Initial Management of Epilepsy

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ABSTRACT

There is no sufficient evidence to prove one anti epileptic drug to be superior to another, so selection of antiepileptic drugs should be individualized according to the patient. Monotherapy should be the goal when anti epileptic drug treatment is instituted for epilepsy.

INTRODUCTION

Epilepsy is the syndrome of two or more unprovoked seizures in person's lifetime. It can also be defined as the tendency to spontaneous excessive neuronal discharge manifesting as seizure. It is a common disorder with an incidence of 50 per 100,000 per year and prevalence of 0.5 to 1%.[1] Seizures affects the quality of life and are also associated with disability and lower rates of employment.[2, 3]

The diagnosis and management of patient with epilepsy is often undertaken by general practitioner, pediatrician, internist and geriatrician. Referral to a neurologist may be necessary if the diagnosis of epilepsy is unclear or if the patient does not respond to initial therapy with antiepileptic drugs. General practitioners may subsequently follow up the patients in order to implement the recommendations of the neurologist. To maximize the likelihood of treatment success, general practitioners should supplement anti epileptic therapy (AED) with patient education and referral for psychosocial and vocational support when needed.[4]

Seizure can be broadly divided into partial or generalized seizure. Partial seizure involves only a portion of the brain in a hemisphere while generalized seizure involves large parts of both hemispheres. Partial and generalized seizure can further be classified into simple and complex. Complex seizure implies that consciousness is impaired.[5]

When to start AED?

The main goals of management of epilepsy are controlling seizure, avoiding and minimizing side effects and maintaining or restoring quality of life.[6-10] AED is not necessary in an individual after a single seizure, particularly if the first seizure is provoked by factors that resolve. AED is generally reserved for patients who are at increased risk for recurrent seizures.

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A prospective randomized trial of individuals with first unprovoked seizure estimates the two year recurrence risk in untreated patient to be 40-50%.[11-13] Three major features for seizure recurrence after first unprovoked seizure are: abnormality in EEG, remote symptomatic causes as identified by clinical history or neuroimaging (e.g. Brain tumor, brain malformation), abnormal neurological examination including focal findings and mental retardation.[11-14] AED treatment after first seizure may be considered in any of this higher risk subgroup.

Randomized control trials have found that immediate treatment reduced risk of seizure recurrence in the first one to two years by 30-50%.[11, 12, 15, 16] However at four and five years after the first seizure, patients had similar rates of complete seizure remission whether AED treatment was initiated immediately after the first seizure or deferred until second seizure occurred.

Selection of AED

No single AED is superior in terms of efficacy or tolerability. So AED should be individualized for each patient,[5] considering drug effectiveness for seizure type, potential adverse effects of drug, interaction with other medication, hepatic and renal diseases, age, gender including child bearing plans and cost.[17]

Medicine	Adverse effect	Excretion	Drug Interaction	Half Life (Hrs)
Valporate	Weight gain, nausea, vomiting, hair loss, easy bruising, Tremor	Hepatic		7-16
Lamotrigine	Rash, nausea, Dizziness, somnolence	Hepatic	Sertraline	12-62
Carbamazepine	Nausea, vomiting, diarrhea, hyponatraemia, rash, pruritis, Drowsiness, dizziness, blurred or double vision, lethargy, headache	Hepatic	Antacid, Clarithromycin, Benzodiazepine, Corticosteroids, Erythromycin, Fluoxetine, OCP, Theophylline, TCA, Warfarin	8-22
Phenytoin	Gingival hypertrophy, body hair increase, rash, lymphadenopathy, Confusion, slurred speech, double vision, ataxia, neuropathy (with long-term use)	Hepatic	Antacid, Benzodiazepine, Corticosteroids, Digoxin, Fluconazole, Fluoxetine, Folate, Omeprazole, OCP, Theophylline, TCA, Warfarin	9-36
Phenobarbitone	Nausea, rash, Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence	Hepatic	Antacid, Benzodiazepine, Corticosteroids, OCP, Theophylline, TCA, Warfarin	75-110
Gabapentin	Somnolence, dizziness, ataxia	Renal	Antacid	5-7
Ethosuxmide	Nausea, vomiting, Sleep disturbance, drowsiness, hyperactivity	Hepatic		60

Table 1: Common AED and its adverse effect, metabolism, drug interaction and half life.

There was little good evidence from clinical trials to support the use of newer monotherapy (Gabapentin, Lamotrigine, Leviterocetim, Oxcarbazepine, Ticgabine, Topiramide and Vigabatrin) or adjunctive therapy over older drugs, or to support the use of one newer AED in preference to another.[17]

In a study involving fifty randomized controlled trial and seven meta analysis, three seizure types had AED with Level A or Level B efficacy of effectiveness as initial immunotherapy; Adults with partial onset seizure (Level A: Carbamazepine and Phenytoin; Level B:

Level of Evidence	Conclusion
A	AED established as efficacious or effective as initial monotherapy
B	AED probably efficacious or effective as initial monotherapy
C	AED possibly efficacious or effective as initial monotherapy
D	AED potentially efficacious or effective as initial monotherapy
E	No RCT data available to assess if AED is effective as initial monotherapy
F	AED considered as ineffective or significant risk of seizure aggravation

Table 2: Level of Evidences

Valporic Acid); Children with partial onset seizure (Level A: Oxcarbazepine; Level B: None) and Elderly Adults with partial onset seizure (Level A: Gabapentin and Lomotrigine; Level B: None). Adult GTCS and Pediatric GTCS and absence seizure had no AED with Level A or Level B efficacy and effectiveness. The absence of rigorous comprehensive adverse effect data makes it impossible to develop an evidence based guideline.[19]

Individual patient data available from 1384 participants from five RCT's for partial seizures showed Lamotrigine was significantly less likely to be withdrawn than Carbamazepine but results for time to first seizure suggested that Carbamazepine may be superior in terms of seizure control. Trials were too short to measure important seizure outcomes such as time to 12 month remission.[19]

Another study involving 684 participants from four randomized or quasi randomized, blinded or unblinded control trials in children and adults with partial onset or GTCS found no overall difference between Carbamazepine and Phenobarbitone for time to 12 month remission or time to first seizure, however, sub group analysis for time to first seizure suggests an advantage with Phenobarbitone for partial onset seizure and a clinical advantage with Carbamazepine with GTCS. Phenobarbitone is significantly more likely to be withdrawn, indicating that it is less well tolerated than Carbamazepine.[21] Carbamazepine can be used as first treatment of choice in partial epilepsies but no evidence to support the choice of Valporate in GTCS.[22]

Data available for a trial comparing Phenytoin verses Valporate in 669 patients from 5 RCT in children and adult with partial seizure and generalized seizure found no evidence to support or overthrow the policy of using Valporate in GTCS and Phenytoin in partial seizure.[23]

A review of 10 RCT's comparing Phenytoin versus Phenobarbitone for partial onset seizure and GTCS favors Phenytoin over Phenobarbitone, as Phenobarbitone was significantly more likely to be withdrawn than Phenytoin. Given that no significant difference for seizure outcomes was found, the higher withdrawal rate with Phenobarbitone may be due to its side effects.[24]

In RCT comparing Ethosuximide, Lamotrigine and Valproic acid for absence seizure, Ethosuximide and Valporic acid were more effective than Lamotrigine.[25]

Monotherapy or Polytherapy?

Mono therapy has been promoted as the ideal epilepsy treatment because of reduced side effects, absence of drug interaction, better compliance, lower cost and in many cases improved seizure control compared to poly therapy.[26] Some patients who have achieved seizure control with poly therapy may be candidates for conversion to mono therapy because there is no conclusive evidence that polytherapy provides better seizure control in majority of cases.[27]

Combination therapy or polytherapy should be attempted only if at least two adequate sequential trials of single agent have failed. Seizure remission is achieved in combination therapy in only a small percentage (10-15%) of patients who have failed monotherapy.[28, 29, and 30]

Special consideration: Pregnancy

Managing epilepsy during pregnancy is to balance maternal and fetal risk associated with uncontrolled seizure against the potential teratogenic effect of AED.[31] Although exposure to AED in utero has been associated with an increased risk of major fetal malformation, most women with epilepsy require medication throughout pregnancy since seizures themselves may be potentially harmful not only to mother but also to the developing fetus.[32]

The overall risk of major malformation is 4 to 6% in exposed infants; Valporate is a major contribution to the risk. While no AED has been definitively safe in pregnancy, the evidence linking Valporate to fetal malformation is sufficiently convincing to recommend avoiding its initiation in pregnancy.[5] Monotherapies are found to be relatively safer than polytherapy. Poly therapy exposure in utero was more commonly associated with poorer outcome.[33]

Summary

AED is usually not started in a first unprovoked seizure with the exception of cases involving associated risk factors. The selection of AED should be individualized considering drug effectiveness for seizure type, partial adverse effect, drug interactions, hepatic and renal diseases, age, gender and cost. No AED has been superior to another as first line therapy or in pregnancy. However Valporate is avoided in pregnancy. Polytherapy has no significant benefit over mono therapy.

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