Selection of Anti-Epileptic Medication in Newly Diagnosed Epilepsy

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INTRODUCTION

Anti-epileptic medications can be divided into two major groups. The traditional antiepileptic drugs, which were released for use prior to 1978, are Phenobarbital, Phenytoin, Primidone, Clonazepam, Ethosuximide, Carbamazapine and Valproate. There was a 15-year period from 1978 to 1993, when no new anti-seizure drug was approved for use. Since 1993, an additional eight new anti-epileptic medications have been approved - Felbamate, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine, Tiagabine, Zonisamide, and Levetiracetam.

The traditional antiepileptic drugs (AEDs) are associated with a number of systemic and cognitive adverse effects. Some side effects are minor and transient; others idiosyncratic reactions with serious implications, such as aplastic anemia and hepatic failure. The complex pharmacokinetic and pharmaceutical properties of traditional antiepileptic drugs make administration difficult at times. Many of these drugs are potent enzyme inducers or inhibitors, and significant drug interactions occur when they are co-administered with other medications.

The newer AEDs were developed in an attempt to overcome the limitations of traditional therapy. All of these drugs are chemically unique, structurally unrelated to the standard antiepileptic drugs and different from one another.

Guidelines are being evolved to address how to integrate the full range of AEDs – including newer therapies – into optimal treatment strategies, based on seizure type and individual patient needs.

AIM OF THERAPY

The first maxim of epilepsy therapy is full seizure control,[1] because this is the most important precondition for worthwhile improvements in the quality of life of the patient, and the only sure way to prevent secondary complications. This maxim must guide all algorithms for the management of epilepsy. The second maxim of epilepsy management is that therapy must not do more harm than good.

For several decades, therapeutic decisions were founded on experience - which was often based on subjectivity. Evidence-based therapy, while desirable, may at times create the myth of objectivity. Limitations include lack of comparison between two or more active therapies in randomized clinical trials (RCTs), the inclusion of treatment-resistant patients in most RCTs, who may not represent a general clinical population, and difficulties in drawing direct comparisons in studies through the meta-analysis process, caused in part by the lack of uniformity in patient populations and study designs. Many studies lack long-term follow-up and comparative studies of add-on therapy after failure of first drug are scant. Most recommendations make optimal use of the modest hard evidence[2,3] and combine it with the best-established experience available.

DRUG SELECTION

While choosing AEDs, the following aspects must be factored in:

1. Efficacy - How good is the drug in stopping the patient's seizures?
2. Safety - What is the risk for a serious idiosyncratic reaction? Is the drug teratogenic?
3. Adverse effects - What side effects may occur? Is there a high therapeutic index?
4. Ease of administration – Frequency of dosing? Initiation of treatment with a regular dose or slow upward titration? Is a parenteral preparation available?
5. Pharmacokinetics - What is the profile of the drug? Is it metabolized by the liver, excreted by the kidneys and is it protein-bound? Is absorption affected by meals or other medicines? Does it cause drug interactions?
6. Drug interactions - Many of the AEDs induce drug interactions by either stimulating or inhibiting the liver P450 mixed enzyme oxidizing system. AEDs may interact with each other and cause changes in other concurrently administered medications.
7. Cost - A particular problem in indigent patients and the elderly.

PRINCIPLES OF AED THERAPY

1. Establish an epilepsy syndrome diagnosis for each patient.
2. Select medications appropriate for that epilepsy syndrome.
3. From the appropriate medications, choose the agent best suited for the patient based on patient and medication characteristics, including age and sex, co-morbidity, concomitant medications.
4. Initiate and titrate the medication at appropriate dosages, increments and rates to enhance tolerability.

Table 1: Drugs for the Treatment of Partial seizures

First-line agents	Second-line agents
Carbamazepine	Valproate
Oxcarbazepine Phenytoin	Gabapentin
	Lamotrigine
	Tiagabine
	Topiramate
	Zonisamide
	Levetiracetam

5. Increase the medication, regardless of serum levels, until complete seizure control is achieved or until persistent, unacceptable side effects occur.
6. Monitor tolerance and compliance with particular drug regimens.
7. Ordering and interpreting appropriate laboratory tests based on knowledge of specific adverse events associated with different drugs.
8. Recognizing changes in seizure characteristics.
9. If satisfactory seizure control is not achieved, change to another agent appropriate for the epilepsy syndrome being treated.
10. Discuss the pros and cons of alternative therapies and to include the patient in the decision-making process.

In treating epilepsy, monotherapy is the current standard. Sequential monotherapy overrides early use of combination therapy Regardless of the category or type of epilepsy, most experts recommend the use of at least two, and possibly three trials with a single AED in a newly diagnosed patient before considering combinations. Seventy percent of patients have either complete control or few seizures with the careful use of a single anti-epileptic drug. The drug which appears most appropriate for a patient's seizure type and epilepsy syndrome should be selected and increased in dose, until seizures are controlled or adverse effects occur. If adverse effects preclude increasing the dose and seizures are not controlled, a second drug should be started and the first drug should be slowly withdrawn. Approximately 20% of patients benefit from a combination of two or more drugs. Adverse reactions are significantly increased with polypharmacy.

SELECTION OF DRUGS ON THE BASIS OF SEIZURE TYPE

Because the pathophysiology of localization-related and generalized epilepsy are different, it follows that the choice of medication also differs. In localization-related epilepsy, an antiepileptic drug's effect on the sodium channel is of critical importance. Normally, the sodium channel opens to allow an action potential to develop and then closes at a certain frequency. During initiation or propagation of epileptic seizures, the sodium channel may fire much more rapidly than normal. Many antiepileptic drugs exert a fairly strong action on the sodium channel. Phenytoin and Carbamazepine act almost exclusively on the sodium channel, whereas other drugs, such as valproic acid, have additional mechanisms. Thus, initial treatment in a patient with localization-related epilepsy is generally with Phenytoin or Carbamazepine.

With generalized epilepsies, such as juvenile myoclonic epilepsy, drugs acting on the sodium-channel will be of little benefit; indeed, they may actually exacerbate the seizures. Similarly, Phenytoin, Tiagabine, and Gabapentin can exacerbate absence seizures in children.

Partial Seizures

About 70% of adult patients with epilepsy have partial-onset seizures, which encompass simple partial, complex partial, and secondarily generalized tonic-clonic seizures. These seizures originate from localized areas of the brain, and the origin and extent of spread within the brain determine the clinical characteristics of the seizures. About 50% of patients have both partial seizures and secondarily generalized tonic-clonic seizures. In general, the latter type of seizure is the easiest to control, followed by complex partial seizures and simple partial seizures, because AEDs are typically more effective in blocking seizure spread than in preventing seizure initiation.

For the majority of patients with newly diagnosed partial epilepsy, initial treatment consists of Carbamazepine, Oxcarbazepine, and Phenytoin. Alternative choices include Divalproex sodium and most of the newer AEDs, including Gabapentin, Lamotrigine, Levetiracetam, Tiagabine, Topiramate, and Zonisamide (Table 1). Barbiturates are usually avoided because of their adverse effects on cognition and mood.

The treatment of choice for patients with partial epilepsy was highlighted by the results of two seminal Veterans Administration clinical trials. The first trial[4] compared the tolerability and efficacy of Phenytoin, Carbamazepine, Primidone, and Phenobarbital, whereas the second trial[5] was a comparative study between Carbamazepine and Valproate. The studies showed that, among these drugs, there was no significant difference in efficacy for complete control of generalized tonic-clonic seizures. However, Carbamazepine was significantly better than the two barbiturates and Valproate in completely controlling partial seizures. There also was a statistical trend favoring Carbamazepine over Phenytoin for complete control of partial seizures, although the difference did not reach statistical significance. These two trials also demonstrated that Phenytoin and Carbamazepine were substantially better tolerated than the barbiturates. On the basis of these results, Carbamazepine and Phenytoin became the drugs of choice for partial epilepsy, followed by Valproate. The barbiturates were relegated to third-line agents predominantly because of their profile of adverse events.

A large study compared Valproate, Phenobarbitone, Phenytoin, and Carbamazepine.[6,7] Few differences were noted in efficacy; however, Phenobarbitone was significantly more toxic, especially in children. Few studies have been done comparing the newer drugs with the older drugs in a double-blinded controlled fashion. Several investigators[8-10] compared Lamotrigine with Carbamazepine and Phenytoin in separate studies. Although efficacy was similar, Lamotrigine was better tolerated. Recent studies comparing Gabapentin and Carbamazepine[11] found no significant differences between them. Gabapentin was better tolerated and carbamazepine was slightly more efficacious.

The usual starting dose of Carbamazepine is 200 mg twice per day, with weekly increases of 200 mg per day and a usual

daily maintenance dose of 600 to 1200 mg. The long-acting formulations of Carbamazepine improve compliance because they can be taken twice daily and are better tolerated than the regular formulation. Carbamazepine is a strong inducer of some of the hepatic cytochrome P-450 isoforms and is associated with a number of clinically significant drug-drug interactions. In addition, Carbamazepine induces its own metabolism (auto-induction), a process that is usually completed in the first 4 to 6 weeks following initiation of treatment. This auto-induction is clinically relevant because, although the patient is on a constant dose, serum Carbamazepine levels can drop substantially in the first few weeks of treatment, requiring dose adjustments. The usual therapeutic range for serum Carbamazepine levels is 6 to 12 mg/L.

Of the newer AEDs, Oxcarbazepine is the only agent approved for initial monotherapy. Comparative trials showed that although Oxcarbazepine did not substantially differ in efficacy from Carbamazepine[12] and Phenytoin,[13] it was significantly better tolerated than either of the latter drugs, making it an attractive first-line therapy for treatment of partial epilepsy. However, elderly patients tolerate Oxcarbazepine less than younger patients. Oxcarbazepine is a keto-analogue of Carbamazepine that is rapidly reduced by cytosolic enzymes to the pharmacologically active mono-hydroxy derivative. As a result, the active metabolite of Carbamazepine, known as 10,11-epoxide, is not produced, which partly explains the better tolerability of Oxcarbazepine and its association with less frequent cutaneous rashes compared with Carbamazepine. Although a starting dose of 300 mg twice daily is recommended, Oxcarbazepine is best tolerated when treatment is initiated at 150 mg twice a day, with weekly increments of 300 mg per day and a target dose of 900 to 1,200 mg for patients with newly diagnosed epilepsy. Compared with Carbamazepine, Oxcarbazepine is associated with substantially fewer drug-drug interactions and does not undergo auto-induction. The conversion ratio between Carbamazepine and Oxcarbazepine is 1.5 mg of Oxcarbazepine to each 1 mg of Carbamazepine. This drug demonstrated significant efficacy as monotherapy in patients newly diagnosed as having partial epilepsy.[14]

For Phenytoin, the usual starting dose is 300 mg daily (4 to 5 mg/kg per day), with a maintenance dose of 200 - 500 mg per day. Depending on the clinical situation, a loading dose of Phenytoin at 18 - 20 mg/kg can be given orally or intravenously. Because of its long half-life, Phenytoin can be given once daily, although it may be administered twice a day to minimize side effects. The therapeutic serum range of Phenytoin is 10 to 20 mg/L. However, the rate of metabolism of Phenytoin is not linear; the drug undergoes first-order metabolism until the hepatic enzymes are saturated, after which the metabolism switches to zero-order kinetics. As a result, the serum level of Phenytoin increases exponentially with higher doses when the hepatic enzymes are saturated. It is therefore recommended that the daily dose of Phenytoin be increased by 100 mg when the serum level is below 10 mg/L and by at most 30 to 50 mg when the level is within the therapeutic range. For elderly patients, increments of 10 mg per day are recommended. Phenytoin, like Carbamazepine, is a strong hepatic enzyme inducer and is prone to a number of significant drug interactions.

If Carbamazepine fails, there is at present no data giving evidence as to the most promising next choice. A failure of Carbamazepine does not predict a failure of oxcarbazepine but it seems more rational first to try another drug which is chemically unrelated. Of the new drugs, Lamotrigine, Topiramate and Levetiracetam can be considered good candidates. Even if monotherapy is the gold standard, a combination of Lamotrigine and Valproate could be an option because of their therapeutic synergistic effect.

Divalproex is usually started at 250 to 500 mg twice daily (10 to 15 mg/kg per day), with weekly increments of 250 to 500 mg per day (5 to 10 mg/kg per day) and a range in daily dose from 1,000 to 3,000 mg. The maintenance dose is typically higher for patients with partial epilepsies than for those who have idiopathic generalized epilepsies. An intravenous formulation is available for acute loading or for replacement maintenance therapy when oral intake is not possible. Although the therapeutic serum range for valproate is 50 to 150 mg/L, there is considerable fluctuation in the serum level when the dose is constant.

The main advantages of Gabapentin are its safety, tolerability, favorable pharmacokinetic profile, and ease of use.[15] It has been used mostly as adjunctive therapy in patients with refractory seizures but is an attractive agent as monotherapy in specific situations, including in patients with severe hepatic disease, cutaneous allergies, porphyria, or acquired immunodeficiency disease and in elderly patients who take a number of medications concomitantly.[16] The effective dose for treatment of epilepsy needs to be individualized but usually ranges between 900 and 4,800 mg per day, divided into three doses.

Lamotrigine is approved as adjunctive therapy and as monotherapy following conversion from hepatic enzyme inducers, such as Carbamazepine and Phenytoin. Although Lamotrigine is not approved for initial monotherapy, some physicians use it in that fashion on the basis of two comparative trials that showed it did not differ substantially in efficacy compared with Phenytoin or Carbamazepine and was better tolerated than Carbamazepine.[17,18] It is imperative to start Lamotrigine therapy at a low dose and to gradually increase the dose in order to minimize the risk of rash. About 10% of patients exposed to this drug can develop a rash, and up to 0.3% of adults and 1% of children can develop a significant, life-threatening idiosyncratic cutaneous reaction. These percentages were derived from trials in which the initial dose and titration schedule were substantially more aggressive than the current recommendations in the drug's package insert. The initial dose and the titration rate of Lamotrigine vary according to the medications being taken concomitantly (hepatic enzyme inducers like Carbamazepine and Phenytoin or hepatic enzyme inhibitors like Valproate) because they can substantially affect Lamotrigine clearance.

Tiagabine is a designer drug that exerts its anticonvulsant effect by inhibiting the reuptake of γ-aminobutyric acid from pre-synaptic terminals. Despite the short half-life, of tiagabine, clinical trials have demonstrated comparable efficacy whether the drug is used on a schedule of two times daily or four times daily.[19] This drug is used as adjunctive therapy, with a usual starting dose of 4 mg per day, weekly increments of 4 mg per day, and a target daily dose between 32 and 64 mg.

Table 2 : Drugs for generalized epilepsy syndromes

• Absence	- Ethosuximide, Valproate
• Juvenile absence	- Valproate, Lamotrigine
• Myoclonic epilepsy	- Valproate, Lamotrigine, Topiramate
• Juvenile myoclonic epilepsy	- Valproate, Lamotrigine
• Young adult onset GTCS	- Phenytoin, Valproate, Gabapentin
• Rolandic seizures	- Carbamazepine, Phenytoin, Gabapentin

Topiramate has significant efficacy when used as adjunctive therapy.[20] Because of potential adverse cognitive events, it should be started at a low dose, with gradual adjustment in dosage thereafter. A starting dose of 25 or 50 mg per day is appropriate, with weekly increments of 25 to 50 mg per day. The usual target dose for adjunctive therapy is 400 mg taken twice daily, with a dose range between 100 and 1,000 mg per day.

Levetiracetam is an attractive AED because of its pharmacokinetic profile, tolerability and ease of use.[21] The recommended starting dose is 500 mg at bedtime, with weekly increments of 500 mg and a total target daily dose between 1,000 and 3,000 mg divided into two doses. Although not approved for use as monotherapy, it can be used as such for the same patient populations as Gabapentin.

Zonisamide is approved as adjunctive therapy.[22] Because zonisamide is a sulfonamide derivative, it should be avoided in patients with sulfa allergies. Zonisamide can be associated with a rash in 3% of patients; rare cases of severe cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, can occur. The recommended starting dose is 100 mg taken once a day, with increments of 100 mg every 2 weeks if needed. This drug has a long half-life (64 hours) and is administered once a day, with a target dose between 100 and 600 mg per day.

Generalized epilepsy syndromes

The traditional drugs for absences are Valproate and Ethosuximide which can be used alone or together (Table 2). If the patient also has generalized tonic-clonic seizures (GTCS) ethosuximide needs to be supplemented by a drug effective in for this type of seizure. Valproate is effective for both these seizure types. Lamotrigine is increasingly replacing Valproate especially in young women, who are at risk for weight gain, teratogenecity and ovarial cysts with Valproate. Topiramate and Levetiracetam are being evaluated as alternatives.

In juvenile myoclonic epilepsy (JME), Valproate is the considered drug of first choice because it is active against myoclonic seizures, GTCS, the occasional absences, and the frequent photosensitivity which are characteristic of this syndrome. Clonazepam is useful for myoclonic seizures, but not for GTCS, and carries a high risk of withdrawal seizures. Lamotrigine is an alternative but is perhaps less effective against myoclonic and GTCS. Carbamazepine and Phenytoin are contraindicated in JME. Topiramate and Levetiracetam are being evaluated as alternatives.

ADVERSE EFFECTS

Adverse effects occur with all of the AEDs. An ideal drug would control seizures without producing any adverse effects. Unfortunately none exist. However, many of the AEDs have a wide therapeutic index and these must be chosen over drugs with a narrow therapeutic index.

Table 3 : AEDs – Dosages and therapeutic concentrations

Drug	Plasma concentration (mg/L)	Daily dose
Phenytoin	10-20	4-6 mg/kg/day (adults); 4-10 mg/kg/day(children)
Carbamazepine	4-12	8-20 mg/kg/day (adults); 10-30 mg/kg/day (children)
Phenobarbital	15-40	1-3 mg/kg/day (adults); 3-6 mg/kg/day (children)
Valproic acid	50-100	10-40 mg/kg/day (adults+children monotherapy) 20-60 mg/kg/day (children-polytherapy)
Primidone	5-15	10-25 mg/kg/day (adults); 10-25 mg/kg/day (children)
Ethosuximide	40-100	15-30 mg/kg/day (adults); 20-40 mg/kg/day (children)
Gabapentin	> 2	900-4800 mg/day (adults); 15-35 mg/kg/day (children)
Lamotrigine	Not established	50 -500 mg/day (adults); 1-15 mg/kg/day (children)

EASE OF ADMINISTRATION

Many of the AEDs require low initial dosing and slow titration of the drug to avoid adverse effects or idiosyncratic reactions. Lamotrigine is a prime example. Initiation of treatment at too high a dose of Lamotrigine will cause a rash in up to 20 to 30% of patients and a number of these patients will develop the Stevens - Johnson syndrome. Carbamazepine must be initiated slowly to avoid GI symptoms, malaise, headache, and other constitutional symptoms. Topiramate must be initiated at a low dose and titrated slowly to avoid significant cognitive impairment. Tiagabine should also be introduced at low doses and be titrated slowly.

Lamotrigine, Carbamazepine, Topiramate, and Tiagabine require low initial dose and slow titration. Phenytoin, Gabapentin, and valproate can be initiated with a calculated dose and titrated to seizure control or toxicity before decreasing the dose.

Frequency of Dosing

Because of variations in absorption rates and drug half-lives dosing schedules vary (Table 3). Carbamazepine should be dosed three times daily; however, slow release formulation of Carbamazepine permits twice a day dosing. Gabapentin, Valproate and Tiagabine should be administered thrice daily. Slow release preparation of valproate which allow once a day and twice a day dosing are available. Phenytoin and Phenobarbital, which have relatively long half-lives, can be administered once daily in most patients.

PHARMACOKINETICS

It is important for the treating physician to be familiar with the pharmacokinetic profiles of these drugs. They predict drug

Table 4 : AEDs – Drug interactions

AED	AED Serum Concentrations Decreased by			AED Serum Concentration Increased by Inhibition of Hepatic Metabolism
	Reduced Oral Absorption	Displacement from Protein Binding Sites	Induction of Hepatic Metabolism	
Carbamazepine			Phenobarbital, Phenytoin, Primidone	Desipramine, Diltiazem, Fluoxetine, Isoniazid, Valproic Acid
Phenytoin	Antacids, Enteral Feedings	Aspirin, Phenylbutazone, Tolbutamide, Valproic Acid	Carbamazepine, Ethanol (chronic), Phenobarbital Primidone, Rifampicin	Allopurinol, Amiodarone, Chloramphenicol, Diltiazem, Disulfiram, Ethanol (acute), Fluoxetine, Isoniazid, Propoxyphene, Sulfonamides, Topiramate, Valproic Acid
Phenobarbital			Carbamazepine, Ethanol (chronic), Phenytoin	Chloramphenicol, Isoniazid, Valproic Acid
Valproic Acid		Aspirin	Carbamazepine, Phenytoin, Phenobarbital, Primidone	Aspirin, Felbamate
Felbamate			Carbamazepine, Phenytoin	Valproic Acid
Gabapentin	Antacids			
Topiramate			Carbamazepine, Phenytoin, Phenobarbital	Valproic Acid
Tiagabine		Valproic Acid	Carbamazepine, Phenytoin, Phenobarbital	
Lamotrigine			Carbamazepine, Phenytoin Phenobarbital, Primidone	Valproic Acid

interactions, dosing schedules, bioactivity and adverse effects. Drugs that are metabolized by the liver are usually enzyme inducers of inhibitors. Drugs which are highly protein-bound are subject to significant fluctuations in free biologically active concentrations in different diseases and physiological states. Any factor which alters plasma proteins will alter free drug levels and hence bioactivity. Only free, unbound drug crosses the blood-brain barrier.

DRUG INTERACTIONS

See Table 4 for drug interactions.

Pharmacodynamic Interactions

1. Potentiation of neurotoxicty : Concurrent use of other AEDs, alcohol, antidepressants, antihistamines, antipsychotics, benzodiazepines, narcotic analgesics, sedatives, and hypnotics
2. Lowering of seizure threshold : Bupropion, clozapine, imipenem-cilastin, isoniazid, reserpine, tricyclic antidepressants, theophylline, and cocaine

Pharmacokinetic Drug Interactions

1. Interference with absorption
2. Reduction in plasma protein binding
3. Enhancement/Inhibition of hepatic metabolism

SPECIAL POPULATIONS

Elderly

Seizures in the elderly pose special problems because of changes in metabolism, decreased hepato-renal function and polypharmacy with other drugs. Phenytoin is the most commonly used drug in this population. However, because of non-linear kinetics and its enzyme-inducing properties, it is often undesirable. Gabapentin offers several advantages: no drug interactions, non-protein-bound, not metabolized by the liver and a low adverse effect profile. Lamotrigine also has favorable characteristics of not provoking drug interactions and having a low adverse effect profile. However, initiation of therapy is prolonged (6 - 8 weeks).

Females

AED selection in reproductive age group females should consider efficacy, tolerability, interactions with contraceptive steroid medications, and teratogenecity. All AEDs, when administered to pregnant females increase the risks of major and minor malformations about two-fold. Malformation rate of offspring of non-epileptic females is about 2% as against 3% in the offspring of epileptic mothers not taking antiepileptic drugs, and 5% in the offspring of epileptic mothers taking antiepileptic drugs. The risks of malformations are increased when mothers are on polypharmacy. Medication changes post-conception do not reduce the risk of fetal malformations. Fetal anticonvulsant syndromes (epicanthal folds, low-set ears, upturned nose, flat nasal bridge, hypoplastic nails, shortened distal phalanges and wide-set eyes) can occur with all of the antiepileptic drugs. Medications should not be discontinued during pregnancy because the serious consequences of seizures on the mother and possibly the fetus. Valproate and carbamazepine are associated with neural tube defects, 1.5 % and 0.75% respectively.[24] All women of child-bearing potential should receive folate supplementation. Withdrawal of AEDs in seizure-free females prior to conception is an option. If at all possible, women contemplating pregnancy should be on monotherapy. There is no specific anti-epileptic drug recommended for the pregnant patient. The drug which controls the epilepsy is the standard of care. Breast feeding for women on is generally safe with all AEDs. Non-enzyme-inducing anti-epileptic drugs are preferable in patients on steroid contraceptives to avoid contraceptive failure.

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