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Comparative efficacy of unique antiepileptic drug regimens in focal epilepsy: An exploratory study

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ABSTRACT

Objective: To compare efficacy of unique antiepileptic drug (AED) polytherapy regimens among patients with focal epilepsy.

Methods: From a longitudinal study of AED treatment, we identified patients with active focal epilepsy who had attempted at least two unique AED regimens (mono-, duo-, or tri-therapy). Efficacy was defined as the presence of at least one six-month period of continuous seizure freedom during exposure to a regimen. To control for individual variations in response and epilepsy severity, we used within-patient comparison approaches, in which we: 1) compared head-to-head unique regimens tried within the same patients; 2) compared one regimen versus aggregate of other regimens attempted in that patient; and 3) compared aggregated monotherapy versus polytherapy regimens.

Results: 757 patients met our criteria and had collectively attempted 170 unique regimens. In the head-to-head analysis, lamotrigine monotherapy was more effective than phenytoin monotherapy. Two regimens were more effective than the aggregate of other regimens attempted: levetiracetam/lamotrigine duotherapy and lamotrigine monotherapy. Two other regimens exhibited slightly better efficacy but did not reach statistical significance: clobazam/levetiracetam/lamotrigine and levetriacetam/oxcarbazepine. Patients who previously attempted at least four regimens had slightly better outcomes on polytherapy than monotherapy, though this was not significant.

Significance: We identified two unique regimens more likely to be associated with ≥6 months of seizure freedom: levetiracetam/lamotrigine duotherapy and lamotrigine monotherapy. Polytherapy may be an effective alternative to monotherapy for patients with focal epilepsy and persistent seizures.

1. Introduction

For those patients who are not rendered seizure free on monotherapy, when in the treatment course and which polytherapy should be considered are unclear. After one failed monotherapy trial, alternative monotherapy has demonstrated similar efficacy to an add-on duotherapy approach (Semah et al., 2014). Some proposed algorithms suggest that AED polytherapy should be attempted after patients fail two monotherapy trials (Brodie, 2005; Kwan et al., 2011; St. Louis, 2009). In these instances, the American Academy of Neurology has recommended the use of several second-generation AEDs to manage focal epilepsy (AAN, 2004). Even after failure of two monotherapy trials, many patients still achieve favorable outcomes with AED treatment (Choi et al., 2016), suggesting a role for a rational polytherapy.

There are many considerations when selecting an appropriate polytherapy combination, including patient history, epilepsy type, previous AED trials, potential side effect profile, safety in pregnancy, and patient preference. Mechanistic and metabolic interactions between AEDs must also be considered. For instance, an enzyme-inducing AED will decrease serum levels of a co-administered AED with inducible metabolism (St. Louis, 2009). Investigators have also suggested (though with little high quality evidence) that combinations are most effective when using AEDs with different mechanisms of action and that broad-spectrum AEDs may be best suited to polytherapy (Kwan and Brodie, 2006). Conversely, combinations of sodium channel blockers may lead to supra-additive (i.e. synergistic) toxicity despite only additive efficacy (Brodie and Sills, 2011). The ideal AED combination should provide supra-additive seizure control with infra-additive

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(antagonistic) toxicity.

Although no standardized paradigm exists for selecting AEDs in polytherapy, several approaches have been used to investigate efficacy of drug combinations. These include animal isobolography studies, prospective comparisons between specific AED combinations, and larger-scale cross-sectional studies in epilepsy care (Brodie et al., 1997; Deckers et al., 2000, 2001; Peltola et al., 2008; Stafstrom, 2010; Stephen and Brodie, 2002; Tallarida, 2006). One specific combination, duotherapy with lamotrigine and valproate, has demonstrated supra-additive seizure control in clinical and in vitro models (Brodie et al., 1997; Taing et al., 2017). No other specific combinations are well established (Brodie and Sills, 2011; Schmidt, 2016).

Within-patient analyses have the advantage of controlling for each patient's unique responsiveness and epilepsy severity. If conducted retrospectively with a large enough sample, it is possible to compare efficacy of several specific AED regimens (Poolos et al., 2012). Many of the second-generation AEDs were specifically approved for seizures with focal onset (Wood et al., 1996). However, there has been no study examining the comparative efficacy of combination drug therapy specifically in focal epilepsy. Such a study could help guide the clinical decision-making process and provide rationale for future prospective studies. With this in mind, we conducted an analysis comparing within-patient efficacy of specific AED regimens in adults with focal epilepsy.

2. Method

The Columbia and Yale Comprehensive Epilepsy Centers (CCEC and YCEC) have an ongoing retrospective, longitudinal observational study of antiepileptic drug response and tolerability. The study is approved by institutional review boards at both sites and is based on medical chart review of 3782 outpatients (at the time of this study). Data collection began on January 1, 2000 and is ongoing. Data abstraction for the existing longitudinal study is based on review of medical records and includes epilepsy history, patient demographics, medical and psychiatric history, concomitant medications, AED dosages, laboratory test results, side effects, and efficacy measures. Data are entered into an electronic database by trained research assistants. The database is designed to reflect the medical chart, so that for each patient appointment an entry is made into the database. That is, for each visit, information about seizure occurrence, medication change, and presence of side effects since the last visit is included. Treatment efficacy measures include average monthly seizure frequency (when indicated in the visit note) and the presence of seizure freedom since the last visit.

For this study, we identified patients with a diagnosis of focal epilepsy, classified by the treating epilepsy attending physician at CCEC based on the International League Against Epilepsy Classification; as Yale patients have only been entered for the past few years, only CCEC patients were included in this study. If patients were diagnosed with focal epilepsy prior to coming to CCEC, they were included only if the CCEC physicians agreed with the diagnosis of focal epilepsy in their assessment. Additional inclusion criteria included: (1) patients had to have tried two or more unique regimens of AEDs consisting of mono-, duo-, or tri-therapy while at CCEC, and (2) each unique regimen consisting of mono-, duo-, or tri-therapy had to have been used continuously for at least six months or discontinued before that time due to lack of complete seizure control. We did not examine regimens attempted for less than six months if patients had discontinued for reasons unrelated to seizure control (such as intolerability or cost). When a new AED was added to an existing regimen (in which the existing medication was not lowered), the initial regimen was considered to have been discontinued due to inefficacy (as evidenced by the need for an additional AED).

We also excluded patients who did not have any reported seizures while being followed at CCEC, thereby eliminating patients with mild or inactive epilepsies. The study observation period began at the time of each patient's first visit to CCEC and ended at the time of last follow up visit. If patients had epilepsy surgery after meeting the inclusion criteria, their observation data were censored at the date of epilepsy surgery.

2.1. Outcome variable

The primary outcome measure was binary and consisted of whether or not patients had a continuous seizure-free period ≥6 months during their time of exposure to a unique regimen. We defined this as a 'remission period.' In cases where a patient tried a unique regimen on several occasions separated in time, the unique regimen was considered to be effective only once even if the patient had multiple remission periods associated with that unique regimen separated in time. Our rationale for using a length of ≥6 months was two-fold; first, seizure control over a 6-month period has been shown to influence quality of life scores (Mehta et al., 2014; Salgado and Cendes, 2009); second, a longer period would have reduced the number of eligible regimens, thereby increasing the risk of type II errors. We also calculated the proportion of remission periods ≥12 months, though we did not incorporate this variable into our statistical analyses.

Because retrospective patient visit notes sometimes might not clearly characterize the type(s) of seizure(s) a patient had since their previous visit, we included focal seizures in addition to secondarily generalized seizures in our overall assessment of seizure freedom. Similarly, we decided not to use seizure frequency (other than seizure freedom) as our primary outcome measure because seizure frequency is not uniformly documented in the medical records. Even when seizure frequency is documented, clinic notes do not necessarily report exact number of seizures for those individuals with multiple seizure types. Such missing data would have complicated an analysis of drug efficacy based on seizure frequency.

2.2. Comparisons between two specific regimens

All unique regimens tried by ≥10 patients were included in this analysis. We used the McNemar test to compare the proportion of patients achieving ≥6 months seizure freedom under one regimen (regimen X) versus the proportion of those same patients achieving ≥6 months seizure freedom when they tried another unique regimen (regimen Y). We also examined whether the occurrence of ≥6 months seizure freedom during a unique regimen compared to another regimen was related to difference in AED dose load. For regimens found to have significantly different proportions of patients achieving remission, we determined the mean drug load for each AED in each regimen. To do this, we first calculated each patient's mean daily AED dose(s) throughout the epoch during which they were taking that unique drug regimen. We then averaged these mean patient doses. Finally, the averaged value of all patient means was used to calculate the drug load, defined as the average daily AED dose divided by the Defined Daily Dose (DDD) of that particular AED. The DDD is the maintenance dose of an AED used for its main indication in adults compiled by the World Health Organization (Organization, 2016). As an example, if three patients took an overall daily average of 400 mg of medication Z, the mean AED load would be calculated as 400 mg divided by the DDD of medication Z. If the DDD was 200 mg, the mean AED load would equal 2. For patients on polytherapy, AED loads for each AED in the regimen were summed. This method of drug load calculation has been used in previous studies of AED polytherapy (Canevini et al., 2010).

When comparing between two specific regimens, we also calculated the mean number of previous attempted regimens prior to the regimen being considered. This calculation (number of previous regimens prior to attempting regimen X and number of previous regimens prior to attempting regimen Y) would inform the chronological sequence of regimens X and Y.

2.3. Comparisons between a unique regimen (regimen X) and all other regimens attempted by patients who attempted regimen X

We first identified all unique regimens that had been tried by ≥10 patients, each of whom had also attempted additional regimens for comparison. Then, for each unique regimen (for example, regimen X), we compared the proportion of patients who achieved remission during regimen X versus the proportion of all other aggregated regimens attempted by those same patients that resulted in seizure freedom. For this analysis, we used Mantel-Haenszel tests. For instance, if regimen X had been attempted by 10 patients, seven of whom had a remission period on regimen X, then we considered the proportion achieving remission during regimen X to be 0.7. If the same group of 10 patients had aggregately attempted 24 other (non-X) regimens, and 12 of the non-X regimens resulted in remission, then we considered the proportion achieving remission during a non-X regimen to be 0.5. In this example, the overall risk ratio would therefore calculated as 0.7/0.5 (remission proportion of X regimens/remission proportion of non-X regimens). Our rationale for utilizing a different statistical test for this portion of the study was that the number of data points per patient was variable: each patient had one data point representing their outcome on regimen X, as well as a data point for each non-X regimen.

2.4. Comparisons between monotherapy and polytherapy

Among patients who had tried both monotherapy and polytherapy (either duo- and/or tri-therapy), we compared the proportion of patients who ever had a remission during monotherapy versus the proportion of patients who ever had a remission during polytherapy. We used McNemar tests to compare the remission proportions between monotherapy and polytherapy, stratifying patients based on the total number of regimens used during the entire follow-up period (2, 3, or ≥4 unique regimens). The rationale for making the comparison within different strata was that the total number of regimens used in a given patient may be a proxy measure of epilepsy severity.

In order to correct for multiple comparisons, we used the Benjamini-Hochberg procedure, which is less conservative than the Bonferroni adjustment. This is a recommended alternative to Bonferroni for health studies with larger numbers of hypotheses (Glickman et al., 2014) and has been used in previous epilepsy research (Park et al., 2015). For the Benjamini-Hochberg procedure, we grouped our hypotheses into three separate families (one for each portion of the study) and assumed a false discovery rate of 0.05. This resulted in three different significance cut-off values, one for each family of hypotheses, allowing for better statistical power. When findings were associated with a p value between the Benjamini-Hochberg adjusted cut-off and 0.05, we considered them to be marginally significant (i.e., possible trend).

3. Results

Of the 3782 patients in the ongoing longitudinal CCEC study, 757 (403 female) met inclusion criteria for this study. A description of the demographics of the sample is displayed in Table 1. There were more females (53.2%) and the mean age of epilepsy onset was 22.9 years (SD = 17.9). The mean duration of epilepsy was 16.17 years (SD = 15.2). The mean age at most recent follow-up was 42.0 years (SD = 18.2). A majority of the 757 patients (84.7%) had attempted at least one AED prior to coming to CCEC.

Five hundred seventy patients (75.3%) had secondarily-generalized seizures reported as one of their seizure types. Of the remaining 187 patients, 139 had at least one type of focal seizure with loss of consciousness. Forty-four patients only had focal seizures without loss of consciousness, while the exact seizure types of four patients in our sample were not clear from the chart. Six hundred seventeen patients (81.5%) suffered from multiple seizure types.

Considering all of the mono-, duo-, and tri-therapy AED regimens used among 757 patients, there were 170 unique AED regimens attempted during the study follow-up. Given our inclusion criteria requiring a minimum of 2 unique AED regimens, patients attempted an average of 2.9 regimens (SD = 1.3). Forty-four unique AED regimens had been attempted by ≥10 patients among whom additional regimens were also tried at different times. As shown in Table 1, 45.9% (348 out of 757) of the study patients never had a continuous six-month period of seizure freedom while being followed at CCEC.

Table 1
Patient Demographics.

Characteristics	Mean (SD)
Age of epilepsy onset	22.9 (17.9)
Age at most recent follow-up	42.0 (18.2)
Number of AED regimens attempted	2.9 (1.3)
	Count (%)
Female	403 (53.2)
Did not have a remission period during follow-up	348 (45.9)
History of status epilepticus	65 (8.6)
Static encephalopathy	71 (9.4)
Had tried ≥1 AED before CCEC visit	641 (84.7)

Of 621 drug regimen attempts (patient-regimen combinations) that resulted in seizure-free periods of ≥6 months, 221 (35.4%) led to complete control of seizures − that is, patients never had a seizure on those regimens. Similarly, of 399 drug regimen attempts that resulted in ≥12 continuous months of seizure freedom, 142 (35.6%) led to complete seizure control.

An average of 46.3 months (range = 0.5–345.4, median = 33.9) of seizure frequency data was available for a subset of 624 patients. They had an average of 3.63 seizures per month during this time (range = 0–200, median = 0.2). After omitting all seizure-free periods ≥6 months from the seizure frequency data, the remaining data from 486 patients revealed an average seizure frequency of 7.34 per month (range = 0–720, median = 1.0).

After calculating p values for each comparison within our study, the Benjamini-Hochberg procedure was used to determine significance cut-off points. These cut-off points were respectively 0.0015, 0.0023, and 0.0083 for the three analyses in our study – comparisons between two specific regimens; comparisons between a specific regimen and the aggregate of other regimens; and comparisons between aggregated monotherapy and aggregated polytherapy regimens.

3.1. Comparisons between two specific regimens

Within data of 757 eligible patients, we identified 34 distinct pairs of AED regimens tried by ≥10 patients (for example, regimen A and regimen B). That is, for each of the 34 distinct pairs, 10 or more patients had attempted regimen A and then regimen B at a different time point, or vice versa. Regimens A and B each constitute a distinct combination of AEDs. The proportion of patients achieving a remission period on one regimen (regimen A) versus the proportion of those same patients achieving a remission period on the other regimen (regimen B) was significantly different for (1) LTG monotherapy (0.75) vs. PHT monotherapy (0.15) ($p < 0.001$). A trend was seen among the following regimens: (2) LTG monotherapy (0.65) vs. LTG/PHT duotherapy (0.23) ($p = 0.02$), and (3) LTG monotherapy (0.61) vs. LTG/GBP duotherapy (0.35) ($p = 0.03$) (Table 2).

To adjust for differences in efficacy which may have been secondary to the amount of medication administered, we compared the mean daily doses and drug loads for the significant comparison – LTG vs. PHT monotherapy – along with the two comparisons in which we found trends. In each case, the LTG monotherapy drug load was higher than any of the individual drug loads compared with it, although both of the less-effective duotherapy regimens (LTG/PHT and LTG/GBP) exhibited a total drug load that exceeded lamotrigine monotherapy. Among these

Table 2
Within-patient head-to-head comparisons of unique AED regimens[a].

AED Regimens (Proportion of patients who had ≥6 months seizure freedom on that regimen)			Total N	P
LTG (0.75)	***vs.***	***PHT (0.15)***	***20***	***< 0.001***
LTG (0.65)	*vs.*	*LTG, PHT (0.23)*	*17*	*0.02*
LTG (0.61)	*vs.*	*GBP, LTG (0.35)*	*23*	*0.03*
LTG (0.44)	vs.	CBZ, LTG (0.25)	32	0.11
LTG (0.31)	vs.	OXC (0.06)	16	0.13
LEV, LTG (0.40)	vs.	LTG, ZNS (0)	10	0.13
LTG (0.52)	vs.	LEV (0.29)	31	0.14
LEV, LTG (0.42)	vs.	LTG (0.34)	77	0.17
CLB, LTG (0.52)	vs.	LTG (0.32)	25	0.18
OXC (0.31)	vs.	LEV (0.06)	16	0.22
LTG (0.45)	vs.	CBZ (0.33)	51	0.24
CBZ (0.29)	vs.	OXC (0.07)	14	0.25
LEV, LTG (0.38)	vs.	CBZ (0.15)	13	0.38
LEV, LTG (0.25)	vs.	CBZ, LTG (0.06)	16	0.38
LTG (0.29)	vs.	LTG, PGB (0.18)	17	0.50
LTG (0.82)	vs.	LTG, VPA (0.64)	11	0.50
CLB, LTG (0.36)	vs.	LEV, LTG (0.18)	11	0.50
LEV, LTG, PGB (0.36)	vs.	LEV, LTG (0.18)	11	0.50
ZNS (0.40)	vs.	LTG (0.20)	10	0.63
LTG (0.60)	vs.	LTG, TPM (0.47)	15	0.63
LEV, LTG (0.33)	vs.	CBZ, LEV, LTG (0.20)	15	0.63
CBZ, LTG (0.30)	vs.	CBZ (0.22)	23	0.63
ZNS (0.40)	vs.	CBZ (0.20)	10	0.63
VPA (0.40)	vs.	LEV (0.20)	10	0.63
CLB, LEV, LTG (0.33)	vs.	LEV, LTG (0.24)	21	0.69
CBZ (0.28)	vs.	LEV (0.17)	18	0.69
CBZ, LEV (0.09)	vs.	LTG (0)	11	> 0.999
LTG (0.30)	vs.	CLB, LEV, LTG (0.30)	10	> 0.999
CBZ (0.38)	vs.	CBZ, LEV (0.33)	24	> 0.999
CLB, LEV, LTG (0.36)	vs.	CLB, LTG (0.29)	14	> 0.999
PHT (0.14)	vs.	LTG, PHT (0.07)	14	> 0.999
LTG (0.27)	vs.	LTG, ZNS (0.27)	11	> 0.999
LEV (0.25)	vs.	LEV, LTG (0.25)	20	> 0.999
LEV (0.36)	vs.	CBZ, LEV (0.36)	11	> 0.999

[a] Significant comparisons ***bolded and italicized*** (significance cut-off value = 0.0015). Trends are *italicized* ($p < 0.05$).

three comparisons, the mean total drug load of LTG monotherapy was 1.37, while the mean total drug load of the less-effective regimens (average of PHT monotherapy, LTG/PHT, and LTG/GBP) was 1.76.

The mean number of previous regimens attempted (prior to and not including the regimen in question) was calculated for each of the significant comparisons. LTG monotherapy was attempted substantially later in the course of treatment (more than one additional prior attempt) than either PHT monotherapy or LTG/PHT duotherapy. See Table 3. Of the 20 patients that attempted both LTG monotherapy and PHT monotherapy, 16 (80.0%) had secondarily-generalized seizures and 15 (75%) had multiple seizure types.

3.2. Comparisons between a unique regimen (regimen X) and all other regimens attempted by patients who attempted regimen X

There were 44 unique AED regimens taken by ≥10 patients among whom one or more additional regimens were also tried at different times. The proportion of patients who achieved a remission during each unique regimen was compared with the proportion of other regimens attempted by the same patients which led to remission. For instance, if 10 patients had attempted regimen A, and additional regimens B–Z had also been attempted between the 10 patients, we first calculated the proportion of patients who had a remission on regimen A. We then divided this value by the proportion of all other regimen trials (trials of regimens B-Z) which led to a remission. Twenty-eight regimens exhibited a ratio above 1.00, while 14 were below 1.00. Five regimens exhibited ratios greater than 2.00. Ratios ranged from 0.00 (CBZ/PGB

Table 3
Mean previous attempts, doses, and drug loads for notable head-to-head comparisons.

Regimen A (Remission Proportion[a])	Mean Daily Dose (mg)	Mean Drug Load	Mean number of previous regimens attempted (Overall mean ± SD[b])		Regimen B (Remission Proportion[a])	Mean Daily Dose (mg)	Mean Drug Load	Mean number of previous regimens attempted (Overall mean ± SD[b])
LTG (0.75)	335	1.11	1.84 (1.06 ± 0.99)	vs.	PHT (0.15)	321	1.07	0.35 (0.52 ± 1.03)
LTG (0.65)	473	1.58	1.41 (1.06 ± 0.99)	vs.	LTG & PHT (0.23)	400 278	1.33 0.93	0.35 (0.69 ± 0.95)
LTG (0.61)	423	1.41	0.87 (1.06 ± 0.99)	vs.	GBP & LTG (0.35)	1278 373	0.71 1.24	1.17 (1.20 ± 1.32)

[a] Proportion of patients that had at least one remission period on regimen.
[b] Mean and standard deviation for that unique regimen among the total cohort.

Table 4
Comparisons of unique AED regimens vs. aggregates of other regimens[a].

Specific AED Regimen	N Pts	Total Regs[b]	Remission Rate (Specific Reg)[c]	Remission Rate (Other Regs)[d]	Risk Ratio	95% CI	Mantel-Haenszel P
LEV, LTG, PGB	14	53	35.7	12.8	2.79	0.95–8.19	0.14
LEV, OXC	*35*	*126*	*25.7*	*9.9*	*2.60*	*1.13–6.01*	*0.05*
LEV, VPA	15	60	33.3	13.3	2.50	0.89–7.02	0.18
LEV, LTG, TPM	11	52	27.3	12.2	2.24	0.63–7.94	0.45
LEV, PGB	18	67	44.4	20.4	2.18	1.02–4.64	0.10
CLB, LEV, LTG	*42*	*141*	*38.1*	*20.2*	*1.89*	*1.09–3.27*	*0.04*
LTG, TPM	30	94	50.0	31.3	1.60	0.96–2.66	0.13
LEV, LTG	***165***	***538***	***36.4***	***22.8***	***1.60***	***1.21–2.10***	***0.0020***
LTG	***283***	***813***	***48.4***	***30.6***	***1.58***	***1.33–1.89***	***< 0.001***
CBZ, TPM	20	82	15.0	9.7	1.55	0.43–5.64	0.80
CLB, LTG	51	170	37.3	24.4	1.53	0.95–2.46	0.13
GBP	28	105	32.1	22.1	1.46	0.74–2.88	0.43
GBP, LEV, LTG	14	46	35.7	25.0	1.43	0.57–3.60	0.70
GBP, LEV	20	80	30.0	21.7	1.39	0.61–3.16	0.65
LEV, ZNS	24	96	16.7	12.5	1.33	0.45–3.94	0.86
ZNS	45	163	26.7	20.3	1.32	0.72–2.39	0.51
OXC	65	230	23.1	17.6	1.31	0.76–2.30	0.44
PB	13	39	30.8	23.1	1.30	0.50–3.91	0.89
LTG, ZNS	37	125	18.9	14.8	1.28	0.56–2.95	0.76
LEV, LTG, VPA	10	38	30.0	25.0	1.20	0.38–3.77	0.91
TPM	25	82	44.0	36.8	1.20	0.68–2.09	0.72
CBZ, LEV	58	211	22.4	19.0	1.18	0.66–2.11	0.71
GBP, LTG	44	147	29.5	25.2	1.17	0.67–2.06	0.74
CBZ	138	440	29.0	28.1	1.03	0.75–1.41	0.95
LTG, PGB	36	110	25.0	24.3	1.03	0.51–2.06	0.87
CBZ, LTG	63	214	25.4	25.2	1.01	0.61–1.67	0.89
CBZ, ZNS	20	67	15.0	14.9	1.01	0.29–3.51	0.72
CBZ, VPA	22	84	22.7	22.6	1.01	0.41–2.47	0.78
OXC, ZNS	12	51	16.7	17.9	0.93	0.22–3.89	0.74
CBZ, GBP	28	116	17.9	19.3	0.92	0.38–2.28	0.92
CBZ, LEV, LTG	21	86	19.0	21.5	0.88	0.32–2.40	0.95
LTG, VPA	26	76	38.5	44.0	0.87	0.49–1.56	0.83
LEV	110	345	29.1	33.6	0.87	0.61–1.22	0.48
PGB	11	48	18.2	21.6	0.84	0.21–3.39	0.86
LTG, OXC	22	66	13.6	18.2	0.75	0.22–2.55	0.91
LEV, LTG, ZNS	10	32	20.0	31.8	0.63	0.16–2.50	0.79
PHT	50	163	20.0	33.6	0.60	0.32–1.10	0.12
VPA	35	112	20.0	33.8	0.59	0.28–1.23	0.21
CBZ, PHT	13	64	7.7	15.7	0.49	0.07–3.58	0.77
LEV, PHT	18	66	11.1	22.9	0.49	0.12–1.98	0.47
LTG, PHT	*42*	*135*	*16.7*	*35.5*	*0.47*	*0.23–0.97*	*0.05*
CBZ, CLB	23	80	13.0	28.1	0.47	0.15–1.44	0.26
PHT, VPA	12	49	8.3	18.9	0.44	0.06–3.23	0.68
CBZ, PGB	13	60	0.0	2.1	0.00	N/A	0.49

Key: AED = antiepileptic drug; CBZ = carbamazepine; CLB = clobazam; GBP = gabapentin; PGB = pregabalin; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; LEV = levetiracetam; PHT = phenytoin; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

[a] Includes regimens attempted by at least 10 patients. Significant regimens are ***bolded and italicized*** (significance cut-off value = 0.0023). Trends are *italicized* ($p < 0.05$).

[b] Total number of regimens attempted by the patients who had taken the specific regimen in question.

[c] Percentage of attempts leading to a remission period in the specific regimen in question.

[d] Percentage of attempts leading to a remission period in other regimens attempted by the same patients.

duotherapy; p = 0.492) to 2.79 (LEV/LTG/PGB tritherapy; p = 0.143).

As seen in Table 4, we found two unique regimens that were significantly more likely to lead to a remission than other regimens taken by the same patients. These effective regimens were (1) LEV/LTG duotherapy (risk ratio = 1.60, p = 0.002) and (2) LTG monotherapy (risk ratio = 1.58, p < 0.001). Two additional regimens showed marginally better efficacy but did not meet significance cut-offs: (1) LEV/OXC duotherapy (risk ratio = 2.60, p = 0.05) and (2) CLB/LEV/LTG tritherapy (risk ratio = 1.89, p = 0.04). LTG/PHT duotherapy exhibited a trend toward poorer efficacy (risk ratio = 0.47, p = 0.05).

As seen in Table 5, mean daily doses and drug loads were calculated for the five regimens that yielded significant or nearly significant risk ratios. Of these, patients on CLB/LEV/LTG tritherapy had the greatest total drug load (3.80). Patients on this regimen also took more daily LTG (mean dose = 543 mg) than patients on LTG monotherapy or LEV/LTG duotherapy.

We also determined seizure types among patients who attempted the two regimens that performed significantly better than other

Table 5
Mean daily doses and drug loads for notable regimens.

Regimen	AED	Mean Daily Dose (mg)	Mean Drug Load	Total Drug Load
LTG	LTG	424	1.41	1.41
LEV, LTG	LEV	1800	1.20	2.83
	LTG	489	1.63	
LEV, OXC	LEV	2376	1.58	3.01
	OXC	1432	1.43	
CLB, LEV, LTG	CLB	19.8	0.99	3.80
	LEV	1504	1.00	
	LTG	543	1.81	
LTG, PHT	LTG	444	1.48	2.56
	PHT	325	1.08	

Key: AED = antiepileptic drug; CLB = clobazam; LTG = lamotrigine; LEV = levetiracetam; PHT = phenytoin; OXC = oxcarbazepine.

Table 6
Within-patient head-to-head comparisons between monotherapy and polytherapy regimens, stratified by number of regimens attempted[a].

Type of Therapy (Proportion of patients that had at least one remission period)			Total Number of Regimens Attempted	Total N[b]	P
Poly (0.46)	*vs.*	*Mono (0.32)*	*≥4*	*117*	*0.012*
Tri (0.24)	vs.	Duo (0.18)	3	72	0.454
Duo (0.34)	vs.	Tri (0.28)	2	58	0.503
Tri (0.36)	vs.	Duo (0.32)	≥4	95	0.556
Poly (0.45)	vs.	Mono (0.42)	3	139	0.677
Mono (0.41)	vs.	Poly (0.39)	2	180	0.791

[a] Trends are *italicized* ($p < 0.05$).
[b] N includes only patients that attempted both types of therapy.

aggregated regimens. Of the 283 patients who attempted LTG monotherapy, 212 (74.9%) had a history of secondarily-generalized seizures, and multiple seizure types were reported in 225 (79.5%). Of the 165 patients who attempted LEV/LTG duotherapy, 130 (78.8%) had secondarily-generalized seizures documented as a seizure type, and 141 (85.5%) had multiple seizure types documented.

3.3. Comparisons between monotherapy and polytherapy

Among patients who had attempted both monotherapy and polytherapy regimens, we compared the number of patients who achieved a remission period on monotherapy with the number of patients who achieved a remission period on polytherapy. We stratified these patients according to the total number of regimens attempted by each patient, a proxy measure of epilepsy severity. None of these comparisons reached statistical significance. Among those patients who attempted four or more regimens, whom we considered as having more severe epilepsies, polytherapy exhibited slightly better efficacy than monotherapy (46% vs. 32%, $p = 0.012$), though this was not statistically significant, as shown in Table 6. No difference was seen between duotherapy and tri-therapy.

4. Discussion

In our cohort of patients with focal epilepsy who attempted at least 2 unique AED regimens, we found that a higher proportion of patients achieved seizure remission on lamotrigine monotherapy compared to phenytoin monotherapy. We also found fewer remissions in lamotrigine/phenytoin duotherapy in both of our analyses. The poor efficacy of lamotrigine/phenytoin duotherapy has also been established in comparison to other lamotrigine duotherapies (Brodie et al., 1997). One explanation for this is phenytoin's cytochrome P450 enzyme-inducing properties. Phenytoin comedication speeds the lamotrigine metabolism, leading to dramatically lower lamotrigine bioavailability (Perucca, 2005; Rambeck and May, 2005) This results in a 125% increase in lamotrigine clearance (Weintraub et al., 2005). Among patients who attempted both LTG monotherapy and comedication with PHT, LTG drug load was actually higher during monotherapy (1.58) than duotherapy (1.33).

Another characteristic of LTG/PHT duotherapy is that both agents have sodium channel blocking properties. When used in combination, they may lead to infra-additive mechanistic actions, meaning that doses required to achieve actions in combination are higher than expected based on data from the individual drugs (Brodie and Sills, 2011). If so, prescribers might have been concerned about potential adverse effects and were consequently less likely to use large enough doses for seizure control. This could explain why LTG drug load among this subset was lower during duotherapy with PHT. In theory, the comparatively worse performance of LTG/PHT duotherapy should also apply to LTG duotherapy with carbamazepine (CBZ), another sodium-channel blocker and cytochrome P450 inducer. Indeed, LTG monotherapy did outperform LTG/CBZ duotherapy in our study, although this head-to-head comparison was not statistically significant. Our results regarding the head-to-head comparison between LTG monotherapy and PHT monotherapy included a small subset of only 20 patients, and therefore should be interpreted with caution.

We also found that gabapentin/lamotrigine duotherapy showed poorer efficacy than lamotrigine monotherapy, although not statistically significant. After assessing whether each patient had been prescribed GBP exclusively for seizure control, we found that 10 of the 23 patients from this comparison had taken GBP for either neuropathic pain or insomnia. Of the remaining 13 patients, four had remission periods on LTG monotherapy but not LTG/GBP duotherapy. This comparison was not significant. The mean daily dose of GBP used by the 23 patients in this analysis was also relatively low (1278 mg; drug load = 0.71). Therefore, this finding should be interpreted with caution.

Our analysis of unique regimens versus aggregated other regimens attempted by the same patients revealed two unique regimens that may be effective: LEV/LTG duotherapy and LTG monotherapy. Two additional polytherapy regimens may have exhibited slightly better efficacy, but were outside the Benjamini-Hochberg cut-offs for significance: LEV/OXC duotherapy and CLB/LEV/LTG tri-therapy. Of the eight AED regimens with the highest overall rate ratios, seven were polytherapy regimens that included levetiracetam. This is consistent with previous studies, which found adjunctive levetiracetam to be more effective than adjunctive placebo at reducing seizure frequency (Lo et al., 2011; Mbizvo et al., 2012). Some have also suggested that broad spectrum AEDs may be more likely to provide additional seizure control if used in combination with a sodium channel blocker (Brodie and Sills, 2011; Kwan et al., 2011). In our study, all three polytherapy regimens for which we found any evidence of greater efficacy (either significance or trend) included levetiracetam and a sodium channel blocker: LEV/LTG, LEV/OXC, and CLB/LEV/LTG. Our results thus provide some support for the use of adjunctive levetiracetam in focal epilepsy. Moreover, given that LEV has not been implicated in pharmacokinetic AED interactions (Perucca, 2005), it may be less likely to exhibit supra-additive (synergistic) toxicity.

Lamotrigine was the only AED that provided superior efficacy when used as monotherapy. It was attempted by 283 patients in our cohort, far more than any other monotherapy or polytherapy regimen. We found that lamotrigine monotherapy was more likely to lead to remission than the aggregate of other regimens attempted, and particularly in comparison to phenytoin monotherapy (along with trends in favor of LTG monotherapy over LTG/PHT and GBP/LTG duo-therapies).

We did not find evidence to support synergism with the use of lamotrigine/valproate duotherapy, which has previously been reported by other investigators (Brodie et al., 1997; Moeller et al., 2009; Pisani et al., 1999; Poolos et al., 2012). This AED combination was attempted by only 26 patients in our cohort, which may account for part of the discrepancy in our results. Furthermore, our study was limited to patients with focal epilepsy types, whereas most of the previous evidence supporting LTG/VPA duotherapy comes from study populations with mixed epilepsy types (Brodie et al., 1997; Moeller et al., 2009; Poolos et al., 2012). One study did indicate strong efficacy of LTG/VPA duotherapy among patients with refractory complex partial seizures (Pisani et al., 1999).

Another finding in our study suggested a slight advantage of polytherapy over monotherapy among patients with severe focal epilepsy. Specifically, those who had previously attempted at least four AED regimens had slightly better outcomes with polytherapy than with monotherapy. This finding may be due to standard treatment practices, where polytherapy is not recommended unless multiple monotherapy trials have failed (Brodie, 2005; Kwan et al., 2011; St. Louis, 2009). On the other hand, the non-significant nature of this finding suggests a paucity of current standards regarding indications for polytherapy.

There were a number of limitations. First, this was a study based on chart review, conducted retrospectively at a single tertiary care center, and our cohort included both prevalent and incident cases. More specifically, only 116 of the 757 patients in our analysis were prescribed their first AED at CCEC. This limits the generalization of our results, as our cohort may be skewed to more severe epilepsies, and our data may be influenced by prescription preferences of the individual physicians at our center. Second, we did not consider changes in either seizure severity or seizure frequency (other than seizure freedom) that may have been associated with specific AED regimen, thereby reducing the granularity of efficacy data of various regimens. A previous retrospective analysis of unique AED regimens used reduction in seizure frequency associated with unique regimens as an outcome variable (Poolos et al., 2012). Assessment of seizure frequency was feasible in the previous study as the study cohort was composed of developmentally-disabled adults living under close supervision in a group home. While we did have some seizure frequency data available in our database, this data was of limited use due to its inconsistent availability among patients and lack of clarity regarding seizure types. Third, neither our study nor the previous retrospective analysis (Poolos et al., 2012) examined side effects or blood levels. These are crucial considerations during clinical selection of AEDs. Although our research database tracks patient-reported side effects, chart review is an indirect means of recording this information and would have been unreliable for our small-sample comparisons. We also omitted data from AED regimens which were attempted briefly and discontinued due to adverse effects, which may have shifted our data in favor of AED regimens with a more tolerable side-effect profile. Our research database does track blood levels when they are available; however, many of the drug regimens in our analysis did not have associated blood level data, rendering the limited data on levels unreliable for our analysis. Some prospective trials of AED polytherapy are limited by using total drug loads that are too low; in practice, ideal drug combinations should allow for a higher total load because they will exhibit infra-additive toxicity. Fourth, we recognize that our outcome of ≥6 months seizure freedom, an endpoint that has been used in drug trials (Brodie et al., 2007), is short, in contrast to outcomes studies that have required a minimum of 12 months or more of seizure freedom (Brodie et al., 2012; Choi et al., 2016). However, given that the comparisons of efficacy between different AED regimens were calculated as within-patient ratios, we hoped to increase the chance of detecting potentially effective polytherapy regimens by using a less restrictive endpoint. Additionally, we found that within our dataset, drug regimens leading to seizure-free periods ≥12 months were almost identical to regimens leading to seizure-free periods ≥6 months in terms of likelihood of complete seizure freedom (respectively 36.6% and 36.4%). This does not imply that our 6-month outcome is superior to a 12-month outcome, or that any binary outcome measure is superior to an assessment of seizure frequency. However, it does suggest that our primary outcome of ≥6 months of seizure freedom may represent an adequate length of time to estimate overall level of control.

5. Conclusions

Our study identified two AED regimens that may be especially effective in management of focal epilepsy: lamotrigine monotherapy and levetiracetam/lamotrigine duotherapy. We also found two more polytherapy regimens with successful outcomes that were slightly below our specific threshold for statistical significance: clobazam/levetiracetam/lamotrigine and levetriacetam/oxcarbazepine.

The unique regimens that were identified in this study are suggestive and will need to be confirmed in prospective studies. This is especially true for the three polytherapy regimens in which we found superior efficacy or a trend toward positive outcomes. None of these regimens has been established in a controlled format. Individual characteristics of each patient's epilepsy type also play an important role in rational AED polytherapy; larger pools of data, which would help match patients based on unique characteristics, have been suggested for this purpose (McCabe, 2015).

Our results indicate that rational AED polytherapy has a bright future in epilepsy care, but much of the work still lies ahead.

Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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