e-ISSN: 0976-822X, p-ISSN:2861-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(5); 473-481

Original Research Article

A Prospective Longitudinal Observational Assessment of Antiepileptic-Drug Tapering and Seizure Recurrence Correlation with Serum Drug Levels and Biomarkers in Persons with Epilepsy

Naveen Kumar[1], Asha Kumari[2], Kanchan Kumari[3]

[1]Tutor, Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India

[2]Assistant Professor and HOD, Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India.

[3]Tutor, Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India

Received: 03-02-2023 / Revised: 11-03-2023 / Accepted: 23-04-2023
Corresponding author: Dr. Kanchan Kumari
Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to investigate antiepileptic-drug (AED) serum level and inflammatory biomarkers assessed during epilepsy treatment for effective seizure control and their correlation with seizure recurrence (SR) following AED-tapering.

Methods: This prospective longitudinal observational study was carried out at DMCH, Laheriasarai, Darbhanga, Bihar, India for one year.

Results: AED dose was reduced by a fixed amount (LEV 250 mg, CBZ 50 or 100 or 150 mg, VPA 100 or 200 mg, and PHT 50 or 100 mg) at a time without taking into consideration the dose just before the commencement of tapering. The amount of dose tapered constitutes about 6.67%–50.0% (median 25%) of the dose just before the commencement of tapering. The median interval between dose reductions was 2 months (range 2–6 months). There was no significant difference in AED levels at SR/stoppage of AED/at 6 months between SR and NSR group in any of the AED monotherapy groups. PWE, in both SR and NSR groups and individual AED monotherapy groups, had significantly high levels of inflammatory mediators (TNF-α, IL-1 β, IL-6, IL-10, and HMGB1) as compared to healthy control subjects at the onset of tapering. The SR group had significantly higher IL-1 β and TNF-α as compared to the NSR group (P = 0.001 and 0.02, respectively).

Conclusion: Low serum AED levels (especially levetiracetam) and raised levels of TNF-α and IL-1 β during tapering commencement had a higher association with SR following AED-tapering.

Keywords: Antiepileptic drug tapering, inflammatory biomarkers, persons with epilepsy, seizure recurrence, serum antiepileptic-drug level

Introduction

Seizure is a transient clinical event that is characterized by abnormal excessive or synchronous neuronal activity in the brain.1 Epilepsy can be defined as the history of at least one seizure and the presence of an enduring brain condition that increases the likelihood of future seizures. [1,2] Epilepsy can occur secondary to brain lesions (e.g.,

traumatic brain injury, cerebrovascular disease, central nervous system infections) as classified by the International League Against Epilepsy. [2] For acquired brain injury (ABI), it has been established that there are two types of seizures; acute symptomatic seizures [3] [previously called early post-traumatic seizures] [4] that occur within the first week after the ABI, and unprovoked remote symptomatic seizures [5] (previously called late post-traumatic seizures) that happen after the first week post-injury. At least two unprovoked remote symptomatic seizures that occur more than 24 h apart or after a single event that occurs in a person who is considered to have a high risk of recurrence (>60% risk in a 10-year period) define post-traumatic epilepsy (PTE) after ABI. [6]

Therapeutic drug monitoring is crucial for surveillance of drug toxicity/overdosage, compliance of drug intake, and thus abet in dose titration during AEDs treatment. Owing to complex pharmacokinetic properties and narrow therapeutic index, extensive variation in AEDs plasma concentration can result in toxicity or loss of therapeutic efficacy. [7,8] Many studies have assessed SR risk in PWE with controlled seizure undergoing tapering and ultimately stoppage of AED, but the comparative efficacy of continuation of lowered down AED doses in this population has not been established. If seizure can be controlled at lower maintenance or "sub-therapeutic" AED doses, this will lead to reduced drug toxicity and reduced treatment costs. [9] However, this does not completely abort the chances of SR, AEs, stigma to the subject being on AED treatment, and the cost of ongoing treatment. Hence, there is no clarity of being on a low dose of AED or complete AED tapering. Although AED dose has been studied concerning SR, there is a lack of evidence focussed on serum AED level and its correlation with SR during AED tapering commenced after at least 2 years of seizure freedom. A strong persistent inflammatory response is one of the key components of epileptogenesis. Upregulation of inflammatory mediators leads to blood–brain barrier breakdown, which facilitates neuroinflammation and subsequently synaptic changes and neuronal hyper-excitability. [10]

Despite these shreds of evidence, there is a lack of studies focusing on serum inflammatory markers assessment during AED tapering where the major concern is the chance of SR. The aim of the present study was to investigate antiepileptic-drug (AED) serum level and inflammatory biomarkers assessed during epilepsy treatment for effective seizure control and their correlation with seizure recurrence (SR) following AED-tapering.

Materials and Methods

This prospective longitudinal observational study was carried out at DMCH, Laheriasarai, Darbhanga, Bihar, India for one year. The study was conducted among clinically diagnosed PWE on treatment with AEDs monotherapy (valproate [VPA], phenytoin [PHT], carbamazepine [CBZ], and levetiracetam [LEV]) coming to the neurology outpatient department, with ≥2 years of seizure freedom and who was going to start AED tapering. PWE excluded from this study include subjects who were either unable to give consent, who had Juvenile myoclonus epilepsy, with the diagnosis of other neurological or psychiatric disorder, chronic disease including inflammatory conditions, on other drugs treatment which can alter seizure threshold, with liver and renal dysfunction requiring AED dose alteration, pregnant or seeking pregnancy. Diagnosis of epilepsy was made by the treating physician according to the International League Against Epilepsy guidelines. A group of healthy control subjects was enrolled to compare the serum level of inflammatory markers with that of PWE.

Study Data Collection

After explaining the study details, each PWE was interviewed according to a well-designed case reporting format to collect the following data: demographic facts; seizure-related information including age at seizure onset, type, number of seizure episodes before control, and time duration of epilepsy (i.e., dates of first seizure episode to the time of tapering onset); and AED treatment information such as dose, duration, and investigational findings if any (like electroencephalography, computed tomography, and magnetic resonance imaging). AED dose at the onset of tapering was represented as a percentage of maximum recommended dose (MRD) of the concerned AED as per the Textbook of Harrison's principles of internal medicine, i.e., PHT (6 mg/kg), CBZ (35 mg/kg), VPA (60 mg/kg), and LEV (60 mg/kg).[20] Strict patient confidentiality was maintained. PWEs were followed up for a minimum of 12 months to look for any SR. This study has done AEs profiling during tapering in PWE using the Liverpool Adverse Event Profile (LAEP) score. LAEP was a patient self-reporting scale to measure the frequency of AED-related AEs. This scale has 19 items/questionnaire with a 4-point Likert scale for each item, i.e., 1 – never a problem; 2 – rarely a problem; 3 – sometimes a problem; and 4 – always a problem. [11] Although the items can be gauged individually for frequency, a global score can be derived from the sum of the ratings. This scale has a total score range from 19 to 76, with more frequent symptoms denoted by a higher score.

Among the PWE, analysis was done for risk factors like higher frequency of seizure episodes before control, longer duration of epilepsy, history of any failed tapering, and history of smoking/alcohol/tobacco intake, which have shown a positive correlation with SR as per a previous study conducted in this setup.11 Patients were called for follow-up visits as per existing hospital treatment protocol for PWE, i.e., at 6 months intervals for a minimum of 1 year/at the time of stoppage of AED/SR. During these visits, monitoring for occurrence of SR and AEs was done. Along with follow-up visits, PWE were contacted telephonically in between for any additional information about SR. [12]

Serum antiepileptic drug level estimation

Serum AED levels for VPA, CBZ, PHT, and LEV were estimated at two visits: A. onset of tapering time, and b. at the time of SR, stoppage of AED, or 6-month follow-up time, whichever is earlier. Blood samples were collected from the subject coming to the neurology outpatient department in the morning before AED intake (trough sample). Subjects with SR were advised to immediately collect a blood sample from a nearby health-care facility as soon as possible and send it to the study center for analysis. The blood sample was processed by cold (4°C) centrifuging at 3500 rpm for 10 min, later serum was collected and stored at −80°C. Serum AED level was estimated using the high-performance liquid chromatography (HPLC) instrument (Agilent 1200 series, Agilent Technologies, USA) and C18 column (Zorbax C18-Merck, Germany). Reagents used for HPLC analysis include potassium dihydrogen orthophosphate, orthophosphoric acid, acetonitrile, methanol, potassium hydroxide, and triethylamine, which are purchased from Merck India Ltd. Standards of AEDs were received from Sun Pharmaceuticals, India as gift samples. Serum was mixed with acetonitrile (for VPA, CBZ, PHT) or methanol (for LEV) and vortexed. It was later centrifuged at 15,000–18,000 rpm (specific for AED) to separate precipitated protein. Then, the supernatant was filtered and injected into the HPLC system through an automatic sampler. The mobile phase comprised the buffer of potassium dihydrogen orthophosphate, methanol, and acetonitrile.

For CBZ and PHT estimation, the mobile phase passed with a 1.2 ml/min flow rate for

15 min runtime. Column compartment with thermostat maintained the temperature at 25°C and UV detector at wavelength 210 nm was used for detection. [13] For LEV estimation, the flow rate was 1 ml/min with a runtime of 15 min by maintaining column temperature at 25°C and measuring peak area and retention time at 205 nm wavelength. [14] VPA was estimated using a PDA detector at wavelength 210 nm. The mobile phase was passed at 1.2 ml/min through a thermostated column compartment at a temperature of 50°C. The mobile phase comprised acetonitrile and phosphate buffer with a run time of 21 min. [15]

Serum biomarkers estimation

Venous blood samples (5 ml) were collected at the onset of tapering (first visit) from all monotherapy subjects enrolled in the study for serum biomarkers level estimation. The serum was separated by centrifugation and stored in a −80°C deep freezer till analysis. The inflammatory biomarkers (TNF-α, IL-1 β, IL-6, IL-10, and HMGB1) were estimated through enzyme-linked immunosorbent assay kits (R and D Systems, Minneapolis, MN 55413, USA). The kits were run as per the instruction manual from the manufacturer and absorbance was recorded through Multi-Mode Microplate Readers (SpectraMax® M Series, Molecular Devices, California, USA). For comparison purposes, blood samples of healthy control subjects (n = 52) were also collected, and the above inflammatory markers were estimated in them.

Statistical Analysis

Analysis of data was conducted using Statistical Package for the Social Sciences (SPSS) software version 23.0 (Chicago, IL, USA). Parametric data were presented as mean ± standard deviation and nonparametric data were by the median and interquartile range or range (minimum–maximum). Mann–Whitney U statistical test was applied for the comparison of nonparametric data. A Chi-square test was used to find out any difference in the distribution frequency among the groups. Statistical significance is considered for $P < 0.05$.

Results

Table 1: Demographics, type of antiepileptic drug, and seizure-recurrence rate among persons with epilepsy undergoing antiepileptic drug tapering

Parameters	**PWE on monotherapy n=100**
Age in years (mean±SD)	24.0±10.5
Gender	
Male	60 (60)
Female	40 (40)
Seizure type	
Focal	58 (58)
Generalized	42 (42)
Seizure free period in years	
Median (range)	3.4 (2–10)
2-4	64 (64)
>4	36 (36)
Family h/o epilepsy	
No	84 (84)
Yes	16 (16)
Previous h/o of tapering	
No	82 (82)
Yes	18 (18)
Education	

Below 10th	25 (25)
Above 10th	75 (75)
Occupation	
Unemployed/student 87	66 (66)
Employed	34 (34)
Smoking/alcoholic/tobacco chewing	
No	90 (90)
Yes	10 (10)
AED treatment parameters **AEDs monotherapy**	
Levetiracetam	40 (40)
Valproate	25 (25)
Carbamazepine	23 (23)
Phenytoin	12 (12)
SR in PWE	24 (24)
SR with time after AED tapering **SR in PWE with time after AED tapering**	
Within 6 months	12 (12)
Within 12 months	16 (16)
Within 24 months	22 (22)
Within 44 months	24 (24)

AED dose was reduced by a fixed amount (LEV 250 mg, CBZ 50 or 100 or 150 mg, VPA 100 or 200 mg, and PHT 50 or 100 mg) at a time without taking into consideration the dose just before the commencement of tapering. The amount of dose tapered constitutes about 6.67%–50.0% (median 25%) of the dose just before the commencement of tapering. The median interval between dose reductions was 2 months (range 2–6 months). The proposed total duration of AED tapering was 7 months (median, range 1.5–22 months). After follow-up (range 12–44 months) in 129 PWE, SR was reported in 24 PWE (24%), while 76 (76%) PWE remained seizure-free. The number of SR with time after AED tapering (% of total PWE with SR) was 12 (12%) within 6 months, 16 (16%) within 12 months, 22 (22%) within 24 months, and 24 (24%) within 44 months of follow-up.

Table 2: Serum antiepileptic drug levels comparison between seizure-recurrence and nonseizure-recurrence persons with epilepsy

LEV (n=40)			
Visits	**Visits AED serum level, median (IQR)**		**P**
	SR (n=10)	**NSR (n=30)**	
Onset of tapering (1st visit)	14.4 (4.1-35.5)	25.5 (13.3-43.7)	0.044
At SR/6 months (2nd visit)	4.60 (2.6-6.3)	8.2 (4.5-19.6)	0.052
VPA (n=25)			
Onset of tapering (1st visit)	58.42 (28.6-85.6)	42.58 (29.45-61.1)	0.40
At SR/6 months (2nd visit)	26.34 (18.9-49.9)	26.64 (13-33.6)	0.48
CBZ (n=20)			
Onset of tapering (1st visit)	10.5 (8.5-13.2)	8.2 (6.65-10.7)	0.44
At SR/6 months (2nd visit)	8.6 (6.2-11.2)	4.6 (2.75-6.9)	0.10
PHT (n=15)			
Onset of tapering (1st visit)	14 (07-19)	6.04 (3.85-10.6)	0.25
At SR/6 months (2nd visit)	4.06 (1.4-6.7)	1.4 (1.0-4.7)	0.64

There was no significant difference in AED levels at SR/stoppage of AED/at 6 months between SR and NSR group in any of the AED monotherapy groups.

Table 3: Comparison of inflammatory biomarkers at onset of tapering among different groups

Groups	Median (IQR)		Median (IQR)		Median (IQR)				P Value
	Control (n=50)	All PWE (n=100)	PWE with SR (n=20)	PWE without SR (n=80)	LEV (n=40)	VPA (n=25)	PHT (n=15)	CBZ (n=20)	
IL-1β (pg/ml)	13.7 (10.4-16.0)	75.5 (49.3-93.6)	84.0 (33.7-97.4)	74.6 (50.5-94.0)	76.6 (56.9-108.3)	80.2 (49.2-98.0)	78.0 (70.9-99.1)	64.6 (35.5-87.4)	<0.001
IL-6 (pg/ml)	75.5 (64.5-82.8)	96.5 (70.7-119.0)	94.4 (68.5-104.2)	96.4 (70.7-126.8)	84.6 (67.6-122.7)	98.2 (70.8-138.8)	104.6 (84.2-112.6)	98.2 (80.6-110.7)	<0.001
IL-10 (pg/ml)	176.4 (140.5-210.4)	60.4 (56.4-70.5)	60.74 (57.4-64.9)	60.8 (56.3-72.7)	62.0 (58.5-74.8)	65.5 (57.1-80.6)	54.6 (54.9-58.7)	55.5 (54.1-60.2)	<0.001
TNF-α (pg/ml)	5.5 (2.9-11.9)	116.4 (86.4-151.3)	126.4 (94.7-146.5)	115.5 (86.1-151.6)	132.8 (92.0-193.6	131.9 (88.8-176.9)	90.7 (80.1-96.7)	110.7 (82.3-141.2)	<0.001
HMGB1 (ng/ml)	6.4 (4.3-11.5)	16.4 (8.3-33.3)	12.8 (7.5-28.0)	18.0 (8.7-34.5)	24.6 (9.4-34.8)	12.8 (7.7-30.5)	8.0 (6.9-16.8)	12.6 (7.8-34.7)	<0.001

PWE, in both SR and NSR groups and individual AED monotherapy groups, had significantly high levels of inflammatory mediators (TNF-α, IL-1 β, IL-6, IL-10, and HMGB1) as compared to healthy control subjects at the onset of tapering. The SR group had significantly higher IL-1 β and TNF-α as compared to the NSR group (P = 0.001 and 0.02, respectively). The comparison of individual AED treatment groups revealed a significant difference between them concerning IL-10, TNF-α, and HMGB1. VPA group had significantly higher IL-10 and TNF-α, whereas the LEV group had higher HMGB1. Among the monotherapy groups, subgroup comparison (SR vs. NSR) was not done due to a limited sample size.

Discussion

Persons with epilepsy (PWE) were considered for antiepileptic drugs (AEDs) tapering if they remain without any seizure episodes for 2 or more years16 because of unendurable adverse drug events (AEs), unbearable treatment cost, and/or often social stigma. [12,17] The decision for AED tapering/stoppage of treatment is shifting from the physician perspective alone to a patient-centered shared decision-making based on the seizure-free probability even after AED tapering. There are no clear recommendations for post-ABI seizure prophylaxis for many etiologies of acquired brain injury such as ischemic stroke, intracerebral and subarachnoid hemorrhages. [18] However, prophylaxis treatment should be applied when the patient is at high risk for acute symptomatic seizure, particularly in the 7-day post-injury period, as for TBI patients.3 Nonetheless, TBI is the only etiology for which there is solid evidence based research examining AED/ASM treatment for seizure prophylaxis for acute symptomatic seizures [19], although the guidelines and

recommendations generated from this evidence were not always followed with regard to decisions on initiation of treatment as well as the timing of initiation and termination of treatment. [20]

AED tapering even after 2–3 years of seizure-free period is still contentious due to the possibility of SR during and after AED tapering which is about 19%–31% as per previous studies conducted in India. [12,21,22] AED dose was reduced by a fixed amount (LEV 250 mg, CBZ 50 or 100 or 150 mg, VPA 100 or 200 mg, and PHT 50 or 100 mg) at a time without taking into consideration the dose just before the commencement of tapering. The amount of dose tapered constitutes about 6.67%–50.0% (median 25%) of the dose just before the commencement of tapering. The median interval between dose reductions was 2 months (range 2–6 months). The proposed total duration of AED tapering was 7 months (median, range 1.5–22 months). After follow-up (range 12–44 months) in 129 PWE, SR was reported in 24 PWE (24%), while 76 (76%) PWE remained seizure-free. The number of SR with time after AED tapering (% of total PWE with SR) was 12 (12%) within 6 months, 16 (16%) within 12 months, 22 (22%) within 24 months, and 24 (24%) within 44 months of follow-up.

There is a lack of previous studies commenting upon serum AED level and its correlation with SR during tapering, so it is tough to establish an accurate sample size. One previous study by Cardoso et al. has compared lower AED dose continuation versus complete tapering of AED dose after being seizure-free for at least 2 years and opined that once PWE decided to taper down their medication, it should be complete. [23] In the same study, they have found a nonsignificant association of serum AED levels and the risk of SR in adults considering two categories, i.e., therapeutic or higher concentration and low concentration.

There was no significant difference in AED levels at SR/stoppage of AED/at 6 months between SR and NSR group in any of the AED monotherapy groups. As per the literature, IL-1 receptor antagonists and IL-10 have an anti-inflammatory effect and exert a protective and anticonvulsant role in seizure models. [24] Similarly, HMGB1 has been positioned as a unique and emerging target against epileptogenesis as per a recent review article. [25] PWE, in both SR and NSR groups and individual AED monotherapy groups, had significantly high levels of inflammatory mediators (TNF-α, IL-1 β, IL-6, IL-10, and HMGB1) as compared to healthy control subjects at the onset of tapering. The SR group had significantly higher IL-1 β and TNF-α as compared to the NSR group ($P = 0.001$ and 0.02, respectively). The comparison of individual AED treatment groups revealed a significant difference between them concerning IL-10, TNF-α, and HMGB1. VPA group had significantly higher IL-10 and TNF-α, whereas the LEV group had higher HMGB1. Among the monotherapy groups, subgroup comparison (SR vs. NSR) was not done due to a limited sample size.

Conclusion

The judgment to start or stop the AED tapering entails a careful assessment of risk factors on an individual basis for reduced risk of SR. The current study result opines the possible association of subtherapeutic serum AED level (especially levetiracetam) and higher inflammatory markers at the onset of tapering with the risk of SR in PWE undergoing AED tapering. These concepts necessitate congregating further evidence regarding the role of monitoring serum AED level and inflammatory markers level along with other established risk factors before onset of AED tapering with an aim of optimal management of epilepsy and reduced risk of SR.

References

1. Fisher RS, Boas WV, Blume W, Elger C, Genton P, Lee P, Engel Jr J. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005 Apr;46(4):470-2.
2. OF THE ILAE DD. ILAE Classification of Epilepsies: Position Paper of the ILAE Commission on Classification and Terminology. Epilepsy. 2017;58(4):512-21.
3. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010 Apr;51(4):671-5.
4. Jennett B. Epilepsy after non-missile head injuries. Heinemann Medical; 1975.
5. Bergey GK. Management of a first seizure. CONTINUUM: Lifelong Learning in Neurology. 2016 Feb 1;22 (1)0020:38-50.
6. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia. (2014) 55:475–82.
7. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239-76.
8. Eadie MJ. Plasma antiepileptic drug monitoring in a neurological practice: a 25-year experience. Therapeutic drug monitoring. 1994 Oct 1;16(5):458-68.
9. Cardoso TA, Cendes F, Guerreiro CA. Is low antiepileptic drug dose effective in long-term seizure-free patients?. Arquivos de neuro-psiquiatria. 2003; 61:566-73.
10. Rana A, Musto AE. The role of inflammation in the development of epilepsy. Journal of neuroinflammation. 2018 Dec;15:1-2.
11. Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. Neurology. 2004 Jan 13;62(1):23-7.
12. Kumar S, Sarangi SC, Tripathi M, Ramanujam B, Gupta YK. Seizure recurrence risk in persons with epilepsy undergoing antiepileptic drug tapering. Acta Neurologica Scandinav -ica. 2020 Jan;141(1):65-76.
13. Sarangi SC, Pattnaik SS, Joshi D, Chandra PP, Kaleekal T. Adjuvant role of Ocimum sanctum hydroalcoholic extract with carbamazepine and phenytoin in experimental model of acute seizures. Saudi Pharmaceutical Journal. 2020 Nov 1;28(11):1440-50.
14. Sarangi SC, Pattnaik SS, Katyal J, Kaleekal T, Dinda AK. An interaction study of Ocimum sanctum L. and levetiracetam in pentylenetetrazole kindling model of epilepsy. Journal of ethnopharmacology. 2020 Mar 1;249: 112389.
15. Sarangi SC, Joshi D, Kumar R, Kaleekal T, Gupta YK. Pharmacokinetic and pharmaco dynamic interaction of hydroalcoholic extract of Ocimum sanctum with valproate. Epilepsy & Behavior. 2017 Oct 1;75:203-9.
16. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia. 1993;34:592–6.
17. Sarangi SC, Kaur N, Tripathi M, Gupta YK. Cost analysis study of neuropsychiatric drugs: Role of National List of Essential Medicines, India. Neurology India. 2018 Sep 1;66 (5):1427.

18. Rowe AS, Goodwin H, Brophy GM, Bushwitz J, Castle A, Deen D, Johnson D, Lesch C, Liang N, Potter E, Roels C. Seizure prophylaxis in neurocritical care: a review of evidence-based support. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2014 Apr;34(4):396-409.
19. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GS, Nakase-Richardson R. Practice guideline update: disorders of consciousness. J Chem Inf Model. 2017;8:1-58.
20. Zaman A, Dubiel R, Driver S, Bennett M, Diggs V, Callender L. Seizure prophylaxis guidelines following traumatic brain injury: an evaluation of compliance. The Journal of Head Trauma Rehabilitation. 2017 Mar 1;32 (2):E13-7.
21. Lamdhade SJ, Taori GM. Study of factors responsible for recurrence of seizures in controlled epileptics for more than 1 years after withdrawal of antiepileptic drugs. Neurology India. 2002 Jul 1;50(3):295.
22. Rathore C, Panda S, Sarma PS, Radhakrishnan K. How safe is it to withdraw antiepileptic drugs following successful surgery for mesial temporal lobe epilepsy?. Epilepsia. 2011 Mar;52 (3):627-35.
23. Cardoso TA, Cendes F, Guerreiro CA. Is low antiepileptic drug dose effective in long-term seizure-free patients?. Arquivos de neuro-psiquiatria. 2003;61 :566-73.
24. Youn Y, Sung IK, Lee IG. The role of cytokines in seizures: interleukin (IL)-1β, IL-1Ra, IL-8, and IL-10. Korean journal of pediatrics. 2013 Jul;56(7) :271.
25. Paudel YN, Semple BD, Jones NC, Othman I, Shaikh MF. High mobility group box 1 (HMGB 1) as a novel frontier in epileptogenesis: from pathogenesis to therapeutic approaches . Journal of neurochemistry. 2019 Dec; 1510020(5):542-57.