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Drug treatment of epilepsy: Options and limitations

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ABSTRACT

The modern antiepileptic drug (AED) era—spanning a period of more than 150 years from the first use of bromide in 1857 to 2008—has seen the introduction into clinical practice of a diverse group of effective and safe drugs. These AEDs have provided considerable benefits for those afflicted with epilepsy of all kinds. In as many as 60–70% of newly treated patients, current AEDs lead to satisfactory control of seizures and a favorable risk–benefit balance for the great majority of patients, albeit with considerable differences in response depending on the type of seizure and epilepsy syndrome and rare serious adverse events. Unfortunately, in 20–30% of patients, epilepsy cannot be controlled. Patients with drug-resistant epilepsy often have serious comorbidity, including injury, depression, anxiety, and increased mortality. The aim of antiepileptic treatment should be to control seizures as quickly as possible with no or minimal side effects and with no negative impact on the quality of life. Improved seizure control is likely to reduce the morbidity and increased mortality associated with uncontrolled epilepsy. In this short overview, the options and the limitations of treating patients with epilepsy are briefly summarized.

1. Introduction

Antiepileptic drugs provide satisfactory control of seizures for most patients with epilepsy. Seizures in about 65% of patients with new-onset epilepsy respond, seizure recurrence occurs in 5%, and 35% have uncontrolled epilepsy. Seizure precipitation can be avoided by lifestyle changes, particularly in adolescents with idiopathic generalized epilepsy. If two or three drug regimens have not brought complete seizure control, the diagnosis of epilepsy and of the epilepsy syndrome should be reevaluated, and if refractory epilepsy is confirmed, surgical options should be considered in suitable candidates. In this short overview, the options and the limitations of treating patients with epilepsy are briefly summarized. For extensive discussion and detailed references, see textbooks and monographs [1–3].

2. Currently used antiepileptic drugs

The following antiepileptic drugs (AEDs) have been approved by regulatory agencies in the United States and Europe: acetazolamide, carbamazepine, clonazepam, clorazepate, ethosuximide, ethotoin, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, methsuximide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, trimethadione, valproate, vigabatrin, and zonisamide. The following additional agents are used mainly for the acute therapy of status epilepticus: diazepam, fosphenytoin, lorazepam, midazolam, and propofol. Pragmatically, the choice of AED among first-line agents needs to be individualized mainly on the basis of the patient profile, including the efficacy for the seizure or the epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics (in consideration of the current or likely future need for concomitant medication for comorbidity), and finally cost. AEDs provide satisfactory control of seizures for most patients with epilepsy. About 65% of patients with new-onset epilepsy respond, seizure recurrence occurs in 5%, and 35% have uncontrolled epilepsy. Seizure precipitation can be avoided by lifestyle changes, particularly in adolescents. If two or three drug regimens have not brought complete seizure control, the diagnosis of epilepsy and of the epilepsy syndrome should be reevaluated, and if refractory epilepsy is confirmed, surgical options should be considered in suitable candidates.

3. Starting treatment

The decision to start drug treatment in a patient with unquestionable epilepsy requires a careful individual risk–benefit assessment. Although AEDs are able to prevent further seizures and reduce the severity of seizures, and treatment is recommended in all persons with a high risk of seizure recurrence, the side effects of AEDs need to be considered. High-risk features for seizure recurrence are symptomatic epilepsy with generalized tonic–clonic seizures (GCTS), complex or simple partial seizures, and idiopathic generalized epilepsies. Early treatment after a first GTCS has, however, not been shown to improve long-term prognosis or lower

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mortality or the risk of injury [4]. A number of patients with good prognoses (e.g., uncomplicated febrile seizures, often benign idiopathic partial epilepsies) may not even require drug treatment. Also, adverse events of AEDs, including central nervous system toxicity and hypersensitivity reactions, have to be balanced against the potential benefit. Psychosocial consequences in case of another seizure (e.g., driver's license or an otherwise seizure-sensitive social setting) may weigh in favor of drug treatment in some patients. Drug treatment is usually not indicated if the diagnosis of epilepsy is uncertain, if provoked seizures occur that can be prevented without drugs, if seizures are rare, and, last not least, if the informed patient or caregiver does not want drug treatment.

Recommendation: Drug treatment of epilepsy is generally advisable if disabling seizures occur or can be reasonably expected to recur sufficiently frequently to adversely affect the individual more than the adverse effects of AEDs. The decision to start treatment after a single seizure needs to be individualized. Even when blocking seizures, AEDs do not seem to favorably affect the course of the underlying epilepsy, which is a serious limitation of current AED treatment.

4. Pharmacokinetics of antiepileptic drugs

From a clinical perspective, the ideal AED does not require monitoring of plasma concentrations, is metabolically inert and is not involved in adverse drug interactions, and can be conveniently given once or twice a day [5]. Unfortunately, a number of currently used classic AEDs induce or, less commonly, inhibit the cytochrome p450 system, such as carbamazepine (CBZ), phenobarbital (PHB), and phenytoin (PHT), or inhibit enzymes involved in glucuronidation, such as valproate (VPA) [6]. Fortunately, modern AEDs are available that are less enzyme inducing, such as oxcarbazepine, or are not metabolized by the oxidative cytochrome p450 system at all, such as gabapentin (GBP), levetiracetam (LEV), lacosamide (LCM), lamotrigine (LTG), pregabalin (PGN), topiramate (TPM), and zonisamide (ZNS), and therefore are less likely to be involved in drug interactions based on enzyme induction. In addition, VPA and LTG inhibit metabolic steps involving glucuronidation and can thus be involved in drug interactions (Table 1).

The absence of drug interactions is a very important advantage for an AED. Most patients with epilepsy are treated for several years, and the majority need to take AEDs for their life. The long-term consequences must therefore be taken into account. For example, a girl may wish to use oral contraceptives at some time in the future, or an adult may become overweight or comorbid with depression, anxiety disorders, migraine, or common serious disorders such as cardiovascular disease, diabetes, and cancer and require additional medication. The increasing incidence of epilepsy in the elderly who commonly have multimorbidity also requires AEDs that do not interact. Finally, one in three patients with new-onset epilepsy requires a combination or a succession of AEDs over her or his lifetime for optimal seizure control. In addition, AEDs that interact with other drugs, for example, through enzyme induction or enzyme inhibition, will also disadvantageously affect endogenous sexual and other hormone metabolism, and may contribute to adverse events. Taking enzyme-inducing CBZ, OXC, PHB, PHT, and primidone (PRM) may, in contrast to GBP, LTG, and TPM, below 200 mg/day, lead to reduced efficacy of comedication including oral contraceptives, AEDs, and other medication. Adding an oral contraceptive may lower the plasma concentrations and efficacy of LTG. Valproate is not involved in interactions with oral contraceptives, but may, however, inhibit glucuronidation of, for example, LTG. Fewer clinically relevant interactions with drugs or endogenous substances occur with OXC, TPM, and VPA instead of classic enzyme-inducing AEDs, which are the least advantageous agents in that respect. Finally, many classic AEDs share the disadvantage of both causing clinically relevant interactions and being affected by other drugs. For all these reasons, absence of enzyme induction or enzyme inhibition is a plus for any AED.

Up to one in three patients with new-onset epilepsy requires a combination of different AEDs for seizure control. In uncommon cases, even more than two AEDs may be needed. During combination therapy, a number of drug interactions may arise with classic AEDs. Drug interactions may interfere with drug efficacy. A prototypic example is the combination of CBZ and VPA. When VPA is added to CBZ, adequate VPA plasma concentrations cannot be achieved in most cases because CBZ lowers the plasma concentration of VPA. However, drug interactions may also increase the plasma concentrations to toxic levels, for example, of LTG in the presence of VPA. Although this combination is beneficial for many patients, tremor may develop and the combination has been shown to be more teratogenic than LTG alone or in combination with another AED, except VPA. However, modern AEDs such as GBP, LEV, LCM, PGN, and tiagabine (TGB) are much better suited for combination therapy as they are much less or not involved at

Table 1
Simplified synopsis of drug interaction properties of common AEDs.

Antiepileptic drug	Enzyme inducer (CYP)	Enzyme inhibitor (CYP, UGT)	Effect of drug on disposition of other AEDs
Clobazam (CLB)	No	No	No relevant change
Felbamate (FBM)	No	No	No relevant change
Gabapentin (GBP)	No	No	No relevant change
Levetiracetam (LEV)	No	No	No relevant change
Lacosamide (LCM)	No	No	No relevant change
Zonisamide (ZNS)	No	No	No relevant change
Topiramate (TPM)	No (<200 mg/day)	No	No relevant change
Carbamazepine (CBZ)	Yes	No	LTG, TGB, VPA (▼▼)
Ethosuximide (ETS)	No	No	PHT, VPA (▲), CBZ (▼)
Lamotrigine (LTG)	Yes	Yes	No relevant change
Oxcarbazepine (OXC)	Yes	No	OXC doses >900 mg (▼); CBZ, LTG, PHT, TGB, VPA (▼▼)
Phenobarbital (PHB)	Yes	No	CBZ, LTG, OXC, PHT, TGB, VPA (▼▼)
Phenytoin (PHT)	Yes	No	CBZ, LTG, PHT, TGB, VPA (▼▼)
Pregabalin (PGN)	No	No	No relevant change
Primidone (PRM)	Yes	No	see PHB
Valproate (VPA)	No	Yes	CBZ-E, LTG, PB, free PHT (▲)
Vigabatrin (VGB)	No	No	PHT (▼), other AEDs (◄►)

Note. CYP, Cytochrome p450 System; UGT, Uridine diphosphate-Glucuronyl Transferase System; CBZ-E, Carbamazepine epoxide; ◄►, no relevant change; ▲, increase in plasma concentration; ▼, decrease in plasma concentration; ▼▼, major decrease in plasma concentration.
Source. Modified from Refs. [6,9].

all in drug interactions among AEDs. Starting epilepsy treatment with modern noninteracting AEDs can prevent such complications.

A large number of patients with epilepsy rely on additional medication other than AEDs for birth control or management of disorders. Depression, anxiety disorders, and migraine are common in patients with epilepsy. Patients with epilepsy are not protected from common diseases such as stroke, myocardial infarction, leukemia, and cancer, which all require medication that may be interfered with by classic enzyme-inducing AEDs. Patients may require treatment with antibiotics, which increases plasma concentration of AEDs and may thus cause toxicity. Initiating epilepsy treatment with modern noninteracting AEDs can prevent such complications.

Recommendation: Adverse drug interactions can be minimized by avoiding enzyme-inducing or -inhibiting classic AEDs and using beneficial combinations of AEDs, if needed, for seizure control.

5. Adverse effects of antiepileptic drugs

Possible adverse effects of AEDs are listed in Table 2 [7–9]. The main advantages of some of the modern AEDs include absence of hypersensitivity reactions, weight problems, and drug interactions that cause central nervous system toxicity. There is no need for routine laboratory monitoring and safety is improved with absence of life-threatening organ damage. Patients receiving carbamazepine should have a CBC once a month for the first year of therapy. If the white or red blood cell count decreases significantly, the drug should be discontinued immediately. Patients receiving valproate should have liver function tests every 3 months for 1 year; if serum transaminase or ammonia levels increase significantly (to >2 times the upper limit of normal), the drug should be discontinued. An increase in ammonia up to 1.5 times the upper limit of normal can be tolerated safely. When an overdose reaction occurs, the amount of drug is reduced until the reaction subsides. When more serious acute poisoning occurs, the patient is given ipecac syrup or, if obtunded, lavaged. After emesis or lavage, activated charcoal is administered, followed by a saline cathartic (e.g., magnesium citrate). Hemodialysis may be considered. The suspect drug should be discontinued and a new anticonvulsant started simultaneously.

Recommendation: Adverse effects of AED treatment can be minimized by slow-dose escalation up to average daily maintenance doses (unless increments are needed for seizure control), by avoiding enzyme-inducing agents and polytherapy, if possible, and by using appropriate well-tolerated modern AEDs for both new-onset cases and refractory epilepsy.

6. Choice of antiepileptic drug

Pragmatically, the choice of AED among first-line agents needs to be individualized, mainly on the basis of the patient profile, including efficacy for the seizure or epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics (including current or likely future need for concomitant medication for comorbidity), and finally cost (Table 3).

6.1. Partial seizures

A number of AEDs are recommended on the basis of their benefit–risk balance (Table 3) [10,11]. The modern AEDs for therapy of previously untreated adolescents and adults with partial epilepsy such as GBP, LTG, LEV, OXC, and TPM have a number of advantages compared with classic AEDs such as CBZ, PHB, PHT, PRM, and VPA. The new AEDs show broadly similar efficacy, with the possible exception of GBP, which seems to be less efficacious than CBZ and at least as tolerable or more tolerable at adequate dosages than classic AEDs for patients with partial epilepsy. However, none of

Table 2
Overview of adverse effects of AEDs.

	CBZ	CLB	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PHB	PHT	TGB	TPM	VPA	VGB	ZNS
Early-onset adverse events																	
Somnolence		++			+	+	+	+		+	++		++	++		+	++
Dizziness		++	+		+	+	+	+	++			++	++	++		+	+
Seizure aggravation	+	+			+					+		+	+			++	
Gastrointestinal	+		++	+	(+)		(+)		+						+		+
Liver failure				+											+		
Hypersensitivity (SJS/TEN[a])	+		+	+				+	+		+	+		+			+
Rash	+							+	+			+					
Late-onset adverse events																	
Sedation		++	+			+					++			(+)			
Encephalopathy												+			+	++	
Depression			+								+	+	+			+	
Behavioral problems							+				++	+	+	++		++	+
Psychotic episodes	(+)		++	(+)	+		(+)				(+)	(+)	(+)	(+)	(+)	++	
Leukopenia	++		+	+					(+)		+	+					
Aplastic anemia	+		+	++							+	+					
Thrombopenia				+											++		
Megaloblastic anemia	(+)										+	+					
Pancreatitis					(+)										+		
Nephrolithiasis														(+)			+
Osteoporosis	(+)										+	+			(+)		
Hyponatremia	(+)								+								
Weight gain	+				+					++					+	+	+
Weight loss														+			
Cognition impaired	+	+									++	+		+			+
Teratogenicity															++		

Note. (+), Minimally increased risk in clinical use; +, risk higher than for AEDs without +; ++, highest risk among AEDs. In general, although exposure to some modern AEDs is still limited, treatment with a number of modern AEDs appears to be advantageous compared with treatment with some of the classic AEDs (see summary of risks). It should, however, be noted that the incidence of many early adverse events shown here can be lowered by using slow titration and avoiding above-average dosages and combination therapy, if possible. For definitions of AEDs see Table 1.

Source. Modified from Ref. [9].

[a] Stevens–Johnson syndrome/toxic epidermal necrolysis.

Table 3
Preferred first-line AEDs for new-onset and refractory epilepsy in adults.

New-onset partial epilepsies	*Refractory partial epilepsies*
Carbamazepine	Lacosamide
Gabapentin	Pregabalin
Lamotrigine	Zonisamide
Levetiracetam	Clobazam
Oxcarbazepine	
Topiramate	
Valproate	
New-onset idiopathic generalized epilepsies	*Refractory idiopathic generalized epilepsies*
Lamotrigine	Clobazam
Topiramate	Levetiracetam
Valproate	

Note. For refractory cases, all first-line AEDs for new-onset cases are also considered unless they have failed during previous treatment.
Source. Modified from Refs. [10,11].

the modern AEDs was more efficacious than CBZ or VPA in their respective comparison groups [12,13]. The first AED leads to complete seizure control in about 50% of patients; subsequent regimens with combination or substitution achieve control in up to 10–15%. One in three patients remains with uncontrolled partial seizures. In addition to the AEDs mentioned, efficacious second-line AEDs such as lacosamide, pregabalin, and zonisamide are available for combination if first treatment failed to control seizures.

If several single-drug or combination regimens with these drugs have failed, surgical options should be considered. If not, third-line agents are available; these are clobazam, phenobarbital, phenytoin, primidone, and tiagabine. Less often used agents with either tolerability or safety problems or no Class I evidence for efficacy (acetazolamide, bromide, felbamate, sulthiame, vigabatrin) should be used as a last resort. Given their similar efficacy for partial seizure control, the choice of AED among first-line agents needs to be individualized based mainly on the patient profile including the epilepsy syndrome, tolerability, gender issues, pharmacokinetics (including current or likely future need for concomitant medication for comorbidity), and cost.

6.2. Generalized seizures

A number of AEDs are recommended on the basis of their benefit–risk balance (Table 3). Despite requiring different treatment strategies, typical absence seizures and juvenile myoclonic epilepsy and related idiopathic generalized epileptic syndromes are often erroneously grouped with partial and other epilepsies under the broad term "epilepsy." Furthermore, AEDs are tested and licensed mainly for partial epilepsies and there may be inappropriate generalizations for their use in "epilepsy." This is exemplified by GBP, CBZ, OXC, and PHT, which induce myoclonic seizures, and VBG and TGB, which induce absences; they are contraindicated in idiopathic generalized epilepsy, which constitutes more than one-third of epilepsy. VPA is still the drug of first choice for patients with idiopathic and symptomatic generalized epilepsy despite its disadvantages, particularly weight gain and teratogenicity, because the efficacy of VPA is unsurpassed by any modern suitable AED such as LTG and TPM [4,13] or LEV. Although LTG and TPM are used for previously untreated adolescents and adults with generalized or unclassified epilepsies, the efficacy of LTG is inferior to that of VPA. Absence seizures are fundamentally different from any other type of seizures and, therefore, unique in terms of pharmacological treatment. Typical absence seizures are often easy to diagnose and treat. VPA, ethosuximide, and LTG, alone or in combination, are first-line agents. VPA controls absences in 75% of patients and also GTCS (70%) and myoclonic jerks (75%); however, it may be undesirable for some women. Similarly, LTG may control absences and GTCS in possibly 50 to 60% of patients, but may worsen myoclonic jerks; skin rashes are common. Ethosuximide controls 70% of absences, but it is unsuitable as monotherapy if other generalized seizure types coexist. A combination of any of these three drugs may be needed for resistant cases. Low dosages of LTG added to VPA may have a dramatic beneficial effect. Clobazam, particularly in absences with myoclonic components, and acetazolamide may be useful adjunctive drugs. Generalized myoclonic seizures are different pharmacologically from absence seizures. If VPA has failed to control myoclonic seizures, LEV is a well-tolerated and effective add-on medication [14]. LEV has, however, not been tested for treatment of previously untreated juvenile myoclonic epilepsy or other idiopathic generalized epilepsies. PRM and PHB, which may be a last resort for treatment of refractory juvenile myoclonic epilepsy, are ineffective and may even worsen absence seizures. The epilepsy syndrome may also play a role. For example, LTG, which is effective in children with typical absence seizures, may worsen myoclonic seizures in infants with severe myoclonic epilepsy. Children are, in general, more vulnerable. Controlled studies of new AEDs in pediatric populations are significantly behind those for adults; consequently, such agents are initially licensed for adults only. Pediatricians have to learn by success or failure in daily practice.

6.3. Advantages of modern AEDs

The most modern AEDs are less enzyme inducing than CBZ, PHT, or barbiturates or less enzyme inhibiting than VPA, or do not influence hepatic enzyme systems at all. This is why, in general, treatment with the new AEDs causes fewer adverse drug interactions. During long-term exposure to some of the newer AEDs, fewer hormonal–metabolic disturbances can reasonably be expected. Based on current evidence, the major malformation rate associated with the use of LTG is similar to that seen during CBZ treatment or in untreated women with epilepsy and is lower than that observed with VPA treatment. A second, very important advantage of some of the modern AEDs is the absence of hypersensitivity reactions. These data suggest, in our view, that a modern AED should be preferred over a classic AED when starting drug treatment in a patient with new-onset epilepsy. In addition, the choice of an AED is also influenced by the individual's characteristics. When first-line AEDs have brought insufficient results, a number of second- and third-line AEDs are available: As these drugs all have quite significant limitations, with respect to either evidence of efficacy or, at least in part, safety concerns (see Section 5), they are recommended only in cases of disabling refractory epilepsy.

Recommendation: The choice of AED among first-line agents needs to be individualized based mainly on the patient profile, including the efficacy for the seizure or epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics (including current or likely future need for concomitant medication for comorbidity), and finally cost and physician preference.

7. Finding the optimal dose of an antiepileptic drug

The drug of choice for a particular type of epilepsy is titrated to the lowest effective dose. If seizures continue, the daily dose is increased by small increments to the average effective dose [9–11]. Except in an emergency, there is no need for rapid titration. Most modern AEDs work within several days to a week of starting treatment. Rapid titration is not only unnecessary, but may even be harmful. It increases the risk of cutaneous hypersensitivity reactions, for example, with CBZ, LTG, and PHT, and adds avoidable central nervous system toxicity, particularly during early PRM therapy. In recent years it was determined that the average effective dose

achieves seizure control in about 70–80% of those who respond at all doses, including above-average doses. As a consequence, a dose increment is useful for only about 20–30% of those whose seizures are not controlled by a well-tolerated average dose. If seizure control cannot be achieved with the maximum tolerated dose, a dose reduction to the previous average dose is recommended. If toxic symptoms or high plasma concentrations indicate an increased risk of toxicity before seizures are controlled, a second AED is added, again guarding against toxicity. Interaction between drugs can interfere with their rate of metabolic degradation. If the patient does not respond sufficiently, the initial, failed anticonvulsant is then withdrawn gradually and transfer to monotherapy with the recently added AED is an option. If the patient responds well, the combination of drugs is usually maintained unless side effects require downtitration to lower the total drug load. Daily dosage for adults and children is summarized in Tables 4 and 5. The time to reach average daily dosages varies considerably among AEDs (Table 4).

Recommendation: Slow titration up to average maintenance doses is generally advisable, because rapid dose escalation and higher-than-average dosages cause adverse events. Higher-than-average doses are more likely to improve seizure control in only an additional 20–30% of all responders. If the therapeutic benefit is not seen after further dose escalation, returning to the previous dose will avoid unnecessary toxicity.

8. Single-drug versus add-on therapy

Once single-drug therapy is not able to control seizures, addition of a second drug and substitution monotherapy are common options. When the initially prescribed AED fails to produce seizure freedom, transfer to monotherapy with an alternative agent (substitution) will lead to seizure control in as many as 15–30% of cases [15,16].Two randomized controlled trials with mostly old, enzyme-inducing AEDs have compared substitution with combination therapy and obtained a rather similar outcome [17,18]. There are no conclusive data favoring either substitution monotherapy or add-on treatment. Except for patients with severe idiosyncratic reactions, where substitution is clearly preferable, a pragmatic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug. This may prevent the substitution of a partially efficacious drug with a nonefficacious drug. Reduction of the first drug prevents unnecessary drug exposure in case of adverse effects. The second drug should be chosen on the basis of which first drug failed. The use of newer-generation AEDs that do not interact with other drugs may possibly provide a better outcome for add-on treatment, which is more vulnerable to adverse drug interactions than substitution monotherapy. The main advantages of substitution versus combination include simplicity allowing clear attribution of observed clinical effect, no unnecessary drug load (overtreatment) as in combination therapy, no detrimental drug interactions, and no adverse effects of specific combinations, for example, increased teratogenicity with a combination of VPA and LTG. Furthermore, transfer to monotherapy has been shown to be useful when combination therapy has failed to provide sufficient seizure control. A safe and well-communicated transfer schedule is as essential as the choice of optimal agent for the success of either combination or substitution.

Recommendation: Except for patients with severe idiosyncratic reactions, where substitution is clearly preferable, a pragmatic choice is to evaluate the combination first and to slowly taper and finally discontinue the first drug if the response to the combination is not impressive. Combining may prevent the substitution of an insufficiently efficacious drug with a nonefficacious drug. Reduction of the first drug prevents unnecessary drug exposure in case of adverse effects. In the decision on the next drug, drugs that have failed in the past should be avoided and modern AEDs that are better suited for combination therapy because of the absence of adverse drug interactions should be considered.

9. Monitoring treatment with antiepileptic drugs

Target plasma AED concentrations are available for a number of drugs [see 9]. However, plasma AED concentrations are less useful to follow than the clinical course. Some patients have toxic symptoms at low concentrations, whereas others tolerate higher concentrations without apparent clinical symptoms. Some patients

Table 4
Dosages and effective plasma concentrations of often used AEDs for adults.

AED	Suggested titration	Suggested range of average target dose (total mg/day; frequency of dosing)	Time to reach average dose (weeks)	Target plasma concentration (mg/L)
Carbamazepine	200 mg every 3 days	600–1200 bid or tid	3	3–12
Clobazam	10 mg per day	10–20 bid	1	[a]
Felbamate	300 mg every 7 days	2400–3600 bid, tid	6	20–45
Gabapentin	300 mg every 1-3 days	900–2400 bid, tid	3	[a]
Lamotrigine	Monotherapy: 25 mg for 2 weeks, 50 mg for the next 2 weeks, then increases of 50–100 mg/week. Add-on in the presence of VPA: 25 mg every other day for 2 weeks, 25 mg/day for the next 2 weeks, then increases of 25–50 mg/week. Add-on in the presence of enzyme-inducing AEDs: 50 mg for 2 weeks, 100 mg for the next 2 weeks, then increases of 50–100 mg/week.	100–400 qd, bid	7–10	2–15
Levetiracetam	500 mg every 1–3 days	1000–3000 bid	2	[a]
Oxcarbazepine	150 mg every 3–7 days	800–1800 bid, tid	2–3	7.5–20 (MHD)
Phenobarbital	50 mg every 7 days	50–200 qd, bid	4	10–40
Phenytoin	50–100 mg every 3–5 days; beyond 200 mg in 25–30 mg steps	200–300 bid, tid	2	5–25
Pregabalin	75–150 mg every 3–7 days	150–600	4	[a]
Primidone	62.5–250 mg every 7 days	500–750 tid	8	10–40 (PHB)
Tiagabine	6 mg every 5–7 days	36–60 tid	5	[a]
Topiramate	25 mg for 1–2 weeks; beyond 100 mg, 25–50 mg per week	100–400 bid	4–6	[a]
Vigabatrin	500 mg every 7 days	500–3000 bid	2	[a]
Valproate	500 mg every 3–7 days	600–1500 bid slow release, tid	2	40-120
Zonisamide	25 mg	300	3	

Note. qd, once a day; bid, two times per day; tid, three times per day; qid, four times per day.
Source. Modified from Ref. [9].
[a] Irrelevant.

Table 5
Dosages of AEDs for children.

AED	Total daily dosage, frequency of dosing, titration
Bromide	300-mg starting dose, average dose (mg/day up to 2100 mg); time to reach average dose is 8 weeks
Acetazolamide	8–30 mg/kg in daily divided doses; not to exceed 750 mg/day
Carbamazepine	<6 years old: initially 5 mg/kg, divided bid, tid, qid; increased every 5–7 days up to 20 mg/kg 6–12 years old: initially 10 mg/kg bid, maximum 200 mg; increased by 100 mg/day at weekly intervals up to 15–30 mg/kg
Clonazepam	Initially 0.01–0.03 mg/kg, maximum 0.05 mg/kg bid, tid; increased by 0.25–0.5 mg/kg every 3 days until seizures are controlled or adverse effects occur; for maintenance, 0.1–0.2 mg/kg tid
Ethosuximide	<6 years old: initially 15 mg/kg divided bid, maximum 500 mg; increased every 4–7 days; for maintenance, 15–40 mg/kg bid, maximum 1500 mg >6 years old: initially 250 mg bid; increased by 250 mg bid as needed every 4–7 days; for maintenance, usually 20–40 mg/kg bid, maximum 1500 mg
Felbamate	4–14 years old: start with 7.5–15 mg/kg per day bid or tid; lower dose of PHT and VPA comedication by 20–30%; increase dose by 7.5 mg/kg per day every 2 weeks, if needed; do not exceed a total daily dose of 45 mg/kg or 3600 mg
Gabapentin	10-50 mg/kg tid, qid
Lamotrigine	<12 years old Add-on with ei-AED, no VPA: initially 0,6 mg/kg/day for 2 weeks, then 1.2 mg/kg/day for 2 weeks, maximum15 mg/kg/day or 400 mg/day Add-on with ei-AED *and* VPA: initially, 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, then 1.2 mg/kg/day in one or two doses,; maximum 5 mg/kg/day or 200 mg/day Add-on with VPA, no ei-AEDs: initially, 0.15 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day, maximum 5 mg/kg/day or 200 mg/day
Levetiracetam	Children aged 4–11/adolescents aged 12–17 weighing <50 kg: initial therapeutic dose 10 mg/kg bid; dose can be increased to 30 mg/kg bid; dose changes should not exceed 10 mg/kg every 2 weeks; children ⩽20 kg should preferably start the treatment with 100 mg/ml oral solution; starting dose of 10 mg/kg daily corresponds to 150, 200, and 250 mg bid for children weighing 15, 20, and 25 kg, respectively; maximum dose of 30 mg/kg bid translates to 450, 600, and 750 mg bid for children weighing 15, 20, and 25 kg, respectively; dosage in children ⩾50 kg is the same as for adults
Oxcarbazepine	⩾6 years old: initially 8–10 mg/kg/day, increased every week by 10 mg/kg/day, maximum 46 mg/kg/day, given bid
Phenobarbital	Neonates: 3–4 mg/kg, then increased Infants: 5–6 mg/kg in one or two divided doses
Phenytoin	Neonates: initially 5 mg/kg, bid; for maintenance, usually 5–8 mg/kg bid, tid
Pregabalin	Use in patients <17 years old is not recommended (EMEA SPC)
Primidone	<8 years: initially 50–125 mg at bedtime, increased by 50–125 mg/day every 3–7 days; for maintenance, usually 10–25 mg/kg tid, qid
Tiagabine	Use in patients <12 years old is not recommended
Topiramate	Initially 0.5–1 mg/kg, increased 0.5–1 mg/kg bid weekly or biweekly; for maintenance, usually 3–6 mg/kg in monotherapy, 5–9 mg/kg in combination, bid
Vigabatrin	Monotherapy for treatment of West syndrome: start with 50 mg/kg per day; up to 150 mg/kg per day has been tolerated
Valproate	Initially 10–15 mg/kg bid, tid, increased by 5–10 mg/kg/day at weekly intervals; for maintenance, usually 30–60 mg/kg bid, tid
Zonisamide	Use in patients <18 years old is not recommended (EMEA SPC)

Note. For target plasma concentrations, see Table 4. ei-AED, enzyme-inducing AED; qd, once a day; bid, two times per day; tid, three times per day; qid, four times per day.
Source. Modified from Ref. [9].

respond at very low concentrations; others do not respond even to very high concentrations. If treatment is ineffective, monitoring of concentration may unmask irregular drug compliance; conversely, a high concentration may indicate that a higher dose increment is not likely to lead to a better response and, in addition, involves a higher risk of drug toxicity. In a patient with unexplained central nervous system toxicity, high plasma AED concentrations may be useful for diagnosis and management of the intoxication. Except for PHT, for which monitoring is strongly recommended, particularly at concentrations above 20 mg/L because of the nonlinear saturation dose kinetics, monitoring of other AED plasma concentrations is optional and should be individualized.

Recommendation: Except for PHT, for which monitoring is strongly recommended, particularly at concentrations above 20 mg/L because of the nonlinear saturation dose kinetics, monitoring of other AED plasma concentrations is optional and should be individualized (e.g., poor drug compliance or adverse events).

10. Management of drug-resistant epilepsy

The definition of drug resistance is elusive. In the broadest sense, all epilepsy is drug resistant, because drugs are a palliative treatment preventing the clinical expression of seizures but cannot affect the underlying pathological state. In a large study of patients evaluated and treated in Glasgow, Scotland, Kwan and Brodie [16] found that of 470 patients who had never before received an AED, 301 (64%) became seizure free for at least 12 months during treatment. Of the 248 patients uncontrolled by the first drug, 113 discontinued the first drug because of lack of efficacy; 69 because of intolerable side effects; 29 because of idiosyncratic reactions; and 37 for other reasons. Only 79 of these 248 patients (32%) subsequently became seizure free. The outcome among these patients was strongly associated with the reason for failure of treatment with the first drug. Another 12 (11%) patients in whom treatment with the first drug was ineffective subsequently became seizure free. Only 4% adequately responded to a third drug. Similarly, only 3% of patients responded to two drugs. However, new evidence from several studies has suggested that the results of Kwan and Brodie [16] may have been too pessimistic. Long-term observations indicate that as many as 20–30% with apparent drug-resistant seizures will eventually enter remission after a change in drug regimen [see, e.g., 19]. The response to newly administered AEDs was highly dependent on past treatment history. The seizure-free rates decreased from 61.8% for the first AED to 41.7, 16.6, and 0% after one, two to five, and six or seven AEDs proved inefficient [19]. Although relative drug-resistant epilepsy can be diagnosed after failure of two AEDs, absolute drug resistance requires failure of six AEDs, as a significant minority of patients (16.6%) are rendered seizure free by addition of newly administered AEDs even after failure of two to five antiepileptic drugs [19]. The good outcome in as many as one of five patients indicated that there is hope, even after many years of having uncontrolled epilepsy.

If epilepsy is considered drug resistant if treatment for ⩾12 months does not achieve seizure freedom, for whatever reason, as many as 36% of newly treated patients are drug resistant [16]. However, if the definition of frequent and severe seizures despite optimal treatment is used so that alternative therapies including surgery might be indicated, only 5–10% of newly diagnosed patients are estimated to be drug resistant [20]. The proportion of uncontrolled epilepsy (seizure frequency at least one per month for 18 months, adopted from [21]) was 15.6%, corresponding to a prevalence of 0.94 per 1000 [22].

There are multiple reasons why patients may be resistant to AED therapy. An incorrect diagnosis may lead to ineffective treat-

ment. For example, use of CBZ in a patient with absence seizures and generalized spike–wave activity could exacerbate seizures. Likewise, treating a patient with complex partial seizures with ethosuximide is unlikely to be helpful. Certain AEDs such as GBP, PGB, VGB, and LTG can exacerbate myoclonic seizures.

It has been suggested that altered drug permeability across the blood–brain barrier (BBB) may be involved in pharmacoresistance to AEDs [23]. ATP-dependent multidrug transporters such as P-glycoprotein are found in the luminal membranes of brain capillary endothelial cells and are known to play a role in BBB function by limiting drug penetration into the brain. Reduced target sensitivity of use-dependent blockade of voltage-dependent Na^+ channels in CBZ-resistant patients is another novel mechanism underlying the development of drug-resistant epilepsy. Current theories on drug resistance in epilepsy include the drug transporter hypothesis, the drug target hypothesis, and a novel approach called the inherent severity model of epilepsy, which posits that the severity of the disease determines its relative response to medication. Valuable as each of these hypotheses is, none is currently a stand-alone theory that is able to convincingly explain drug resistance in human epilepsy. As a consequence, it may be of interest to update and integrate the various hypotheses of drug resistance and to explore possible links to the severity of epilepsy. The observation that a high frequency of seizures prior to onset of treatment is prognostic of increased severity and future drug refractoriness suggests that common neurobiological factors may underlie both disease severity and pharmacoresistance. Such a link has been proposed for depression; however, the evidence for a direct mechanistic link, genetic or otherwise, between drug response and severity of human epilepsy remains elusive. Although emerging data from experimental studies suggest that alterations in $GABA_A$ receptors may represent one example of a mechanistic link, clearly more work is needed to explore whether common neurobiological factors may underlie both epilepsy severity and drug refractoriness [23].

It is now clear that although the new-generation AEDs are very useful, they are not able to reverse drug-resistant epilepsy in the vast majority of patients [24]. The medical, social, and economic consequences of poorly controlled seizures can be enormous. Recurrent seizures are associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Frequent seizures not only influence quality of life, morbidity, and mortality in epilepsy, but also significantly increase costs.

Recommendation: Although the exact mechanism(s) of drug resistance remains elusive, we know that a change in regimen in apparently refractory epilepsy will eventually lead to seizure freedom in as many as one in five patients. Avoiding resignation on the side of the patient and complacency on the side of the physician is essential to the success of medical treatment. Drug-resistant epilepsy is associated with significant risks for death, physical injury, cognitive impairment, and psychosocial problems. Early referral for exploring surgical treatment is advisable; two-thirds of patients respond to AEDs after surgery, and one-third remain seizure-free after AEDs have been withdrawn. If surgery is not an option, change in medical regimens and palliative vagus nerve stimulation are good options.

11. Limitations of current drug treatment

11.1. Prophylactic treatment

Head injuries with skull fractures, intracranial hemorrhages, focal neurological deficits, and amnesia cause posttraumatic epilepsy in 25 to 75% of cases. Prophylactic treatment with anticonvulsant drugs after the head injury reduces the probability of early posttraumatic seizures during the first few weeks after the injury, but does not prevent the development of permanent posttraumatic epilepsy months or years later. Early treatment after a second tonic–clonic seizure does not improve the long-term outcome of the epilepsy. It is now clear that although the new-generation AEDs are very useful, many patients in whom previous drug regimens were ineffective will not respond to the drugs. A challenge for the scientific community is to determine the causes of these drug failures and circumvent obstacles to seizure control by developing novel treatment strategies.

11.2. Seizure aggravation

Seizure aggravation is an important limitation of current AEDs. Idiopathic generalized epilepsies (IGEs) are particularly prone to pharmacodynamic aggravation: typical absences are consistently increased by CBZ, VGB, TGB, and GBP, whereas PHT is less aggravating. Juvenile myoclonic epilepsy is aggravated often by CBZ and less frequently by PHT and other AEDs. The GTCS that occur in IGEs may respond to AEDs that aggravate the other seizure types. Nonconvulsive status epilepticus has been associated with TGB. GBP-associated myoclonus appears to be relatively frequent. It is usually mild and can easily be overlooked. Discontinuation of therapy is not necessary in most cases. Patients with symptomatic generalized epilepsies often have several seizure types that respond differently to AEDs: myoclonias are generally aggravated by the same drugs that aggravate IGEs; tonic seizures in the Lennox–Gastaut syndrome respond to CBZ, which, however, may aggravate atypical absences. In severe myoclonic epilepsy of infancy, LTG has a nearly constant aggravating effect. In some patients with benign Rolandic epilepsy, clear aggravation may be produced by CBZ, with occurrence of negative myoclonias, atypical absences, drop attacks, and, at the maximum evolution, a state of electrical status epilepticus during sleep. Only a few medications can control IGEs without potentially causing seizure aggravation. Broad-spectrum AEDs such as VPA, LTG, and TPM are extremely effective at controlling a variety of seizures without causing excessive seizure aggravation. Among these drugs, VPA has the longest clinical experience history and the largest body of published data.

11.3. Loss of effect (tolerance)

Development of tolerance (i.e., reduction in response to a drug after repeated administration) is an adaptive response of the body to prolonged exposure to the drug, and tolerance to AEDs is no exception. Tolerance develops to some drug effects much more rapidly than to others. The extent of tolerance depends on the drug and individual (genetic?) factors. Tolerance may lead to attenuation of side effects but also to loss of efficacy of AEDs and is reversible after discontinuation of drug treatment.

Different experimental approaches are used to study tolerance in laboratory animals. Development of tolerance depends on the experimental model, drug, drug dosage, and duration of treatment, so that a battery of experimental protocols are needed to evaluate fully whether tolerance to effect occurs. Two major types of tolerance are known. Pharmacokinetic (metabolic) tolerance, resulting from induction of AED-metabolizing enzymes, has been shown for most first-generation AEDs and is easy to overcome by increasing dosage. Pharmacodynamic (functional) tolerance is due to "adaptation" of AED targets (e.g., by loss of receptor sensitivity) and has been shown experimentally for all AEDs that lose activity during prolonged treatment. Functional tolerance may lead to complete loss of AED activity and cross-tolerance to other AEDs. Convincing experimental evidence indicates that almost all first-, second-, and third-generation AEDs lose their antiepileptic activity during prolonged treatment, although to different extents. Because of diverse confounding factors, detecting tolerance in patients with

epilepsy is more difficult, but can be done with careful assessment of decline during long-term individual patient response. After exclusion of confounding factors, tolerance to antiepileptic effect for most modern and old AEDs can be shown in small subgroups of responders by assessing individual or group response.

Development of tolerance to the antiepileptic activity of an AED may be an important reason for failure of drug treatment. Knowledge of tolerance to AED effects as a mechanism of drug resistance in previous responders is important for patients, physicians, and scientists [25].

11.4. Unpredictability of effects

Drug treatment of epilepsy is characterized by unpredictability of efficacy, adverse drug reactions, and optimal doses in individual patients, which, at least in part, is a consequence of genetic variation. Since genetic variability in drug metabolism was reported to affect treatment with PHT more than 25 years ago, the ultimate goal of pharmacogenetics has been to use the genetic makeup of an individual to predict drug response and efficacy, as well as potential adverse drug events. However, determining the practical relevance of pharmacogenetic variants remains difficult, in part because of problems with study design and replication. This article reviews the published work with particular emphasis on pharmacogenetic alterations that may affect the efficacy, tolerability, and safety of AEDs, including variation in genes encoding drug target (SCN1A), drug transport (ABCB1), drug metabolism (CYP2C9, CYP2C19), and human leukocyte antigen (HLA) proteins. Although the current studies associating particular genes and their variants with seizure control or adverse events have inherent weaknesses and have not provided unifying conclusions, several results, for example, that Asian patients with a particular HLA allele, HLA-B*1502, are at higher risk of developing Stevens–Johnson syndrome when using CBZ, are helpful in increasing our knowledge of how genetic variation affects the treatment of epilepsy. Although genetic testing raises ethical and social issues, a better understanding of genetic influences on epilepsy outcome is key to developing the much needed new therapeutic strategies for individuals with epilepsy [26].

Recommendation: Although AED treatment is beneficial for most patients, AEDs do not prevent epilepsy in persons at risk or drug-resistant epilepsy even when given early. Aggravation of mostly myoclonic or absence seizures by drugs for partial seizures is another problem. Unpredictability of effect and loss of effect during prolonged treatment are further issues in drug treatment.

12. Avoidable treatment errors

12.1. Overtreatment

The most common avoidable treatment errors stem from misdiagnosis and inadvertent overtreatment. Common forms of misdiagnosis occur early in the management of a patient who is thought to have epilepsy, but in fact has syncope with myoclonia or psychogenic nonepileptic seizures. Subsequent AED use provides no benefit, even at higher doses, which invariably result in adverse events. Overtreatment may, however, also occur in patients with unequivocal epileptic seizures. Although complete seizure control is the ultimate goal of pharmacological therapy, it should not be sought at all costs, and no patient with epilepsy should suffer more from the side effects of treatment than from the consequences of the underlying disease. Overtreatment is not uncommon in patients taking AEDs, and it may occur in many forms and by a variety of mechanisms. Long-term use (or continuation) of AED therapy in situations where it is not indicated (e.g., in children with simple febrile seizures or in seizure-free patients who have undergone brain surgery) constitutes an overt case of overtreatment. Other forms of overtreatment include the use of unnecessarily rapid dose escalation rates, which may expose the patient to potentially serious or severe side effects, or the prescription of unnecessarily high maintenance dosages. The latter may result from inadequate understanding of dose–response relationships, from misinterpretation of serum drug concentrations (e.g., targeting concentrations within the "range" in patients who are well controlled at lower concentrations), or, less often, from failure to recognize a paradoxical increase in seizure frequency as a sign of drug toxicity. The most common form of overtreatment, however, involves the unnecessary use of combination therapy (polypharmacy) in patients who could be treated optimally with a single drug. Adverse effects associated with polypharmacy often result from undesirable drug–drug interactions. Although pharmacokinetic interactions are somewhat predictable and can be minimized or controlled by monitoring serum drug concentrations and/or dose adjustment, pharmacodynamic interactions leading to enhanced neurotoxicity (as seen, e.g., in some patients given a combination of LTG and CBZ) can be identified only by careful clinical observation. There is evidence that not all AED combinations are equally adverse, and that the combined use of specific drugs (e.g., LTG and VPA) may even exhibit an improved therapeutic index in some patients compared with either agent given alone, provided appropriate dose adjustments are made. In women of childbearing potential, however, the same combination is associated more often with fetal malformations than either drug alone. Unless and until we better understand the complexities of drug combinations, single-drug therapy may avoid inadvertent overtreatment associated with polypharmacy.

12.2. Undertreatment

Unfortunately, treatment of patients with uncontrolled epilepsy with suboptimal doses may prevent seizure remission. In every patient with uncontrolled epilepsy a dose increment should be considered unless the patient has symptoms and signs of incipient central nervous system or other organ drug toxicity. It has been shown that in as many as one in three patients presenting with uncontrolled seizures, increasing the dose led to seizure remission [27].

Recommendation: Keep it simple; avoid unnecessary diagnostic or therapeutic interventions with an unfavorable risk–benefit balance. It is advisable to withhold drug treatment until the diagnosis of epilepsy is certain. Avoid combination therapy and enzyme-inducing agents if possible. Both overtreatment and undertreatment with AEDs should be avoided.

13. Special treatment needs

One of the standards of good clinical care is to individualize the treatment of epilepsy to the special needs of the individual with epilepsy. Here we focus on the elderly and those with mental health problems. Other important patient groups are discussed elsewhere [9].

13.1. The elderly

The change in pharmacokinetics and higher sensitivity to adverse events of many AEDs usually require more cautious dosing in the elderly. In addition, high comorbidity in the elderly often requires additional medication. To avoid disturbing drug interactions, AED monotherapy and the use of modern AEDs that are not involved or subject to drug interactions, such as GBP [28], low-dose TPM [29], and LEV (no evidence class I study available), are preferable. Compliance may be more difficult in the elderly

with cognitive decline. Multimorbidity with many comedications is common. The elderly may have an increased susceptibility for adverse events, especially when treated with CBZ. Ataxia may be more frequent in the elderly, and discontinuation of AEDs because of adverse events is more common in the elderly than in younger adults. Lower doses of AEDs are often sufficient because treatment response may be better in the elderly. Lower glomerular filtration rates in the elderly require much lower doses of renally excreted AEDs; body fat, albumin, and cytochrome p450 changes also occur in the elderly, and OXC-related hyponatremia may be more frequent in the elderly. Osteoporosis should not be overlooked in the elderly with epilepsy who are on enzyme-inducing AEDs or VPA. Elderly women with epilepsy present several unique management challenges. They have an elevated risk for osteoporotic fracture because of the adverse effects of AEDs on bone metabolism, combined with the chance of trauma during seizures and the subtle effects of AEDs on coordination that promote falling.

Recommendation: Epilepsy in the elderly is increasing although specialists see surprisingly few elderly patients with epilepsy. It is advisable to prefer non-metabolized, non-enzyme inducing new AEDs such as GBP and LTG in the elderly instead of classic enzyme-inducing CBZ, if possible. Slow dose escalation and lower-than- average dosages are recommended; AED combination therapy should be avoided, and clear written instructions are important.

13.2. Patients with mental health disorders

The lifetime community-based prevalence of depression, suicidal ideation, and generalized anxiety disorder is twofold higher in patients with epilepsy than in the general population [30] (Table 6). Suicide is a leading cause of death in patients with refractory epilepsy. Depression and, less well known, anxiety disorders are the leading causes of suicidal death in epilepsy. Severity of depression (not seizure frequency) seems to be the most important correlate for quality of life. Serotonin reuptake inhibitors can be given for depression in persons treated with AEDs for epilepsy without worsening of seizure control. Treatment of depression does not seem to affect seizure control either way. Reboxetine and citalopram are good candidate antidepressants for people with epilepsy. Anxiety can be treated with anxiolytic agents such as buspirone (10–20 mg/day) [31]. In patients with uncontrolled epilepsy and anxiety who require a change in AED regimen, add-on treatment with an anxiolytic AED such as PGB may be considered. In patients with dysthymia and mood instability, mood-stabilizing AEDs such as lamotrigine and valproate should be considered, particularly when a change in regimen is considered to improve seizure control. Conversely, treatment with PHT or PHB has been shown to be associated with depression in some patients, even when treatment has resulted in seizure freedom. In case both seizure control and mood stability are proving resistant to AEDs, vagus nerve stimulation should be considered. Vagus nerve stimulation has been shown to improve seizure control and mood, particularly postictal mood changes. In patients undergoing resective surgery for refractory epilepsy, particularly refractory temporal lobe epilepsy, those becoming seizure free after surgery often report improved mental well-being. It is difficult to say at present if the improvement in mood is a specific effect of surgery or if it also occurs when a change in AED regimen has led to seizure freedom in apparently refractory partial epilepsy.

Table 6
Psychiatric comorbidity in people with epilepsy and the general population.

Psychiatric disorder (lifetime)	Percentage (95% CI)	
	Epilepsy, $N = 253$	No epilepsy $N = 36{,}717$
Major depressive disorder	17.4% (10.0–24.9)	10.7% (10.2–11.2)
Mood disorder	24.4% (16.0–32.8)	13.2% (12.7–13.7)
Anxiety disorder	14.1% (7.2–21.1)	11.2% (10.8–11.7)
Mood disorder/anxiety disorder/dysthymia	34.2% (25.0–43.3)	19.6% (19.0–20.2)
Panic disorder/agoraphobia	6.6% (2.9–10.3)	3.6% (3.3–3.9)
Suicidal ideation	25.0% (17.4–32.5)	13.3% (12.8–13.8)
Any mental health disorder	35.5% (25.9–44.0)	20.7% (19.5–20.7)

Source. Modified from Ref. [30].

Recommendation: Depression and particularly anxiety are often underdiagnosed in patients with epilepsy, particularly drug-resistant epilepsy. Treatment with selective serotonin reuptake inhibitors and anxiolytic agents such as buspirone are as safe and effective as in a patient without epilepsy. It is advisable to avoid classic AEDs such as PHT and PHB, which may contribute to depressive mood, and to prefer new, mood-stabilizing AEDs such as LTG or anxiolytic AEDS such as PGB. Vagus nerve stimulation should be considered if seizures and depression prove to be drug resistant.

14. Stopping therapy with antiepileptic drugs

Starting an AED is much easier than stopping treatment. The possibility that the patient may have developed serious or cognitive adverse events is an argument in favor of discontinuing AEDs. On the other hand, a seizure relapse may have grave social consequences, particularly in an adult. Drug discontinuation after seizure freedom results in relapse in one-third of patients. Reinstitution of a medication that worked for years fails to achieve control in one of four patients. These risks need to be considered, although there is no evidence that discontinuation is responsible for the poor prognosis of treatment of seizure recurrence in some patients [32]. However, women in their childbearing years who are seizure free should also be encouraged to stop medication that may cause malformations. Studies have shown that the risk of seizure recurrence becomes lower with the duration of prior seizure remission [33]. Patients who had been in remission for at least 2 years were prospectively randomized into a group that continued drug treatment and another group in which drugs were gradually withdrawn. Two years after the study commenced, 78% who continued treatment remained seizure free compared with 59% who had stopped treatment. However, 5 years after withdrawal, there were no differences in seizure relapse rate between the withdrawal and no withdrawal groups. A meta-analysis of several studies suggests that this figure may be as low as 30% [34]. The MRC study identified age over 16, concurrent therapy with one or more AEDs, seizures after starting AED therapy, history of secondarily generalized seizures or myoclonic seizures, short period of freedom from seizures, and abnormal EEG as significant factors predicting recurrence. Etiology is important, and patients with brain lesions or cerebral palsy may be more prone to recurrence. Although there is no class I evidence, most patients with juvenile myoclonic epilepsy are advised to continue medication for life. It is probably advisable to wait until seizures have been in remission for at least 3 years in remission before considering withdrawal of AED therapy. However, in children with benign epilepsies that have well-defined natural histories, such as those with centrotemporal spikes, shorter periods may be sufficient.

Withdrawal of AED therapy should be planned, gradual, and always one drug at a time. Status epilepticus is possible, although uncommon, with abrupt cessation. No clear guidance is available as to how fast AEDs should be withdrawn. It has been suggested that cessation of therapy over a period less than 6 months results in higher rates of relapse [35]. However, recent studies have shown that more rapid tapering over periods as short as 6 weeks [36] may be just as safe as slow withdrawals over 6 or more months.

15. Conclusion

The majority of patients with epilepsy will achieve lasting remission on drug treatment. Of those who do not, significant risks of mortality and morbidity exist due to uncontrolled seizures. Seizure freedom is therefore very important. Several new drugs have been added to the armamentarium and these should be tried in each refractory patient. These are not always effective, however, and surgical options should be explored.

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