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Clinical guideline: antiepileptic drugs of choice for epileptic syndromes and epilepsies in pediatric patients

Juan C. Reséndiz-Aparicio[1], Jesús M. Padilla-Huicab[2], Iris E. Martínez-Juárez[3], Gustavo Hernández-Martínez[4], Eunice López-Correa[5], Benjamín Vázquez-Juárez[6], Rosana Huerta-Albarrán[7] and Claudia Rivera-Acuña[8]

[1]PPE, Instituto Nacional de Neurología y Neurocirugía Dr. Manuel Velasco Suárez y Hospital Psiquiátrico Infantil Dr. Juan N. Navarro, Mexico City; [2]Hospital General de Especialidades Dr. Javier Buenfil Osorio, Campeche; [3]Instituto Nacional de Neurología y Neurocirugía Dr. Manuel Velasco Suárez Mexico City; [4]Centro de Alta Especialidad del Estado de Veracruz Dr. Rafael Lucio, Jalapa, Veracruz; [5]Hospital General Dr. Gaudencio González Garza, Centro Médico La Raza, IMSS, Mexico City; [6]Hospital para el Niño Poblano, Puebla; [7]Hospital General de México Dr Eduardo Liceaga, Mexico City; [8]Hospital Regional de Alta Especialidad ISSSTE, Puebla. México

Abstract

Approximately 65% of children with newly diagnosed epilepsy achieve sustained control of their epileptic seizures with the antiepileptic drug (AED) initially prescribed, and 15-20% require the combination of other AEDs. To begin treatment with an AED, basic aspects should be considered, such as the capacity for absorption, distribution, metabolism, and elimination of each AED. Treatment with an AED in pediatric patients, as for any age, must be personalized, but in these cases, the biological age and its degree of development are fundamental. Furthermore, the type of seizure, type of epileptic syndrome, comorbidity, in many cases the etiology, and even other aspects such as tolerability and availability of use must be considered. If adequate seizure control is not achieved, synergistic combinations could be used, making sure that adverse effects are not increased. Remember that a high percentage of patients initiate their epilepsy in the pediatric stage, which is why management in this age group is fundamental, and doses must always be calculated in relation to the weight of the patient.

Key words: *Antiepileptic drug. Monotherapy. Polytherapy. Childhood. Pediatric.*

Introduction

This is a clinical guide for the pharmacologic treatment of epilepsy in pediatric patients. It consists of establishing PICO-based questions and setting forth answers. The levels of evidence are based on articles published in peer-reviewed indexed articles and other international guidelines, such as the guides published by the International League Against Epilepsy, the National Institute for Health Care Excellence, and the Guidelines from the Sociedad Andaluza de Epilepsia (Andalusian Epilepsy Society). In addition, we emit recommendations from the Programa Prioritario de Epilepsia (Priority Epilepsy Program).

Correspondence:
Juan Carlos Reséndiz Aparicio
PPE, Instituto Nacional de Neurología y Neurocirugía Dr. Manuel Velasco Suárez
Hospital Psiquiátrico Infantil Dr. Juan N. Navarro
Mexico City, Mexico
E-mail: jc_doc@yahoo.com

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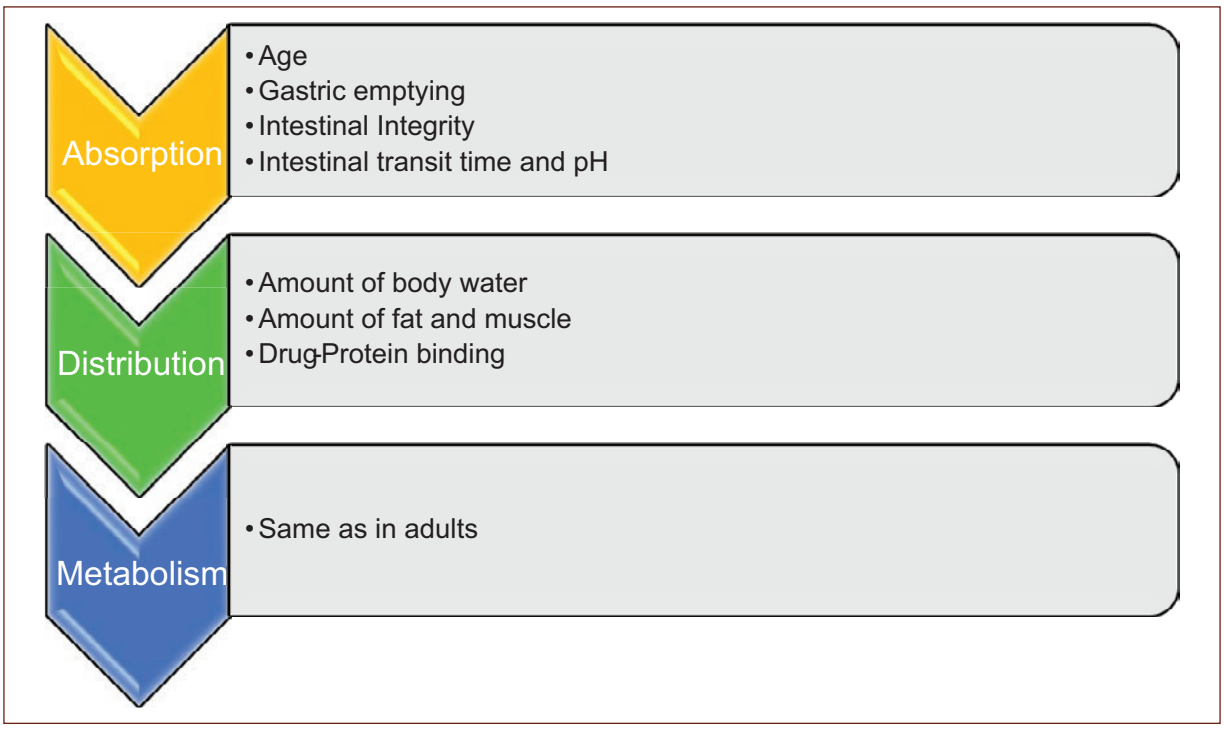

Figure 1. Pharmacokinetic and pharmacodynamic variables in pediatric age and use of antiepileptic drugs[1-6].

Question 1. What are the pharmacokinetic and pharmacodynamic differences in pharmacologic management of epilepsy between the pediatric patient and the adult?

Pediatric patients have a broad range of variations in their ability for absorption, distribution, metabolism, and clearance of antiepileptic drugs (AEDs) (Fig. 1). Clearance of AED is much faster than in adults, which makes it important to calculate the dose depending on the weight or body surface area and to be careful of the toxic effects (Tables 1 and 2)[1-6].

Question 2. Should treatment with antiepileptics be based on the type of epileptic syndrome that a patient presents?

To establish a diagnosis of epilepsy, it is sufficient if we can define an epileptic síndrome[7] that, in the current classification, would correspond to a Level III diagnosis[8]. By definition, an epileptic syndrome presupposes a disease that incorporates characteristics in common such as the type of seizure, the electroencephalographic findings, the shared imaging study results, age of onset and/or remission, when applicable, seizure triggering factors, diurnal variations, and sometimes the prognosis[8].

Question 3. What is the evidence for treating epileptic syndromes described for newborns: benign familial neonatal epilepsy (BFNE), early myoclonic encephalopathy (EME), and Ohtahara syndrome?

The first thing to understand is that neither systematic reviews nor clinical guides exist for the management of the syndromes that have been described in newborns; thus, the evidence for treatment is Level IV, and in all these cases, the recommendation is U.

BFNE

For cases with frequent seizures or status epilepticus, it could be necessary to provide therapy with drugs such as carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), levetiracetam (LEV), oxcarbazepine (OXC), and valproate (VPA). CBZ, even at low doses, is considered to be a good option for BFNE, even in status epilepticus[9,10]. In general, patients require treatment during the first 6-12 months of life.

Table 1. Traditional antiepileptic drugs and their pediatric use

AED	Initial dose (mg/kg/day)	Maintenance dose	Daily dose	Presentation
Diazepam	2-5 years: 1.5 6-11 years: 0.9	Same Same	3 times	Solution: 5 mg/5 ml Tablets: 10 mg
Carbamazepine	5-10	15-20 mg/kg/day	2 or 3 times	Suspension: 100 mg/5 ml Tablets: 200 mg
Clobazam	0.25	1 mg/kg/day	Once or twice	Tablets: 10 mg
Clonazepam	0.01	0.1 mg/kg/day	2 or 3 times	Suspension: 0.1 mg/1ml Tablets: 2 mg
Phenytoin	4-5	4-8 mg/kg/day	2 or 3 times	Suspension: 37.5 mg/5 ml Tablets: 100 mg
Phenobarbital	5	Same	Once or twice	Tablets: 100 mg
Gabapentin	10-15	30-100 mg/kg/day	2 or 3 times	Capsules: 300 and 400 mg
Lamotrigine	0.5	2-10 mg/kg/day	Twice	Tablets: 25, 50, and 100 mg
Levetiracetam	10	40-60 mg/day	Twice	Solution: 100 mg/ml Tablets: 250, 500, and 1000 mg 500 mg extended release
Oxcarbazepine	5-10	20-30 mg/kg/day	Once or twice	Suspension: 300 mg/5 ml Tablets: 300 and 600 mg 150, 300, and 600 mg extended release
Pregabalin	3.5-5	15-20 mg/kg/day	Twice	Capsules: 75 and 150 mg
Topiramate	0.5-1.0	4-8 mg/kg/day	Twice	Tablets: 25, 50, and 100 mg
Valproic acid	10-15	15-30 mg/kg/day	2 or 3 times	Syrup: 250 mg/5 ml Sprinkle: 125 mg Capsules: 250 mg and 500 mg 250 mg and 500 mg extended release
Vigabatrin	40	80-100 mg/kg/day (150 mg/kg/per day for childhood spasms)	2 or 3 times	Tablets: 500 mg

Table 2. New antiepileptic drugs and their use in pediatric age patients

Drug	Initial dose (mg, kg, day)	Maintenance	Daily dose	Secondary effects	Formulation
Lacosamide	1-2	6-9	2	Dizziness, cephalea, double vision, nausea	Tablets: 50 and 100 mg
Lamotrigine/monotherapy With enzyme inducing AED With Valproate	0.5 2 0.2	2-10 5-15 1-5	2 2 1-2	Skin rash, drowsiness, dizziness, nausea, double vision	Tablets: 5, 25, 50, and 100 mg
Levetiracetam	10	20-60	2	Cephalea, anorexia, drowsiness, behavior problems	Tablets: 250, 500, and 1000 mg Suspension: 100 mg/1 ml
Oxcarbazepine	5-8	10-30	2	Dizziness, ataxia, drowsiness, hyponatremia	Tablets: 300 and 600 mg Suspension: 300 mg/5 ml
Topiramate	1	6-9	2	Weight loss, lethargy, anorexia, hyperthermia, kidney stones	Tablets: 25, 50, and 100 mg
Vigabatrin	20-50	50-150	2	Hyperkinesis, weight gain, insomnia, visual field defects	Tablets: 500 mg

AED: antiepileptic drugs

Table 3. Treatment for west syndrome*

	Evidence	Recommendation
Insufficient data to determine whether ketogenic diet, immunoglobulin, LEV, NZP, TPM, VPA, or vitamin B6 are effective for treating infantile spasms	III and IV	U
Using rapid ACTH or prednisolone in unknown cause West syndrome improves long-term cognitive results	II and III	C
Insufficient studies to establish what other forms of corticosteroids are as effective and recommended as ACTH to treat short-term infantile spasms	III and IV	U
Low-dose ACTH (20-30 UI) versus high dose (150 UI/m^2) shows similar efficacy	I and II	B
ACTH is more effective than VGB for infantile spasms not associated with tuberous sclerosis	III	C
VGB is more effective for infantile spasms associated with tuberous sclerosis	III	C
First-line drugs are ACTH, steroids, or VGB and second-line drugs are BZD, ketogenic diet, TPM, and VPA	IV	R-PPE

*The AEDs are in alphabetical order and are available in Mexico[12,13], LEV: levetiracetam, NZP: nitrazepam, TPM: topiramate, VPA: valproate, VGB: vigabatrin, BZD: benzodiazepines, TPM: topiramate, VPA: valproate

EME

Early onset with a burst suppression pattern in the EEG, various types of seizures, and psychomotor retardation. Metabolic etiologies are often a cause of EME. The burst suppression pattern in EME is different from that of Ohtahara since, in general, the burst is shorter and the suppression is longer. The use of steroids and ACTH may be effective in some cases[11].

Ohtahara syndrome

It has been calculated that 75% of these cases evolve into West syndrome between the 2nd and 6th months of age. Treatment is difficult, but in some cases, ACTH, LEV, and high doses of PB have been shown to be effective[11].

Question 4. What is the evidence for treating West syndrome?

There are insufficient data to determine the effectiveness of ketogenic diet, intravenous immunoglobulin, LEV, nitrazepam, topiramate (TPM), VPA, or Vitamin B6, for treating infantile spasms[12].

Early control of spasms could improve development in those who do not have a proven underlying etiology[13]. For West of unknown cause, providing treatment quickly with ACTH or prednisolone, above using vigabatrin (VGB), can improve cognitive results in the long term[12]. Both steroids and VGB have potentially serious secondary effects, and the patient must be carefully observed.

The current studies are not enough to establish whether other types of corticosteroids, such as prednisolone, dexamethasone, or methylprednisolone, may be as effective or recommendable as ACTH for short-term treatment of infantile spasms[12].

First-line treatment medications are considered to be ACTH, steroids, or VGB, while second-line treatment can be benzodiazepines, ketogenic diet, TPM, and VPA, although the long-term benefits of the different therapies are still uncertain, and more research is needed on this subject (Table 3)[13].

Question 5. What is the evidence for treating Lennox-Gastaut syndrome?

To choose the treatment, one must consider the behavioral and psychiatric comorbidities, such as depression, anxiety, and psychosis. One must also take into account that the patient may have different types of seizures and some drugs may diminish some types of seizures while increasing others. Some combinations can be synergistic and reduce the number of seizures, but it is important to monitor the possible increase in adverse effects (Table 4)[14,15].

Valproate is a first-line drug, while CLB, ketogenic diet, lamotrigine (LTG), LEV, and TPM are effective as adjunct (add-on) therapies[15-19]. Other options for resistant seizures are cannabidiol, resective surgery, stimulation of the vagus nerve, callosotomy, or transcranial stimulation[20-22].

Table 4. Treatment for LGS*

	Level evidence	Recommendation
VPA is the first-line drug for LGS	II and III	B
CLB, LTG, LEV, and TPM are effective as adjunct therapy	II and III	B
Ketogenic diet is recommended for drug-resistant seizures in LGS	III	C
Cannabidiol is useful for resistant seizures in LGS	I and III	A
Callosotomy is useful for atonic seizures in LGS	III	C
Vagus nerve stimulation is useful for drug-resistant seizures in LGS	III	C
The use of CBZ, GBP, OXC, PGB, or VGB is not recommended in LGS	IV	R-PPE

*The AED are in alphabetical order and are available in Mexico[15-22]. LGS: Lennox-Gastaut syndrome, VPA: valproate, CLB: clobazam, LTG: lamotrigine, LEV: levetiracetam, TPM: topiramate, CBZ: carbamazepine, GBP: gabapentin, OXC: oxcarbazepine, PGB: pregabalin, VGB: vigabatrin

Table 5. Treatment in Doose syndrome[23-25]

	Evidence	Recommendation
LTG	II	B
VPA	IV	R-PPE
Ketogenic diet	IV	U

LTG: Lamotrigine, VPA: valproate

Question 6. What drugs are the most effective for pediatric patients with myoclonic astatic epilepsy or Doose syndrome?

VPA is considered the first choice AED, and it can be combined with BZD, ethosuximide (ESM), LTG, LEV, and TPM[23].

The ketogenic diet can be very effective. The anti-epileptics that should be avoided are CBZ, gabapentin (GBP), OXC, pregabalin (PGB), tiagabine, and VGB since these increase myoclonic epileptic seizures (ES) (Table 5)[24,25].

Question 7. What pharmacological treatment is recommended for pediatric patients with Dravet syndrome?

ESs in these patients are refractory. A good combination is VPA with TPM, which has shown improvement, especially for focal seizures and generalized tonic-clonic ES. In some cases, ACTH or corticoids, ketogenic diet, ESM, or intravenous immunoglobulin has shown satisfactory results[26]. CBZ, GBP, LTG, OXC, PHT, PGB, and VGB should not be used, as they can aggravate myoclonic ES (Table 6)[15].

Question 8. What drugs should be used for early onset occipital epilepsy or Panayiotopoulos syndrome?

Evidence places OXC at Level A, while CBZ, PB, PHT, TPM, VPA, and VGB are Level C, and CLB, CZP, and LTG are potentially Level D, with respect to efficacy/effectiveness, as initial monotherapy in children with focal onset epilepsy that have been recently diagnosed or without previous therapy[27].

Question 9. What drug must be used for juvenile myoclonic epilepsy?

TPM and VPA are potentially effective (Level D) for any type of seizure within this syndrome. Avoid administering CBZ, GBP, OXC, PHT and VGB, since they can aggravate or trigger absence seizures, myoclonus, and in some cases, generalized tonic-clonic seizures. Furthermore, LTG may exacerbate myoclonic seizures in some cases (Level F)[28,29].

Question 10. What is the evidence for treating generalized epilepsy with generalized tonic-clonic ES in pediatric patients?

There are no Class I or II studies on pediatric-aged patients, leaving us with only class III studies, and thus, Level C evidence that suggests that monotherapy with CLB, LTG, LEV, TPM and VPA may be effective[30-33].

Table 6. Treatment in Dravet syndrome*

	Level evidence	Recommendation
VPA is effective for myoclonic seizures	IV	R-PPE
LTG may worsen or trigger myoclonic ES in patients with Juvenile myoclonic epilepsy or Dravet syndrome	IV	R-PPE
CLB, CNZ, LTG, LEV, and TPM are also effective for myoclonic seizures	IV	U

*The AED are in alphabetical order and are available in Mexico[15,26], VPA: valproate, LTG: lamotrigine, CLB: clobazam, CNZ: clonazepam, LTG: lamotrigine, LEV: levetiracetam, TPM: topiramate, ES: Epileptic seizures

Table 7. Treatment in epilepsy for generalized tonic-clonic epileptic seizures only in pediatric age patients*

	Level of evidence	Recommendation
Initial CLB monotherapy may be slightly more effective in treating epilepsy with GTCS than PHT. No advantage over CBZ	II	B
CBZ and LTG may be effective as monotherapy for epilepsy with GTCS. There is greater treatment failure with CBZ but quicker response in controlling seizures (6 months)	II	B
CBZ and PHT can be effective as monotherapy for treating epilepsy with GTCS, no difference between them when comparing effectiveness and adverse effects	II	B
LEV, TPM, and VPA can be effective in treating epilepsy with GTCS	III	R-PPE

*The AED are in alphabetical order and are available in Mexico[29-33], CLB: Clobazam, PHT: phenytoin, CBZ: carbamazepine, LTG: lamotrigine, LEV: levetiracetam, TPM: topiramate, VPA: valproate

Table 8. Meta-analysis from the Cochrane library among first-generation AEDs for the treatment of focal ES*

Study	Conclusions
Tudur 2002	CBZ and PHT show similar effectiveness in treating focal ES
Tudur 2003 Tudur 2007	PB is less tolerated than CBZ (with similar effectiveness)
Nolan 2013	PB is less tolerated than PHT (with similar effectiveness)
Nolan 2013	PHT and VPA present similar effectiveness to control ES
Glauser 2006	CBZ and PHT show efficacy and effectiveness with good quality evidence VPA show efficacy and effectiveness with low-quality evidence

*The AEDs are in alphabetical order and are available in Mexico[28,37,42-44,] CBZ: carbamazepine, PHT: phenytoin, ES: epileptic seizures, PB: phenobarbital, PHT: phenytoin, VPA: valproate

CBZ and PHT must be avoided since they can aggravate or trigger GTCS (Table 7)[29].

Question 11. Which AED is considered to be first choice for recently diagnosed focal epilepsy in the pediatric patient?

Around 65% of children with recently diagnosed epilepsy achieve sustained control of their ES with the AED prescribed initially. An additional 15-20% of these patients require combination with other AEDs to achieve control. The remaining percentage does not achieve control with the available medicines, becoming a drug-resistant focal epilepsy[34,35].

For childhood focal seizures, first-line monotherapy with GBP, LCM, LEV, LTG, OXC, PGB, and TPM is recommended. Alternative monotherapy includes CBZ or VPA, and as coadjuvant therapy CLB or LCM or one

Table 9. Comparative studies between traditional and new AEDs in treating focal ES*

Study	Conclusions
Glauser 2006	Second-generation AEDs (GBP, LTG, OXC, and TPM) are not inferior in effectiveness compared with first-generation AEDs Second-generation AEDs (GBP, LTG, OXC, and TPM) show similar efficacy
Privitera 2003	TPM (doses 100 or 200 mg/day), CBZ (600 mg/day), and VPA (1250 mg/day) show similar efficacy results
Gamble 2006	LTG has better tolerability and adherence to treatment than CBZ
Nolan 2013 Arya 2013	OXC shows similar efficacy compared to PHT, but it is tolerated better
Koch 2009	OXC presents similar efficacy and effectiveness compared with CBZ
Marson 2007 Tudur 2007	LTG shows greater effectiveness over CBZ, GBP, and TPM but not over OXC CBZ demonstrates greater efficacy in seizure remission during 12 months compared to GBP but not greater than that observed with LTG, OXC, and TPM The AED with the lowest efficacy is GBP and the least tolerated is TPM CBZ, LTG, and OXC show better adherence and better control during treatment of focal ES VPA shows similar adherence as CBZ but with lower efficacy PHT and TPM are less effective than LTG and have lower efficacy than CBZ
Brodie 2007 Perry 2008	LEV demonstrates similar efficacy and tolerability CBZ for recently diagnosed focal epilepsy
CSGCE 1998 Bawden 1999	CLB shows similar efficacy as PHT and CBZ as monotherapy for the control of focal ES and GTCS There are no differences in the results of cognitive tests applied to children at 12 months of treatment receiving CBZ or CLB
Rosenow 2012	There are no differences in efficacy or tolerability with LEV or LTG for control of focal ES or GS as monotherapy at 26 weeks of treatment in patients older than 12 years

*The AEDs are in alphabetical order and are available in Mexico[28,37,42-52], AEDs: antiepileptic drugs, CBZ: carbamazepine, PHT: phenytoin, OXC: oxcarbazepine, VPA: valproate, GBP: gabapentin, LTG: lamotrigine, LEV: levetiracetam, TPM: topiramate, CLB: clobazam

Table 10. Treatment for epilepsy with focal epileptic seizures in pediatric age patients*

	Level of recommendation
CBZ, GBP, LTG, OXC, PB, PHT, TPM, and VPA can be used as monotherapy for the initial treatment of focal onset ES in children	A
LEV can be used as monotherapy for initial treatment of focal onset ES in children	C

*The AEDs are in alphabetical order and are available in Mexico[28,37,42-52], GBP: gabapentin, LTG: lamotrigine, LEV: levetiracetam, TPM: topiramate, VPA: valproate, OXC: oxcarbazepine, PB: phenobarbital, PHT: phenytoin, LEV: levetiracetam

of the AEDs used as monotherapy can be used. When using VPA, remember the teratogenic risks for fertile-aged patients, especially when used in high doses (Tables 8-10)[28,36-44].

Question 12. Which AEDs are considered to be the first choice for recently diagnosed generalized epilepsy in the pediatric patient?

Choosing an AED for generalized seizures must be personalized according to age, type of seizure, tolerability, availability for use, and other aspects.

VPA continues to be the drug of choice as monotherapy for all types of generalized ES in children, after assessing the risk-benefit and taking into special consideration patients with cognitive deficits, risk of overweight, and teratogenic effects in fertile-aged adolescents. Other options include LEV and TPM. Administration of CBZ, GBP, LTG, OXC, PHT, and VGB should be avoided since they could precipitate generalized tonic-clonic seizures and myoclonic seizures[15,29,35].

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