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Association between antiepileptic drug dose and long-term response in patients with refractory epilepsy

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ABSTRACT

Seizures in patients with medically refractory epilepsy remain a substantial clinical challenge, not least because of the dearth of evidence-based guidelines as to which antiepileptic drug (AED) regimens are the most effective, and what doses of these drugs to employ. We sought to determine whether there were regions in the dosage range of commonly used AEDs that were associated with superior efficacy in patients with refractory epilepsy. We retrospectively analyzed treatment records from 164 institutionalized, developmentally disabled patients with refractory epilepsy, averaging 17 years of followup per patient. We determined the change in seizure frequency in within-patient comparisons during treatment with the most commonly used combinations of 12 AEDs, and then analyzed the response to treatment by quartile of the dose range for monotherapy with carbamazepine (CBZ), lamotrigine (LTG), valproate (VPA), or phenytoin (PHT), and the combination LTG/VPA. We found that of the 26 most frequently used AED regimens, only LTG/VPA yielded superior efficacy, similar to an earlier study. For the monotherapies, patients who were treated in the lowest quartile of the dose range had significantly better long-term reduction in seizure frequency compared to those treated in the 2nd and 3rd quartiles of the dose range. Patients with paired exposures to CBZ in both the lowest quartile and a higher quartile of dose range experienced an increase in seizure frequency at higher doses, while patients treated with LTG/VPA showed improved response with escalation of LTG dosage. We conclude that in this population of patients with refractory epilepsy, LTG/VPA was the most effective AED combination. The best response to AEDs used in monotherapy was observed at low dosage. This suggests that routine exposure to maximally tolerated AED doses may not be necessary to identify those patients with drug-resistant seizures who will have a beneficial response to therapy. Rather, responders to a given AED regimen may be identified with exposure to low AED doses, with careful evaluation of the response to subsequent titration to identify non-responders or those with exacerbation of seizure frequency at higher doses.

1. Introduction

Medically refractory epilepsy, defined as continuing seizures despite adequate trials of at least two antiepileptic drugs (AEDs), remains a significant health burden, affecting one-third of the approximately three million people in the US with epilepsy [1]. Despite the prevalence of refractory epilepsy, there are few evidence-based guidelines for its optimal treatment. Most prospective studies have focused on the initial monotherapy of new-onset epilepsy [2–5]. The American Academy of Neurology has published a consensus statement assessing the efficacy of individual AEDs when used as adjunctive therapy in refractory epilepsy, but no guidelines have been issued on the comparative efficacy of AEDs, either used as monotherapy or in combination [6]. Thus neurologists and other clinicians have little guidance but their own experience as to which AEDs are most effective in refractory epilepsy, and what doses to employ.

In a previous study, we addressed the question of the comparative efficacy of AED regimens in an analysis of treatment records from developmentally disabled patients at two Washington State institutions [7]. This unique database recorded the monthly convulsive seizure occurrences in a population of 146 patients, the AEDs used, and their daily dosages. A strength of this database was its extended longitudinal followup, averaging at that time 12 years per patient, with analysis of the eight most frequently used AEDs in regimens of as many as three drugs given at a time. We analyzed the comparative efficacy of differing regimens in within-patient comparisons, thus normalizing for inherent

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differences in seizure frequency among patients. The principal conclusion of this study was that only one AED regimen, the combination of lamotrigine (LTG) and valproate (VPA), demonstrated significant superiority in antiepileptic efficacy. The efficacy of LTG and VPA together greatly exceeded the sum of the efficacies of the component drugs used in monotherapy, and it was suggested that this represented pharmacodynamic synergy, that is, superior efficacy based on as yet unclear cellular or molecular mechanisms of action of the two drugs. Other, more focused studies have also supported the superiority of the LTG/VPA combination [8,9].

Our prior study analyzed AED efficacy without reference to the dosages used. This leaves open the question of whether some AEDs, even if failing to show overall superior efficacy, might be more effective when used in some region of their usual range of daily doses. Common clinical practice is to introduce an AED and escalate dosage to maximal tolerated levels while assessing response. In new-onset epilepsy, however, several studies have shown that the majority of patients who will become seizure-free do so at low doses of AEDs, and that the benefits of further dose escalation are modest [10,11]. Outside of clinical trials, there is a paucity of studies examining the relationship of AED dose and long-term response to therapy in patients with refractory epilepsy.

To address these questions, we first re-analyzed the overall efficacy of frequently used AED regimens using an expanded database comprising the responses to 12 different AEDs alone and in combination over an average of 17 years of followup per patient. We then analyzed the efficacy of the four AEDs most frequently used in monotherapy in our database (carbamazepine [CBZ], VPA, phenytoin (PHT), and LTG), as well as the combination LTG/VPA, with respect to daily dosage by dividing the entire range of daily dosages into quartiles, and determining the comparative efficacy in each dosage quartile for the AED regimens studied. This allowed us to determine how AED efficacy varied with dosage in a retrospective analysis.

2. Material and methods

2.1. Data collection

We obtained epilepsy treatment records for 164 developmentally disabled adults residing at two state-run institutions, the Fircrest Residential Habilitation Center in Shoreline, WA (86 patients) and the Rainier Residential Habilitation Center in Buckley, WA (78 patients). Approval was obtained from the Washington State Institutional Review Board allowing records-based research without patient consent, owing to the patients' diminished cognitive status. Records dating from 1980 to 2015 documented monthly seizure occurrence (primarily convulsive seizures) observed by nursing staff, AED dosages, and basic demographic and diagnostic data. A rotating staff of consulting neurologists who specialized in epilepsy (including author N.P.P.) made epilepsy diagnoses and treatment recommendations. Treatment decisions as to AED regimen composition, dosage level, and rate of introduction of each AED had been made according to each clinician's preferences, and not according to any formal protocol.

Patients included in the study were diagnosed with epilepsy and their seizures were medically refractory, defined as at least one seizure per year despite at least two different treatment trials with AEDs. We studied the 12 most frequently used AEDs as shown in Table 1. We excluded patient data in months with exposure to AEDs other than the study AEDs; months with exposure to more than three concurrent AEDs; months where AED dose was not constant; or data obtained after epilepsy surgery or vagal nerve stimulator implantation. We only analyzed data where there was at least four 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.

Table 1
Antiepileptic drug exposures in the study population including both monotherapy and polytherapy exposures. LTG, VPA, CBZ, and PHT were the most frequently used AEDs.

AED	Abbreviation	No. of patients exposed
Lamotrigine	LTG	128
Valproate	VPA	128
Carbamazepine	CBZ	126
Phenytoin	PHT	95
Topiramate	TPM	87
Levetiracetam	LEV	78
Gabapentin	GBP	59
Phenobarbital	PB	59
Oxcarbazepine	OXC	45
Lacosamide	LAC	38
Zonisamide	ZNS	36
Pregabalin	PGB	17

2.2. Analysis methods

We calculated the average seizure frequency (seizures/month) during the entire time of exposure to each AED combination. Comparisons of efficacy for different AED regimens were calculated as within-patient ratios of the average seizure frequency on that index regimen divided by the baseline average seizure frequency. This baseline seizure frequency was calculated as the average seizure frequency on all other AED regimens to which the patient had been exposed, irrespective of when the exposure to the index regimen occurred; that is, the baseline average included AED exposures potentially both before and after exposure to the index regimen. This seizure frequency ratio (SFR) of index/baseline seizure frequency provided a within-patient metric of AED regimen efficacy that normalized for differences in seizure frequency among patients. We also calculated SFR for each index regimen subdivided by quartile of dosage range: we averaged seizure frequency during exposure to the index AED only for the months when the drug was given in the specified quartile of daily dosage, and compared to the baseline on all other AED regimens except for the index regimen. To make our results comparable to the metric usually reported in AED clinical trials, we report the percent reduction in normalized seizure frequency as $(1\text{-}SFR) * 100$. For AED trials where no seizures were recorded, seizure frequency was set as: 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 two 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). We used log-transformation of SFR statistics so as to provide a metric that was symmetrical around SFR = 1 (representing no change); that is, so that small SFRs (say, 0.1, reflecting a highly effective trial) would be equally weighted against highly ineffective trials where SFR was large (say, 10). After log-transformation, SFRs for all AED regimens were distributed normally, allowing use of parametric statistics. Statistics on demographic data are expressed as means $\pm$ standard errors. Statistical significance was calculated using one-way ANOVA with Tukey post-hoc tests, or with one-sample *t*-tests. Significance was set at $\alpha = 0.05$.

3. Results

3.1. Comparative efficacy of commonly used AED regimens

We sought to extend our prior study on the comparative efficacy of AEDs used in a developmentally disabled patient population with refractory epilepsy. The demographic characteristics of this population are shown in Table 2. The patients were characterized as having developmental disability largely of unknown cause, with a predominance of

Table 2
Demographic characteristics of study patients.

Number of patients	164
Male patients (%)	57.9
Female patients (%)	42.1
Mean age at last data collection (y)	54.3
Neurologic diagnosis (% of total)	
Genetic	9.8
Perinatal hypoxic/ischemic	8.5
Lennox-Gastaut syndrome	7.9
CNS infection	6.1
CNS structural	6.1
Unknown	61.6
EEG findings (% of total)	
Focal/multifocal epileptiform abnormality	45.7
Generalized epileptiform abnormality	20.7
Mixed focal/generalized epileptiform abnormalities	9.2
Nonepileptiform abnormality	14.6
Normal	3.1
No data	6.7
Functional status (% of total)	
Ambulatory/verbal	11.6
Ambulatory/nonverbal	14.6
Nonambulatory/verbal	11.0
Nonambulatory/nonverbal	43.9
Insufficient data	18.9

focal epilepsy based on routine EEG recordings. Treatment records consisting of monthly seizure frequency and AED dose were analyzed. The top 12 AEDs to which patients were exposed (either in monotherapy or in combination therapy) are shown in Table 1. On average, each patient was exposed to a median of 6 AED regimens (range 2–13) over an average 206 months (± 8.0, $n = 164$) or about 17 years of followup each. Patients had an average seizure frequency of 2.8 seizures per month (± 0.31, $n = 164$).

We determined the average seizure frequency for each patient during exposure to each combination of one, two, or three study AEDs at a time. Table 3 shows the mean SFR (and 95% CIs) and reduction or increase in seizure frequency from baseline for the top 26 AED regimens with at least $n = 10$ exposures. (There were a total of 53 AED regimens with at least $n = 5$ exposures, but only those with at least $n = 10$ exposures are shown here.) Similarly to our previous study [7], only patients treated with LTG/VPA showed a statistically significant improvement in seizure frequency, averaging a 52% reduction in seizure frequency compared to their baseline seizure frequency during treatment with other AED regimens. LTG/VPA demonstrated superior efficacy in those patients with focal epileptiform EEG findings (mean 44% reduction in seizure frequency, 95% CIs [24.2%, 59.2%], $n = 15$, $p = 0.001$), while those with generalized EEG findings showed a reduction of borderline statistical significance (mean 53% reduction [18% increase, 81% reduction], $n = 10$, $p = 0.097$). None of the other AED regimens showed a statistically significant reduction in seizure frequency from baseline, including treatment with the most frequently used monotherapies CBZ, VPA, PHT, and LTG. Treatment with CBZ/PB and CBZ/TPM showed trends towards superior responses that were of borderline statistical significance, while LTG/CBZ showed a trend towards worsened seizure frequency. The

Table 3
Comparative efficacy of the most frequently used AED regimens. SFR represents the ratio of seizure frequency during exposure to the AED regimen shown, divided by baseline seizure frequency. Only the combination LTG/VPA yielded a statistically significant improvement in average seizure frequency compared to baseline seizure frequency. CBZ/VPA was significantly inferior. *p* value is shown without correction for multiple comparisons.

AED combination	No. of pts	Average no. of months exposure (± SEM)	Average SFR [95% CIs]	Average % decrease (increase) in seizure frequency vs. baseline	*p*
CBZ	66	55 ± 7.0	1.18 [0.936, 1.48]	(18)[a]	0.158
CBZ/VPA	55	45 ± 6.2	1.39 [1.06, 1.84]	(39)[a]	0.018
VPA	53	36 ± 5.1	1.33 [0.940, 1.88]	(33)[a]	0.106
LTG/VPA	40	58 ± 8.3	0.481 [0.355, 0.652]	52[b]	<0.0001
VPA/PHT	40	43 ± 7.0	1.17 [0.907, 1.53]	(17)[a]	0.212
CBZ/PHT	38	39 + 5.9	1.26 [0.929, 1.70]	(26)[a]	0.133
PHT	35	35 ± 6.4	1.17 [0.782, 1.76]	(17)[a]	0.429
LTG	32	33 ± 5.4	0.820 [0.568, 1.18]	18[b]	0.277
LTG/CBZ	26	35 ± 8.1	1.37 [0.988, 1.89]	(37)[a]	0.058
LTG/LEV	20	37 ± 7.1	0.764 [0.389, 1.50]	24[b]	0.416
LTG/PHT	19	32 ± 6.0	1.09 [0.774, 1.53]	(9)[a]	0.609
PB	18	91 ± 20	0.732 [0.409, 1.31]	27[b]	0.275
CBZ/PB	17	38 ± 11	0.577 [0.313, 1.06]	42[b]	0.074
VPA/GBP	17	17 ± 6	1.42 [0.900, 2.26]	(42)[a]	0.122
PHT/PB	17	72 ± 17	0.781 [0.506, 1.20]	22[b]	0.245
LTG/TPM	16	22 ± 6.4	1.16 [0.861, 1.56]	(16)[a]	0.303
OXC	16	40 ± 9.3	1.17 [0.573, 2.40]	(17)[a]	0.640
CBZ/TPM	16	40 ± 9.2	0.607 [0.338, 1.09]	39[b]	0.090
LTG/VPA/TPM	13	36 ± 11	0.469 [0.182, 1.21]	53[b]	0.107
LTG/PB	11	25 ± 6.6	0.891 [0.544, 1.46]	11[b]	0.616
VPA/TPM	11	15 ± 3.5	0.901 [0.490, 1.65]	9.9[b]	0.710
LTG/VPA/PHT	11	15 ± 6.1	1.03 [0.722, 1.47]	(3)[a]	0.855
CBZ/VPA/PHT	11	22 ± 6.8	1.06 [0.617, 1.82]	(6)[a]	0.816
TPM	10	28 ± 11	1.47 [0.742, 2.92]	(47)[a]	0.233
PHT/GBP	10	26 ± 3.7	1.08 [0.539, 2.16]	(8)[a]	0.810
LTG/VPA/LEV	10	17 ± 3.8	0.633 [0.326, 1.23]	37[b]	0.155

[a] Denotes increased seizure frequency. [b] Denotes decreased seizure frequency.

combination of CBZ/VPA appeared to yield an increased seizure frequency over baseline.

3.2. Response to CBZ monotherapy by dose quartile

Even though the four monotherapies failed to demonstrate significant improvement compared to other AED regimens, we hypothesized that improved efficacy might be seen in some region of the dosing range. We therefore determined the range of AED doses for each studied regimen, and set four quartiles that approximately spanned the entire dose range. We then calculated SFR and percent change in seizure frequency by measuring average seizure frequency for patients exposed in each quartile of the AED dose range, compared to each patient's baseline average seizure frequency on all other AED regimens. This yielded a within-patient metric of comparative AED efficacy subdivided by quartile of each drug's dose range.

We first studied CBZ monotherapy. 66 patients were exposed to CBZ monotherapy, averaging 55 months of exposure each. Daily CBZ dosages ranged from 200 to 3400 mg/d, with a median dose of 1600 mg/d (Fig. 1A). To determine whether there were differences in epilepsy severity among patients represented in the various quartiles, we first calculated the baseline seizure frequency (i.e. on all AED regimens other than CBZ) for patients who had been exposed in each quartile of CBZ dose range (Fig. 1B). This showed a trend towards increasing baseline seizure frequency in patients treated with higher doses of CBZ, although this was not statistically significant. We then calculated the percent

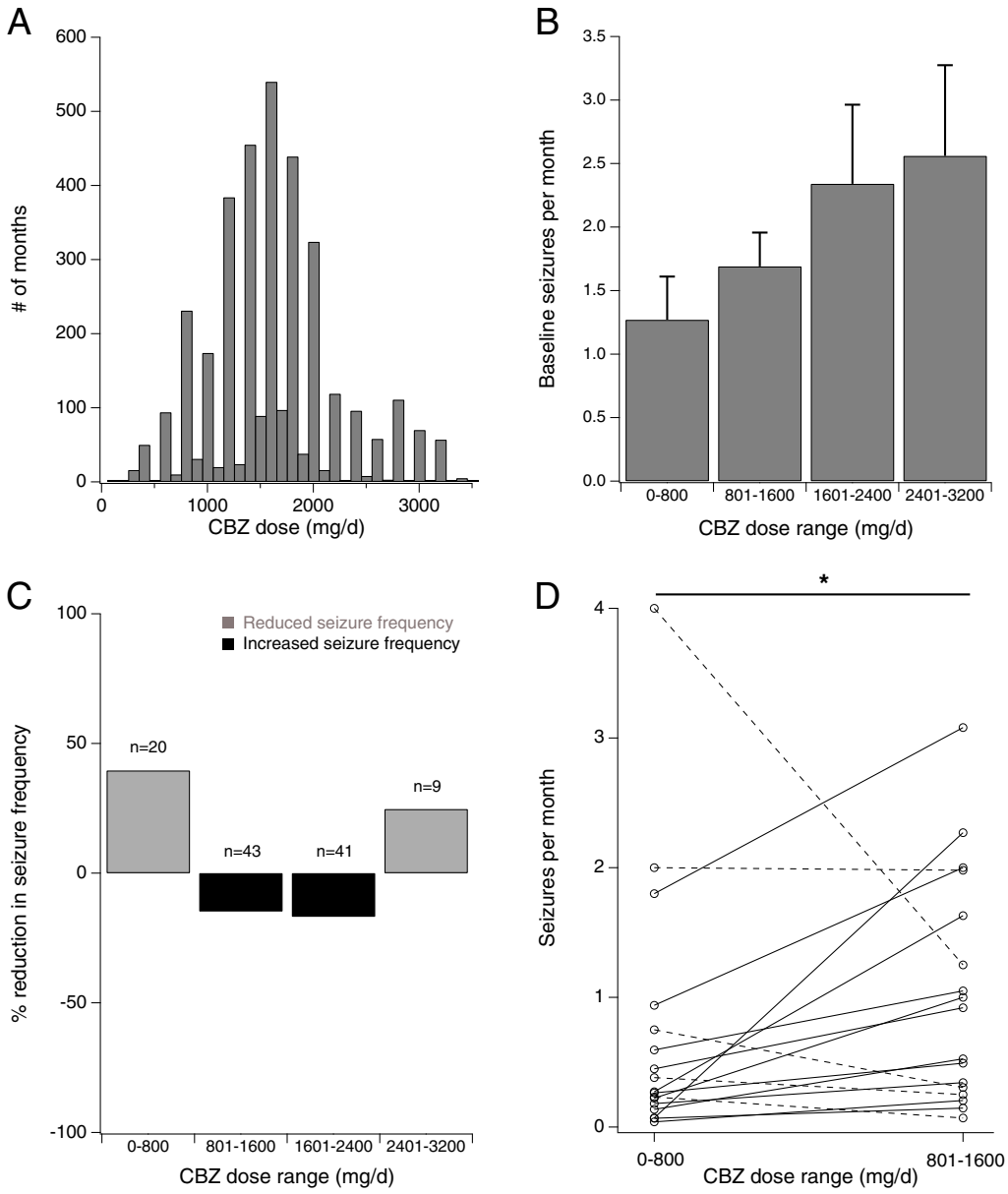

Fig. 1. Response to CBZ monotherapy by dose range quartile. A. Distribution of CBZ doses used in all patients. Median CBZ dose was 1600 mg/d. B. Baseline seizure frequency on all other AED regimens except CBZ for patients exposed in each dose quartile of CBZ. Patients exposed in higher CBZ dose quartiles tended to have higher baseline seizure frequency, although this was not statistically significant. C. Patients exposed to the lowest CBZ dose quartile tended to have a better response to treatment, although no statistically significant differences were seen among the four dose ranges. D. Data from individual patients exposed to both the first and second quartiles of CBZ dose range showed that the majority of patients exhibited an increase in seizure frequency (*solid traces*) when exposed to the higher CBZ dose range, instead of the expected decrease in seizure frequency (*dashed traces*), demonstrating a statistically significant negative dose-response relationship (* = $p < 0.05$).

reduction in seizure frequency for CBZ in each dose quartile against the baseline average of all other AED regimens to which each patient had been exposed (Fig. 1C). There were no statistically significant differences in the change in seizure frequency among dose quartiles; however, the 20 patients treated in the lowest dose quartile (0–800 mg/d) showed a trend towards improved seizure frequency from baseline, whereas those in the second quartile (801–1600 mg/d) and third quartile (1601–2400 mg/d) showed trends towards worsened seizure frequency. Patients treated in the highest quartile (2401–3200 mg/d) showed a trend towards improved response. To examine whether there was a negative relationship between change in seizure frequency and CBZ dose in the lowest two quartiles, we identified patients who had been exposed to CBZ in both quartiles (Fig. 1D). 17 out of the 20 patients exposed to the lowest quartile of CBZ dose were also exposed to the second quartile. 12 out of these 17 patients showed increased seizure frequency at the higher dose range compared to the lower, while five patients improved at the higher dose; on average, patients exhibited a significant 88% increase ([2%, 245%], $n = 17$, $p < 0.05$) in seizure frequency when exposed to CBZ monotherapy in the second dose quartile compared to the first quartile. No significant differences in seizure frequency were observed in patients exposed to other neighboring quartiles of the CBZ dose range.

This surprising finding demonstrated a negative dose-response relationship for CBZ between two dose quartiles spanning a clinically relevant range from 0 to 1600 mg/d. Because it is known that CBZ can exacerbate generalized epilepsy syndromes [12], we categorized the EEG findings in this group to determine if these patients were disproportionately diagnosed with generalized syndromes. The EEG diagnoses were 41% focal, 17% non-epileptiform, 12% generalized, and 12% mixed, and were not different from the patient population as a whole (Table 1). This suggests that the negative dose-response seen with CBZ monotherapy did not represent exacerbation of seizures in patients with generalized epilepsy.

We then asked whether there was a correlation between response to low-dose CBZ and the presence of a positive dose-response relationship. Out of the 20 patients exposed to low-dose CBZ, 12 were identified as "responders," meaning at least a 25% decrease in seizure frequency from baseline. 11 of these 12 had been further exposed to higher dose quartiles of CBZ. All 11 of these patients exhibited a negative dose-response, meaning that seizure frequency worsened with higher dosage. On the other hand, eight of the 20 patients exposed to low-dose CBZ were identified as non-responders. Of these, six had been exposed to higher-dose CBZ: four showed a positive dose-response, and two a negative dose-response. We conclude from this analysis that at least for CBZ, response to low doses of the drug did not correlate with a positive response to higher doses. Conversely, some patients did not show a response to low-dose CBZ, but had improved response with dosage escalation, although not enough to result in an improvement as a group compared to baseline.

3.3. Response to LTG monotherapy by dose quartile

Having identified a negative dose-response relationship in the lower half of CBZ dose range, we turned to patients exposed to LTG monotherapy. 32 patients were exposed to LTG monotherapy for an average duration of exposure of 33 months. Daily doses ranged from 100 to 1200 mg/d, with a median dose of 500 mg/d (Fig. 2A). There were no significant differences in baseline seizure frequency among the LTG treatment groups (Fig. 2B). (Note that only one patient fell into the 901–1200 mg/d dose range and so was not included in the analysis.) Although patients exposed to LTG monotherapy demonstrated an overall nonsignificant 18% decrease in seizure frequency compared to baseline seizure frequency (Table 3), differences were seen when the response was divided by quartile of LTG dose. The six patients treated in the lowest quartile of LTG dose exhibited a significantly better response than those in the second and third quartiles (Fig. 2C). The data on baseline seizure frequency (Fig. 2B) showed that this result was not confounded by a selection bias where only patients with less frequent seizures were being treated with low-dose LTG. No significant differences in seizure frequency were observed in patients who had paired exposures to neighboring quartiles of the LTG dose range.

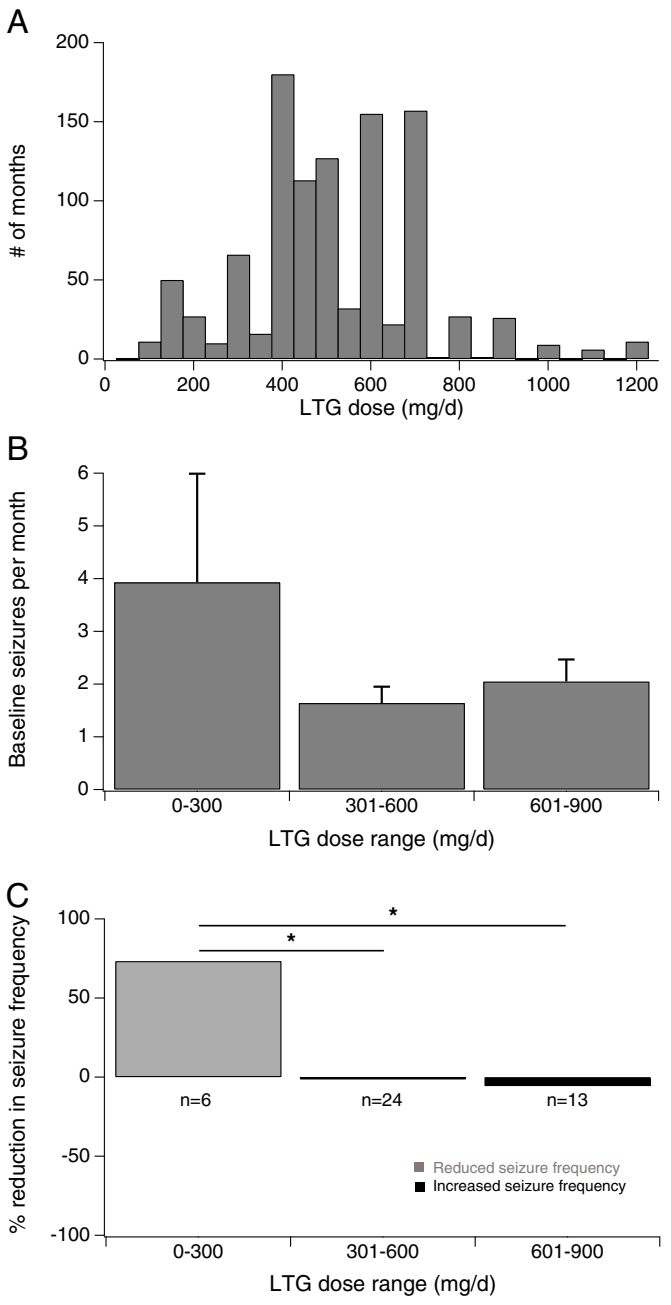

Fig. 2. Response to LTG monotherapy by dose range quartile. A. Distribution of LTG doses used in all patients. Median LTG dose was 500 mg/d. B. Baseline seizure frequency on all other AED regimens except LTG for patients exposed in each dose quartile of LTG monotherapy. There were no significant differences in baseline seizure frequency among the groups. (Note that only one patient fell into the 901–1200 mg/d dose range and so was not included in the analysis.) C. Patients treated in the lowest dose range quartile of LTG monotherapy exhibited a significantly better mean response than patients treated in the second and third dose quartiles (* = $p < 0.05$ by one-way ANOVA).

3.4. Response to VPA monotherapy by dose quartile

We next analyzed patients exposed to VPA. 53 patients were exposed to VPA monotherapy, for an average 36 months each. VPA daily

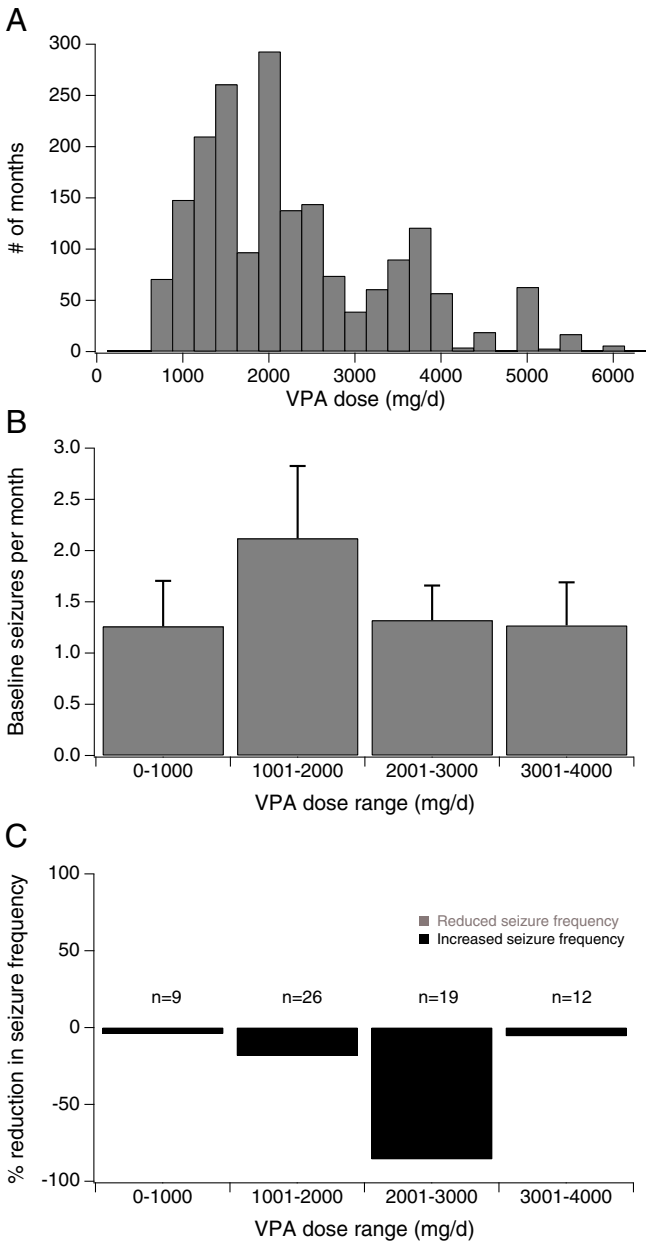

Fig. 3. Response to VPA monotherapy by dose range quartile. A. Distribution of VPA doses used in all patients. Median VPA dose was 2000 mg/d. B. Baseline seizure frequency on all other AED regimens except VPA for patients exposed in each dose quartile of VPA. No significant differences in baseline seizure frequency were seen among the groups. C. The mean response to VPA monotherapy was negative in each quartile of dose range, but patients exposed to in the lowest quartile tended to have the least negative response. However, no statistically significant differences were seen among the four dose ranges.

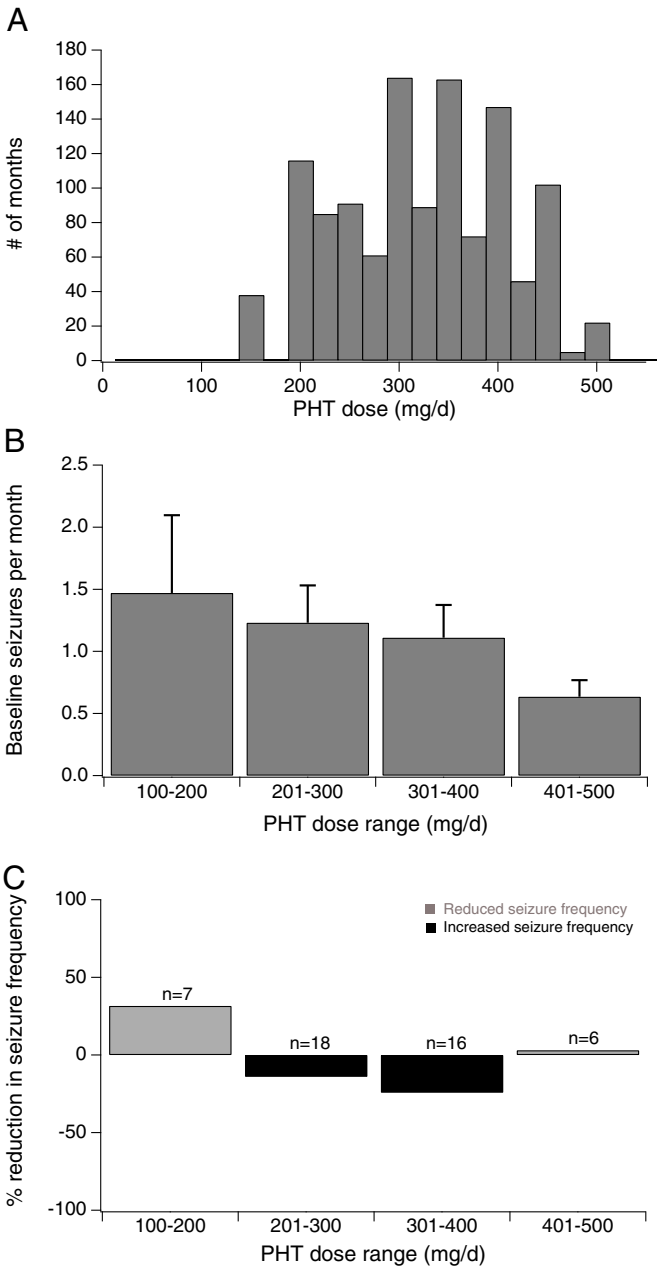

Fig. 4. Response to PHT monotherapy by dose range quartile. A. Distribution of PHT doses used in all patients. Median PHT dose was 325 mg/d. B. Baseline seizure frequency on all other AED regimens except PHT for patients exposed in each dose quartile of PHT. A trend of decreasing baseline seizure frequency with increasing PHT dose range quartiles was seen, but there were no significant differences among the groups. C. Patients exposed to PHT monotherapy in the lowest dose quartile tended to have a better response that those in higher dose ranges, but no statistically significant differences were seen among the four dose ranges.

doses spanned the range of 500–6000 mg/d, with a median dose of 2000 mg/d (Fig. 3A). Baseline seizure frequency was without significant differences among the VPA dose quartiles (Fig. 3B). Analysis of patients' response by quartile of VPA dose (Fig. 3C) showed uniform trends towards poorer responses in all quartiles, but without statistically significant differences among any dose quartile. The best relative response to VPA occurred in patients in the lowest dose quartile, consistent with the pattern seen with other AEDs. No significant differences in seizure frequency were observed in patients exposed to neighboring quartiles of the VPA dose range.

3.5. Response to PHT monotherapy by dose quartile

We then analyzed the 35 patients exposed to PHT monotherapy. Patients were exposed to PHT for an average duration of 35 months. PHT dosing ranged from 60 to 500 mg/d, with a median dose of 325 mg/d (Fig. 4A). The baseline seizure frequency for patients exposed to PHT did not show any significant differences among the groups (Fig. 4B). When analyzed by quartile of PHT dose, there were no significant

differences among the four dose ranges, although similarly to the response to the other monotherapies, the patients exposed to the lowest dose range tended to have the best response. No significant differences in seizure frequency were observed in patients exposed to neighboring quartiles of the PHT dose range.

3.6. Overall response to AED monotherapy by dose quartile

The responses to all four monotherapies showed a consistent pattern where patients exposed to the lowest quartile of the AED dose range appeared to have the best response compared to those given higher AED dosages. We combined the responses in each quartile for the four monotherapies to yield an aggregate average. As shown in Fig. 5A, these combined data demonstrated that patients exposed to monotherapy with either CBZ, LTG, VPA or PHT exhibited significantly better response in the lowest quartile of the AED dose range compared to those in the 2nd and 3rd quartiles. Out of 270 exposures to monotherapies among the four quartiles of the dose range, only 42 of these exposures (16% of the total, and representing 37 unique patients, or 23% of all patients) occurred in the lowest quartile of each AED dose range. In the aggregate, these patients showed a 38% reduction in seizure frequency from baseline, whereas patients exposed in the 2nd and 3rd quartiles showed 13% and 29% increases in seizure frequency, respectively. This confirms the trend shown for individual monotherapies that the best patient responses were associated with treatment in the lowest dosage quartiles. The aggregated baseline seizure frequency for patients exposed to these monotherapies was similar across all dose quartiles, demonstrating no difference in seizure severity among the groups (Fig. 5B). EEG findings in each group were also similar, with focal EEG findings in 38%, 43%, 46%, and 39% of patients in quartiles 1–4, respectively.

3.7. Response to LTG/VPA combination therapy

We next turned to analysis of the LTG/VPA combination therapy. A total of 40 patients were exposed to LTG/VPA for an average of 58 months. LTG doses spanned the range of 6–600 mg/d, with a median of 200 mg/d (Fig. 6A). The median dose of LTG used in monotherapy (500 mg/d) was 2.5 times higher than the median dose used in combination with VPA, suggesting that clinicians adjusted their dosing to accommodate the known 2–3 fold inhibition of LTG clearance by concomitant VPA administration [13]; thus it is likely that comparable serum LTG levels were achieved in the two patient populations. The range of VPA doses in combination with LTG was 30–5500 mg/d, with a median dose of 1500 mg/d, somewhat lower than the median 2000 mg/d dose for VPA used in monotherapy (Fig. 6B).

The combination LTG/VPA displayed significantly better efficacy than other AED regimens in our study, with an average 52% reduction in seizure frequency that was highly statistically significant (Table 3). We divided the dose ranges of both LTG and VPA into halves yielding four groups in a 2×2 comparison, comparable to the quartiles of dose range analyzed for AEDs given in monotherapy. When the efficacy of LTG/VPA was analyzed in this way, all four groups showed an improvement in seizure frequency; however, no significant differences among the groups were seen. We then identified 9 patients who had been treated with LTG in both the lower and upper halves of the dose range, along with VPA in the lower dose range. Eight of these nine patients demonstrated a decrease in seizure frequency at the higher LTG dose range compared to the lower, showing an average 61% ([19%, 81%], $n = 9$, $p < 0.05$) decrease in seizure frequency. This demonstrates that LTG used in combination with lower-dose VPA exhibited a positive dose-response relationship.

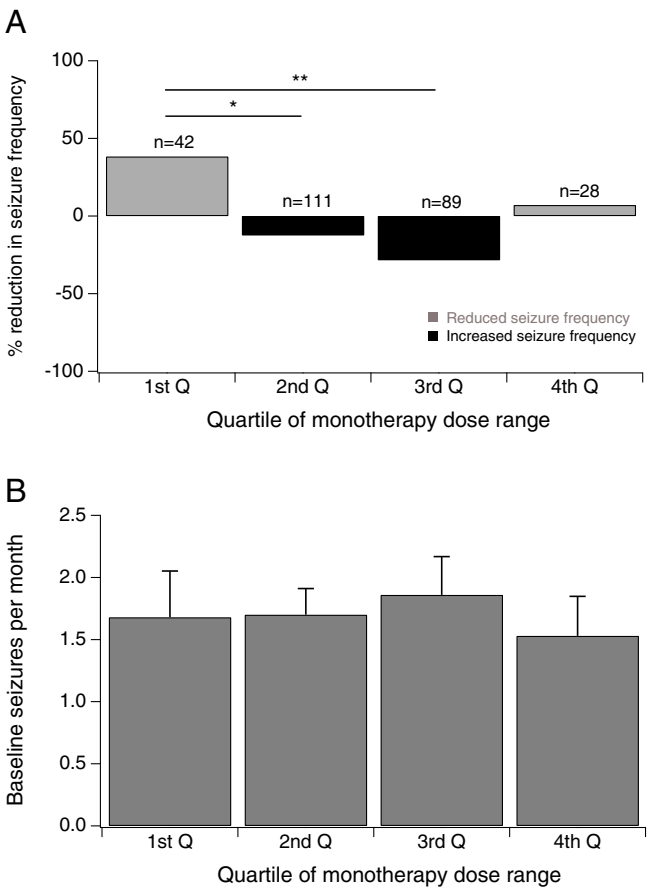

Fig. 5. Aggregate response to all monotherapies by dose range quartile. A. Significant differences were seen in the aggregate response to monotherapy (CBZ, LTG, VPA, and PHT) among dose range quartiles. Patients exposed to the lowest quartile had significantly better response than those in the 2nd and 3rd quartiles ($^{*} = p < 0.05$; $^{**} = p < 0.01$ by one-way ANOVA). B. There were no significant differences in baseline seizure frequency among patients exposed to the various AED dose range quartiles.

4. Discussion

In this study, we extended a previous analysis of the treatment records of institutionalized, developmentally disabled patients with refractory epilepsy [7]. Access to these records has allowed us to compile a database of AED efficacy with remarkable longitudinal followup, averaging 17 years per patient, and encompassing a wide variety of differing AED regimens to which patients had been exposed according to various clinicians' preferences. The institutional setting ensured rigor in the recording of patients' seizures and their compliance with medical therapy. These qualities of the dataset have allowed us to ask questions about AED efficacy with minimal a priori assumptions about which drugs or drug combinations to analyze. Because our previous study had shown superior efficacy only for the combination LTG/VPA but not for any of the four monotherapies, we wished to determine whether there were regions of the AED dosing range that show improved patient response in these therapies with limited overall efficacy. Our presumption was that higher doses of AEDs should be associated with incremental improvement in seizure frequency, reflecting the traditional wisdom that an AED should be dosed to maximal tolerated amounts before assessing its effectiveness in seizure control [14]. However there is little empirical evidence supporting these practices in patients with refractory epilepsy. Thus we felt that this dataset represented an opportunity to comprehensively examine the

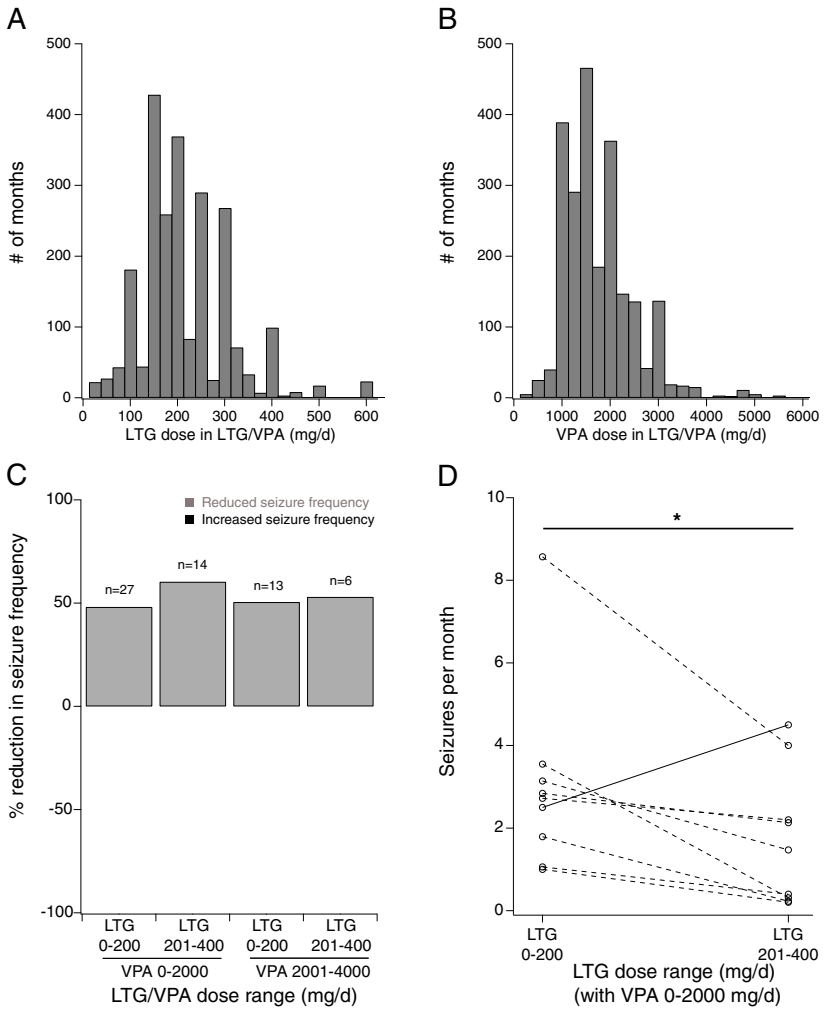

Fig. 6. Response to LTG/VPA combination therapy by dose range quartile. A. Distribution of LTG doses used in combination with VPA for all patients. Median LTG dose was 200 mg/d. B. Distribution of VPA doses used in combination with LTG. Median VPA dose was 1500 mg/d. C. The response to LTG/VPA in all four combinations of dose ranges was positive, but no statistically significant differences were seen among the four groups. D. Data from individual patients exposed to both low and high LTG dose ranges in combination with low dose VPA show that eight of nine patients exhibited an decrease in seizure frequency (*dashed traces*) while a single patient showed increased seizure frequency (*solid trace*), demonstrating a statistically significant positive dose-response relationship ($* = p < 0.05$).

relationship between AED dose and the long-term response in patients with refractory epilepsy.

Our analysis showed that when CBZ, LTG, VPA or PHT were used in monotherapy, the best long-term reductions in seizure frequency were seen for those patients treated in the lowest quartiles of the dose ranges. Patients treated with the four monotherapies in aggregate in the lowest quartile of AED dose range had significant reductions in seizure frequency from baseline compared to those treated in the second and third quartiles. This surprising finding contradicts the expectation that patients treated with higher AED dosages should demonstrate at least incremental improvement in seizure frequency compared to those treated with lower dosages. In fact, those treated in the 2nd and 3rd third quartiles of the monotherapy dose ranges had a significantly inferior response in within-patient comparisons against their baseline seizure frequency on other AED regimens.

An important question is why an association between low-dose AED treatment and improved response was observed. We cannot necessarily conclude that this observation represents a negative dose-response relationship in the strict pharmacological definition of this term, since patients were not randomized into groups of AED dosage and prospectively followed as they would have been in a clinical trial. Such clinical trials have tended to show positive dose-response relationships over the typical 8- to 12-week periods of clinical trials (e.g. [15,16]; but see [17]). However, at least for CBZ monotherapy, a negative dose-response relationship was observed for patients who received paired exposures in the lowest and 2nd quartiles of CBZ dose, with increased seizure frequency observed in those treated with higher CBZ doses. This suggests that at least for patients treated with CBZ up to 1600 mg/d, exacerbation of seizure frequency occurred at higher doses, consistent with the observation for the entire group of patients that the best response to CBZ monotherapy occurred in the lowest quartile of the dose range, and an inferior response occurred in the 2nd quartile. It is unclear whether a negative dose-response relationship underlies the relatively poorer response of patients exposed to LTG, VPA, and PHT monotherapy in the higher end of the dose range since we did not have sufficient numbers of patients exposed to paired quartiles of AED dose range.

A possible explanation for the discrepancy between the positive dose-response relationships usually observed in clinical trials and our results may lie with the short duration of clinical trials (typically a three-month observation period) compared to the long study periods here, ranging from 33 to 58 months. There have been anecdotal

observations of a "honeymoon" period with new AED exposures that remits with prolonged therapy [18]. It is possible that the positive dose-response relationships observed for most new AEDs given as adjunctive therapy in clinical trials may reflect short-term improvements in seizure frequency that are not sustained with chronic administration.

It might be hypothesized that the superior response of patients treated with low-dose AEDs was the result of selection bias in the clinicians' dosing decisions, with the populations of patients in higher dose quartiles being enriched with patients whose seizures did not respond to respond in the lowest quartile. This possibility is unlikely to explain the results, since out of all patients treated with one of the four monotherapies, only 23% were ever exposed to the lowest quartile of AED dose range. This shows that clinicians did not systemically assess most patients at low dosages of AEDs before moving them to dosages in higher quartiles of the range, but instead usually began exposure at higher dosages. Nor does it appear that patients exposed to higher dosages of these drugs had more severe epilepsy, as baseline seizure frequency was comparable across the dosage quartiles. EEG findings were also similar across dosage groups, showing that differences in epilepsy syndrome did not likely account for differential response to AED dosage. We can also exclude that differences in compliance varied by AED dose, as compliance was assured in these institutionalized patients. It is possible that some factor other than epilepsy severity or syndrome influenced the treating clinicians' decisions on what dosages to employ and led to systematic bias, but if so, this is not apparent from our data.

A positive dose-response relationship was seen for LTG given in conjunction with low-dose VPA. It is interesting that this positive dose-response relationship was observed with the only AED regimen in our study with superior overall efficacy, and suggests that the unique efficacy of LTG and VPA together depends on pharmacodynamic synergy. The alternative hypothesis, that the well-known pharmacokinetic interaction whereby VPA elevates LTG serum concentration accounted for the improved efficacy of LTG, would predict that similar improved efficacy of LTG in monotherapy would be achieved by escalating dosages of LTG alone. This is contrary to what was observed in the group of patients as a whole treated with LTG monotherapy; in this group, higher LTG doses did not lead to improved efficacy.

For all four drugs studied in monotherapy, the best responses to treatment were achieved in the lowest ranges of AED dose. This is consistent with reports in new-onset epilepsy that found the greatest proportion of patients who achieved seizure freedom did so at low AED doses [10,11], or that patients with established juvenile myoclonic epilepsy were equally likely to be seizure-free with daily doses of valproate less than or equal to 1000 mg/d as those taking >1000 mg/d [19]. A practical implication of these results is that patients with refractory epilepsy who will respond favorably to a given AED regimen might also be identified with exposure to low doses of medication. This would appear to contradict the usual recommendation that assessment of AED efficacy requires exposure to dosages that produce symptomatic toxicity [14]. Those patients who do not respond at low-dose can then be cautiously assessed at higher doses to determine whether they are non-responders to that regimen, or perhaps demonstrate exacerbation of seizure frequency.

There are several limitations to this study. First is its retrospective design. While this allowed us to analyze our dataset without a priori assumptions, it also introduces the possibility of confounding variables. For example, it is possible that the treating clinicians who made drug dosing decisions exposed patients to different AED doses based on some clinical characteristics (aside from seizure frequency or EEG findings, which were similar across dosing groups) that biased assignment into low- or high-dose groups. Prospective, randomized studies, with long-term exposure to AED monotherapies on a fixed schedule of dosage escalation, would be helpful to confirm the findings shown here. A second limitation is the developmentally disabled study population, and the possibility that this group has differing responses to AED therapy. However, like the general population with epilepsy, our study cohort predominantly was diagnosed with focal not generalized epilepsy, and we are not aware of literature that shows differential efficacy of AEDs in a developmentally disabled population compared to the general population. Third, we only analyzed the most frequently used AEDs in our dataset, representing predominantly older drugs. It is possible that newer AEDs may exhibit different characteristics than the four AEDs studied here. Fourth we analyzed AED efficacy by dose and not serum concentration. We took this strategy because the much sparser representation of serum concentration data in our dataset would have significantly decreased the statistical power of the analysis. Finally seizures observed by caregivers, while meticulously documented, largely represented convulsive seizures, and it is possible that more subtle non-convulsive seizures went underreported.

5. Conclusions

Evidence-based guidance is needed to identify the optimal AED regimens in refractory epilepsy. In this study, treatment records from a developmentally disabled patient population with an average 17 years of followup allowed retrospective analysis of the most effective AED regimens. LTG/VPA was the only AED combination out of the 26 most frequently used to produce a significant improvement over baseline seizure frequency, and was most effective in patients with focal epilepsy syndromes. For the four most commonly used monotherapies, the best response tended to be observed in the lowest quartile of the dosage range. This suggests that responders to a given AED regimen in refractory epilepsy may be initially identified at low dose without routine escalation of all patients to maximally tolerated doses. Those patients whose seizures do not respond at low dose can then be cautiously evaluated for evidence of response during further dosage escalation, with the goal of identifying non-responders or patients whose seizure frequency is exacerbated at higher dose.

Disclosure of conflicts of interest

The authors report no conflicts of interest.

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