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Refining General Principles of Antiepileptic Drug Treatments for Epilepsy

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Antiepileptic drugs (AEDs) are the primary treatment strategy for epilepsy. As the use of AEDs has become more widespread and diverse over the past century, it has become necessary to refine the associated prescription strategies. This prompted the Drug Committee of the Korean Epilepsy Society to perform a systemic review of both international and domestic guidelines as well as literature related to medical treatment of epilepsy, and prepared a series of reviews to provide practical guidelines for clinicians to follow. This article is the first in a series on AED treatments for epilepsy in South Korea.

Key Words epilepsy, antiepileptic drugs, anticonvulsants, therapeutics.

INTRODUCTION

Epilepsy is a common neurological disease that affects more than 70 million people worldwide.[1] It is characterized by recurrent seizures, and the primary treatment is antiepileptic drug (AED) medication. About two-thirds of patients with epilepsy can control their seizures if they are appropriately diagnosed and treated.

Since potassium bromide was first used in the 19th century, various AEDs have been developed and numerous studies have been published on pharmacological treatments for epilepsy. More than 20 AEDs are currently used to treat epilepsy, which makes it prudent to reconsider how to effectively prescribe and administer them. To this purpose, the International League Against Epilepsy (ILAE) began developing evidence-based guidelines for clinicians in 1998. However, despite 2 decades having passed, treatment guidelines for epilepsy are still not used in many countries.[2]

The prevalence of epilepsy among the general population in South Korea is approximately 0.4%.[3] Most AEDs used in other countries are also available for use in South Korea, and in 2015 the Korean Epilepsy Society (KES) provided clinical guidelines for AED treatment in patients with epilepsy.[4] Early experts in South Korea who provided treatment and research for epilepsy contributed to this guideline. However, the guidelines are quite limited, since (as the original authors mentioned) the publication was a proposal rather than an agreed-upon set of rules. The authors also stated that the list of AEDs was not exhaustive and needed to be updated. The Drug Committee of KES subsequently prepared a series of reviews to provide practical guidelines for clinicians. Members of that committee discussed the contents relevant to AED treatments in South Korea through both online discussions and offline meetings.

This review is an additional attempt to further clarify and improve these guidelines so that clinicians can make informed decisions when treating epilepsy, while also taking into

account circumstances that may be unique to patients in South Korea. This article is the first in a series, and will describe the general principles of AED treatments for epilepsy.

GENERAL PRINCIPLES OF AEDS

When a pharmacological treatment is first being considered, the clinician should address 1) whether the medication is necessary and 2) which AED to prescribe. It is also important to confirm that the event being treated was actually an epileptic seizure through careful and detailed history-taking and sufficient evaluations.

At least one confirmed seizure is necessary to clinically diagnose epilepsy. There is no disease-specific symptom or sign for epilepsy, and a neurological examination is normal in most patients. According to the latest definition,[5] epilepsy can be identified if any of the following are present:

1) Two or more unprovoked seizures occurring more than 24 hours apart.

2) An unprovoked seizure, after which the probability of further seizures is similar to that of two unprovoked seizures over the next decade (e.g., more than 60%).

3) Diagnosis of an epilepsy syndrome.

This three-line definition contains answers to several clinically significant questions, which we discuss below.

Beginning AED treatment

AED treatment should be considered once it meets the diagnostic criteria for epilepsy or status epilepticus; in short, it should be treated only after it has been confirmed. However, there is some controversy about whether a patient with a single seizure should receive medication. The immediate administration of an AED is sometimes not necessary after a single seizure, especially if a curable cause provoked the seizure. In addition, without risk factors for recurrent seizure (e.g., abnormal EEG, neurological deficit, or a causative structural brain lesion), only one in four patients will experience a second seizure within the following 2 years.[6-8] The overall risk of recurrence after a seizure is 40−52%.[5] Immediately administering an AED reduces the occurrence of seizures during the next 1−2 years but it does not influence the probability of long-term remission.[9,10] Moreover, reflex epilepsy caused by avoidable stimuli such as light or sound does not necessarily require medication, while removing the cause and controlling the trigger are more important factors for seizures provoked by alcohol or substance abuse.

The decision to begin AED treatment should be made on an individual basis, considering the patient's needs and circumstances as well as the specifics of the disease itself. Even if the diagnostic criteria are not met, AED initiation can be considered when epilepsy is strongly suspected, including since recurrent seizures affect the mood, quality of life, employment, and social relationships of the patient. For patients who experience their first unprovoked seizure, the effect on the quality of life might be better for immediate AED treatment than for deferred treatment.[11] In addition, given the social complications and stigma related to epilepsy and seizure,[12] immediate AED treatment may be considered if the patient fears the social repercussions of a public episode. The clinician should therefore consider the risks and benefits of diagnosing epilepsy and prescribing an AED separately in each case.

Treatment of status epilepticus requires special care since this condition leads to abnormally prolonged seizures, and is considered a neurological emergency.[13,14] The treatment of status epilepticus should be initiated when generalized tonic-clonic seizures and focal seizures last longer than 5 and 10 minutes, respectively.[15] Given the urgency of treating status epilepticus, a ready-made teamwork-based treatment cascade should be set up depending on the circumstances of individual hospitals.

Choosing an appropriate AED

The most appropriate AED can be difficult to define in each case, but the most-common definition involves choosing an AED while considering the circumstances, situations, and conditions of the patient.[1,6,16] The ultimate goal of treatment is seizure remission without adverse effects.

Several factors should be considered when selecting the appropriate AED. First of all, it is crucial to determine the epilepsy classification and seizure type. For example, carbamazepine and vigabatrin may aggravate myoclonic seizures, while ethosuximide and valproic acid are recommended for absence seizures. Drug efficacy and tolerability (potential adverse effects that may have occurred or may occur in the future) are essential factors to consider, and interactions with other medications and medical comorbidities (e.g., depression, dementia, and hepatic and renal problems) should also be considered. In addition, the patient's age, sex, and life plan should be taken into account. Lastly, the cost of the drug relative to the financial status of the patient should be examined.

The immediate administration of intravenous lorazepam is highly recommended for status epilepticus,[17,18] and the subsequent AED strategy should be determined under intensive care that includes continuous EEG monitoring. Since up to 40% of status epilepticus cases cannot be controlled with first-line drugs,[14] it is recommended that a well-trained neurologist (ideally an epileptologist) participates in the treatment process.

Since choosing an appropriate AED is a critical issue with a wide variety of possible approaches, all of the details can-

not be covered in one section. The subsequent articles in this review series will therefore expand on more-detailed treatment strategies and considerations, which will include assessing AEDs according to the type of seizure and epilepsy, the age of the patient (e.g., elderly versus pediatric), medical comorbidities, sex, and specific treatment strategies for status epilepticus.

Determining the dosage, titration, and maintenance therapy

When it is determined that medication is necessary, the clinician must also decide what dose to administer and how rapidly the dosage may be increased. The initial treatment strategy is monotherapy, and approximately half of newly diagnosed epileptics achieve complete remission after taking the first prescribed AED.[1,2,5,11,19] In order to minimize adverse effects, it is recommended to start at a low dose and increase the dose gradually until the maintenance dose (or target dose) is reached. The recommended initial dose and the range of maintenance doses for representative AEDs in South Korea are summarized in Table 1.[20]

The maintenance dose varies between patients and is determined as the optimal trade-off between maximizing the benefit and minimizing the adverse effects. A loading dose is often also necessary in cases of status epilepticus or very frequent seizures. If the seizure recurs, the dosage may be increased further within the limits of the maximum allowable dose of the AED. Optimal doses are different for each patient due to the differences in pharmacokinetic parameters and drug–drug interactions, which makes it necessary to carefully determine the dose on an individual basis for each patient. Moreover, AEDs should be administered at a frequency that will keep the blood levels stable. Drugs in a modified-release dosage formulation obtained from the immediate-release dosage formulation can keep the AED concentration within the target range with less variation, and may enhance AED adherence thanks to improving the convenience to the patient.[21,22] A modified-released dosage formulation can optimize the risk–benefit ratio and improve tolerability.

Regular follow-up EEG sessions as well as monitoring the blood levels related to the AED are recommended. EEG and blood levels can be checked repeatedly and more frequently when the AED is initiated, when drug–drug interactions are suspected, when the impact of comorbid medical illness is considered, and when the combination of drugs is modified.

Sometimes patients are unaware of their seizures, and in these cases the clinician will have to assess the symptoms based on the eyewitness reports of caregivers. However, a caregiver cannot always be with a patient, and may even not be aware of the seizures in some cases. In other words, the seizure frequency may be underestimated due to nonspecific characteristics, short-term symptoms, and absence of witnesses.[23] This so-called unrecognizability is a unique feature of epilepsy, and clinicians should always keep in mind that the symptoms of epilepsy can be underestimated.

Table 1. Recommended initial dosages and ranges of maintenance dosages for different AEDs

AED	Initial dosage	Maximal maintenance dosage (per day)
Carbamazepine*	100–200 mg b.i.d.	1200 mg
Ethosuximide	250 mg b.i.d.	1000 mg
Gabapentin	100 mg t.i.d.	2400 mg
Lacosamide	50 mg b.i.d.	400 mg
Lamotrigine	25 mg q.d. (monotherapy)	400 mg
	25 mg every other day (with valproic acid)	100 mg
	25 mg b.i.d. (with enzyme inducer)	500 mg
Levetiracetam*	250 mg b.i.d.	3000 mg
Oxcarbazepine	150–300 mg b.i.d.	2400 mg
Perampanel	2 mg h.s.	12 mg
Phenobarbital	60 mg per day	240 mg
Phenytoin	100 mg or 150 mg b.i.d.	600 mg
Pregabalin*†	≤75 mg b.i.d.	600 mg
Topiramate*	25 mg q.d. or b.i.d.	500 mg for monotherapy, 800 mg for combination therapy
Valproic acid*	10–15 mg/kg/day (divalproex) 20–30 mg/kg/day (sodium valproate)	60 mg/kg/day
Vigabatrin	500 mg b.i.d.	3000 mg
Zonisamide	100 mg q.d.	600 mg

*Modified-release dosage formulations (controlled release and extended release) are available in South Korea, †The modified-release dosage formulation of pregabalin is not currently approved for epilepsy in South Korea.
AED: antiepileptic drug.

Adverse effects of AEDs

Once an AED is prescribed, the clinician should be prepared to address any adverse effects that may occur. An adverse effect refers to any undesired harmful effect that results from treatment, including that involving medication. Such an effect is frequently unexpected, and can include morbidity, mortality, dysfunction, or loss of function. It may be difficult to detect, such as being identifiable only based on symptoms reported by the patient. The clinician should therefore monitor the patient for adverse effects resulting from the AED at

every visit. Table 2 summarizes the representative adverse effects of AEDs.[20,24,25]

In order to prevent adverse effects, the clinician should titrate slowly from low doses and maintain the lowest dose possible while still achieving effective treatment. The patient may adapt to an adverse effect of the AED over time, or the effect may go away on its own.[24] Therefore, if an adverse effect is tolerable, it may be considered optimal to maintain the AED at its current dosage. However, adverse effects such as weight gain and loss of bone mineral density are closely related to the cumulative AED dose,[26,27] and replacement of the AED may be needed to eliminate these effects. An AED may also cause cognitive dysfunction. Adverse effects that require an immediate cessation of AED treatment include

Table 2. Representative adverse effects and contraindications of AEDs

AED	Adverse effects	Contraindications and adverse effects that require AED cessation
Carbamazepine*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia General: hyponatremia, GI problems, leukocytopenia, LFT elevation, rash, osteoporosis	SJS, DRESS, bone-marrow suppression, AVB, MAOI medication
Ethosuximide	Neurological: somnolence, dizziness, ataxia, anorexia, psychosis General: GI problems, weight loss, leukocytopenia, anemia	SJS, DRESS, pancytopenia, lupus, porphyria
Gabapentin*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, tremor General: GI problems, weight gain	Pancreatitis, absence seizure
Lacosamide*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, headache General: cardiac arrhythmia	
Lamotrigine*	Neurological: ataxia, dizziness, diplopia, aseptic meningitis General: rash, osteoporosis	SJS, DRESS
Levetiracetam	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, mood disorders, psychosis	Suicidal ideation, pancytopenia
Oxcarbazepine*	Neurological: somnolence, lethargy, dizziness, ataxia, headache General: hyponatremia, GI problems	SJS, AVB, bone-marrow suppression, MAOI medication
Perampanel*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, falling, hostility, psychosis, mood disorder	Suicidal or homicidal ideation
Phenobarbital*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, headache, rash, psychosis, mood disorder, cognitive slowing General: osteoporosis, anemia	SJS, DRESS
Phenytoin*	Neurological: somnolence, lethargy, dizziness, diplopia, ataxia, nystagmus, cerebellar atrophy General: gingival hypertrophy, osteoporosis, pancytopenia, lymphadenopathy	SJS, bone-marrow suppression, recent myocardial infarction, second- or third-degree AVB
Pregabalin	Neurological: somnolence, lethargy, dizziness, ataxia General: dry mouth, weight gain, edema	Angioedema
Topiramate*	Neurological: cognitive slowing, dizziness, anorexia General: weight loss, GI problems	Glaucoma, hyperammonemia, hypohidrosis with hyperthermia, urolithiasis
Valproic acid*	Neurological: dizziness, diplopia, ataxia, tremor General: hyperammonemia, thrombocytopenia, alopecia, GI problems, weight gain	Urea-cycle disorder, unfulfilled PPP, significant hepatic or pancreatic dysfunction, porphyria, coadministration with carbapenems or mefloquine
Vigabatrin	Neurological: somnolence, lethargy, diplopia, ataxia, nystagmus, cognitive slowing General: anemia, weight gain, arthralgia	Permanent bilateral visual field constriction, blurred vision
Zonisamide*	Neurological: somnolence, lethargy, dizziness, ataxia, mood disorders, anorexia, cognitive slowing General: weight loss	SJS, DRESS, urolithiasis, hypohidrosis with hyperthermia

*Contraindicated in galactose intolerance, Lapp lactose deficiency, and glucose/galactose malabsorption.
AED: antiepileptic drug, AVB: atrioventricular block, DRESS: drug reaction with eosinophilia and systemic symptoms, GI: gastrointestinal, LFT: liver function test, MAOI: monoamine oxidase inhibitor, PPP: pregnancy prevention program, SJS: Stevens-Johnson syndrome.

rash, Stevens-Johnson syndrome, hepatic dysfunction, aplastic anemia, and agranulocytosis. Such cases will require a detailed patient evaluation and appropriate treatment changes.

It is known that several human leukocyte antigen (HLA) gene types are associated with adverse effects. In particular, HLA-B*15:02 and HLA-A*31:01 are well-known genetic factors for the drug rash related to several AEDs, especially carbamazepine.[28-30] This has prompted suggestions to perform genetic testing before prescribing carbamazepine.[25,31] However, the conclusions from these studies remain unclear, and there is a lack of research in this area in South Korea. Moreover, genetic tests cannot be performed on all patients with epilepsy, and they cannot predict all of the possible adverse effects.

The clinician must be aware of all the known negative effects of an AED, and properly inform the patient about them. Adverse effects of AEDs are an issue that the clinician and the patient should address together.

Failure of the initial treatment and the concept of rational polytherapy

AED treatment failure refers to the occurrence of unexpected breakthrough seizures despite the administration of regular medication at a sufficient dose. Drug intolerance due to adverse effects may be considered a failure, with the exception of drug-resistant epilepsy.[32]

If the seizure is not controlled with a sufficient dose of the AED, the clinician should check whether the diagnosis is correct and whether the AED has been prescribed appropriately. Other factors such as insufficient adherence, sleep deprivation, and alcohol abuse should also be considered. The next step is to decide whether to switch to a different AED or to add a another AED to the existing prescription. There is no evidence that either of these two strategies is superior in all situations. Combination therapy may allow for the rapid control of seizures, but drug interactions may increase adverse effects. If the clinician decides to substitute a drug rather than add another one, the ideal strategy is to add and gradually increase the dose of the new drug, and then taper off the existing one.

The fundamental action of all AEDs is to reinforce inhibition or attenuate excitation of neuronal hypersynchrony to prevent seizure, and their detailed mechanisms of action and chemical subtypes have expanded enormously over the past 20 years. Although the mechanisms underlying the effects of all AEDs are not known in detail, it is known that each drug inhibits seizures in its own way. The concept of rational polytherapy has not yet been fully established, and so in-depth discussion is necessary to further refine the underlying concepts. The authors of this study propose the following concept of rational polytherapy:

1) Set the optimal doses of the ongoing AEDs.
2) Avoid AEDs with similar action mechanisms.
3) Avoid increasing the number of prescribed AEDs.
4) If a change in dosage is needed, titrate or taper off slowly.
5) Consider drug–drug interactions to achieve synergy and avoid adverse effects.
6) If a new AED is suboptimal, replace it with another.
7) If a new AED is effective, withdraw the previous one.

While several experts have praised the benefits of combination therapy and raised clinical expectations for its effectiveness,[33-35] there is little evidence to support this opinion. It is recommended for the patient to be referred to an epileptologist if the additional AED also fails to control the seizures, since this is likely to indicate the presence of drug-resistant epilepsy. While AEDs are the backbone of treatment for epilepsy and monotherapy is the most-responsible initial treatment, rational polytherapy may be a way to increase treatment options while still minimizing adverse reactions.

Duration of AED therapy and the concept of resolved epilepsy

AED therapy may be temporary or lifelong. Several studies have investigated AED discontinuation. However, if the patient has a high risk of recurrent seizure, drug discontinuation might not be the best course of action. Risk factors that can predict recurrent seizures include perinatal injury, uncontrolled seizure after receiving medication, taking multiple drugs, significant epilepsy duration before remission, short seizure-free intervals, family history, sex, and epileptiform discharges in EEG.[36-38] There have also been reports that drug withdrawal may improve the intelligence quotient and quality of life,[39,40] but this does not affect the long-term prognosis of epilepsy.[41,42]

The concept of resolved epilepsy was used by the ILAE in 2014.[5] This phrase means that seizures are not expected to occur anymore, although this is not guaranteed. The choice of the word "resolved" instead of "cure" suggests that once diagnosed, and even well-controlled, the probability of recurrent seizure will always be higher in an epileptic than in a person with no history of epilepsy. The ILAE suggested that epilepsy is resolved when the following criteria are met:[5] 1) age-dependent epilepsy syndrome has past the applicable age, or 2) being free of seizures for at least 10 years while being free of AED use for at least 5 years. Although the evidence is lacking and not without controversy, the Drug Committee of KES recommends that withdrawing an AED may be considered after 5 years of being seizure free.

Nonetheless, and as mentioned above, the goal of AED treatment is remission without adverse effects. Resolved

epilepsy might not be a possible or realistic goal for all patients. Decisions about whether or not to continue AEDs should be considered carefully and on an individual basis. In addition, the final decision depends not only on the clinician but also on the wishes of the patient and caregivers.

There is no definitive strategy for withdrawing AED treatment. A strategy of tapering off slowly is generally recommended, since the sudden discontinuation of an AED may induce withdrawal seizures. A tapering period of at least 6 months is generally recommended.

SUMMARY AND RECOMMENDATIONS

- The most important step when addressing epilepsy is to confirm that a bona fide seizure event has occurred.
- Once the event meets the diagnostic criteria for epilepsy or status epilepticus, AED treatment should be initiated.
- The primary pharmacological treatment strategy for epilepsy is monotherapy.
- A ready-made treatment strategy should be prepared for status epilepticus, and implemented using a team-based approach.
- The primary goal of AED treatment for epilepsy is lasting remission without significant adverse effects.
- Adverse effects of AEDs should be addressed by the clinician and patient together.
- In the light of the concept of resolved epilepsy, we recommend waiting for a seizure-free period of at least 5 years before considering AED withdrawal.

Author Contributions

Conceptualization: all authors. Investigation: all authors. Writing—original draft: Keun Tae Kim, Yong Won Cho. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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