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Development of an electronic decision tool to support appropriate treatment choice in adult patients with epilepsy – Epi-Scope®

Benjamin Legros [a,*], Paul Boon [b], Berten Ceulemans [c], Thomas Coppens [d], Karine Geens [e], Henri Hauman [f], Lieven Lagae [g], Alfred Meurs [h], Leon Mol [i], Michel Ossemann [j], Kenou van Rijckevorsel [k], Michel Van Zandijcke [l], Pascal Vrielynck [m], Daniëlla Wagemans [n], Thierry Grisar [o]

[a] *Hôpital Erasme, Université Libre de Bruxelles, Centre de Référence Pour le Traitement de l'Épilepsie Réfractaire, 808, Route de Lennik, 1070 Bruxelles, Belgium*
[b] *Reference Center for Refractory Epilepsy, Ghent University Hospital, Belgium*
[c] *University Hospital, University of Antwerp, Antwerp, Belgium*
[d] *Hôpital Civil de Charleroi, Charleroi, Belgium*
[e] *AZ KLINA, Brasschaat, Belgium*
[f] *AZ St-Maarten-CEPOS, Duffel, Belgium*
[g] *University Hospitals KUL, Leuven, Belgium*
[h] *Universitair Ziekenhuis Gent, Universiteit Gent, Gent, Belgium*
[i] *Vlaamse Liga tegen Epilepsie, Turnhout, Belgium*
[j] *Cliniques Universitaires UCL de Mont-Godinne, Université Catholique de Louvain, Yvoir, Belgium*
[k] *Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium*
[l] *AZ Sint-Jan Brugge-Oostende, Bruges, Belgium*
[m] *Centre Neurologique William Lennox, Reference Center for Refractory Epilepsy, Ottignies, Belgium*
[n] *Medical Department, Pfizer Belgium, Belgium*
[o] *GIGA Neurosciences Centre, Université de Liège, Liège, Belgium*

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ABSTRACT

Background: Given the continuous knowledge progression and the growing number of available antiepileptic drugs (AEDs), making appropriate treatment choices for patients with epilepsy is increasingly difficult. While published guidelines help for separate clinical aspects, patients with a combination of specific characteristics may escape proper guidance. This study aimed to determine the appropriateness of AEDs for particular clinical variables and to offer treatment recommendations for adult patients with epilepsy in a user-friendly format for practicing neurologists.
Methods: Using the RAND/UCLA Appropriateness Method, the appropriateness of AEDs as initial/second mono-therapy and combination therapy was assessed in relation to selected clinical variables by a Belgian panel of 13 experts in epilepsy. Panel recommendations for particular patient profiles were determined by the outcome of these separate ratings.
Results: The appropriateness outcome of individual AEDs was not substantially different between first and second mono-therapy; valproate was considered appropriate for all types of generalised and partial seizures. The outcome for combination therapy was highly dependent on the type of AED and seizures. With respect to co-morbidities and co-treatments, levetiracetam and pregabalin proved to have the least contra-indications. For the elderly and with respect to factors related to the female reproductive system the appropriateness of AEDs showed a more diffuse pattern. Although caution was deemed necessary for some combinations, the AEDs were never considered inappropriate regarding their drug interaction profile.
Conclusions: The Epi-Scope® tool that displays appropriateness recommendations for highly specific, possibly complex cases, supports optimal treatment choices for adult patients with epilepsy in daily practice.

1. Introduction

The epilepsies are a widespread and heterogeneous group of chronic neurological diseases for which pharmacotherapy is still the mainstay treatment.[1] Considerable efforts have been made

* Corresponding author. Tel.: +32 2 5553429; fax: +32 2 5553942.
E-mail address: blegros@ulb.ac.be (B. Legros).

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over the last decades to develop new antiepileptic drugs (AEDs) and formulations.[2,3] Consequently, the pharmaceutical arsenal of AEDs has enlarged considerably and has become increasingly complex with respect to mechanism of action and safety/tolerability. In daily clinical practice, many different treatment strategies are used consecutively, often by "trial and error". A less directive approach could play a role in the relatively large population of medically refractory patients (about one third of those with newly diagnosed epilepsy) that still exists.[4] In addition, recent clinical insights have influenced the definition of epileptic syndromes and led to the identification of novel therapeutic indications.[5]

The continuous evolution in knowledge and drug development makes it challenging for the general neurologist to keep track of the different (contra-)indications of AEDs and their combinations in relation to particular patient characteristics. Making appropriate treatment choices in face of an individual patient with epilepsy may be increasingly difficult, despite the existence of renowned and high-quality guidelines from leading neurological associations such as the International League Against Epilepsy (ILAE) and the American Academy of Neurology and the American Epilepsy Society (AAN/AES).[6,7] Also the National Institute for Clinical Excellence and the Scottish Intercollegiate Guidelines Network published a management guide.[8,9] Current therapeutic guidelines, however, present somewhat conflicting recommendations and are very meticulously focussed on the indication itself, leaving other clinical aspects (apart from advanced age[6,7]) largely unattended because of scant evidence. Moreover, they usually do not cover complex patient profiles that present with co-existing morbidities, concomitant treatments and other parameters that complicate disease management. It is fairly unlikely that these types of complex patients will be studied in randomised controlled trials, leading to evidence-based data. Nevertheless, some kind of guidelines to help physicians treating these patients would be welcomed.

It therefore felt desirable as well as useful to develop recommendations on the appropriate use of AEDs in relation to relevant clinical aspects in adult patients with epilepsy and secondly, to embed these into a user-friendly software program to allow easy access for neurologists in daily clinical practice.

2. Methods

2.1. Panel process

The appropriateness of AEDs for particular patient profiles was assessed using the RAND/UCLA Appropriateness Method (RAM).[10,11] This modified Delphi method consists of an iterative process of individual rating rounds and plenary discussions, and has been applied in various fields of medicine.[12] The RAM has been extensively tested for its internal consistency and external validity.[12] The panel process consisted of the following steps.

A panel of 13 Belgian neurologists accepted to participate. The rationale for this number is a trade-off between permitting diversity of representation/opinion and involving all in group discussions. Panel selection was based on expertise in the field of epilepsy and geographical distribution in order to ensure regional representation across Belgium.

Panellists convened for a first panel meeting to discuss the conceptual framework and starting points of the study. The panel distinguished between 7 groups of clinical variables that determine treatment choice in adult (16+) patients with epilepsy (Fig. 1). These variables were further specified (e.g. age 16–64 or ≥65 years, different co-morbidities, different co-treatments, etc.). Treatment decisions were divided into 3 categories: initial mono-therapy, second mono-therapy, and combination of 2 AEDs. It was decided to consider only AEDs that are commonly available for the indication of epilepsy in Belgium. The appropriateness of these medications was then individually rated by the panellists for every option included (in total 1128 ratings per panel member), using a 9-point scale (1 = inappropriate, 9 = appropriate). To facilitate an efficient scoring process, an electronic rating program was used.

Individual ratings were aggregated to panel statements for each of the options, using the mathematical rules that are typically applied in RAM studies.[11] An option was considered 'appropriate' if the median panel score was between 7 and 9 without disagree-

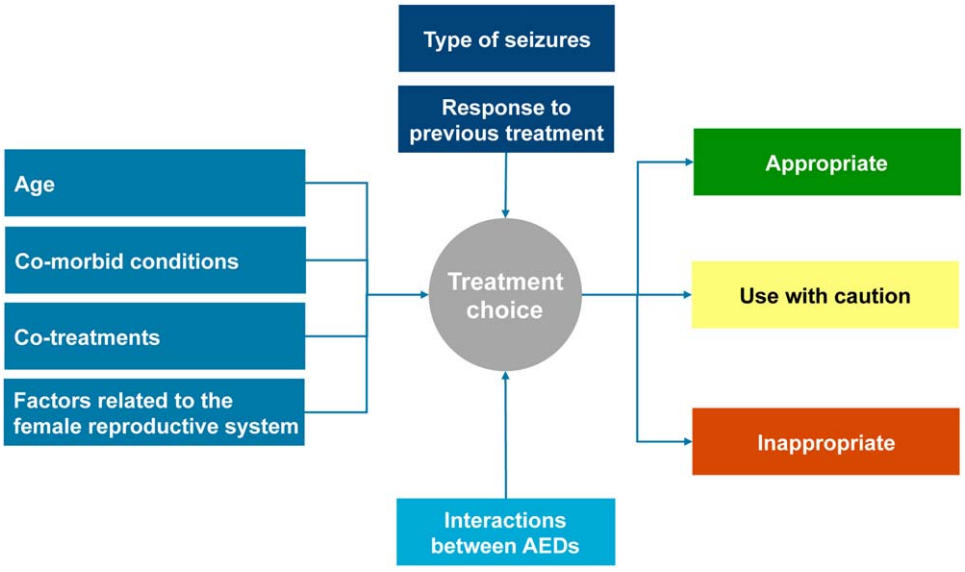

Fig. 1. Conceptual model of the panel study. Treatment recommendations for adult (16+) patients with epilepsy were formulated based on the appropriateness of antiepileptic drugs (AEDs) with respect to particular clinical variables.

Table 1
Clinical variables and medications included in the final ratings.

Clinical variables		
Age		
16–64 years	≥65 years	
Type of seizures		
•*Initial and second mono-therapy*		
a. Generalised	Tonic–clonic	
	Absence	
	Myoclonic	
b. Focal	Not secondary generalised	
	Secondary generalised	
•*Combination therapy*		
a. Generalised		
b. Focal		
Response to previous treatment (second mono-therapy)		
a. Initial medication		
b. Reason of treatment failure	Insufficient response (despite optimal doses)	
	Poor tolerance	
Co-morbid conditions		
Renal insufficiency	Cardiovascular disease	Psychosis
Kidney stones	Diabetes mellitus	Migraine
Hepatic disease	HIV	Insomnia
Porphyria	Osteoporosis	Somnolence
Auto-immune disease	Obesity	Mental retardation/low IQ
Mitochondriopathy	Depression/anxiety	
Co-treatments		
Chronic anticoagulants	Chemotherapy	Radiotherapy
Psychopharmaca	Corticosteroids	PPI/antacids
Antibiotics	Diuretics	Lipid-lowering drugs
Factors related to the female reproductive system		
Child bearing factors (pregnancy, child wish, breast feeding)		
Use of oral contraception		
Interactions		
All potential interactions between the AEDs listed below		
Medications		
Mono-therapies		
Carbamazepine	Levetiracetam	Phenytoin
Ethosuximide	Oxcarbazepine	Topiramate
Lamotrigine	Phenobarbital	Valproate
Combination therapies		
Baseline	**Add-ons**	
Carbamazepine	Benzodiazepines	Phenytoin
Lamotrigine	Carbamazepine	Pregabalin
Levetiracetam	Ethosuximide	Primidone
Oxcarbazepine	Gabapentin	Tiagabine
Phenobarbital	Lamotrigine	Topiramate
Phenytoin	Levetiracetam	Valproate
Topiramate	Oxcarbazepine	Vigabatrin
Valproate	Phenobarbital	

ment between panellists, and 'inappropriate' if the median was between 1 and 3. Agreement corresponds with at least 9 individual scores within the same category (1–3, 4–6 or 7–9). Disagreement is defined as the situation in which at least 4 panel members (i.e. one third of the panel) had scores in each of the sections 1–3 and 7–9. Options for which disagreement existed or for which the median score was between 4 and 6 were deemed 'use with caution'.

The panel then convened to discuss the results, focusing on the interpretation of definitions and clinical variables used, and on potentially redundant or missing conditions and medications. The discussion led to some adaptations of the rating model (addition of some conditions and deletion of others, refinement of some definitions), after which a second individual rating round was conducted (1428 ratings per panellist). Based on the second round ratings, a prototype of the electronic decision support tool was developed (see next section), which was piloted during educational meetings for Belgian general (non-specialised) neurologists, and chaired by the panel members.

Based on the feedback of these meetings, a third rating round was conducted, in which some new clinical variables were added and other options were re-rated. The final rating structure, including 1529 options, is summarised in Table 1.

2.2. Electronic decision tool

The recommendations were embedded in an electronic decision support tool, structured around the main treatment decisions: initial mono-therapy, second mono-therapy (after insufficient response to, or poor tolerability of the initial mono-therapy), and combination therapy (after unsatisfactory response to mono-therapy). Appropriateness ratings of the panel for the separate conditions were combined to overall panel recommendations for any patient profile to be selected, using the following rules:

1. If the treatment is appropriate for all conditions, the outcome is 'appropriate'
2. If any of the panel ratings of the treatment for the separate conditions is inappropriate, the outcome is 'inappropriate'
3. All other situations result in the outcome 'use with caution'

	Generalised			Focal	
	Tonic-clonic	Absence	Myoclonic	Secondary generalised	
				No	Yes
1. Carbamazepine	6.0	1.0	1.0	8.5	8.5
2. Ethosuximide	2.0	8.0	5.0	1.0	1.0
3. Lamotrigine	8.0	7.5	6.0	8.0	8.0
4. Levetiracetam	8.0	6.0	8.0	8.5	8.5
5. Oxcarbazepine	6.5	1.0	1.0	8.0	8.0
6. Phenobarbital	3.0	1.5	2.0	3.5	4.0
7. Phenytoin	3.0	1.0	1.5	4.5	4.5
8. Topiramate	7.0	5.0	6.5	7.5	7.5
9. Valproate	9.0	9.0	9.0	7.0	8.0

Fig. 2. Appropriateness of antiepileptic drugs as initial mono-therapy in relation to the type of seizures. Red, inappropriate; green, appropriate; yellow, use with caution. Figures in boxes represent the median panel scores. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

3. Results

Disagreement amongst the panellists was low and dropped from 2.6% in the first round to 0.5% in the final round (all options together).

3.1. Initial mono-therapy

The panel ratings on the appropriateness of 9 AEDs as initial mono-therapy show marked patterns in relation to the type of seizures (Fig. 2). Valproate was the only medication considered appropriate for all types of seizures. Phenobarbital and phenytoin were deemed inappropriate for all types of generalised seizures, and were also less favoured in focal disease.

3.2. Second mono-therapy

Although the panel rated all 9 AEDs also separately as second mono-therapy by taking into account the initial medication and type of treatment failure (insufficient response or poor tolerability) for each of these, the figures differ only slightly from those of the initial mono-therapy. In 52 out of the 720 ratings (7.2%) the outcomes differed from those in Fig. 2, but never with more than 1 appropriateness class, and mostly with less than 1 point difference on the 9-point scale. The most pronounced differences were found for phenobarbital (always inappropriate as a second mono-therapy, regardless of the type of seizures), phenytoin (mostly inappropriate in focal, not-secondary generalised disease), and topiramate (appropriate in myoclonic seizures).

3.3. Combination therapy

The rating results for combination therapy are summarised in Table 2. Although the panel chose to include primidone and vigabatrin in the ratings, their use as an add-on was consistently rated inappropriate. Four out of 15 AEDs were deemed appropriate for generalised seizures, versus 7 for focal disease. These were all AEDs that could also be used as mono-therapy with the exception of pregabalin (for focal disease).

3.4. Co-morbidities and co-treatments

The ratings for co-morbidities and co-treatments show diffuse patterns for the 15 AEDs considered (Table 3). The vast majority of non-appropriate ratings concerns 'use with caution', while around 10% relates to 'inappropriate' use. Both for co-morbidities and co-treatments, least (relative) contra-indications were seen for levetiracetam and pregabalin, while phenobarbital, phenytoin, and primidone showed the poorest profiles in this respect.

3.5. Advanced age and factors related to the female reproductive system

The panel considered advanced age (≥65 years) to be a contra-indication for the use of phenobarbital, phenytoin, and primidone. Benzodiazepines, carbamazepine, ethosuximide, oxcarbazepine, tiagabine and vigabatrin were recommended to be 'used with caution' in elderly patients. Concerning child-bearing factors (breast feeding, pregnancy or planning to become pregnant), all AEDs warrant at least cautious use, while phenobarbital, phenytoin and primidone were deemed 'inappropriate'. For women using oral contraceptives, benzodiazepines, gabapentin, levetiracetam, pregabalin, tiagabine, valproate and vigabatrin were considered to be safe options. All other AEDs were advised to be 'used with caution', except for phenobarbital and primidone (both inappropriate).

3.6. Interactions between AEDs

The ratings on interactions between AEDs (Table 4) revealed no inappropriate combinations, although cautious use was recommended for some. Best results were seen for levetiracetam and topiramate. For the add-ons, gabapentin and pregabalin showed the most favourable interaction profiles.

3.7. Epi-Scope®

The final rating results formed the basis for the development of an electronic decision support program, called Epi-Scope®. A patient profile can be chosen by selecting the different clinical variables (Fig. 3). In total, the tool allows around 45 billion different combinations of patient profiles. The appropriateness of AEDs for a selected profile is displayed using corresponding colours; green indicates that the medication is appropriate in the given situation, yellow means 'use with caution', while red corresponds to an inappropriate choice (Fig. 4). (For interpretation of the references to colour in this figure, the reader is referred to the web version of the article.) By clicking on any of the AED boxes, the reasons behind the recommendations are explained (Fig. 4). Additional information on indications and reimbursement conditions (specifically for Belgium) is available via links to governmental sites on pharma-

Table 2
Appropriateness of add-ons to 8 initial (baseline) antiepileptic drugs.[a]

Add-on	Generalised seizures	Focal disease
Benzodiazepines	Mostly inappropriate, except with carbamazepine and valproate (caution)	Inappropriate
Carbamazepine	Inappropriate with phenobarbital and phenytoin; others: caution	Appropriate except with oxcarbazepine (caution)
Ethosuximide	Use with caution	Inappropriate
Gabapentin	Inappropriate	Use with caution
Lamotrigine	Appropriate	Appropriate
Levetiracetam	Appropriate	Appropriate
Oxcarbazepine	Use with caution, except with phenytoin (inappropriate)	Appropriate, except with carbamazepine (caution)
Phenobarbital	Inappropriate	Use with caution
Phenytoin	Inappropriate	Use with caution
Pregabalin	Inappropriate	Appropriate
Primidone	Inappropriate	Inappropriate
Tiagabine	Inappropriate	Use with caution
Topiramate	Appropriate	Appropriate
Valproate	Appropriate	Appropriate
Vigabatrin	Inappropriate	Inappropriate

[a] Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate.

Table 3
Antiepileptic drugs rated by the panel as 'use with caution' or 'inappropriate' in light of co-morbidities and co-treatments. Inappropriate medications are marked with an *.

Co-morbidities	
Renal insufficiency	BZD, CBZ, GBP, LEV, OXC, PB, PHT, PGB, PRM, TPM, VGB
Kidney stones	TPM*
Hepatic disease	BZD, CBZ, ESM, LTG, OXC, PB, PHT, PRM, TGB, TPM, VPA
Porphyria	BZD, CBZ, ESM, LTG, OXC, PB*, PHT*, PRM*, TGB, TPM, VPA*, VGB
Auto-immune disease	CBZ, ESM, LTG, OXC, PB, PHT, PRM, TGB, VPA
Mitochondriopathy	BZD, CBZ, OXC, PB, PHT, PRM, TGB, TPM, VPA*, VGB
Cardiovascular disease	CBZ, OXC, PB, PHT, PRM
Diabetes mellitus	PHT, VPA
HIV	BZD, CBZ, ESM, OXC, PB, PHT, PRM, TPM, VPA
Osteoporosis	CBZ, OXC, PB*, PHT*, PRM, TPM, VPA
Obesity	GBP, PB, PGB, VPA, VGB
Depression/anxiety	ESM, GBP, PB, PRM, TGB, TPM, VGB
Psychosis	BZD, ESM, GBP, LTG, LEV, PB, PHT, PRM, TGB, TPM, VGB
Migraine	–
Insomnia	LTG
Somnolence	BZD*, CBZ, ESM, GBP, LEV, OXC, PB*, PHT, PGB, PRM*, TGB, TPM, VPA, VGB
Mental retardation/low IQ	BZD, ESM, GBP, LEV, PB, PHT, PGB, PRM*, TGB, TPM, VGB
Co-treatments	
Chronic anti-coagulants	BZD, CBZ, ESM, OXC, PB*, PHT*, PRM*, VPA
Psychopharmaca	BZD, CBZ, OXC, PB, PHT, PRM, TPM, VPA
Antibiotics	CBZ, ESM, LTG, OXC, PB, PHT, PRM
Chemotherapy	CBZ, ESM, LTG, OXC, PB, PHT, PRM, TPM, VPA
Corticosteroids	CBZ, ESM, OXC, PB, PHT, PRM
Diuretics	CBZ, OXC, PB, PHT, PRM, TPM
Radiotherapy	CBZ*, LTG, PB*, PHT*, PRM*
PPI/antacids	CBZ, GBP, OXC, PB, PHT, PRM, TGB
Lipid-lowering drugs	CBZ, ESM, OXC, PB, PHT, PRM, TGB, TPM, VGB

BZD, benzodiazepines; CBZ, carbamazepine; ESM, ethosuximide; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PGB, pregabalin; PRM, primidone; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate.

cotherapy. A demonstration of Epi-Scope® can be viewed in English via: http://www.e-hims.com/episcope_demo/.

4. Discussion

Using a modified RAND approach, the study summarised expert opinion, i.e. clinical evidence combined with personal experience where the medical literature is insufficient to determine the appropriateness of different AEDs in relation to particular patient-specific clinical conditions. Following logical principles, treatment recommendations were then formulated based on the combination of panel outcomes for these separate aspects. When at least one aspect was deemed not appropriate (uncertain or inappropriate), the final outcome for a patient profile with that aspect was considered accordingly. Recommendations were calculated by this methodology for all patient profiles that can be created with the clinical variables selected in this study. The total number of distinct cases with epilepsy that the study covers reaches 45 billion.

To provide a clear and concise display of the results, the data were embedded into an electronic tool, which is a real asset to further broaden the applicability and usefulness of the study outcome. In contrast to tables and listings, the tool allows easy extraction of the panel's recommendations in a few 'clicks'. In addition, when encountering a patient with epilepsy, the Epi-Scope® program could be used as 'professional mirror' in the consultation office; physicians can compare their own treatment decisions with that of the panel. The Epi-Scope® decision support tool does not replace clinical judgement; it merely indicates

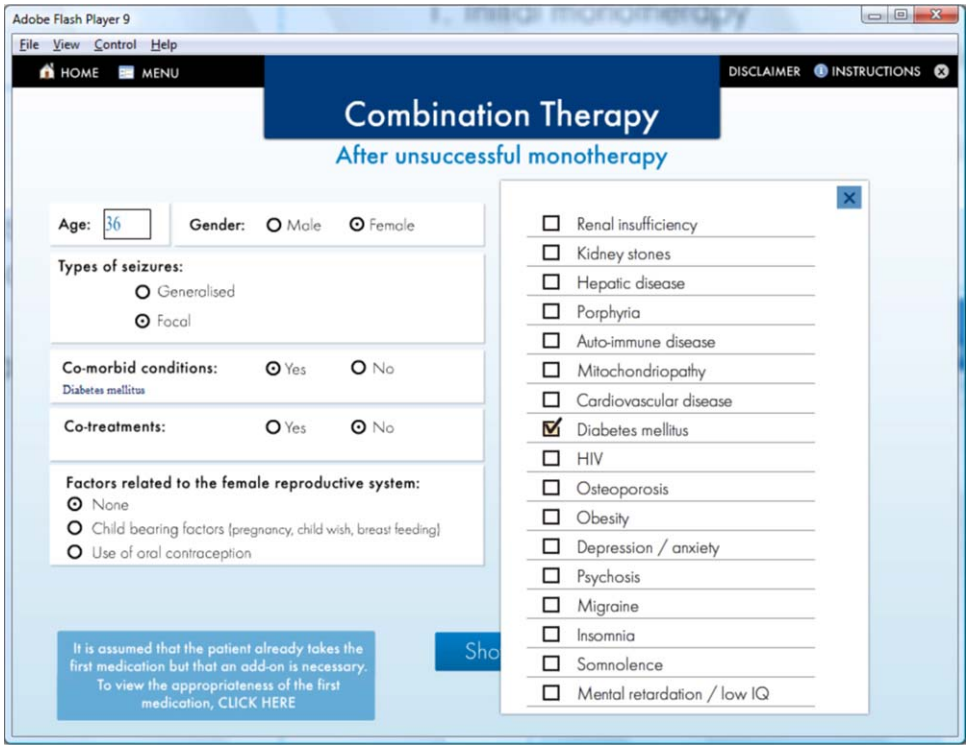

Fig. 3. User interface of Epi-Scope®. Example of a patient profile.

potential treatment options and points to contra-indications for individual patient profiles. Furthermore, the display of reasons behind the given recommendation is an additional advantage and allows using the tool for educational purposes. Besides at the personal level the tool can be deployed to discuss patient cases within the framework of continuing medical education.

In some respects, the study recommendations (and Epi-Scope® program) are relatively similar to the recommendations of the ILAE and AAN/AES, that have been published some years ago[6,7] and which, inherent to the methodology of study qualification, merely reflect evidence-based data. For an adult patient with partial seizures for instance, the ILAE guidelines considered CBZ and PHT

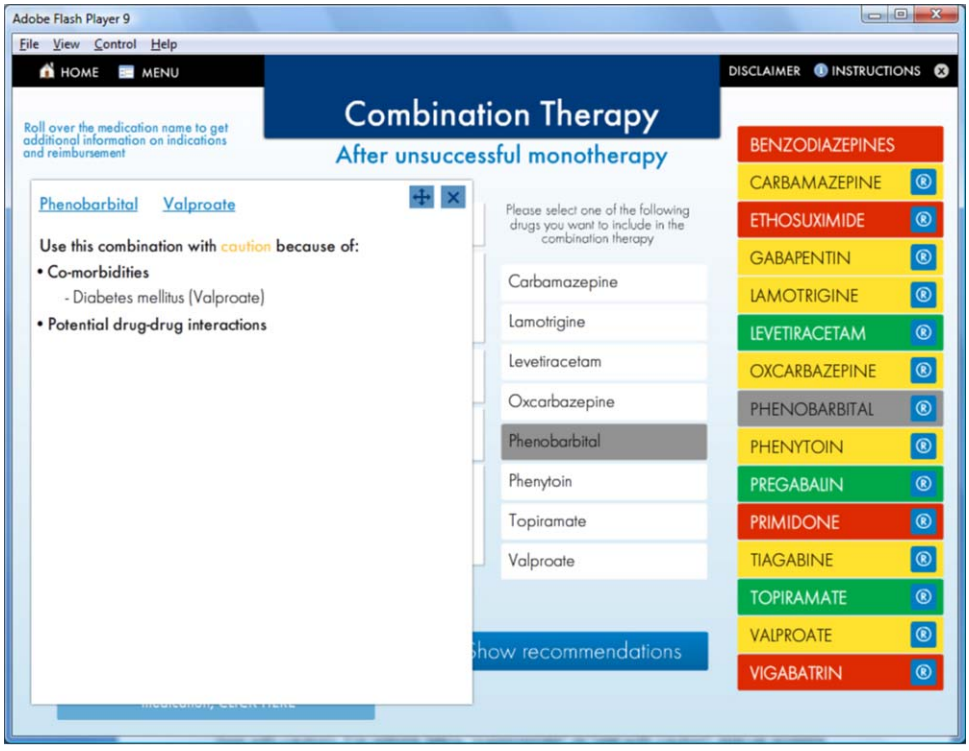

Fig. 4. Display of the medication recommendations (right) and considerations behind a selected recommendation for combination therapy as pop-up (left).

Table 4
Potential interactions between antiepileptic drugs[a] (use with caution). None of the combinations was rated inappropriate.

Carbamazepine	BZD, ESM, LTG, OXC, PB, PHT, PRM, TGB
Lamotrigine	CBZ, PB, PHT, PRM
Levetiracetam	–
Oxcarbazepine	CBZ, ESM, PB, PHT, PRM
Phenobarbital	BZD, CBZ, ESM, LTG, OXC, PHT, PRM, TGB, VPA
Phenytoin	BZD, CBZ, ESM, LTG, OXC, PB, PRM, VPA
Topiramate	VPA
Valproate	LTG, PB, PHT, PRM, TPM, VGB

[a] See Table 3 for explanation of medication abbreviations.

with level A evidence and VPA with level B. While the AAN/AES guidelines give recommendations only for newer AEDs, GBP, LTG, OXC and TPM received a level A or B for use. In comparison, our study recommends CBZ, LEV, LTG, OXC, TPM and VPA for a 30-year-old man with partial seizures and no co-morbidity/co-medication. These drugs are indicated to be used as mono-therapy in Belgium, which is not the case for GBP. The panel considered PHT (as well as PB) as to be 'used with caution' due to long-term safety issues. LEV was included as appropriate based on the more recently published study of the drug in new-onset partial seizures.[17] Similar results were obtained in previously published expert opinion studies conducted in the US[13,14] and in Belgium,[15,16] which recommended CBZ, OXC, LTG and LEV.[14,16] As such, the study outcome is a combination of existing clinical data (causing similarities with the current guidelines) and experiences/opinion of experts in the field.

One of the major strengths of this study/tool, making it unique versus guidelines and other expert panel studies is that guidance is given for composite clinical cases, e.g. with multiple co-morbidities, co-treatments and other patient variables that are important for treatment choice (e.g. advanced age, breast feeding, etc.). The vast majority of these special populations are excluded from participation in clinical studies, which causes evidence-based medicine and current guidelines to be rather limited in this respect. Consequently, the recommendations for complex cases in this study reflect rather medicine-based evidence than evidence-based medicine, and panel recommendations could be considered a useful complement to existing international guidelines. To illustrate this with a patient profile that is relatively common in practice, valproate is considered as an appropriate first mono-therapy in our study for a 32-year-old female patient with generalised tonic–clonic seizures who takes oral contraception, similar to established guidelines and other panel studies (level C, no AED has level A or B).[6,7,14,16] When this patient also presents with kidney stones and obesity and takes PPI/antacids, the tool's recommendation for valproate turns into 'use with caution' due to obesity as co-morbidity, leaving levetiracetam as an appropriate treatment option. Specific recommendations for such a case cannot be extracted from existing literature sources.[6,7,14,16]

One of the limitations of the study – inherent to the methodology – is that the recommendations reflect ''expert opinion'', which may change very rapidly. Therefore, the results of this study could be considered a 'snapshot' of the current situation in Belgium. Given the continuous advances of clinical science and experiences, periodical updates are warranted to keep the treatment recommendations up-to-date. Therefore, annual re-ratings are taking place based upon the publication of novel relevant data, retrieved from regular literature searches by a steering committee of 3 panel members. Obviously, new AEDs need to be included as well (e.g. lacosamide, which has been available in Belgium since March 2010). Compared to distributing study results in printed version, using software in an internet environment allows timely and easy updates once new rating results become available. A further constraint relates to the included co-morbidities and co-treatments. While these constitute the most frequent/relevant ones for patients with epilepsy, not all existing could be covered. To ensure a reasonable balance between rating feasibility and the extent of recommendations, some categories such as 'cardiovascular disease' have been kept fairly large, covering multiple conditions (e.g. hypertension, arrhythmia, ischaemic cardiomyopathy, etc.).

Another limitation that could be envisioned relates to the development of patient profiles by combining selected clinical variables, which could lead to hypothetical cases that rarely occur in daily practice. However, recommendations for these theoretical cases might never appear.

Furthermore, the outcome of such kind of approach is less subject to validation. The ultimate validation study would be a patient outcome study, which is theoretically feasible but practically very extensive, complex and time-consuming. Other types of validation studies could include inter-panel comparisons (national versus international, epileptologists versus general neurologists, etc.).

5. Conclusions

The Epi-Scope® tool is a unique and easy reference format to view the panel's treatment recommendations for adult patients with epilepsy. Because of the validity of the RAM used and the broad applicability of the study results in terms of patient characteristics, the electronic decision tool supports practicing neurologists in making appropriate treatment decisions for highly specific patients with epilepsy.

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