8-2016

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Jon Marc Finamore
Thomas Jefferson University

Michael R. Sperling
Thomas Jefferson University

Tingting Zhan
Thomas Jefferson University

Maromi Nei
Thomas Jefferson University

Christopher T. Skidmore
Thomas Jefferson University

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Jon Marc Finamore[1], Michael R. Sperling[2], Tingting Zhan[3], Maromi Nei[2], Christopher T. Skidmore[2], Scott Mintzer[2]

[1]Sidney Kimmel Medical College, [2]Department of Neurology, [3]Division of Biostatistics, Department of Pharmacology, Thomas Jefferson University, Philadelphia, PA

Corresponding author: Scott Mintzer, Department of Neurology, Thomas Jefferson University, 901 Walnut Street Suite 400 Philadelphia, PA 19107. Phone: 215-955-1222. Fax: 215-955-0606. E-mail: scott.mintzer@jefferson.edu

Running title: Outcome after AED Switch

Number of words: **3,967**

Number of figures: 1

Number of tables: 4

Summary

OBJECTIVE: Outcomes after changing anti-epileptic drugs (AEDs) have largely been studied in single cohort series. We recently reported the first study to examine this question in a controlled manner. Here, we expand on these results by using a matched, prospective methodology applied to both uncontrolled and well-controlled patients taking any AED.

METHODS: We reviewed all outpatient notes over a 9-month period and identified patients with focal epilepsy on monotherapy. We classified those who switched AED as case patients, with those remaining on the same drug serving as controls. We matched cases with controls for seizure status (seizure-free in the preceding six months or not), current AED, and number of failed AEDs. We subsequently assessed outcome six months later.

RESULTS: Seizure-free patients who switched drug (n=12) had a 16.7% rate of seizure recurrence at six months, compared to 2.8% among controls remaining on the same drug (n=36, p=0.11). There was a 37% remission rate among uncontrolled patients who switched drug compared to 55.6% among controls (n=27 per group, p=0.18). Uncontrolled patients who had previously tried more than one AED were somewhat less likely to enter remission (p=0.057). Neither AED mechanism of action nor change in dosage impacted outcome.

SIGNIFICANCE: Here we provide further estimation of the modest risk (~14%) associated with switching AEDs in patients in remission compared to being maintained on the same regimen. Uncontrolled patients were no more likely to enter remission after a drug switch than they were after remaining on the same drug, suggesting that spontaneous changes in disease state, and not drug response, underlie remission in this population.

Keywords: Antiepileptic drugs, Seizure recurrence, Seizure remission

Key Points:

- Seizure-free patients who switch drug have approximately a 14% additional risk of seizure recurrence compared to remaining on the same drug.

- Uncontrolled patients who remain on the same drug are just as likely to go into remission as

those who switch to a different drug.

Introduction

With the increasing availability of pharmacologically distinct antiepileptic drugs (AEDs) comes an increasing need to understand their efficacy relative to each other. Randomized head-to-head trials in newly-diagnosed patients, a number of which have been performed in recent years[1-4] provide crucial data to inform initial treatment decisions, but leave us none the wiser about treatment decisions that might be necessary later, if the chosen drug fails or is not tolerated. Essentially, the question is not just whether one drug works *better* than others, but whether one drug works *in different patients* than others. The only way to ascertain this is to have the same patient serially treated with several agents to see if there are differences in outcome.

Such studies have been performed[5-8], and have established the rate of seizure control over multiple AED trials. But all of these are single cohort studies, without a control group of any kind. Furthermore, looking at serial outcome after initial AED failure tells only half the story of differences between AEDs. The other half is serial outcome after AED success; this remains largely unstudied, as physicians and patients are understandably disinclined to alter therapy when seizures are not occurring. Nonetheless, in clinical practice it is frequently necessary to change AEDs in seizure-free patients due to side effects, pregnancy planning, or concerns about long-term consequences[9].

Our group recently published the first study to provide data regarding these two issues[10]. We found first, that seizure-free patients had a modest but clinically important risk of seizure recurrence when switched to a different AED; and second, that patients who were not seizure-free were as likely to have a remission of seizures if left on the same drug as they were if switched to another agent. Yet that study had a number of important limitations. It was

retrospective, and as with any such study, the groups compared had noteworthy differences between them in ways that could have changed outcome, such as the number of prior AEDs failed. Furthermore, the group who were changing drugs was entirely composed of patients taking carbamazepine or phenytoin who were being switched to newer-generation AEDs; thus, the generalizability of these data to other types of AED switches remains uncertain.

Here we report the outcome of AED switching in both seizure-free and non-seizure-free patients in a methodologically improved manner that makes the results more widely applicable to the epilepsy population. We looked at patients switching from any AED to any other, rather than merely from older to newer drugs; we assessed outcome prospectively rather than retrospectively; and we matched the case and control patients by the AED they were taking - to eliminate any effects pertaining to specific drugs - and the number of prior AEDs they had failed, as this is the most important prognostic factor in treatment).

Methods

We reviewed all outpatient encounter notes at the Jefferson Comprehensive Epilepsy Center between February and October 2012. Study design is outlined in Figure 1. Inclusion criteria were a diagnosis of focal epilepsy and treatment with a single AED; selection of patients was done in a retrospective manner. Neither patients nor providers were made aware of inclusion in this study. We then classified patients as seizure-free or non-seizure-free as of the index date. For case patients, the index date was the date in which the patient switched medications; for controls, the appointment date when identified was used. Patients were considered seizure-free if they had had no seizures in the six months prior to the index date while taking the single AED (generalized tonic-clonic, focal with impairment of consciousness and focal with observable

manifestations were counted; isolated auras were not); other patients were considered not seizure-free. Patients for whom a discernible seizure status on monotherapy at six months could not be established were excluded. We recorded patient age, gender, current AED and number of AEDs previously failed. The latter were tabulated from chart review. All medications previously tried were counted, regardless of the reason of discontinuation. In the case of patients who had previously undergone surgical resection for epilepsy, we counted only drugs failed since surgery.

Patients were then categorized according to AED management. We classified patients who had their AED changed to a different (single) AED during the recruitment period as cases. Patients who remained on the same AED during this period were categorized as controls. Cases were then matched with controls according to seizure-status as of the index date, with seizure-free cases matched with seizure-free controls, and non-seizure-free cases with non-seizure-free controls (see Figure 1). Seizure-free patients were matched with three controls, while non-seizure-free patients were each paired with one control. Matching ratios differed because of the number of available controls within each group. Cases were matched with controls taking the same AED before the index date and who had failed the same number of AEDs. If multiple candidates matched a given case in these parameters, a control was chosen chronologically from the earliest index date. When no exact match for previous number of AEDs was available, a control on the same drug with the closest number of failed AEDs was used; if multiple candidates remained at this point, the control with the index date closest to the case's was used.

Finally, patients were prospectively followed for at least six months from the index date to assess seizure status. For case patients, the follow-up period was counted from the date in which they started monotherapy with the new AED; if no known date was available, we assumed a four week period for medication titration. Seizure status was evaluated beginning at six

months, and patients' outpatient notes were periodically re-evaluated by the authors over the following year. Patients were considered seizure-free at six months if they had no seizures (excluding auras) during this follow-up period. In order to maximize outcome data and avoid bias, patients not seen in clinic for follow-up were telephoned and asked to report on seizure recurrence and medication changes. There were six case patients who were rapidly switched off of their new AED due to side-effects or cost, and put on another new drug. For these patients, we ignored the intervening brief treatment, with the rationale that this would not bias efficacy outcome in either direction, and considered them to have switched from their original to the latest AED. Patients with no follow-up at six months were removed from the study. Cases who did not ultimately switch drugs were also removed. For removed cases, their corresponding controls were also excluded. Controls with no follow-up were replaced (preserving the 3:1 and 1:1 matching ratios for seizure-free and non-seizure-free groups, respectively). New controls were selected from the initial pool of controls that remained un-matched, using the same matching algorithm described above. For patients who underwent further medication changes, had neurosurgical procedures or passed away, outcomes were recorded if a six month seizure status on monotherapy could be established. As a secondary outcome measure, we examined outcomes one year after index date, but did so only in those for whom monotherapy seizure status could be determined for a full year prior to the index to avoid introducing a bias due to asymmetry of observation times.

A logistic regression model was used to analyze seizure freedom and the effects of other variables on seizure freedom. The covariates considered were seizure status before index date (seizure-free vs. refractory), cohort type (case vs. control), number of AEDs failed, duration of AED trial (log transformed), number of days seizure-free before index date (log transformed, for

seizure-free patients only), and gender. The final parsimonious model, selected in stepwise fashion using Akaike Information Criterion, included seizure status before index date, cohort type, and number of AEDs failed. There was a significant association between number of AEDs failed and seizure status before index date, so an interaction term between these was also included. An interaction term between cohort type and seizure status before index date was also included because both variables were critical to the study's design. Analyses of seizure type, dose increase, and drug mechanism of action were done using Chi-squared or Fisher's exact tests as appropriate. This study was approved by the Institutional Review Board of Thomas Jefferson University.

Results

Appointment records of 2,734 patient visits were reviewed, with 547 patients meeting inclusion criteria. After matching, 102 patients were included in this study. There were 39 case patients (those who had their AED changed), of whom 12 were seizure-free at the index date. The remaining 63 patients were controls, comprised of 36 seizure-free (matched to the 12 seizure-free cases) and 27 non-seizure-free patients (matched to the 27 non-seizure-free cases). Baseline characteristics for both groups are presented in Table 1. Age and gender were similar across the two populations. The groups were also similar for age of onset and duration of epilepsy. Among non-seizure-free patients, there was a large difference in seizure frequency between cases and controls. However, this effect was due to two cases having upwards of three seizures per day during the six month recruitment period. (The next highest frequency, after these two, was 32 seizures in six months.) When these two case patients are excluded, seizure frequency is comparable between the two groups, as shown in Table 1. Case and controls also

had similar number of previously failed drugs. The most common reason for drug switch was seizure, followed by side-effects. Case patients were significantly less likely to be seizure-free at the index date (95% CI 0.14-0.76; p=0.011); this is expected, as a change in AED would often be prompted by continued seizures.

Data on drug prevalence is shown in Table 2. The distribution of AEDs before switch between cases and controls was largely comparable, with levetiracetam being the most common AED in both groups. The disparity in gabapentin prevalence between cases and controls was due to the fact that there were no control patients on the drug. A lack of controls for certain case patients also accounts for the difference in zonisamide and valproate prevalence. For cases, the most common drug to switch to was lamotrigine, followed by levetiracetam.

Raw data on seizure outcomes at six months are shown in Table 3. Of 12 seizure-free case patients, there were 2 (16.7%) who had a recurrent seizure within six months of the drug change, compared to 1 of 36 controls who had a spontaneous recurrence within 6 months of the index date (2.8%). This difference was not statistically significant, likely due to the small sample size, but may be viewed as clinically important, as the incremental risk of seizure recurrence with drug switch, compared with remaining on the existing agent, was 13.9%. For non-seizure-free patients, 10 of 27 (37%) cases became seizure-free at six months, while 15 of 27 controls (55.6%) achieved seizure remission. This difference was not significant.

Odds ratios are shown in Table 4. For seizure-free patients, odds of remaining seizure-free were not significantly different in cases relative to controls, nor was the number of previously failed AEDs a significant predictor of seizure outcome. For non-seizure-free patients, the odds of becoming seizure-free at six months were also no different for cases than for controls. There was a trend toward non-seizure-free patients having failed 2 or more drugs being

less likely to enter a 6-month remission compared than those who had failed only a single drug (OR 0.19, 95% CI: 0.03-1.04, p=0.057). A similar trend was seen for rising number of failed drugs being less associated with remission (Chi-square test for trend, p=0.061). We also examined whether the number of seizures a patient had had during the 6 months prior to index date predicted the likelihood of remission, and found a trend toward patients having three or more seizures during this period being less likely to become seizure-free in follow-up compared to those having only one or two seizures (OR 0.22, 95% CI 0.05-1.06, p=0.062). Neither age, nor gender, nor type of seizure (focal motor, complex partial, generalized tonic-clonic) was found to be a significant predictor of outcome in either group.

We followed patients out to one year when sufficient follow-up data were available. For seizure-free patients, we restricted this analysis to those who had been seizure-free for one year prior to their index date so that there was no bias created by assessment of longer duration post-index than pre-index. The 1-year outcomes are shown in Table 5. Overall, the results were fairly similar to those seen at six months. Again, there was a trend toward those having failed 2 or more AEDs being less likely to enter remission (OR 0.18, 95% CI 0.03-1.09, p=0.065). However, number of seizures in the prior 6 months was no longer found to be significant predictor (OR 0.39, 95% CI 0.08-1.8, p=0.38).

Medication titration is a potential reason for seizure recurrence, so we reviewed our cohort to determine whether any patients had seizures during their medication titration period; we found 4 instances of this. In one case, the patient had a seizure while on low doses of both their original and new AEDs (levetiracetam and lamotrigine, respectively) but became seizure-free for over 6 months once a therapeutic dose of lamotrigine was reached. Three other patients

had seizures during the titration period but continued to have seizures once titration was finished; thus, the event occurring during the titration period did not affect their eventual outcome status.

In the 27 patients who were not seizure-free but remained on the same drug, 11 had a dose increase, while 16 remained on the same drug at the same dose. Seven (64%) of the former became seizure-free at six months, compared to 8 (50%) of the latter. At one year, remission rates were 45% and 38% respectively. There was no clear evidence that dose increase had any bearing on likelihood of remission ($p>0.5$ for 6 month and 1 year comparisons). The difference in outcome between patients with symptomatic epilepsy and non-symptomatic was also investigated. A similar proportion of symptomatic patients were identified within both case and control groups, and seizure recurrence rate at six and twelve months was found to be similar between symptomatic and non-symptomatic patients (data not shown).

To determine if drug mechanism of action played a role, we categorized drugs as being sodium channel (phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide and zonisamide) or non-sodium channel agents (all others) and investigated whether those switching between categories were more likely to have a change in seizure outcome (seizure-free to non-seizure-free, or vice versa) than those switching within a drug category. There was a trend toward more changes in outcome with switch in drug category ($p=0.076$), but this borderline result was driven overwhelmingly by the tendency of patients on sodium channel drugs to have similar outcomes when changed to other sodium channel drugs, and the numbers in individual categories are too small to allow for meaningful conclusions.

Discussion

The present investigation is the first to utilize a prospective, matched design to study

seizure outcome in patients treated with different AEDs serially in monotherapy. There were two major findings. Regarding those who were not seizure-free, we found that the likelihood of 6-month remission was equally high if the patient were left on the same medication than if switched to another. In contrast to our prior study[10], all AEDs were included in this investigation, and cases and controls were matched for initial AED; thus, this is not a phenomenon related to specific drugs. Furthermore, since cases and controls were matched by number of AEDs failed, which is the most important prognostic factor in serial treatment outcome[8], our result is not an artifact of the controls being "easier" patients than the cases. Thus, there was no evidence that changes in drug therapy led to improvements in outcome in the non-seizure-free population.

Thus, our findings suggest that "successes" in serial AED studies may be spontaneous remissions rather than true drug effects. This is line with the results of a recent investigation which utilized natural history to simulate drug trials and also found that presumptive treatment effects, and placebo effects, are instead likely due to natural fluctuations in the disease[11]. Some serial AED treatment studies involved a more treatment-resistant cohort than ours[5,7], but others, like us, examined patients throughout the spectrum of treatment resistance[8,12]. Our non-seizure-free patients had a high rate of subsequent 6-month remission in comparison to other studies; this is likely due to the fact that a considerable fraction of our patients had had only a single seizure in the prior 6 months, which may make them more somewhat likely to remit whether there is a new drug or not. Nonetheless, the lack of effect of AED switching on outcome appears to hold regardless of seizure frequency.

The second major result pertains to the seizure-free patients. Our findings suggest about a 14% risk of seizure recurrence when a patient who has been free of seizures is switched to another agent. This is a clinically meaningful difference which likely did not reach statistical

significance due to our sample size; yet validation of this finding comes from our prior investigation, which yielded very similar results[10]. While the previous study included as cases only patients taking phenytoin or carbamazepine, the present one includes patients taking any AED; this makes the results much more generalizable to the population of adults with focal epilepsy. Furthermore, since we matched patients by the specific AED they were taking, and by the number of prior AEDs failed, our new data are not biased by variations in AED effects, nor by prior difficulty in obtaining seizure control. Thus, in counseling seizure-free patients with focal epilepsy, the additional risk of recurrence upon switching to a new agent, based upon two separate studies, appears to be approximately 14% over 6 months. Recurrence in a seizure-free patient has the potential for a number of negative consequences, including injury, social embarrassment, employment difficulty, and loss of driving privileges. This must be weighed against the potential benefits of AED switch in certain circumstances, including improved quality of life from reduction in side effects[13], improved compliance with less frequent dosing intervals[14], reduced teratogenicity in patients trying to conceive[15], and reversal of chronic AED-related metabolic conditions such as hyperlipidemia or polycystic ovary syndrome[9, 16-18]. Additional studies with larger cohorts will be needed going forward to further validate the results our two investigations, and perhaps ascertain whether certain subgroups are at greater or lesser risk of seizure recurrence with drug switch.

Patients taking sodium-channel-blocking AEDs had a tendency to remain in the same outcome class when switched to other sodium channel agents, though these were only statistical trends, and the findings may have been limited by the sample sizes of groups taking various AEDs. Thus, evaluation of what might be called “rational sequential therapy”, based upon mechanism of action, will require larger studies with greater numbers of patients. We found no

evidence that dose increases had impact upon outcome, consistent with findings from prior studies that the large majority of patients who become seizure-free do so at modest AED doses[19]. This implies that good outcomes in patients after AED dose increase are also more likely to be spontaneous remissions than true drug effects.

Our study is limited by the modest sample size of the seizure-free group who switched drugs; however, our findings in seizure-free patients are strikingly similar to those obtained in our prior, unmatched study[10], suggesting that the results are reproducible despite the sample size. Our study is also limited by being non-randomized; there are doubtless unmeasured differences between those patients who were left on the same drug and those who were switched, as such decisions are highly individualized. Such differences might include the presence or absence of isolated auras, variability in seizure frequency, and the underlying etiology of epilepsy. Performing the ideal study would entail randomizing patients to remain on their current AED or switch to another one; such a study would require large numbers, and recruitment would be daunting. Thus, despite its limitations, the present type of study may be the only feasible means to obtain data regarding serial efficacy of AEDs.

We have previously posited two models of relative AED efficacy[10]. In one model, each AED "covers" a somewhat different segment of the epilepsy population, such that efficacy may sometimes be dependent upon the individual agent. This is the model implicitly employed by many practitioners, including drug trialists, who continue to try one AED after another in resistant patients in hopes of finding the "magic bullet" to stop a given patient's seizures. This model is appealing for its refusal to succumb to therapeutic nihilism[7], though whether hope should supplant data is an ethically fraught issue. In the second model, the various agents are almost wholly overlapping in their patient spectra, such that, effectively, "if you've failed one,

you've failed them all". This model fits with the practice algorithm of epilepsy surgery proponents, who point to data showing the very low remission rate with serial AED trials in resistant patients[8,12], and whose perspective is bolstered by our data in the non-seizure-free population, for whom alterations in therapy had no apparent effect on outcome.

There could conceivably be differing segments of the population for which each model is accurate. It is also possible that the truth is at neither end of the spectrum, but somewhere in between: in other words, with AEDs having moderate, but not large, differences in their coverage. Our data suggest that for most patients, most drugs will work, with perhaps one in seven having an outcome dependent upon a certain AED. But failure of 2 or more AEDs identifies a subset for whom there is no evidence of genuine drug efficacy, even with serial trials, consistent with the second model described above.

Two further goals, then, present themselves to advance the field of AED clinical pharmacology. The first is to determine whether certain drugs are more or less "overlapping" in their efficacy spectra than others; this would allow for rational serial AED therapy, as opposed to the current practice of choosing based upon physician preference or other clinical factors. The second is to address the conundrum that no progress has been made in attacking AED resistance, with similar proportions of patients remaining treatment-resistant over time despite the development of many new AEDs, some with novel mechanisms[6,12]. This suggests that many patients with epilepsy have a disease whose mechanism is radically different from the ones addressed by all currently available AEDs, which appear to largely treat the same group of drug-amenable patients.

In summary, our data suggest that most outcome changes seen in patients with resistant epilepsy may be spontaneous rather than due to therapeutic alterations. Changes in therapy may

still sometimes be worthwhile to achieve a palliative goal, such as reduction in generalized tonic-clonic seizures, or prevention of status epilepticus. Most treatment-amenable patients appear likewise to have similar responses to various AEDs -- in this case, positive responses -- but perhaps one in seven may depend upon a particular agent or agents for seizure freedom, and the risk of seizure recurrence must be balanced against various potential benefits (e.g. mitigation of side effects) when there is reason to believe that such benefits may accrue.

Tables

Table 1
Patient demographics

	Cases	Controls	p-value
Number of patients	39	63	
Age (years)	44.8±17.4	47.8±14.4	0.335
Gender (male)	22 (56.4%)	30 (47.6%)	0.389
Age of seizure onset (years)	35.6±19.7	34.5±18	
Duration of epilepsy (months)	124.3±130.9	141.55±159.3	
Number seizure-free	12 (30.7%)	36 (58.1%)	0.011
Monthly seizure-frequency (if non-seizure-free) (seizures/month)	7.9±26.3	0.6±1.1	0.023
After removal of two outlier cases*	0.9±1.2	0.6±1.1	0.055
Seizure-free period (if seizure-free) (months)	39.8±29	71.4±81.3	0.197
Number of drugs failed	0.9±1.1	1.16±1.8	
Reason for switch			
Seizures	20 (51.3%)		
Side-effects	14 (35.9%)		
Cost	2 (5.1%)		
Long-term health effects	1 (2.6%)		
Unknown	2 (5.1%)		

*See main text

Table 2
Drug usage

	Before switch		After switch
Drug	Cases (n=39)	Controls (n=63)	Cases (n=39)
LEV	15	23	8
PHT	6	8	0
CBZ	4	8	2
ZNS	2	8	8
LTG	3	3	12
LAC	1	1	6
OXC	2	5	1
GBP	2	0	1
TPM	2	6	0
VPA	2	1	0
PHB	0	0	1

LEV=levetiracetam, PHT=phenytoin, CBZ=carbamazepine, ZNS=zonisamide, LTG=lamotrigine, LAC=lacosamide, OXC=oxcarbazepine, GBP=gabapentin, TPM=topiramate, VPA=valproate, PHB=phenobarbital

Table 3

			6 months		12 months	
Status at index date	Group	N	Seizure-free	Recurrent seizures	Seizure-free	Recurrent seizures
Seizure-free	Cases	12	10 (83.3%)	2 (16.7%)	7 (77.8%)	2 (22.2%)
	Controls	36	35 (97.2%)	1 (2.8%)	27 (96.4%)	1 (3.6%)
Non-seizure-free	Cases	27	10 (37%)	17 (63%)	8 (29.6%)	19 (70.4%)
	Controls	27	15 (55.6%)	12 (44.4%)	11 (44%)	14 (56%)

Outcomes at six and twelve months

Table 4
Six month outcome analysis

Status at index date	Comparison	Odds ratio	95% CI	p-value
Seizure-free	Cases versus controls	0.13	(0.01, 1.53)	p = 0.11
	Previous failed AED	*	*	p = 0.579
Non-seizure-free	Cases versus controls	0.47	(0.15, 1.38)	p = 0.18
	Previous failed AED, ≥2	0.19	(0.03, 1.04)	p = 0.057
	Number of seizures†, ≥2	0.22	(0.05, 1.06)	p = 0.062

*Calculated using Fisher's Exact test; odds ratio not determinable. †In six months prior to index date.

Disclosures

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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