



## TREATMENT OF NEW ONSET EPILEPSY: IN VIEW OF THE LACK OF EVIDENCE-BASED RECOMMENDATIONS

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### Introduction

Antiepileptic drugs (AEDs) are the initial treatment modality for the vast majority of patients with epilepsy. Once the decision to treat is made, most patients will take medications for at least 1-2 years, and some will continue therapy for their entire lives. The treatment of epilepsy with AEDs is associated with several specific issues and challenges of long-term therapy. These includes: (1) choice of AEDs, (2) initial definition of end point of therapy and adequate drug trial, (3) monitoring of adverse drug reactions, (4) in patients whose seizures remain uncontrolled, the appropriate sequence of drugs and drug combinations, and (5) definition and management of intractable epilepsy. In this review, we would focus on the first three issues.

### Choice of Antiepileptic Drugs

The last decade has witnessed the licensing of a range of new, highly effective AEDs. We now have almost 20 diverse agents with different mechanisms of action. This provides genuine choice. The goal of therapy is not just seizure control, we can now afford to take a more holistic approach to patient management. Factors determining AED choice fall into three categories (Table 1): patient factors, types and syndromes of epilepsy, and pharmacology of drugs themselves. When long-term treatment was decided, the patient would be started on monotherapy. Table 2 depicts choice of AED based on seizure or syndrome diagnosis. New AEDs might have better or equal efficacy when compared to the older AEDs and probably be better tolerated.

When one tries to assess the evidence of AED treatment, according to a recently published article, in which 50 randomized controlled trials and seven meta-analyses over 60 years were studied, there was an alarming lack of well-designed, properly conducted epilepsy randomized

controlled trials, especially for treatment of epilepsies in children. There was only one Class I study for children with partial-onset seizures, in which oxcarbazepine was compared to phenytoin. There was no Class II study in this area. Even worse, for treating children with generalized tonic-clonic, absence seizures, benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy, both Class I and II studies was not available. The recommendation of drug treatment in children with different epilepsies was most of the time either based on adult data or Class III studies. For the role of new AEDs, the absence of rigorous comprehensive adverse effects data makes it equally impossible to develop an evidence-based guideline in initial monotherapy.

### Initial Definition of End Point of Therapy and Adequate Drug Trial

Progressivity of dosage in initiation of drug is an essential rule. The drug should be introduced at low dosage and

**Table 1.** Factors affecting AED choice

#### *Patient factors*

Comorbidities (e.g. attention deficit, psychosis, depression, anxiety neurosis, migraine)

Compliance

Life style

Concomitant disease (e.g. renal disease, liver disease)

Weight status

Cost

#### *Type of epilepsy*

Idiopathic

Localization-related

Syndromic

#### *Drug-related factors*

Mechanism

Pharmacokinetics

Efficacy

Toxicity

Interactions

Teratogenicity

**Table 2.** Use of antiepileptic drugs in the treatment of seizures and epileptic syndromes in children

<b>Partial seizures</b>	
First choice	carbamazepine, oxcarbazepine, phenytoin
Second choice	gabapentin, lamotrigine, topiramate, valproate
Third choice	tiagabine, phenobarbital, primidone
Others	benzodiazepine, acetazolamide, vigabatrin, felbamate
<b>Generalized tonic-clonic seizures</b>	
First choice	valproate, carbamazepine, phenytoin
Second choice	lamotrigine, topiramate
Third choice	phenobarbital, primidone
<b>Absence seizures</b>	
First choice	valproate, ethosuximide
Second choice	lamotrigine
Third choice	topiramate, benzodiazepine, acetazolamide
<b>Juvenile myoclonic epilepsy</b>	
First choice	valproate
Second choice	lamotrigine, topiramate, benzodiazepine
Third choice	phenobarbital, primidone
Consider	felbamate
<b>Lennox-Gastaut syndromes</b>	
First choice	valproate
Second choice	lamotrigine, topiramate
Third choice	ketogenic diet, felbamate, benzodiazepine, phenobarbital
Consider	ethosuximide, pyridoxine, vigabatrin, steroids or corticotropin
<b>Infantile spasms</b>	
First choice	corticotropins, vigabatrin
Second choice	valproate
Third choice	topiramate, lamotrigine, tiagabine, benzodiazepine
Consider	pyridoxine, felbamate
<b>Benign epilepsy with centrotemporal spikes</b>	
First choice	gabapentine, valproate carbamazepine, phenytoin
Second choice	phenobarbital, primidone, benzodiazepine
Consider	lamotrigine, topiramate

increased gradually until control is obtained or the limit of tolerance reached. It is generally accepted that the optimal maintenance dose should be as high as necessary and as little as possible. One should initially aim for a lower than average dose or drug level. This will provide opportunity to identify patients whose seizures can be controlled at a relatively low dose. It is recommended to keep the dose as low as possible, provided clinical control is gained, even though the level is sub-therapeutic. However, this advice is difficult to apply in clinical practice, especially in patients with infrequent seizures, as it is hard to be sure that control is obtained. At the same time, initiating drug with a very low dose carries the impact of recurrent seizures. Examination of response to AEDs at different dose levels in adults with newly diagnosed epilepsy has not been explored in randomized studies. Even more so in the treatment of epilepsy in children, a population with the greatest needs, is supported by the least amount of information about safe and effective use of AEDs. Infants and children have different pharmacokinetics and susceptibility to anticonvulsants. The therapeutic serum concentration ranges for AEDs in children are so far based on results of studies in adults. Because long-term effects and toxicity of antiepileptic drugs in developing children are largely unknown and

because subtle effects may occur even at drug levels within the optimal range, it has been strongly recommended that the lowest possible dose of anticonvulsant that prevents seizures be used, regardless of plasma level. Table 3 summarizes the average doses of AEDs in children.

**Table 3.** Average dose of antiepileptic drugs in children

Drug	Average dose mg/kg		
	Neonates	Infants	Children
Phenobarbitone	3-4 qd	2.5-3 q12h	2-4 q12h
Phenytoin	2.5-4 q12h	2-3 q8h	2.3-2.6 q8h
Carbamazepine		3-10 q8h	3-10 q8h
Valproate		5-10 q8h	5-10 q8h
Ethosuximide			10-20 q12h
Felbamate			5-15 q8h
Gabapentine			5-15 q8h
Topiramate			2-5 q12h
Lamotrigine			2-5 q12h
Tiagabine			0.5-2 qd
Oxcarbazepine			5-15 q8h
Levetiracetam			5-20 q12h
Vigabatrin		50-100 q12h	25-75 q12h

An adequate drug trial must be defined in terms of both dose and duration. The current tendency is to consider drug failure when seizures persist at the maximal tolerated (or sub-toxic) dose of an AED, regardless of the plasma drug levels. The appropriate duration of drug treatment varies as a function of the baseline seizure frequency. A reasonable trial duration for a given drug would be about 5-10 times the average seizure interval at baseline before the drug was introduced. This time frame, however, may not apply to very high and very low seizure frequencies.

### Drug Monitoring

Monitoring is an attempt to detect serious systemic toxic reactions of AED in time to intervene and protect patients. Adverse events have led to legal actions that have affected treatment, monitoring and the need to document patient care. The process begins with disclosure of information within the framework of risks and benefits. Documentation of the discussion is important. Issues of informed consent have also required adjudication. This is especially relevant in the area of drug-associated teratogenicity. The patient must be informed of the nature of side effects, what must be tolerated, and how side effects will influence titration. Serious, life threatening, idiosyncratic effects must be clearly explained, but within the context of rarity.

So far, evidence-based scientific criteria fail to support routine monitoring. One study of 199 children evaluated liver, blood and renal function at initiation of therapy and at 1, 3, and 6 months. Screening studies repeated every 6 months disclosed no serious clinical reactions from phenobarbital, phenytoin, carbamazepine or valproate. One way to minimize the risk of serious adverse effects is to identify high-risk patients. Baseline biochemical studies before drug initiation help to identify patients with special risk factors, e.g. renal or liver dysfunction, that could influence drug selection. Risk factors for valproate related hepatotoxicity are: patients <2 years, being treated with multiple AEDs, and known metabolic disease with delayed development. Patients fitting this profile need detailed laboratory screening and monitoring strategy. Patients who are unable to communicate, e.g. handicapped, institutionalized, may also require regular monitoring. Table 4 summarizes screening laboratory tests that may

aid in detection of adverse effects of AEDs. Clotting studies for patients on valproate before surgery should be obtained. Tests of bone metabolism (e.g. calcium, alkaline phosphatase) every 2-5 years for those taking enzyme-inducing drugs may be required especially in non-ambulatory patients.

For many years, monitoring of plasma levels of AEDs has been used extensively. There have also been many critical reappraisals of the clinical value of such monitoring. One of the weaknesses of the concept of the therapeutic range is that it does not take into account the great variations that exist among children in their susceptibility to drugs. When active metabolites exist, or when the relationship between blood levels and clinical activity is weak, the value of blood level monitoring is further undermined. In case of well-controlled epilepsy, regular clinical supervision is the only essential measure. The main indications for obtaining blood levels include the followings:

- Verification of the patient's compliance.
- Persistence of seizures despite a correctly prescribed therapy.
- Presence of toxic effects.
- Occurrence of breakthrough seizures in previously well-controlled patients.
- Use of polytherapy.
- Use of drugs that had low therapeutic ratio or with the phenomenon of saturation kinetics, especially phenytoin.
- In patients with physical or mental handicaps, such that clinical manifestations of toxicity are difficult to elicit.
- Young age of patients, e.g. neonate.
- Before changing to another agent when labeling the prescribed drug ineffective.
- After a loading dose of drug was given.
- Specific clinical conditions, e.g. status epilepticus, organ failure, or pregnancy.

The time of sampling is important when drug level is monitored. In general, when toxicity is suspected, it is best to sample at maximal blood level. Conversely, if a low blood level is suspected because of ineffective treatment, sampling at time of trough level is

**Table 4.** Screening laboratory tests to detect adverse drug reactions

Antiepileptic drugs	Laboratory tests
Phenytoin	Complete blood picture, liver enzymes
Phenobarbitone	Complete blood picture, liver enzymes
Carbamazepine	Complete blood picture, liver enzymes, serum sodium
Valproate	Complete blood picture, liver enzymes, amylase and lipase, ammonia, carnitine
Oxcarbazepine	Complete blood picture, liver enzymes, serum sodium
Topiramate	Urine for microscopic hematuria, renal ultrasound, intraocular pressure, venous blood gas

recommended. With drugs that have a short half-life, the use of blood levels to check patient's compliance is limited. Trough level of AEDs should be measured after steady state was achieved (i.e. 4-5 half-lives of drug). The time of blood sampling was also affected by drug that undergoes auto-induction, the clearance of carbamazepine increases by 300% within 30 days after therapy begins. Interpretation of drug level is not always straightforward, especially in cases of drug interactions, and for drugs whose protein-binding vary with resultant change in unbound drugs, and for those that have active metabolites.

### Conclusion

Drug treatment is, by far, the most common form of treatment of epilepsies. Newer AEDs might have equal or better efficacy and might be better tolerated. All AEDs have side effects, and their use should therefore be limited to the smallest amount of single agent as possible. A better knowledge of the pharmacokinetics of drugs have permitted a more rational use. Although useful in determined circumstances, blood level measurements are not a substitute to clinical judgment. The aim of treatment is to render the patient seizure-free with a minimum of side effects, not to achieve any predetermined therapeutic drug level.

### Summary

- New AEDs might have better or equal efficacy when compared to the older AEDs and probably be better tolerated.
- It is recommended to keep the dose as low as possible, provided clinical control is gained, even though the level is sub-therapeutic. The aim is to treat the patient and not the drug level.
- Adverse events have led to legal actions that have affected treatment, monitoring and the need to document patient care.
- Evidence-based scientific criteria fail to support routine monitoring. Baseline biochemical studies

before initiation of drug and monitoring of AED adverse effects in patients at risk are recommended.

- In well-controlled epilepsy, regular clinical supervision is the only essential measure.
- Drug level monitoring can provide useful information under valid indications. The time of sampling is important when the clinician interprets the drug level.

### Further Reading

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