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Clinical guideline: antiepileptic drugs of choice for focal and generalized seizures in adult patients with epilepsy

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Abstract

The mainstay of treatment in patients with epilepsy is antiepileptic drugs (AEDs). Currently, there are a significant number of AEDs in Mexico. For the pharmacological management of the patient with epilepsy, it is important to know the pharmacokinetics, dosage, mechanism of action, and formulations of the AED. 70-80% of patients with either focal or generalized seizures are completely seizure free on AED monotherapy. When, despite the use of AED in monotherapy, seizure freedom is not achieved, a second AED should be used; AEDs with different mechanisms of action are empirically combined for this purpose. If a patient persists in having seizures with the use of an adequate AED, at appropriate doses and with therapeutic adherence, a correct diagnosis of the seizure type and a differential diagnosis should be reconsidered, using a new clinical evaluation and auxiliary diagnostic tests.

Key words: *Antiepileptic drug. Monotherapy. Polytherapy. Adult.*

Introduction

This is a clinical guide for the pharmacologic treatment of epilepsy in adults at first and second level treatment centers. 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 and the National Institute for Health Care Excellence, as well as emitting recommendations from the programa prioritario de epilepsia (priority epilepsy program).

Question 1. What are the pharmacokinetics of antiepileptic drugs (AEDs)?

In general, newer AEDs have more predictable kinetics and lower risk of drug interaction. This is because serum protein binding is low or null, they are mainly eliminated by renal excretion or metabolized by isoenzymes lacking P450, and they have a lower potential

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Table 1. Dose, mechanism of action, formulation, and pharmacokinetics for adults of AEDs available in Mexico[1]

AED	Initial dose	Final dose	Mechanism of action	Extended release formulation	Parenteral formulation	Bioavailability (%)	T. Max (h)	Distribution volume (L/kg)	PP binding 37°C (%)	Half-life (h)	Clearance (L/kg/h)
BRV	50 mg 1 dose	25-100 mg 2 doses	SV2	No	Yes	100	0.25-3	0.5	≤ 22	9	3.6 L/h
CBZ	100-400 mg 2-3 doses	600-1200 2-3 doses	SC	Yes	No	75-85	2-24	0.8-2	70-80	16-24	0.133
CLB	5 mg 2 doses	5 mg 2 doses	G	No	No	90-100	2	0.9-0.4	87-90	20	-
CLZ	-	1-20 mg 1-3 doses	G	No	No	80-90	1-4	3	80-90	20-60	0.09
DZP	Oral and intravenous 0.15-0.2 mg/kg maximum 10 mg/dose	-	G	No	Yes	75-100	1-4	1.1	95	32-47	-
ESM	250 mg 2 doses	1500 2-3 doses	CC	No	No	90-95	3-7	0.65	0	30-60	0.01-0.015
GBP	300 mg 3 doses	600 mg 3 doses	G	No	No	60	2-4	0.9	0	4-6	0.12-0.13
LCS	100 mg 2 doses	200 mg 2 doses	SC	No	Yes						
LEV	125-500 mg 2 doses	1000-3000 mg 2 doses	SV2	Yes	Yes	95-100	0.6-1.3	0.5-0.7	< 10	6-8	0.6 mL/min/kg
LTG	12.50 mg 1-2 doses	100-600 mg 1-2 doses	SC	No	No	95-100	2-5	0.9-1.22	55	24-35	0.044-0.84
OXC	300-600 mg 2 doses	600-2400 mg 2 doses	SC	Yes	No	95-100	4.5	0.7-0.8	40	4-9	-
PB	25-50 mg 1-2 doses	100-200 mg 1-2 doses	G	No	yes	95-100	8	0.42-0.75	45-60	50-140	0.006-0.009
PGB	150 mg 2 or 3 doses	200-600 mg 2 or 3 doses	G	No	No	90-100	<1	0.56	0	6.3	0.083
PHT	200-300 mg 2 or 3 doses	300-500 mg 2 or 3 doses	SC	No	Yes	85-90	10-15	0.5-0.8	70-95	7-48	0.003-0.02

(continue)

Table 1. Dose, mechanism of action, formulation, and pharmacokinetics for adults of AEDs available in Mexico[1] *(Continued)*

AED	Initial dose	Final dose	Mechanism of action	Extended release formulation	Parenteral formulation	Bioavailability (%)	T. Max (h)	Distribution volume (L/kg)	PP binding 37°C (%)	Half-life (h)	Clearance (L/kg/h)
PRM	100-125 mg 1-2 doses	750-2000 mg 1-2 doses	G	No	No	90-100	3-4	0.6-1	20-30	5-18	0.006-0.009
TPM	25-50 mg 2 doses	125-200 mg 2 doses	M	Yes	No	80-100	3.7	0.55-0.8	9-17	15-23	0.022-0.036
VGB	500 mg 2 doses	1500 mg 2 doses	G	No	No	60-80	2-3	0.8	-	4-7	0.102-0.114
VPA	200-500 mg 2-3 doses	1000-3000 mg 2-3 doses	M	Yes	Yes	<100	1-8	0.1-0.4	88-92	15-17	0.01-0.115

AED: antiepileptic drug; BRV: brivaracetam; CBZ: carbamazepine; CLB: clobazam; CLZ: clonazepam; DZP: diazepam; ESM: ethosuximide; GBP: gabapentin; LCS: lacosamide; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PGB pregabalin; PHT: phenytoin; PRM: primodone; TPM; topiramate; VGB: vigabatrin; VPA: valproate.
Mechanism of action: SV2: protein binding SV2; SC: sodium channel blocker; G: GABA analogue; CC: T-type calcium channel blocker; M: multiple mechanism.

for inducing/inhibiting various hepatic enzyme systems[1] (Table 1).

Question 2. What are the advantages and limitations of monotherapy for the control of epilepsy in the adult?

It was not until the 70s that the practice of beginning therapy with polypharmacy began to come into question due to its toxic effects and by recognizing that there was no scientific evidence that two or three AEDs were more effective than a single AED. Conversely, the first observational studies of that era reported that when patients with epileptic seizures went from polytherapy to monotherapy, they tended to have fewer secondary effects and even better seizure control[2].

The ideal AED must be effective for controlling any type of epileptic seizure, have perfectly known mechanisms of action, simple pharmacokinetics and pharmacodynamics, no plasma protein binding, and without active metabolites to avoid interactions with other AEDs or other drugs, given the comorbidities found in people with epilepsy[7,8] (Tables 4 and 5). It must have an optimal efficacy and tolerability/safety relationship. In addition, it should be inexpensive, since it is of chronic use. Currently, AEDs are very far from the ideal AED profile[3].

In 2018, Brodie et al. reported results from a prospective study including 1795 English patients, with an average age of 32 years (range 9-93 years), without previous treatment that received their first AED, followed from 1982 to 2012. Of the 63.7% of the patients without seizures, 57.3% were seizure free on monotherapy and 6.4% were seizure-free on polytherapy. The other 36.3% were considered as refractory and were taking two or more AEDs without control of their seizures, with a Class IV level of evidence (Fig. 1 and Table 2)[3].

Monotherapy is the gold standard to begin treatment of focal and generalized seizures in adults, with the goal of obtaining 100% control; however, it is important to realize that about 20-30% do not achieve this goal[3].

Question 3. What is the AED of choice for focal onset seizures and what is the first-line AED for generalized onset seizures in adults?

To begin treatment, based on pharmacokinetics and pharmacodynamics, one must start with a gradually

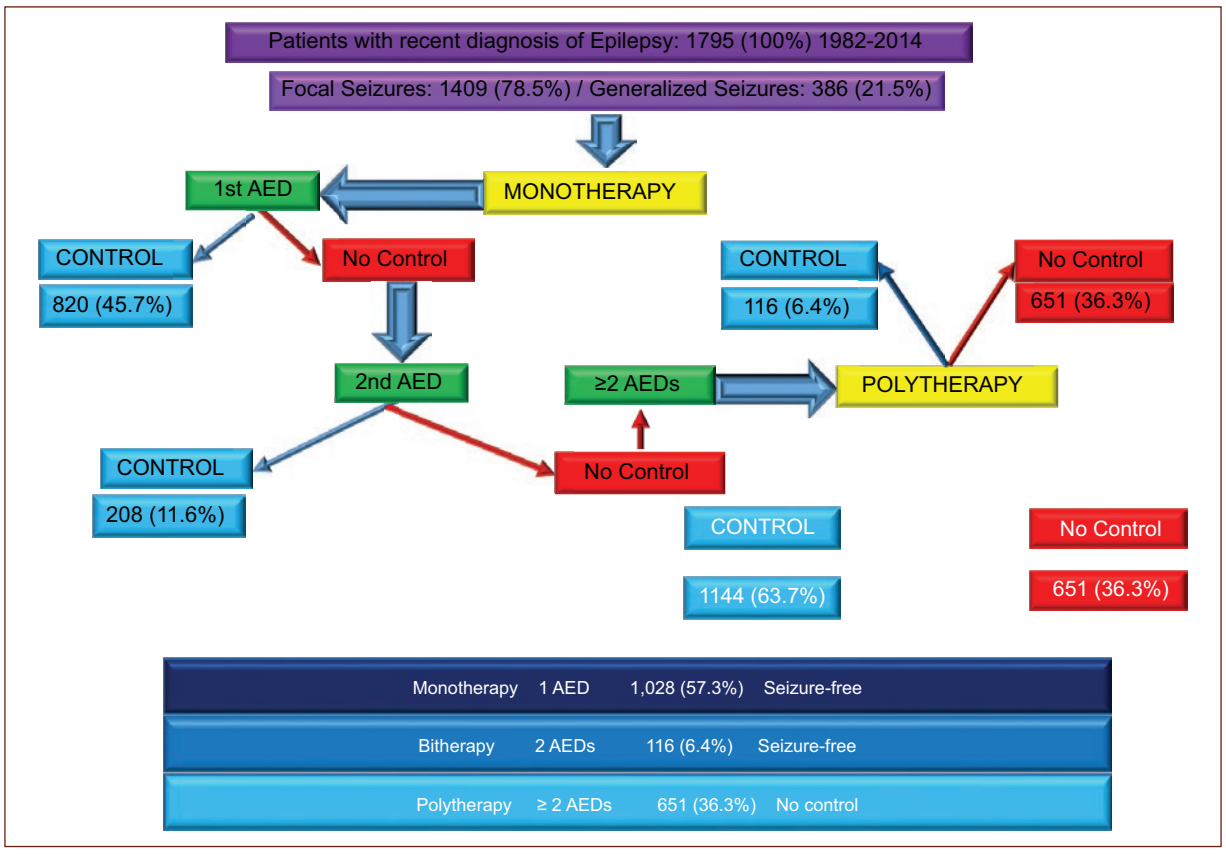

Figure 1. Pharmacologic control of epileptic seizures.

Table 2. Data for monotherapy in adults

Data	Evidence	Recommendation
The goal of AEDs is the complete control of epileptic seizures, and they are effective if prescribed correctly for the syndrome or type of seizure	I and III	A
The recommendation is to begin treatment with a single AED	I and III	A
The dose of the AED must be reached slowly and progressively until arriving at the recommended therapeutic dose	IV	R-PPE
Consistency in taking the treatment is very important, and the patient must be informed of the gravity of suspending it abruptly	IV	R-PPE

AEDs: antiepileptic drugs; PPE: priority epilepsy program.

progressive dose to arrive at the recommended therapeutic dose. In the adult, you do not always calculate the milligrams per kilogram of weight, especially for the new generation AED, but must consider the aspects related to the particular AED, the characteristics of the patient, as well as cost and bioavailability[6] (Table 3). The AED of the first choice will fundamentally depend on clinical confirmation of epilepsy. First, by recognizing the type of epileptic seizure; second, the type of epilepsy, if possible, third to determine a diagnosis of the epileptic syndrome presented by the patient, and on a fourth level, to be able to determine the etiology of the epilepsy.

Table 3. Variables to consider when choosing the AED as first-line monotherapy[6]

Variables related to the AED	Variables related to the patient	Other variables
Primary AED for the type of seizure	Genetic history	Availability of the AED
Idiosyncratic Reactions	Age at seizure onset	Cost of the AED
Dose dependent adverse effects	Gender	
Pharmacokinetics	Comorbidities	
Pharmacodynamics	Concomitant medication	
Teratogenicity	Ability to swallow	
Interactions		
Immediate/extended release formulation		

Modified form. AED: antiepileptic drug.

Table 4. Data for monotherapy in focal onset seizures in adults*[9-19]

Data	Evidence	Recommendation
The AEDs of choice to begin monotherapy treatment in focal onset seizures are CBZ, PHT, LTG and LEV	I and III	A
The evidence level for VPA is from Class II and III studies for control of focal onset seizures	II and III	B
Evidence for monotherapy for focal onset seizures with PB or with PRM is class II and III, without statistically significant differences compared with the adverse effects of CBZ and PHT	II and III	C
VGB, currently having only one Class I study, has insufficient data to recommend it for monotherapy in focal onset seizures, given the risk-benefit of visual field affectation	I and IV	C
For BRV, GBP, OXC, PGB, and TPM, the data are insufficient to recommend as monotherapy for epilepsy with focal onset seizures	IV	U

*The AEDs are in alphabetical order and are available in Mexico[6,10-18]. PHT: phenytoin; CBZ: carbamazepine; LEV: levetiracetam; VPA: valproate; PB: phenobarbital; PRM: primidone; VGB: vigabatrin; BRV: brivaracetam; GBP: gabapentin; OXC: oxcarbazepine; PGB: pregabalin; TPM: topiramate; AEDs: antiepileptic drugs; LTG: lamotrigine

Table 5. Data for monotherapy in generalized onset seizures in adults*[9-21]

Data	Evidence	Recommendation
LTG, LEV, and VPA are first choice AEDs for monotherapy management of generalized onset motor and non-motor seizures in adults	II and III	A
To treat generalized onset non-motor seizures, first-line AEDs are ESM and VPA; LTG may also be useful	II and III	A
TPM can be useful as monotherapy in generalized onset motor seizures: tonic-clonic, tonic, and clonic	II and III	B
Generalized onset seizures, motor (myoclonic), and non-motor (absences) are aggravated with CBZ, GBP, PTH, OXC and VGB	IV	R-PPE
When treating childbearing-aged women, the teratogenic potential of the AED must be considered, especially for TPM and VPA		R-PPE

*The AEDs are in alphabetical order and are available in Mexico[19-21]. LTG: lamotrigine; LEV: levetiracetam; VPA: valproate; AEDs: antiepileptic drugs; ESM: ethosuximide; TPM: topiramate; CBZ: carbamazepine; GBP: gabapentin; PHT: phenytoin; OXC: oxcarbazepine; VGB: vigabatrin.

Table 6. Data for using a 2nd AED in monotherapy[6,12,20-22]

Data	Evidence	Recommendation
If the first AED is not well tolerated at low doses, another AED from among those recommended for first-line therapy must be used	IV	R-PPE
When an average therapeutic dose of the chosen AED is reached, without achieving 100% control in a maximum period of 6 months, another AED with a different pharmacological profile must be used	IV	R-PPE
When changing the AED is necessary, the other AED must be introduced gradually at the recommended dose, and the gradual and progressive suspension of the first AED must be evaluated	IV	R-PPE

AED: antiepileptic drug; PPE: priority epilepsy program.

Table 7. Data for bitherapy for focal onset seizures in adults[24,25]

Data	Evidence	Recommendation
If monotherapy with one or various regimens of AED with A-B recommendation was not effective, two AEDs with recommendation A-B and different mechanisms of action can be combined: (SC)+(M), (SC)+(SV2), (SC)+(G) or (SV2)+(M)	I-III	A
VPA inhibits the glucuronidation process, increasing the half-life of LTG. Thus, when combined with valproate, the dose of LTG must be increased slowly until arriving at a minimal therapeutic dose to avoid adverse effects	I-III	A
There are insufficient data for combining 2 AEDs with the same mechanism of action, like two with multiple mechanisms (M)+(M)	IV	U
Combination of 2 AEDs with the same mechanism of action, such as SC blockers (SC)+(SC) or GABA analogs (G)+(G), is not recommended because of reports of inefficacy and increase in adverse effects	IV	R-PPE
The most effective combination of two AEDs with different mechanisms of action to control focal onset seizures in adults that did not respond to monotherapy is (SC)+(M): LTG (LTG) recommendation A + VPA recommendation B	IV	R-PPE

SC: sodium channel; VPA: valproate; AED: antiepileptic drug; PPE: priority epilepsy program; LTG: lamotrigine.

Table 8. Data for bitherpay in generalized onset seizures in adults

Data	Evidence	Recommendation
If monotherapy with one or more regimens of AED with recommendation A was not enough, two AEDs with recommendation A, with different mechanisms of action, must be combined: (SC)+(M), (SC)+(SV2), or (SV2)+(M)	IV	R-PPE

Modified from[3]. AED: antiepileptic drug; PPE: priority epilepsy program; SC: sodium channel.

Question 4. When do you recognize that the first-line AED is not effective to treat epilepsy in the adult patient and what are the recommendations for monotherapy with a second AED?

When despite taking a first-line AED at adequate doses and therapeutic adherence by the patient, it is not effective to control epilepsy in the adult, and we must reconsider the correct diagnosis of the type of seizure and the differential diagnosis by conducting a new clinical evaluation and clinical tests[6,12,20-22] (Table 5).

Question 5. At the moment when monotherapy with two or more drugs has not been enough to control all the seizures, what AEDs are adequate when you want to combine two AEDs, in the adult?

The fact is that there are no existing Class I, II, or III studies for bitherapy. The possibility that the 4-25% of patients who do not respond to monotherapy will be seizure free with bitherapy, that is, that they require administration of two AEDs to completely control their seizures, only has class IV evidence.[3,23]

Empirically, a combination of AED with different mechanisms of action, minimum interaction between the AED, and a different spectrum of adverse effects has been proposed[24,25] (Tables 1 and 6).

The bitherapy that has been demonstrated to be the most effective is the combination of a sodium channel blocker with a wide spectrum AED with multiple (M) mechanisms of action: such as lamotrigine and valproate, keeping in mind the teratogenic potential (Tables 7 and 8) [23-36]

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