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Management of Newly Diagnosed Epilepsy

A Practical Guide to Monotherapy

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Abstract

With the emergence of several new antiepileptic drugs (AEDs) in recent years, choosing an agent to initiate monotherapy in newly diagnosed epilepsy has become increasingly complicated. We provide a succinct guide intended for general clinicians to assist in this clinical situation. General features of AEDs, differences between first- and second-generation drugs, and characteristics specific to each medication are discussed. The emphasis is on tailoring treatment to the individual patient with epilepsy because each case has specific features that must be accounted for, including the type of seizure and epilepsy, medication-specific characteristics, co-morbid conditions, drug-drug interactions, patient drug tolerance, and special population factors, all of which must be balanced and optimized when choosing initial therapy in this setting. Finally, this information is conveniently summarized in a set of tables and illustrated by way of case scenarios.

Epilepsy is a chronic neurological disorder characterized by the tendency for recurrent seizures. It is typically diagnosed after the occurrence of at least two unprovoked seizures. Worldwide incidence ranges from 50 to 120 cases per 100 000 per year, with a prevalence rate of 4–10 cases per 1000 people, with higher rates in underdeveloped countries as well as in lower socioeconomic classes. These rates are similar between different ethnic groups and slightly higher for men when compared with women. Across age, there is a bimodal distribution with higher incidence at the extremes of age, specifically before the age of 1 year, and in the elderly, among whom the incidence is currently accelerating the fastest.[1]

When choosing initial therapy for newly diagnosed epilepsy, it is important to first distinguish epilepsy from provoked seizure(s) or a single unprovoked seizure. A first seizure may occur in the setting of newly diagnosed epilepsy, but may also happen to people without epilepsy. Provoked seizures do not necessarily represent epilepsy and are the result of acute, reversible systemic or neurological conditions, including but not limited to such examples as electrolyte disturbances, effects of drugs or effects of toxins. Examples of provoked seizures include those secondary to alcohol withdrawal or hypoglycaemia. Provoked seizures are relatively frequent events with lifetime prevalence rates (up to the age of 80 years) of 5–10% in patient populations. Unlike epileptic seizures, they resolve with treatment of the underlying condition.[2]

The diagnosis of epilepsy is typically made only after the occurrence of at least two unprovoked seizures because the incidence of recurrence after a single unprovoked seizure is estimated at a rate of approximately 35% over the subsequent 5 years, but steeply increases to over 70% after the occurrence of a second unprovoked seizure.[3]

It is imperative to make this distinction because in the setting of a provoked or single unprovoked seizure, long-term treatment with antiepileptic drugs (AEDs) is not indicated and may lead to potentially serious adverse reactions, as well as unnecessary costs.

This article is written for an audience of practising general clinicians and is intended to provide succinct, practical recommendations regarding the initiation and use of monotherapy in the treatment of newly diagnosed epilepsy. In deciding on initial therapy, multiple factors must be considered, including: (i) the complex nature of epilepsy as illustrated in section 1; (ii) the multitude of available AEDs and their specific characteristics; and (iii) variable patient traits including demographic factors, co-morbidities and coadministered medications. The choice of AED needs to be tailored to the patient and typically requires adjustment over time based on the degree of seizure control and the patient's tolerability of the AED.

For the purposes of this article, the term 'first-generation AEDs' includes carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid, and 'second-generation AEDs' encompasses felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide and pregabalin.

1. Classification of Epileptic Disorders

The accepted classification of epileptic seizures and syndromes was developed by the International League against Epilepsy (ILAE) and most recently revised in 1989. This classification is based on aetiology and region of origin, and categorizes seizures as partial (i.e. of focal origin), generalized (i.e. with an electrographic onset over both hemispheres) or unclassified. Partial seizures are further classified as either simple partial, complex partial or partial with secondary generalization, also known as secondarily generalized tonic clonic (GTC) seizures. Simple partial seizures do not involve an alteration in consciousness, while complex partial seizures do. Generalized seizures include both convulsive and non-convulsive events. In this system, both partial and generalized seizures are further subdivided as illustrated in figures 1, 2 and 3.[4,5]

While there is no specific AED for a given type of epilepsy, some general treatment guidelines are available for broad classes of seizures. Some of the AEDs have been shown to be effective only against

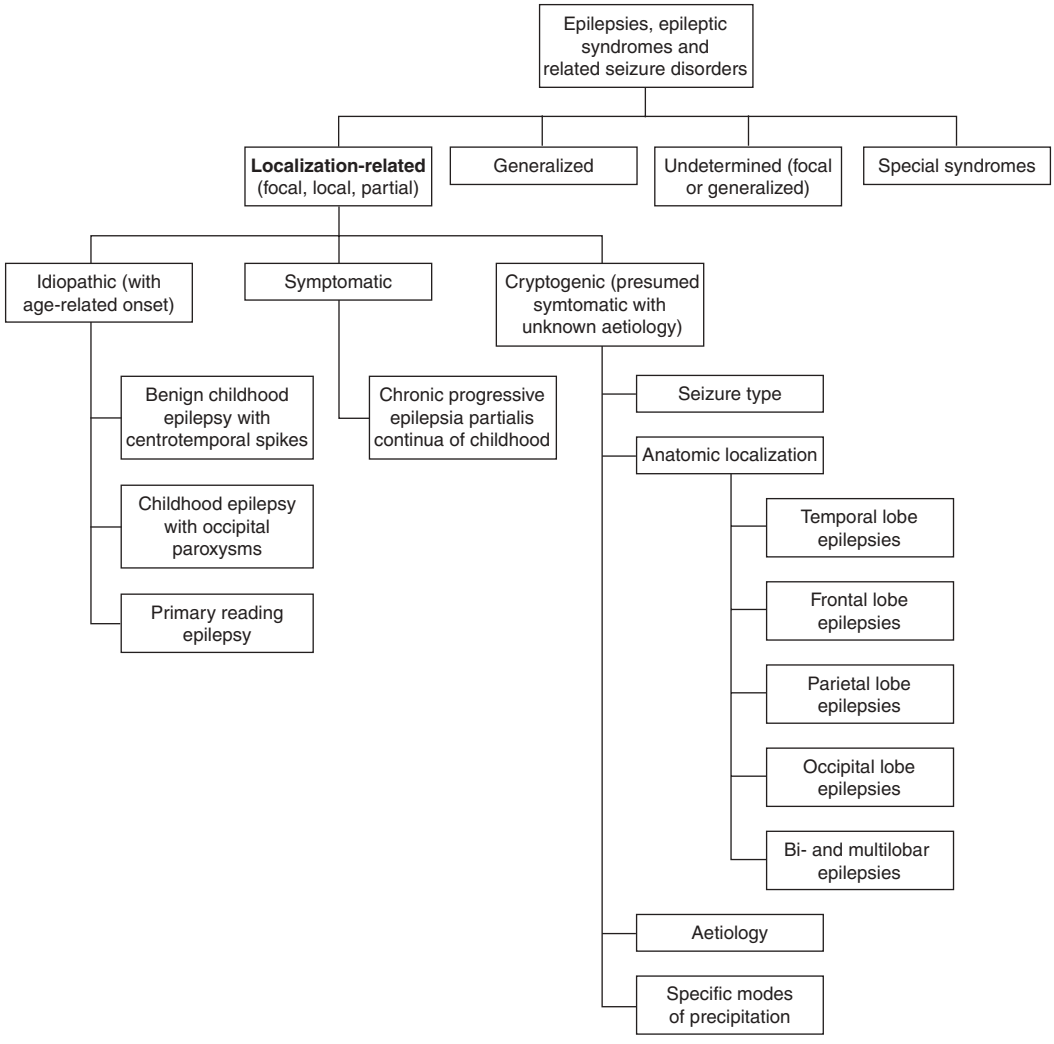

Fig. 1. International League against Epilepsy (ILAE) classification, localization-related epilepsies and epileptic syndromes.

partial with or without secondarily generalized seizures, while others, considered broad spectrum, are effective against both partial and primary generalized seizures, and one, namely ethosuximide, is specifically effective for absence seizures. AEDs are listed by effectiveness for seizure types in table I.

It is important to note that of the AEDs indicated for partial with or without secondarily generalized seizures, some may actually worsen absence or myoclonic seizures, and their use should be limited in this setting. This is shown in table I.

2. Expected Therapeutic Response to Monotherapy

Within 5 years of diagnosis of epilepsy, 50–60% of patients will be in long-term seizure remission, while at the other end of the spectrum, approximately 20% of these patients never experience remission.[1] Regarding the degree of

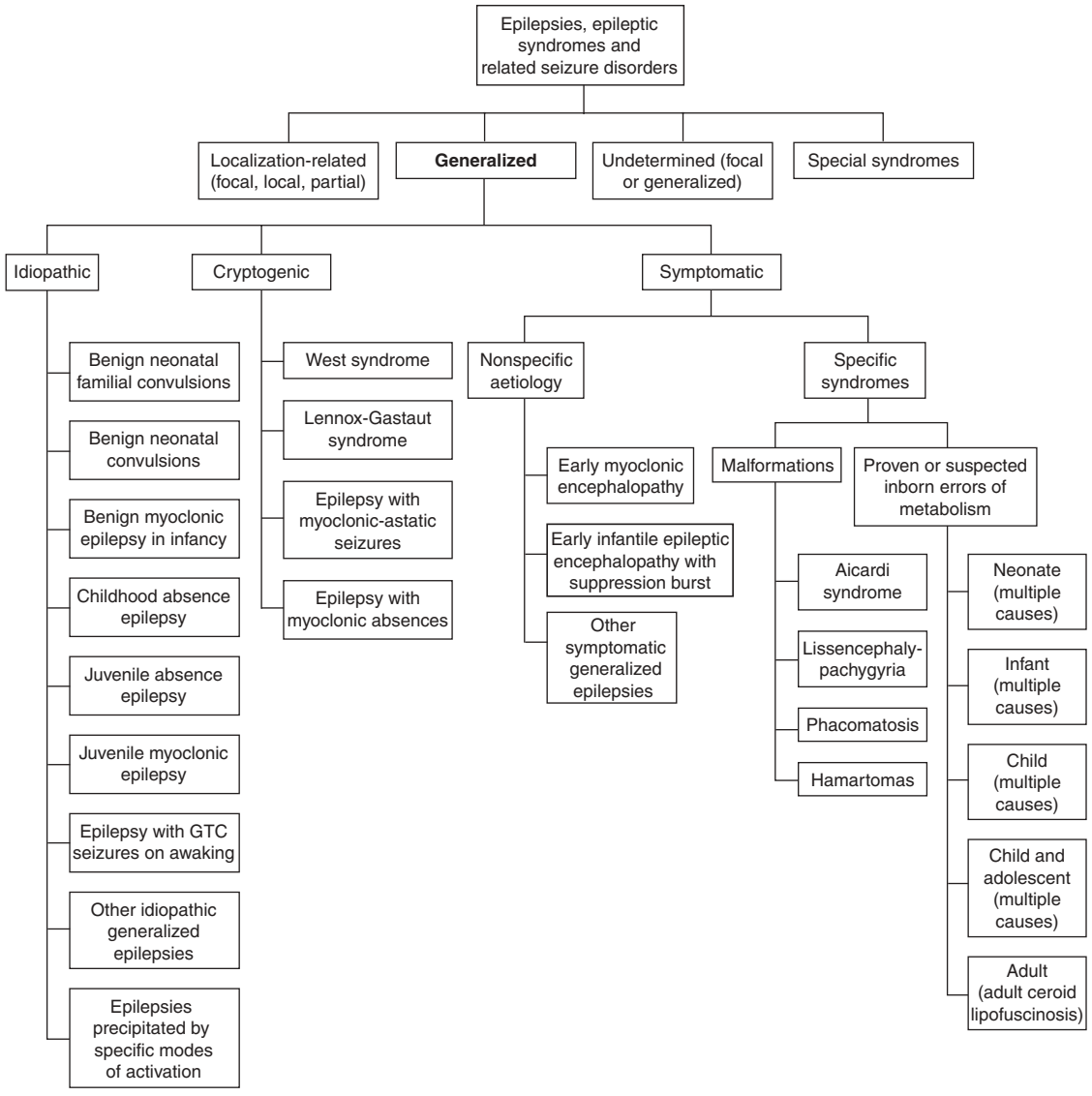

Fig. 2. International League against Epilepsy (ILAE) classification, generalized epilepsies and epileptic syndromes.[4,5] **GTC** = generalized tonic clonic.

seizure control in patients receiving medical treatment for epilepsy, over the course of 1 year, about 10% experience more than one seizure per week, approximately 40% have between one event per week and one per year, and about 50% remain seizure free.[1]

Studies have shown that seizure control varies with type of epilepsy. While approximately two-thirds of cases of newly diagnosed epilepsy are localization-related, GTC seizures have been shown to be more fully controlled than partial seizures, with 70–80% of patients being controlled within 1 year of starting monotherapy.[6]

The ILAE classification outlined in figures 1–3 categorizes both localization-related and generalized epilepsies as idiopathic, cryptogenic or

symptomatic. Idiopathic epilepsies are those that are presumed to be genetic in origin. Symptomatic epilepsies, on the other hand, occur as the result of a known process directly or indirectly affecting the CNS and leading to seizures, such as the development of a chronic seizure disorder secondary to a brain tumour. Finally, cryptogenic epilepsies are those in which signs, symptoms and diagnostic results indicate a symptomatic process, but the underlying cause is yet to be identified.

A large, observational study prospectively followed 525 patients with newly diagnosed epilepsy for a period of 2–16 years and showed that 63% of these patients remained seizure-free after beginning AED treatment. Among these patients, 40% of those with symptomatic or cryptogenic epilepsy continued to have seizures despite treatment, compared with 26% of those with idiopathic epilepsy. In other words, those with symptomatic or cryptogenic epilepsy were significantly more likely than those with idiopathic epilepsy to have persistent seizures despite medical treatment. Of the 470 patients in this study who had never received AEDs before entry to the study, 64% became seizure-free with treatment: 47% after monotherapy with the first AED, an additional 14% after switching to monotherapy with an alternative second or third agent, and 3% on combination AED therapy (figure 4).[7]

More refined information on the degree of seizure control is described in an observational study of 1696 adult patients with epilepsy followed for 1–7 years. However, nearly all of the subjects in this study had an established diagnosis of epilepsy at the time of entry, with only 8% of the participants being seen at the time of their first seizure. In this sample population, 45% of the subjects were seizure-free with medical treatment, including 82% with idiopathic generalized

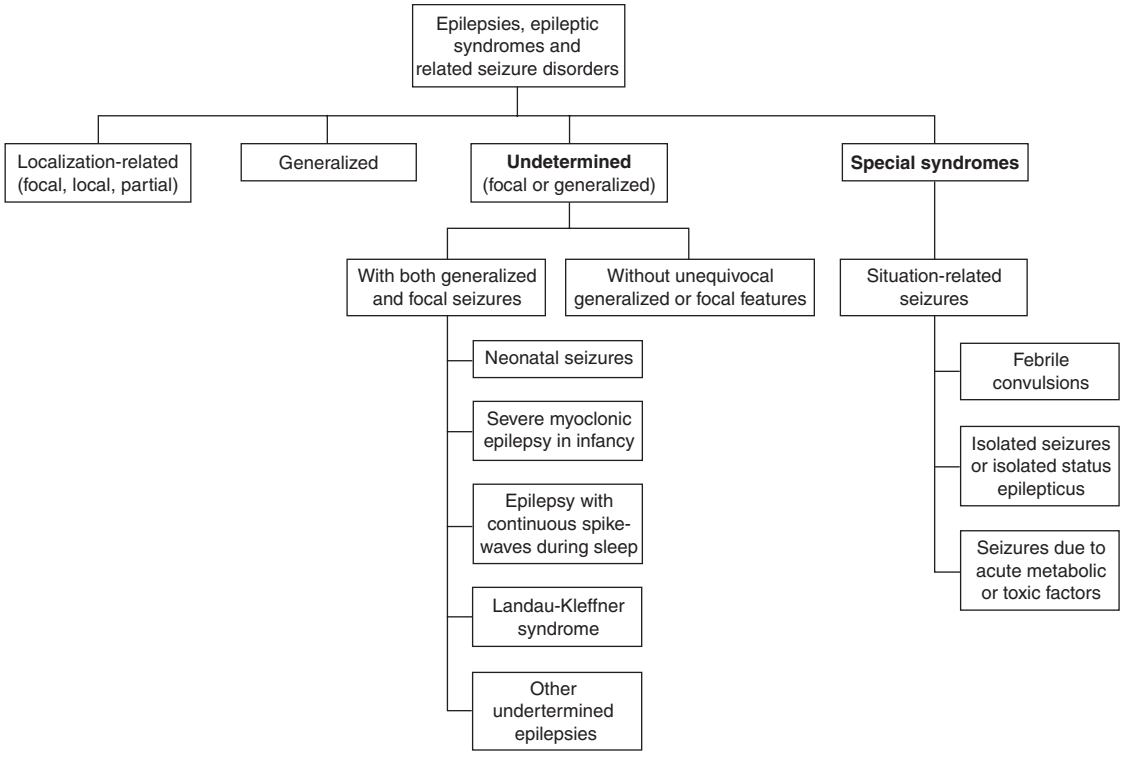

Fig. 3. International League against Epilepsy (ILAE) classification, undetermined epilepsies and epileptic syndromes and special syndromes.[4,5]

Table I. Antiepileptic drugs and seizure type

Antiepileptic drug	Seizure type	Comments
Carbamazepine	Partial ± secondarily GTC	May worsen absence or myoclonic seizures
Ethosuximide	Absence > myoclonic, atonic seizures	May worsen GTC seizures
Phenobarbital	Partial ± secondarily GTC	
Phenytoin	Partial ± secondarily GTC	May worsen absence or myoclonic seizures
Primidone	Partial ± secondarily GTC	
Valproic acid	Broad spectrum	Effective in LGS
Felbamate	Broad spectrum	Effective in LGS
Gabapentin	Partial ± secondarily GTC	May worsen absence or myoclonic seizures
Lamotrigine	Broad spectrum	Effective in LGS
Levetiracetam	Broad spectrum	
Oxcarbazepine	Partial ± secondarily GTC	
Tiagabine	Partial ± secondarily GTC	May worsen absence or myoclonic seizures. May cause absence stupor
Topiramate	Broad spectrum	Effective in LGS
Vigabatrin	Partial ± secondarily GTC	Effective in the treatment of infantile spasms. May worsen absence or myoclonic seizures
Zonisamide	Broad spectrum	
Pregabalin	Partial ± secondarily GTC	

GTC = generalized tonic clonic; **LGS** = Lennox-Gastaut syndrome.

epilepsy, 35% with symptomatic partial epilepsy and 45% with cryptogenic partial epilepsy. Analysis of further defined subgroups showed that of the patients with localization-related epilepsy, those with temporal lobe epilepsy (TLE) were more likely to be refractory to treatment than those with extratemporal lobe epilepsy (ETLE), with 20% of the TLE group becoming seizure-free, compared with 36% in the ETLE group. Within the TLE group, those with hippocampal sclerosis (HS) were significantly less likely than those without to obtain seizure freedom (10% vs 31%). Of the patients with partial epilepsy in this study with known structural lesions, the degree of seizure control varied with the type of lesion. Rate of seizure freedom was lowest in those with HS (10%) or cortical dysgenesis (24%). In contrast, the relatively highest degree of seizure freedom was seen in patients with stroke (54%), vascular malformation (50%) or tumour (46%).[8]

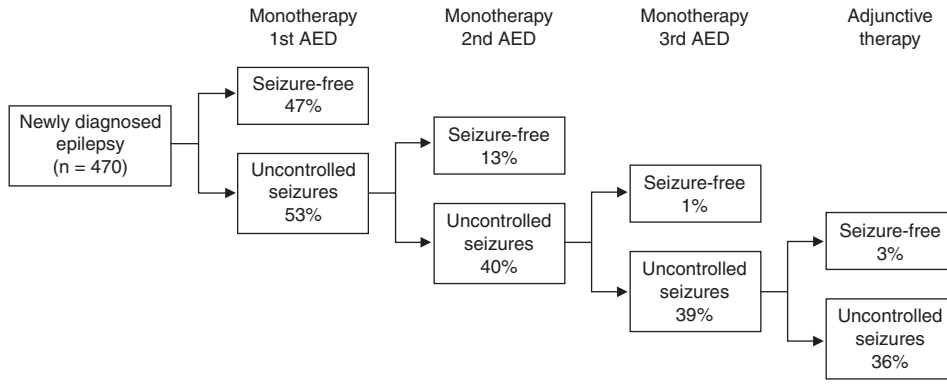

Fig. 4. Efficacy of antiepileptic drugs (AEDs). Results from a large, observational study prospectively following patients with newly diagnosed epilepsy.[7]

3. Other Treatment Modalities

When seizures continue despite trials with multiple agents in monotherapy, combination therapy may be tried. However, as discussed in section 2, the odds of seizure control with combination therapy after failure with two to three agents in monotherapy are very low. Patients who continue to have seizures despite treatment with multiple AEDs (those with medically intractable epilepsy or pharmacoresistence) may require surgical intervention for improved seizure control, provided they are appropriate surgical candidates. The determination of which patients are appropriate surgical candidates is a complex, multifactorial problem and is not discussed further here.

In considering this progression from monotherapy to polytherapy, to surgery, the concept of pseudoresistance must be kept in mind. This refers to poor seizure control as a result of inappropriate drug selection or dose administration, misdiagnosis or poor compliance.[9] This is in contrast to continued seizures despite optimized therapy with a specific agent. The difference between these two scenarios is often not discernable without a detailed history, but is of utmost importance in clinical decision making because a drug cannot be considered ineffective unless its use has been optimized. In other words, if a patient is assumed to be resistant to a specific medication when they are indeed experiencing pseudoresistance, they may be unnecessarily switched to different agents or even undergo avoidable epilepsy surgery along with its inherent risks.

4. Goals of Treatment

In treating epilepsy, the goal is seizure freedom while minimizing adverse effects of treatment, ''so the person can lead as normal a life as possible''.[2] For each of the aforementioned forms of treatment, the goal is complete seizure control. This is important not only because of the increased morbidity and mortality associated with epilepsy, but also because of the potential for this condition to progressively worsen with continued seizures. Patients with epilepsy have a mortality rate approximately twice as high as that of the general population due to accidental and non-accidental causes.[9] Sudden unexpected death in patients with epilepsy (SUDEP) accounts for the largest seizure-related proportion of this increase and occurs in the setting of GTC seizures. Rates of SUDEP vary greatly with degree of seizure control, with an incidence of approximately 1 per 2500 in those with well controlled epilepsy, compared with about 1–2 per 100 in those with severe intractable epilepsy.[1]

Unfortunately, despite optimization of all potential forms of therapy, complete seizure control is not always obtainable, and maximal reductions of seizure frequency and severity in the absence of toxicity become the objectives.

Before addressing the choice of a specific AED in treating newly diagnosed epilepsy, some general principles of AEDs are discussed.

5. Additional Principles Applied in the Selection of Antiepileptic Drugs

Once the clinician has identified the type of epileptic seizure and syndrome at hand, selection of the appropriate AED must factor in the following other variables: (i) pharmacokinetic properties and pharmacodynamic interactions with concomitant medications or intrinsic molecules such as hormones; (ii) tolerability and safety of the AED; and (iii) specific needs of special patient populations, including paediatric and geriatric patients as well as women of childbearing age.

5.1 Pharmacokinetic Properties

In choosing a specific AED, drug absorption, distribution, metabolism and elimination must be considered. The combined effect of these factors is reflected in the serum concentrations of the drug. The ideal AED is one with the following pharmacokinetic properties: availability of multiple formulations, linear absorption, minimal or no protein binding (specifically albumin binding), and linear kinetics metabolism. Quantitative

Table II. Pharmacokinetic properties of antiepileptic drugs: absorption and distribution[1,6,9][a]

Antiepileptic drug	Absorption	Oral bioavailability (%)	Protein binding (%)	Vd (L/kg)[b]	Therapeutic drug concentration (μg/mL)	Comments
Carbamazepine	Linear	70–79	75	0.8–2	4–12	Subject to autoinduction
Ethosuximide	Linear	>90	<10	0.62–0.72		
Phenobarbital	Linear	80–100	45–60	*0.5–0.75*[c] *0.8–1*[d]	10–40	
Phenytoin	Non-linear	70–100	85–95	*0.6–0.8*[c] *1–1.5*[d]	10–20	Changes in dose do not yield proportional changes in serum concentrations It is necessary to know the serum albumin concentration to interpret phenytoin level
Primidone	Linear	90–100	20–30	0.4–1	5–12	
Valproic acid	Linear	90	85–95	*0.15–2*[c] *0.2–0.4*[d]	50–100	It is necessary to know the serum albumin concentration to interpret valproic acid level Free fraction increases exponentially above serum levels >70 μg/mL
Felbamate	Linear		22–25	0.7–1		
Gabapentin	Non-linear	60 maximum	<3			
Lamotrigine	Linear	98	55	0.9–1.3	4–18	Questionably subject to autoinduction
Levetiracetam	Linear	Nearly 100	<10	*0.7*		
Oxcarbazepine	Linear		40–60			
Tiagabine	Linear	90	96			
Topiramate	Linear	80	10–40	0.6–0.8		
Vigabatrin	Linear	50	0	0.8		
Zonisamide	Linear	>90	40–60	0.8–1.6	20–30	
Pregabalin	Non-linear	>90	0	0.5		

a All values are based on use as monotherapy.

b Parenteral Vd in italics.

c Adults and children.

d Neonates and infants.

Vd = volume of distribution.

pharmacokinetic measures of the AEDs are listed in tables II and III.

5.1.1 Absorption

Among AEDs, an agent with linear absorption is preferable because of the predictability of its bioavailability (defined as the proportion of the amount of drug absorbed relative to the total dose). Nearly all of the oral formulations of AEDs in use today are passively absorbed from the gastrointestinal lumen to the serum in a nearly linear fashion. Exceptions include gabapentin, pregabalin and perhaps phenytoin, which utilize an active transport mechanism.[1] With an active transport, absorption is linear at low and moderate doses, but becomes nonlinear when the system is saturated. For example, at high doses of gabapentin (>1800 mg/day), serum concentration will plateau because little additional drug will be absorbed once the L-amino acid transporter becomes saturated.[10,11] Absorption is also affected by the degree of lipid solubility of a drug, with more lipid-soluble compounds showing increased absorption.

As shown in table IV, various AEDs are available in different formulations including parenteral solutions, oral syrups, elixirs and suspensions, immediate- (IR), delayed- (DR) and extended-release (ER) formulations, sprinkle capsules and chewable tablets.

Parenteral administration is needed in emergency situations including status epilepticus, as well as in cases where frequent seizures necessitate rapid treatment. Seven AEDs are available for intravenous administration, three of which are of the benzodiazepine family. Among these parenteral formulations, only fosphenytoin and diazepam are favoured for intramuscular administration. On the other hand, intramuscular administration of phenytoin is contraindicated as it causes fatty tissue necrosis. Phenobarbital and the benzodiazepines other than diazepam have a more erratic absorption. In general, intramuscular use is limited by relatively slow absorption and should be considered only in emergency situations in which there is no venous access.[12]

The advantage of AEDs available in solution is the ability to administer them via nasogastric, gastric or rectal tubes to patients who are unable to reliably swallow. Examples of patients in whom this may be helpful include infants, people who refuse to take their medication by the oral route and those with gastrointestinal disturbance. Solutions also have the advantage of more rapid absorption than capsules or tablets, and for some drugs, may be administered rectally in emergency situations. Similarly, sprinkles and chewable formulations may aid in successful administration of AEDs in certain clinical situations, such as in patients with swallowing problems who cannot reliably take capsules or tablets.

The other oral formulations available include IR, DR and ER. The IR formulations are characterized by rapid dissolution of the tablet/capsule in the upper gastrointestinal tract followed by rapid absorption of the drug. A DR formulation is one in which the tablet remains intact in the gastrointestinal tract for several

Table III. Pharmacokinetic properties of antiepileptic drugs: metabolism and elimination[1,6,9][a]

Antiepileptic drug	Metabolism	Active metabolites	Renal excretion (%)	Eliminated unchanged (%)	Elimination half-life (h)	Predominantly enzyme inducer, inhibitor or neither
Carbamazepine	Hepatic	Carbamazepine-10,11-epoxide 9 hyroxymethyl-10-carbamoyl acridan	72	3	10–20	Inducer
Ethosuximide	Hepatic		10–20		30–60	Neither
Phenobarbital	Hepatic		20	20	50–120	Inducer
Phenytoin	Hepatic		2		7–60	Inducer
Primidone	Hepatic	Phenylethyl-malonamide Phenobarbital	75	65	3–12	Inducer
Valproic acid	Hepatic		70–80	<3	6–20	Inhibitor
Felbamate	Hepatic		90	40–50	14–23	Inhibitor
Gabapentin	None		100 (of that absorbed)	100	5–7	Neither
Lamotrigine	Hepatic		94	10	10–35	Neither
Levetiracetam	Nonhepatic		90	66	6–8	Neither
Oxcarbazepine	Hepatic	10-monohydroxy-carbazepine	95	<1	1–2.5 (8–15 for metabolite)	Dose dependent (see section 5.1.3)
Tiagabine	Hepatic		25	2	5–9	Neither
Topiramate	Hepatic		60–100	60–100	18–25	Dose dependent (see section 5.1.3)
Vigabatrin	None		60–80	60–80	4–7	Neither
Zonisamide	Hepatic		62	35	50–70	Neither
Pregabalin	None		90–99	90–99	5–6.5	Neither

a All values are based on use as monotherapy.

Table IV. Antiepileptic drug formulations

Antiepileptic drug	Tablet	Capsule	Extended-release tablet and/or capsule	Delayed-release tablet	Chewable tablet	Sprinkle capsule	Suspension, syrup or elixir	Parenteral solution
Carbamazepine	•		•		•		•	
Ethosuximide		•					•	
Phenobarbital	•	•					•	•
Phenytoin		•	•		•		•	•
Primidone	•						•	
Valproic acid		•	•	•		•	•	•
Felbamate	•						•	
Gabapentin	•	•					•	
Lamotrigine	•				•			
Levetiracetam	•		•				•	•
Oxcarbazepine	•						•	
Tiagabine	•							
Topiramate	•					•		
Vigabatrin	•							
Zonisamide		•						
Pregabalin		•						

hours, after which upon exposure to a predetermined pH it dissolves, releasing the drug, which is then rapidly absorbed. An ER formulation is one in which the capsule or tablet has a drug delivery system spanning a specific period, typically in the order of 12–24 hours. This leads to more steady drug delivery and hence concentration over time.

Every AED that has an IR formulation is subject to transient adverse events within 1–3 hours of its administration, particularly when the serum concentrations are already high. This is known as a peak of dose effect, which is likely to result in poor compliance. The advantage of DR over IR formulations is less irritation of the gastrointestinal mucosa and fewer gastrointestinal adverse events. Nonetheless, peak of dose effects can occur even with DR formulations once the drug is released to the intestinal lumen and rapidly absorbed.

The advantages of ER formulations include avoidance of peak of dose effect, the ability to administer the drug on a daily or twice-daily schedule, and simplification in interpretation of serum concentrations because of stable concentrations over a 24-hour period. The decreased fluctuations in peak and trough blood concentrations result in better tolerability of the drug.

In theory, while generic and brand formulations should have nearly identical bioavailability, this is not always the case. Thus, switching from brand to generic or among generic formulations can lead to undesirable consequences for patients including toxicity and breakthrough seizures. While this problem can occur with any of the AEDs, it is most pronounced with phenytoin because it is characterized by zero-order kinetics. In this setting, small dose-to-dose fluctuations, as are commonly encountered with generic formulations, can cause large and unpredictable changes in serum concentration, which, in turn, can lead to toxicity and/or breakthrough seizures.[1,6,9]

5.1.2 Distribution

Once a drug is absorbed, it is selectively distributed to different tissue compartments based primarily on lipid solubility and protein binding. In general, the more lipid soluble the drug, the

greater the tissue penetration. The blood-brain barrier is characterized by tight intercellular junctions and it dictates which drugs are able to reach the CNS and to what degree. In addition to this passive distribution across lipid membranes, there is some evidence that specific active transporters are involved in certain AEDs reaching the CNS.[1]

AEDs circulate in the blood either partially bound to proteins, including albumin and glycoproteins, or as free drug. The free fraction of a drug in plasma is distributed, and this is the portion that crosses the blood-brain barrier and is bioactive. Binding to albumin but not to glycoproteins can be of clinical significance.

Among AEDs, there is a broad range in degree of albumin binding as shown in table II. This is important because drugs that are highly albumin bound are characterized by a significant difference between free and total plasma concentrations. This occurs because these proteins have a limited number of receptors that can act as carriers for the drug in circulation. Under normal conditions, saturation of drug receptors in albumin occurs at serum concentrations above 60–70 mg/L. However, any condition resulting in decreased serum albumin, such as renal and hepatic disease or protracted malnutrition, will limit the available albumin receptors to which the AED is bound, leading to higher free fraction of the drug and, accordingly, higher concentrations crossing to the CNS.

Clinically, this comes into play for the highly protein-bound AEDs in a number of ways. First of all, in this setting initial dosage based on weight alone is likely to lead to acute toxicity. Also, if multiple highly protein-bound drugs are coadministered, there will be competition for protein binding, and active, free fractions of each of the drugs will be unpredictable, leading to complicated re-dosing decisions as well as difficulty in interpretation of serum concentrations.

The degree of distribution of a drug into tissue is quantified by a constant, the apparent volume of distribution (Vd), with higher values of Vd corresponding to a higher concentration of drug in tissue. The units of Vd are litres per kilogram and the serum concentration of a drug can be grossly approximated as dose (mg/kg)/Vd.[1]

5.1.3 Elimination

Most AEDs are biotransformed prior to excretion, although a few are cleared unchanged. The majority of AEDs are metabolized by hepatic enzymes, and therefore are subject to drug-drug interactions with other hepatically metabolized agents, antiepileptic and others, primarily through the effects of induction and inhibition.

All of the first-generation AEDs are at least in part hepatically metabolized, followed by renal elimination. Carbamazepine, phenytoin, phenobarbital and primidone are inducers, while valproic acid is an inhibitor of specific isoenzymes within the hepatic cytochrome P450 (CYP) enzyme system as well as the glucuronidation process. Their coadministration may affect the concentrations of other AEDs, other medications and/or hormones. In contrast with first-generation AEDs, two of the second-generation AEDs, topiramate and oxcarbazepine, have inducing properties at high doses, but modest inhibiting properties at lower doses. Table III outlines the characteristic effects on these enzymes of the various AEDs.

Historically, it is the first-generation AEDs with enzyme-inducing properties that are referred to as 'enzyme-inducers'. As a group, there are many factors relating to these drugs that may have significant and, at times, untoward clinical impact, including interaction with antiepileptic and other medications, effects on intrinsic and administered hormone-containing compounds, and detrimental effects on bone health.

Enzyme inducers increase clearance and subsequently lower the concentration of medications metabolized in the liver, with potentially serious and unexpected clinical outcomes.[6] Compounds that may be affected include other AEDs and other hepatically metabolized medications, and in some cases an AED may induce its own metabolism through autoinduction. The list of medications that may interact with the enzyme-inducing AEDs is extensive, including, but not limited to, many antipsychotic drugs, antidepressants, antimicrobials, calcium channel antagonists, theophylline, ciclosporin and warfarin. Therefore, it is important to check for

the potential for interaction whenever starting treatment with one of these agents in a patient on any other medication(s).[1]

The enzyme inducers also have effects on intrinsic hormones and hormone-containing compounds. Their coadministration may lead to decreased serum concentration and effectiveness of estrogen-containing contraceptives. In addition, they have the potential to alter levels of androgens and their metabolites. This decrease in androgen levels has been associated with sexual dysfunction in men taking these medications.[13] These drugs, and possibly valproic acid, which is an enzyme inhibitor, are also associated with the potential for decreased bone density due to increased clearance of vitamin D.[1,6] Therefore, patients taking these medications should be advised to take supplemental calcium and vitamin D, and undergo periodic bone density screening.

Most AEDs and their metabolites are excreted by the kidneys. Those that are excreted without hepatic metabolism, as listed in table III, may require decreased dosage in the setting of severe renal dysfunction to avoid accumulation of the drug and associated toxicity.

Most AEDs follow linear, first-order kinetics, and therefore changes in dosage lead to proportional changes in serum concentrations of the drug. In these cases, routine monitoring of serum concentrations is not necessary.

However, in the case of phenytoin, which is metabolized by zero-order kinetics, changes in dose do not necessarily result in proportional changes in serum concentration. This leads to a degree of unpredictability within the range of commonly used dosages. In fact, with phenytoin, at times small increases in dose can lead to toxicity, and smaller decreases in dose can result in breakthrough seizures. In these instances, it is important to closely monitor serum concentrations during changes in dosage or with coadministration of drugs with the potential for interaction.

5.1.4 Serum Concentrations

While seizure control is related to serum concentration for many of the AEDs, interpretation of serum concentrations and therapeutic ranges must be tailored to the individual. Therapeutic ranges are based on populations rather than individuals, and it is not uncommon for a patient to achieve adequate seizure control at a 'subtherapeutic' concentration or for a patient to tolerate a 'supratherapeutic' concentration without experiencing adverse effects. Conversely, for a given patient, adverse reactions may occur at low serum concentration or breakthrough seizures may continue despite 'supratherapeutic' concentrations.

Other factors to keep in mind when interpreting serum concentrations include effects of albumin concentration, as well as drug-drug interactions related to competition for protein-binding sites as discussed in section 5.1.2.

It is also important to take into account diurnal fluctuations in serum concentrations of drugs with short elimination half-lives. To clarify, since the serum concentration for these agents varies throughout the day, comparisons between concentrations should always be based on samples from the same time of day. The serum concentration associated with maximum drug concentration or systemic exposure during a dose administration cycle is referred to as the peak value and that of the minimum or lowest concentration as the trough value. When adjusting dose administration to increase seizure control based on serum concentrations, it is best to use trough values because these represent the lowest serum concentration attained during the course of the day. Blood for measurement of trough concentrations are drawn immediately before a scheduled dose.

Because most AEDs are metabolized by linear kinetics, it is sufficient to obtain a baseline serum concentration after steady state is reached. Subsequent changes in concentration can be estimated with dose changes simply by assuming a linear relationship with no need to repeat serum concentration measures. The exception is phenytoin, which is characterized by saturation kinetics, and therefore a non-linear relationship between dose and serum concentration, as described in section 5.1.3. In this case, it is important to monitor serum concentrations with changes in dose or when coadministering drugs with the potential for interaction.

Table V. Equations for determining loading dose[a]

Purpose of equation	Equation	Reference
Initial IV loading dose	IV dose = Vd × desired concentration + maintenance dose for desired concentration	9
IV reloading dose needed for desired change in concentration	IV dose = (desired concentration − measured concentration) × Vd + maintenance dose for desired concentration	9
Correction to phenytoin concentration for low albumin state	Corrected concentration = measured concentration/(0.1 + 0.2 × albumin level)	14
Correction to phenytoin concentration in the setting of significant renal disease	Corrected concentration = measured concentration/(0.1 + 0.1 × albumin level)	15

a Units used in equations are as follows: IV dose (mg/kg), Vd (L/kg), concentration (mg/L).

IV = intravenous; **Vd** = volume of distribution.

Appropriate times to check serum AED concentrations include when initiating therapy, and when starting medications with potential interactions when there is evidence of drug toxicity or compliance is in question. Routine, serial testing is not necessary for AEDs characterized by linear kinetics in the absence of a specific clinical question.

Table V provides equations that may be used to determine dose administration for desired concentrations of AEDs in normal and special circumstances.

5.2 Tolerability and Safety

Every drug has associated adverse reactions, affecting tolerability or safety. Specific reactions associated with AEDs are outlined in table VI.

5.2.1 Tolerability

Not infrequently, tolerability of AEDs is poor, leading to suboptimal compliance. In some instances, a change of AED may be necessary; in others, dose adjustments, change in titration schedule or dose administration frequency, and/or formulation of the drug may be sufficient to avert the need to discontinue the drug. Premature discontinuation should be avoided when adverse events can be expected to be transient to avoid abandoning a potentially useful drug.

As an example of a tolerability issue, all AEDs have the potential for unwanted CNS effects, including cognitive, memory or mood disturbance. The likelihood of such reactions varies among the AEDs and is typically dose-dependent, although they may occur at therapeutic doses. These effects may be subtle, requiring formal neuropsychological testing to detect, and difficult to distinguish from the effects of the disease.[2]

5.2.2 Safety

Safety issues are rare, but may have serious and even life-threatening clinical consequences. These require patient education and vigilance on the part of both the patient and the clinician for early identification and response, with prompt discontinuation of the drug and appropriate treatment as necessary.

5.3 Special Populations

Specific issues arise for patients in special populations regarding epilepsy and its treatment. These populations include women of childbearing age, older individuals, patients with developmental disabilities, and those with comorbidities. Some of these issues are illustrated in the case scenarios in section 7.

6. Limitations of Available Data

As mentioned, the number of available AEDs is growing, and the choice of the initial agent to use in monotherapy is complicated for a number of reasons. In making this decision, a number of sources of data are available as resources, including clinical trials from regulatory agencies, clinical guidelines from professional organizations and individual studies. Each has advantages and limitations, and the information they provide

Table VI. Potential adverse drug reactions (ADRs) of antiepileptic drugs[1,6,9]

Antiepileptic drug	Serious ADRs	Comments	Other ADRs	Comments
Carbamazepine	Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia		Hyponatraemia, leukopenia, hypersensitivity reaction	
Ethosuximide	Stevens-Johnson syndrome, toxic epidermal necrolysis, psychosis		Headache, irritability, depression, anxiety, weight loss	
Phenobarbital	Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia, hepatic failure		Connective tissue disorders, cognitive impairment, somnolence, hypersensitivity reaction	Connective tissue disorders including Dupuytren's contractures and frozen shoulder occur with long-term use at a rate of 5–40%
Phenytoin	Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia, hepatic failure, hypotension, bradycardia and/or tissue irritation with intravenous formulation, pseudo lymphoma and lupus-like reaction		Hirsutism, gingival hyperplasia, peripheral neuropathy, cerebellar degeneration, hypersensitivity reaction	Hirsutism and gingival hyperplasia are associated with long-term use
Primidone	Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia, hepatic failure		Connective tissue disorders, cognitive impairment, somnolence, hypersensitivity reaction	Intense dizziness, nausea and sedation at start-up with primidone may occur due to crossed tolerance with phenobarbital. Initial adverse events can be averted by starting patients on phenobarbital for a 10-day period before introducing primidone
Valproic acid	Pancreatitis, hepatic failure, prolonged bleeding time, thrombocytopenia, other coagulation disorders, polycystic ovaries and polycystic ovary syndrome	Increased risk of hepatic failure in children aged <2 years, those with metabolic disorders, mental retardation and/or patients taking multiple AEDs Effects on coagulation may be clinically significant in those taking medications, which affect coagulation and those undergoing surgery	Hyperammonaemic encephalopathy, tremor, weight gain, alopecia	
Felbamate	Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic failure, aplastic anaemia, leukopenia, thrombocytopenia and agranulocytosis		Nausea, anorexia, insomnia, headache	
Gabapentin	Stevens-Johnson syndrome		Weight gain, peripheral oedema	

Continued next page

Table VI. Contd

Antiepileptic drug	Serious ADRs	Comments	Other ADRs	Comments
Lamotrigine	Stevens-Johnson syndrome, toxic epidermal necrolysis		Hypersensitivity reaction	
Levetiracetam	Psychosis		Agitation, hostility, anxiety	
Oxcarbazepine	Stevens-Johnson syndrome, toxic epidermal necrolysis		Hyponatraemia, leukopenia, hypersensitivity reaction	
Tiagabine	Non-convulsive status epilepticus	Mostly occurs in patients with spike and wave epilepsy	Dizziness, fatigue, anxiety, depression, tremor	
Topiramate	Nephrolithiasis, acute angle closure glaucoma, metabolic acidosis, hypohidrosis	Because of the increased incidence of renal stones, patients should be encouraged to remain well hydrated	Cognitive impairment, irritability, paraesthesias, weight loss	Cognitive impairment including verbal memory deficits may occur in up to 15% of patients and may be worsened if coadministered with valproic acid
Vigabatrin	Visual field defects, psychosis, depression	Visual field defects may occur in up to 30% of cases and may be irreversible. Use requires periodic formal visual field testing	Weight gain, sedation	
Zonisamide	Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, aplastic anaemia, agranulocytosis and other blood dyscrasias, nephrolithiasis, hypohidrosis	Zonisamide is a sulfa drug	Cognitive impairment	
Pregabalin	Angioedema		Weight gain, peripheral oedema, dizziness, somnolence, blurred vision	

should therefore be thought of as complementary.

In the US, the FDA does not regulate physicians' use of medications; however, a survey showed that many general practitioners, including some neurologists, are influenced by FDA labelling when choosing therapy for the treatment of epilepsy. In addition, in some European countries, physicians are further discouraged from off-label use of medications because national insurance may not pay for such treatment. The indications for a given AED by the regulatory agencies are based only on the type of studies carried out by the manufacturer. Thus, many AEDs do not get an indication for paediatric use, ever, or only several years after the drug has been released in the market.

Clinical trial designs for approval of AEDs for a monotherapy indication vary from country to country. In the US, the FDA requires evidence of superiority of the study drug over placebo. This requirement raises ethical dilemmas because it puts the patients at risk of unnecessary seizures. To overcome this problem, the FDA has allowed for the use of 'pseudo-placebos', which consist of a comparator AED at a 'low dose'. On the other hand, the European Medicines Agency (EMEA) requires evidence that the study drug is non-inferior to an optimized dose of an established comparator drug. Thus, it is not surprising that

monotherapy indication is obtained earlier in Europe than in the US. Such has been the case with lamotrigine, oxcarbazepine, topiramate and levetiracetam.[16] In fact, in the US, several manufacturers elect not to seek a monotherapy indication because of the logistical difficulties of the FDA stipulations. Thus, most studies showing safety and efficacy of monotherapy regimens in new onset epilepsy have been conducted outside the US.

Conversion to monotherapy studies have been conducted in patients with refractory epilepsy, many of whom may not even be candidates for epilepsy surgery. However, the data of these studies do not reflect the problems that clinicians have to face in their practice. This is clearly illustrated in the study converting patients with refractory partial epilepsy from polytherapy to lamotrigine monotherapy.[17] From the data of that study, lamotrigine received an indication for monotherapy only if the patient is converted from polytherapy with enzyme-inducing AEDs but not from other types of polytherapy regimen.

To demonstrate superiority of monotherapy over placebo in patients with refractory epilepsy, inpatient studies have been designed to compare 'time-to-exit' in patients randomized to study drug versus placebo in the course of a video-EEG monitoring study in which all concomitant AEDs have been discontinued. This design clearly does not reflect clinical practice. Thus, data from monotherapy studies conducted in this patient population may not be applicable to patients typically seen in the clinic.

In recent years, professional organizations such as the American Academy of Neurology (AAN), the American Epilepsy Society (AES), the Child Neurology Society and the ILAE have recognized the need to develop clinical guidelines with evidence-based data, with a primary objective of providing clinically applicable recommendations. The methodology used by the various organizations may vary. For example, the guidelines generated by the AAN and AES make their recommendations only in the presence of data derived from methodologically sound studies.[18] The AAN guidelines recognize the safety and efficacy of an AED based on noninferiority trials provided the studies were multicentre and carried out under double-blind, randomized conditions. Thus, clinicians can support their decision to prescribe an AED based on the recommendations made by these guidelines, even in the absence of FDA or EMEA indications. These documents are a valuable tool for all clinicians, as they fill in the gap between the lack of regulatory agency indications and the needs encountered in daily clinical practice.

In general, the guidelines published by the various professional societies agree that the second-generation AEDs are better tolerated and provide equal efficacy when compared with standard agents. They point out that, as a class, the second-generation agents have simpler pharmacokinetics, less interaction with concomitant drugs and endogenous compounds (e.g. hormones, vitamins), are safer and require less laboratory monitoring. Although they acknowledge that these second-generation AEDs are more expensive than standard agents, they point out that the lack of formal cost-benefit analyses clouds true cost comparisons. Taking this into account, they recommend considering first-generation, as well as second-generation AEDs when starting monotherapy in newly diagnosed epilepsy, with the specific agent chosen based on the characteristics of the individual being treated.[18]

In England and Wales, the National Institute for Health and Clinical Excellence (NICE) interprets available study evidence as support that there is no significant difference in efficacy between second-generation and first-generation AEDs, that there are insufficient data to evaluate differences in quality of life associated with them, and that first-generation agents are considerably less expensive than second-generation medications. Therefore, in contrast with AAN recommendations, NICE suggest starting monotherapy for newly diagnosed epilepsy with one of the first generation AEDs unless they have been shown to be ineffective for the patient, the patient cannot tolerate them, they interact with other medications the patient is receiving, or the patient is a woman of childbearing potential, in which case they suggest initiating treatment with one of the second-generation AEDs.[2]

More recently, results of the multicentre Standard and New Antiepileptic Drugs Trial (SANAD) were published. This study attempted to bridge the gap between regulatory trials and clinical guidelines, and provide both methodologically sound and clinically applicable data comparing newer and older AEDs. It was composed of two arms, with arm A designed to evaluate the treatment of partial epilepsy and arm B generalized and unclassifiable epilepsies.[19,20] Two major criticisms of this study are that it was non-blind and the method that was chosen for assignment as partial, generalized or unclassifiable epilepsy. This classification was made by the practitioner based on whether they felt that carbamazepine or valproic acid was more appropriate for initial management. If carbamazepine was chosen, the patient was enrolled in arm A of the study, and if valproic acid was selected, they were assigned to arm B. Clearly, this represents an imprecise method for determination of epilepsy type and these studies may more accurately reflect a comparison of carbamazepine with a subgroup of the newer AEDs, and valproic acid with a different subgroup for mixed populations of patients with epilepsy rather than the desired evaluations of populations of patients with well defined partial and generalized or unclassifiable epilepsies. While these studies do have technical shortcomings as pointed out in several commentaries,[21-26] they do nonetheless represent large studies of significant duration providing an earnest attempt to address the inadequacies of prior studies that has plagued the literature over the past few decades.

The SANAD study of the treatment of partial epilepsy assessed the effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine and topiramate through a non-blind randomized controlled trial design, with neither patients nor clinicians masked to treatment.[19] It involved 1721 randomized subjects with up to 6 years of follow-up. In this study carbamazepine was chosen as the standard older drug and compared with the other, newer agents. Because oxcarbazepine was added to the study later than the other medications, conclusions on its use are more limited. Two primary outcomes were assessed, time to treatment failure, which combines in one measure both seizure control and tolerability, and time to 12-month remission.

Regarding time to treatment failure, lamotrigine was found to be significantly better than the other AEDs studied, with carbamazepine and oxcarbazepine next best, and gabapentin and topiramate performing poorest. Further analysis showed that carbamazepine and topiramate were most frequently associated with treatment failure due to adverse events, while gabapentin was most often associated with failure due to inadequate seizure control. Importantly, the difference between lamotrigine and carbamazepine appeared to be a higher incidence of treatment failure due to adverse effects with carbamazepine, while the two drugs performed similarly in terms of rate of failure due to inadequate seizure control. With respect to time to 12-month remission, carbamazepine was favoured compared with all other drugs studied, with gabapentin performing the poorest. In this study, adverse events were reported by patients and classified as clinically significant or not by clinicians. While the differences in adverse event rates were small between the AEDs, qualitative adverse effect profiles emerged for individual drugs. For example, gabapentin was associated with dizziness, ataxia and weight gain, while patients taking topiramate more frequently complained of anxiety, weight loss and paraesthesias.

Arm B of the SANAD study evaluated the treatment of generalized and unclassifiable epilepsies.[20] It assessed the effectiveness of valproic acid, lamotrigine and topiramate through a non-blind randomized controlled trial design, with neither patients nor clinicians masked to treatment. A total of 716 subjects were studied for up to 7 years, utilizing the same primary outcome measures as for arm A. For this study, valproic acid was considered to be the older, standard drug and was compared with the other two, newer drugs.

With regard to time to treatment failure, valproic acid was significantly better than topiramate, with no significant difference between valproic acid and lamotrigine. However, for the subgroup of patients with idiopathic generalized epilepsy, valproic acid outperformed both

topiramate and lamotrigine on this measure. In terms of time to 12-month remission, valproic acid performed better than lamotrigine overall as well as for those with idiopathic generalized epilepsy, with no significant difference between valproic acid and topiramate for either of these groups. The most frequent adverse events associated with treatment failure with topiramate were psychiatric and cognitive complaints, as well as tiredness and fatigue. Rash was the most common with lamotrigine and weight gain with valproic acid.

Overall, the authors felt that their findings suggested that valproic acid is better tolerated than topiramate and more efficacious than lamotrigine for patients with generalized and unclassifiable epilepsy, and should be used as first-line treatment in these populations. They stressed that the relatively increased risks for teratogenicity associated with valproic acid use should be taken into account when treating women of childbearing potential, and that this group of patients must be educated about these relative risks and benefits so they may make an informed choice.

7. Case Scenarios

These general factors relating to AEDs, together with AED-specific characteristics, which are outlined in the tables, must be kept in mind when tailoring monotherapy for the patient with newly diagnosed epilepsy.

In order to illustrate this process of initiating monotherapy, a few fictional case scenarios are presented. When reading these scenarios, the concept of 'tailoring therapy to the individual' cannot be stressed enough, reflecting the multiple variables encompassing (i) individuals with epilepsy, (ii) epilepsy types and (iii) specific AEDs, all of which must be balanced in choosing therapy.

7.1 Case #1

A 23-year-old woman presents to clinic because of new onset of spells over the previous 3 months that have been witnessed by her fiancé. The patient states that she knows when she will have one of these episodes because they are always preceded by a rising sensation in her stomach, after which she loses awareness. Her fiancé has seen three of these events and reports that they are stereotypical. He describes that during these events the patient is unable to speak or follow commands, and that she smacks her lips and has abnormal movements of her right hand. After these spells, the patient reports feeling confused and fatigued. The most recent event occurred after an evening of poor sleep and progressed to GTC activity associated with loss of bladder control, for which paramedics were called and the patient was taken to her local emergency department (ED), treated with intravenous lorazepam, and instructed to follow up in the neurology clinic the following morning.

The patient has a medical history of febrile seizures as an infant, with no other significant medical history, and is on no medications. She plans on marrying within the next few months, and starting a family in the near future. An MRI scan of the brain shows findings consistent with left mesial temporal sclerosis. A routine EEG shows occasional sharp waves over the left anterior temporal region, superimposed on intermittent, left temporal focal slowing. The patient is diagnosed with left temporal, localization-related epilepsy secondary to presumed mesial temporal sclerosis, and experiences complex partial seizures with and without secondary generalization.

The choice of initial agent for seizure control in this patient is, in large part, dictated by the epileptic syndrome and the fact that she is a woman of childbearing age. Most AEDs have been found to yield a therapeutic effect in this type of epilepsy, so the choice must be based on the AED with the least teratogenic effects. Women with epilepsy taking AEDs have twice the risk of giving birth to a baby with major malformation compared with the risk of a healthy woman on no medication (2–4%).[27] While the specific prevalence rates vary from study to study, a consistent trend has been seen across several observational and epidemiological studies, including those based on data from several pregnancy registries regarding the risk for major congenital malformations (MCMs) associated

with AEDs. Specifically, there is an increased risk for MCMs for women taking AEDs during pregnancy compared with healthy women not taking AEDs. Also, when compared with women taking all other AEDs, those taking valproic acid during pregnancy have a significantly higher and dose-dependent risk to deliver a baby with an MCM including neural tube defects (NTDs), or to experience neurocognitive impairment.[28-31] For example, one study reports a prevalence rate for MCMs of 10.7% in women taking valproic acid, compared to 2.9% in those taking any other AED, and 1.6% in healthy women not using AEDs.[30] A smaller number of studies have shown a similar trend of increased risks with phenobarbital when compared with the other AEDs, but to a lesser degree than reported with valproic acid. Finally, while women taking carbamazepine during pregnancy have a similar risk for MCMs as those taking AEDs as a group, carbamazepine use in pregnancy has been associated with an increased relative risk for NTDs.[29] While not consistently replicated, there is preliminary data to suggest that the risk of MCMs with lamotrigine use may be lower than that associated with other commonly used AEDs.[31] While preliminary data suggests that the overall risk of MCMs with lamotrigine is equal to or lower to the other AEDs as a group, there is evidence suggesting an increased relative risk of cleft lip or cleft palate for infants exposed *in utero*.[32]

Therefore, the patient was started on lamotrigine with the dose slowly titrated up. Once on a maintenance dose of 150 mg twice daily, the patient became seizure free. Shortly thereafter her serum lamotrigine concentration was 8 mg/L. However, it should be emphasized that there are very scant data on the safety of all the other second-generation AEDs in pregnancy.

She is also started on supplemental folic acid. There is evidence that in children born to women without epilepsy, supplemental folic acid use decreases the risk of NTDs.[33] In addition, many AEDs have antifolate properties. Therefore supplemental folic acid is recommended for women of childbearing potential taking AEDs. It is important to start this prior to conception, since the embryonic structures affected develop early in pregnancy.[34] The recommended dose varies widely depending on the source, from 0.4 mg/day to as much as 5 mg/day. The American College of Obstetrics and Gynecology as well as the Society of Obstetricians and Gynaecologists of Canada provide risk-stratified recommendations on folic acid dose administration. For women with epilepsy taking either valproic acid or carbamazepine, they recommend 4–5 mg/day. Vitamin B12 deficiency should be ruled out before initiating high-dose folic acid to avoid masking such a deficit.[35]

In the time prior to clinical follow-up 6 months later, the patient has married and just found out that she is pregnant. She voices concerns about birth defects related to AED use and asks if she can discontinue lamotrigine because she has remained seizure free. It is explained to the patient that although there is an increased risk of birth defects with AED use, the obstetric risks leading to early miscarriage and harm to the fetus and mother from breakthrough convulsions outweigh the risks associated with AED use. Furthermore, women with epilepsy have a 20% risk of worsening of their seizures during pregnancy, with respect to both frequency and type. Thus, this patient needs to factor in that increased risk in any decision to discontinue AEDs.

During the eighth week of her pregnancy, the patient experiences a habitual, complex partial seizure. Her serum lamotrigine concentration is found to have dropped to 3 mg/L. Her lamotrigine dosage is increased, with serum concentrations returning to the mid-therapeutic range, and she subsequently remains seizure free with monthly monitoring of serum concentrations and dose adjustments throughout the pregnancy to maintain the baseline concentration.

In this case, the initial drop in serum concentrations and associated breakthrough seizure were the result of the well described increase in lamotrigine clearance associated with pregnancy. This effect is related to the increase in estrogen levels, which accelerates the glucuronidation process responsible for much of the metabolism of lamotrigine. Because of this, it is important to have a pre-conception baseline serum lamotrigine

concentration at a dosage that provides optimal seizure control. During pregnancy, monthly or at times biweekly serum concentration assays allow for dose adjustment, using the established baseline for that individual as a target serum concentration. Also, post-partum lamotrigine clearance will normalize, and concentrations may rapidly rise and lead to acute toxicity if dosage is not appropriately decreased again within the first 10 days after birth. Decrement of the dose can be guided with serum concentration measurements.[36] However, as a rule of thumb, it is safe to decrease the dose of lamotrigine by 30% on the day after birth and by 30% decrements every 4 days to a pre-conception baseline dosage.

The patient's epilepsy remains well controlled on lamotrigine monotherapy for 6 months, after which she develops a rash associated with fever, which prompts its discontinuation. Once the rash has cleared completely, she is switched over to carbamazepine given as an ER formulation at a dose of 600 mg/day and she remains seizure free.

Several months later, she decides to begin oral contraceptive pills (OCPs) as a birth control method and she is placed on an OCP containing ethinylestradiol and a synthetic progesterone. It is explained to the patient that carbamazepine has enzyme-inducing properties, and its coadministration with ethinylestradiol-containing OCPs will probably decrease their efficacy as a contraceptive, as the serum ethinylestradiol concentrations would decrease. She is advised to use an OCP with the highest concentration of ethinylestradiol and to use additional forms of contraception, or she is given the option to be switched to an alternative AED that is devoid of enzyme-inducing properties. The patient is started on levetiracetam with gradual dose titration because this drug is not known to interact with OCPs. When she is on a full maintenance dose of levetiracetam of 1000 mg twice daily, she is gradually weaned from carbamazepine and continues to remain seizure free.

7.2 Case #2

A 77-year-old gentleman with a long history of hypertension presents to the ED with a new onset of spells. He describes an aura of a rising sensation in his stomach. His wife, who accompanies him, states that she witnesses staring spells associated with lip smacking, as well as repetitive utterance of the phrase ''what's wrong?''. These events last approximately 30 seconds. She estimates that the patient has had three such spells over the past 6 months, most recently the night before coming to the ED. She has not witnessed GTC seizures.

The patient takes metoprolol, tocopherol (vitamin E), cyanocobalamin (vitamin B12) and a multivitamin, and is on no other medications. He is a retired teacher and lives at home with his wife. She states that their health insurance requires a significant co-payment for medications and requests that the most inexpensive medications be prescribed if he needs to go on medication for the treatment of these spells.

The patient experiences a habitual spell while undergoing an EEG in the ED. The ictal and interictal findings are consistent with right temporal, localization-related epilepsy. Because of concerns about cost and since its efficacy has been widely accepted in localization-related epilepsy, the patient is started on carbamazepine at a dose of 200 mg twice daily and admitted for evaluation of potential aetiologies of his seizures. Imaging results are negative and he is diagnosed with cryptogenic, right temporal, localization-related epilepsy.

On the second day of hospitalization, the patient complains of palpitations and lightheadedness. An ECG reveals atrial fibrillation (AF) with a rapid ventricular rate, and the patient is transferred to a telemetry unit and given intravenous verapamil, which quickly controls his ventricular rate, although he remains in AF. He is started on an oral maintenance dose of verapamil 80 mg three times daily. Later that evening, the patient complains of nausea and double vision. His serum carbamazepine concentration is measured at 13.5 mg/L. Because carbamazepine is mainly metabolized by the CYP3A4 isoenzyme, which is inhibited by verapamil, his carbamazepine dose is not given that night and his maintenance dose is lowered to 100 mg twice daily for the following 5 days. His toxicity symptoms

gradually clear and the serum carbamazepine concentration decreases to 6 mg/L.

Because the patient remains in AF, he is started on anticoagulation therapy, initially bridging with intravenous heparin while starting warfarin until the target international normalized ratio (INR) is reached. In this setting, a higher warfarin dose may be required because the clearance of warfarin will be increased by carbamazepine given that it is metabolized by several isoenzymes of the CYP system including 1A2, 2C*, 2C18, 2C9, 2C19 and 3A4. The patient remains seizure free and is discharged home a few days later, with a dose of carbamazepine 100 mg every morning and 200 mg every evening, which he is to take for 1 week and then increase to a target dose of 200 mg twice daily.

Two weeks later he is readmitted with recurrent episodes of tachycardia of up to 170 beats/min and an ECG continues to show the persistence of AF. The maintenance dose of verapamil is increased to 120 mg three times daily.

The patient remains healthy and his seizures well controlled on this regimen for several months, at which point he experiences symptoms of fever, vomiting and diarrhoea and is unable to take food or medications by mouth. Over the course of 2 days, he begins to experience progressively more frequent habitual seizures and then becomes lethargic. The patient's wife witnesses a GTC seizure and calls paramedics to bring the patient to the ED.

On examination, he is lethargic and nonverbal, moaning spontaneously. He has a low-grade fever, an irregular cardiac rhythm and weighs 60 kg on admission. His sodium level is elevated at 148 mEq/L, albumin level is decreased at 2 g/dL and the serum carbamazepine concentration is low at 3 mg/L. An EEG is conducted because of the patient's decreased level of consciousness and reveals right temporal status epilepticus. The patient is treated with intravenous lorazepam 0.1 mg/kg and loaded with intravenous fosphenytoin at a dose of 20 mg/kg phenytoin equivalents (PE), followed by a maintenance dose of 300 mg/day, and admitted to the medical intensive care unit. Shortly after starting fosphenytoin, the patient's electrographic seizures remit. However, the patient remains lethargic and the total serum phenytoin concentration is 22.0 μg/mL. Because the patient is hypoalbuminaemic, a free serum phenytoin concentration is checked, and measured at 3.75 μg/mL (normal range 1–2 μg/mL). A few doses of fosphenytoin are deferred, free serum concentrations are monitored, and the drug is restarted at a lower dose of 200 mg PE/day (approximately 3 mg PE/kg/day). Free serum phenytoin concentrations gradually decrease to the mid-therapeutic range. The patient's mental status gradually improves and he is converted from fosphenytoin to oral phenytoin. He remains febrile and work-up reveals pneumonia, for which he is started on clarithromycin. Throughout the next few days, free phenytoin concentrations and INR values fluctuate unpredictably, illustrating the aforementioned complication of dose administration of phenytoin particularly in the setting of coadministration with other hepatically metabolized agents.

With this in mind, when the patient is medically stabilized, he is gradually switched over to lamotrigine monotherapy from phenytoin to reduce the chance for these potential complications in the future. Although, as mentioned, carbamazepine is considered the gold standard for efficacy in localization-related epilepsy, there is some evidence suggesting that lamotrigine may be equal in efficacy and better tolerated in older patients with epilepsy.[37] The patient remains seizure free on lamotrigine monotherapy and his INR values remain stable.

7.3 Case #3

An 18-year-old college freshman is brought to the ED by paramedics after his friends witness him experience a GTC seizure. The patient has no significant past medical history and was up late at night drinking with friends when the seizure occurred. He has no recollection of the event. On examination, he is initially disoriented and somnolent, but easily arousable. A CT scan of the head and laboratory tests are within normal limits, except for an elevated serum alcohol concentration. The patient is observed in the ED and

over a few hours becomes more lucid. No further seizure activity is witnessed and he is discharged home with instructions to follow up with a neurologist in clinic the following day, with a diagnosis of provoked seizure versus new-onset epilepsy.

In clinic, the patient denies jerking spells; however, his girlfriend, who accompanied him, states that she frequently notices that he has jerking spells as he is falling asleep. She also notices that objects such as his toothbrush or eating utensils frequently appear to spontaneously fly out of his hand. An MRI of the brain with thin cuts through the temporal lobes is normal, and EEG reveals frequent, interictal, generalized, high voltage, 4–5 Hz, polyspike and slow wave discharges.

The patient is diagnosed with juvenile myoclonic epilepsy (JME). He is instructed to start zonisamide 100 mg once daily and to titrate up by 100 mg every week, until a maintenance dose of 300 mg once daily is reached. As shown in figure 2, JME is a form of primary generalized epilepsy, and therefore a broad-spectrum agent is appropriate (see table I). Indeed, as also shown in table I, some of the AEDs that are effective in treating partial seizures may actually worsen myoclonic seizures and should be avoided in the treatment of JME. It is reasonable to start with a second-generation AED because as a class these have fewer adverse drug reactions and simpler pharmacokinectics. He is also counselled on the importance of avoiding sleep deprivation and alcohol use because these are likely to provoke seizures. Finally, he is instructed about local state law, which mandates that he not drive for a minimum of 6 months of seizure freedom.

A month later, the patient is again brought to the ED for witnessed GTC seizure activity. The event occurred while the patient was attending a fraternity party. His serum alcohol concentration is again found to be elevated. He is discharged home and instructed to follow up with his neurologist.

Two weeks later, the patient is brought to the same ED by paramedics after being involved in a motor vehicle accident in which the vehicle he was driving rear-ended another vehicle. On the scene, and in the ED, he is found to be disoriented. Blood is drawn for serum zonisamide concentration measurement. The patient gradually recovers and is discharged home. The incident is reported to the state and he loses his driving privileges for driving against medical advice. The patient is seen in clinic a few days later. His serum zonisamide concentration from the ED was zero. The patient states that he was not taking zonisamide as instructed because he did not think he would have another seizure. The patient is counselled on the importance of AED compliance, as well as the risks associated with GTC seizures including SUDEP. He is once again instructed to refrain from alcohol use and sleep deprivation.

The patient relates that after his accident he began to realize the importance of following medical advice, and since that time he has abstained from alcohol use and become compliant in taking zonisamide as instructed. He subsequently remains seizure free on zonisamide monotherapy.

8. Conclusion

When choosing initial monotherapy for newly diagnosed epilepsy, it is clear that multiple factors need to be taken into account and that therapy needs to be tailored to the individual patient with epilepsy. The most important factors include characteristics of the AED and the type of seizure disorder, co-morbid medical, neurological and/or psychiatric disorders and concomitant medications.

Table VII. Additional non-epilepsy indications for antiepileptic drugs

Antiepileptic drug	Additional uses
Carbamazepine	Mood disorders Neuralgia
Valproic acid	Mood disorders Migraine headaches
Gabapentin	Peripheral neuropathy Neuralgia
Lamotrigine	Mood disorders[38]
Topiramate	Migraine headaches
Pregabalin	Peripheral neuropathy Neuralgia Fibromyalgia

Table VII lists additional non-epilepsy indications for AEDs that are important to take in to account when treating patients with epilepsy and co-morbidities. In some countries, the healthcare system mandates the use of first-generation AEDs before a second-generation drug can be prescribed because of cost considerations. Conversely, if price of the medication is not a significant concern, in most cases a second-generation agent may be appropriate because of improved tolerability. As more studies with AEDs are completed, including quality-of-life outcome measures and comprehensive cost analyses taking into account costs of treating breakthrough seizures due to noncompliance with treatment and costs of treatment of adverse events, this relationship between cost and second-generation versus first-generation agent may become less of a factor.

In terms of the AED, pharmacokinetics play an important role in the initial choice of treatment. If the patient is receiving other medications, drug-drug interactions need to be considered, and if compliance problems are likely, daily scheduling concerns need to be weighed in the decision. Available formulations may also play a role in choosing specific therapy in selected cases as described in section 5.1.1 because not all agents are offered in multiple forms.

Finally, and perhaps most importantly, characteristics of the individual being treated play a large role in the initial choice of treatment. Comorbid medical conditions, inclusion in one of the special populations listed in section 5.3 and type of epilepsy all need to be considered and balanced in choosing initial therapy.

By taking all of these factors into consideration, a rational choice of initial monotherapy can be made for cases of newly diagnosed epilepsy. This selection must be tailored to the individual being treated with the understanding that close, longitudinal clinical follow-up, with evolution of treatment over time, is necessary in most cases. This relationship between the patient with epilepsy and the physician allows for optimization of therapy by balancing efficacy and tolerability, by either adjusting dosage or scheduling of the agent, or changing to an alternative agent.

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