

## CLINICAL AND PATHOLOGICAL SCIENCES

## REVIEW ARTICLE

**Considerations in the treatment of the patient with epilepsy. A review article**  
**Consideraciones en el tratamiento del paciente con epilepsia. Artículo de revisión**

Juan E. Bender del Busto<sup>1,II</sup>, Liuba Hernandez Toledo<sup>II</sup>

<sup>I</sup>Universidad de Ciencias Médicas de La Habana. La Habana, Cuba.

<sup>II</sup>Centro Internacional de Restauración Neurológica (CIREN). Habana, Cuba.

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**ABSTRACT**

**Introduction:** Epilepsy is as old as mankind, and for some people, the second neurological disease. It has gone through different cultures and epochs, following different treatments until the 19th century when the scientific and modern therapy began, which currently maintains in absolute development.

**Objective:** To present and reflect on the use of antiepileptic drugs described up to the present, the ones which are under investigation, and the future development trends.

**Material and Method:** A bibliographic review was performed by searching different online databases, related to antiepileptic therapy. The

reports of original prospective or retrospective researches, and review works were included in the information search. The 79-year period reviewed extended from 1937 to 2016.

**Results:** The importance of the positive diagnosis of epilepsy for a correct management of the patient is described. Antiepileptic treatment is approached, with a specificity on the drugs described up to the present time, the ones that are under complete development, and the general principles of treatment and worries in the field of neurosciences, with a view to achieve an efficient therapy.

**Conclusions:** The current antiepileptic therapy is

symptomatic and not curative, being necessary to keep in mind the general aspects in the management of the epileptic patient, in an

### RESUMEN

**Introducción:** La epilepsia es considerada tan antigua como la humanidad y para algunos, la segunda enfermedad neurológica. Ha transitado a través de las diferentes culturas y épocas, con la utilización de diversos tratamientos, hasta el siglo XIX en que se inició la terapia científica y moderna, la cual se mantiene en pleno desarrollo hasta nuestros días.

**Objetivo:** Exponer y reflexionar sobre el uso de las drogas antiepilépticas descritas hasta el momento, las que están en investigación y las tendencias futuras de desarrollo.

**Material y Metodo:** Se realizó una revisión bibliográfica en diversas bases de datos en línea, relacionadas con la terapia antiepiléptica. Se incluyeron en la búsqueda de la información los reportes de investigaciones originales prospectivas o retrospectivas y trabajos de revisión. El período revisado fue de 79 años y se

### INTRODUCTION

It is considered that epilepsy can occur in any person without distinction of age, sex, race, social origin or geographical characteristics. It is a global public health problem that requires an adequate response. According to reports from the World Health Organization (WHO), an estimated 50 to 69 million people suffer from this disease, most of them living in developing countries.<sup>1-3</sup>

It can be asserted that epilepsy affects 1-2% of the population.<sup>4-7</sup>

Epilepsy is one of the most frequent disorders of the Central Nervous System (CNS); considered to

integral and individualized way.

**Keywords:** epilepsy, scientific therapy, antiepileptic drugs.

extendió desde 1937 hasta 2016.

**Resultados:** Se describe la importancia del diagnóstico positivo de la epilepsia para un correcto manejo del paciente. Se aborda el tratamiento antiepiléptico, con especificidad en las drogas descritas hasta la actualidad, las que están en pleno desarrollo, así como los principios generales del tratamiento y las inquietudes en el campo de las neurociencias, con vistas a lograr una terapéutica eficaz.

**Conclusiones:** La terapia antiepiléptica actualmente es sintomática y no curativa, siendo necesario tener en cuenta los aspectos generales en el manejo del paciente epiléptico, de forma integral e individualizada.

**Palabras claves:** Epilepsia, terapia científica, farmacos antiepilépticos.

be the second neurological disease, which is seen more frequently (72,5%) in primary health care worldwide, after headache (73,5%). It is, at the same time, the fourth cause of neurological disability (7,9%) after Migraine (8,3%), Dementia (12,0%) and Cerebrovascular Disease (55,0%).<sup>8</sup>

It is currently considered by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) as a disease, not a disorder.<sup>9,10</sup>

The knowledge of this disease dates back more than 3 000 years. Its history can be traced to the

same history of man, since it has left its mark engraved in each of the different civilizations. It was known by the name "Morbo Sacro" or "Sacred Disease" and "attacks" or epileptic crises with the term "epilambaneim" which means "attack", "surprise", "to take possession", or "to fall over itself" (manifestations that caused fear), from which derives the term through which this disease is known at present: Epilepsy. Hypocrates described it for the first time in his book: "The Sacred Disease".<sup>11</sup>

The most frequent age of onset is childhood and adolescence due to obstetric trauma before or during childbirth, cranial trauma, encephalitis or meningoencephalitis; and it is attributable in some countries of Latin America to cerebral parasitism, for example cysticercosis. However, as the longevity of the planet increases, the incidence and prevalence of epilepsy have also increased due to cerebrovascular diseases, brain tumors or demential diseases, which are more frequent in the elderly.<sup>12</sup>

### OBJECTIVE

To comment and reflect on the use of antiepileptic drugs described so far, the ones under investigation, and future development

### MATERIAL AND METHODS

A bibliographic review was performed by searching various online bibliographic databases, including PubMed, Cochrane Library, EBSCO, Clinical Key, Springer, MedScape and ScieLo, among others related to antiepileptic treatment and the general principles of the management of these patients. To review the literature, the key words epilepsy and treatment were used.

The first treatments included from the exorcism to the practice of bloodletting and trepanation.<sup>11</sup> However, scientific therapy dates back to the 19<sup>th</sup> century with the accidental discovery of bromide salts.<sup>11</sup> From then on, a variety of drugs were incorporated into the therapeutic arsenal of this disease.

Different techniques and alternative methods have also been included in the management of this disease more recently.

It is important to point out that, since it is fully associated with alterations in the psychological and social sphere of the patients who suffer from it, and it has frequent psychiatric manifestations, the management of these conditions is essential.<sup>13,14</sup>

Therefore, we consider that; because of the complexity of this pathology, its social implication, and its psychobiological and even economic consequences, the patient with epilepsy must be managed with a multidisciplinary approach.

trends in order to guide the patient therapeutically in an appropriate manner, and minimize the complications of this disease.

The reports of prospective or retrospective original investigations and revision works were included in the search for the information, as well as articles published in Spanish and English languages.

The 79-year period reviewed extended from 1937 to 2016.

## RESULTS

There are concerns or questions that the doctor should consider in the management of a patient with suspected epilepsy: *Are we in front of an epileptic event? What type of crisis does the patient suffer? What is the cause of the crisis/epilepsy? What therapeutic behavior should we follow?*<sup>15</sup>

After making the correct diagnosis of a patient, but before prescribing a specific antiepileptic drug, the doctor must take into account a number of additional issues. A complete understanding of these issues should allow for the best outcome for the patient, regardless of the drug or any other therapy chosen.<sup>16,17</sup>

However, before entering into the complexities of treatment strategies, we need to make a brief reminder about the accuracy of the patient's diagnosis. The correct diagnosis is, after all, the foundation on which the therapy is based on. An inadequate diagnosis is likely to lead to insufficient and potentially harmful treatment.

This is a complex issue, given that epilepsy is a heterogeneous set of syndromes with innumerable causes and a wide variety of clinical expressions.

So, how are we going to make a correct diagnosis of the patient with the disease? We can only do this by recognizing that multiple levels of diagnosis are present and they must be identified in each patient, which can be summarized as follows: etiological diagnosis, diagnosis of seizures, and diagnosis of epileptic syndrome (if possible);<sup>18</sup> and those diagnoses that are based, in turn, on the chronopathogram of the comicial events, the physical examination, and the necessary complementary investigations.

Once the patient's diagnosis is safely made, we

should ask ourselves: what are the treatment issues that should be considered to optimize the outcome for the individual?

To do this we must consider that the treatment of epilepsies can be summarized in three major groups: prophylactic/preventive, pharmacological, and non-pharmacological: surgery and alternative treatment, without forgetting the psychological / psychiatric management.

We will approach the pharmacological treatment and the general aspects of its management and we will ignore the other topics, to deal with the specific purposes of this review.

### **Pharmacotherapy**

Regarding this topic, it should be kept in mind, that the therapy of this disease is still suppressive, symptomatic and not curative.<sup>19</sup>

From 1909, the year of the foundation of the International League Against Epilepsy (ILAE), modern approaches to the medicinal therapy of epilepsy were formulated and many novel drugs were introduced.<sup>19</sup>

There were the studies of Tracy Putnam (1894-1975) and H. Houston Merritt (1902-1978) the ones that marked the end of the empirical use of substances, in search of new antiepileptic drugs.<sup>20-22</sup>

The introduction of different drugs / procedures in clinical practice is detailed in each period:

- 1850: Bromides/chloral hydrate/Borax
- 1910: Phenobarbitone
- 1930: Ketogenic diet
- 1938: Phenytoin
- 1941: Acetazolamide
- 1944: Trimethadione
- 1950: Adrenocorticotrophic hormone (ACTH)

- 1954: Primidone
- 1957: Methosuximide
- 1958: Ethosuximide
- 1962: Sulthiame
- 1963: Diazepam
- 1965: Carbamazepine
- 1967: Valproic Acid
- 1968: Clonazepam
- 1975: Clobazam.<sup>23,24</sup>

**Drugs introduced between 1989 and 1994:**

Vigabatrin (1989), Lamotrigine (1990), Oxcarbazepine (1990), Felbamate (1993) y Gabapentin (1994).<sup>25</sup>

**Drugs introduced between 1995 and 2008:**

Topiramate (1995), Tiagabine (1996), Levetiracetam (1999), Zonisamide (2000), Pregabalin (2004), Stiripentol (2007), Rufinamide (2007), Lacosamide (2008).<sup>26</sup>

**Other antiepileptic drugs that are currently in active development:**

Retigabine, Eslicarbazepine acetate, Fluorofelbamate, Remacemide, Valprocemide and Propylsopropyl acetamida, Brivaracetam, Seletracetam, Carisbamato, Ezogabine, Ganaxoxone, Perampanel, T-2000, 2-Deoxy-D-glucose, Huperzine A, JZP-4, ICSC 700-008, NAX-5055, NS1209, Tonabersat and YKP3089.<sup>27-32</sup>

**Other drugs in experimental phase:**<sup>33-35</sup>

- CPP-115 (Vigabatrin derivatives) (1S,3S)-3-amino-4-difluoromethylenecyclopentanecarboxylic acid.
- Antinflammatory agents: HE3286 (Triolex) androstene-3 $\beta$ ,7 $\beta$ ,17 $\beta$ -triol ( $\beta$ AET); VX-765 (S)-1-(S)-2-3,3-dimethyl-butanoyl-pyrrolidine-2-carboxylic acid.
- Other new components: 2-Deoxy-D-Glucose, Cannabinoids, Everolimus, NAX 810-2, Propofol

Hemi-Succinate, Isovaleramide, Losigamone, Safinamide and Talampanel.

There is interest and recent public debate about the potential use of marijuana and one of its active substances, cannabidiol (CBD) (non-psychoactive compound) in the treatment of various neurological conditions such as chronic pain, multiple sclerosis, which is especially positive in patients with refractory seizures and catastrophic epilepsies such as Dravet's syndrome.<sup>36-38</sup>

Mention is also made of intravenous immunoglobulin (IVIG), composed of products purified from human blood. The products generally contain more than 95% unmodified IgG and traces of IgA or IgM.<sup>39,40</sup>

The mechanism of action of IVIG in epilepsy appears to be primarily immunological, but the therapeutic effects of IVIG can also have an impact on immune system pathways, including modulation of plasma levels of interferon, interleukin-6 (IL-6), and IL-828.<sup>39,40</sup>

Considering the didactic purposes of this review, we have avoided those aspects related to pharmacokinetics, indications, doses, interactions and adverse reactions of antiepileptic drugs.

Our criterion is that we should not be satisfied with the advances of today's epileptology and we should continue in the search for an effective therapy.

There is a clear need to insist on the study of conventional animal models and to explore other fields that include molecular research, in which neuronal hyperexcitability can be reduced and, in addition, components with antiepileptogenic and neuroprotective properties are identified.<sup>41</sup>

Recent research shows that genetic differences in patients could influence the response to treatment.<sup>42</sup>

Several novel approaches to the treatment of epilepsy are also studied, including the transfer of different genes and stem cell transplantation. On the other hand, multiple therapeutic targets are described, including neuropeptides, neurotrophic factors and inhibitory neurotransmitters.<sup>43</sup> For all this, it is important to take advantage of the results that are continually being made available to the scientific community thanks to the synergy of basic and clinical multidisciplinary research.

This means that the clinical applicability of the neurobiological results must be evaluated in such a way that the new information can be translated into diagnostic and therapeutic terms, and consequently the guidelines and recommendations will be produced.

Important actions have been carried out by the International League against Epilepsy (ILAE) through its various committees (in genetics, neurobiology, psychobiology, epidemiology, therapeutic strategies, diagnostic methods and care policy of health) to help developing countries in establishing research and projects geared to their specific problems.<sup>44</sup>

#### **General Aspects of Treatment.**<sup>45</sup>

Having epilepsy commonly suggests several consequences that are relatively unique, including:

- restrictions on driving and unsafe activities, persistent stigma, and the small but real possibility of sudden death.
- undesired chronic effects of AEDs on cognitive ability, mood, weight (both gain and loss), childbearing, and sexual function.

- cultural and financial stress, and some AED regimens can be inconvenient and threaten compliance.

Such issues are just as important, and can be as complex in patients with mild epilepsy (or even a first seizure) as they are in those with intractable seizures.

#### ***The doctor should never forget that:***<sup>18</sup>

- The diagnosis of Epilepsy is eminently clinical; so, the pharmacological management should begin when the diagnosis of Epilepsy is made, even when the etiology has not been determined yet.
- Successful treatment requires therapeutic management plans that are individualized for each patient.
- The goal is to provide each patient with maximum control of seizures without significant adverse effects from AEDs and psychiatric comorbidity; especially depression, which profoundly affects quality of life.
- Independence, driving, employment, safety, and social stigma are very real and serious concerns for a patient with epilepsy.
- "no seizures, no side effects" should be the primary goal in management.
- The pharmacokinetic principles of antiepileptic treatment must be taken into account (absorption, apparent volume of distribution, protein binding, elimination, control of serum levels).<sup>46</sup>
- The older AEDs produce alteration of hepatic metabolism via alteration of the cytochrome P450 system. Strong hepatic enzyme inducers are: Phenytoin, Carbamazepine, Phenobarbital, and Primidone.
- The newer antiepileptic drugs either have no

hepatic-inducing properties or are only minimally inducing.

**Recommendations to the patient:**<sup>10,18</sup>

- No alcoholic beverage intake.
- Not to drive vehicles (except being 3 years or more without crisis).
- Sleep no less than 8 hours at night.
- Avoid stressful situations and additional responsibilities.
- Not to work unprotected in heights, or in places that offer danger in case of crisis.
- Avoid great physical efforts.
- Do systematic, but not exhausting study.
- Avoid spear fishing and swimming (unless watched).
- The patient must know that the effectiveness of the treatment is the suppression of the crises and not the disappearance of the inter-critical electroencephalographic anomalies.
- The patient should register number, duration, time and severity of epileptic seizures.

**Errors in the antiepileptic treatment:**<sup>18</sup>

- Make an inappropriate positive diagnosis.
- Not to start treatment when the diagnosis is made (to wait for the EEG or imaging studies to impose it).
- Prescribe maximum starting dose in the initial phase and not to design a progressive dosing.
- Initial use of polytherapy.
- Not to choose the drug according to the type of attack, syndrome or special group.
- Indicate treatment for a single crisis without individualized analysis.
- Interrupt treatment during puberty, without crisis-free period, or suddenly (sudden replacement).<sup>47</sup>
- Not to take into account the half-life of antiepileptics and their plasma levels.

- Not to take into account the interaction of drugs, or the combination of drugs with similar effects.
- Use drugs that lower the epileptogenic threshold.
- Not to consider the side effects of antiepileptic drugs.
- Consider the effectiveness of the treatment: disappearance of the inter-critical electroencephalographic anomalies, and not the suppression of the crises (with normal functionality).

**Must we treat all epileptic patients?**

*A single seizure in adults or children usually does not require treatment unless:*

- There is evidence of a brain lesion or major abnormalities on the EEG (particularly generalized spike-and-wave discharges).
- A first nonfebrile seizure between 2 and 5 years may be the first manifestation of epilepsy (myoclonic-astatic type) that will require vigorous treatment to prevent the development of epileptic status or epileptic encephalopathy.
- Rolandic spikes in children do not indicate the need for drug treatment unless seizures are frequent and upsetting to the family.
- If a second seizure would be hazardous to an adult for reasons related to employment or driving, treatment may be warranted after a first isolated seizure, provided that excellent compliance can be anticipated and the seizure is not related to precipitating factors such as sleep deprivation.<sup>48</sup>

The risk of recurrence followed by a first unprovoked crisis in children and adults varies from 27 to 71%. Most recurrences occur early, with approximately 50% of recurrences 6 months after the initial crisis and more than 80% in the

first 2 years of the initial crisis. Late recurrences are unusual, but they can occur 10 years after the initial event.<sup>49</sup>

A relatively small number of factors are associated with the risk of recurrence of the crises. The most important ones are the etiology of the crises, the electroencephalogram, and whether the first crisis occurred during wakefulness or sleep. Factors that are not associated with a significant change in the risk of recurrence include the age of debut, the number of crises in the first 24 hours, and the duration of the initial crisis.

According to current concepts, the diagnosis of epilepsy after a single unprovoked crisis, associated with a high risk of recurrence, may give rise to the decision to initiate treatment or not.

It must be borne in mind that a therapeutic decision is not the same as a diagnosis and must be customized according to the wishes of the patient, the risk-benefit ratio in each specific case, and the available options.

The physician should weigh the possibility of avoiding a second crisis and the risks that it entails, against the risk of adverse drug reactions and costs for the patient.

When to start treatment with antiepileptic drug after a simple crisis:<sup>10,18</sup>

**Definitely:**

- With structural damage: Brain tumors; arteriovenous malformation; and infection such as abscess, herpetic encephalitis.
- Without structural injury: History of epilepsy in siblings (but not in parents); electroencephalogram with defined epilepsy pattern; history of previous symptomatic convulsion (convulsion in the context of an illness

or childhood); febrile crisis, which is a very controversial topic; history of an anterior brain injury; cerebral hemorrhage; infection of the Central Nervous System (CNS), head trauma; and initial epileptic status.

**Possibly:**

- Unprovoked seizure without any of the risk factors mentioned above.

**Not Probably** (although short-term therapy can be used):

- Alcohol abstinence.
- Drugs abuse.
- Epileptic crisis in the context of an acute illness (i.e, high fever that can trigger simple febrile seizures, dehydration, hypoglycemia).
- A crisis immediately after an acute trauma to the head.
- Specific benign epilepsy syndromes, such as benign epilepsy with centrotemporal tips.
- Crisis caused by excessive sleep deprivation (e.g, college student at exam time)

**Aspects to be considered after a single crisis** (which creates a real uncertainty in the attending physician):<sup>18</sup>

- Was it really an epileptic seizure?
- Was the first crisis safe?
- Are there risk factors for a second attack?
- Is the neurological examination abnormal?
- Is the EEG pathological?
- Is the structural study abnormal?
- Is the story of the siblings and parents known? Do they have epileptic seizures, too?
- Should this person be allowed to drive?
- Should there be limitations in the patient's work?
- What are the risks of not treating the patient?
- What are the risks of treating the patient?

Indication of studies after a crisis:



The indication for a brain imaging study should be considered, depending on the clinical context (history and physical examination).

The electroencephalogram (EEG) in general, should be obtained as soon as possible after the crisis.

Pseudoseizures can sometimes be difficult to diagnose and require prolonged video-EEG monitoring.

**Beginning of treatment:**<sup>10,50</sup>

- After establishing the diagnosis of an epileptic seizure and not a pseudoseizure, such as a syncopal episode.

- After a correct identification of the type of epilepsy.

- When the doctor is certain that the patient has a high risk of recurrence.

- The selection of DAE therapy should be carefully performed in relation to the type of seizure, severity, type of epilepsy or epileptic syndrome, the etiology, and the triggering factor.

- Therapy should be initiated (preferably as monotherapy) at a low dose, gradually increasing it to reach an effective level to avoid side effects ("start low, go slow").<sup>47,51</sup>

- If there is toxicity with low doses that may be ineffective, the first AED should be gradually replaced by a second drug.

- Some antiepileptic drugs usually require prolonged titration.

- If the attacks continue (without toxicity), the dose should be increased according to tolerance.

- If epileptic seizures still persist, the transition to another first-line drug (in a second monotherapy) can be assessed.

- If anticonvulsant monotherapy is not successful, adjuvant treatment with a second-line drug should be considered (biotherapy).

- Rational polytherapy (selecting the association that best suits the characteristics of the patient and their epilepsy, taking into account the pharmacokinetic and pharmacodynamic characteristics of each DAE) has been defended, but remains speculative in relation to the best efficacy based on the use of AED with different modes of action.

- For the association of AED to imply increasing efficacy without increasing toxicity, the theoretical basis of rational combination therapy proposes to consider the mechanism of action of each drug, its spectrum, tolerability, and pharmacodynamic and pharmacokinetic interactions.

- In the event of continuous epileptic seizures, a reassessment of the differential diagnosis should be made and surgery should be considered.

**Interruption of treatment:**<sup>52</sup>

There are no rules defined as to the best time or even the best way to proceed when deciding to interrupt treatment.

At 12 months, 60 -70% of treated patients will be crisis-free.

According to the recent considerations of a group of ILAE experts, it is estimated that epilepsy is resolved in subjects with an age-related epileptic syndrome who have reached the corresponding age or in those who have remained without seizures during the last 10 years and have not taken antiepileptic medication for at least during the last 5 years.<sup>49</sup>

**Predictive factors for relapse:**<sup>18,49</sup>

- Epileptic syndrome, for example, juvenile myoclonic epilepsy (JME).

- Underlying structural pathology.

- Continuous epileptiform EEG abnormality

- Severe prolonged epilepsy before remission.

- Age increase.

In children, it is possible to try to stop the medication after having no seizures for 2 years, while for adults the interval of absence of seizures before reducing and suspending an AED is from 3 to 5 years.

The risk of recurrence of crises after having suffered unprovoked crises diminishes with time, although it never reaches the level of people who have never suffered a crisis. Most recurrences are early. Late recurrences are rare after 5 years. After 10 years without antiepileptic medication it is likely that the annual risk of crisis is very low.

Common precipitating factors of epileptic crisis:<sup>18</sup> Stress, sleep deprivation, fatigue and exercise, stroboscopic lighting (photosensitive epilepsy), alcohol consumption, omitting antiepileptic medication, medications that can reduce the seizure threshold, metabolic factors, menstruation (catamenial epilepsy), fever (infection), and hyperventilation.

#### ***Serum dosage of antiepileptic drugs.***<sup>53</sup>

Although there are no randomized studies, a positive impact of pharmacological analysis on the clinical outcome in epilepsy has been demonstrated; the evidence from non-randomized studies and above all clinical experience does indicate that the measurement of serum concentrations of antiepileptic drugs (AED) of old and new generation may have an important role to guide the management of the patient, provided that the concentrations are measured with a clear indication and interpreted in a critical manner, taking into account the entire clinical context, which in our opinion is essential. Situations in which measurements of AED are more likely to be beneficial should include:<sup>47</sup>

(1) when a person has reached the desired clinical

result, with a view to establishing an individual therapeutic concentration, which can be used later to evaluate possible causes for a change in the response to drug.

(2) as an aid in the diagnosis of clinical toxicity.

(3) to assess compliance, especially in patients with uncontrolled seizures.

(4) to guide dose adjustment in situations associated with pharmacokinetic variability (e.g, children, the elderly, patients with associated diseases, formulation of drug changes).

(5) when the pharmacological change is foreseen (for example, in pregnancy, or when in other clinical circumstances a drug is added or eliminated).

(6) to guide dose adjustments of antiepileptics with dose-dependent pharmacokinetics, especially phenytoin.

#### ***Some general indications for the measurement of serum concentrations of antiepileptic drugs.***<sup>53</sup>

1. After the beginning of treatment or after adjusting the dose, when the doctor decides to aim for a pre-selected concentration for that patient.

2. Once the desired clinical response has been achieved, to establish the "individual therapeutic range."

3. To assist the physician in determining the magnitude of an increase in dose, especially with AED that shows a dose-dependent pharmacokinetics (most notably, phenytoin).

4. When there are uncertainties in the differential diagnosis of signs or symptoms suggestive of AED toxicity related to concentration, or when toxicity is difficult to assess clinically (for example, in young children or in patients with mental disabilities).

5. When epileptic seizures persist despite an

apparently adequate dosage.

6. When a pharmacokinetic alteration is suspected, due to factors related to age, pregnancy, associated diseases or drug-drug interactions.

7. To evaluate possible changes in the concentration of DAE in stable state, when a change is made in the formulation of drugs, including switches that have generic formulations.

8. Whenever there is an unexpected change in the clinical response.

9. When a bad compliance is suspected.

The therapeutic monitoring of the antiepileptic drug has been used as a tool to optimize the treatment of epilepsy for almost 50 years. Although solid evidence for its usefulness in improving clinical outcomes is scarce, it continues to play a role in the treatment of this disease.<sup>54</sup> However, the physician must take into account that, due to individual variation, many patients

may require concentrations outside the reference ranges.

In many situations, patient's management is best guided by the determination of "individual therapeutic concentration" defined as the concentration with which an individual is free from epileptic seizures, with good tolerability, or the best compromise between improvement in control of the crises and the adverse effects related to the concentration.

In this regard, serum monitoring of DAEs can provide important information for decisions about dose adjustments of most antiepileptic drugs in patients with unexpected treatment outcomes or in situations associated with pharmacokinetic disorders, e.g. during pregnancy, in different disease states, in conjunction with drug interactions, and in certain age groups (children and the elderly), where the clinical evaluation of the effects of treatment can be particularly difficult.

## CONCLUSIONS

There are general principles that the modern physician must take into account about the proper use of antiepileptic drugs to achieve a scientific management of the disease, with judgment and individuality. There are different

drugs in active development, but even without any effective therapy; all this demonstrates that it is necessary to continue doing research on this topic.

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**Juan E. Bender del Busto. Universidad de Ciencias Médicas de La Habana. La Habana, Cuba.**

**E-mail: [jebender@infomed.sld.cu](mailto:jebender@infomed.sld.cu)**