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Treatment of epilepsy in adults

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ABSTRACT – Epilepsy is a chronic neurological disorder in adults and requires treatment with antiepileptic medication. While the majority of patients with epilepsy can be treated with medication, about one third will fail on medical treatment. Therefore, other treatment options such as surgery, devices, and the ketogenic diet are other options to consider, in addition to medical treatment. The treatment of epilepsy requires many other factors to be taken into consideration, and these include, but are not limited to, age, gender, coexistent medical conditions, and the use of concomitant medications. The goal of treatment is to provide optimal seizure control while using the least possible number of medications, particularly for young females at reproductive age or the elderly who may suffer from other medical diseases and receive other concomitant medications. Certain conditions may co-exist with epilepsy, such as migraine, mood disorder, and memory disturbances, therefore the decision to choose the most appropriate medication for epilepsy patients should also involve treatment of these conditions. Here, we review current clinical practice in epilepsy and focus on the most common problems and conditions that clinicians face on a daily basis to treat adult patients with epilepsy. Side effect profiles, spectrum of efficacy and optimal choices per predominant type of seizures are summarized and can be used for educational purposes.

Key words: epilepsy, treatment, adult, elderly, efficacy spectrum, protein binding, side effects

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Epilepsy is one of the most common chronic neurological conditions worldwide. The prevalence of epilepsy in the United States has been reported at 6 to 8 per 1,000 people, with an incidence of 26 to 40 per 100,000 person-years (Hauser *et al*., 1993).

About 10% of people will have at least one seizure in their lifetime, and about a third of them will go on to develop epilepsy (Hesdorffer *et al*., 2011). The incidence of epilepsy has a bimodal distribution, with the highest risk during infancy and old age. About two thirds of the epilepsies are localization-related or focal and a third are generalized (Sillanpää and Shinnar, 2010).

When to treat

The diagnosis of epilepsy is clinical and based on history-taking, from the patient and ideally from a witness. EEG, neurological examination, and brain imaging studies are supportive for diagnosing patients with epilepsy (PWE). Epilepsy is defined as an enduring predisposition of the brain to seizures (Fisher *et al*., 2005).

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Epilepsy diagnosis is typically made only after the occurrence of at least two unprovoked seizures. Concepts around this are changing, however. Recently, there has been consideration of diagnosing epilepsy after a single seizure if the risk of recurrence is sufficiently high. For example, if the epilepsy is remote symptomatic, due to a previous brain insult, or associated with a focal abnormality on EEG, it is considered to have a moderate to high risk of recurrence (Hauser *et al*., 1982; Hauser *et al*., 1990; Berg and Shinnar, 1991). The incidence of recurrence after a single unprovoked seizure is about 35% over the subsequent five years, in the absence of an abnormal EEG or MRI, or a remote symptomatic cause of epilepsy. The recurrence rate increases to 70% after the occurrence of a second unprovoked seizure (Shorvon, 2005).

Before deciding on antiepileptic drug (AED) therapy for newly diagnosed epilepsy, it is important to distinguish between epilepsy and provoked seizures. Long-term treatment with AEDs is not indicated in the setting of provoked seizures. Typical examples are provoked seizures secondary to alcohol withdrawal or hypoglycaemia.

AED treatment is indicated after two unprovoked seizures or a single unprovoked seizure if there is an increased risk of a second unprovoked seizure. The main risk factors include abnormal EEG (epileptiform discharges), abnormal neurological examination, or evidence of a structural CNS abnormality presumed to be the underlying cause of the seizure (Hauser *et al*., 1998; Brodie *et al*., 2012).

Two large open-label, randomized controlled trials showed that treatment of epilepsy with AEDs can be effective in preventing recurrence after a single unprovoked seizure (First Seizure Trial Group, 1993; Marson *et al*., 2005).

In the First Seizure Trial Group (FIRST) and Multicenter Study of Early Epilepsy and Single Seizures (MESS) study, patients were randomly assigned to immediate treatment or deferred treatment. In the FIRST study group of patients randomized to immediate treatment, 24% had a recurrence within the first two years, compared with 42% of patients who were untreated until recurrence. In the MESS study, the rate of seizure recurrence in the immediate group versus the delayed treatment group was 32% versus 39%. However, there is no evidence that treatment altered the long-term course in both groups in terms of seizure remission and recurrence (Hauser *et al*., 1998; Brodie *et al*., 2012).

Treating epilepsy: a long-term approach

Although AEDs are the initial step for treating PWE, treatment of epilepsy can be complex. In addition to AEDs, hormonal therapies, diet, surgery (resective or functional), neurostimulation, and behavioural modification techniques can be utilized to optimize seizure control.

Not infrequently, epilepsy management evolves over a lifespan. Clinicians should remember that treatment of PWE is a dynamic process due to possible changes in the patient's medical, social, and occupational conditions. It does not only relate to medical treatment, but also to surgical treatment. PWE refusing surgical treatment as an option may reconsider it in the future. Management of PWE not only requires seizure control but also treatment of coexistent medical conditions, in addition to attention disorder, sleep disorder, chronic psychiatric diseases, and intellectual impairment. A multidisciplinary team approach is often needed for treatment of PWE. This team should ideally include a neurologist, neuropsychologist, and psychiatrist to control seizures and underlying frequent psychiatric or neurodevelopmental comorbidities.

About two thirds of patients with new-onset epilepsy may become seizure-free with the first or second AED administered. (Kwan *et al*., 2010) This has not substantially changed in the last several decades. If there is failure to respond to the first two AEDs, at adequate doses in sequential monotherapy or combination therapy, the patient is considered to have treatment-resistant epilepsy, and referral to an epilepsy centre should not be delayed.

Which AED to choose?

Medical therapy is by far the most common approach. In the past two decades, over a dozen new AEDS have been approved by the Food and Drug Administration (FDA) or other regulatory bodies (*table 1*).

AEDs can be divided into two groups: broad-spectrum and narrow-spectrum.

Narrow-spectrum drugs are typically effective against focal seizures, whether or not they generalize to tonic-clonic seizures, but can exacerbate absence or myoclonic seizures. Broad-spectrum drugs show good efficacy against focal and generalized seizure types, and should be the AED of choice when the epilepsy syndrome has not yet been determined (*table 2*). To date, there is no evidence to support any difference among AEDs with different mechanisms of action, in terms of efficacy in treating focal seizures.

A large body of literature, including head-to-head and pivotal clinical trials, suggests that AEDs have a fairly similar relative efficacy against focal seizures (Brodie *et al*., 2012).

However, AEDs differ in efficacy regarding the treatment of patients with idiopathic generalized epilepsy. In a large, randomised study (SANAD) of patients with new-onset seizures which were predominantly

Table 1. Antiepileptic drugs and year of approval.

Drug	Year Approved in USA	Year Approved in Europe
Clobazam	2011	1979
Eslicarbazepine	2013	2009
Felbamate	1993	1993
Gabapentin	1994	1993
Lacosamide	2009	2008
Lamotrigine	1994	1991
Levetiracetam	1999	2000
Oxcarbazepine	2000	1990
Retigabine	2011	2011
Rufinamide	2008	2007
Perampanel	2012	2012
Pregabalin	2005	2004
Tiagabine	1997	1996
Topiramate	1996	1997
Vigabatrin	2009	1973
Zonisamide	2000	2005

Table 2. Spectrum of efficacy of antiepileptic drugs.

AEDs with narrow spectrum efficacy	AEDs with broad spectrum efficacy
Focal seizures with or without secondary generalized tonic-clonic seizures	Focal and generalized seizures
• Carbamazepine • Phenytoin • Gabapentin • Lacosamide • Oxcarbazepine • Pregabalin • Tiagabine • Vigabatrin • Retigabine • Eslicarbazepine	• Valproate • Benzodiazepines • Perampanel • Phenobarbital • Primidone • Lamotrigine • Levetiracetam • Topiramate • Zonisamide • Rufinamide • Felbamate

generalized, valproate (VPA) was found to be more successful than lamotrigine (LTG) or topiramate (TPM) (Marson *et al*., 2007). Specifically, VPA was more efficacious than lamotrigine and better tolerated than TPM. One might question the open-label design of the SANAD study, however, it is unique due to the use of multigroup comparisons and a follow-up period of up to six years.

The type of seizure and AED of choice is summarized in *table 3*. In addition to relative efficacy and tolerability, there are many other factors to bear in mind when considering initial AED therapy, such as age, gender, ease of use, serious toxicity, concomitant medications, the presence of comorbid conditions, and, least but not last, cost.

The choice of AED should be tailored to each patient, with consideration of the multiple variables, as mentioned above. When treating an epilepsy patient, the goal should be to use the least possible number of AEDs, along with the smallest doses, in order to provide seizure freedom with optimal tolerability and minimal side effects. Typically, treatment with AEDs requires adjustment over time depending on the degree of seizure control and the patient's ability to tolerate the AED.

Seizure aggravation can be caused by some AEDs. Generalized genetic epilepsies (GGE; formerly known as idiopathic generalized epilepsies or IGEs) can worsen with certain AEDs. Typical and atypical absences are aggravated by carbamazepine (CBZ), vigabatrin (VGB), tiagabine (TGB), gabapentin (GBP), and, to some extent, phenytoin (PHT).

Juvenile myoclonic epilepsy can be aggravated by CBZ and to some degree by PHT and other AEDs. GBP can cause myoclonus. Lamotrigine (LTG) can worsen myoclonus in some individuals.

Pharmacokinetics of AEDs

When choosing AEDs, the following pharmacokinetic factors should be considered; drug absorption, distribution, metabolism, and elimination. An ideal AED should show linear absorption with a low level of protein binding. AEDs with multiple available formulations offer ease of use.

With the exception of GBP and pregabalin (PGB), almost all AEDs are passively absorbed from the gastrointestinal lumen in a nearly linear fashion. GBP and PGB utilize an active transport mechanism to be absorbed. This active transport is saturated at higher doses of medication, therefore linear bioavailability is only seen when these AEDs are used at low and moderate doses.

AEDs have different degrees of albumin binding. The unbound fraction is the active drug, which is capable of

Table 3. Antiepileptic drugs and types of seizures.

Antiepileptic drug	Focal seizures with or without generalization	Primary generalized tonic-clonic	Myoclonic	Typical and atypical absences
Carbamazepine	Yes	Unclear	No	No
Felbamate	Yes	Yes	Possible	Possible
Gabapentin	Yes	Unclear	No	No
Lacosamide	Yes	Unclear	Unclear	Unclear
Lamotrigine	Yes	Yes	Unclear	Yes
Levetiracetam	Yes	Unclear	Unclear	Unclear
Oxcarbazepine	Yes	Yes	No	No
Perampanel	Yes	Yes	Unclear	Unclear
Phenobarbital	Yes	Yes	No	No
Phenytoin	Yes	Yes	No	No
Rufinamide	Yes	Unclear	Possible	Unclear
Tiagabine	Yes	Unclear	No	No
Topiramate	Yes	Yes	Possible	Possible
Vigabatrin	Yes	Unclear	No	No
Zonisamide	Yes	Yes	Yes	Yes

crossing the blood/brain barrier and engage brain targets. Protein binding is especially important in patients with hypoalbuminaemia and decreased renal clearance. Highly protein-bound AEDs will interact with other highly protein-bound drugs due to competition for protein binding. This can result in unpredictable free fractions of each drug, and can lead to difficulty in interpreting levels, as only the total (bound and unbound) is usually measured. PHT, VPA and perampanel (PP) exhibit the highest degree of protein binding. Most second-generation AEDs do not exhibit this feature.

Most AEDs undergo biotransformation in the liver prior to renal excretion, although a few AEDs are cleared unchanged. All of the first-generation AEDs and some new AEDs, such as PP, LTG, and oxcarbazepine (OXC), are at least partially hepatically metabolized, mainly by cytochrome p-450 enzyme systems, followed by renal elimination. Therefore, the majority of AEDs are subject to interactions with other drugs that are hepatically metabolised.

CBZ, PHT, phenobarbital (PB), and primidone (PRM) are hepatic enzyme inducers, while VPA is an inhibitor of specific isoenzymes within the hepatic cytochrome P450 (CYP) enzyme system as well as the glucuronidation process. Therefore, co-administration of first-generation AEDs may affect the concentrations of other AEDs, other medications, and/or hormones.

On the other hand, the second-generation AEDs do not have an inducing or inhibiting effect on cytochrome P450 enzymes or glucuronidation, with the exception of TPM and OXC which are mildly inducing at high doses. Therefore, second-generation AEDs should be considered in PWE on chronic non-epilepsy co-medications due to a lack of drug-drug interaction potential.

Parenteral administration is necessary in emergency situations, including status epilepticus, frequent seizures, or when the patient cannot have oral preparations, such as postoperatively or secondary to gastrointestinal problems. Intravenous formulations are available for PHT, fosphenytoin, VPA, levetiracetam (LEV), lacosamide (LCM), PB, lorazepam, and midazolam.

Optimal dose

To achieve optimal dosing, the AED of choice for a given patient should be titrated to the lowest effective dose. If seizures are not controlled, then the daily

Table 4. Therapeutic levels and protein binding of antiepileptic drugs.

AED	Suggested reference range (μg/ml)	Suggested reference range (μmole/l)	Protein binding (%)
Carbamazepine	4-12	16.9-50.8	40-90
Clobazam	N/A	0.1-1.0	70-90
Clonazepam	20-70	0.06-0.22	85
Ethosuximide	40-100	280-700	0
Phenobarbital	10-40	65-94	50
Phenytoin	10-20	40-79	90
Primidone	5-10	23-46	0-20
Valproic acid	50-100	350-700	90-95
Felbamate	30-60	126-252	22-36
Gabapentin	2-20	12-117	0
Lacosamide	10-40	47-188	<15
Lamotrigine	2.5-15	10-58	55
Levetiracetam	12-46	25-50	<10
Oxcarbazepine	3-35		40
Perampanel	N/A		95-96
Pregabalin	N/A		0
Rufinamide	N/A		26-34
Tiagabine	20-200		95-97
Topiramate	5-20		9-17
Vigabatrin	N/A		0
Zonisamide	10-40		40-50

dose can be increased gradually to seizure cessation, or until tolerability issues ensue.

Most AEDs work within a few days to a week after starting an effective dose, although some AEDs need to be titrated slowly to avoid toxicity, thus an effective dose may not be reached immediately. Rapid titration should be avoided, unless warranted by frequent seizures. Serious hypersensitivity reactions and central nervous system toxicity can be reduced by using the recommended titration schedule. It is well known that higher-than-average doses may improve seizure control for only an additional 20-30% of all responders (French *et al*., 2004a, 2004b; Elger and Schmidt, 2008).

Measuring blood levels of AEDs enables clinicians to monitor the drug response while avoiding toxicity due to high levels. Therapeutic response to AEDs differs from patient to patient. There are two main factors that determine the response to AEDs; pharmacokinetic and pharmacodynamic. Pharmacokinetic factors affect the levels of AEDs in the brain tissue and blood. Pharmacodynamic factors cause different responsiveness of the brain tissue to AEDs. The goal of monitoring AED levels is to keep them within the "individual" therapeutic range. "Population" therapeutic ranges (TR) are defined as the range of serum concentration of a drug found to be associated with optimal clinical response with minimal adverse effects in a given population of patients (*table 4*). Population therapeutic ranges are useful when initially selecting a treatment dose. However, if a patient does not achieve optimal therapeutic response within this range, it is appropriate to adjust dosing until optimal effect (taking both efficacy and safety into account) is achieved. Once this effect has been achieved, AED concentration can again

be assessed, and this will determine the patient's "individual" therapeutic range. Once individual range has been ascertained for a given patient, serum concentrations can be followed to ensure that therapeutic range is maintained over time. Some PWE may need to maintain AED levels above the population TR, while some will be seizure-free with AED levels below the population TR. It is very helpful to identify each patient's individual TR, which may be used as a reference level in the future, if needed, to treat recurrent seizures and rule out non-compliance with treatment.

Timing of blood sampling to determine drug blood levels is very important, especially if non-sustained release or short half-life drugs are used. The blood levels will vary depending on the timing of blood draw. Therefore, the timing of blood sampling should be at similar time points. Usually, samples are collected at the time of trough, in the morning before intake of the first daily dose.

Monitoring of AED levels is not available in all countries, but should be utilized whenever available, especially when there is a question over dose-related toxicity or compliance. Establishing individual AED level for each patient, relative to the best treatment response, provides a future reference in the event of switching between AED formulations or using generic forms, or breakthrough seizures. AED levels should be followed if a new coexistent medical condition occurs, such as critical illness, pregnancy, or use of concomitant medication with drugs that may potentially interact with AEDs.

Tolerability and side effect profiles of AEDs

Tolerability is one of the most important factors when selecting AEDs, since this will affect treatment compliance, but also because it may be impossible to select drugs based on efficacy, which is less predictable. Dose adjustments, changes in titration schedule, or change in dose frequency may be needed to increase tolerability. CNS side effects can have a significant negative effect on the quality of life of the patient.

There are two types of adverse effects: common and rare. Besides behavioural and cognitive effects, weight gain or loss, nausea, incoordination, dizziness, and gait disturbance are common adverse effects reported with AEDs.

Serious adverse effects, such as hepatic failure, Stevens-Johnson syndrome (SJS), and pancreatitis can be life-threatening. These and other serious and common adverse events are summarised in *table 5*. CBZ has been associated with life-threatening cutaneous adverse drug reactions, such as toxic epidermal necrolysis (TEN) and SJS in Asians patients with HLA-B*1502 and in Caucasians and Japanese patients with HLA-A3101 genes (Man *et al*., 2007; Ozeki *et al*., 2011).

AEDs and comorbidities

PWE often have comorbidities. Based on several population studies, a higher prevalence of stroke, diabetes, heart disease, high blood pressure, asthma, chronic bronchitis, gastrointestinal ulcers, arthritis, thyroid conditions, migraine, Alzheimer's disease, and cancer in persons with a history of epilepsy have been reported (Boro *et al*., 2003; Gaitatzis *et al*., 2012). Also, PWE were found to have increased prevalence of mental health disorders, such as anxiety and depression. Treatment of PWE requires optimal identification and management of comorbidities, while the primary goal is to provide seizure freedom. Therefore, AEDs should be chosen carefully since potential side effects and interactions with other medications can be prevented when special consideration is given to underlying comorbidities and comedications (Téllez-Zenteno *et al*., 2005a; Ryvlin, 2006; Elliott *et al*., 2009; Hinnell *et al*., 2010).

For example, TPM and VPA, which mitigate migraine, could be considered as treatment for patients with this comorbidity, while zonisamide (ZNS) or TPM can be considered for obese PWE because these AEDs can promote weight loss. Similarly, VPA and PGB should not be the drug of choice in obese PWE, as these can cause weight gain.

Coexistent hepatic or renal insufficiency can decrease elimination of some AEDs, leading to toxicity. Drugs that are eliminated predominantly by the affected organ should be avoided. First-generation AEDs mostly undergo hepatic metabolism, therefore second-generation AEDs should be considered in patients with liver disease.

Mood disorders and increased suicidality have been reported to be more common in PWE. The causes are the underlying epilepsy and side effects of AEDs. Therefore, PWE should be assessed for coexistent mood disorders. Unfortunately, evaluation by a psychiatrist is not possible for every PWE, and initial screening should be performed by neurologists. For self-administered questionnaires, the patient and their families should also be questioned separately regarding signs of depression and suicidality. If there is a concern of suicidality, appropriate measures should be taken, such as referral to a crisis centre.

AEDs associated with a higher risk of depression, such as LEV, PB, PRM, TPM, VGB, and ZNS, should be used with caution and avoided when possible in PWE with mood disorders, such as depression and anxiety.

Table 5. Side effect profiles of antiepileptic drugs.

	Common side effects	Serious side effects
Carbamazepine	Dizziness, diplopia, ataxia, leukopenia	Rash, agranulocytosis, hepatic failure, Stevens-Johnson syndrome, hyponatraemia
Ezogabine	Dizziness, somnolence, fatigue	Confusion, vertigo, tremor, abnormal coordination, urinary retention
Oxcarbazepine	Fatigue, dizziness, nausea, ataxia, diplopia	Rash, Steven-Johnson syndrome, hyponatraemia, anaphylaxis
Gabapentin	Sedation, fatigue, dizziness, weight gain	None
Perampanel	Somnolence	Agitation, hostility, severe life-threatening psychiatric disorders
Pregabalin	Sedation, fatigue, dizziness, weight gain, ataxia, oedema	None
Phenytoin	Fatigue, dizziness, ataxia, confusion, diplopia	Rash, Steven-Johnson syndrome, pseudolymphoma, lupus-like syndrome, hepatic failure
Phenobarbital	Fatigue, dizziness, ataxia, confusion, hyperactivity (in children)	Blood dyscrasias, hepatic failure, rash, Stevens-Johnson syndrome
Valproate	Weight gain, thrombocytopenia, tremor, drowsiness, nausea, vomiting	Hepatic failure, pancreatitis, hyperammonaemia, thrombocytopenia, aplastic anaemia, teratogenicity
Lacosamide	Dizziness, nausea, vomiting, visual disturbance	Prolonged PR interval, other ECG changes, atrial fibrillation, atrial flutter
Lamotrigine	Dizziness, blurred vision, headache, insomnia	Rash, Stevens-Johnson syndrome, hypersensitivity, hepatic failure
Levetiracetam	Mood swings, irritability, anxiety	Psychosis
Retigabine	Dizziness, somnolence	Skin discolouration
Rufinamide	Somnolence, nausea, vomiting, headache	Shortened QT, multiorgan hypersensitivity
Tiagabine	Fatigue, dizziness, somnolence, irritability	Spike-wave status epilepticus
Topiramate	Drowsiness, paresthesia, word finding difficulty, anorexia, weight loss, metabolic acidosis, oligohydrosis	Nephrolithiasis, heat stroke, metabolic acidosis, acute close-angle glaucoma
Vigabatrin	Somnolence, trembling, swallowing, motor difficulties	Irreversible, bilateral concentric peripheral field constriction
Zonisamide	Drowsiness, difficulty with concentration, anorexia, weight loss, oligohydrosis	Stevens-Johnson syndrome, nephrolithiasis, oligohydrosis, heat stroke, aplastic anaemia

Irritability and aggressive behaviour can be triggered by certain AEDs, such as LEV and PB. In this population, AEDs with a positive psychotropic effect, such as CBZ, LTG, OXC, and VPA, are preferred.

Enzyme-inducing AEDs can lead to unsuccessful treatment of coexisting medical conditions by lowering exposure to comedications to subtherapeutic levels. Therefore, consideration should be given to

avoiding enzyme-inducing AEDs in patients on concomitant medications that are inducible. If they are used, levels of comedications may need to be monitored. Similarly, enzyme-inducing AEDs can lead to unsuccessful treatment with anti-retroviral drugs. If the patient is on antiretroviral treatment, non-enzyme-inducing AEDs are recommended; LEV, PGB, TPM and GBP can be used safely.

A recent AAN guideline recommends limiting the use of enzyme-inducing AEDs, specifically PHT in epilepsy patients with HIV on retroviral treatment (Birbeck *et al*., 2012).

Women with epilepsy

Women with epilepsy should be consulted whether they are considering pregnancy or not. For example, contraception and plans for contraception should be discussed either soon after beginning care, or soon after menarche. It should be emphasized that unplanned pregnancy can be very problematic. Enzyme-inducing AEDs can interact with oral contraceptives with the potential to cause contraception failure. AEDs can also impact the hormonal milieu. Enzyme-inducing AEDs can reduce oestrogen and testosterone-binding globulin. VPA, an enzyme inhibitor, has been linked to polycystic ovarian syndrome. Antiepileptic drugs, such as PB, CBZ, PHT, TPM, PRM, rufinamide (RUF), and OXC, are capable of inducing the metabolism of drugs that are cleared by the CYP3A4 enzyme system. Induction of the 3A4 system increases the metabolism of both the oestrogenic and progestogenic components of oral contraceptives and reduces their levels by as much as 50%, leading to a potential risk of failure of contraception and unplanned pregnancies. Enzyme-inducing AEDs can cause reduced efficacy of all hormonal contraceptives, including pills and hormone-releasing subdermal progestogen patches and implants (Crawford *et al*., 1990; Crawford, 2002). OXC, RUF and TPM are only mildly inducing, compared to the older AEDs. Other forms of contraception, such as IUDs and diaphragms, should be considered as alternatives.

It is very important to discuss with women their plans to have children, even if they may not have plans to bring the child up themselves. Any changes in AEDs should be made well before pregnancy. A woman who is considering to have a child should be weaned off potentially teratogenic AEDs if at all possible, and the AED regimen should be simplified to a minimum number of AEDs that control seizures. However, maintaining seizure control should be the primary focus for treating a woman with epilepsy, whether contemplating pregnancy or not. The teratogenicity of AEDs is one of the main challenges when treating female patients with epilepsy. Several pregnancy registries have reported higher rates of major congenital malformations with the use of VPA during pregnancy, compared to other AEDs, such as CBZ or LTG (Wide *et al*., 2004; Artama *et al*., 2005; Wyszynski *et al*., 2005; Morrow *et al*., 2006; Vajda *et al*., 2007; Harden *et al*., 2009; Veiby *et al*., 2009). VPA has been recently reported to be associated with an increased risk of spina bifida, atrial septal defects, cleft palate, and craniosynostosis (Jentink *et al*., 2010). There is a direct relationship between VPA dose and teratogenicity.

Recently, observational studies by Meador *et al*. indicated that prenatal exposure to VPA can adversely affect the cognitive development of offspring. Children of mothers who were treated with VPA during pregnancy had significantly lower IQ at the age of 3 years compared to children exposed to CBZ, LTG, or PHT (Meador *et al*., 2009). Moreover, in the report of Baker *et al*. (2015), children with prenatal VPA exposure scored lower on measures of motor skills, language comprehension, and language expression, with an increased frequency of educational interventions, but did not show a decrease in IQ; this effect was seen even in those exposed to VPA at low doses (<800 mg/day). Children who had prenatal exposure to VPA had a higher incidence of autism spectrum disorders (ASDs). Moreover, 8.9% of children exposed to VPA monotherapy and 15% to VPA polytherapy met the diagnostic criteria for ASD (Rasalam *et al*., 2005, Bromley *et al*., 2013). Due to all the reasons reported above, VPA is not the drug of choice for women with epilepsy of childbearing potential, unless absolutely necessary.

Serum concentrations (and therefore exposure) of most of the AEDs can vary during pregnancy. This is particularly true for LTG, which can show a pronounced increase in clearance throughout pregnancy. Therefore, frequent blood level monitoring and dose adjustments may be necessary during pregnancy (Ohman *et al*., 2008; Fotopoulou *et al*., 2009).

Teratogenicity of second-generation AEDs is still not well known, although preliminary data from observational studies indicate potential teratogenicity with TPM (Hunt *et al*., 2008; Mølgaard-Nielsen and Hviid, 2011; Vajda *et al*., 2012).

Also, polytherapy is associated with a higher risk of teratogenicity, therefore, it should be avoided as much as possible in women with epilepsy at childbearing age (Holmes *et al*., 2011). The goal for women with epilepsy at childbearing age is to achieve seizure freedom with the least teratogenic antiepileptic medication or combination. However, although teratogenicity of AEDs is a significant concern during pregnancy, the impact of having generalized tonic-clonic seizures in a pregnant woman can be serious.

Elderly patients with epilepsy

The incidence of epilepsy is higher in the elderly and the issues of management are somewhat unique in this population. Relative to the general population, elderly individuals more commonly live by themselves or in nursing homes, and this may impact appropriate therapy. For some individuals, seizures may manifest as confusional episodes which can be confused with early dementia. Changes in pharmacokinetics associated with aging make elderly patients more susceptible to the side effects of many AEDs. Lower glomerular filtration rates and changes in albumin, body fat, and liver enzymes can decrease the metabolism and clearance of AEDs. Choosing and dosing AEDs in the elderly requires caution, and elderly patients usually have comorbidities which are treated with many comedications.

Lower doses of AEDs are often sufficient in elderly patients. Compliance is sometimes lower in the elderly due to low tolerance to side effects. Ataxia, hyponatraemia, and cognitive decline are among common side effects of AEDs. Also, an elevated risk of osteoporosis due to the adverse effects of AEDs, in addition to increased risk of bone fracture due to trauma during seizure, is another challenge in the elderly.

In the elderly with epilepsy, AED monotherapy and second-generation AEDs, such as GBP, low-dose TPM, and LEV, are preferable (Rowan *et al*., 2005; Ramsay *et al*., 2008).

What to do when epilepsy becomes refractory?

Failure to respond to the first two AEDs, at adequate doses as monotherapy, is defined as refractory epilepsy. The International League Against Epilepsy task force defined drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (monotherapy or in combination) to achieve sustained seizure freedom" (Kwan *et al*., 2010).

Once a patient's epilepsy is recognized to be drug-resistant or refractory, referral to a comprehensive epilepsy centre is advisable. As epilepsy becomes treatment-resistant, non-drug therapies should be considered. These include surgery, a change in diet, hormones, and devices.

Surgical treatment decisions are critically important and require an individualised risk-benefit assessment. Anterior temporal lobectomy is a well-known and well-defined surgical procedure for epilepsy; in a randomised controlled trial, it was shown to be more effective than medical therapy, achieving seizure freedom in up to 70% of adults with refractory temporal lobe epilepsy (Wiebe *et al*., 2001; Téllez-Zenteno *et al*., 2005b). In a study by de Tisi *et al*. (2011), (28)% of postsurgical patients off antiepileptic drugs were seizure-free after anterior temporal lobectomy.

Other surgical procedures for epilepsy include resection of structural lesions (lesionectomy), corpus callosotomy, and less commonly used multiple subpial transections (Maehara and Shimizu, 2001; Benifla *et al*., 2006).

The ketogenic diet contains high fat, low protein, and low carbohydrate. Although it has been found to be effective for many types of epilepsy, it is difficult to maintain over time, particularly in adults. It has been used in children with drug-resistant epilepsy. Modified versions of the ketogenic diet have also been used in adults with refractory epilepsy (Kossoff and Dorward, 2008). The ketogenic diet was shown to decrease seizure frequency more than 50% in about half of patients (Neal *et al*., 2008). The ketogenic diet can be tried for all seizure types.

Neurostimulation devices have been used for the treatment of refractory epilepsy. The vagus nerve stimulator has been approved as adjunctive therapy for the treatment of adults and adolescents with refractory epilepsy (Milby *et al*., 2009). It consists of a pacemaker-like/battery device implanted on the patient's upper chest, while the lead carries electrical stimulation to the left vagus nerve.

Deep brain stimulation is an intracranial device, delivering electrical stimulation on a scheduled basis bilaterally to the anterior nucleus of the thalamus. A two-year follow-up of a randomised trial involving 100 patients showed a mean seizure reduction of 56%, while 14 patients were seizure-free for at least six months (Anderson *et al*., 2008; Fisher *et al*., 2010).

Counselling patients with epilepsy

Initial consultation between a patient and a physician is an essential step in order to build a relationship of trust. Patients may feel very scared and anxious about being labelled with epilepsy, and there is fear of many unknowns regarding the disease. Patients require comprehensive counselling and education at the first visit, and it is very important to provide patients with educational material and an opportunity to be able to interact with other patients through local epilepsy foundation support groups and social media. Counselling at the first visit should include issues such as driving, employment, SUDEP, safety measures in daily life, first aid for seizures, and education for family and friends.

For self-education, patients should be encouraged to use online resources locally and internationally, such as www.epilepsy.com. Use of an

online diary should be advised (examples can be found at www.myepilepydiary.com and www.seizuretracker.com).

At each visit, PWE should be asked about reported seizure frequency in their diary, as well as tolerability and adverse side effects of their therapy. Lists of comorbidities and concomitant medication should be updated at each visit in order to reduce the risk of drug-drug interactions and optimise the care for their coexistent medical condition.

In the USA, in certain states such as Pennsylvania, New Jersey, Delaware, California, Oregon, and Nevada, seizures have to be reported to the Department of Motor Vehicles (DMV) by the physician. In other states, it is the patient's responsibility to report to the DMV. To be able to resume driving, the required period of seizure freedom differs from state to state and varies from three months to two years. In a study by Drazkowski *et al*. (2003), shortening of a seizure-free period from one year to three months was not shown to affect the rate of motor vehicle accidents due to seizures.

Conclusion

For PWE, epilepsy can be managed with very little impact on overall personal goals and quality of life. Caring for a person with epilepsy requires an excellent line of communication between doctor and patient, with continuing consideration to optimise seizure control and quality of life. Often, there will be a long-term relationship, and it is important to continually reassess whether therapeutic goals have changed, and whether therapy is optimised. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Which antiepileptic should be avoided for a young woman with epilepsy?
A. Levetiracetam
B. Carbamezepine
C. Phenobarbital
D. Lamotrigine
E. Oxcarbazepine

(2) Which antiepileptic is known to worsen myoclonic seizures?

(3) Which antiepileptic does not have any effect on oral contraceptive efficacy?
A. Carbamezepine
B. Phenytoin
C. Phenobarbital
D. Lacosamide
E. Rufinamide

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".