Acta neurol. belg., 2008, **108**, 118-130

Guideline

Recommendations for the treatment of epilepsies in general practice in Belgium

Paul BOON[1], Sebastiaan ENGELBORGHS[2], Henri HAUMAN[3], An JANSEN[4], Lieven LAGAE[5], Benjamin LEGROS[6], Michel OSSEMANN[7], Bernard SADZOT[8], Etienne URBAIN[9] and Kenou VAN RIJCKEVORSEL[10]

[1]Ghent University Hospital,& Ghent University, Gent, Belgium ; [2]Department of Neurology and Memory Clinic, ZNA-Middelheim and ZNA-Hoge Beuken, Faculty of Medicine, University of Antwerp, Antwerpen, Belgium ; [3]Sint-Maarten Hospital, Duffel, Belgium ; [4]University Hospital Brussel, Vrije Universiteit Brussel, Belgium ; [5]University Hospital, Leuven, Belgium ; [6]Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Belgium ; [7]University Clinic UCL de Mont-Godinne, Yvoir, Belgium ; [8]University Hospital Centre Sart-Tilman, Liège, Belgium ; [9]Grand Hôpital de Charleroi, Charleroi, Belgium ; [10]Saint Luc University Hospital, Université Catholique de Louvain, Bruxelles, Belgium

Abstract

The large choice of antiepileptic drugs (AEDs) in Belgium complicates the selection of the appropriate product for the individual patient. International guidelines on the treatment of epilepsy have been published, but are not tailored to the Belgian situation. This publication presents recommendations from a group of Belgian epilepsy experts for the practical management of epilepsy in general practice in Belgium. It includes recommendations for initial monotherapy and add-on treatment in adult patients (≥ 16 years) and initial monotherapy in paediatric patients (< 16 years). For these three situations a first choice AED is recommended. One or more alternative first choice AEDs are defined for patients in which certain patient- or AED-related factors preclude the use of the first choice product. Selection of compounds was based on the registration and reimbursement status in Belgium, the level of evidence of efficacy, common daily practice and the personal views and experiences of the authors. The paper reflects the situation in 2008.

In addition to the treatment recommendations, other relevant points to consider in the treatment of epilepsy with AEDs are addressed, including comorbidity and age of the patient, the interaction potential, pharmacokinetic properties and safety profile of the AEDs, and generic substitution.

Introduction

Epilepsy is one of the most common neurological conditions, affecting about 1 in 150 to 200 people (1). Epileptic seizures can be classified as focal (about 60% of the patients (2)) or generalized seizures (3, 4). Focal seizures start in a localized part of the brain. In some patients the electrical abnormalities may subsequently spread throughout the brain. In patients with generalized seizures, such as absences, myoclonic seizures and tonic-clonic seizures, abnormal electrical activity is bilateral and synchronous.

Epilepsy may also be classified by epileptic syndrome (i.e. a unique combination of disease characteristics such as seizure type, typical age of onset, EEG findings, and prognosis ; examples are Lennox-Gastaut syndrome and West syndrome), sometimes by genetic cause (Ring chromosome 20 associated epilepsy), or by aetiology (e.g. idiopathic versus symptomatic/cryptogenic epilepsy).

Epilepsy is commonly treated with antiepileptic drugs (AEDs). AED treatment is aimed primarily at prevention of new seizures and/or decrease of the severity of the seizures. Treatment generally starts with a single drug (monotherapy) at the lowest effective dose (5). If the efficacy of this first AED is considered insufficient, the dose is gradually increased until seizures are controlled or adverse effects become unacceptable. About 50% of the patients are adequately treated with the first single AED (6). If seizure control is considered insufficient and further increase of the AED dose is inadvisable because of side effects, another AED is started as monotherapy in the majority of cases (5). If seizures are still not adequately controlled, which occurs in about 30% of the patients, combination therapy with two (or more) AEDs is usually considered (6).

The number of AEDs registered in Belgium is considerable. Some of these products have been available for decades (e.g. carbamazepine, phenytoin, valproate, phenobarbital, primidone), whereas others have been introduced in the 1990s (e.g. gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate).

The choice of an AED is based on patient-related factors, such as seizure type or epileptic syndrome, age of the patient, liver and kidney function, use of concomitant medication, concomitant diseases, and AED-related factors such as the expected efficacy of the AED in the diagnosed type of epilepsy, the ease of use, dosing frequency, tolerability and safety, pharmacokinetics, and reimbursement status.

The authors have been listed alphabetically. All authors have made equal contributions to this article. This paper has been prepared under the auspices of the Belgian League against Epilepsy.

The large number of available AEDs makes the selection of the appropriate AED for the individual patient a complicated task. In 2002 a group of Belgian epilepsy experts published an article with common and practical strategies to start treatment of newly diagnosed epilepsy (7). Since then, guidelines on the treatment of new-onset epilepsy have been published by the International League against Epilepsy (ILAE, 2006) (8), the American Academy of Neurology and the American Epilepsy Society (AAN, 2004) (9), the Scottish Intercollegiate Guidelines Network (SIGN, 2003) (100), and the UK National Institute for Clinical Excellence (NICE, 2004) (11). Guidelines on the treatment of refractory epilepsy have been published by the AAN (2004) (12). All guidelines were published some years ago, and do not include results of recently published clinical studies. In addition, these guidelines may not always be applicable to the Belgian situation, since they do not take into account the Belgian registration and reimbursement status of the AEDs or common clinical practice in Belgium.

The current publication provides recommendations for the treatment of epilepsy in general clinical practice, focusing on the Belgian situation. The recommendations are based on the registration and reimbursement status of the AEDs in Belgium in 2008, the level of evidence of efficacy, common daily practice and the personal views and experiences of the authors. For an extensive discussion of the available scientific data, the reader is referred to textbooks or review articles on the treatment of epilepsy.

Methodology

The recommendations for treatment of epilepsy presented in this paper were prepared in 2008 by a group of Belgian epilepsy experts. Starting point for the discussions were the published guidelines on the treatment of new onset epilepsy (ILAE, 2006 (8) ; AAN, 2004 (9) ; SIGN, 2003 (10) ; NICE, 2004 (11)) and refractory epilepsy (AAN, 2004) (12). In addition a literature search was performed to identify relevant controlled clinical trials with AEDs published after the cut-off dates used in these guidelines. The criteria used to determine the relevance of the studies were similar to those used in the published guidelines. The recommendations from the published guidelines and the relevant publications identified in the literature search were evaluated for their applicability to the Belgian situation (registration status, reimbursement, clinical practice).

The discussions resulted in recommendations for :

– Initial monotherapy for seizures in adult patients (≥ 16 years)
– Add-on treatment of refractory seizures in adult patients (≥ 16 years)
– Initial monotherapy for seizures and epileptic syndromes in paediatric patients (< 16 years)

The following criteria were used to select the recommended compounds :

– The AED is registered and reimbursed in Belgium (this criterion could not always be met in the recommendations for paediatric patients) ;
– The AED with the highest level of evidence of efficacy is recommended as first choice (using the ILAE classification of levels of evidence for monotherapy and the AAN classification of levels of evidence for add-on treatment ([1])) ;
– If the level of evidence for different AEDs is the same or if there is only limited evidence, recommendations are based on personal views and experiences of the authors.

(1)

	ILAE definitions (8)	AAN definitions (12)
Level of evidence	Criteria	Criteria
A	≥ 1 class I studies or meta-analysis meeting class I criteria sources or ≥ 2 class II studies	≥ 1 convincing class I studies or ≥ 2 consistent, convincing class II studies
B	1 class II study or meta-analysis meeting class II criteria	≥ 1 convincing class II study or ≥ 3 consistent class III studies
C	≥ 2 class III double-blind or open-label studies	≥ 2 convincing and consistent class III
D	1 class III double-blind or open-label studies	–
Class study	Criteria	Criteria
I	Randomized, controlled study ; double-blind design ; no forced exit criterion ; either superiority demonstrated or detectable noninferiority boundary ≤ 20% ; treatment duration ≥ 48 weeks	Prospective, randomized, controlled clinical trial with masked outcome assessment. The following criteria should be fulfilled : primary outcome(s) clearly defined ; patient selection clearly defined ; adequate accounting for drop-outs and cross-overs (numbers sufficiently low) ; baseline characteristics sufficiently equivalent or appropriate statistical adjustment for differences
II	Randomized, controlled study ; double-blind design ; no forced exit criterion ; either superiority demonstrated or detectable noninferiority boundary ≤ 30% ; treatment duration ≥ 24 weeks	Prospective matched group cohort study with masked outcome assessment meeting the criteria mentioned above or a randomized controlled trial that lacks one of these criteria.
III	Randomized, controlled study	All other controlled trials where outcome assessment is independent of patient treatment
IV	Other studies	Other studies, case series, case reports, or expert opinion

The following definitions will be used :

First choice = First treatment choice in the "**ideal patient**", i.e. a patient without any specific factors precluding the use of this AED (e.g. no relevant comorbidity or concomitant medication).

Alternative first choice = Product recommended when certain patient factors (e.g. comorbidity, concomitant medication) or AED-related factors (e.g. pharmacokinetic properties, interaction potential, contraindications, adverse event profile) preclude the use of the first choice product.

Recommendations for treatment

Initial monotherapy in adults (≥ 16 years)

Recommendations for initial monotherapy in adults are presented in Table 2.

Focal seizures with/without secondary generalization

Registered and reimbursed treatment options for monotherapy in this indication are : carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, pheneturide, phenytoin, primidone, topiramate, and valproate (Table 1).

Of these treatment options *carbamazepine* is considered first choice in the "ideal patient". Carbamazepine is a narrow spectrum AED with level A evidence of efficacy in partial onset seizures (8). It has been exhaustively tested in clinical practice for several decades.

Of the recommended alternative first choices *levetiracetam* is the only compound with level A of efficacy in focal seizures in the entire age group of adults over 16 years of age (13). Levetiracetam has a more favourable safety profile than carbamazepine, superior pharmacokinetics and no known potential for drug interactions (Table 5). The only drawback is that it has been less exhaustively tested in clinical practice than carbamazepine.

Alternative first choice *lamotrigine* has level C evidence of efficacy in the general (adult) population. Level A evidence of efficacy was only demonstrated in elderly patients (8). The recently published SANAD study demonstrated that, with non-inferior efficacy, lamotrigine is better tolerated than carbamazepine (level C evidence) (14). Lamotrigine is not likely to affect the pharmacokinetics of other compounds (including other AEDs ; Table 5), but the metabolism of lamotrigine is accelerated by enzyme-inducing drugs and decreased by enzyme-inhibiting drugs (e.g. valproate). Clinical experience with lamotrigine is less than that with carbamazepine.

Primary generalized tonic-clonic seizures

Registered and reimbursed treatment options for monotherapy in this indication are : carbamazepine, lamotrigine, phenytoin, phenobarbital, primidone, topiramate and valproate (Table 1). There are no AEDs with level A or B evidence of efficacy in this indication (8). Valproate, carbamazepine, lamotrigine and topiramate all have level C evidence of efficacy (8). In the recent SANAD study valproate was more effective than lamotrigine and better tolerated than topiramate in patients with generalized and unclassified epilepsy (level C evidence) (15). The choice of *valproate* as first choice is based on all level C evidence, personal experience of the authors and on its ease of use. *Carbamazepine*, *lamotrigine* and *topiramate* are considered suitable alternative first choices in situations where valproate can not be used (see Table 5). It should be noted that carbamazepine and lamotrigine may induce or aggravate myoclonic seizures and that carbamazepine may also induce or aggravate absences. Phenytoin and phenobarbital are not recommended as first choice because of their unfavourable side effect profile.

Juvenile myoclonic epilepsy (JME)

JME starts during adolescence but usually requires lifelong therapy with AEDs. Registered and reimbursed treatment options for monotherapy in JME are primidone and valproate (Table 1). *Valproate* is recommended as first choice, although it has only level D evidence of efficacy (there are no AEDs with level A, B or C) (8). Its tolerability and (long-term) safety have been well established. In some cases *lamotrigine* may be a valuable alternative first choice, despite the fact that it is not registered in Belgium for this indication. It also has level D evidence of efficacy. It should be noted that lamotrigine may worsen myoclonias in some patients. The results of treatment should therefore be monitored carefully.

The other registered/reimbursed AED (primidone) is not recommended because its level of evidence of efficacy is lower and because it has an inferior safety profile.

Type of seizures not (yet) established

Adequate diagnosis of epilepsy with proper classification of seizures is very important for the selection of an AED. If the seizure type has not yet been established but the start of AED treatment is required, a broad spectrum AED should be used. *Valproate* is recommended as first choice because of its well-established efficacy and safety and its ease of use. The use of carbamazepine is not recommended in this situation.

Add-on treatment of refractory seizures in adult patients (≥ 16 years)

Treatment options for this group of patients are presented in Table 3. All AEDs listed in the table for add-on treatment in focal seizures with/without

Table 1

AEDs (ATC code N03) registered and reimbursed in Belgium (Source: RIZIV/INAMI - 01-08-2008 (18))

AED	Focal seizures with/without secondary generalization	Primary generalized tonic-clonic seizures	Juvenile myoclonic epilepsy	Other indications (reimbursed)	Other registered indications (not reimbursed)[a]
Carbamazepine	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children			
Ethosuximide				Absence epilepsy; atonic seizures, myoclonias	
Felbamate				Add-on treatment in patients with Lennox Gastaut syndrome in adults and children ≥ 4 y (when not responding to any other relevant AED)	
Gabapentin	Add-on treatment Adults + children[b]				Monotherapy of partial-onset epilepsy with/without secondary generalization in adults and children > 12 y
Lamotrigine	Monotherapy Adults + children ≥ 12 y Add-on treatment Adults + children[c]	Monotherapy Adults + children ≥ 12 y Add-on treatment Adults + children[c]		Add-on treatment of Lennox Gastaut syndrome in adults and children[c]	
Levetiracetam	Monotherapy Adults + children ≥ 16 y Add-on treatment Adults + children ≥ 4 y		Add-on treatment Adults + children ≥ 12 y		Add-on treatment of primary generalized tonic-clonic seizures in adults and children > 12 y
Oxcarbazepine	Mono- and add-on therapy Adults + children ≥ 6 y				
Pheneturide	Adults + children ≥ 2 y				
Phenobarbital[d]	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults and children			
Phenytoin	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children			
Pregabalin	Add-on treatment Adults + children ≥ 17 y				
Primidone	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children		
Tiagabine	Add-on treatment Adults + children ≥ 12 y				
Topiramate	Monotherapy Adults + children ≥ 6 y Add-on treatment Adults + children ≥ 2 y	Monotherapy Adults + children ≥ 6 y Add-on treatment Adults + children ≥ 2 y		Add-on treatment in patients with Lennox Gastaut syndrome in adults and children ≥ 2 y	
Valproate	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children	Mono- and add-on therapy Adults + children	Mono- and add-on therapy in patients with Lennox syndrome, West syndrome, absence epilepsy in adults and children	
Vigabatrin	Add-on treatment (last choice) Adults + children			Monotherapy of infantile spasms (West syndrome)	

[a]The mentioned indications are not always registered for all brands/products ; [b]Age limit varies among brands. Reimbursement criteria do not specify an age limit ; [c]Age limit varies among brands ; [d]Available as Gardenal (partly reimbursed) and as magisterial preparation for paediatric use (fully reimbursed). The available combination products (Epipropane tablets) are not recommended.

Table 2

Initial monotherapy of seizures in adults (≥ 16 years)

	First choice[a]	Level of evidence of efficacy[b]	Alternative first choice[a]	Level of evidence of efficacy[b]	Remarks
Focal seizures with/without secondary generalization	Carbamazepine	A	Levetiracetam	A	– *Levetiracetam* has a better pharmacokinetic and safety profile than *carbamazepine*, with no potential for drug interactions. – For *lamotrigine* the overall level of efficacy is C. Level A evidence of efficacy was only obtained in elderly patients.
			Valproate	B	
			Lamotrigine Oxcarbazepine Topiramate	C	
Primary generalized tonic-clonic seizures	Valproate	C	Carbamazepine	C	– *Carbamazepine* may induce or aggravate myoclonic seizures and absences – *Lamotrigine* may induce or aggravate myoclonic seizures
			Lamotrigine		
			Topiramate		
Type of seizures not (yet) established	Valproate	–		–	– The use of *carbamazepine* is not recommended
Juvenile myoclonic epilepsy	Valproate	D	Lamotrigine	D	– *Lamotrigine* is not registered and not reimbursed for juvenile myoclonic epilepsy; – *Lamotrigine* may exacerbate myoclonias

[a] First choice = First treatment choice in the "ideal patient", i.e. a patient without any specific factors precluding the use of this compound (e.g. comorbidity, concomitant medication)
Alternative first choice = Product recommended when certain patient factors (e.g. comorbidity, concomitant medication) or compound-related factors (e.g. pharmacokinetic properties, interaction potential, adverse event profile) preclude the use of the first choice product.

[b] Level of evidence of efficacy : the criteria used to establish the level of evidence of efficacy are taken from Glauser T. *et al.* (2006).

Table 3

Add-on treatment of refractory seizures in adults (≥ 16 years)

	Recommended AEDs	Remarks
Focal seizures with/without secondary generalization	Carbamazepine	– All AEDs are efficacious as add-on treatment of refractory epilepsy in adults[a], and are considered first choice. The AEDs are listed in alphabetical order. – *Carbamazepine* has been used in clinical practice for over 30 years, but has a high potential for pharmacokinetic interactions – *Gabapentin, levetiracetam* and *pregabalin* have the most favourable pharmacokinetic and safety profile, and no potential for drug interactions – *Vigabatrin* is also registered and reimbursed for add-on treatment of refractory partial-onset epilepsy, but should only be used when all other compounds are ineffective, because it has a very unfavourable safety profile (concentric visual field defects).
	Gabapentin	
	Lamotrigine	
	Levetiracetam	
	Oxcarbazepine	
	Pregabalin	
	Tiagabine	
	Topiramate	
	Valproate	
Primary generalized tonic-clonic seizures	Carbamazepine	– All AEDs are efficacious as add-on treatment of primary generalized tonic-clonic seizures in adults[b], and are considered first choice. The AEDs are listed in alphabetical order.
	Lamotrigine	
	Levetiracetam	
	Topiramate	
	Valproate	

[a] For all newer AEDs the level of evidence of efficacy is A (the criteria used to establish the level of evidence of efficacy are taken from French J.A. *et al.* ; 2004). No add-on studies have been performed with the older AEDs ; efficacy of these compounds is considered to be established during long-term clinical experience.

[b] For all newer AEDs the level of evidence of efficacy is A (the criteria used to establish the level of evidence of efficacy are taken from French J.A. *et al.* ; 2004). No add-on studies have been performed with the older AEDs ; efficacy of these compounds is considered to be established during long-term clinical experience.

secondary generalization (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and valproate) are considered to be equally efficacious. Vigabatrin, which is also registered and reimbursed for this indication, is not recommended because it can induce irreversible visual field defects.

The compounds recommended for add-on treatment of primary generalized tonic-clonic seizures (carbamazepine, lamotrigine, levetiracetam, topiramate, valproate) are also considered to be equally efficacious.

Selection of the optimal compound for add-on treatment in the individual patient should be based on patient-specific variables and AED-specific variables. The pharmacokinetic parameters, availability of different pharmaceutical formulations and other factors important in choosing an AED are summarized in Table 5. Of all compounds recommended for add-on therapy, gabapentin, levetiracetam and pregabalin are the least likely to interact with other AEDs (see *Interaction potential and pharmacokinetic profile of AEDs* section) (16).

Initial monotherapy of epilepsy in children (< 16 years)

In Table 4a recommendations are presented for the treatment of epilepsy in children, classified by seizure type (focal seizures, generalized seizures). Randomized, controlled clinical studies on monotherapy of seizures in children are scarce (8). The recommendations for the treatment of seizures in children are therefore largely based on the personal experience of the authors.

As in adult patients, *carbamazepine* is considered first choice in children with focal seizures with or without secondary generalization. Based on personal experience of the authors, *valproate* (approved and reimbursed for all age groups), *oxcarbazepine, topiramate and lamotrigine* (only reimbursed in certain age groups), and *levetiracetam* (off label use) are recommended as alternative first choices.

For all types of generalized seizures (tonic-clonic seizures, typical absence seizures and myoclonic seizures) *valproate* is considered first choice. Recommendations for alternative first choices depend on the type of generalized seizures.

The recommendations for treatment of children in whom the type of epilepsy has not (yet) been established are the same as those for adult patients (first choice *valproate*).

Febrile seizures (occurring during an episode of high fever) occur in about 2-5% of all children. If atypical febrile seizures occur (or febrile seizures are frequent, severe or of long duration), prophylactic treatment with *valproate* may be considered.

Neonatal seizures (seizures occurring during the first month of life) have many characteristics that are quite different from other types of epilepsy, and may often be associated with other conditions, such as perinatal asphyxia, metabolic disorders and CNS or systemic infections. In addition to adequate treatment of the underlying conditions, neonatal seizures may be treated with AEDs. However, little scientific progress has been made in this respect. Though phenobarbital has its drawbacks, it is still the drug of choice for the treatment of neonatal seizures.

Table 4b lists the first choice AEDs for treatment of the most frequently occurring epileptic syndromes in children. Identification of the syndrome type is useful to estimate the impact of the epilepsy on childhood development. Frequency of seizure recurrence and prognosis with respect to cognition, memory and overall morbidity and mortality may vary considerably among syndromes.

Points to consider

Interaction potential and pharmacokinetic profile of AEDs

Most patients with epilepsy are treated for several years and many need life-long treatment with AEDs. Epilepsy is often associated with other (CNS-related) conditions (see below), and patients with epilepsy may also develop diseases unrelated to their epilepsy. All these concomitant diseases may require pharmacological treatment. In addition, women of childbearing potential may also wish to use oral contraceptives.

Therefore the absence of a potential for drug interactions is an important positive feature of an AED. Factors contributing to an increased likelihood of drug interactions are low bioavailability, high plasma protein binding, extensive metabolism, a capacity to induce or inhibit drug metabolizing enzymes, and excretion by active processes. Table 5 shows that *gabapentin*, *levetiracetam* and *pregabalin* have the lowest potential for drug interactions.

In addition to potential drug interactions, other pharmacokinetic properties may be relevant when choosing an AED, such as linear pharmacokinetics, a sufficiently long elimination half life to allow once or twice daily dosing, and the absence of active metabolites. The pharmacokinetic properties of the AEDs are also presented in Table 5.

Adverse events

Treatment with AEDs is often associated with side effects. For a complete overview of all adverse events the reader is referred to the summaries of product characteristics (SmPCs) or package inserts of the individual AEDs. There are considerable differences between the various sources of information (such as published review articles, repertorium) on the most important (or clinically most relevant)

Table 4a

Initial monotherapy of seizures in children (< 16 years)

	First Choice[a]	Alternative First Choice[b]			Remarks
		Approved for the indication	Only approved in certain age groups	Off-label	
Focal seizures with/without secondary generalization	Carbamazepine	Valproate	Lamotrigine (≥ 12 y) Oxcarbazepine (≥ 6 y) Topiramate (≥ 6 y)	Levetiracetam	
Generalized seizures					
* Tonic-clonic seizures					
– *with other generalized seizure types*	Valproate		Lamotrigine (≥ 12 y) Topiramate (≥ 6 y)	Levetiracetam	
– *without other seizure types*	Valproate	Carbamazepine	Lamotrigine (≥ 12 y) Topiramate (≥ 6 y)	Levetiracetam	
* Typical absence seizures	Valproate	Ethosuximide		Lamotrigine	– *Carbamazepine*, *oxcarbazepine* and *phenytoin* may worsen seizures
* Myoclonic seizures	Valproate	Ethosuximide		Levetiracetam Topiramate	– *Carbamazepine*, *oxcarbazepine, phenytoin* and sometimes *lamotrigine* may worsen seizures – *Benzodiazepines* may be a treatment option for (sub)acute use
Type of seizures not yet established	Valproate				– The use of *carbamazepine* is not recommended
Febrile seizures	-			Valproate	– *Valproate* should not be used in patients with metabolic disease
Neonatal seizures	Phenobarbital			Benzodiazepines Phenytoin	– In difficult cases referral to a specialized centre is recommended

[a] First choice = First treatment choice in the "ideal patient", i.e. a patient without any specific factors precluding the use of this compound (e.g. comorbidity, concomitant medication).

[b] Alternative first choice = Product recommended when certain patient factors (e.g. comorbidity, concomitant medication) or compound-related factors (e.g. pharmacokinetic properties, interaction potential, adverse event profile) preclude the use of the first choice product.

Table 4b

Initial monotherapy of frequent epileptic syndromes in children (< 16 years)

	First Choice[a]	Remarks
Childhood absence epilepsy (CAE)	Valproate	
Juvenile absence (JAE) or myoclonic epilepsy (JME)	Valproate	– *Carbamazepine*, *oxcarbazepine* and *phenytoin* may worsen seizures
Benign childhood epilepsy with centrotemporal spikes (BCECTS)	No treatment Carbamazepine	– *Carbamazepine* may provoke ESES[b]
Childhood occipital epilepsy (Panayiotopoulos type and Gastaut type)	Carbamazepine	
Late onset childhood occipital epilepsy (Gastaut type)	Carbamazepine	
West syndrome	Vigabatrin	
Lennox-Gastaut syndrome (LGS), Doose syndrome	Valproate	– For refractory cases of Lennox-Gastaut syndrome *felbamate* is a treatment option
Epileptic encephalopathy with ESES including Landau-Kleffner syndrome (LKS)	Valproate	
Progressive myoclonic epilepsies (PME)	Valproate Levetiracetam (off-label)	– *Carbamazepine*, *oxcarbazepine* and *phenytoin* may worsen seizures – *Valproate* is contraindicated in patients with mitochondriopathies – *Lamotrigine* may worsen some myoclonias

[a] First choice = First treatment choice in the "ideal patient", i.e. a patient without any specific factors precluding the use of this compound (e.g. comorbidity, concomitant medication).
[b] ESES = Electrical Status Epilepticus during slow wave Sleep.

Table 5

Important factors in determining the choice of an AED

AED[a]	Presence of Favourable Pharmacokinetic Properties[b]							Interaction potential				Pharmaceutical formulations			Contraindications[d]	Caution in patients with[d]
	High bioavailability	Low plasma protein binding	Long half-life	Significant renal excretion in unchanged form	Absence of oxidation or conjugation	Absence of active metabolites	Linear kinetics	Uncommon target of drug interactions[b]	Uncommon cause of drug interactions[b]	Enzyme inducer (CYP)[c]	Enzyme inhibitor (CYP, UGT)[c]	Tablet/capsule	Liquid oral formulation or dispersible tablet	i.v. formulation		
Carbamazepine	✓	✓	[e]							✓		✓	✓		Atrioventricular block ; History of bone marrow depression ; History of aplasia medullaris or acute intermittent porphyria	History of heart, liver or kidney disease, history of drug-induced haematological reactions or oxcarbazepine- or phenytoin-induced hypersensitivity reactions ; Increased intraocular pressure Latent psychosis, mental confusion or agitation (in elderly)
Ethosuximide	✓	✓	✓			✓	✓		✓				✓		–	Liver and kidney disease
Gabapentin		✓		✓	✓	✓		✓	✓			✓			–	–
Lamotrigine	✓	✓	✓			✓	✓		✓	✓[i]	✓[i]	✓	✓		–	Impaired kidney function (may lead to accumulation of glucuronide metabolite)
Levetiracetam	✓	✓	[f]	✓	✓	✓	✓	✓	✓			✓	✓	✓	–	Impaired kidney function
Oxcarbazepine	✓	✓				✓	✓	✓		✓		✓			–	History of carbamazepine-induced hypersensitivity reactions ; low plasma sodium levels or treatment with sodium-lowering drugs (e.g. diuretics) ; disturbances in cardiac conduction (atrioventricular block, arrhythmia)
Phenobarbital	✓	✓	✓	✓		✓	✓			✓		✓			Porphyria ; Severe respiratory insufficiency Severe renal or hepatic impairment	Impaired kidney function (dose reduction required) Impaired liver function (dose reduction required)
Phenytoin	✓		✓			✓				✓		✓			Absolute: porphyria, chronic cardiac disorders Relative: liver and kidney disease, viral hepatitis	Decreased protein binding capacity (dose reduction required) ; diabetes
Pregabalin[h]	✓	✓		✓	✓	✓	✓	✓	✓			✓			–	Diabetes (adaptation of antidiabetic medication may be required) ;
Tiagabine	✓					✓	✓		✓			✓			Severe hepatic impairment	History of severe behavioural disturbances including generalized anxiety and depression ;
Topiramate	✓	✓	✓	✓		✓	✓		✓[g]	✓[g]		✓			–	Presence of risk factors for kidney stones or use of medication with a risk of increasing kidney stone formation. Impaired liver function
Valproate	✓		[e]			✓					✓	✓	✓	✓	Acute and chronic hepatitis ; History or family history of severe hepatitis ; Hepatic porphyria	Haemorrhagic diathesis ; AIDS ; renal insufficiency (may require dose adaptation), lupus erythematosus, disturbances in enzymes involved in urea metabolism, history of pancreatitis
Vigabatrin	✓	✓	[f]	✓	✓	✓	✓	✓	✓			✓			–	Impaired kidney function History of clinically significant visual field defects ; History of psychosis, depression or behavioural problems.

[a]This table only includes the AEDs mentioned in Tables, 2, 3 and 4a/b ; [b]Data taken from Perucca, 2003 (16) ; [c]Data taken from Elger, 2008 (6) . [d]Taken from "contraindications and "special warnings and precautions" sections of Summary of Product Characteristics. All products are contraindicated in patients with known hypersensitivity to the active substance or structurally related compounds, or to one of the excipients of the product ; [e]Sustained release formulations suitable for twice daily dosing ; [f] Prolonged effect despite short half-life allows twice-daily dosing ; [g]< 200 mg/day ; [h]For pregabalin data on pharmacokinetics and interaction potential are taken from the Summary of Product Characteristics ; [i]No relevant effect on disposition of other AEDs.

Table 6

Most important adverse events of AEDs

AED[a]	Central Nervous System	Behavioural/Cognitive	Skin	Blood	Gastrointestinal	Other
Carbamazepine	Dizziness	Behavioural	Rash	Leucopenia		Hyponatriemia
Ethosuximide	Drowsiness	Behavioural	Rash	Aplastic anemia	GI disturbances	
Gabapentin	Somnolence/sleepiness					Weight gain
Lamotrigine	Headache	Behavioural	Rash			
Levetiracetam	Somnolence/sleepiness	Behavioural				
Oxcarbazepine	Dizziness	Behavioural		Leucopenia		Hyponatriemia
Phenobarbital	Drowsiness	Cognitive				Osteoporosis
Phenytoin	Ataxia	Cognitive	Rash			Gingival hypertrophy, osteoporosis
Pregabalin	Somnolence/sleepiness					Weight gain
Tiagabine	Dizziness	Cognitive				
Topiramate	Dizziness	Cognitive			Anorexia	Weight loss
Valproate	Tremor	Behavioural			GI disturbances	Weight gain

[a] This table only includes the AEDs mentioned in Tables, 2, 3 and 4a/b.

side effects. The conclusions of the authors regarding the clinically most relevant adverse effects of the recommended AEDs are presented in Table 6.

The adverse event profile of an AED may play a role in the selection of treatment. It is for instance not advisable to treat elderly patients with AEDs with a considerable sedative effect, or to treat patients with a history of psychiatric conditions with AEDs known to induce depression or psychosis.

Comorbidity

Epilepsy is often associated with other CNS-related conditions, including anxiety, suicidal thoughts, depression, cognitive decline, migraine, and psychogenic non-epileptic seizures (6). Depression is estimated to occur in about 50% of patients with refractory partial epilepsy (6). Memory function may decline 10 years earlier than in age-related controls (6). Other less common psychiatric comorbid conditions include autism and psychosis. Migraine also seems to be more common in patients with epilepsy, particularly in those with a history of head trauma or a family history of migraine (6). In addition, injuries, sexual dysfunction and endocrine reproductive disorders also have a higher prevalence in patients with epilepsy (6).

The presence of comorbid conditions is an important parameter in the selection of an AED. Some AEDs are contraindicated in patients with certain conditions, and other AEDs should only be used with caution in specific groups of patients (see Table 5).

Elderly

Treatment of epilepsy in elderly patients should be done with caution. In elderly patients with new-onset epilepsy, focal seizures are the most common type of seizures (often related to stroke). For this type of seizures *lamotrigine* is first choice, having level A evidence of efficacy (8). *Levetiracetam* is a good alternative first choice, because of its favourable safety and pharmacokinetic profile (16). In elderly patients with new-onset generalized seizures (which may occur in patients with Alzheimer's disease or other neurodegenerative dementias) *valproate* is recommended as first choice.

In all cases, slower than usual dose escalation and lower-than-average maintenance doses are recommended. It should be noted that AEDs may have a different pharmacokinetic behaviour in elderly patients (due to lower protein binding, decreased liver and kidney function, changes in distribution volume) and elderly patients may have an increased susceptibility of the nervous system leading to an increase in adverse effects. In addition, elderly patients are more likely to have comorbid diseases or use concomitant medication.

Generic substitution

In this publication AEDs are referred to by their generic name. Some compounds are marketed by several pharmaceutical companies. When a patient is successfully treated with a particular brand it is advised to continue treatment with that same product. Switching from one brand to another may lead to differences in bioavailability of the antiepileptic compound, and therefore to differences in clinical efficacy and safety (17).

Acknowledgements

This work was supported by an unrestricted grant from UCB Pharma SA/NV, Brussels, Belgium. UCB facilitated the organization of the expert meetings, but was not involved in the actual preparation of the recommendations.

REFERENCES

1. Belgian League against Epilepsy (www.epilepsieliga.be ; www.ligueepilepsie.be).
2. Hauser W. A., Annegers J. F., Rocca W. A. Descriptive epidemiology of epilepsy : Contributions of population-based studies from Rochester, Minnesota. *Mayo Clin. Proc.*, 1996, **71** : 576-586.
3. From the Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures.. *Epilepsia*, 1981, **22** (4) : 489-501.
4. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*, 1989, **30** : 389-399.
5. Legros B., Boon P., Dejonghe P., Sadzot B., Van Rijckevorsel K., Schmedding E. Opinion of Belgian neurologistss on antiepileptic drugs : Belgian Study on Epilepsy Tretament (BESET). *Acta Neurol. Scand.*, 2007, **115** : 97-103.
6. Elger C. E., Schmidt D. Modern management of epilepsy : A practical approach. *Epilepsy & Behavior*, 2008, **12** : 501-539.
7. De Borchgrave V., Delvaux V., de Tourchaninoff M., Dubru J. M., Ghariani S., Grisar Th., Legros B., Ossemann M., Sadzot B., Tugendhaft P., van Bogaert P., Van Rijckevorsel K. Therapeutic strategies in the choice of antiepileptic drugs. *Acta Neurol. Belg.*, 2002, **102** : 6-10.
8. Glauser T., Ben-Menachem E., Bourgeois B., Cnaan A., Chadwick A., Guerreiro C. *et al.* ILAE Treatment Guidelines : Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes. *Epilepsia*, 2006, **47** (7) : 1094-1120.
9. French J. A., Kanner A. M., Bautista J., Abou-Khalil B., Browne T., Harden C. L. *et al.* Efficacy and tolerability of the new antiepileptic drugs I : Treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee

of the American Academy of Neurology and the American Epilepsy Society. *Neurology*, 2004, **62** : 1252-1260.

10. Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Epilepsy in Adults. A national clinical guideline. April 2003. ISBN 1 899893 58 X.
11. NHS. National Institute for Clinical Excellence. The epilepsies. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. Clinical Guideline 20, October 2004. ISBN 1-84257-808-1.
12. French J. A., Kanner A. M., Bautista J., Abou-Khalil B., Browne T., Harden C. L. *et al.* Efficacy and tolerability of the new antiepileptic drugs II : Treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*, 2004, **62** : 1261-1273.
13. Brodie M. J., Perucca E., Ryvlin P., Ben-Menachem E., Meencke H. J ; Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology*, 2007, **68** (6) : 402-8.
14. Marson A. G., Al-Kharusi A. M., Alwaidh M., Appleton R., Baker G. A., Chadwick D. W., Cramp C., Cockerell O. C., Cooper P. N., Doughty J., Eaton B., Gamble C., Goulding P. J., Howell S. J., Hughes A., Jackson M., Jacoby A., Kellett M., Lawson G. R., Leach J. P., Nicolaides P., Roberts R., Shackley P., Shen J., Smith D. F., Smith P. E., Smith C. T., Vanoli A., Williamson P. R ; SANAD Study group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy : an unblinded randomised controlled trial. *Lancet*, 2007, **369** (9566) : 1000-15.
15. Marson A. G., Al-Kharusi A. M., Alwaidh M., Appleton R., Baker G. A., Chadwick D. W., Cramp C., Cockerell O. C., Cooper P. N., Doughty J., Eaton B., Gamble C., Goulding P. J., Howell S. J., Hughes A., Jackson M., Jacoby A., Kellett M., Lawson G. R., Leach J. P., Nicolaides P., Roberts R., Shackley P., Shen J., Smith D. F., Smith P. E., Smith C. T., Vanoli A., Williamson P. R ; SANAD Study group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy : an unblinded randomised controlled trial. *Lancet*, 2007, **369** (9566) : 1016-26.
16. Perucca E., Johannesen S. I. The ideal pharmacokinetic properties of an antiepileptic drug : how close does levetiracetam come ? *Epileptic Disord.*, 2003, **5** (Suppl. 7) : S17-S26.
17. Krämer G., Biraben A., Carreno M., Guekht A., de Haan G. J., J drzejczak J., Josephs D., van Rijckevorsel K., Zaccara G. Current approaches to the use of generic antiepileptic drugs. *Epilepsy & Behavior*, 2007, **11** : 46-52.
18. Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV) ; Institut national d'assurance maladie-invalidité (INAMI) ; (www.inami.fgov.be ; www.riziv.fgov.be).

Prof. dr. Paul Boon,
Ghent University Hospital,
185 De Pintelaan,
B-9000 Gent (Belgium).
E-mail : Paul.Boon@Ugent.be