Review Article
Volume 7:5, 2021

Epilepsy Journal

ISSN: 2472-0895 Open Access

What is Epilepsy – when do we Start Treatment and with what?

Roy G Beran*

Professor, School of Medicine, Grifiith University, Broad Beach, Queens land, Australia; and Professor, Chair Medical Law Sechenov Moscow First State University, Moscow, Russia

Abstract

Introduction: Epilepsy comprises ≥ 2 unprovoked seizures (>24 h apart), 1 unprovoked seizure with probability of recurrence (≥ 60%) or an epilepsy syndrome. What follows is consideration of treatment.

Background: Newer ASMs offer adjunctive treatment but none has better efficacy than carbamazepine (CBZ) although possibly less adverse effects. Valproate (VPA) is preferred for generalised epilepsy (except child-bearing age women) with increased preference for the levetiracetam and lamotrigine (LTG). Despite decline for older ASMs, Beran supported CBZ.

First unprovoked seizure has 30-50% chance of recurrence, rising to 70-80% with a second seizure. Percentages increase with abnormal neurologic examination, focal spikes on electroencephalography (EEG) and focal seizures.

Most common epilepsy presentation to the emergency department is non-compliance causing breakthrough seizures, having: shorter duration seizure control; worse adherence to ASM; more frequent polytherapy; more abnormal EEGs; and cerebral imaging abnormalities.

Discussion: Epilepsy presentations comprise 2 categories; first ever or recurrent seizures. Factors, such as infections or alcohol withdrawal, demand intervention and on-going seizures must be aborted. Recurrent seizures require blood levels before administering the current ASM(s).

Treating first ever focal seizure favoured newer, and tendency to ignore older, ASMs, despite support for CBZ. VPA is favoured in non-childbearing age women for generalised epilepsy. Trials advocated LTG.

Conclusion: Epilepsy represents a tendency to seizure recurrence, including a single seizure, assuming ≥ 60% risk of recurrence. Treatment of first focal seizures favours the newer ASMs (the author advocating CBZ); VPA was preferred in non-childbearing aged women with generalised seizures. For non-compliance, restarting the previous ASM(s), after sampling for ASM levels, seems optimal.

Keywords: Epilepsy • Treatment • Epidemiology • Diagnostic criteria • Medications

Introduction

Working in a major teaching hospital, one would expect that all those in the Accident and Emergency Department (AED) knew exactly what constituted a definition of epilepsy. Personal experience suggests that this is far from reality. British research has suggested that 3.3% of all emergency ambulance calls, resulting in AED attendance were related to epilepsy and epileptic seizures [1]. Evidence suggests that attendance at the AED for patients with seizure is, more often than not, clinically unnecessary [1-3] and is often a result of poor outpatient care [4]. These should result in better care once the patient reaches the AED but how can this be the case if those in attendance are unfamiliar with what the diagnosis of epilepsy represents?

Epilepsy is simply defined as a tendency to recurrence of seizures. In 2005 the International League Epilepsy (ILAE), the international body representing professionals with a special interest in epilepsy, defined epilepsy as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures". Its application usually required "two unprovoked seizures >24 h apart." [5]. More recently, the ILAE altered the practical definition for special circumstances that do not meet the two unprovoked seizures criteria [6]. "The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: [1] At least two unprovoked (or reflex) seizures occurring >24 h apart; [2] one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; [3] diagnosis of an epilepsy syndrome." [6] This revised definition translates to the possibility of a person being diagnosed, as having epilepsy, on the basis of their first seizure, if the prevailing circumstances suggest that there exists a real propensity to recurrence of seizures.

Having defined the definition of epilepsy, according to the information provided by the ILAE and the International Bureau for Epilepsy (IBE), representing the lay bodies interested in the management of people with epilepsy, what follows is a consideration of when to treat patients and what to do when the patient presents to the AED of a major teaching hospital.

Background

It is accepted that epilepsy remains a life shortening condition which, if treated effectively, can be properly managed, in the majority of affected individuals, using anti-seizure medications (ASMs), either in mono therapy or a combination of ASMs [7]. Approximately 70% of newly diagnosed people, with adult-onset epilepsy, will achieve a lasting remission in seizures, once commenced on appropriate ASMs, although approximately half of them will report mild to moderately severe unwanted treatment emergent adverse effects (TEAEs) from the ASMs [7]. Approximately 20-30% of those with epilepsy will not be seizure-free despite being treated with ASMs and these individuals are considered medication resistant and have a significantly increased risk of death plus psychiatric and somatic comorbidities, with or without TEAEs from their ASMs [7].

Over recent years, there have emerged newer ASMs which widen the treatment options to manage those who present with seizures. It has been argued that these newer ASMs are better tolerated although they do not

***Address for Correspondence:** Beran GR, Professor, School of Medicine, Grifiith University, Broad Beach, Queens land, Australia; and Professor, Chair Medical Law Sechenov Moscow First State University, Moscow, Russia, E-mail: Roy.Beran@unsw.edu.au*

Received 09 August 2021; **Accepted** 23 August 2021; **Published** 30 August 2021

reduce the prevalence of medication resistant epilepsy nor do they preclude the development of epilepsy, in those at risk, such as following traumatic brain injury [7]. While there have been many new ASMs, approved to treat focal epilepsy, based on clinical trial data, there have been very few head-to-head trials of ASMs, to determine which is preferred and in what situations they should be trialled [8,9]. Lattanzi, et al. [9] via a meta-analysis of various trials, which compared newer ASMs to controlled release carbamazepine (CBZ-CR), in monotherapy studies, found no significant difference in the 6 or 12 months' seizure freedom, when compared with levetiracetam (LEV), zonisamide (ZNS), lacosamide (LCM) or eslicarbazepine acetate (ESL). LCM was associated with fewerTEAE provoked medication withdrawals, when compared with CBZ-CR, and all 4 comparative medications were efficacious as monotherapy to treat newly diagnosed focal epilepsy.

In an earlier study, reported in 2007, Marson and colleagues (10) conducted an open label comparison of ASMs, comparing the effectiveness of CBZ with gabapentin (GPT), lamotrigine (LTG), oxcarbazepine (OXC) and topiramate (TPM) and concluded that LTG was favoured "for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with partial onset seizures" [10]. The study recognised that, at the time, CBZ was recommended as the first line ASM, for the treatment of newly diagnosed patients with focal epilepsy [11,12]. At the same time, French, et al. [13] also assessed the efficacy, tolerability and safety of seven of the new ASMs, including GPT, LTG, TPM, tiagabine, OXC, LEV and ZNS when managing adults and children with either focal or generalised epilepsy. They showed that all of the newer ASMs could be used as effective adjunctive treatment for refractory epilepsy in adults. GPT was shown to be efficacious for mixed seizure disorders while GPT, LTG, OXC and TPM were all efficacious for refractory focal epilepsy in children. Based on limited evidence, it was concluded that LTG and TPM were efficacious as adjunctive treatment of generalised epilepsies, in both adults and children, and may have a role in the treatment of Lennox Gastaut Syndrome [13]. None of these studies showed significant efficacy benefits, comparing these newer ASMs with CBZ, although it was argued that the TEAEs may be less intrusive as compared with CBZ, as was shown with LTG [11]. When considering generalised epilepsy, sodium valproate (VPA) was both clinically and cost effectively a viable alternative to either LTG or TPM [8, 10].

Shih and colleagues [14] surveyed 42 epileptologists, in the United States of America, regarding treatment options for patients with epilepsy, with particular reference to either genetically mediated generalised epilepsy and focal epilepsy, including scenarios in which patients were pregnant, elderly, had cerebral tumours, were post-transplant patients or who had serious comorbidities. They concluded that VPA was considered the ASM of choice for generalised epilepsy, with the exception of women of child- bearing age, due to the risks of teratogenicity [14]. Ethosuximide was favoured in absence seizures while LEV was considered favourably in genetically mediated tonic-clonic seizures and myoclonic epilepsy. LTG, LEV and OXC were identified as first line agents for focal seizures while LTG and LEV were favoured in women of child-bearing age [14]. LEV and LTG were selected in the elderly while LTG was favoured in those with depression as comorbidity [14]. Compared to the 2005 and 2001 surveys, there was increased preference for the LEV and LTG, and a decline in the use of phenytoin (PHT), GPT, phenobarbital (Pb) and CBZ [14].

Beran recently reported a reappraisal of CBZ [15,16] which supported its use recognising that it was developed through the research and development of imipramine (Tofranil), a tricyclic antidepressant, thereby providing it with psychotropic benefits. None of the newer ASMs, as reported above, proved more efficacious than did CBZ and some of the favoured ASMs, such as LEV, being shown to have a serious and significant negative impact on quality of life. This was demonstrated in a clinical trial of LEV, when used to treat patients with chronic daily headaches, as compared with placebo, acknowledging that the patients had a with very prolonged headache history over decades [17].

Having reviewed some of the available ASMs, and their comparisons to other medications, it is important to consider when is it appropriate to start ASMs, especially within the context of the newly diagnosed patient with seizures, attending the AED. The majority of those with epilepsy who present to hospital will do so after their first convulsive seizure [18]. This is accepted that this is a frightening experience although population studies have confirmed that there exists an 8-10% lifetime risk of a patient having at least one seizure [19] and 3% chance of developing epilepsy [20]. If there is a provocative cause for the seizure, causing disturbed cerebral function (an acute symptomatic/provoked seizure), there is a 3-19% risk of recurrent seizures [18]. If the first seizure is unprovoked, meta-analysis suggests a 30-50% chance of recurrence and, after a second unprovoked seizure; this figure rises to 70-80% [21-23]. Recurrence rates increased in those with abnormal neurologic examination, focal spikes on electroencephalography (EEG) and if they experienced focal seizures [21]. The rates of recurrence were much less following a generalised tonic-clonic seizure, combined with normal EEG and normal neurologic examination [21]. Camfield, et al. [22] found that, in a study of children with epilepsy, prescription of ASMs did not alter the recurrence rate. Hauser and colleagues [22] found that, in a study of more than 200 patients with a first seizure, >30% (64) had a second seizure, 20% (41) had a third seizure and ~13% [26] had a fourth seizure. Of those who experienced a second seizure, there was >70% chance of a third seizure and, of them, one in four experienced a further seizure. Most seizures recurred within the first year from the second or third seizure and the risk of recurrence was increased where there was a known or suspected cause for the seizures [22].

In a cohort of >400 children, Shinnar et al, [23] reported that 45% (182) experienced a second seizure, of whom, 72% (131) had a third seizure, 58% (105) had ≥4 seizures and 29% (53) had ≥ 10 seizures, the cohort being followed for a mean period of ~10years. In a Western Australian study, Lawn, et al. [24] followed almost 800 adults, seen in hospital after their first seizure, for more than a decade, to examine duration of seizure freedom, aetiology of the seizures, EEG and cerebral imaging. They confirmed that the rate of recurrence was ≥ 60%, if the patient had an epileptiform abnormality on their EEG or abnormal cerebral imaging, thereby confirming the relevance of the changed definition of epilepsy (6, 24). They confirmed that the risk of recurrence was time dependent and, if the patient remained seizure free for ≤12 weeks, no patient group continued to fulfill the new definition of epilepsy. Of the 407 patients within the cohort, who had a second seizure, the likelihood of a third seizure at 4 years was 68% (95% CI 63–73%) and at 10 years was 85% (95% CI 79–91%) [24]. the authors concluded that the duration of seizure freedom, following the first-ever seizure, greatly affected the risk of recurrence, with no patients fulfilling the new definition of epilepsy if they had ≤ 12 weeks of seizure freedom. When a threshold was applied, based on the 10-year risk of a third seizure, no first-seizure patient group ever had epilepsy [24].

Wang et al, [25] evaluated >1700 patients who presented to hospital following their first ever seizure, of whom 18% had epileptiform EEG changes and 28% had possible epileptogenic abnormalities on neuroimaging. The peak time for seizures was midday, for those with their first unprovoked seizure, being less likely to be reported during the night or during sleep [25], despite common wisdom suggesting that epilepsy is more common during sleep. When evaluating the relationship between epilepsy and sleep, typical epileptiform discharges are more common during non-Rapid Eye Movement (REM) sleep together with traditional drowsy EEG arousal periods, because this is the more synchronised state, with sleep spindles and high amplitude delta waves [26]. Focal onset seizures in adults are the most common types of epilepsy occurring out of sleep. Of these, frontal and temporal lobe seizures are most common, with frontal lobe classically being the most common epilepsy to occur out of sleep [26]. Classically, nocturnal frontal lobe seizures are characterized by paroxysmal arousals with hyper motor complex movements, lasting a brief amount of time [26]. In about half of the time, the EEG is normal, interictally, and can even be normal during the seizures. Sleep-related temporal lobe seizures are also quite frequent, representing one third of overall temporal lobe seizures in epilepsy monitoring units [27]. Many of these patients awaken from sleep with an 'aura', representing a focal seizure with awareness, and then progress to a typical focal seizure with altered awareness and they may be amnestic for the event [27].

Considering when to treat patients diagnosed with epilepsy, moving on from those who present with their first ever seizure, the most common reason for people with epilepsy to present to the AED, having been seizure free for some time, is following a lapse in compliance/adherence with their treatment regimen, thereby producing sub-therapeutic blood level of ASMs [28-30]. In their Ugandan study, Kaddumukasa and colleagues [28] found that non-compliance was by far the most common cause ofr hospital presentation ($p < 0.0001$), followed by: duration of treatment ($p < 0.0001$); infections ($p < 0.044$) and menses among female study participants ($p < 0.0001$). They also found that "the level of education, sleep deprivation, alcohol and substance abuse, and flickering lights were not associated with breakthrough seizures" [28]. In an Egyptian study, Al-Kattan et al. [29] also confirmed that non-compliance/adherence was the most common cause for breakthrough seizures, accounting for more than half of their sample of 90 patients. Other relevant factors in their study included: sleep deprivation (~40%) and psychological stress (~35%). Those who experienced breakthrough seizures were found to have lower durations of seizure control, adherence to ASMs and were more frequently on ASM polytherapy, than was the case for those who did not report breakthrough seizures [29]. Those presenting with breakthrough seizures also had a higher percentage of abnormal EEGs and more frequent focal epileptiform discharges [29]. Al-Kattan, et al. [29] found no significant difference between the two groups regarding age, gender, age at onset of epilepsy, duration of disease or the type of seizures being experienced. Another Egyptian study [30], found no significant difference between those with and without breakthrough seizures with regards to: age; gender; age at onset of epilepsy; occupation; and marital status, thereby confirming the findings of the previous study. They also showeld that those with breakthrough seizures had: longer duration of epilepsy and lower adherence to ASMs ($p = 0.001$); reduced adherence resulting in more missed doses of ASMs ($p = 0.0001$); more TEAE with ASMs ($p = 0.0005$); more sleep deprivation and lower blood levels of their ASMs ($p = 0.0006$); more frequently taking ASM polypharmacy ($p = 0.0002$); and a greater exposure to flickering lights ($p = 0.04$), the latter just reaching significance at $p=0.04$ (30). They also confirmed that those with breakthrough seizures had a greater propensity to abnormal EEGs with more frequent epileptiform discharges ($p=0.003$) and more abnormalities on magnetic resonance imaging of the brain ($p=0.005$). They did not find a difference with regards to emotional stress, generic brand substitution, concurrent illnesses or the use of non-ASMs [30]. The question of generic brand substitution, when considering the treatment of epilepsy, has been reported to cause problems [31,32] but it is usually unable to be addressed by the AED because hospital formularies will usually stock the cheapest ASM which usually equates to a generic alternative with no regard to what brand the patient was taking prior to admission [32].

Discussion

When considering, what is 'epilepsy' and when to start treatment and with what, the first step is to make the correct diagnosis of the epilepsy. The patient who comes to the AED will usually present following a convulsive seizure which is, in the majority of cases, as a consequence of a focal becoming generalise tonic-clonic seizure [33]. Those with less dramatic seizures usually take much longer to be diagnosed and hence to be treated [18].

It is now possible to diagnose epilepsy on the basis of a single seizure if there exist other circumstances which raise the propensity for recurrence of seizures up to ≥ 60% [6,24]. The diagnosis of epilepsy still rests on the taking of an adequate history and is essentially a clinical diagnosis, complemented by various investigations, administered to confirm it [34,35]. The attending doctor needs to appreciate that epilepsy, being a 'tendency to recurrence of seizures', may take many forms, depending on the type of seizures that the patient is experiencing [33] and, when in doubt, it is imperative to seek advice from others, to confirm the clinical impression.

Having diagnosed epilepsy, this does not constitute the final step in the diagnostic pathway and, where possible, it is important to determine the seizure type, essentially whether the seizures are generalised or focal [33] and, if so, whether one can identify contributing circumstances which provoked the seizure. Patients presenting with seizures, to the AED, fall into 2 main categories, namely those who have experienced their first ever seizure and those who have breakthrough or recurrent seizures. By far the more common is the category of those known to be prone to seizures that have had a breakthrough episode. Having determined that the person is known to have epilepsy, it is important to find the cause of the recent breakthrough event. One must consider some of the causes of seizures, such as infections [36] or alcohol withdrawal [37]. The reported risk of unprovoked seizures, in population-based cohorts of survivors of CNS infections, from developed countries is between 6.8 and 8.3% and is much higher in resource-poor countries [36]. When a patient presents to the AED with a first ever seizure, it is imperative to look for possible infection as the treatment of choice, within this scenario, is to treat the underlying infection and only then to treat the seizure, assuming that the patient is no longer seizing when being assessed. Should the patient be having on-going seizures, at the time of assessment in the AED, the treatment must focus on aborting those seizures and, for that, one needs to have a developed and acceptable approach to the management of status epilepticus [38], the discussion of which is outside the scope of this overview. Where the presenting seizure is as a consequence of excessive alcohol or sudden alcohol withdrawal [37], attention must be focused on the management regarding the use of alcohol and modifying those alcohol related issues which require directed intervention to stop further seizures occurring. Should the patient still be seizing, at the time of presentation to the AED, treatment, along the lines of the treatment of status epilepticus must be employed but ultimately it is questionable whether the patient will accept advice regarding the use of ASMs, once the initial seizure has stopped. Each case will have to be determined on its merits having developed a therapeutic relationship with the patient.

With alcohol related seizures, the brain substrates that trigger these seizures are thought to be largely in the brainstem and are distinct from those believed to be responsible for other clinically important seizures [37]. Because the alcohol withdrawal seizures are pharmacologically induced, the pathophysiologic mechanisms almost certainly are different from those of the seizures that occur in genetic and acquired epilepsies [37]. As a result, the approach to treatment may also need to be different with the focus being to manage the dependence on the alcohol, rather than the use of ASMs [39]. It follows that the answer to the question posed in the title, namely, 'when do we start treatment and with what?' is largely determined by both the type of seizure presenting as epilepsy and the underlying aetiology.

Having dealt with the management of conditions that may provoke seizures, and the necessity to first treat them, the next most common problem is the management of the patient who presents with recurrent seizures, provoked as a consequence of non-compliance with medical advice and a failure to adhere to the treatment regimen. Having been previously diagnosed with epilepsy, the patient will, more likely than not, have been prescribed at least one ASM. The efficacy of ASM(s), to control seizures, has been estimated to be approximately 70% [2,7-11] which translates to the fact that it is, more likely than not, that the patient who presents to the AED was prescribed at least one of these. Having determined that the patient is known to have epilepsy, the next step is to take blood samples to determine the ASM levels which will also demonstrate whether the patient is in the therapeutic range and, if so, whether all his/her ASMs are within the appropriate range [40]. Once the blood sample has been taken and sent to the laboratory for measurement, it is advisable to administer doses of the ASM(s) that the patient had already been prescribed. It makes absolutely no sense to add a new ASM, rather than administer the ASM the patient was already prescribed, as this will only confound the picture. As the patient is already in a medical facility, there is little reason to be worried about causing the patient ASM toxicity, by administering additional ASMs which the patient was theoretically taking, as any experienced toxicity can be properly managed within the hospital. Based on the assumption that the patient has been non-compliant, it is highly unlikely that the patient will experience symptoms of toxicity.

The medication to be selected, for the treatment of the patient with a first ever seizure, will be influenced by the preferences and practices of the practitioner. Allowing for the influences, set out above, [7-17] each doctor will have his/her favoured ASM. There has been a tendency to ignore the older ASMs, such as PHT, CBZ or Pb due to the perception that the newer ASMs are better, if not for seizure prevention then for less TEAE [11-14]. Based on personal preference, there remains considerable support for CBZ in those patients presenting with focal epilepsy, on the basis of cost, positive psychotropic effects and the ability to easily measure blood levels that allow simple therapeutic monitoring of patients who have presented due to non-compliance [15,16,40]. For those patients who have generalised epilepsy, VPA remains a favoured ASM in women who are not of childbearing age [14], acknowledging that both VPA and LTG have positive psychotropic benefits, with the SANAD trial [10] favouring LTG. For the patient presenting with his/her first ever seizure, it may not be necessary for the clinician to be in a hurry to start any medication as up to 30% may not have a further seizure and hence there should be sufficient time to properly evaluated the patient, with such tests as, EEG and cerebral imaging, to determine if (s) he qualifies for a diagnosis of epilepsy [7,11,12,18,24,25].

Conclusion

Epilepsy is a tendency to recurrence of seizures which has been modified to include a single seizure if the prevailing circumstances provide a considered opinion that the risk of further seizures is ≥ 60%. When treatment is started is determined by the establishment of the diagnosis, conforming to the ILAE/ IBE definition. For those with a first ever focal seizure there is a preference for the newer ASMs, although the author favours CBZ as an initial trial ASM and for first ever generalised seizures there is a preference for VPA in non-childbearing aged patients and LTG if this be the case. Where the patient is non-compliant, it being the most common reason for recurrent seizures presenting to AED, restarting the ASM that proved efficacious, prior to the non-compliance, seems to offer the best option and should be started immediately after taking a blood sample to determine blood levels of ASMs.

References

1. Male, Leanne Rachel, Adam Noble and Darlene Ann Snape, et al. "Perceptions of emergency care using a seizure care pathway for patients presenting to emergency departments in the North West of England following a seizure: a qualitative study." BMJ open 8 (2018): 1-10.
2. Dickson, Jon Mark, Hannah Dudhill, and Jane Shewan, et al. "Cross-sectional study of the hospital management of adult patients with a suspected seizure (EPIC2)." BMJ open 7 (2017): 1-9.
3. Reuber, M, L. Hattingh, and P. J. Goulding. "Epileptological emergencies in accident and emergency: a survey at St James's university hospital, Leeds." Seizure 9 (2000): 216-220.
4. Dixon, Peter A, Jamie J. Kirkham, Anthony G. Marson, et al. "National Audit of Seizure management in Hospitals (NASH): results of the national audit of adult epilepsy in the UK." BMJ open 5 (2015): 1-7
5. Fisher, Robert S, Walter Van Emde Boas, and Warren Blume, et al."Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)." Epilepsia 46 (2005): 470-472.
6. Fisher, Robert S, Carlos Acevedo, and Alexis Arzimanoglou, et al. "ILAE official report: a practical clinical definition of epilepsy." Epilepsia 55 (2014): 475-482.
7. Schmidt, Dieter, Steven C, and Schachter. "Drug treatment of epilepsy in adults." Bmj 348 (2014).
8. Cross, J. Helen, and Torbjorn Tomson. "Newer versus older antiseizure medications: further forward?." The Lancet 397 (2021): 1327-1329.
9. Lattanzi, Simona, Gaetano Zaccara, and Fabio Giovannelli, et al. "Antiepileptic monotherapy in newly diagnosed focal epilepsy. A network meta-analysis." Acta Neurologica Scandinavica 139 (2019): 33-41.
10. Marson, Anthony G, Asya M. Al-Kharusi, and Muna Alwaidh, et al. "The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial." The Lancet 369 (2007): 1016-1026.
11. National Institute for Clinical Excellence. "The diagnosis and management of the epilepsies in adults and children in primary and secondary care." (2004).
12. French, J. A, A. M. Kanner, J. Bautista, and B. Abou-Khalil, et al. "CME Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy." Neurology 62 (2004): 1261-1273.
13. French, J. A, A. M. Kanner, J. Bautista, and B. Abou-Khalil, et al. "Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society." Neurology 62 (2004): 1261-1273.
14. Shih, Jerry J, Julia B. Whitlock, and Nicole Chimato, et al. "Epilepsy treatment in adults and adolescents: expert opinion, 2016." Epilepsy & Behavior 69 (2017): 186-222.
15. Beran, Roy G. "Carbamazepine- An oldie but a goodie - A clinician's perspective." Seizure-European Journal of Epilepsy 83 (2020): 243-245.
16. Beran RG. "Carbamazepine (Tegretol) - An half century of survival". J Pharmacol and Clin Toxicology (In Press) (2021).
17. Beran, Roy G, and Paul J Spira. "Levetiracetam in chronic daily headache: A double-blind, randomised placebo-controlled study: (The Australian KEPPRA Headache Trial [AUS-KHT])." Cephalalgia 31 (2011): 530-536.
18. Pohlmann-Eden, Bernd, Ettore Beghi, and Carol Camfield, et al. "The first seizure and its management in adults and children." Bmj 332 (2006): 339-342.
19. Hauser, W. Allen, Stephen S. Rich, and John F. Annegers, et al. "Seizure recurrence after a 1st unprovoked seizure: an extended follow-up." Neurology 40 (1990): 1163-1163.
20. Hauser, W. Allen, John F. Annegers, and Leonard T. Kurland. "Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984." Epilepsia 34 (1993): 453-458.
21. Camfield, Peter R, Carol S. Camfield, J. M. Dooley, et al."Epilepsy after a first unprovoked seizure in childhood." Neurology 35 (1985): 1657-1657.
22. Hauser, W. Allen, Stephen S. Rich, and Ju R-J. Lee, et al., "Risk of recurrent seizures after two unprovoked seizures." New England Journal of Medicine 338 (1998): 429-434.
23. Shinnar, Shlomo, Anne T. Berg, and Christine O'Dell, et al. "Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure." Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 48 (2000): 140-147.
24. Lawn, Nicholas, Josephine Chan, and Judy Lee et al. "Is the first seizure epilepsy—and when?." Epilepsia 56 (2015): 1425-1431.
25. Wang, Shuyu, Ray Boston, and Nicholas Lawn, et al. "Temporal patterns in the first unprovoked seizure." Epilepsy & Behavior 115 (2021): 107625.
26. Lanigar, Sean, and Susanta Bandyopadhyay. "Sleep and epilepsy: a complex interplay." Missouri medicine 114 (2017): 453.
27. Karafin, Matthew, Erik K. St Louis, and M. Bridget Zimmerman, et al.

"Bimodal ultradian seizure periodicity in human mesial temporal lobe epilepsy." Seizure 19 (2010): 347-351.

28. Kaddumukasa, Martin, Mark Kaddumukasa, and Steven Matovu, et al. "The frequency and precipitating factors for breakthrough seizures among patients with epilepsy in Uganda." BMC neurology 13 (2013): 1-7.
29. Al-Kattan, Manal, Lamia Afifi, and Reham Shamloul, et al. "Assessment of precipitating factors of breakthrough seizures in epileptic patients." The Egyptian Journal of Neurology, Psychiatry and Neurosurgery 52 (2015): 165.
30. Esmael, Ahmed, Mohammed Gomaa, and Mohammed Saad. "Triggering Factors for Breakthrough Seizures among Epileptic Patients. Cross Sectional Study in Epileptic Patients Attending Epilepsy Clinic Mansoura University Hospital, Egypt." International Neuropsychiatric Disease Journal (2019): 1-10.
31. Beran, Roy G. "Generic Substitution and Advice to Patients- Potential Legal Medicine Consequences- From A (Australia) to U (United Kingdom or United States of America)." Seizure (2021).
32. Manser, David, and Roy G. Beran. "Clinical letter: Brand substitution with generics-A potential mine field." Seizure 83 (2020): 232-233.
33. Scheffer, Ingrid E, Samuel Berkovic, and Giuseppe Capovilla, et al. "ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology." Epilepsia 58 (2017): 512-521.
34. Tan M. “Epilepsy in adults”. Aust Fam Physician 43 (2014):100-104.
35. Perucca, Piero, Ingrid E. Scheffer, and Michelle Kiley. "The management of epilepsy in children and adults." Medical Journal of Australia 208 (2018): 226-233.
36. Vezzani, Annamaria, Robert S. Fujinami, and H. Steve White, et al. "Infections, inflammation and epilepsy." Acta neuropathologica 131 (2016): 211-234.
37. Rogawski, and Michael A. "Update on the neurobiology of alcohol withdrawal seizures." Epilepsy Currents 5 (2005): 225-230.
38. Beran, Roy G. "An alternative perspective on the management of status epilepticus." Epilepsy & Behavior 12 (2008): 349-353.
39. Crowley, and Philip. "Long-term drug treatment of patients with alcohol dependence." Australian prescriber 38 (2015): 41.
40. Stepanova, Daria, and Roy G. Beran. "The benefits of antiepileptic drug (AED) blood level monitoring to complement clinical management of people with epilepsy." Epilepsy & Behavior 42 (2015): 7-9.

How to cite this article: Roy G Beran. "What is Epilepsy – when do we Start Treatment and with what?" *Epilepsy J* 7 (2021): 141.