



Treatment registry in focal epilepsy (TRIP): Multicenter observational study in Lebanon



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ABSTRACT

Purpose: Treatment of newly diagnosed epilepsy with a single antiepileptic drug (AED) is the favored approach for seizure management. This observational study aimed to assess, under daily practice conditions, remission and retention rates with the first AED prescribed as monotherapy in patients newly or recently diagnosed with focal epilepsy.

Methods: The treatment registry in focal epilepsy (TRIP) study was conducted on 234 Lebanese patients with newly or recently diagnosed focal epilepsy, requiring treatment with an AED. Demographics, baseline focal seizure characteristics and results of the Clinical Global Impression (CGI) scale at the 12-month visit were reported. The primary objective of this study was to assess the percentage of patients who achieved a 6-month terminal seizure remission at the 12-month visit following treatment with a first AED administered as monotherapy. Secondary outcome variables included the calculation of the 6-month terminal seizure remission according to the baseline seizure types and patient retention at the 12 and 18 month visits. In addition, bivariate and multivariate analyses were conducted to identify independent predictors of 6-month terminal seizure remission at the 12-month visit.

Results: The mean age of the 234 eligible patients was 31.6 years and the majority were males (62%). At baseline, the most common type of focal seizures was focal seizures with impairment of consciousness (45%), and the most frequent topographical localization was in the temporal lobe (47%). In total, 77.6% of the patients achieved a 6-month terminal seizure remission at the 12-month visit. Patients with an epileptogenic lesion on neuroimaging were significantly less likely to achieve a 6-month remission compared to those with no identifiable pathological substrate. Patients with focal motor seizures without impairment of consciousness at baseline had significantly lower odds of achieving a 6-month terminal seizure remission compared to patients with a combination of seizure types. There was no significant association between age or gender and 6-month terminal seizure remission. The retention rates were 95.7% and 88.5% at months 12 and 18 respectively with the great majority of patients (90.7%) reporting marked improvement on the CGI scale.

Conclusions: A substantial proportion of patients with newly diagnosed epilepsy achieved a 6-month terminal seizure remission following treatment with a first AED administered as monotherapy. Patients with an epileptogenic lesion on neuroimaging and those with focal motor seizures without

Abbreviations: ADR, Adverse Drug Reactions; AED, Antiepileptic Drug; CGI, Clinical Global Impression; CI, Confidence Interval; CRF, Case Report Form; CT, Computerized Tomography; EEG, Electroencephalogram; ILAE, International League Against Epilepsy; MRI, Magnetic Resonance Imaging; OR, Odds Ratio.

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impairment of consciousness at baseline were significantly less likely to achieve a 6-month terminal seizure remission. This study demonstrated the feasibility of conducting long-term multicenter studies in Lebanon and will hopefully serve as an impetus to conduct randomized studies in the field of epilepsy.

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1. Introduction

Epilepsy is one of the most common serious neurological disorders, affecting about 50 million people worldwide. In developed countries, its annual incidence ranges from 16 to 50 cases per 100,000 people [1–4], while it is in the range of 100–190 per 100,000 in developing countries [1,4–6]. Globally, epilepsy accounts for 1% of the disease's burden; 80% of the burden of epilepsy is in the developing world, where in some areas 80 to 90% of people with epilepsy receive no treatment at all [7].

Studies have shown that up to 70% of newly diagnosed children and adults with epilepsy can be successfully treated (seizure remission for several years) with antiepileptic drugs (AED) [8]. However, up to 30% of patients will not respond to AED treatment [8]. For patients with focal epilepsy, a number of variables, including age, number of seizures prior to treatment initiation, seizure types and presence of an epileptogenic lesion on neuroimaging were found to be independent predictors of response to AED treatment [9,10].

Up till the year 2013, there was no registry of cases of epilepsy or seizures in Lebanon. The following study is a national, prospective, multicenter, observational study conducted on a cohort of patients newly or recently diagnosed with focal epilepsy. The primary objective of the study was to assess the proportion of Lebanese patients who achieved a 6-month terminal seizure remission at month 12 following treatment with a first AED administered as monotherapy. The secondary objectives were to evaluate the retention rates at months 12 and 18, to determine the AED efficacy according to the types of focal seizure (focal motor seizures without impairment of consciousness, focal seizures with impairment of consciousness, and focal seizures evolving to a bilateral convulsive seizure), to evaluate the safety of the AED and to assess the discontinuation rate due to adverse events. In addition, bivariate and multivariate analyses were conducted to identify independent predictors of 6-month terminal seizure remission at the 12-month visit.

2. Methods

2.1. Study design

This was a national, prospective, multicenter, observational study conducted on patients newly or recently diagnosed with focal onset seizures and who, in the opinion of the treating physician, required treatment with an AED. The recruitment period started in November 2008 and ended in September 2010. Each patient was followed for up to 18 months from their enrolment date and the last patient visit occurred in March 2012.

2.2. Study population

Twenty eight randomly selected neurologists from across Lebanon participated in the study. Their number was determined based on the sample size and the recruitment period. Each physician was requested to enroll the first 10 eligible patients. Patients who met the eligibility criteria and signed the written informed consent, by themselves or their legal representatives for children, were enrolled in the study. Eligible participants for this study were adults and children 6 years and older, newly or recently

diagnosed with focal onset seizures and requiring treatment with an AED. Women of childbearing potential had to be practicing efficient contraception. Previous treatment with benzodiazepines for a period not exceeding three months was allowed, but benzodiazepines were to be discontinued not later than 1 week after entering the study.

Patients (or parents of children) had to be able to complete the patient's seizure diary and to follow study procedures. All patients were required to have an EEG and neuroimaging study (head computerized tomography (CT) or brain magnetic resonance imaging (MRI) performed within the last six months before entering the study, and blood tests drawn within the last 3 months prior to the enrolment date.

A newly or recently diagnosed patient was defined as having experienced two focal onset seizures with or without evolution to a bilateral convulsive seizure in the previous 6 months or a single focal onset seizure if clinical and ancillary data (EEG, brain MRI, head CT) fulfilled the diagnosis of epilepsy and required AED treatment as determined by the treating physician [11]. Patients with more than 10 focal seizures during the previous 6 months were excluded. Focal motor seizures without impairment of consciousness were counted toward inclusion. Focal seizures without impairment of consciousness and involving subjective sensory or psychic phenomena only were not counted toward inclusion nor in the efficacy analysis.

The investigators classified the type of seizure according to the proposed classification by the International League Against Epilepsy (ILAE) [12–14]. When possible, the investigators were asked to determine the topographic localization of the seizure (temporal, frontal, parietal, or occipital) based on the seizure semiology, EEG findings and neuroimaging.

Patients with primarily generalized seizures or an idiopathic generalized epilepsy syndrome, history of non-epileptic seizures, contraindication to the use of AED or taking benzodiazepines for anxiety, were excluded from the study. Also excluded were patients with an active infection of the central nervous system, demyelinating disease, any progressive neurological disorder, severe acute or chronic disease (hematological, renal, cancer, acquired immunodeficiency syndrome), history of drug or alcohol abuse, pregnancy, trying to become pregnant, lactation, and intake of an investigational drug within 30 days prior to the first study visit.

2.3. Source of information and quality control

Data were collected and filled on case report forms (CRF) at baseline and during four follow-up visits at months 1, 6, 12 and 18 (M1, M6, M12 and M18) that were prescheduled at the end of each previous visit. Regular site-visits were performed to ensure the accuracy and completeness of the data collected. In addition, quality control was performed at 10% of the sites to verify the accuracy of data reported on CRF versus source data. In addition, a review of CRF completeness and signed informed consent was performed for all patients enrolled in the study.

2.4. Data collection

At baseline or inclusion visit, the following data were collected: date of visit, verification of the patient's eligibility for the study,

written informed consent, demographic data, results of brief neurological examination, disease history and characteristics of epilepsy, evaluation of the type, etiology, topographic localization of seizures and prescribed AED. In addition, the investigator reviewed with the patients the study procedures and provided them with the seizure diary. The choice of the initial AED administered as monotherapy was left to the treating physician's discretion.

The following clinical data were collected at the four follow-up visits (M1, M6, M12 and M18): date of visit, compliance by questioning patients (evaluating the number of missed doses on average per week), efficacy assessment (evaluating number of seizures on the seizure diary since the previous visit), results of brief neurological examination, and prescribed AED. At the last three follow-up visits (M6, M12 and M18), patients (or their parents) were asked to fill the Clinical Global Impression Scale (CGI). The CGI is a categorical scale rating patient satisfaction with his current state as compared to his baseline condition.

Being a disease registry, only spontaneously reported adverse drug reactions (ADRs) were documented.

2.5. Premature discontinuation of the study

The reasons for drop-outs were documented by the investigator on the CRF. For patients lost to follow-up, the CRF had to be filled up to the last visit.

2.6. Endpoints assessment

The primary efficacy variable was the percentage of patients who achieved a terminal seizure remission at least 6 months at the 12-month visit (M12) on their first AED administered as monotherapy. Secondary outcome variables included the calculation of the 6-month terminal seizure remission according to the baseline seizure types, patient retention at the 12 and 18 month visits and the CGI scale assessed at the time of the last three visits. Safety was determined by an assessment of the spontaneously reported ADR by the patients. Discontinuation rates were calculated and classified according to their causes.

2.7. Statistical analysis

Demographics, baseline focal seizure characteristics and results of the CGI scale at the 12-month visit were summarized using descriptive statistics. They were expressed as means, standard deviation and range for numeric variables and frequency distributions n (%) for categorical variables.

The primary outcome consisting of the percentage of patients who achieved a 6-month terminal seizure remission at the 12-month visit was computed along with its 95% confidence interval (CI) using the binomial exact distribution. It was calculated that the enrollment of 250 patients will allow us to estimate with a 90% confidence the frequency of patients who achieved a 6-month terminal seizure remission within an error of 5%. In addition, assuming a loss to follow-up of 20%, this number of enrolled patients will allow us to estimate with a 90% confidence the frequency of patient retention at the 18-month visit within an error of 5%.

Secondary outcomes included the calculation of 6-month terminal seizure remission according to the baseline seizure types and patient retention at the 12 and 18 month visits. In addition, bivariate and multivariate analyses were conducted to identify independent predictors of 6-month seizure remission at the 12-month visit. The initial full model with 6-month terminal seizure remission as the outcome variable included the following set of covariates/predictor variables: age, gender, weight of patients, results of the brief neurological exam, total number of seizures at

baseline, topographic localization, etiology and baseline type of seizures. Odds ratios (OR) with corresponding 95% CIs were used to report the association between variables and the 6-month terminal seizure remission at month 12. A two-tailed P -value <0.05 was considered statistically significant. The statistical analysis was carried out using IBM[®]-SPSS[®] software for Windows Release (IBM[®]-SPSS[®], Armonk, New York, USA, version 20.0).

2.8. Ethical considerations

The Institutional Review Board approved the study protocol before initiating the study. The study was performed in compliance with the guidelines for Good Epidemiology Practice [15]. All persons who accepted to participate in the study were interviewed after signing their written informed consent. Data collection and analysis were performed respecting their autonomy and anonymity.

3. Results

3.1. Recruitment of the patients

Of the 246 patients enrolled in the study, 234 who fulfilled the inclusion criteria, none of the exclusion criteria and who signed an informed consent at the baseline visit prior to enrollment were eligible for efficacy analysis (Fig. 1). Twelve patients were excluded for various reasons: one patient was below the inclusion age of 6 years, four had the consent date recorded after the date of visit 1, and seven had no data recorded about age. The safety analysis was conducted on the 246 patients enrolled, regardless of eligibility. The initial AED prescribed at baseline included carbamazepine, lamotrigine, phenytoin, topiramate and valproate.

3.2. Participation per period of the registry

The percentages of patients completing each visit from baseline to month 18 is shown in Fig. 2. There were 234 patients at baseline and M1, 221 patients at M6, 219 at M12 and 207 at M18.

3.3. Demographic characteristics of the patients

The mean age of the 234 eligible patients was 31.6 ± 21.9 years. The majority of the patients were males (62.0%; $n = 145$) with an average weight of 62.0 ± 20.6 kg, ranging from 11 to 120 kg. Data about gender was missing for three patients. The brief neurological examination documented evidence of abnormal findings in 26.1% of patients.

3.4. Frequency of different focal seizure types at baseline

Of the 234 patients, the most common type of focal seizures at the baseline visit was focal seizures with impairment of consciousness only (45%), followed by focal seizures evolving to a bilateral convulsive seizure only (20%) and focal motor seizures without impairment of consciousness only (13%). Twenty-two percent of patients had more than one seizure type at the baseline visit. The physicians were able to determine the topographic localization of the seizures in 190 patients (81%). The seizures were classified as temporal in 46.6%, frontal in 19% and parietal or occipital in 15%. Regarding etiology, 31% of patients were found to have an epileptogenic lesion detected on neuroimaging, while the rest had no detectable pathological substrate (Table 1).

3.5. Main outcome analyses

At month 12, 77.6% of the patients achieved a 6-month terminal seizure remission (95% CI = 72.1–83.1%). When data were stratified

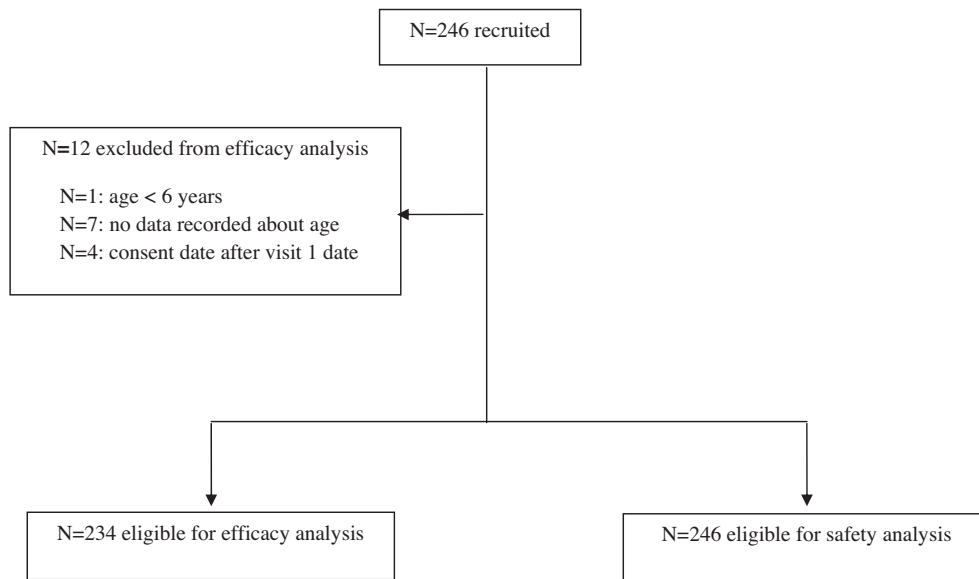


Fig. 1. Patient flow diagram.

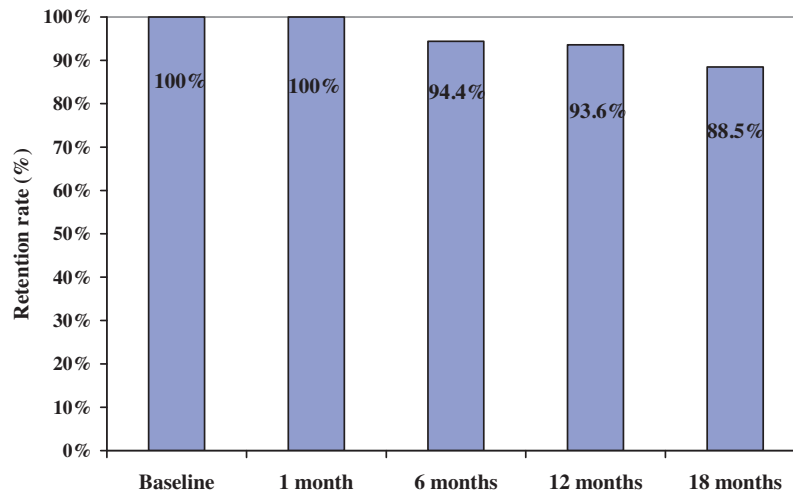


Fig. 2. Retention rate per visit.

Table 1
Baseline seizure types, topographic localization of seizures and neuroimaging findings (N=234).

Variable	N (%)
Type of focal seizure	
Focal motor without impairment of consciousness	30 (12.8%)
With impairment of consciousness	106 (45.3%)
Evolving to a bilateral convulsive	46 (19.7%)
Combination	51 (21.8%)
Data not recorded	1 (0.4%)
Topographic localization	
Temporal	109 (46.6%)
Frontal	45 (19.2%)
Parietal/occipital	36 (15.4%)
Not determined	39 (16.7%)
Data not recorded	5 (2.1%)
Epileptogenic lesion on neuroimaging	
No	151 (64.5%)
Yes	73 (31.2%)
Not determined	8 (3.4%)
Data not recorded	2 (0.9%)

according to baseline seizure type, patients with a combination of seizures had the highest percentage of achieving a terminal remission (85%), followed by patients with focal seizures with impairment of consciousness (78%) and focal seizures evolving to a bilateral convulsive seizure (78%). The lowest percentage of terminal seizure remission (66%) occurred in patients with focal motor seizures without impairment of consciousness at baseline (Table 2). At the one-month follow-up visit, the proportion of patients who were seizure-free was 76%, and after 6 months it was 79%. The percentage of patients who remained seizure free from enrollment to the 12-month visit was 57%.

3.6. Predictors of 6-month terminal seizure remission at month 12

Etiology was a significant predictor of the 6-month terminal seizure remission at month 12. The results indicate that, as compared to the patients with no detectable pathological substrate on neuroimaging, those with an epileptogenic lesion had significantly lower odds of achieving a 6-month terminal seizure remission (adjusted OR = 0.37, 95% CI = 0.17 to 0.81, P = 0.013). When patients were stratified into those with cortical dysplasia

Table 2
Main and secondary outcomes analyses.

Variable	N (%)	95% confidence interval
6-Month terminal seizure remission	170/219 (77.6%)	72.1–83.1%
6-Month terminal seizure remission stratified by baseline seizure type		
Focal motor without impairment of consciousness	19/29 (65.5%)	48.2–82.8%
Focal with impairment of consciousness	80/102 (78.4%)	70.4–86.4%
Focal evolving to a bilateral convulsive Combination	31/40 (77.5%)	64.6–90.4%
Combination	39/46 (84.8%)	74.4–95.2%
Retention rate at month 12	219/234 (93.6%)	90.5–96.7%
Retention rate at month 18	207/234 (88.5%)	84.4–92.6%

and/or hippocampal sclerosis (7 patients) compared to those with other types of pathological substrates (66 patients), there was no significant difference between the two groups in the likelihood of achieving a 6-month terminal seizure remission (OR = 2.92, 95% CI = 0.33 to 26.04, $P = 0.336$). The type of seizure at baseline was also found to be a significant predictor of a 6-month terminal seizure remission at the 12-month visit. As compared to patients with a combination of seizure types, those with focal motor seizures without impairment of consciousness had significantly lower odds of achieving a 6-month a terminal seizure remission (OR = 0.22, 95% CI = 0.06 to 0.77, $P = 0.02$). Age and gender were not found to be significant predictors of achieving a 6-month terminal seizure remission (Table 3).

3.7. Discontinuation and safety

Of the 246 patients enrolled in the study, 207 (84.1%) participants completed the study while 28 (11.4%) prematurely discontinued it. The main reasons for discontinuation were lack of efficacy ($n = 11$), loss to follow-up ($n = 6$), adverse events ($n = 4$) and poor compliance ($n = 1$). As for safety, six ADRs were

Table 3
Multivariate analyses of 6-month terminal seizure remission at month 12.

Variable	Adjusted OR (95% CI)	P-value*
Age (years)		
<21	1	–
21–59	0.45 (0.20, 1.01)	0.052
>59	1.11 (0.32, 3.84)	0.875
Gender		
Male	1	0.182
Female	1.70 (0.78, 3.71)	
Epileptogenic lesion on neuroimaging		
No	1	–
Yes	0.37 (0.17, 0.81)	0.013*
Baseline seizure type		
Focal motor without impairment of consciousness	0.22 (0.06, 0.77)	0.02*
Focal with impairment of consciousness	0.45 (0.15, 1.33)	0.15
Focal evolving to a bilateral convulsive Combination	0.57 (0.15, 2.11)	0.40
Combination	1	–

OR = odds ratio; CI = confidence interval.

* Significant at the 5% level.

spontaneously reported, namely hair loss, fatigue, vertigo, tremors, increased appetite and migraine headaches.

3.8. CGI index

Data on the CGI index are summarized in Table 4. CGI was completed by 92% of patients at the 12-month visit. The majority of patients (90.7%; $n = 195$) reported a marked improvement on the CGI.

4. Discussion

The TRIP is the first study conducted in Lebanon to report pragmatic outcomes (efficacy and safety) of first prescribed AED as monotherapy in a cohort of patients newly or recently diagnosed with focal epilepsy.

Our results indicate that 77.6% of patients achieved a 6-month terminal seizure remission at the 12-month visit. This result is concordant with a number of observational and double-blind studies conducted in children and adults with newly diagnosed epilepsy [16–20]. Since this study was not designed nor powered as a comparative trial to evaluate the efficacy and tolerability of different AED, the results were not stratified according to the choice of first AED. The main purpose of this study was to evaluate the feasibility of conducting a large prospective long-term multicenter study from different geographical locations in Lebanon that might serve as the basis of conducting large double-blind trials in the field of epilepsy.

We also found that patients with an epileptogenic lesion on MRI were significantly less likely to achieve a 6-month terminal seizure remission compared to those with a cryptogenic localization

Table 4
Clinical Global Impression at month 12 ($N = 215$).

CGI at month 12	N (%) ^a
Marked improvement	195 (90.7%)
With no side effects	166 (77.2%)
With side effects that do not significantly interfere with patient's functioning	27 (12.6%)
With side effects that significantly interfere with patient's functioning	2 (0.9%)
With side effects that outweighs therapeutic effect	0 (0.0%)
Moderate improvement	13 (6.0%)
With no side effects	7 (3.3%)
With side effects that do not significantly interfere with patient's functioning	4 (1.9%)
With side effects that significantly interfere with patient's functioning	2 (0.9%)
With side effects that outweighs therapeutic effect	0 (0.0%)
Minimal improvement	5 (2.3%)
With no side effects	3 (1.4%)
With side effects that do not significantly interfere with patient's functioning	2 (0.9%)
With side effects that significantly interfere with patient's functioning	0 (0.0%)
With side effects that outweighs therapeutic effect	0 (0.0%)
Unchanged	2 (0.8%)
With no side effects	1 (0.4%)
With side effects that do not significantly interfere with patient's functioning	1 (0.4%)
With side effects that significantly interfere with patient's functioning	0 (0.0%)
With side effects that outweighs therapeutic effect	0 (0.0%)

^a Nineteen patients had missing values for CGI at month 12.

related epilepsy. The importance of the pathological substrate as one of the variables impacting on achieving seizure remission has been recognized in patients with refractory as well as newly diagnosed epilepsy [21–23]. A recent review determined that patients who respond well to AEDs have no or minor MRI abnormalities, and among those with underlying lesions there is an inverse correlation between outcome and extent of MRI defined neuronal damage outside the main lesion, which may be undetectable by visual analyses of routine MRI [23]. Although mesial temporal sclerosis and cortical dysplasia were shown to be associated with pharmacoresistance [21,22], the lack of statistical difference in our study between patients with those pathological substrates compared to the rest of the cohort is most likely due to the small number of patients with those pathologies.

Furthermore, the baseline seizure type was a significant predictor of seizure remission. As compared with patients who had mixed seizure types, those with focal motor seizures without impairment of consciousness had significantly lower odds of achieving a 6-month seizure remission at month 12. Those results are not concordant with the results obtained in a number of studies that showed that newly diagnosed patients with epilepsy experiencing multiple seizure types at baseline appear to have worse outcomes in adults and children [9]. However, a recent review suggested that the effect of seizure types is less important than other factors including early response to treatment in determining eventual outcome [10].

Our results also documented high retention rates of 93.6% and 88.5% at months 12 and 18, respectively. Those high retention rates are concordant with those reported in other observational studies. For instance, a large observational study conducted in adults and children newly or recently diagnosed with focal onset epilepsy reported a retention rate of 90% at 1 year [15]. Those high retention rates are due to a number of factors, including tolerability and efficacy of the prescribed AED and the overall patients satisfaction with the treatment they are receiving. This is corroborated by the low drop-out rate from our study and the results of the CGI index that reflected a high level of satisfaction with the treatment they received. The low frequency of adverse events documented in this study is most likely a reflection that only the spontaneously reported side effects were recorded in the CRF.

This study has a number of weaknesses including its open label design and lack of stratification of results by type and dose of AEDs. Nevertheless, it indicated the feasibility of conducting multicenter long-term trials in Lebanon and will hopefully provide the impetus to conduct randomized clinical trials in the field of epilepsy.

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Conflict of interest statement

Marie-Therese Sawaya and Fariha Younes are employees of Sanofi-Aventis, Lebanon.

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References

- [1] Kotsopoulos IA, Van Merode T, Kessels FG, de Krom MC, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. *Epilepsia* 2002;43:1402–9.
- [2] Sridharan R. Epidemiology of epilepsy. *Curr Sci* 2002;82:664–70.
- [3] Forsgren L, Beghi E, Oun A, Sillampaa M. The epidemiology of epilepsy in Europe – a systematic review. *Eur J Neurol* 2005;12:245–53.
- [4] Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy – a review. *Epilepsy Res* 2009;85:31–45.
- [5] Carpio A, Hauser WA. Epilepsy in the developing world. *Curr Neurol Neurosci Rep* 2009;9:319–26.
- [6] Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry* 1996;61:433–43.
- [7] World Health Organization. Atlas: epilepsy care in the world 2005. Geneva, Switzerland: World Health Organization; 2005. Available from http://www.who.int/mental_health/neurology/epilepsy_atlas_introduction.pdf [last accessed 31.10.14].
- [8] World Health Organization. Epilepsy. Fact sheet N7. 999, October 2012. © WHO; 2013. Available from <http://www.who.int/mediacentre/factsheets/fs999/en/> [last accessed 31.10.14].
- [9] Abimbola S, Martiniuk AL, Hackett ML, Glozier N, Mohamed A, Anderson CS. Early predictors of remission in newly diagnosed epilepsy: a systematic approach to reviewing prognostic factor studies. *Neurol Res* 2014;36:1–12.
- [10] Mohanraj R, Brodie MJ. Early predictors of outcome in newly diagnosed epilepsy. *Seizure* 2013;22:333–44.
- [11] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–512.
- [12] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005–2009. *Epilepsia* 2010;51:676–85.
- [13] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for classification of epilepsies, and epileptic syndromes. *Epilepsia* 1985;26:268–78.
- [14] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;30:389–99.
- [15] Good epidemiology practice (GEP) – IEA guidelines for proper conduct of epidemiologic research. Prepared for the IEA European Federation. Adopted by the IEA and “societies” in 2004. Updated in June 2004. IEA European Federation; 2014. Available from http://www.gmwebtesting.com/ucimed/website/images/descargas/comite_etico/normativas/2004-European-Federation-GoEpidPrac.pdf [last accessed October 31].
- [16] Jedrzejczak J, Kunciková M, Magureau S, VIPe Study Group. An observational study of first-line valproate monotherapy in focal epilepsy. *Eur J Neurol* 2008;15:66–72.
- [17] Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AL, et al. Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *J Neurol Neurosurg Psychiatry* 1995;58:44–50.
- [18] de Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Neville BC, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 1996;347:709–13.
- [19] Jannuzzi G, Cian P, Fattore C, Gatti G, Bartoli A, Monaco F, Perucca E. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. *Epilepsia* 2000;41:222–30.
- [20] Brodie MJ, Perucca E, Rylvlin P, Ben-Menachem E, Meecke HJ. Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology* 2007;68:402–8.
- [21] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256–62.
- [22] Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001;42:357–62.
- [23] Cendes F. Neuroimaging predictors of AED resistance in new-onset epilepsies. *Epilepsia* 2011;52(Suppl. 4):7–9.