Review

Treatment of epilepsy in adults

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Case vignettes

1. *A 60-year old patient with long standing temporal lobe type epilepsy was taking carbamazepine 800 mg a day in divided doses of 200, 200 and 400 mg. He was tolerating the dose well, but his seizures were not controlled well. He had an exacerbation of seizures and saw a neurologist. He was advised to take an extra tablet of 200 mg of carbamazepine every time he had a seizure and over the next two weeks he ended up taking 400 mg three times a day. When he was seen at this stage he was very ataxic, had diplopia and was feeling very sleepy.*

2. *A 25-year old female was taking 600 mg of sodium valproate for juvenile myoclonic epilepsy. She was well controlled without any seizures. A physician who saw her changed her medication to carbamazepine as she was pregnant 18 weeks. She ended with relapse of her seizures and had to be put back on 400 mg valproate with good results.*

3. *A 13-year old boy was started on valproate by a neurologist after having two seizures during sleep. Despite increasing the dose to 800 mg daily he was getting seizures about once a month. EEG showed centro-temporal spikes and after changing over to oxcarbazepine 150 mg twice a day his seizures completely stopped.*

Above examples show practical problems in the management of epilepsies today. Some of us still base our treatment decisions on large scale studies done in the 1980s when seizures were lumped together and treatment was solely based on seizure type. New knowledge has shed light on basing treatment on the epileptic syndromes rather than seizure types for more effective and rational treatment. The Ceylon College of Physicians guidelines on epilepsy is very brief and is based on seizure types and makes naïve statements like "if under 25 years use valproate and if over 25 years use carbamazepine". A comprehensive update of these guidelines is needed. Even NICE UK guidelines are at times outdated when published and their undue emphasis on cost-effectiveness results in their recommendations at times being not the best for an individual patient. Most recent 2012 updated NICE guidelines are undecided on the value of levetiracetam because of its current cost. This review is an attempt to overcome these problems and to make some clinically useful recommendations based on current evidence and personal experience.

Global prevalence of epilepsy is about 3 to 9 per 1000 population[1]. Globally 10% of people will have at least one seizure and one third of them will develop epilepsy[2,3]. The prevalence of epilepsy in Sri Lanka is around 9 per 1000 population[4]. Epilepsy is one of the commonest neurological diseases in our country and patients are managed by both specialist neurologists as well as general physicians. Optimal management of epilepsy should encompass both optimal seizure control as well as minimal adverse effects. Antiepileptic drugs have many side effects but the availability of more than 20 antiepileptic drugs give the physician a wide array to choose from. Further it is also important to choose the most efficacious drug for the particular seizure type or the syndrome. In this review we would discuss the current evidence based treatment for epilepsy in adults addressing the indications for starting treatment, drug selection, epilepsy in pregnancy and in the elderly, failure of treatment, duration of treatment and the withdrawal of treatment.

Epilepsy is not a single disease entity but consists of many syndromes and diseases, which have a multitude of clinical manifestations and aetiology. Classification of epileptic seizures and syndromes are required for the appropriate management and prognosis. The short and long term management of epilepsy varies with the disorders manifesting with the seizures. This emphasizes the need for accurate diagnosis as the first step in the treatment of epilepsy.

Details of seizure types and classification are not discussed here but in brief there are three steps required in the process of diagnosis – **to confirm the paroxysmal event as a seizure, to identify the type of seizure and finally to find the cause and the epileptic syndrome or disease.** Once epilepsy is diagnosed and the type of seizure and aetiology is identified appropriate therapeutic interventions are required. Total seizure freedom without clinically significant adverse effects is the aim of therapy. Antiepileptic drugs form the mainstay of management while some now benefit from neurosurgical interventions, stimulation techniques and ketogenic diet.

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Should therapy be commenced after the first unprovoked seizure?

After confirming the event to be a seizure the next step is to decide when to commence antiepileptic therapy. The decision to treat is based on the balance between the likelihood of further seizures and the risk of adverse effects of treatment. Once therapy is commenced the goal is to maintain freedom from seizures with minimal drug related adverse effects and is usually achieved with a single appropriately selected anti-epileptic drug at target therapeutic dose. Poly therapy is best avoided and commenced only in those who fail to respond to several trials of single AED at therapeutic dose.

The usual practice is to commence antiepileptic therapy after the second unprovoked seizure. There is evidence from two large open labeled, randomized clinical trials - First Seizure Trial Group (FIRST) study[5] and the Multicentre Study of Early Epilepsy and Single Seizure (MESS) study[6] showing that immediate treatment after the first seizure reduced the recurrence rates of subsequent seizures, but the risk reduction at 2 years was 42% in the FIRST study and 18% in the MESS study. Reanalysis of the MESS study showed that the recurrence at 2 years varied from 30% in the low risk group to 73% in the high risk group.

Thus the decision to treat the first seizure should be based on the risk category including the severity of the seizure, time of occurrence and individual characteristics. A patient with a high risk of recurrence could be commenced on an appropriate antiepileptic after the first unprovoked seizure. One should also consider that the restrictions imposed by seizures on everyday activities are of greater relevance to an adult than to a child. More than 50% of patients will not have a recurrence after the first unprovoked seizure and, thus treatment can be differed except in patients with a high risk of recurrence, severe seizures and patients with seizures following a stroke or other identifiable lesions and in elderly patients.

In all other patients antiepileptics are commenced after the second unprovoked seizure, if the severity of the seizure is significant to the individual, if it occurs within 2 years of the first and if the patient wishes to take treatment.

Which antiepileptic drug should be commenced?

The choice of antiepileptic drug would be based on the efficacy of the drug for the seizure type and the tolerability based on the results of well conducted randomized controlled clinical trials. But unfortunately due to the availability of only very few well conducted trials[7] the current leading guidelines differ in their recommendations. Adverse effects including idiosyncratic reactions, teratogenicity, chronic side effects and enzyme inducing effects and potential for side effects influence the choice of antiepileptics in addition to efficacy and effectiveness. All current guidelines consider individual patient characteristics, seizure types and characteristics of special relevance such as child bearing potential, old age and co-morbidities when choosing the appropriate antiepileptic[8,9,10].

In general the older AEDs which have stood the test of time are generally preferred over the newer AEDs. The newer AEDs like gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin are recommended in patients who have not benefited from treatment with the older AEDs or for those in whom the older AEDs are unsuitable because of contraindications, drug interactions, and poor tolerance[9]. General recommendations are for monotherapy and if initial therapy is unsuccessful monotherapy with another drug is tried and combination therapies tried only when attempts at monotherapy have failed.

Seizures are broadly categorized into partial and generalized seizures. The commonly prescribed antiepileptics are sodium valproate and carbamazepine along with phenytoin. Carbamazepine is used as first line for partial seizures and is also used as second line for generalized tonic clonic seizures. Sodium valproate is used as first line AED in primary generalized seizures, absence and myoclonic seizures. Valproate may also be considered in atypical absence, atonic and tonic seizures. Phenytoin is efficacious for tonic clonic seizures, partial seizures and for prevention and treatment of seizures occurring during or following neurosurgery and severe head injury.

Phenobarbital is used for tonic clonic and partial seizures and sometimes in atypical absence, atonic and tonic seizures. Ethosuximide is primarily used in absence seizures but when absences coexist with other seizure types valproate is preferred. Clonazepam is efficacious in tonic clonic or partial seizures. Clobazam is used as an adjunctive therapy in partial seizures.

All AEDs have CNS side effects which are dose related and may be apparent at therapeutic doses. Of particular concern is the effect of AEDs on cognitive functions. AEDs may have subtle effects on mood, cognition and memory that is usually apparent only on formal testing. Carbamazepine, phenytoin and barbiturates are enzyme inducers while valproate is an enzyme inhibitor.

Of the newer antiepileptics, studies have shown that lamotrigine, oxcarbazepine and topiramate can be used as monotherapy, while these three along with levetiracetam and gabapentin are used in combination therapy. The newer drugs are attributed to have a more acceptable adverse-effect profile, less drug interactions and convenient dosing regimens. On the other hand there

is very limited data on the effects of these drugs on the fetus and thus they are not widely prescribed during pregnancy.

Lamotrigine is used as monotherapy in partial seizures as well as in primary and secondarily generalized tonic clonic seizures. It is also used for seizures in Lennox-Gastaut syndrome. Carbamazepine is best avoided in L-G syndrome as it can aggravate generalized seizures while controlling partial seizures.

Oxcarbazepine is a carbamazepine analogue which is used as monotherapy or combination therapy for partial seizures with or without secondary generalization. It has a lower potential for drug interactions compared to carbamazepine. **Both carbamazepine and oxcabazepine are ineffective against, and can exacerbate absence and myoclonic seizures and therefore are best avoided in primary generalized epilepsies.**

Topiramate is recommended as combination therapy for those who are inadequately controlled with the conventional anti epileptic drugs and who have partial seizures with or without secondary generalization, seizures associated with Lennox-Gastaut syndrome, or primary generalized tonic clonic seizures. It is also recommended as monotherapy for patients with newly diagnosed epilepsy who have generalized tonic clonic seizures or partial seizures with or without secondary generalization. Users of topiramate should be well aware of its side effect profile as it has many potentially serious side effects. Levetiracetam is approved for combination therapy of partial seizures with or without secondary generalization and is a drug that is well tolerated.

In summary when considering the current guidelines the AAN (American Academy of Neurology) recommends for partial seizures with or without generalization carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate and valproate. The NICE (UK National Institute for Health and Clinical Excellence) recommends carbamazepine, lamotrigine, oxcarbazepine, topiramate and valproate while the SIGN (Scottish Intercollegiate Guideline Network) recommends carbamazepine, lamotrigine, oxcarbazepine, phenytoin and valproate. The ILAE (The International League Against Epilepsy) recommends carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproate.

Carbamazepine, lamotrigine, oxcabazepine and valproate have been recommended by all four major guidelines while topiramate is recommended in 3 of the major guidelines as first line therapy for adults with partial seizures, with or without secondary generalization[11].

If therapeutic doses need to be reached rapidly drugs such as levetiracetam, valproate or phenytoin which can be started or rapidly titrated to the fully effective dose are recommended while lamotrigine or topiramate which require slow titration are generally avoided.

Treatment of idiopathic generalized epilepsies

Valproate has superior efficacy in all seizures and syndromes of IGEs but its use in women of childbearing age is highly problematic. The adverse effects of valproate and its lack of efficacy in 20% of patients have prompted the search for newer drugs. Lamotrigine, levetiracetam, topiramate and zonisamide appear to be effective. Levetiracetam, because of its efficacy in all types of seizures and safer adverse reaction profile, seems to be the best substitute for valproate.

Carbamazepine, oxcarbazepine and phenytoin too can be considered but exacerbate absences and myoclonic jerks. Vigabatrin exacerbate absences. Gabapentin is ineffective in all types of idiopathic generalized epileptic seizures. Clonazepam is effective for myoclonic jerks, but is ineffective for GTCS. Lamotrigine is effective in primarily GTCS and absences, but may exacerbate myoclonic jerks.

Juvenile myoclonic epilepsy

Valproate has been recognized as the most effective drug with full control of seizures in about 80% of patients with JME. The effective dose may vary from 600 to 3000 mg a day. Phenobarbitone is extensively used in Europe for treatment of JME. It is effective in controlling GTCS and myoclonic jerks, but may exacerbate absences. Phenobarbitone 60-90 mg daily is sufficient. When myoclonic jerks persist clonazepam can be added to valproate and when only myoclonic jerks are the presentation, clonazepam can be the initial therapy. Lamotrigine is not suitable as it can exacerbate myoclonic jerks in JME though it would control generalized seizures and absences. **Levetiracetam is probably the best new AED in the treatment of JME.** The results of treatment of JME with levetiracetam are very impressive. In three independent studies 62%, 67%, and 63% of patients with JME became seizure free with levetiracetam monotherapy or polytherapy.

Antiepileptics and pregnancy

Several observational studies as well as a population based study report increased risk of congenital malformations such as spina bifida, atrial septal defects, cleft palate and craniosynostosis with valproate compared with other AEDs such as carbamazepine and lamotrigine[12,13,14]. Studies also show that valproate affects cognitive development[15]. The teratogenic effects of valproate are dose dependent especially at higher daily doses of 1000 mg or more.

For focal seizures carbamazepine is used as a first line drug. The choice of drugs for primary generalized seizures is more difficult with lamotrigine being the first choice with levetiracetam and topiramate being the possible alternatives to valproate.

Lamotrigine is less efficacious than valproate especially in syndromes associated with myoclonic seizures and absence seizures. Further the pharmacokinetics of lamotrigine requires frequent dose adjustments during pregnancy.

Data on levetiracetam and topiramate with regard to teratogenicity is insufficient and the adverse effects of topiramate on cognition raise concern[16, 17].

Antiepileptics in the elderly

Choice of an appropriate antiepileptic in the elderly is challenging, as they are more prone to adverse effects. Carbamazepine, an enzyme inducer is not recommended in the elderly as it is likely to cause drug interactions as well as impaired bone health, cause endocrine dysfunctions and changes in serum cholesterol levels as well as markers of cardiovascular risk factors[18].

Carbamazepine remains the drug of choice in focal seizures but lamotrigine and levetiracetam are preferred in patients on other medications where drug interactions and enzyme induction may cause problems as well as in patients in whom bone health is a concern.

In a retrospective review carried out comparing the effectiveness of 10 antiepileptics in elderly adults with epilepsy, lamotrigine was the most effective with levetiracetam being the next most effective[19].

Selection of formulation of AED

Currently with the introduction of sustained release preparations only carbamazepine sustained release preparation when given twice daily has shown to be superior with regard to tolerability compared to immediate release formulations[20]. Evidence is not strong for the other AEDs.

Optimal dosage

The lowest dose that provides seizure freedom should be used in order to increase tolerability and minimize the adverse effects. Evidence suggests that newly diagnosed patients respond to relatively low doses of AED. Optimal starting doses being 400 mg per day for carbamazepine, 1000 mg per day for levetiracetam, 100 to 200 mg per day for lamotrigine and 600 to 1000 mg per day for valproate[21,22]. Sometimes a starting dose of carbamazepine 200 mg in the morning may be difficult to tolerate and then the morning dose may have to be titrated from 100 mg up or use the controlled release formulations. Our personal experience is levetiracetam 500 mg daily is effective as adjuvant therapy in most cases. Factors such as age, comorbidities, attitudes towards potential side effects and risk of seizure recurrence should be taken into account when deciding the optimal dosage. Further gradual dose titrations increases tolerability and reduce idiosyncratic adverse reactions. Thus starting with a low dose and titrating to optimal dose is recommended unless an immediate anti seizure effect is required. The optimal duration of titration period depends on the type of AED, maintenance dose and individual response.

If seizures recur when the patient is stabilized on the selected initial maintenance dose, the dose is increased depending on the clinical response.

Current recommendations promote the identification of a serum concentration with the best response to an individual and its use as a reference to adjust dosage with anticipated pharmacokinetic changes such as in pregnancy or when a potentially interacting drug is added or removed or to assess unexpected changes in clinical response[23].

Failure of initial monotherapy

Failure of initial monotherapy could be either due to lack of efficacy or due to adverse effects. If the AED was discontinued due to idiosyncratic reactions, another AED has to be tried avoiding the use of drugs which have cross reactivity.

If the failure is due to lack of efficacy after titrations to the highest tolerated dose, non compliance, incorrect diagnosis and inappropriateness of the AED needs to be considered. If AED needs to be changed, it should be switched gradually to monotherapy with an alternative drug[24,25]. Some trials advocate monotherapy with an alternative drug before adjuvant therapy while others suggest combination therapy specially if the first AED was partially effective and tolerated[26].

Duration of treatment

Duration of treatment depends on prognostic factors, adverse effects of medication, patient's lifestyle and attitude towards continuation of medication and the possibility of relapse. The risk of relapse is greater in adults and so is the impact of a relapse with regard to driving and certain occupations. Further the psychosocial issues associated with long term medication may be significant.

Adolescent onset of seizures, focal seizures, underlying neurological illness and abnormal EEG when withdrawing the drugs predict a higher risk of recurrence while childhood epilepsy, idiopathic generalized epilepsy and normal EEG are associated with a lower risk of recurrence[27]. Discontinuation may be considered after 2 to 4 years of seizure freedom after discussing the potential risk and benefits with the patient. Symptomatic epilepsy, focal epilepsy and cognitive deficits are associated with poor outcome after a recurrence.

Evidence recommends that discontinuation should be individualized and gradual over a 3 month period and preferably over 6 months when withdrawing barbiturates and benzodiazepines.

Conclusion

Epilepsy is one of the most common neurological disorders and causes significant morbidity and mortality especially amongst the adult population who make up the working population of our society and is a cause of physical and social burden. Appropriate pharmacological treatment will be of immense benefit to the patient and one should keep in mind to prescribe an appropriate antiepileptic, which is also available and affordable to the patient.

Search strategy

References for this Review were identified through searches of PubMed until January 2012 with the search items “epilepsy”, “treatment”, “antiepileptic drugs”. References were also identified from relevant review articles. Only articles published in English were reviewed.

References

1. Kurtzke JF, Kurland LT. The epidemiology of neurologic disease. In: Joynt RJ, ed. Clinical Neurology, Volume 4. Philadelphia: Lippincott 1993.
2. Epilepsy Foundation. Epilepsy and seizure statistics. http://www.epilepsy foundation.org/about/statistics.cfm.
3. Hesdorffer DC et al. Estimating risk for developing epilepsy. A population based study in Rochester, Minnesota. *Neurology* 2011; **76**: 23 -27.
4. Senanayake N. Epilepsy control in a developing country – the challenge of tomorrow. *Ceylon Medical Journal* 1987; **32**: 181-99.
5. First Seizure Trial Group (FIRST group). Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic clonic seizure. *Neurology* 1993; **43**: 478-83.
6. Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial. *Lancet* 2005; **365**: 2007-13.
7. Glauser T, Menachem B, et al. ILAE treatment guidelines: evidence based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006; **5**: 317-22.
8. Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. National Institute for Clinical Excellence. 2012. http://guidance.nice.org.uk/CG137.
9. Scottish Intercollegiate Guideline Network. Diagnosis and management of epilepsy in adults. A national clinical guideline. April 2003, updated Oct 20, 2005. http://www.sign.ac.uk/pdf/sign70.pdf
10. French AJ, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, 1: treatment of new onset epilepsy: report of the TTA and QSS subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2004; **45**: 401-9.
11. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. *Lancet Neurology* 2011; **10**: 446-56.
12. Wyszynski DF, Nambisan M, Surve T, et al. Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; **64**: 961-5.
13. Morrow J, Russel A, Guthrie E, et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *Journal of Neurology, Neurosurgery and Psychiatry* 2006; **77**: 193-8.
14. Jentink J, Loane MA, Dolk H, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *New England Journal of Medicine* 2010; **362**: 2185-93.
15. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *New England Journal of Medicine* 2009; **360**: 1597-605.
16. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study on effectiveness of valproate, lamotrigine or topiramate for generalized and unclassifiable epilepsy. an unblinded randomized controlled trail. *Lancet* 2007; **369**: 1016-26.
17. Nicolson A, Appleton RE, Chadwick DW, Smith DF. The relationship between treatment with valproate, lamotrigine and topiramate and the prognosis of generalized idiopathic epilepsies. *Journal of Neurology, Neurosurgery and Psychiatry* 2004; **75**: 75-9.
18. Mintzer S, Mattson RT, Should enzyme inducing antiepileptics drugs be considered first line agents? *Epilepsia* 2009; **50** (Suppl 8): 42-50.
19. Hiba Arif, Richard Buchsbaum, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. *Archives of Neurology* 2010; **67**(4): 408-15.
20. Perucca E. Extended release formulations of antiepileptic drugs: rationale and comparative value. *Epilepsy Currents* 2009; **9**: 153-7.
21. Brodie MJ, Perucca E, et al. Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled release carbamazepine in newly diagnosed epilepsy. *Neurology* 2007; **68**: 402-8.

22. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; **42**: 1255-60.

23. Patsalos PN, Berry DJ, et al. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: a position paper by the subcommision on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008; **49**: 1239-76.

24. Leach JP, Lauder R, Nicolson A, Smith DF. Epilepsy in the UK: misdiagnosis, mistreatment and under treatment? The Wrexham area epilepsy project. *Seizure* 2005; **14**: 514-20.

25. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effects of past treatment history. *Neurology* 2008; **70**: 54-65.

26. Beghi E, Gatti G, Tonini C, et al. Adjunctive therapy versus alternative monotherapy in patients with partial epilepsy failing on a single drug: a multicentre, randomized, pragmatic controlled trial. *Epilepsy Research* 2003; **57**: 1-13.

27. Jacoby A, Johnson A, Chadwick D. Psychosocial outcomes of antiepileptic drug discontinuation. The Medical Research Council Antiepileptic Drug Withdrawal: A study Group. *Epilepsia* 1992; **33**: 1123-31.