.97	2(0-7)	0.090
V3 HAM autonomic	17	2±1.7	2(0-5)	17	2.12±1.73	1(0-6)	0.874
V5 HAM autonomic	17	1.24±1.09	1(0-3)	16	1.94±1.73	1.5(0-5)	0.283
V2-3 HAM autonomic	17	-0.35±1.87	0(-4-3)	17	0.53±1.42	1(-2-3)	0.080
V2-5 HAM autonomic	17	0.41±1.58	0(-2-4)	16	0.81±1.42	1(-2-3)	0.312
p-value for within group **			0.404			0.052	

* *p*-value for between group using Mann-Whitney U Test

** *p*-value for within group for visit 2,3 and 5 using Friedman Test

Ω *p*-value for within group for visit 2 and visit 5 using Wilcoxon Signed Rank test

Visit 2 = week-0, Visit 3 = week-4, Visit 5 = week

Table 3.2 HAM-A score: compare between enzyme inducer and non-enzyme inducer use

	Enzyme inducer does not use				Enzyme inducer use			
	Etifoxine (n=3)		Placebo (n=9)		Etifoxine (n=14)		Placebo (n=8)	
	n	%	n	%	n	%	n	%
% Change Ham_V2_V3_50								
reduction <50%	2	66.7	7	77.8	13	92.9	5	62.5
reduction >50%	1	33.3	2	22.2	1	7.1	3	37.5
Ham_V2_V5_50								
reduction <50%	2	66.7	9	100.0	11	78.6	5	71.4
reduction >50%	1	33.3	0	0.0	3	21.4	2	28.6

Visit 2 = week-0, Visit 3 = week-4, Visit 5 = week 12

3. The reduction of depression scores using PHQ-9 and the quality of life using QOLIE-10

The assessment of depression and quality of life assessment were shown in Table 4. There was no significant difference between the etifoxine group and the placebo group.

Table 4 Comparison of PHQ-9 between etifoxine and placebo

	Etifoxine			Placebo			
	n	mean±sd	Median (min-max)	n	mean±sd	Median (min-max)	*p*-value for between group*
Visit 2-PHQ-9	17	8.41±4.95	10(0-16)	17.000	7.35±4.46	8(1-21)	0.324
Visit 3-PHQ-9	17	9.24±5.17	10(1-19)	17.000	6.59±4.2	6(1-13)	0.178
Visit 5-PHQ-9	17	7.76±5.4	8(1-18)	16.000	5.25±3.55	5(1-11)	0.193
p-value for within group			0.117			0.229	
Visit 2-QOL	17	24.29±5.83	23(9-34)	17.000	21.47±5.5	22(12-29)	0.162
Visit 3-QOL	17	23.71±5.63	24(12-35)	17.000	20.76±6.33	21(11-33)	0.227
Visit 5-QOL	17	22.65±4.61	23(12-32)	16.000	19.44±4.79	19(12-28)	0.076
p-value for within group			0.528			0.175	

p-value for between group* using Mann-Whitney U Test

p-value for visit 2,3 and 5** using Friedman Test

Visit 2 = week-0, Visit 3 = week-4, Visit 5 = week 12

4. The reduction in seizure frequency after taking etifoxine and placebo

Our drug-resistant epilepsy was not difference in reduction of average seizure frequency after adding etifoxine, Table 5.1.

From incident rate ratio analysis for efficacy of etifoxine, it was found that using etifoxine (200) 2x2 oral pc provide benefit from previous antiseizure medications of 13.7% when compared to placebo, Table 5.2.

Table 5.1 Seizure frequency for the etifoxine group and the placebo group

Seizure frequency (SF)	Etifoxine			Placebo			*p*-value for
	n	mean±sd	median(IQR)	n	mean±sd	median(IQR)	between group*
Visit 2-total SF/month	16	3.88±3.26	3(3-4)	16	8.0±18.30	3(2-4.75)	0.863
Visit 3-total SF/month	16	6.31±6.25	4(1.5-8.5)	16	8.38±20.73	1.5(1-5)	0.266
Visit 4-total SF/month	16	6.25±6.54	3.5(2-12.75)	16	7.44±16.69	2(0.25-3.75)	0.151
Visit 5-total SF/month	16	5.56±6.54	3(0-12.5)	16	5.94±12.39	1.5(1-4.5)	0.789
p-value for visit 2,3, 4 and 5**			*0.000***			*0.000***	
Visit 2-SPS/month	16	1.00±1.46	0(0-2.75)	16	4.75±12.85	0.5(0-2.75)	0.466
Visit 3-SPS/month	16	2.00±3.50	0(0-3.5)	16	5.31±14.36	1(0-2.75)	0.589
Visit 4-SPS/month	16	1.50±2.73	0(0-2.5)	16	5.56±15.85	0(0-2.5)	0.963
Visit 5-SPS/month	16	1.38±2.96	0(0-2.25)	16	4.56±12.32	0.5(0-2.75)	0.250
p-value for visit 2,3, 4 and 5**			*0.018***			*0.002***	
Visit 2-CPS/month	16	0.69±1.40	0(0-1)	16	2.13±5.47	0(0-2.75)	0.765
Visit 3-CPS/month	16	2.75±5.31	0.5(0-2.75)	16	1.88±5.51	0(0-1)	0.243
Visit 4-CPS/month	16	2.25±4.75	0.5(0-2)	16	1.31±3.46	0(0-1)	0.415
Visit 5-CPS/month	16	1.94±4.86	0(0-0.75)	16	0.44±1.03	0(0-0.75)	0.823
p-value for visit 2,3, 4 and 5**			*0.002***			*0.007***	
Visit 2-SGTC/month	16	2.19±3.90	0(0-0)	16	1.13±1.62	0(0-2)	0.692
Visit 3- SGTC /month	16	1.56±2.58	0(0-2.75)	16	1.19±1.94	0(0-1)	0.983
Visit 4- SGTC /month	16	2.50±4.77	0(0-2.75)	16	0.56±1.15	0(0-0.75)	0.324
Visit 5- SGTC /month	16	2.25±4.32	0(0-2.75)	16	0.94±2.05	0(0-1)	0.373
p-value for visit 2,3, 4 and 5**			0.215**			*0.028***	

Table 5.2 Incident rate ratio and efficacy of etifoxine for seizure control

	SZ frequency		Incidence rate	IRR (95%CI)	Efficacy(95%CI)
	SZ frequency	Follow-up time (month)			
Etifoxine	290	43.54	6.66	0.863	13.7% (-1.1-26.4)*
Placebo	348	45.11	7.71		

IRR – incidence rate ratio, * *p*-value=0.027, SZ – seizure

5. Safety analysis of etifoxine for patients with drug-resistant epilepsy

There were 3 patients per each group reporting adverse event and 4 patients per group were early discontinued, Table 6.

Table 6 Adverse event and early discontinuation in each group

After randomization	Etifoxine (n = 20)		Placebo (n = 20)	
	Adverse event	Early discontinuation	Adverse event	Early discontinuation
4-week	1 (drug rash)	1 (1 from AE)	1 (over sedated) 1 (aggressive behavior)	2 (2 from AE)
8-week (telephone)	1 (aggressive and PNES)	2 (1 from AE, 1 loss F/U unclear reason)	1 (PNES)	1 (1 from AE)
Before 12-week	1 (pregnancy)	1 (1 pregnancy)	1 (pregnancy)	1 (1 pregnancy)

PNES- psychogenic non-epileptic seizures

Discussion

Etifoxine in drug-resistant epilepsy (DRE) reduced HAM-anxiety score over the study time, the benefit appeared especially on subtypes of anxiety which were fear and sleep. In this study, etifoxine didn't reduced depression, quality of life and seizure frequency. The adding on efficacy of seizure reduction of etifoxine in DRE patients compared with placebo was 13.7%. Etifoxine was safe in DRE population.

Strength of the study: this was the first study of etifoxine as an adjunctive treatment in patients with drug-resistant focal epilepsy with comorbid anxiety symptoms. Weakness of the study: the study population of this study was small that would affect the result of the study for example the efficacy for seizure reduction was not achieve statistically significant difference. Also, the patients with drug-resistance epilepsy are always very difficult to treat which the dosage of etifoxine in this study (4 tablets a day) would be inadequate and that the higher dosage would be required. Moreover, this study was conducted during the COVID-19 pandemic which absolutely affected patients' physical and mental heaths. Future direction: the further study should be increased for the sample size, study period, and higher dosages of etifoxine.

Conclusion

Etifoxine in drug-resistant epilepsy (DRE) reduced HAM-anxiety score over the study time, and the benefit appeared especially on fear and sleep subtypes of anxiety scores

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