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Brief Insight about Recurrence of Seizures after Anti-Seizure Drugs Withdrawal

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Abstract: Epilepsy was one of the most frequent severe brain diseases. It can affect people of all ages and has a wide range of symptoms and causes. Anti seizure drugs (ASDs) were potentially an effective treatment for epileptic patients. However, treatment failure and poor adherence were very common in patients experiencing side-effects due to ASDs. In approximately 25% of patients, side-effects of ASDs lead to treatment discontinuation and negative impact on the quality of life. Tapering or discontinuation is considered an important step in controlled epileptic patients with long term use of anti-epileptic drugs after they are seizure-free for period of 2 years or more because of compelling complications like adverse drug effects, cost of treatment, and social stigma. In recent decades, many studies have focused on the risk of seizure recurrence after ASD withdrawal, which varies from 12% to 67%.

Keywords: Recurrence of Seizures, Anti-Seizure Drugs Withdrawal

Introduction: Epilepsy was one of the most frequent severe brain diseases. It can affect people of all ages and has a wide range of symptoms and causes**.** Epilepsy has been known from the beginning of time. It was one of the most prevalent and terrifying neurological diseases that affects millions of individuals throughout the world. The term came from a Greek word that meaning "to seize" or "to grab hold of "**(1).**

Epilepsy was a condition associated with high levels of stigma. Quality of life was reportedly diminished in people with epilepsy worldwide. Studies showed a decreased quality of life self-perception in people with epilepsy (PWE). In addition to anxiety and depression, early identified affected domains included those directly related to seizures and

antiseizure medication adverse effects, and those associated to the experience of living with epilepsy**(2)**.

In everyday life, epilepsy was strongly linked to significant psychological and social problems. According to the World Health Organization (WHO), people with epilepsy face civil and human rights violations and restrictions **.** Epileptic patients were more likely to find difficulty in gaining satisfactory employment. Remission of seizures enhances their chance at work and this acts as a pressure to continue therapy **(3).**

Epilepsy, like many other mental health disorders was often associated with substantial stigma particularly in poor areas. Most people with epilepsy in these regions were less likely to be sent to school, find employment, or marry**(4)**.

Epilepsy was a complex brain disease which causes the prominent clinical sign called seizures characterized by motor, autonomic or behavioral features. A seizure was a brief episode of signs or symptoms in the brain caused by abnormally high or synchronized neuronal activity. The clinician's first duty was to assess whether an occurrence resembles a seizure and is not one of its mimics **(5)**.

Seizures occur when there was abnormal synchronous neuronal firing in a section of the brain, or throughout the entirety of the brain, when networks are irregularly formed by a structural, infectious, or metabolic disturbance. In children, the most common causes of seizures were genetic, injury due to perinatal insults, and malformations of cortical development **(6).**

Epilepsy was a chronic disease of the brain characterized by an enduring predisposition to generate seizures, unprovoked by any immediate central nervous system insult, and although characterized by the neurobiologic, cognitive, psychological, and social consequences **(7).**

Anti seizure drugs (ASDs) were potentially an effective treatment for epileptic patients. However, treatment failure and poor adherence were very common in patients experiencing side-effects due to ASDs. In approximately 25% of patients, side-effects of ASDs lead to treatment discontinuation and negative impact on the quality of life**(8)**.

The most common obstacle to reaching completely effective doses of ASDs was its side effects. As a result, an ASDs effectiveness profile is complexly linked to its potential for toxicity. Adverse effects of ASDs negatively impact quality of life **(9)**.

Anti seizure Drugs can affect how the brain works in other ways. Since ASDs lower the excitability of nerve cells in the brain, they can also affect normal activity, Cognitive function, problems with thinking, remembering, paying attention or concentrating and finding the right word **(9).**

Basically, all anticonvulsants can have a negative impact on cognitive performance. If any cognitive deficits before treatment existed, these deficits may be exacerbated. The most common negative effect of anticonvulsants is a decrease in information processing speed, reaction speed and concentration. Most treatment related cognitive disorders are reversible and fade after dose reduction or completely disappear after a change in substance **(9)**

Many people were concerned with ASDs adverse effects, particularly because they affect the quality of their life. ASDs may cause unwanted side effects in some patients. The common side effects of ASDs were feelings of tiredness, stomach upset, dizziness and blurred visions, which usually happen in the first few weeks of taking ASDs**(10)** .

The most common occurring side-effects of ASDs were memory problems, fatigue, tremors, gastrointestinal symptoms, osteoporosis, depression, drowsiness, dizziness, weight change and nause**(11)**.

Recurrence of Seizure after Anti-Seizure Drugs Withdrawal

Approximately two-thirds of epileptic patients treated with ASDs can expect remission of seizures. The decision process of whether to withdraw ASDs in patients who have been seizure-free is similar to the decision to initiate treatment in patients with a single seizure. The decision must be based on the risk of seizure relapse **(12).**

Tapering or discontinuation is considered an important step in controlled epileptic patients with long term use of anti-epileptic drugs after they are seizure-free for period of 2 years or more because of compelling complications like adverse drug effects, cost of treatment, and social stigma **(13).**

In recent decades, many studies have focused on the risk of seizure recurrence after ASD withdrawal, which varies from 12% to 67%**.** approximately 2/3rd of controlled epileptic patients will have long remission and half of them will have successful ASDs withdrawal**.** Most recurrences occurred in the first 2 years (79.8%) after the beginning of withdrawal, especially in the first 12 months (48.5%) **(14)**

Recurrence rate of epilepsy after therapy discontinuation was 25%-40% in children and 28%-66% in adults**.** More than 70% of the children in whom ASD treatment was withdrawn will remain seizure free. A young age at onset of seizures, idiopathic aetiology without neurological disorder, and absence of EEG abnormalities were associated with a lower relative risk of relapse after discontinuation, but do not guarantee lasting seizure freedom **(15).**

Risk factors of recurrent epileptic seizures after remission:

Age at onset of epilepsy

Age at onset of epilepsy was often cited as an important prognostic factor for long remission. Childhood onset is associated with the best prognosis compared with adolescent onset epilepsy accordingly,Mastropaolo et al., said that epileptic children stand a good chance of being seizure free after ASDs withdrawal after seizure free period of two years **(16)**

Epilepsy started in children and in adults, the relapse rate was highest in the first 12 months (especially in first 6 months) after ASD withdrawal and tended to decrease thereafter **(7).**

Shinnar et al., (31) in their study classified their epileptic patients according to age of epilepsy into 3 groups; patients before 2 years old, those with epilepsy onset between 2 and 12 years old, and those with onset after 12 years old and they found that risk of seizures recurrence was 73% in those with onset after 12years old, 45% in those with onset before 2 years old and 26% in those with onset between ages 2 and 12 years.

(16),reported in their study that the relation between age of epilepsy onset and seizure recurrence was U shaped relation with an elevated risk at birth that falls to a nadir by about age 3–4 years when it begins to rise again until age 10 years and plateaus until age 25 years.

It has long been known that the response to ASDs treatment in newly diagnosed epilepsy patients was better than that in chronic epilepsy patients**.(17)**

Berg and Shinnar, (18) conducted a meta-analysis of 25 studies published in 1952–1994 on epilepsy recurrence after ASD withdrawal that included 5354 patients with epilepsy of all ages. The 1-year recurrence risk in patients with epilepsy onset during adolescence or adulthood was 1.79 or 1.34 times higher than in patients with onset in childhood. Since then, many studies have reported the highest recurrence rate after ASD withdrawal in patients with onset in adolescence, followed by adult onset and childhood onset **(7).**

Etiology of Epilepsy

The type of epilepsy should always be included in the decision-making process before treatment is discontinued. The risk of seizure recurrence even after many years of being seizure-free was particularly high for patients with juvenile myoclonic epilepsy or focal epilepsy with a structural aetiology, which are the most common epilepsies in adults ***(16).***

The Etiology of epilepsy proved to be a highly significant factor in predicting outcome in recurrence after ASDs discontinuation. The risk of relapse is significantly increased in both cryptogenic and remote symptomatic etiology as compared with idiopathic etiology **(18)**.

The recurrence rate after ASD withdrawal varies among patients with secondary epilepsy, and the outcomes are significantly improved by treating the etiology and removing lesions. **(16)**

Studies in patients with glioma-induced epilepsy have also shown that the etiology plays an important role in withdrawal success or failure***. Kerkhof et al, (19)*** evaluated the recurrence rate after AED withdrawal in 71 patients with histologically confirmed low-grade or anaplastic (grades II–III) glioma who were seizure-free for at least 1 year after antitumor treatments, including surgery, radiotherapy, and chemotherapy. The patients were followed for an average of 22 years. Among 46 patients undergoing withdrawal, 12 (26%) experienced recurrent seizures, and 58% of these patients exhibited tumor progression. Among the patients with no recurrent seizures, 15% exhibited tumor progression. The recurrence rate was 8% in patients who did not withdraw from ASDs, 50% of whom experienced tumor progression. Among the patients with no recurrent seizures, 9% experienced tumor progression. Thus, tumor progression is closely related to ASD withdrawal failure and uncontrolled seizures.

Dunin-Wasowicz et al (20) conducted a prospective withdrawal study in 32 infants with a CMV infection combined with seizures. Notably, 59.4% of the patients achieved a seizure-free state, 34.4% of whom successfully withdrew from ASDs over 30–36 months with no recurrence observed during 1 to 6 years of follow-up.

Gender

Emerson et al., (21), mentioned in their study that there was no significant difference in the rates of relapse between male and female patients or black and white patients**.**

Altunbasak et al., (22), found that being female was a significant risk factor of seziures recurrence with 30.8% relapse rate. Seizure frequency and severity may change at puberty, over the menstrual cycle, with pregnancy, and at menopause. Estrogen is known to increase the risk of seizures **(23)**

Type of Seizure

Several studies have shown that patients with focal seizures are susceptible to recurrence after ASD withdrawal***.*** According to ***Hawash and Rosman (24).*** three-quarters of patients with recurrence after ASD withdrawal experienced focal seizures with or without generalized seizures. ***Schmidt and Löscher (25)*** conducted a meta-analysis of 14 studies in children and adult patients with epilepsy and found that focal epilepsy was a risk factor for recurrence after ASD withdrawal in patients with epilepsy.

He et al., (14) conducted a study with a follow-up period of 1 year or more in 200 adult patients with focal epilepsy who were seizure-free for at least 2 years. The overall recurrence rate was 49.5% after ASD withdrawal, and 79.8% of patients with recurrence experienced the recurrence during the first 2 years, whereas few patients experienced recurrence after 5 years of withdrawal (<1%). Moreover, the recurrence risk is also related to the duration of remission before withdrawal. The recurrence rates in patients with remission periods of 2–3, 3–4, and 4–5 years were 2.08, 2.33, and 1.53 times higher than in patients with a remission period of ≥5 years.

Among the patients with generalized seizures, the rate of withdrawal success was 70% to 80% for patients with absence seizures or generalized tonic–clonic seizures and was as low as 35% for patients with both absence seizures and generalized tonic–clonic seizures ***(15).***

Afshari & Moradian, (26) observed in their study that the greatest rate of recurrence in focal epilepsy 71.3%, while 35.5% of patients with generalized epilepsy had developed recurrent epileptic fits. Among different types of generalized epilepsy. Patients with myoclonic epilepsy had the highest rate of recurrence 89.5%.

Juvenile myoclonic epilepsy and focal slowing on the initial EEG were associated with an increased risk of relapse. **(18)**.Partial seizures,nocturnal seizures and mixed seizure types are thought to have a worse prognosis for seizure control than generalized seizures **(27)**.

<u>Number of ASDs & Response to ASDs</u>

Patients taking two or more drugs at the time of discontinuation have a higher risk of relapse compared with patients on monotherapy. Therefore, patients on polytherapy should be warned about their increased risk, but slow tapering, and subsequently, drugs withdrawal could be considered if no other concurrent negative prognostic factors occur **(7).**

Higher risk of relapse is associated with multiple AEDs. Afshari agreed with Y. Li , patients with multidrug therapy experienced higher recurrence rate 81.5% **(26)**.

The correlation between the early response to treatment with ASDs and the long-term prognosis of patients with epilepsy has been highlighted in recent years. The early ASD response time was defined as starting a 12-month seizure-free remission period within 6 months of treatment.**(28)**

Ou et al., (29), found in their study that patients whose seizures were not completely controlled within the first 6 months of initiation of ASD therapy were more likely to relapse than those patients whose seizures were controlled within the first 6 months of treatment. The failure to achieve remission within one year and >10 generalized tonic clonic (GTC) seizures prior to the initiation of therapy were also found to be significant factors predictive

of a poor prognosis. The response to the first AED was the strongest predictor of long-term prognosis in adults and children. **(28)**

The UK Medical Research Council (MRC) trial found that an increased risk of seizure recurrence was associated with: a shorter duration of seizure-free period prior to study entry, seizures after starting antiepileptic drug treatment, patients taking multiple antiepileptic drugs at the time of study entry ***(25).***

EEG:

Electroencephalogram, particularly prolonged EEG monitoring, is often used to predict the risk of ASD withdrawal***.*** Several retrospective studies, prospective studies, and meta-analyses have analyzed EEG abnormalities, particularly the effects of interictal epileptiform discharges (IEDs) on postdwithdrawal relapse, with controversial conclusions***.*** Only a few studies showed that IEDs may predict the recurrence risk, with varying significance for IEDs occurring before withdrawal and during withdrawal ***(30).***

Family History

Tirteen percentage of children with idiopathic seizures had positive family history and was associated with increase risk of recurrence after ASDs withdrawal**(31)**.

Approximately, 15% of people with epilepsy have a positive family history. **(32)** showed fourdold increase in the incidence of the epilepsy in those patients with a positive family history .**Babtain, (33)** showed that one from four epileptic patients has a positive family history. Epilepsy can arise directly or indirectly from genetic disorders related to a specific gene, a combination of genetics and environmental factors. Genetic (formerly idiopathic or primary) generalized epilepsies account for 15 – 20 % of all epilepsies**.** Incidence of seizure in first-degree relatives is an important indicator of involvement of genetic factors in the incidence of the disease**(34)**

Severity of Epilepsy and Seizures Frequancy

The frequency and total number of seizures before or during ASD treatment were identified as significant risk factors for seizure relapse.Frequency of seizures at the onset of the disorder is predictive of remission. A worse prognosis has been reported in those who experienced high frequency tonic–clonic seizures before receiving any treatment**(27)**.

Number of seizures occurred before control and length of time required to control fits considered measures of epilepsy severity so, Emerson et al founed a relation between number of seizure and relapse rate**(21)**.also, Callaghan et al found that number of seizures occurred before control was a significant factor of relapse**(35)**.

Cases of epilepsy that involve multiple seizure types might indicate the severity of epilepsy, and this feature has been identified as an important risk factor in relapse. The occurrence of many seizures before therapy and an insufficient response to initial ASD treatment are indicators of refractory epilepsy. Severity of epilepsy affects successful ASDs withdrawal. The longer the duration of active epilepsy before remission the greater the likelihood of relapse.**(36)**

Depression

Epileptic patients show an increased prevelance of comorbid depressive and anxiety disorders. Previous study found that the lifetime prevelance of depression in epileptic patients was ranging from 30% to 55%.Indeed, a recently published meta analysis of several well designed studies of depression in epileptic patients reported that the risk of depression increases several folds in epileptic patients, when compared to the general population. The cause of the increased risk of depression in patients with epilepsy is multifactorial. Genetic , neurochemical , anatomical , neurologic and iatrogenic factors are among the most common studied etiologies.**(37)**.

There are positive associations between high seizure frequency and depression, according to results of study of **Carson et al., (38)**,approximately , 20% - 40% of epileptic patients with recurrent seizures and 6% - 9% of controlled epileptic seziures are found to be depressed.

Anxiety

Despite the fact that some patients with epilepsy have normal lives, devoid of cognitive or emotional dysfunction, a significant number of epileptic patients suffered from psychiatric disturbance, including mood disorders. Anxiety could be classified as a common psychiatric disorder occurring in 25% of epileptic patients. Previous studies have attributed interictal anxiety to a combination of biological factors such as seizure induced alterations of neuronal circuits in the amygdala region via a kindling-like mechanism **(30)**.

Another study showed that anxiety in epileptic patients could be related to the psychological worries concerning, for instance , the possibility seizure related injuries or the impact of epilepsy on employment and marital status **Wiglusz et al., (39)** pointed to a strong association between seizures frequency and anxiety as this study reported that 33% of drug resistant epilepsy were clinically anxious by using Hmilton Anxiety and Depression scale.

Imaging Finding

Abnormalities in the brain, including brain tumors or vascular malformations such as arteriovenous malformations (AVMs) and cavernous malformations, can cause epilepsy. On brain magnetic resonance imaging (MRI), a focal abnormality in the cortical or limbic regions that indicates a possible substrate for an epileptogenic zone is the finding that most often

suggests increased risk for seizure recurrence. Diffuse abnormalities, such as hydrocephalus, may increase the risk by injuring the cerebral cortex **(37)**

History of Febrile Seizure:

Febrile seizure was the most common type of childhood seizure disorder, it occur in 2% to 5% of children 6 months to 5 years of age. These seizures have a familial tendency in some cases and are sporadic in others, suggesting that both genetic and environmental elements contribute to their generation **(18)**.

Approximately one-third of children with a first febrile seizure experience one or more recurrent FS **(18)**.A family history of epilepsy and the occurrence of a complex febrile seizure were found to be associated with increased risk of subsequent epilepsy**.** Children with simple febrile seizure have approximately the same risk (i.e., 1%) of developing epilepsy by the age of 7 as the general population. However, children with a history of multiple simple febrile seizure, younger than 12 months at the time of their first febrile seizure, and a family history of epilepsy, are at higher risk to develop epilepsy**(400**.

Sleep Deprivation

Sleep quality was not correlated to the frequency of seizure, while the degree of insomnia was found to be correlated to the frequency of seizure. The frequency of seizure in moderate insomnia was higher compared to the frequency in patients without insomnia. Sleep deprivation had little or no influence on the likelihood of seizure recurrence after a first unprovoked seizure, and it is not an independent predictor of seizure recurrence. Unprovoked seizures associated with sleep deprivation have a markedly higher likelihood of recurrence when compared with seizures provoked by a clearly defined proximate cause**(41)**

Age at Anti Epileptic Drugs Withdrawal

Annegers et al., (42),reported that certain types of seizures (particularly absence and generalized tonic clonic childhood seizures) may remit. This may explain why discontinuance of medication was more frequent among patients in whom the onset of seizures had occurred in childhood. Patients who may require chronic medication for other diseases (particularly the elderly) and patients who are handicapped by central nervous system disturbance and so are under close medical supervision may be less likely to discontinue ASDs.

Factors influencing relapse:

Table (1): clinical factors which might predict seizure recurrence following antiepileptic drug withdrawal ***(43).***

Table 1

Factors predicting seizure recurrence following antiepileptic drug withdrawal

Associated with increased risk	Associated with reduced risk
Juvenile myoclonic epilepsy Partial seizures with secondary generalisation Abnormal electroencephalogram Epileptogenic lesion on neuroimaging	Childhood absence epilepsy Benign rolandic epilepsy Normal electroencephalogram Normal neuroimaging Onset in childhood No seizures for more than two years prior to antiepileptic drug withdrawal Monotherapy No seizures following introduction of antiepileptic drug Normal intellect

References:

1. Blair R. D. G, (2012): Temporal Lobe Epilepsy Semiology. 2012.
2. Braga P, (2021): Exploring quality of life perception in people with epilepsy and people imagining life with epilepsy. Seizure, 90(December 2020), 182–185.
3. Sander J. (2015): Stopping antiepileptic drug treatment. Epilepsy, 343.
4. Newton C. R, Garcia H. H. (2012): Epilepsy in poor regions of the world. The Lancet, 380(9848), 1193–1201.
5. Fisher R. S, Bonner A. M. (2018): The Revised Definition and Classification of Epilepsy for Neurodiagnostic Technologists. Neurodiagnostic Journal, 58(1), 1–10.
6. Falco-Walter J, (2020): Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. Seminars in Neurology, 40(6), 617–623.
7. Beghi E. (2020): "The Epidemiology of Epilepsy."Neuroepidemiology 54(2): 185-191.
8. Kinderen R. J. A. De, Evers S. M. A. A, Rinkens R, Postulart D, Vader C. I, Majoie M. H. J. M, Aldenkamp A. P. (2014): Side-effects of antiepileptic drugs : The economic burden. Seizure: European Journal of Epilepsy, 23(3), 184–190.
9. Carter J, Vahle V, (2009): Adverse antiepileptic drug effects Toward a clinically and neurobiologically relevant taxonomy. 047551, 1223–1230.

10. Mutanana N, Tsvere M, Chiweshe M. K. (2020): General side effects and challenges associated with anti-epilepsy medication: A review of related literature. African Journal of Primary Health Care and Family Medicine, 12(1), 1–5.
11. Mattson R.H. (1989): Comparison of carbamazepine,... N Engl J Med, 321(19), 1306–1311.
12. Shih J. J, Ochoa J. G. (2009): A systematic review of antiepileptic drug initiation and withdrawal. Neurologist, 15(3), 122–131.
13. Kumar S, Sarangi S. C, Tripathi M, Ramanujam B, Gupta Y. K. (2020): Seizure recurrence risk in persons with epilepsy undergoing antiepileptic drug tapering. Acta Neurologica Scandinavica, 141(1), 65–76.
14. He R. Q, Zeng Q. Y, Zhu P, Bao Y. X, Zheng R. Y, Xu H. Q. (2016): Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy. Epilepsy and Behavior, 64, 233–238.
15. Bouma P. A. D, Peters A. C. B, Brouwer O. F, (2002): Long term course of childhood epilepsy following relapse after antiepileptic drug withdrawal. Journal of Neurology Neurosurgery and Psychiatry, 72(4), 507–510.
16. Lamberink H. J, Otte W. M, Geerts A. T, Pavlovic M, Ramos-Lizana J, Marson A. G, Overweg J, Sauma L, Specchio L. M, Tennison M, Cardoso T. M. O, Shinnar S, Schmidt D, Geleijns K, Braun K. P. J. (2017): Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. The Lancet Neurology, 16(7), 523–531.
17. Reynolds E. H. (1988): The Early Treatment and Prognosis of Epilepsy. Psychiatry and Clinical Neurosciences, 42(3), 429–435.
18. Berg A. T, Shinnar S, Levy S. R, Testa F. M, Smith-Rapaport S, Beckerman B, Ebrahimi N, (2001): Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. Epilepsia, 42(12), 1553–1562.
19. Kerkhof M, Benit C, Duran-Pena A, & Vecht C. J . (2015):Seizures in oligodendroglial tumors. CNS oncology, 4(5), 347–356
20. Dunin-Wasowicz D, Kasprzyk-Obara J, & Jóźwiak S. (2010):Successful antiepileptic drug withdrawal in infants with epilepsy and cytomegalovirus neuroinfection: longitudinal study. Epilepsia, 51(7), 1212–1218
21. Emerson R, D'Souza B. J, Vining E. P, Holden K. R, Mellits E. D, Freeman J. M. (1981): Stopping Medication in Children with Epilepsy. New England Journal of Medicine, 304(19), 1125–1129.
22. Altunbasak S, Artar Ö, Burgut R, Yildiztas D, (1999): Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures. Seizure, 8(7), 384–389.
23. Shuster E. A. (1996): Epilepsy in women. Mayo Clinic Proceedings, 71(10), 991–999.
24. Hawash K. Y, & Rosman N. P. (2003): Do partial seizures predict an increased risk of seizure recurrence after antiepilepsy drugs are withdrawn? Journal of child neurology, 18(5), 331–337.
25. Schmidt D, & Löscher W. (2005): Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. Acta neurologica Scandinavica, 111(5), 291–300.
26. Afshari D, and Moradian N, (2012): Evaluating the rate of recurrence of epilepsy after therapy discontinuation in 2-year seizure-free epileptic patients. International Journal of Neuroscience, 122(10), 598–601.
27. Macdonald B. (2001): The prognosis of epilepsy. 347–358.
28. Brodie M. J, Barry S. J. E, Bamagous G. A, Norrie J. D, Kwan P. (2012): Patterns of treatment response in newly diagnosed epilepsy. Neurology, 78(20), 1548–1554.

29. Ou S, Xia L, Li R, Wang L, Xia L, Zhou Q, Pan S. (2018): Long-term outcome of seizure-free patients and risk factors of relapse following antiepileptic drug withdrawal. Epilepsy and Behavior, 88, 295–300.
30. Doležalová I, Brázdil M, Hermanová M, Janoušová E. and Kuba, R. (2014):"Effect of partial drug withdrawal on the lateralization of interictal epileptiform discharges and its relationship to surgical outcome in patients with hippocampal sclerosis." Epilepsy Res 108(8): 1406-1416.
31. Shinnar S, Berg A. T, Moshe S. L, Kang Y. H, Odell C, Alemany M, Goldensohn E. S, Hauser W. A. (1994): Discontinuing Antiepileptic Drugs in CMdren with Epilepsy : A Prospective Study.
32. Chentouf A, Dahdouh A, Guipponi M, Oubaiche M. L, Chaouch M, Hamamy H, Antonarakis S. E, (2015): Familial epilepsy in Algeria: Clinical features and inheritance profiles. Seizure, 31, 12–18.
33. Babtain F. A, (2013): Impact of a family history of epilepsy on the diagnosis of epilepsy in southern Saudi Arabia. Seizure, 22(7), 542–547.
34. Ghiasian M, Daneshyar S, Khanlarzadeh E, Novin M. B. (2020): Investigating the relationship of positive family history pattern and the incidence and prognosis of idiopathic epilepsy in epilepsy patients. Caspian Journal of Internal Medicine, 11(2), 219–222.
35. N. Callaghan A. Garret, T. G. (1988): Withdrawal of anticovulsant drugs in patients free of seizures for two years. A prospective study. The New England Journal of Medicine, 318(15), 942–946.
36. Canevini M. P, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V, Saltarelli A, & Canger R. (1992): Juvenile myoclonic epilepsy of Janz: clinical observations in 60 patients. Seizure: European Journal of Epilepsy, 1(4), 291–298.
37. Tellez-Zenteno J. F, Patten S. B, Jetté N, Williams J, Wiebe S. (2007): Psychiatric comorbidity in epilepsy: A population-based analysis. Epilepsia, 48(12), 2336–2344.
38. Carson A. J, Postma K, Stone J, Warlow C, Sharpe M, (2003): The outcome of depressive disorders in neurology patients: A prospective cohort study. Journal of Neurology Neurosurgery and Psychiatry, 74(7), 893–896.
39. Wiglusz M. S, Landowski J, Michalak L, Cubała W. J. (2016): Validation of the Hospital Anxiety and Depression Scale in patients with epilepsy. Epilepsy and Behavior, 58, 97–101.
40. Chung S, (2014): Febrile seizures. Korean Journal of Pediatrics, 57(9), 384–395.
41. Lawn N, Lieblich S, Lee J, Dunne J. (2014): Are seizures in the setting of sleep deprivation provoked? Epilepsy and Behavior, 33, 122–125.
42. Annegers J. F, Hauser W. A, Elveback L. R. (1979): Remission of Seizures and Relapse in Patients with Epilepsy. Epilepsia, 20(6), 729–737.
43. Laue-Gizzi H. (2021): "Discontinuation of antiepileptic drugs in adults with epilepsy." Aust Prescr 44(2): 53-56.