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Antiepileptic Drug Selection According to Seizure Type in Adult Patients with Epilepsy

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Epilepsy is a common neurological disorder that is mainly treated using antiepileptic drugs. Several antiepileptic drugs such as phenobarbital, phenytoin, primidone, and ethosuximide were developed in the early 20th century. More than 10 types of antiepileptic drugs have been developed since the 1990s, and there are now more than 20 antiepileptic drugs in active clinical use. The choice of antiepileptic drugs is based on the clinical features of the seizure types, electroencephalogram findings, epileptic syndrome, and drug stability. Currently there are 19 antiepileptic drugs approved by the Korean Food and Drug Administration, 18 of which (with the exclusion of brivaracetam) are covered by the National Health Insurance Service in Korea. We reviewed the selection of antiepileptic drugs according to the classification of epileptic seizures.

Key Words antiepileptics, seizure, epilepsy, adults.

INTRODUCTION

Epilepsy is a common neurological disorder for which antiepileptic drugs are the main treatment. Several antiepileptic drugs such as phenobarbital, phenytoin, primidone, and ethosuximide were developed in the early 20th century. More than 10 types of antiepileptic drugs have been developed since the 1990s, and there are now more than 20 antiepileptic drugs in active clinical use.[1] These so-called new antiepileptic drugs were rarely used in the early stage of development as a monotherapy alone, instead normally being used as an add-on therapy. However, they are now increasingly being used as a monotherapy because their underlying mechanisms have many properties that differ from those of conventional antiepileptic drugs, they have less-severe adverse effects, and they are superior in terms of drug interactions. These drugs include vigabatrin, zonisamide, lamotrigine, gabapentin, topiramate, fosphenytoin, tiagabine, oxcarbazepine, levetiracetam, pregabalin, lacosamide, rufinamide, eslicarbazepine, perampanel, and brivaracetam.

The history of antiepileptic drugs is summarized in Fig. 1 based on their approval dates in the Republic of Korea. For example, ethosuximide was first introduced in 1989, then discontinued in before being used again from 2012 after being approved by the Korean Food and Drug Administration (FDA). Since 1990, more than a dozen new antiepileptic drugs with various mechanisms have been introduced, thereby greatly expanding the range of drug choices for treating epilepsy.

Several considerations such as the type of epilepsy and seizure, drug-related factors, and the patient's characteristics should be taken into account when selecting the most-suitable drug. However, it remains unclear which treatments are best for a certain patient with epilepsy. Although randomized controlled trials (RCTs) provide the strongest evidence, very

few RCTs directly compare multiple active treatments in a single trial. Instead, most studies have compared treatments with placebos when assessing the effectiveness and safety of antiepileptic drugs.[2,3] Moreover, most RCTs have investigated patients with drug-resistant seizure.[4] Under these circumstances, appropriate treatment guidelines can help both clinicians as well as nonspecialists in epilepsy to choose antiepileptic drugs. Treatment guidelines have been suggested by some epilepsy societies: the American Academy of Neurology,[5] National Institute for Health and Care Excellence,[6] the Scottish Intercollegiate Guidelines Network,[7] and the International League Against Epilepsy (ILAE).[8] The Korean Epilepsy Society provided the "clinical guideline for antiepileptic drug treatment in patients with epilepsy" in 2015 (Table 1).[9] The experts leading the medical care for and research into epilepsy in the Republic of Korea contributed to the guidelines. However, the guidelines are quite limited (as also stated by their authors), in terms of them essentially representing proposals rather than guidelines, not being exhaustive, and needing to be updated.

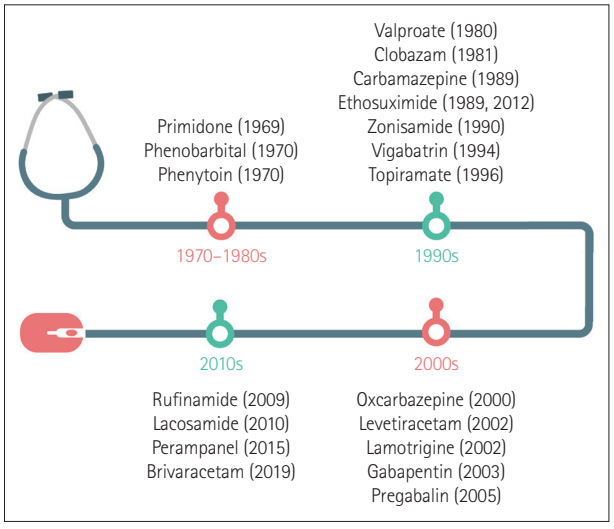

Fig. 1. Timeline of antiepileptic drugs, showing the dates on which their use by patients was approved by the Korean Food and Drug Administration.

Currently there are 18 antiepileptic drugs approved by the Korean FDA and covered by the National Health Insurance Service in Korea (Table 2). Here we focus on the selection of antiepileptic drugs according to the type of seizure as part of a series of articles on antiepileptic drug treatment for epilepsy.

Table 2. Available antiepileptic drugs in Korea and their effects on seizure types

	Focal	GTCS	Absence	Myoclonic	Atonic or tonic
PB	1st	1st	X	1st	
PHT	1st	1st	W	W	1st
PRM	1st	1st	X		
ESM	X	X	1st	X	X
CBZ	1st	1st	W	X	X
CLB	2nd	2nd	W	W	W
VPA	1st	2nd	1st	1st	1st
VGB	2nd	2nd	W	W	U
ZNS	1st	1st	U	1st	U
LTG	1st	1st	2nd	2nd	2nd
GBP	1st	X	W	W	X
TPM	1st	2nd	U	2nd	2nd
OXC	1st	1st	X	X	X
LEV	1st	2nd		2nd	
PGB	2nd	X	X	X	X
LCM	2nd	U	U	U	U
RFN					2nd
PRP	2nd	2nd	U	U	U
BVC	2nd				

BVC: brivaracetam, CBZ: carbamazepine, CLB: clobazam, ESM: ethosuximide, GBP: gabapentin, GTCS: generalized tonic-clonic seizure, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PGB: pregabalin, PHT: phenytoin, PRM: primidone, PRP: perampanel, RFN: rufinamide, TPM: topiramate, U: unknown effect and mechanism, VGB: vigabatrin, VPA: valproate, W: worsening effect, X: no effect, ZNS: zonisamide, 1st: first choice, 2nd: second choice.

Table 1. Clinical guideline for selecting AEDs according to seizure type in patients with epilepsy in the guideline of the Korean Epilepsy Society published in 2015

Seizure type	First-line AEDs	Second-line AEDs	Adjunctive AEDs	Considered additional AEDs	Not recommended
Focal	CBZ, OXC, LTG	LVT, VPA	CBZ, GBP, LTG, LVT, OXC, VPA, TPM	LCM, PB, PHT, PGB, VGB, ZNS	
GTCS	VPA, LTG		CLB, LTG, LVT, VPA, TPM		
Absence	ESM, VPA	LTG		CLB, CZP, LVT, TPM, ZNS	CBZ, OXC, GBP, PHT, PGB, VGB
Myoclonic	VPA	LVT, TPM		CBZ, CZP, ZNS	CBZ, OXC, GBP, PHT, PGB, VGB
Atonic or tonic	VPA	LTG		TPM	CBZ, OXC, GBP, PHT, PGB, VGB

AED: antiepileptic drug, CBZ: carbamazepine, CLB: clobazam, CZP: clonazepam, ESM: ethosuximide, GBP: gabapentin, GTCS: generalized tonic-clonic seizure, LCM: lacosamide, LTG: lamotrigine, LVT: levetiracetam, OXC: oxcarbazepine, PB: phenobarbital, PGB: pregabalin, PHT: phenytoin, TPM: topiramate, VGB: vigabatrin, VPA: valproate, ZNS: zonisamide.

GENERAL CONCEPTIONS OF ANTIEPILEPTIC DRUGS

The mechanisms of antiepileptic drugs were previously divided into four categories: 1) modulation of voltage-dependent ion channels, including Na^+, Ca^{2+}, and K^+ (phenytoin, carbamazepine, lamotrigine, oxcarbazepine, ethosuximide, and zonisamide), 2) potentiation of γ-amino butyric acid (GABA) (phenobarbital, benzodiazepines, vigabatrin, and tiagabine), 3) multiple mechanisms of action (sodium valproate, gabapentin, felbamate, and topiramate), and 4) another mechanism of action (levetiracetam).[10] For example, valproate works via multiple mechanisms that are similar to those of phenytoin, such as the frequency-dependent prolongation of Na^+-channel inactivation, weak attenuation of T-type Ca^{2+} channels, and augmentation of release of GABA by increasing its synthesis from the excitatory neurotransmitter glutamic acid.[11] Levetiracetam and lacosamide may act as antiepileptic drugs with a modulating mechanism—the exocytolic function of synaptic vesicle protein SV2A—that could enhance the release of inhibitory neurotransmitters such as GABA.[12] Lacosamide has another additional mechanism, which is enhancing the modulation of the slow inactivation of Na^+ channels without affecting the fast inactivation of voltage-gated Na^+ channels.[12] Perampanel has a novel mechanism of action as a noncompetitive agonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.

Pharmacokinetics is the study of drug absorption, distribution, metabolism, and excretion. The concentrations of anti-

Table 3. Pharmacokinetics of antiepileptic drugs

	F (%)	T_{max} (h)	V_d (L/kg)	Protein binding (%)	Renal excretion* (%)	Metabolic organ (%)	$T_{half-life}$ (h)	T_{SS} (d)	Therapeutic range (mg/L)
PB	70–90	0.5–8.6	0.6–0.9	55	20–25	Hepatic (50–80) Renal (20–50)	53–118	10–15	15–40
PHT	90–100	8–12	0.7–0.8	87–93	-5	Hepatic (95) Renal (5)	6–60	15–20	10–20
PRM	60–80	4–6	N/A	20–45	-65	Hepatic (60–70) Renal (30–40)	7–22	2–3	-
ESM	>90	1.5–7.0	0.6–0.7	0	-20	Hepatic	25–60	5–15	50–100
CBZ	85	3–8	0.8–2.0	76	<2	Hepatic	12–17	2–6	4–12
CLB	>95		0.9–1.4	85	-	Hepatic	18		100–400
VPA	>95	4–17	0.1–0.2	90	1–3	Hepatic (95) Renal (5)	6–17	2	50–100
VGB	60–80	1	0.8	0	100	Renal	5–8	2	-
ZNS	90	2–6	1.0–1.9	40	-35	Hepatic (70) Renal (30)	27–70	10–40	10–40
LTG	>95	1–4	0.9–1.3	55	10	Hepatic	15–35	5–6	-
GBP	35–60	2–4	0.85	0	100	Renal	5–7	2	-
TPM	80	1.4–4.3	0.6–0.8	15	20–60	Hepatic (30) Renal (70)	20–30	4–6	2–13
OXC	90	4.5–6.0	0.75	60	<1	Hepatic (80) Renal (20)	8–15	1	-
LEV	95	0.3–2.0	0.5–0.7	<10	-66	Renal	6–8	5	6–21
PGB	90	1.3	0.57	0	-98	Renal	5–7	2	3.0–9.5
LCM	100	1–4	0.5–0.8	<30	40	Hepatic (60) Renal (40)	13	2–3	-
RFN	85	4–6	0.71–1.14	35	-4	Hepatic	6–10	1–3	5–30
PRP	100	0.5–2.5		≤95	2	Hepatic	70		-
BVC	100	1	0.5	≤20	9	Hepatic (20)	9	2	0.2–2.0

*Unchanged excretion.
BVC: brivaracetam, CBZ: carbamazepine, CLB: clobazam, ESM: ethosuximide, F: drug fraction, GBP: gabapentin, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PGB: pregabalin, PHT: phenytoin, PRM: primidone, PRP: perampanel, RFN: rufinamide, T_{max}: time to reach maximum plasma concentration, TPM: topiramate, T_{SS}: time to reach steady-state plasma concentration, V_d: volume of distribution, VGB: vigabatrin, VPA: valproate, ZNS: zonisamide.

Table 4. Recommended titration rate and maintenance dose for AEDs in adult patients with epilepsy

AED	Titration rate	Initial target maintenance dose (mg/day)	Usual maintenance dose (mg/day)	Frequency of administration
PB	Start at 30–50 mg at bedtime and increase if indicated after 10–15 days	50–100	50–200	1 time/day
PHT	Start at 100–300 mg/day and increase to target dosage over 3–7 days at up to 50 mg/day	200–300	200–400	1–2 times/day
PRM	Start at 62.5 or 125 mg/day and increase to target dosage over about 3 weeks A faster titration may be used in patients on enzyme-inducing comedication	500–750	500–1500	2–3 times/day
ESM	Start at 500 mg/day and increase at 5- to 7-day intervals in increments of 250 mg/day	500–750	500–1500	
CBZ	Start at 200 or 400 mg/day and increase to target dosage over 1–4 weeks at up to 200 mg/day	400–600	400–1600	2–3 times/day
CLB	Start at 5–10 mg/day and increase to 20 mg/day after 1–2 weeks	10–20	10–40	1–2 times/day
VPA	Start at 500 mg/day and increase at 5- to 7-day intervals in increments of 500 mg/day	500–1000	500–2500	2–3 times/day
VGB	Start at 250 or 500 mg/day and increase by 500 mg/day over 1–2 weeks	1000	1000–3000	1–2 times/day
ZNS	Start at 50–100 mg/day, increase to 100 mg/day at interval of 1–2 weeks	200–300	200–500	2 times/day
LTG	Monotherapy: start at 25 mg/day for 2 week, then increase to 50 mg/day for 2 weeks. Further increases of 50 mg/day every 2 weeks Valproate comedication: start at 25 mg on alternate days for 2 weeks, then 25 mg/day for 2 weeks. Further increases of 25–50 mg/day every 2 weeks. Enzyme-inducing comedication: start at 25 or 50 mg/day for 2 weeks. Further increases of 50–100 mg/day every 2 weeks	50–150 (monotherapy) 50–100 (add-on valproate) 200–300 (add-on enzyme inducers)	50–150 (monotherapy or add-on valproate) 200–500 (add-on enzyme inducers)	2 times/day (once daily possible with monotherapy and valproate comedication)
GBP	Start at 300–900 mg/day and increase to target dosage over 5–10 days	900–1800	900–3600	2–3 times/day
TPM	Start at 25–50 mg/day and increase in 25- or 50-mg/day increments every 2 weeks	100	100–400	2 times/day
OXC	Start at 300 mg/day and increase at 2-day intervals by 150 mg/day to target dosage over 1–3 weeks	600–900	600–3000	2–3 times/day
LEV	Start at 500 or 1000 mg/day and increase at 1- to 2-week intervals at up to 500 mg/day after 2 weeks	1000–2000	1000–3000	2 times/day
PGB	Start at 50 or 75 mg/day and increase at 3- to 7-day intervals at up to 50–300 mg/day	150–300	150–600	2–3 times/day
LCM	Start at 100 mg/day and increase to target dosage in increments of 100 mg/day every week	200–300	200–400	2 times/day
RFN	Start at 400 mg/day and increase every 2–4 days by 400 mg/day	1200	1200–3200	2 times/day
PRP	Start at 2 mg and increase by 2 mg/day to target dosage at 2-week intervals	4–8	4–12	1 time/day
BVC	Start at either 50 or 100 mg/day and increase to target dose at intervals of 1–2 weeks	50–200	50–200	2 times/day

AED: antiepileptic drug, BVC: brivaracetam, CBZ: carbamazepine, CLB: clobazam, ESM: ethosuximide, GBP: gabapentin, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PGB: pregabalin, PHT: phenytoin, PRM: primidone, PRP: perampanel, RFN: rufinamide, TPM: topiramate, VGB: vigabatrin, VPA: valproate, ZNS: zonisamide.

epileptic drugs in vivo are determined by complex interactions of the basic processes of the absorption, distribution, metabolism, and elimination of drugs. Drug concentrations are the primary determinants of therapeutic and toxic effects, and the rational use of antiepileptic drugs therefore requires an understanding of their pharmacokinetics (Table 3), the dosage and medication intervals (Table 4), drug interactions, and monitoring the level of the drug in the plasma.

After an antiepileptic drug is administered via a specific route, its serum concentration is determined by various pharmacokinetic parameters. The serum concentration of the drug, which influences its therapeutic effects, is determined by absorption, distribution, and conversion processes in the human body, and the rate of excretion, bioavailability, and protein binding. The main pharmacokinetic parameters are summarized in Table 3. Older antiepileptic drugs generally show strong protein binding and clinically significant changes in drug effects resulting from changes in the drug-free fractions. As one example of a clinical application, the effect of drugs exhibiting strong protein binding (e.g., phenytoin and valproate) could be reduced when the serum level of albumin is low, such as in renal or hepatic disease, pregnancy, and malnutrition with various medical conditions.[11] On the other hand, newer antiepileptic drugs exhibit fewer drug interactions and more-predictable pharmacokinetics.[13] Antiepileptic drugs have different half-lives, which in general are related to the time taken to reach the steady-state plasma concentration. This is a useful indicator to consider when determining the maintenance dosage of a specific antiepileptic drug. The titration rates and maintenance doses for the various antiepileptic drugs are listed in Table 4.

The pharmacokinetic properties of an antiepileptic drug determine the time course of its serum concentration after its administration, while pharmacodynamics describes the relationship between the drug concentration and its therapeutic effect. When applying combination therapy of antiepileptic drugs, pharmacokinetic and/or pharmacodynamic interactions can occur between multiple drugs, which could be either beneficial or harmful. Adding an antiepileptic drug with different pharmacodynamic properties is recommended in combination therapy because antiepileptic drugs such as carbamazepine, phenytoin, oxcarbazepine, lamotrigine, and lacosamide that act on Na^+ channels have more adverse effects. On the other hand, the synergistic combination of valproate and lamotrigine elicits beneficial drug interactions and is often recommended when monotherapy fails. Combination therapy should be considered when there are few side effects, since seizure control using this method is superior to that in monotherapy.

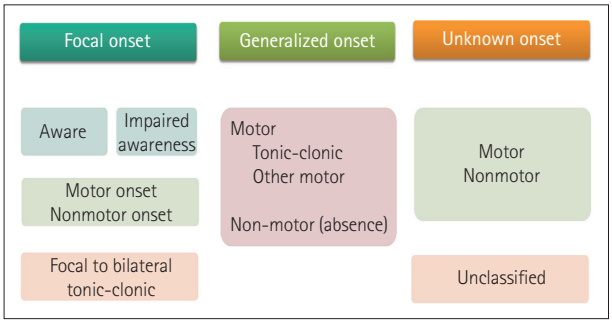

Fig. 2. ILAE 2017 classification of seizure type. In the guidelines of the ILAE revised in 2017, seizures are classified into focal, generalized, and unknown based on their onset. ILAE: International League Against Epilepsy.

SEIZURE TYPE AND EPILEPSY CLASSIFICATION

The ILAE guidelines revised in 2017 classify seizure into focal, generalized, unknown, or unclassifiable based on its onset (Fig. 2).[14] The old term "partial" was changed to "focal" seizure, while the term "generalized seizure," in which seizure begins in both hemispheres, was retained. If the onset of seizure is unknown, but subsequent seizure types are known, the seizure is classified as "unknown." A seizure event that does not belong to any of the above categories is designated as "unclassified." Depending on whether consciousness in lost during a seizure event, the old terms "simple" and "complex" were changed to the new terms of "aware" and "impaired awareness." After classifying the loss of consciousness, the next step is to assess the "motor" or "nonmotor" category at the onset of seizure. A secondary generalized seizure was newly named "focal to bilateral tonic-clonic seizure."

Epilepsy is classified into the following four types: "focal," "generalized," "combined generalized and focal," and "unknown." A few epileptic syndromes that involve both focal and generalized seizure types (e.g., Dravet syndrome and Lennox-Gastaut syndrome) were included in "combined generalized and focal epilepsy." Epilepsy events in which information about the type of seizure and patient is insufficient are categorized as "unknown."

In order to select appropriate drugs, the diagnosis of the patient must first be accurate, in terms of the cause, seizure type, and epilepsy syndrome. The most useful diagnostic classification for antiepileptic drug selection is based on the seizure type (Fig. 2 and Table 2). Most antiepileptic drugs are effective against focal seizures and generalized tonic-clonic seizures, but special medications are needed for absence and myoclonic seizures, for which broad-spectrum antiepileptic drugs such as valproate are effective. In contrast, ethosuximide has a small indication range and can only be used in absence

seizures. Therefore, diagnosing the seizure type is most important when initiating treatment for patients with epilepsy.

ANTIEPILEPTIC DRUG SELECTION ACCORDING TO SEIZURE TYPES

Focal onset seizure with awareness or impaired awareness

First single drug

Carbamazepine,[15] oxcarbazepine,[15] and lamotrigine[16] are recommended for patients with their first diagnosed focal seizures. In the 2019 Expert Opinion Survey in Korea, the first choices for focal seizure were levetiracetam, oxcarbazepine, and lamotrigine.[17] Carbamazepine is the most-frequent antiepileptic drug used in RCTs for patients with focal seizures. A 2007 large-scale, open-label RCT with carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate involving 1,721 patients with partial-onset seizures found that lamotrigine exhibited noninferiority compared with carbamazepine.[18]

If carbamazepine, oxcarbazepine, and lamotrigine are not suitable or the patient does not tolerant them, levetiracetam[19] or valproate[20] can be used. A meta-analysis of 17 trials involving 3,205 patients found levetiracetam to be an effective antiepileptic drug for partial-onset refractory seizures.[21]

Additional drug

If the primary treatment is ineffective or the patient does not tolerate it, the frequently chosen options for additional treatment are carbamazepine, clobazam,[22] gabapentin,[23] lamotrigine,[24] levetiracetam,[25] oxcarbazepine,[26] valproate,[27] tiagabine,[28] and topiramate.[29] If the additional treatment is ineffective or the patient cannot tolerate it, the patient can be transferred to a tertiary institution. Lacosamide, phenobarbital, phenytoin, pregabalin, vigabatrin, and zonisamide can be considered as the next step in the process. Lacosamide[30] has been used as a single drug for controlling the first focal seizure in Europe and the United States, but has only been approved as an additional antiepileptic drug for focal seizure in Korea.[31] In a 2-year follow-up of 322 patients with partial-onset seizure, lacosamide monotherapy produced a favorable outcome and safety profiles.[30]

Brivaracetam increases the binding affinity of the synaptic vesicle protein SV2A by 10-fold more than levetiracetam. It was approved by the Korean FDA in 2019, and has been available for prescribing as an additional treatment in patients with focal seizure since 2020.[32] The voltage-gated Na^+-channel antagonist eslicarbazepine acetate is a novel antiepileptic drug that is used as an additional therapy for patients with focal seizure in the United States and Europe, but it has not yet been released in Korea.[33] Retigabine is another novel antiepileptic drug approved for use in patients with refractory focal seizure in the United States and Europe that has not been introduced into Korea.[34]

GENERALIZED ONSET SEIZURE

Generalized tonic-clonic seizure

First single drug

Valproate[35] is recommended for patients who are first diagnosed with generalized tonic-clonic seizure. When valproate is administered to females of childbearing age, there is a risk of the development of fetal deformities and neurodevelopmental disorders. The use of valproate should therefore be minimized as much as possible. If valproate is not suitable, lamotrigine, levetiracetam, zonisamide, and topiramate are considered as a first-line treatment.[31] In the 2019 Expert Opinion Survey in Korea, valproate and lamotrigine were frequently selected for generalized tonic-clonic seizure.[17] However, care is need with lamotrigine since this can aggravate myoclonus.[35]

There is double-blind and open-label RCT evidence for the effectiveness of carbamazepine, levetiracetam, lamotrigine, phenytoin, and valproate as first-line antiepileptic drugs in patients with generalized tonic-clonic seizures. A large-scale RCT compared lamotrigine, valproate, and topiramate in 716 patients with generalized-onset and unclassifiable seizures.[36] The subgroup analysis of idiopathic generalized epilepsy showed that valproate was more effective and had a lower failure rate than lamotrigine and topiramate.

Additional drug

If the primary treatment is not effective or tolerated, clobazam,[37] lamotrigine, levetiracetam,[38] valproate, topiramate,[35] and perampanel[39] can be considered as additional drugs. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, and vigabatrin are not used in cases of absence or myoclonic seizure. A randomized trial showed that adjunctive therapy with perampanel was well tolerated and improved the control of drug-resistant generalized tonic-clonic seizure in patients with idiopathic generalized epilepsy.[39]

Nonmotor (absence) seizure

First single drug[16]

Ethosuximide or valproate[40] is recommended for absence seizures. Lamotrigine[31] can be considered if ethosuximide or valproate is inappropriate, ineffective, or not tolerated by the patient. A large study of ethosuximide, valproate, and la-

Table 5. Recommendations of antiepileptic drugs from Korean Expert-Opinion Surveys

	Monotherapy		Adjunctive therapy		Not recommended
	Treatment of choice	First-line treatment	Treatment of choice	First-line treatment	
Focal seizure			LEV, LTG, LCM	OXC, TPM, ZNS, CBZ, VPA	
Without dyscognitive seizure	LEV, OXC, LTG	CBZ			
With dyscognitive seizure	LTG, OXC, LEV	CBZ			
With bilateral convulsion	LEV, OXC, LTG	CBZ, LCM, VPA			
Generalized seizure			VPA, LEV	LTG, TPM, ZNS	
GTCS	VPA, LEV	LTG, TPM, ZNS			
Absence	ESM, VPA	LEV			CBZ, OXC, GBP, PHT, PGB, VGB
Myoclonic	VPA, LEV	ZNS, TPM			CBZ, OXC, GBP, PHT, PGB, VGB

CBZ: carbamazepine, ESM: ethosuximide, GBP: gabapentin, GTCS: generalized tonic-clonic seizure, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PGB: pregabalin, PHT: phenytoin, TPM: topiramate, VGB: vigabatrin, VPA: valproate, ZNS: zonisamide.

motrigine demonstrated the superior effectiveness of ethosuximide and valproate compared with lamotrigine as a first-line treatment for patients with absence seizure.[41] A 2010 double-blind trial of 446 patients with absence seizure found that the rate of seizure-free outcomes was 58% for valproate, 53% for ethosuximide, and 29% for lamotrigine.[40] If the patient has coexisting generalized tonic-clonic seizures, valproate should be considered in preference to ethosuximde.[42]

Additional drug

If the primary treatment is not effective or is not tolerated by the patient, two of the following drugs can be considered: ethosuximide, lamotrigine, and valproate. If the additional treatment is ineffective or the patient cannot tolerate it, the patient can be transferred to a tertiary institution. Clobazam,[37] clonazepam,[43] levetiracetam,[44] topiramate,[35] and zonisamide[45] can be considered as a next step.

Myoclonic seizure

First single drug[16]

Valproate[35] is recommended as the primary treatment for myoclonic seizures. Levetiracetam,[46] zonisamide,[31] and topiramate[35] can be considered as first-line antiepileptic drugs if valproate is inappropriate. An unblinded RCT performed in the United Kingdom over 5 years found that valproate was better tolerated than topiramate and more effective than lamotrigine.[34]

Additional drug

If the first single antiepileptic drug fails to control myoclonic seizures, lamotrigine[47] or zonisamide[48] can be considered as an additional drug. A prospective RCT involving patients with juvenile myoclonic epilepsy found that lamotrigine was effective and better tolerated than valproate, even though lamotrigine often elicited idiosyncratic reactions such as skin eruption.[46] Carbamazepine, oxcarbazepine, phenytoin, gabapentin, vigabatrin, and tiagabine worsen myoclonic seizure.

Tonic or atonic seizure[16]

Phenytoin and lamotrigine[36] are effective at treating tonic seizures. Valproate[35] is the drug of choice for atonic seizure, especially in Lennox-Gastaut syndrome, but it is less effective in controlling tonic seizure. Antiepileptic drugs with broad-spectrum effects such as lamotrigine,[35] topiramate,[35] zonisamide, and levetiracetam are used for mixed seizures that include tonic seizure.

Lamotrigine,[49] topiramate,[50] and rufinamide[51] are also used as adjunctive treatment for atonic seizure. However, rufinamide has recently been reported to aggravate atonic seizure.[52] Levetiracetam and zonisamide, which are broad-spectrum antiepileptic drugs, are expected to be useful in the treatment of atonic seizure, although the data regarding outcomes are currently insufficient.

CONCLUSION

Recently developed antiepileptic drugs act via various novel mechanisms that increase their effectiveness while minimizing side effects. Since there is a wide range of antiepileptic drug available, selecting appropriate treatments requires broadening our understanding of the use of antiepileptic drugs based on seizure types in order to provide customized treatments for patients with epilepsy. This review has summarized the antiepileptic drugs that are available in Korea for different seizure types based on medical evidence and Korean expert opinions (Table 5). The most-important reference information when treating with antiepileptics is medical evidence. Expert opinion cannot be a substitute for the medical literature, and should only be consulted in specific clinical situations.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: Hyeyun Kim, Yong Won Cho, Kwang Ik Yang. Investigation: all authors. Methodology: Hyeyun Kim, Yong Won Cho, Kwang Ik Yang. Supervision: Yong Won Cho, Kwang Ik Yang. Validation: all authors. Visualization: Hyeyun Kim, Yong Won Cho, Kwang Ik Yang. Writing—original draft: Hyeyun Kim. Writing—review & editing: Hyeyun Kim, Yong Won Cho, Kwang Ik Yang.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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