

RESEARCH PAPER

Reducing versus stopping antiepileptic medications after temporal lobe surgery

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Abstract

Objective: To study the safety of antiepileptic drug (AED) withdrawal after temporal lobe epilepsy (TLE) surgery. **Methods:** We reviewed patients who underwent TLE surgery from 1995 to 2011, collecting data on doses, dates of AED initiation, reduction, and discontinuation. Predictors of seizure outcome were defined using Cox-proportional hazard modeling and adjusted for, while comparing longitudinal seizure-freedom in patients for whom AEDs were unchanged after resection as opposed to reduced or stopped. **Results:** A total of 609 patients (86% adults) were analyzed. Follow-up ranged from 0.5 to 16.7 years. Most (64%) had hippocampal sclerosis. Overall, 229 patients had remained on their same baseline AEDs, while 380 patients stopped (127 cases) or reduced (253 cases) their AEDs. Mean timing of the earliest AED change was shorter in patients with recurrent seizures (1.04 years) compared to those seizure-free at last follow-up (1.44 years; P -value 0.03). Whether AEDs were withdrawn 12 or 24 months after surgery, there was a 10–25% higher risk of breakthrough seizures within the subsequent 2 years. However, 70% of patients with seizure recurrence after AED discontinuation re-achieved remission, as opposed to 50% of those whose seizures recurred while reducing AEDs ($P = 0.0001$). Long-term remission rates were similar in both AED discontinuation and “unchanged” groups (82% remission for AEDs withdrawn after 1 year and 90% for AEDs withdrawn after 2 years), while only 65% of patients whose recurrences started during AED reduction achieved a 2-year remission by last follow-up. **Interpretation:** AED withdrawal increases the short-term risk of breakthrough seizures after TLE surgery, and may alter the long-term disease course in some patients.

Introduction

The debate is ageless on how to manage antiepileptic drugs (AED)s after epilepsy surgery. Several factors underlie a need to reduce medications, including concerns about toxicity of polytherapy,^{1,2} a perpetuation of the “sick role” with seizure-free patients continuing a complicated medication regimen years after surgery,^{3,4} and ballooning AED costs.^{5,6} Conversely, many epileptologists fear the unknown risk of provoking a breakthrough seizure or recurrence of refractory epilepsy, and most would not consider stopping AEDs before at least 2 years of postoperative seizure-freedom.^{7,8} Seizures do recur in 10–

30% of all patients by one postoperative year. Seizure-free rates continue to decline by 2–4% per year beyond three to five postoperative years, despite ongoing AED polytherapy.^{9–18} It is unknown whether these rates of seizure recurrence would be any higher if patients were on no or less AEDs instead.

There is little information guiding decision-making on postoperative AED management. Multiple retrospective series,^{19–25} and two observational prospective studies are available.^{25,26} All added valuable information, but some were restricted to children,^{19,22} most did not include a control group where AEDs were continued,^{24,25,27–29} none distinguished patients with AED reduction from those

with AED discontinuation, and none were adequately powered to answer this basic question: expecting that seizures will recur over time in some patients after surgery, do they recur more often solely because AEDs are tapered? Furthermore, even if breakthrough seizures occur with AED withdrawal, do they herald the recurrence of intractable epilepsy^{30,31}?

In this manuscript, we evaluate the immediate and long-term implications of AED reduction, AED discontinuation, or continuation of preoperative AED regimen in patients who underwent temporal lobe epilepsy (TLE) surgery.

Methods

Patient selection

With approval from our Institutional Review Board, patients of all ages who had TLE surgery between September 1995 and June 2011 were reviewed. Prior to surgery, patients had failed at least two AEDs, completed a presurgical workup and were selected for surgery after a multidisciplinary patient management conference. Routine postsurgical follow-up involved outpatient visits at 6 weeks, 3 months, 6 months, 1 year, and then yearly thereafter for seizure-free patients, with more frequent visits in patients with recurrent seizures. Patients who were not seen in clinic were contacted yearly by phone to update their clinical and medication status. The decision to withdraw AEDs was generally made under physician guidance, and if made by the patient was reported to the physician.

Data collection

We collected data on clinical, imaging, and electrophysiological patient characteristics, focusing on variables previously associated with seizure outcome after TLE surgery.

The doses of AEDs used at the time of surgery, at seizure recurrence, and at last available follow-up were recorded. Dates of initiation, reduction, and termination of AEDs were collected. When the precise date of medication change between two clinic encounters was not found, it was approximated to a midway point between these two visits. This approximation was made in 18% of the cases. The “AED status” for every patient was then classified into one of three categories: “unchanged” if the AED regimen (medication type and dose) was the same from surgery through the last follow-up; “reduced” if the number of AEDs or their doses were reduced at some point after surgery; or “stopped” if all AEDs were discontinued at some point.

Outcome definition

The primary outcome is complete seizure-freedom after surgery. In patients with acute postoperative seizures, the timing of the first seizure occurring beyond the acute postoperative period (>1 week) was considered as the timing of recurrence. We also performed a separate analysis defining a favorable seizure outcome as an “Engel class I” to allow comparisons regarding the probability of achieving an eventual 2-year remission.

Statistical methods and variable definition

Descriptive statistics were used for each variable and data were analyzed using Wilcoxon rank sum, Chi square and Fisher’s exact tests to compare between seizure-free and seizure recurrent patients to provide potential prognostic factors. Variables with a significance level of 5% on univariate analysis were then tested in a multivariate Cox-proportional hazards regression model (again at 5% significance level). Multicollinearity was addressed and controlled for when appropriate. Predictors of AED outcome (reduced vs. stopped vs. unchanged) were similarly defined using a multivariate regression model. These two analyses (predictors of seizure outcome and predictors of AED management) identified the confounding variables to be considered with the subsequent analysis of the seizure outcomes in the various AED management groups.

Kaplan–Meier survival analysis was then done to calculate the probability of favorable seizure outcomes in patients who were seizure-free at 1 or 2 years and had their AEDs subsequently either reduced, stopped, or unchanged. These time-points were chosen as they clinically represent the various cutoffs discussed in the literature for “safe” AED withdrawal. The survival analysis included the subgroup with unchanged AEDs so that outcomes in the AED withdrawal categories can be put in perspective with a control group in place. Statistical significance was tested using the log-rank test and comparison of 95% confidence intervals.

Results

A total of 609 patients (including 85 children) fulfilled study criteria and were analyzed. The cohort’s clinical, imaging, and surgical characteristics are summarized in Table 1.

AED management

By last follow-up, there was no change in baseline preoperative AEDs in 229 patients (38%). AEDs were stopped completely at some point in 127 (21%) patients, and were

Table 1. Overall baseline cohort characteristics.

<i>Baseline cohort characteristics</i>	
Clinical characteristics	
Female (%)	52
Left-sided surgery (%)	54
Mean preoperative seizure-frequency/month (SD, range)	25.4 (74.3, 0.5–900)
Mean age at seizure onset, years (SD, range)	15.5 (13.8, 0.5–16.7)
Mean age at surgery, years (SD, range)	34.7 (14.8, 1–74.3)
Mean follow-up duration, years (SD, range)	4.62 (3.48, 0.5–16.7)
MRI findings (N = 609)	
Normal, number (%)	81 (13)
Unilateral temporal lobe abnormality, number (%)	453 (75)
Extratemporal abnormality, number (%)	75 (12)
PET findings (N = 608)	
Normal, number (%)	17 (3)
Abnormal, number (%)	492 (81)
Not done, number (%)	99 (16)
Type of surgery (N = 601)	
Standard temporal lobectomy, number (%)	571 (95)
Selective amygdalohippocampectomy, number (%)	17 (2.8)
Tailored cortical resection, number (%)	13 (2.2)
Etiology (N = 608)	
Hippocampal sclerosis, number (%)	389 (64)
Malformations of cortical development, number (%)	103 (17)
Tumors, number (%)	78 (13)
Vascular malformations, number (%)	21 (4)
Others, number (%)	17 (3)

N = total number of patients with available data on variable of interest.

reduced in 253 (42%) patients. The number of AEDs at the time of surgery ranged from one to five (mean 1.95, SD 0.7; median 2), and from zero to five AEDs at last follow-up (mean 1.42; SD 0.92; median 1). Tables 2, 3 detail the dosing of the most commonly used AEDs.

Patient characteristics in various AED management groups

Patients within the “reduction,” “discontinuation,” and “unchanged” cohorts had similar baseline seizure burden, epilepsy duration and imaging (MRI and positron emission tomography [PET]) findings, but differed in relation to: (1) etiology, (2) the number of AEDs being used at the time of surgery, and (3) presence of spikes on routine electroencephalography (EEG) done 6 months after surgery (Table 4).

The “AED reduction” category included 128 patients who had the number of their AEDs reduced, 78 whose number of AEDs was unchanged, but daily doses were decreased, and 47 who had both number and dose of AEDs reduced. The AED reduction involved a conversion into monotherapy from two to four baseline AEDs in 123 patients, a conversion into two AEDs in 23 patients, and a reduction from four to three AEDs in three patients.

Time frame of AED change

The exact dates of AED changes were available in 311 patients (82%) who had any AEDs withdrawn (253 reduced and 127 stopped).

Table 2. Anti-epileptic drug (AED) usage at the time of surgery.

Drug	#Patients (%)	Min dose (mg/day)	Max dose (mg/day)	Mean (mg/day)	Median (mg/day)	SD
LEV	253 (42)	500	6000	2406	2500	1047
LTG	217 (36)	12	900	447	400	195
CBZ	169 (28)	200	2400	1144	1200	439
TOP	113 (19)	45	1800	385	300	295
PHT	110 (18)	50	1000	403	400	152
OXC	93 (15)	300	3000	1496	1500	664

LEV, levetiracetam; LTG, lamotrigine; CBZ, carbamazepine; TOP, topiramate; PHT, phenytoin; OXC, oxcarbazepine.

Table 3. Antiepileptic drugs patients were taking at the point of last follow-up.

Drug	#Patients (%)	Min dose (mg/day)	Max dose (mg/day)	Mean (mg/day)	Median (mg/day)	SD
LEV	186 (31)	250	5500	2290	2000	1086
LTG	197 (32)	50	2250	487	425	260
CBZ	109 (18)	200	2400	982	900	420
TOP	67 (11)	50	800	330	300	183
PHT	52 (9)	100	1200	370	342	157
OXC	71 (12)	375	2400	1425	1500	503

LEV, levetiracetam; LTG, lamotrigine; CBZ, carbamazepine; TOP, topiramate; PHT, phenytoin; OXC, oxcarbazepine.

Table 4. Relationship between baseline patient characteristics and AED management decisions.

	AED reduced (N = 253)	AED stopped (N = 127)	AED unchanged (N = 228)	P-value
Etiology N (%)				
MTS	173 (68%)	66 (51%)	150 (66%)	<0.0001
MCD	47 (19%)	19 (15%)	37 (16%)	
Tumor	17 (7%)	35 (28%)	26 (12%)	
Vascular	10 (4%)	5 (4%)	6 (2%)	
Other	6 (2%)	2 (2%)	9 (4%)	
Baseline # of AEDs				
Mean \pm SD error	2.13 \pm 0.04	1.69 \pm 0.06	1.89 \pm 0.05	<0.0001
Ipsilateral spikes on postoperative EEG				
Present	29 (11%)	19 (15%)	42 (18%)	0.02
Absent	212 (84%)	96 (75%)	152 (67%)	
Type of surgery				
ATL	238 (94%)	116 (92%)	217 (95%)	0.88
SAH	7 (3%)	5 (4%)	5 (2%)	
Neocortical	6 (3%)	2 (2%)	5 (2%)	
Age group				
Adults	226 (89%)	102 (80%)	189 (84%)	0.06
Children	25 (10%)	21 (17%)	38 (17%)	
Side of surgery				
Left	137 (54%)	68 (53%)	116 (51%)	0.67
Right	114 (45%)	55 (43%)	111 (49%)	
MRI findings				
Unilateral temporal abnormality	191 (75%)	98 (77%)	160 (70%)	0.34
Normal	34 (13%)	13 (10%)	32 (14%)	
Temporal + extratemporal abnormalities	26 (10%)	12 (9%)	34 (15%)	
PET scan				
Abnormal	210 (83%)	94 (74%)	183 (80%)	0.16
Normal	5 (2%)	3 (2%)	9 (4%)	
History of generalized tonic clonic seizures				
Present	193 (76%)	83 (65%)	177 (77%)	0.11
Absent	57 (23%)	38 (30%)	48 (21%)	
Baseline seizure-frequency mean (\pm SD)	23.0 (\pm 4.7)	17.4 (\pm 6.7)	31.5 (\pm 4.9)	0.20
N patients (%) with any seizure recurrence	143 (57%)	59 (48%)	130 (58%)	0.17

MTS, mesial temporal sclerosis; MCD, malformation of cortical development; AED, antiepileptic drug; ATL, anterior temporal lobectomy; SAH, selective amygdalohippocampectomy.

In these 311 patients, the mean *interval from surgery to starting AED withdrawal* was 1.34 years (range 0–13.0 years, SD 1.70, median 0.67 years). This interval was longer in patients with >20 preoperative seizures/month (1.43 years vs. 0.95 years; $P = 0.04$), and it tended to be shorter in children (mean 0.88 years vs. 1.40 years in adults; $P = 0.08$).

The mean *interval from surgery to the latest AED change* was 1.64 years (range 0–12.2 years, SD 1.87 years, median 1.07 years). This interval correlated with age group (shorter in children 0.95 years vs. 1.76 years in adults; $P = 0.002$), suggesting a higher sense of “urgency” to stop AEDs in children compared to adults. We were unable to reliably determine from reviewing the records whether medications were being reduced with the eventual intent of complete discontinuation or solely to reduce side effects. On average though, the latest AED change

occurred earlier in patients within the “AED reduction” category (1.57 ± 0.14 years after surgery) compared to 1.94 (± 0.19) years in those with the discontinuation category ($P = 0.11$) suggesting that many patients were in the process of being tapered off medications when this was halted due to seizure recurrence.

The mean *interval between surgery and seizure recurrence* was 1.59 years \pm 0.19 in patients with seizure recurrence in context of reduction versus 2.58 years \pm 0.26 in the AED discontinuation group ($P = 0.004$). The mean interval between surgery and recurrence was 1.19 \pm 0.19 years in those with no AED change.

Seizure outcome in overall cohort

A total of 338 patients (55%) had breakthrough seizures after surgery. However, 429 (71%) were in remission by

last follow-up (Engel I), 81 cases (13%) had an Engel II (rare seizures), 68 (11%) had Engel III, and 30 (5%) had Engel IV. In fact, of the 338 patients who experienced any seizure recurrence, 163 (48%) were seizure-free by last follow-up (Engel I), 78 (23%) were significantly improved (Engel II), 67 (20%) had no worthwhile improvement (Engel III) and 30 (9%) were worse off (Engel IV).

In the subgroup with recurrence in the setting of AED reduction or discontinuation (112 patients), 75 were able to eventually achieve remission (68%), 26 had an Engel score of II at last follow-up, eight had Engel score III, and two had Engel score IV.

After multivariate modeling, two independent seizure outcome predictors were identified: ipsilateral spiking on postoperative EEG and preoperative seizure-frequency (whole model P -value <0.0001). These variables predicted outcome in the group as a whole, and within each subgroup of AED management individually.

Seizure outcome and AED management

The mean timing of the earliest AED change was shorter in patients with recurrent seizures (1.04 years) compared to those who were seizure-free (1.44 years after surgery; P -value=0.03). A similar trend ($P = 0.08$) was observed correlating the interval to the latest AED change with seizure outcome.

Subsequent analyses focused on patients who were seizure-free at 12 months (Fig. 1A and B) and 24 months (Fig. 2A and B) before undergoing AED withdrawal. We report seizure outcomes as A-complete seizure-freedom since surgery and B-Engel score I (allowing patients to have some breakthrough seizures) as long as they eventually achieve 2-year remission.

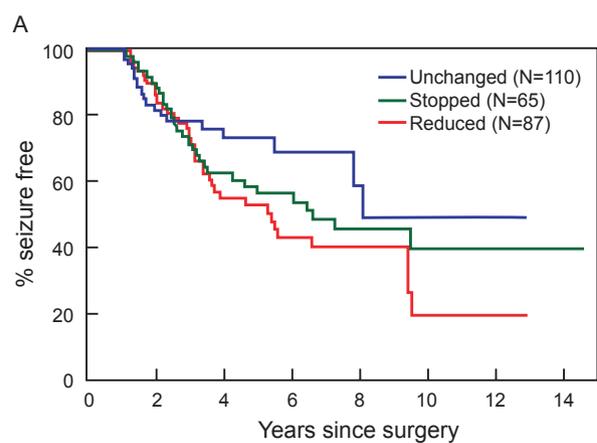
Subgroup analyses in tumors versus other pathologies, and in patients with or without spikes on postoperative EEG showed the same findings as those illustrated in Figures 1, 2.

Discussion

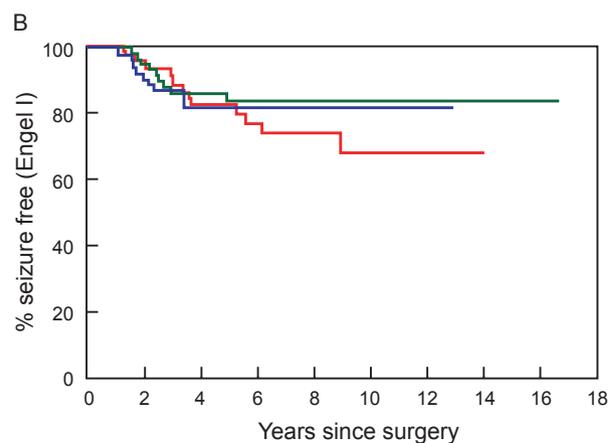
While recognizing that no definite guidelines on postoperative AED management can be derived from this retrospective observational cohort study, the work presented here provides both confirmatory and novel knowledge about this difficult subject.

AED management decisions

An adequate assessment of the reasons underlying patient and physician decision-making about AED withdrawal could not be reliably derived from our record review. Our findings suggest though that postoperative AED



Time since surgery	1 yr	2 yrs	4 yrs	6 yrs	10 yrs
AEDs Reduced	100% (± 0)	85% (± 3)	55% (± 6)	43% (± 7)	20% (± 9)
AEDs Stopped	98% (± 1)	87% (± 4)	63% (± 6)	54% (± 7)	40% (± 8)
AEDs Unchanged	98% (± 1)	82% (± 4)	73% (± 5)	69% (± 6)	49% (± 12)



Time since surgery	1 yr	2 yrs	4 yrs	6 yrs	10 yrs
AEDs Reduced	100% (± 0)	93% (± 3)	82% (± 4)	77% (± 6)	68% (± 8)
AEDs Stopped	100% (± 0)	93% (± 3)	86% (± 4)	83% (± 5)	83% (± 5)
AEDs Unchanged	98% (± 1)	90% (± 3)	82% (± 5)	82% (± 5)	82% (± 5)

Figure 1. This figure illustrates the rates of a favorable seizure outcome as defined by complete seizure-freedom after surgery (A) and by Engel score of 1 (B) in the various medication management categories for patients who were seizure-free at one postoperative year. Median timing of the actual earliest AED change was 1.90 years.

management in this TLE cohort may reflect a compromise between needing to relieve patients from significant medication-related side effects and confidence about surgical success. Patients with brain tumors (and thus an

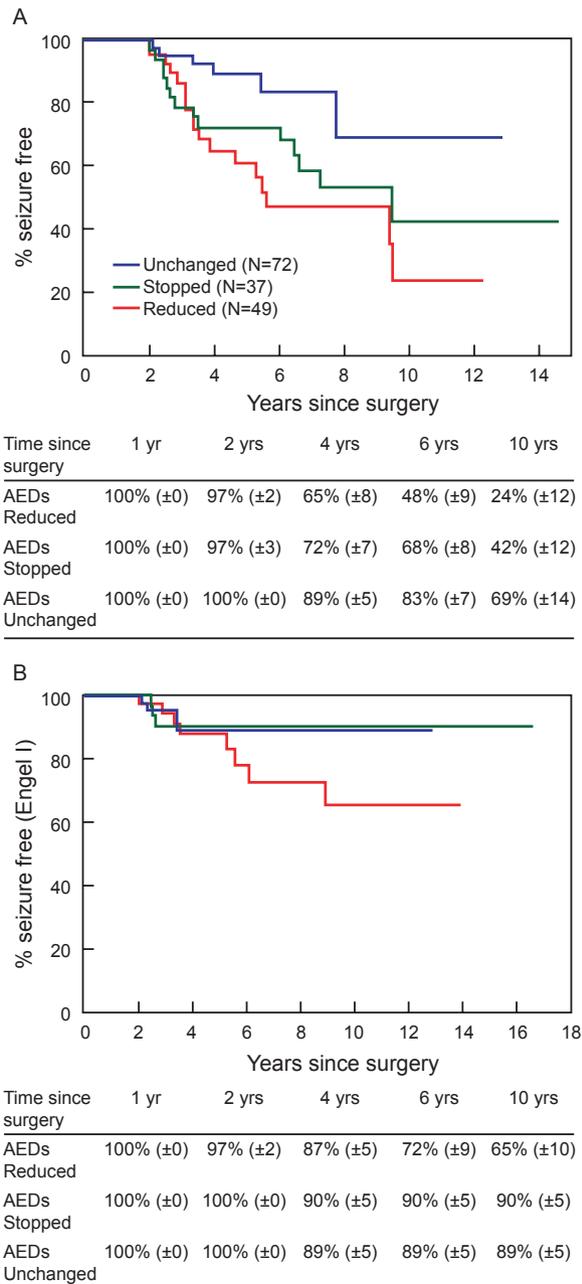


Figure 2. This figure illustrates the rates of a favorable seizure outcome as defined by complete seizure-freedom after surgery (A) and by Engel score of 1 (B) in the various medication management categories for patients who were seizure-free at two postoperative years.

easily ascertainable complete removal of the epileptic focus) were at least twice as likely as those with any other epilepsy pathology to have their AEDs completely discontinued after surgery, while those with spikes on postoperative EEG (and thus an easily ascertainable presence of an epileptic focus) were almost twice as likely to continue

their AEDs unchanged (Table 4). The baseline number of AEDs (and potentially the degree of medication side effects) was, however, higher in this group with unchanged AEDs compared to that where AEDs were stopped, suggesting that the need to reduce side effects may have been mitigated by concerns over recurrence risk with higher baseline seizure severity. This finding aligns well with earlier studies suggesting that AEDs are often continued in patients felt to be at “high risk” of postoperative seizure recurrence.^{19,22,25} A thorough understanding of this issue requires a prospective study evaluating both the patient and physician perspectives as the decisions to continue or stop AEDs are being made.

Short-term implications of AED withdrawal

Whether AEDs were withdrawn after 1 or 2 years following successful surgery, patients whose AEDs were withdrawn were less likely to remain completely seizure-free within the subsequent 1–2 years compared to those whose AEDs were unchanged (Figs. 1A, 2A). When patients within the 1-year withdrawal category were evaluated 2 years later, 72% (±5%) within the AED reduction group and 69% (±6%) within the AED discontinuation group had remained completely seizure-free as opposed to 79% (±4%) when AEDs were unchanged. Similarly, when patients whose AEDs were withdrawn at least 2 years after surgery were evaluated at four postoperative years, 55% (±6%) were seizure-free within the AED reduction group and 63% (±6%) within the AED discontinuation group as opposed to 73% (±5%) within the “unchanged AED” group. These observations are consistent with previous work, including a randomized clinical trial³² that evaluated AED withdrawal in the larger population of medically treated seizure-free patients, and found that medication withdrawal may slightly increase the risk of breakthrough seizures within the subsequent 12–24 months. They also concur with a large prospective observational cohort study comparing patients who reduced their medications either from two to one AED or from one to no AED after successful epilepsy surgery and found similarly increased relapse rates in both groups.²⁵

Long-term implications of AED withdrawal

Published data suggest that AED withdrawal (lumping AED reduction and AED discontinuation) after surgery may not alter long-term rates of remission. One prospective observational study reporting the rates of seizure recurrence after AED taper initiated 3 months or 1 year after surgery found an eventual rate of seizure recurrence similar to a small group of historical controls.²⁶ In our cohort, a “withdrawal group” lumping reduction and

discontinuation had comparable late outcomes to that with continued AEDs (data not shown). However, examination of the Engel scores at 6 and 10 years shows that the AED discontinuation group typically regained seizure-freedom and achieved long-term remission rates (Engel I) that were similar to the “unchanged AED” group, while patients whose seizures recurred in the context of AED reduction persistently had lower chances of long-term remission (Figs. 1B, 2B). This again occurred whether AEDs were withdrawn after 1 or 2 years. In addition, 70% patients with seizure recurrence after AED discontinuation were able to reach remission, as opposed to 50% of those whose seizures recurred while reducing AEDs and 37% of the recurrences whose AEDs had remained unchanged since surgery ($P = 0.0001$). These findings reproduce an earlier study where postoperative seizures in the context of AED reduction were more likely to become intractable than those starting after AED discontinuation.³³ Of note, the poor prognostic implications of recurrence during AED reduction occurred regardless of the underlying pathology. Put together, these findings suggest an inherently different pathophysiology and implications of seizures recurring while AEDs are being reduced versus after discontinuation, a pathophysiology that most likely transcends individual medications or traditional epilepsy characteristics and is rather “substrate”-dependent. A high seizure-frequency is associated with poor drug response in both humans and animal models of new-onset epilepsy.³⁴ Variations in the timing of initial exposure to some AEDs following the induction of kindling alters the subsequent effectiveness of these drugs.³⁵ In fact, potential genetic mechanisms of variation in epilepsy severity have been identified, including subclinical mutations in ion channels that increase or reduce epilepsy severity in mice, regardless of underlying pathology.³⁶ Within this framework, our results suggest that similar potential genetic mechanisms may underlie the “rekindling” of intractable epilepsy after breakthrough seizures in some patients, but not others.

On the upside, our results allow the clinician to reassure patients whose seizures recur after completely stopping AEDs about their long-term prognosis. On the downside, we could not identify specific clinical predictors that can adequately distinguish a priori patients who will successfully complete AED withdrawal. This highlights our limitations in understanding the mechanisms of postoperative seizure outcomes and emphasizes the need for specific and reliable biomarkers of disease and treatment response.

Early versus late AED withdrawal

Earlier AED withdrawal in our group was associated with a higher rate of initial seizure recurrence: (1) the mean

timing of the earliest AED change was shorter in patients with recurrent seizures compared to those who remained seizure-free, and (2) patients in the 1-year withdrawal category had about 10% lower chance of being seizure-free at 4 years when compared to the 2-year withdrawal category. Specifically, at the 4-year time point (Figs. 1A, 2A), 55% were seizure-free in the AED reduction group and 63% in the AED discontinuation group in the 1-year withdrawal cohort, as opposed to 65% and 72%, respectively, in the 2-year withdrawal group. This is consistent with earlier literature,^{7,28} and intuitively expected. However, the long-term rates of remission were the same within each AED management category, whether the AEDs were withdrawn at 1 or 2 years. For example, evaluating the “AED reduction” category, the 6-year seizure-freedom rate was 77% when AEDs were reduced at 1 year (Fig. 1B) and 72% when AEDs were reduced at 2 years (Fig. 2B). Similarly, the 10-year seizure rates were also comparable (65–68%) whether AEDs were reduced at 1 or 2 years. These results are consistent with an observational study in children in which earlier time to AED reduction or discontinuation increased the risk of breakthrough seizures but did not affect remission by last follow-up.¹⁹ The practical implication becomes that we cannot necessarily mitigate the risk of epilepsy recurrence after AED withdrawal simply by waiting longer after surgery.

Limitations

This is a retrospective cohort study with several limitations and biases. The actual reasons and motivation underlying individual patient and physician decisions to change AEDs cannot be ascertained in this design, and the cohorts evaluated differed with regard to their etiology, baseline number of AEDs, and occurrence of postoperative EEG spiking. We attempted to mitigate for these problems by: (1) studying a large, well-characterized sample; and (2) performing a detailed comparison of the three study groups (AEDs reduced vs. stopped vs. unchanged) and adjusting in subsequent analysis for the baseline differences identified in etiology and EEG findings. We cannot, however, rule out that some unmeasured underlying differences between the different study groups may have accounted for some of the observed outcome differences.

Conclusions

Regardless of its timing, AED withdrawal (reduction or discontinuation) increases the short-term risk of breakthrough seizures after TLE surgery. Seizures occurring after AED discontinuation are usually controlled with

reinstitution of medications and long-term prognosis is not altered. Seizures starting while AEDs are being reduced are more difficult to control. These findings and their significance need to be validated in a prospective randomized controlled study.

Conflict of Interest

None declared.

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