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Comparative efficacy of combination drug therapy in refractory epilepsy

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ABSTRACT

Objective: We retrospectively examined treatment records of developmentally disabled adults with highly refractory epilepsy to determine whether any combinations of 8 of the most commonly used antiepileptic drugs (AEDs) possessed superior efficacy.

Methods: We obtained the treatment records from 148 developmentally disabled adults with refractory epilepsy cared for in 2 state-run institutions. These records charted monthly convulsive seizure occurrence and AED regimen over 30 years. We studied the effects of 8 commonly used AEDs alone and in combination on seizure frequency in within-patient comparisons.

Results: Out of the 32 most frequently used AED combinations, we found that only the combination of lamotrigine and valproate had superior efficacy, measured against both an aggregate measure of other AED regimens to which patients were exposed, and in head-to-head comparisons with other AED combinations. We also found that while use of 2 concurrent AEDs provided improved efficacy over monotherapy, use of 3 AEDs at a time provided no further benefit over two.

Conclusions: These results suggest that at least one AED regimen provides significantly better efficacy in refractory convulsive epilepsy, and that AEDs should be used no more than 2 at a time. Limitations of the study include its retrospective design, lack of randomization, and small sample sizes for some drug combinations. Future prospective trials are needed in this challenging clinical population. *Neurology*® 2012;78:62–68

GLOSSARY

AED = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **DD** = developmentally disabled; **LTG** = lamotrigine; **OXC** = oxcarbazepine; **PB** = phenobarbital; **PHT** = phenytoin; **SFR** = seizure frequency ratio; **TPM** = topiramate; **VPA** = valproate; **ZNS** = zonisamide.

The majority of patients with epilepsy have good control of seizures, defined as at least 12 months of continuous seizure freedom. Several large prospective trials studying antiepileptic drug (AED) retention as their primary outcome measure (the likelihood that an AED will not be discontinued due to poor efficacy or intolerable side effects) in either new-onset or established epilepsy found significant differences among AEDs used in monotherapy, with less pronounced differences in efficacy alone (the impact of AEDs on seizure frequency).[1–4] However, about one-third of patients with epilepsy are medically refractory, defined as uncontrolled seizures despite multiple AED trials.[5,6] Refractory patients are usually treated with combinations of 2 or more AEDs, and while there have been small prospective or retrospective studies that have evaluated the efficacy of selected AED combinations, there has been little evidence from large-scale studies or from consideration of AED mechanisms of action to guide clinical decision-making.[7,8] Thus the question of whether any AED combination yields superior efficacy in patients with refractory epilepsy remains open. Because of this longstanding clinical challenge, identification of any AED regimen with superior efficacy in patients with refractory epilepsy would be a substantial advance.[9,10]

Supplemental data at www.neurology.org

Supplemental Data

From the Department of Neurology and Regional Epilepsy Center (N.P.P.), Neurobiology Program (L.N.W.), and School of Pharmacy (S.Z.H.), University of Washington, Seattle; Fircrest Residential Habilitation Center (S.Z.H.), Shoreline; and Rainier Residential Habilitation Center (S.W.), Buckley, WA.

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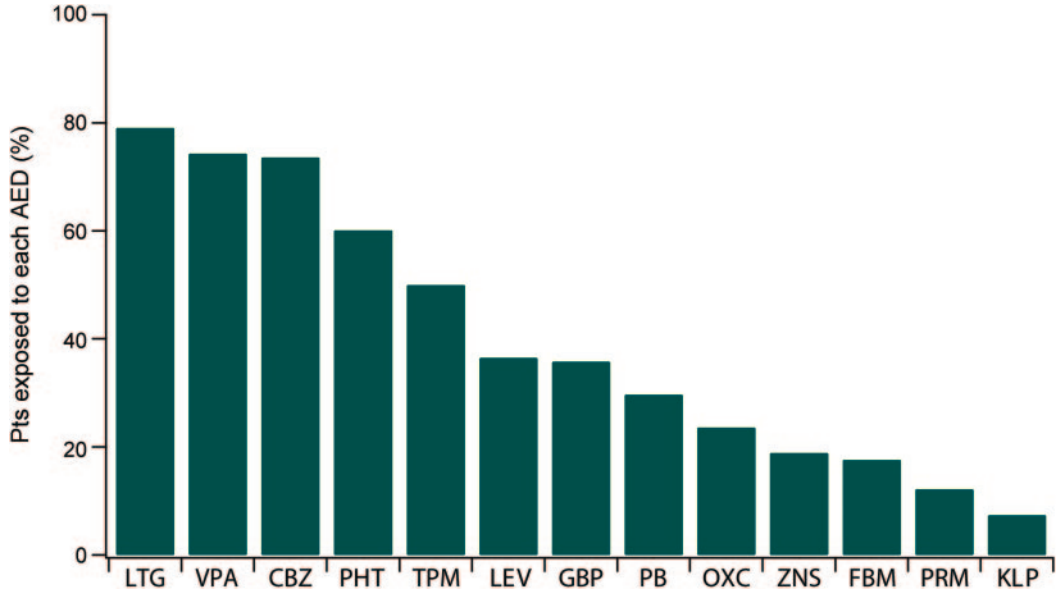
Figure 1 Antiepileptic drug (AED) exposures of study patients



The drugs studied here, from most to least frequently used, were lamotrigine (LTG) . . . gabapentin (GBP), and zonisamide (ZNS). CBZ = carbamazepine; FBM = felbamate; KLP = clonazepam; LEV = levetiracetam; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PRM = primidone; TPM = topiramate; VPA = valproate.

To address this question, we examined records collected over 30 years documenting the treatment of 2 populations of institutionalized developmentally disabled (DD) patients with refractory epilepsy, and compared the efficacy of various AED regimens, including both older and newer-generation drugs.

METHODS We obtained epilepsy treatment records for a population of severely DD adults residing at 2 state-run institutions: the Fircrest Residential Habilitation Center in Shoreline, Washington (85 patients), and the Rainier Residential Habilitation Center in Buckley, Washington (63 patients). Records dating from 1980 to the present documented monthly seizure occurrence (primarily convulsive seizures) observed by nursing staff, AED dosages, and basic demographic and diagnostic data. AED serum level data were not consistently recorded for all drugs and were not used in this analysis. Epilepsy diagnoses and treatment recommendations were made by a rotating staff of consulting neurologists who specialized in epilepsy (including author N.P.P.).

Patients included in the study were diagnosed with epilepsy and were medically refractory, defined as at least 1 seizure per year despite at least 2 different treatment trials with AEDs. There were 13 drugs to which at least 5% of patients had been exposed, as shown in figure 1. We studied the 8 most frequently used AEDs (in decreasing order of frequency): lamotrigine (LTG) through zonisamide (ZNS). We excluded phenobarbital (PB) and oxcarbazepine (OXC) because these drugs were primarily used at only 1 institution, preventing independent comparison of results at both institutions. We excluded patient data in months with exposure to AEDs other than the study AEDs; months with exposure to more than 3 concurrent AEDs; or data obtained after epilepsy surgery or vagal nerve stimulator implantation. We only used data where there was at least 4 months of exposure to a given AED combination to avoid the variability inherent in short-term trials where AEDs were likely discontinued for tolerability issues.

We calculated the average seizure frequency (seizures/month) during the entire time of exposure to each AED combination. We did not account for changes in AED dosing during each period of exposure since the average exposure duration for each combination was in excess of 2 years, and AED dosages were at steady-state for the majority of the period. Comparisons of efficacy between different AED regimens were calculated as within-patient ratios of the seizure frequency (seizure frequency ratio [SFR]). SFR < 1 implied superiority of the index regimen compared to another, whereas SFR > 1 implied inferiority. This method normalized for differences in average seizure frequency among patients. For AED trials where no seizures were recorded, seizure frequency was set as follows:

1/(number of months of treatment with that regimen)

This avoids the possibility of division by zero in calculations of the ratio of seizure frequencies between 2 regimens. (For example, in a 12-month trial with no seizures, seizure frequency was set as 0.083.) Statistics on SFR data were performed after log-transformation of the data and are expressed as means $\pm$ 95% confidence intervals (CIs). Statistics on demographic data are expressed as means $\pm$ standard errors. Statistical significance was calculated using 2-sided t tests with $\alpha = 0.05$ and without correction for multiple comparisons.

Standard protocol approvals, registrations, and patient consents. Approval was obtained from the Washington State Institutional Review Board. This included approval to perform records-based research without patient consent, owing to the patients' severely diminished cognitive status.

RESULTS Demographic characteristics of this DD patient population are shown in table 1. Genetic syn-

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Table 1 Characteristics of study patients

Demographics	Values
No. of patients	148
Male patients, %	60.8
Female patients, %	39.2
Mean (SD) age at entry into study, y	51.1 (±0.86)
Neurologic diagnosis, % of total	
Genetic syndromes	12.8
Lennox-Gastaut syndrome	8.1
Perinatal insult	8.1
CNS infection	6.1
Congenital CNS structural abnormality	2.7
Unknown or idiopathic	52.7
EEG findings, % of total	
Focal or multifocal abnormality	38.8
Generalized abnormality	16.3
Mixed focal/generalized abnormalities	8.2
Nonepileptiform abnormality	19.0
Normal	2.7
No information	15.0

dromes, idiopathic Lennox-Gastaut syndrome, and perinatal hypoxic-ischemic insults were common neurologic diagnoses. However, most patients carried the idiopathic diagnosis of "static encephalopathy." Routine EEG testing showed that 63% of all patients had epileptiform abnormalities, or 74% of patients for whom EEG results were available. There was a predominance of focal (or multifocal) over generalized EEG abnormalities, along with nonepileptiform but abnormal findings such as slowing.

We analyzed an average of 140 months (±5.8, n = 148) of epilepsy treatment data for each patient. Mean seizure frequency was 3.2 per month (±0.39, n = 148). Patients were exposed to a median of 4 (interquartile range 3–6; mean 4.7) different combinations of 1-drug (monotherapy), 2-drug (duotherapy), or 3-drug (tritherapy) regimens. Like most refractory epilepsy patients, they were predominately exposed to combinations of AEDs (145 out of 148 patients) as opposed to monotherapy regimens only.

It is a tenet of epilepsy treatment that increased number of concurrent AEDs used in combination should produce improved seizure control. We tested this hypothesis by calculating for each patient the ratio of the average seizure frequency observed during all duotherapy regimens to that seen during all monotherapy regimens. Because this ratio was calculated as a within-patient comparison, it normalized for seizure frequency differences among patients. We found that the average seizure frequency during duotherapy was 0.81 ([0.68–0.98], n = 145, $p = 0.03$) of that during monotherapy, a 19% decrease. This accords well with adjunctive trials of new AEDs in refractory epilepsy patients that have typically shown 15%–30% improvement in seizure frequency when corrected for placebo effect (reviewed in[11]). Unexpectedly, seizure frequency during tritherapy was 1.07 ([0.88–1.30], n = 76, $p > 0.05$) times that seen during duotherapy, demonstrating no benefit on the average of a third drug added to a regimen already containing 2 drugs. Patients treated with 3 drugs had more severe epilepsy than those who were only exposed to 1 or 2 drugs, with average seizure frequency of 4.6 seizures per month (±0.69, n = 76), compared to patients who received only monotherapy or duotherapy (1.7 ± 0.23, n = 72, $p = 0.0001$). Correspondingly, patients who received only monotherapy and duotherapy showed a seizure frequency on duotherapy that was 0.72 ([0.54–0.96], n = 67, $p = 0.02$) of that on monotherapy, a 28% decrease that was a larger improvement with duotherapy than was seen in the population as a whole.

We then examined whether there were any AED combinations that produced superior efficacy when compared to all other AED regimens a given patient had received. We sequentially calculated the ratio of the average seizure frequency observed during each AED combination to the aggregate average seizure frequency during all other AED combinations to which the patient had been exposed. Thus, if a patient had been exposed to 3 different AED combinations "A," "B," and "C," we calculated the ratio of seizure frequency during regimen A to the average seizure frequency during both B and C; then compared seizure frequency during B to the average during A and C; and so forth. Out of 32 different combinations of 1, 2, or 3 AEDs with at least 5 patient exposures (shown in table 2), only the combination of LTG and valproate (VPA) produced decreased seizure frequency compared to the aggregate average of all other combinations to which each patient had been exposed (0.52 [0.40–0.66], n = 40, $p = 3 \times 10^{-6}$). A similar effect magnitude was seen independently in the Fircrest (0.51 [0.39–0.65], n = 31, $p = 4 \times 10^{-6}$) and the Rainier populations (0.54 [0.23–1.23], n = 9, $p > 0.05$). Several other AED combinations showed improved efficacy that did not quite achieve statistical significance, including LTG/VPA/topiramate (TPM) and carbamazepine (CBZ)/TPM. Although we did not correct the p values in table 2 for multiple comparisons, the effect of LTG/VPA remained highly significant even with Bonferroni correction ($\alpha = 0.002$).

There were only 6 AED trials of 12 months or longer where no seizures were recorded (average trial length 31 ± 9.0 months). The AED combinations

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Table 2 Comparative efficacy of individual AED combinations to the aggregate average of other regimens to which each patient had been exposed[a]

AED combination	No.	SFR average	CI	*p*
CBZ	66	1.06	0.82-1.37	0.66
CBZ/VPA	54	1.08	0.83-1.40	0.56
VPA	50	1.20	0.91-1.59	0.18
VPA/PHT	41	1.10	0.85-1.41	0.47
LTG/VPA	40	0.52	0.40-0.66	3×10^{-6}
CBZ/PHT	38	1.20	0.88-1.64	0.24
PHT	33	1.21	0.81-1.80	0.34
LTG	30	0.76	0.50-1.17	0.20
LTG/CBZ	28	1.25	0.90-1.73	0.18
LTG/PHT	20	0.99	0.76-1.29	0.94
VPA/GBP	18	1.40	0.93-2.12	0.10
LTG/TPM	16	1.06	0.75-1.49	0.74
LTG/LEV	15	0.77	0.33-1.78	0.51
CBZ/TPM	15	0.53	0.26-1.08	0.08
LTG/VPA/TPM	13	0.46	0.20-1.06	0.07
LTG/VPA/PHT	11	0.98	0.71-1.37	0.91
VPA/TPM	11	0.81	0.46-1.42	0.42
CBZ/VPA/PHT	11	1.02	0.54-1.93	0.93
PHT/GBP	10	1.04	0.53-2.05	0.90
LTG/VPA/LEV	9	0.66	0.34-1.26	0.18
CBZ/GBP	9	0.92	0.36-2.34	0.85
LTG/VPA/GBP	9	0.76	0.48-1.20	0.20
LTG/TPM/LEV	9	1.15	0.63-2.10	0.60
TPM/PHT	8	0.79	0.35-1.79	0.52
TPM	7	1.44	0.84-2.46	0.15
VPA/LEV	7	0.71	0.38-1.31	0.22
LTG/CBZ/PHT	7	0.91	0.48-1.74	0.74
LTG/ZNS	6	0.93	0.78-1.11	0.32
CBZ/LEV	5	1.19	0.42-3.40	0.67
CBZ/PHT/GBP	5	2.09	0.79-5.49	0.10
TPM/LEV	5	0.64	0.30-1.38	0.18
LTG/CBZ/VPA	5	1.42	0.47-4.23	0.43

AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval; LEV = levetiracetam; LTG = lamotrigine; PHT = phenytoin; SFR = seizure frequency ratio; TPM = topiramate; VPA = valproate; ZNS = zonisamide.
[a] SFR <1 indicates decreased seizure frequency for the combination listed vs the aggregate average; SFR >1 indicates increased seizure frequency. *p* Value is for comparison vs SFR = 1.0.

Table 3 Statistically significant head-to-head comparisons of AED combinations[a]

Combination 1	Combination 2	SFR average (no. 1/ no. 2)	*p*	No.
LTG/VPA	VPA	0.48	0.004	20
LTG/VPA	CBZ/VPA	0.45	4×10^{-5}	19
CBZ/TPM	CBZ	0.48	0.043	14
LTG/VPA	LTG	0.54	0.029	13
LTG	VPA	0.31	0.026	10
LTG/VPA	VPA/GBP	0.45	0.035	9
LTG/VPA/GBP	VPA/GBP	0.55	0.041	8
CBZ/PHT	CBZ/VPA/PHT	0.71	0.042	7
LTG	VPA/PHT	0.36	0.025	6
LTG/VPA	CBZ/VPA/PHT	0.39	0.012	5

AED = antiepileptic drug; CBZ = carbamazepine; LTG = lamotrigine; PHT = phenytoin; SFR = seizure frequency ratio; TPM = topiramate; VPA = valproate.
[a] In this table, combination 1 is shown as the superior regimen in each row, with decreased seizure frequency compared to combination 2.

(and the number of patients exposed) that produced these periods of seizure freedom were as follows: LTG/VPA (2); LTG (2); VPA (1); and CBZ/phenytoin (PHT) (1). The patients in whom seizure-free periods were observed had a much lower baseline seizure frequency (on all other drug regimens aside from the one producing seizure freedom) than the average patient (0.42 ± 0.13 seizures/month).

Comparing the seizure frequency seen with a given AED combination to the average of all other combinations to which a patient has been exposed is a pragmatic metric of AED regimen efficacy as it identifies a regimen that appears to stand out in clinical practice. But because the composition of the regimens differs from patient to patient, what each combination is being compared to varies. Thus, to identify regimens with superior efficacy in head-to-head comparisons, we calculated the SFR seen with each AED regimen sequentially to every other in within-patient comparisons. There were 86 different head-to-head comparisons with at least 5 exposures, shown in table e-1 on the *Neurology*® Web site at www.neurology.org. In this list, it can be seen that the majority of head-to-head comparisons of frequently used AED combinations produced only modest differences in efficacy (<20%) that did not achieve statistical significance. However, 10 comparisons achieved statistical significance and are listed in table 3. In this list, combinations containing LTG/VPA were superior to 6 other AED combinations, including either LTG or VPA used in monotherapy. Example data in figure 2 show an individual patient's response to LTG and VPA in monotherapy and in combination, demonstrating markedly improved response to the drugs in combination. The results of the head-to-head comparisons appear to validate the finding that identified LTG/VPA as uniquely efficacious when tested against the aggregate average of

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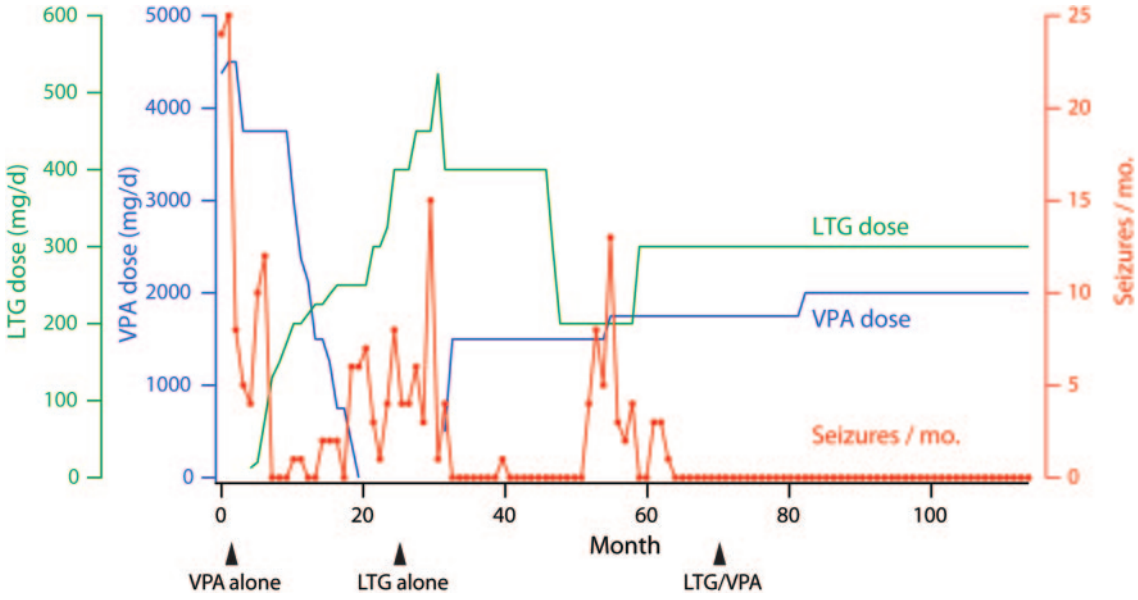
Figure 2 Example patient data show dramatically decreased seizure frequency in response to lamotrigine (LTG)/valproate (VPA) combination therapy compared to either VPA or LTG monotherapy



other AED combinations. And although the p values shown in table 3 were not corrected for multiple comparisons, it would appear highly unlikely that the predominance of LTG/VPA-containing regimens would arise by chance.

We asked whether there were features of the LTG/VPA-exposed cohort that predisposed them to an improved response with this combination. The average seizure frequency of LTG/VPA-exposed patients during all AED regimens except LTG/VPA was comparable (4.2 ± 0.92 seizures/mo, n = 40) to patients not exposed to LTG/VPA (3.0 ± 0.43, n = 108, $p > 0.05$). However, the efficacy of LTG/VPA compared to the aggregate average of all other AED combinations differed by EEG findings: patients with focal or multifocal EEG abnormalities showed a more improved SFR (0.55 [0.43–0.69], n = 15, $p <$ 0.0001 vs SFR = 1) than those with generalized abnormalities (0.72 [0.40–1.30], n = 9, $p > 0.05$). Finally, we asked whether the superior effectiveness of LTG/VPA arose from a pharmacokinetic or a pharmacodynamic interaction between the 2 drugs. VPA decreases the hepatic clearance of LTG to ~1/3rd its value in monotherapy, thus increasing LTG steady-state serum level by about a factor of 3.[12] There were few determinations of LTG serum levels, thus we could not definitively evaluate this question. However, paired comparisons in patients who underwent trials of both LTG monotherapy and LTG/VPA duotherapy showed that the average LTG dose in monotherapy was 2.90 (±0.13, n = 13) times the LTG dosage used in combination with VPA, suggesting that serum LTG levels in these 2 conditions were similar. Since patients receiving LTG/VPA had ~50% of the seizure frequency of patients receiving LTG alone (table 3), it does not appear that a pharmacokinetic effect of VPA on LTG steady-state serum concentration explains its increased efficacy in comparison to LTG alone.

DISCUSSION We used an extensive database of the treatment of DD, medically refractory epilepsy patients to determine whether there were any AED combinations with improved efficacy. We found that a single AED combination, LTG with VPA, was superior to others tested, both in comparison to an aggregate average of other AED regimens and in head-to-head regimen comparisons. In both measures, LTG/VPA reduced seizure frequency by 50% or greater in comparison to other regimens, although only rarely produced seizure freedom. We also found, somewhat to our surprise, that patients who were poorly controlled on a 2-drug AED regimen were not benefitted by the addition of a third drug.

This study examined AED therapy in refractory patients in a broad-based fashion without prior assumptions as to which regimens to test. Previous large, prospective studies of AED retention and efficacy have studied new-onset epilepsy, or a mixture of new and established (but not necessarily refractory) patients treated with monotherapy regimens. However, refractory patients are largely treated with combinations of AEDs, thus the problem of identifying which combination might be most effective is subject to daunting arithmetic. Considering the 8 most commonly used drugs in this study, there are 92 unique

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combinations of these AEDs taken 1, 2, or 3 at a time, and more than 4,000 possible head-to-head comparisons of those combinations. To assess the differential efficacy of all of these combinations solely in head-to-head comparisons would require tens of thousands of patient exposures.

Our study, with approximately 700 AED combination patient exposures, circumvented this problem by first comparing individual AED combinations to an aggregate measure of all other combinations to which a patient had been exposed, allowing greater statistical power to assess the efficacy of individual combinations. LTG/VPA stood out in remarkable fashion from all other regimens using this measure. Head-to-head comparisons supported this finding, with LTG/VPA constituting the majority of all superior head-to-head comparisons. A number of other frequently used AED combinations, consisting of both older and newer drugs, showed little difference in efficacy whether in aggregate or head-to-head comparisons.

The advantages of our approach to this study include a comprehensive database of AED exposures in highly refractory patients that extended back some 3 decades and on the average tracked patient outcomes over nearly 12 years each. Patients' epilepsy diagnoses were established by consulting epileptologists, and supported by epileptiform abnormalities in 74% of patients with EEG testing. Seizures were objectively recorded by nursing staff and not self-reported as in most trials. The use of within-patient comparisons normalized for differences in seizure frequency among patients.

There are several limitations of this study, including its retrospective nature, lack of randomization, inclusion of only the 8 most commonly used AEDs, lack of correlation of effects with drug dosage or serum levels, and the lack of sufficient patient numbers to assess many of the AED combinations with adequate statistical power. Our study focused on efficacy and did not assess AED regimen tolerability, an important factor in AED retention over time. Nursing staff almost exclusively reported convulsive seizures (presumably both primarily and secondarily generalized in onset); therefore whether nonconvulsive complex partial or generalized seizures would show similar responses to the various AED combinations is unknown. And since the study population consisted of DD adults, it is possible that their response to AEDs may not be representative of refractory epilepsy patients in the general population. Our study patients had a predominance of focal over generalized EEG abnormalities (~2:1 ratio), similar to that in other large studies of DD children and adults with refractory epilepsy.[13,14] This might suggest that our patients have a predominance of localization-related over generalized epilepsy syndromes, although since not all seizure types were characterized in our patients, their epilepsy syndrome diagnosis is unclear. Some studies have suggested that in DD children and adults, symptomatic generalized epilepsy syndromes such as Lennox-Gastaut syndrome predominate (reviewed in[15]). Thus, epilepsy in DD populations likely differs from the general refractory epilepsy population where there is a large predominance of localization-related over generalized epilepsy syndromes (about 5:1),[16] and this may limit the applicability of our findings to the general population. Of note, in our study LTG/VPA was more effective in patients with focal EEG abnormalities than in those with generalized abnormalities, suggesting that its superior efficacy in this population was not due to a preferential action on generalized epilepsy syndromes.

There is support in the literature for the superior effectiveness of the LTG/VPA combination in the general population in comparison to LTG/CBZ and LTG/PHT,[17,18] or to either LTG or VPA in monotherapy.[19] LTG/VPA was also the most-frequently used duotherapy combination in a large survey of DD adults with epilepsy.[13] It has been suggested that LTG/VPA may be more effective based on pharmacodynamic synergism between the 2 drugs' mechanisms of action.[17] VPA exerts a well-known pharmacokinetic effect on LTG metabolism, reducing its hepatic clearance[12,20]; however, prior studies of the effectiveness of the LTG/VPA combination did not control for this phenomenon. Our study data suggest that the effectiveness of LTG/VPA was not explained by a pharmacokinetic effect of VPA on LTG serum concentration. In the absence of serum drug level data, however, this question remains unresolved.

The present study suggests that the combination of LTG/VPA possesses superior efficacy in refractory epilepsy, a condition for which there has been little evidence-based guidance on which to base treatment decisions. This conclusion should ideally be confirmed in a prospective study of refractory patients, preferably from the general population. The current study does not rule out the existence of other AED regimens with improved efficacy, such as CBZ/TPM, for which the numbers of observations were small. Our results also suggest that since 3-drug AED combinations did not provide additional benefit over 2-drug combinations, use of AED combinations in clinical practice might best involve no more than 2 drugs at a time. This approach may lessen the increased toxicity that accompanies increasing number of AEDs, while not sacrificing efficacy.

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AUTHOR CONTRIBUTIONS

Nicholas Poolos conceived of the study, analyzed the data, and drafted the manuscript. Lindsay Warner analyzed the data and revised the manuscript. Sophia Humphreys analyzed the data and revised the manuscript. Stephen Williams analyzed the data and revised the manuscript.

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DISCLOSURE

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