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Anti-seizure medication treatment trials prior to pre-surgical evaluation

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ABSTRACT

Purpose: Our study evaluates patterns of anti-seizure medication (ASM) usage prior to pre-surgical evaluation in drug resistant epilepsy (DRE).
Methods: We conducted a retrospective study of patients with DRE presenting for pre-surgical evaluation from 1/1/2017 to 12/31/2018. We abstracted demographic data, ASM usage, MRI and EEG findings, and distance from home to our center.
Results: In total, 54 patients (23 female) were included. The mean number of ASM trials at the time of pre-surgical evaluation was 5.62 (±3.3; range 1–15). A mean of 0.4 ASMs (±1.1; range 0–6) were initiated at our center prior to pre-surgical evaluation. MRI localization to regions other than the hippocampal or temporal region ($p = 0.002$) was associated with higher numbers of ASM trials. A trend for a larger number of ASM trials was seen for increased distance of patient primary residence from our center, right-sided ictal EEG laterality, and posterior quadrant or non-localized ictal EEG patterns.
Conclusions: Only 17% of patients were referred for pre-surgical evaluation after a trial of 1–2 ASMs. On average, patients tried 5.6 different ASMs with most of those trials predating referral to our center. Temporal lobe lesions were associated with fewer ASM trials prior to referral. Female sex was associated with an average of two more ASM trials than males. Our data do not allow us to determine how access to care, patient choice, and physician opinions impact the variability of ASM trials prior to referral for surgical evaluation. Our data indicate that delays to pre-surgical evaluation continue to occur.

Introduction

A definition for drug resistant epilepsy (DRE) was established based on empiric data, including the work of Kwan and Brodie [1], as well as expert opinion. This definition, as outlined in a consensus proposal by the International League Against Epilepsy, requires failure of adequate trials of two tolerated, appropriately chosen and used anti-seizure medications (ASMs) (monotherapy or in combination) to achieve sustained seizure freedom [2].

Surgical resection has been established as an effective potential treatment option for patients with DRE [3–5]; for appropriately chosen candidates, it can represent the best chance for seizure freedom. Although the benefits of this approach have been clearly demonstrated, surveys among neurologists in Europe and North America have revealed inconsistent attitudes and practice patterns regarding the utility of epilepsy surgery [6]. The elapsed time from seizure onset to epilepsy surgery was essentially unchanged despite the publication of an American Academy of Neurology Practice Parameter recommending epilepsy surgery as a safe and effective treatment in focal DRE [7,8].

One potential factor contributing to the extended time from seizure onset to pre-surgical evaluation may be the patient's or treating physician's threshold for the minimum number of ASM trials necessary prior to referral to a comprehensive epilepsy center. With the continued approval of new ASMs, there is at least the potential for patients to be in a cycle of seemingly endless ASM trials prior to proceeding to the pre-surgical evaluation despite the recommendation to consider pre-surgical evaluation after failure of two ASMs [4,9]. To explore the potential contribution of ASM trials to the duration of time between seizure onset and pre-surgical evaluation, we studied the relationship between the number of ASM trials and demographic as well as clinical epilepsy variables in a consecutive cohort of patients. Our primary hypothesis was that patients have failed more than two ASMs prior to referral for pre-surgical evaluation. Our primary goal was to assess the number of ASMs tried prior to pre-surgical evaluation. Secondarily, we sought to identify factors that may contribute to the number of ASMs tried prior to pre-surgical evaluation.

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Material and methods

This study was approved by the Medical College of Wisconsin Institutional Review Board (PRO00034529). All patients discussed at the Froedtert & the Medical College of Wisconsin Comprehensive Epilepsy Center (FCEC) multidisciplinary surgery conference (MDSC) or admitted to the Froedtert Hospital Epilepsy Monitoring Unit for pre-surgical evaluation from 1/1/2017 to 12/31/2018 were included in our analysis.

After identifying patients, we abstracted demographic data including the patient's age at the time of evaluation, age at seizure onset, duration of epilepsy, gender, race, ethnicity, and distance from registered home to FCEC. Relevant clinical data regarding treatment were abstracted including the current and previous ASMs and which ASMs were trialed following referral to FCEC versus those trialed prior to referral. The reason for discontinuation (e.g. efficacy versus tolerability) and maximum dose or level were not uniformly available for all ASMs. Diagnostic data were abstracted including MRI findings, interictal EEG findings, and ictal EEG findings. We recorded the results of these diagnostic tests as normal or abnormal and, if abnormal, the lateralization and localization of findings.

Additional potentially relevant factors including what year they were referred to the FCEC, whether they were referred from a primary care provider or a Neurologist to the FCEC, and how many outpatient visits they had with an epileptologist at the FCEC were also collected. All data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the Medical College of Wisconsin [10]. REDCap is a secure, web-based application designed to support data capture for research studies. Data analysis was conducted in SPSS 26 utilizing the de-identified data from REDCap. Our primary outcome was assessed by calculating the mean number of ASMs failed at the time of pre-surgical evaluation. Secondary exploratory analyses were undertaken to identify potential factors contributing to additional ASM trials. Student's t - tests and ANOVA were utilized to compare means between two or and more than two samples respectively. The Holm-Bonferroni method was utilized to correct for multiple comparisons.

Results

A total of 31 male and 23 female patients met inclusion criteria. The mean number of ASMs trialed at the time of presentation to FCEC for pre-surgical evaluation was 5.62 (±3.3; median:5; range 1–15). Nine patients (17%) were tried on only one or two ASMs at the time of referral to the FCEC. A mean of 0.4 ASMs were initiated by epileptologists at our center following referral to FCEC and prior to beginning the pre-surgical evaluation (±1.1; range 0–6). Female gender ($p = 0.002$) was associated with a higher number of ASM trials whereas the self-reported race and ethnicity had no significant impact (Table 1). Among the clinical factors assessed, only MRI localization to regions other than the hippocampal or temporal region ($p = 0.002$) was associated with a higher number of ASM trials. Increased distance of the patient's primary residence from the FCEC ($p = 0.015$), right-sided ictal EEG laterality ($p = 0.016$), and posterior quadrant or non-localized ictal EEG patterns ($p = 0.008$) demonstrated a trend for higher number of ASM trials, but these were not significant after correction for multiple comparisons (Table 2 shows the adjusted alpha values for significance).

Discussion

This study demonstrates that most patients (83%) were tried on more than two ASMs prior to their pre-surgical evaluation; on average, these patients were tried on 5–6 ASMs prior to progressing to the pre-surgical evaluation. The majority of these ASM trials occurred prior to referral to a comprehensive epilepsy center.

There are likely numerous factors which contribute to the number of ASM trials prior to pre-surgical evaluation. One potential factor was distance from our center; longer distance (>60 miles) had a higher number (~7) of ASM trials prior to pre-surgical evaluation although this was not statistically significant after correction for multiple comparisons. The potential impact of distance on ASM trials prior to pre-surgical evaluation may reflect access to care, patient preference, and/or physician preference. Access to care limitations could include transportation factors (e.g. unable to travel to a comprehensive epilepsy center) as well as insurance factors (e.g. insurance considered our center out of network) [11]. Medical transport services and telemedicine may help to alleviate access to care due to transportation factors. Patient preferences may include a desire to receive all health care locally or a desire to not explore non-pharmacologic treatments for seizures. Referring physician factors could include a belief that more ASM trials are necessary prior to pre-surgical evaluation or a reluctance to refer patients for pre-surgical evaluation [6]. Systems-based barriers to referring patients as well as barriers to patients completing the pre-surgical evaluation may also be a contributing factor and addressing these factors has been shown to improve the epilepsy surgery referral process [12].

Another potential patient and physician factor may be the perceived severity of seizures; Steinbrenner and colleagues identified a perceived low seizure frequency as one reason why patients were not referred by epileptologists for epilepsy surgery [6]. The changing response to ASMs over time may also lead to both patient and physician decisions to proceed with additional trials versus pursuing possible surgical treatments. Trials of ASMs in patients with DRE may result in periods of six months or more of seizure freedom in up to 20% of patients, although the reported number of

Table 1
Demographic characteristics of study cohort.

Characteristics		n	Mean number of ASMs trialed	sig
Gender				
	Female	23 (43%)	6.9	0.002
	Male	31 (57%)	4.7	
Race				
	White	39 (72%)	6	0.317
	Black or African American	9 (17%)	4.1	
	Hispanic or Latino	6 (11%)	5.5	
Ethnicity				
	Hispanic	6 (11%)	5.5	0.296
	Not Hispanic	48 (89%)	5.7	

Abbreviations: ASM, anti-seizure medication; sig = significance (reported in p-value).

Table 2
Potential factors impacting the number of ASM trials.

Characteristics		n	Mean number of ASMs trialed	Sig	Adjusted α
Distance to Froedtert				0.015^	0.006
	<15 miles	15 (28%)	3.7		
	15–60 miles	19 (35%)	5.8		
	>60 miles	20 (37%)	6.9		
MRI Findings				0.391	0.02
	Normal	10 (19%)	6.2		
	Multiple lesions	6 (11%)	4.3		
	Focal lesion	31 (57%)	5.4		
	Diffuse findings	1 (2%)	3		
	Nonspecific findings	6 (12%)	7.7		
MRI Laterality of Lesion				0.254	0.008
	N/A	18 (33%)	6.2		
	Left	18 (33%)	4.3		
	Right	14 (26%)	6.5		
	Bilateral	3 (6%)	5.3		
	Unknown	1 (2%)	9		
MRI Localization of Lesion				0.002*	0.005
	Normal	19 (35%)	6.3		
	Temporal or hippocampal	19 (35%)	3.7		
	Other lobar	7 (13%)	8.9		
	Hemispheric, multifocal, or other	9 (17%)	5.8		
Interictal EEG Result				0.424	0.03
	Normal	10 (19%)	5.9		
	Single epileptiform focus	27 (50%)	5.2		
	Two epileptiform foci	13 (24%)	5.7		
	Multifocal epileptiform discharges	2 (4%)	10		
	Slowing only	2 (4%)	5		
Interictal EEG Laterality				0.323	0.013
	N/A	11 (20%)	6.4		
	Left	16 (30%)	4.4		
	Right	14 (26%)	6		
	Bilateral	10 (19%)	5.4		
	Generalized	3 (6%)	8.3		
Interictal EEG Localization				0.765	0.05
	N/A	14 (26%)	6.7		
	Frontal	3 (6%)	5.7		
	Temporal	30 (56%)	5		
	Fronto-temporal	2 (4%)	6		
	Posterior quadrant	1 (2%)	5		
	Hemispheric	1 (2%)	8		
	Multifocal	1 (2%)	9		
	Other	2 (4%)	4.5		
Ictal EEG Result				0.322	0.01
	No seizures	55 (10%)	3.6		
	Single ictal onset focus	41 (76%)	5.9		
	Two ictal onset foci	7 (13%)	4.9		
	Multifocal ictal onsets	1 (2%)	9		
Ictal EEG Laterality				0.016^	0.006
	N/A	7 (13%)	3.7		
	Left	23 (43%)	4.8		
	Right	15 (28%)	7.4		
	Bilateral	7 (13%)	5.3		
	Generalized	2 (4%)	10		
Ictal EEG Localization				0.008^	0.005
	Non-localized or N/A	9 (17%)	5.1		
	Temporal or Fronto-temporal	33 (61%)	5.2		
	Frontal	2 (4%)	5.5		
	Posterior quadrant	3 (6%)	12.3		
	Hemispheric, multifocal, or other	7 (13%)	5.4		
Referral				0.155	0.007
	Other or unknown	6 (11%)	3.8		
	Self	2 (4%)	10		
	PCP	4 (7%)	5.8		
	Outside neurologist/neurosurgeon	34 (63%)	6		
	Internal neurologist/neurosurgeon	8 (15%)	4.4		

Abbreviations: Other lobar, frontal, parietal, insular, or occipital.
The * designates statistical significance following Holm-Bonferroni correction and the ^ designates a trend for significance that was not significant based on the adjusted alpha value from the multiple comparisons correction shown in the final column.

patients achieving a remission and the duration of the remission varies between studies [13–15].

While differences in the number of ASMs based upon the referral source to our institution was not statistically significant, we did note that the number of ASM trials in patients who were self-referred was higher. This raises the possibility of a potential role of patient choice in the number of ASMs trialed, the factors that may lead to self-referral and the limited number of such patients

(and the number of patients with unknown referral sources) require caution in interpreting this finding.

While the presence or absence of MRI abnormalities did not significantly impact the number of ASM trials (Table 2), patients with MRI findings that localize to the temporal or hippocampal region had fewer ASM trials. This is consistent with the large body of evidence to support temporal lobectomy as safe and effective [3–5]. Unexpectedly, with regard to ictal EEG laterality, we found a higher number of ASMs were tried in patients with right-sided or diffuse findings (Table 2) although this trend was also not significant after correction for multiple comparisons. While we would expect greater numbers of ASMs trialed in patients with poorly lateralized and diffuse ictal onsets, the finding of higher numbers of ASM trials in patients with right-sided ictal onsets was not expected. If any difference was observed, we had expected to see greater numbers of ASM trials in left-hemispheric ictal onsets (hypothesizing that concerns about language dominance may play a role in reluctance to proceed with pre-surgical evaluation on the part of the physician or patient). We explored the potential for right-hemispheric ictal onsets to be over-represented in patients further from our center, but this was not the case (40% of right hemispheric and 43.5% of left hemispheric ictal onset cases were from>60 miles from our center). One potential explanation is the associated MRI findings; 47.8% of patients with left-hemispheric ictal onsets had hippocampal or temporal MRI findings and 26.1% had unremarkable imaging. In contrast, only 13.4% of the right-hemispheric ictal onsets had hippocampal or temporal MRI findings and 60% had unremarkable imaging. We suspect the higher rate of favorable image findings in the patients with left-hemispheric ictal onsets may be driving this observation. The possibility of other factors which were not captured retrospectively such as seizure semiology possibly with features such as ictal speech changes or atypical behavioral manifestations cannot be ruled out.

Although our study is limited by its retrospective nature, we utilized a consecutive cohort of all patients that met our inclusion criteria to minimize selection biases. The retrospective nature limits the ability to explore patient-based factors in more detail. The retrospective nature, combined with many ASM trials occurring outside of our health system, precluded assessing whether all ASM trials captured here truly met the criterion of an adequate trial. The relatively small number of patients is also a limiting factor and this likely contributes to the factors that show a trend for significance but do not make adjusted significance levels when correcting for the multiple comparisons. Lastly, there may be factors that are unique to certain geographic or institutional settings (e.g. access to public transportation, need for long-distance travel to be seen at the center, and systems in place to facilitate pre-surgical evaluations for patients traveling from a distance). As our data represent only a single center, we may over-represent or under-represent some of these factors due to our setting; multicenter data to identify regional and institutional factors would help identify additional factors. Future prospective studies would also benefit from exploring patient perceptions on the number of ASM trials prior to considering surgical interventions.

Conclusions

Our data demonstrate that patients were tried on over five ASMs at the time of referral for pre-surgical evaluation. This suggests additional ASM trials may be a factor contributing to delays in patients undergoing epilepsy surgery. The causative relationship cannot be determined in this retrospective dataset (i.e. was referral delayed to allow for additional ASM trials or were other factors delaying referral leading to additional ASM trials in the interim). The degree to which patient preference as opposed to physician practice drives these choices could not be determined. Further exploration of the factors that drive multiple ASM trials in a diverse sample across centers may lead to strategies to mitigate these factors ultimately leading to more expedient referral to comprehensive epilepsy centers.

Ethical statement

All work in this study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study was approved by the Medical College of Wisconsin Institutional Review Board (PRO00034529).

Declaration of Competing Interest

Vishal Pandya, Patrick Bauer, Serena Thompson, Christopher T. Anderson, Manoj Raghavan: These author has no conflicts of interest to disclose. Chad Carlson: This author has served as a consultant for Greenwich Biosciences; payments for consultation services were made to the Department of Neurology. Dr. Carlson received no direct payments and has no relevant disclosures.

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