

Chapter 3

Drug Therapy for Adult Epilepsy

CQ 3-1

Should drug therapy be started after the first epileptic seizure?

Summary

After a first unprovoked seizure, treatment with antiepileptic drugs should not be started, except under the following circumstances. Even after a first seizure, treatment initiation is considered if there is a neurological abnormality, an abnormal electroencephalogram, a lesion shown by neuroimaging studies, or a family history of epilepsy, because the recurrence rate is high under the above conditions. Treatment may be started after a first seizure in some patients in consideration of the patient's social situation or desire. In the elderly, treatment is considered after a first seizure since the risk of recurrence after the initial seizure is high. After a second seizure, starting antiepileptic drug is recommended because the risk of seizure recurrence within one year is high.

Comment

Patients with a first unprovoked seizure have approximately 35% risk of recurrence in the subsequent 5 years, whereas patients with a second attack have a risk of recurrence of 73% within one year^{1, 2)}.

At the start of treatment, especially for a long-term treatment policy, patients should be given explanations of their disease condition, treatment period, adverse effects of drugs, etc., and given due respect of self-determination of their own treatment³⁻⁵⁾.

The risk of recurrence after the first seizure is high (66–90%) in elderly people compared to young people. Therefore, treatment is often started after the first seizure⁶⁾.

When comparing starting drug therapy immediately after the first seizure, after the first recurrence, and after the fifth recurrence, there is a slight difference among the three timings of treatment initiation in the seizure control rate during the subsequent 2 years, but no difference in more long-term seizure outcome. In a study of 525 epilepsy patients (mean age 29 years; mean onset age 26 years; idiopathic epilepsy in 27%, symptomatic epilepsy in 29%, and cryptogenic epilepsy in 45%) followed for an average of 5 years, 37% of the patients with more than 20 seizures before starting treatment (n = 185) had recurrence within one year, compared with 29% among patients with 20 or less seizures before treatment initiation, and the difference was significant⁴⁾. In addition, the prevalence of persistent seizures was higher in patients with symptomatic or cryptogenic epilepsy than in those with idiopathic epilepsy (40% vs. 26%)

■ References

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- 2) Hauser WA, Anderson VE, Loewenson RB, et al. Seizure recurrence after a first unprovoked seizure. *N Engl J Med.* 1982; 307(9): 522-528.
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What are the recommended drugs for new-onset partial epilepsy?

Summary¹⁻⁷⁾

The recommended first-line drugs are carbamazepine, lamotrigine and levetiracetam, followed by zonisamide and topiramate. The recommended second-line drugs are phenytoin, valproate, clobazam, clonazepam, phenobarbital, gabapentin, lacosamide and perampanel.

Comment

For new-onset epilepsy, treatment with antiepileptic drug usually starts with monotherapy. The drugs are selected taking into consideration the conditions of individual patients based on the diagnosis of seizure type and epilepsy. Basically, antiepileptic drugs are started at low doses, and the doses are increased gradually until seizures are controlled. If seizures are not controlled by the first antiepileptic drug, review the diagnosis of epilepsy, check the status of compliance with drug taking, and confirm whether the maximum tolerated dose has been reached. If the initial drug (first-line drug) is judged to be ineffective, prescribe the next drug (another first-line drug or a second-line drug) (**Table 1**).

In February 2018, clobazam, gabapentin, topiramate, and perampanel were approved for adjunctive use with other agents in Japan.

■ References

- 1) Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007; 369(9566): 1016-1026.
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Table 1. Recommended drugs for partial seizures.

Drug name	Abbreviation	Major mechanism of action	Major adverse reactions
First-line drugs			
Carbamazepine	CBZ	Voltage-dependent Na channel inhibition	Dizziness, diplopia, nystagmus, ataxia, drowsiness, hyponatremia, rash, cytopenia, liver dysfunction, SJS, DIHS, TEN
Lamotrigine	LTG	Voltage-dependent Na channel inhibition	Drowsiness, dizziness, diplopia, rash, cytopenia, liver injury, SJS, DIHS, TEN
Levetiracetam	LEV	SV2A binding	Dizziness, headache, psychotic symptoms, (bad mood, irritability, etc.)
Zonisamide	ZNS	Na channel blockade, Ca channel blockade, GABA enhancement, CA inhibition	Drowsiness, lethargy, anorexia, hypohidrosis, urolithiasis, rash, liver dysfunction
Topiramate	TPM	Na channel blockade, Ca channel blockade, GABA _A enhancement, excitatory amino acid receptor inhibition, CA inhibition	Drowsiness, lethargy, anorexia, hypohidrosis, urolithiasis
Second-line drugs			
Phenytoin	PHT	Voltage-dependent Na channel inhibition	Dizziness, diplopia, nystagmus, ataxia, drowsiness, rash, cytopenia, liver dysfunction, SJS, DIHS, TEN
Gabapentin	GBP	Binds Ca channel to modulate neurotransmitter release	Drowsiness, dizziness, malaise, headache, diplopia, myoclonus
Valproate	VPA	Enhancement of GABA _A -mediated inhibition, inhibition of glutamate-mediated excitability	Thrombocytopenia, obesity, alopecia, tremor, diuresis, fibrinogen decrease, liver dysfunction, acute pancreatitis
Phenobarbital	PB	GABA _A -Cl ⁻ benzodiazepine receptor, Na/Ca channel inhibition, glutamate receptor blockade	Drowsiness, sedation, restlessness, excitability, hyperactivity, ataxia, rash, liver dysfunction, cytopenia
Clobazam	CLB	Enhancement of GABA _A -mediated inhibition	Drowsiness, salivation, ataxia, abnormal behavior, airway hypersecretion, rash
Clonazepam	CZP	Enhancement of GABA _A -mediated inhibition	Drowsiness, salivation, ataxia, abnormal behavior
Perampanel	PER	Non-competitive AMPA receptor inhibition	Drowsiness, ataxia, psychotic symptom
Lacosamide	LCM	Na channel inhibition (promote slow inactivation)	Drowsiness, ataxia

CA: carbonic anhydrase, TEN: toxic epidermal necrolysis, DIHS: drug induced hypersensitivity syndrome, SJS: Stevens-Johnson syndrome

1. In February 2018, clobazam (Mystan), gabapentin (Gabapen), topiramate (Topina) and perampanel (Fycompa) were approved for adjunctive use with other agents in Japan.
2. Although topiramate (Topina) has been approved in America and Europe for both focal and generalized seizures, this drug was approved only for partial seizure in Japan in February 2018.

What are the recommended drugs for new-onset generalized epilepsy?

Summary¹⁻¹¹⁾

- (1) For generalized tonic-clonic seizures, valproate is recommended as the first-line drug. Lamotrigine, levetiracetam, topiramate, zonisamide, clobazam, phenobarbital, phenytoin, and perampanel are recommended as second-line drugs. In women of child-bearing ages, drugs other than valproate are more recommended.
- (2) For absence seizures, valproate and ethosuximide, followed by lamotrigine are recommended.
- (3) For juvenile myoclonic epilepsy, valproate, clonazepam, levetiracetam, and topiramate are recommended.

Comment

For generalized seizures, the seizure control effect of valproate is superior to the other drugs. However, due to the adverse effects of valproate, including teratogenicity and effect on neonatal IQ, drugs other than valproate should be considered for women of child-bearing ages⁹⁻¹¹⁾. During pregnancy, valproate should be avoided when possible, and if valproate is used, a dose of 600 mg per day or lower is preferable.

■ References

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- 11) Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009; 360(16): 1597-1605.

Which antiepileptic drugs should be avoided for generalized epilepsies?

Summary ¹⁾

Since carbamazepine exacerbates myoclonic seizures and absence seizures, it should not be used for idiopathic generalized epilepsy. Phenytoin worsens tonic-clonic seizures, and gabapentin exacerbates myoclonic seizures. Benzodiazepines occasionally exacerbates tonic seizures in Lennox-Gastaut syndrome.

Comments

Unverricht-Lundborg's disease is a representative disease of progressive myoclonus epilepsy (PME). In a large-scale study, treatment of Unverricht-Lundborg's disease with phenytoin effectively controlled current seizures but worsened survival rate ²⁾. Phenytoin is recommended not to be used for the treatment of PME, because it induces marked cerebellar ataxia or deteriorates cerebellar ataxia.

■ References

- 1) Perucca E, Gram L, Avanzini G, et al. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia*. 1998; 39(1): 5-17.
- 2) Eldridge R, Iivanainen M, Stern R, et al. "Baltic" myoclonus epilepsy: hereditary disorder of childhood made worse by phenytoin. *Lancet*. 1983; 2(8354): 838-842.

Table 1. Recommended drugs and drugs that should be used with caution for new-onset epilepsies.

Seizure type	First-line drugs	Second-line drug	Drugs that should be used with caution
Partial seizure	Carbamazepine, lamotrigine, levetiracetam, zonisamide, topiramate	Phenytoin, valproate, clobazam, clonazepam, phenobarbital, gabapentin, perampanel, lacosamide	
Tonic clonic seizure, clonic seizure	Valproate (excluding women of child-bearing potential)	Lamotrigine, levetiracetam, topiramate, zonisamide, clobazam, phenobarbital, phenytoin, perampanel	Phenytoin
Absence seizure	Valproate, ethosuximide	Lamotrigine	Carbamazepine, gabapentin, phenytoin
Myoclonic seizure	Valproate, clonazepam	Levetiracetam, topiramate, piracetam, phenobarbital, clobazam	Carbamazepine, gabapentin, phenytoin
Tonic seizure, atonic seizure	Valproate	Lamotrigine, levetiracetam, topiramate	Carbamazepine, gabapentin

What are the recommended drugs for patients with a risk of psychiatric symptoms?

Summary

- (1) Patients with intractable epilepsy, limbic seizures, and a family history or past history of psychiatric disorders are at risk of concomitant psychiatric symptoms. In such patients, we should be cautious with using multiple antiepileptic drugs, rapid dose increase, and high dose administration.
- (2) For patients with depressive disorder, bipolar disorder, anxiety disorder, and psychotic disorder, some antiepileptic drugs should be avoided while use of some other antiepileptic drugs may be considered in individual patient.

Comment

Some psychiatric symptoms are caused by antiepileptic drugs, and they are sometimes overlooked¹⁾. Antiepileptic drugs such as ethosuximide, zonisamide, primidone, high-dose phenytoin, topiramate, and levetiracetam may cause acute psychosis^{1,2)}. Potent antiepileptic drugs given at high doses by rapid up-titration may cause forced normalization psychosis, and rapid withdrawal of benzodiazepines may induce acute psychosis. Depressive state and declined mental performance due to phenobarbital; depressive state due to ethosuximide, clonazepam, zonisamide, topiramate, and levetiracetam; and hypomania due to clobazam have been reported^{1, 2)}. Levetiracetam has been reported to increase aggressiveness, and lamotrigine to cause insomnia, anxiety and irritation²⁾.

- The risk of concomitant psychiatric symptoms is high in patients with intractable epilepsy, limbic seizures, and a past history or family history of psychosis³⁾.
- For patients with depressive disorder, phenobarbital, zonisamide, topiramate, or levetiracetam should not be used, and use of lamotrigine may be considered²⁾.
- For patients with bipolar disorder, use of phenytoin, carbamazepine, lamotrigine, or oxcarbazepine may be considered²⁾.
- For patients with anxiety disorder, lamotrigine or levetiracetam should not be used, and use of benzodiazepines or gabapentin may be considered²⁾.
- For patients with psychiatric disorder, phenytoin, ethosuximide, zonisamide, topiramate, or levetiracetam should not be used²⁾.
- To prevent antiepileptic drug-induced psychiatric symptoms, when adding or changing potent antiepileptic drug, do it over an adequately long duration and provide guidance to patients to maintain compliance with medication^{1, 4)}.

■ References

- 1) Matsuura M, Fujiwara T, Ikeda A. Diagnostic and treatment guideline for psychotic comorbidities in adult epilepsy. Tenkan Kenkyu 2006; 24(2): 74-77 (in Japanese).
- 2) Perucca P, Mula M. Antiepileptic drug effects on mood and behavior: Molecular targets. Epilepsy Behav. 2013; 26(3): 440-449.
- 3) Kerr MP, Mensah S, Besag F, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia. 2011; 52(11): 2133-2138.
- 4) Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet. 2012; 380(9848): 1180-1192.

■ Search formula and secondary reference sources

((("Epilepsy/drug therapy" [Majr]) AND "adverse effects" [Subheading])) OR "Anticonvulsants/adverse effects" [Majr] Filters: Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese PubMed = 119

Table 1. Antiepileptic drugs that may be considered or should be avoided in patients with concomitant psychiatric disorders.

	Depressive disorder	Bipolar disorder	Anxiety disorder	Psychiatric disorder
To be avoided	PB, PRM, ZNS, TPM, LEV		LTG, LEV	PHT, ESM, ZNS, TPM, LEV
Use may be considered	LTG	PHT, CBZ, LTG, OXC	CZP, CLB, GBP	

(For abbreviations of drugs, see **Table 1** on page v of the Revised Clinical Practice Guideline For Epilepsy)

(Modified from: Perucca P, Mula M. Antiepileptic drug effects on mood and behavior: Molecular targets. Epilepsy Beh. 2013; 26(3): 440-449.)

What are the recommended drugs when complicated with medical diseases?

Summary¹⁻⁴⁾

- (1) In patients complicated with renal or liver dysfunction, antiepileptic drugs should be selected considering hepatic degradation (valproate, phenytoin, carbamazepine, phenobarbital, benzodiazepines), hepatorenal degradation (topiramate, lamotrigine), and renal degradation (gabapentin, levetiracetam) of antiepileptic drugs.
- (2) There are serious concerns over deterioration of cardiac conduction abnormalities by phenytoin and carbamazepine, as well as exacerbation of hyponatremia by carbamazepine and valproate.
- (3) The effects of phenytoin and carbamazepine on immune disorders; the decline of cognitive function caused by phenobarbital, zonisamide, carbamazepine, and topiramate; and the induction of Parkinsonian symptoms by valproate have been reported.
- (4) When phenytoin is used in patients with hypoalbuminemia, the effect of phenytoin is augmented because free (non-albumin binding) phenytoin increases due to the reduced albumin binding rate.

Comment

Many of the existing antiepileptic drugs are metabolized by the liver. On the other hand, a number of new antiepileptic drugs are metabolized by the kidney.

Phenytoin is the drug with the most serious concern regarding the increase in the fraction of free (non-albumin binding) drug in patients with hypoalbuminemia. Although valproate shares a similar situation, the clinical significance is less marked compared with phenytoin. In addition, when valproate is used in combination with phenytoin, strong binding of valproate with albumin results in further increase in free phenytoin.

■ References

- 1) Karciski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav.* 2005; 7(Suppl 1): S1-64.
- 2) Leppik IE, Cloyd JC. General principles, epilepsy in the elderly. In: *Antiepileptic drugs*. 5th ed, Philadelphia: Lippincott Williams & Wilkins, 2002, p.149-158.
- 3) Gugler R, Shoeman DW, Huffman DH, et al. Pharmacokinetics of drugs in patients with the nephritic syndrome. *J Clin Invest.* 1975; 55(6): 1182-1189.
- 4) Rane A, Wilson JT. Clinical pharmacokinetics in infants and children. *Clin Pharmacokinet.* 1976; 1(1): 2-24.

What are the recommended drugs for elderly-onset epilepsy?

Summary

- (1) Carbamazepine, lamotrigine, levetiracetam, and gabapentin are recommended for partial seizures in elderly patients without complications or comorbidities.
- (2) Levetiracetam, lamotrigine, and gabapentin are recommended for partial seizures in elderly patients with complications or comorbidities.
- (3) Lamotrigine, valproate, levetiracetam, and topiramate are recommended for generalized seizures.

Comment

A group of 593 patients (mean age 72 years) with elderly-onset epilepsy (defined as patients aged 65 years or older with new-onset epilepsy) having seizure frequency of more than once every three months were randomly allocated to lamotrigine 150 mg/day, gabapentin 1,500 mg/day, or carbamazepine 600 mg/day, and observed for 12 months. Carbamazepine showed a slightly higher seizure control rate, whereas lamotrigine and gabapentin were superior in terms of tolerability and lower medication dropout rate ¹⁾. A subsequent study reported that there was no difference in seizure control rate between levetiracetam and lamotrigine ²⁾.

■ References

- 1) Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy. *Neurology*. 2005; 64(11): 1868-1873.
- 2) Werhahn KJ, Trinka E, Dobesberger J, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia*. 2015; 56(3): 450-459.

What are the combined drugs that require special caution for epilepsy patients?

Summary

- (1) Caution is required regarding decreased blood concentration and poor seizure control when antiepileptic drugs are used in combination with an inhibitor of intestinal absorption (phenytoin with an antacid, gabapentin with magnesium oxide) or drugs that lower the epileptic seizure threshold (Table 1)¹⁻³⁾.
- (2) Caution is required regarding the drug interaction effects on blood concentration by induction or inhibition of hepatic metabolizing enzymes (Figure 1)⁴⁾.

Comment

Many of the antiepileptic drugs in current use show great interactions between the antiepileptic drugs and with other drugs. Given the complicated relations as shown in **Figure 1**, they are one of the reasons for monotherapy recommendation. However, even with monotherapy, autoinduction of metabolic enzymes is a characteristic of carbamazepine. There is a concern over the phenomenon of a decrease in blood concentration from approximately one month after treatment initiation or an increase in blood concentration when the drug is restarted after temporary interruption (see CQ12-4 on page 108).

Gabapentin, levetiracetam, and topiramate (200 mg/day or lower) show little interaction between antiepileptic drugs.

Drugs that lower the epileptic seizure threshold as shown in **Table 1** are commonly involved in drug interaction.

■ References

- 1) Ikeda A. Functional diseases and neurological/motor diseases. In: Imura Y (Ed.) Easy Guide to Internal Medicine, third Edition. Tokyo: Bunkodo Co., Ltd. 2008. p. 826-837 (in Japanese).
- 2) Gilman JT. Drug interaction. In: Pellock JM, Dodson WE, Bourgenus BF eds. Pediatric Epilepsy, Diagnosis and Therapy, 2nd edition. New York: Demos Medical Publishing. 2001. p.555-562.
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- 4) Sato T, Ikeda A, Shibasaki H. Symptoms and treatment: epilepsy. In: Treatment Guide for Neurosurgery. Tokyo: Chugai Igakusha. 2002. p. 20-33 (in Japanese).

Table 1. Drugs that lower the threshold of epileptic seizure.

During alcohol, barbiturate or benzodiazepines withdrawal
Anti-depressants (imipramine, amitriptyline, SSRI [mild])
Anti-psychotics (chlorpromazine, thioridazine)
Bronchodilators (aminophylline, theophylline)
Antimicrobials (carbapenems, antimicrobial and NSAID combination)
Local anesthetics (lidocaine)
Analgesics (fentanyl, cocaine)
Antitumor agents (vincristine, methotrexate)
Muscle relaxants (baclofen)
Anti-histamines

(Modified from: Ikeda A. Functional diseases and neurological/motor diseases. In: Imura Y (Ed.) Easy Guide to Internal Medicine, Third Edition, Tokyo: Bunkodo Co., Ltd. 2008. p. 826-837.)

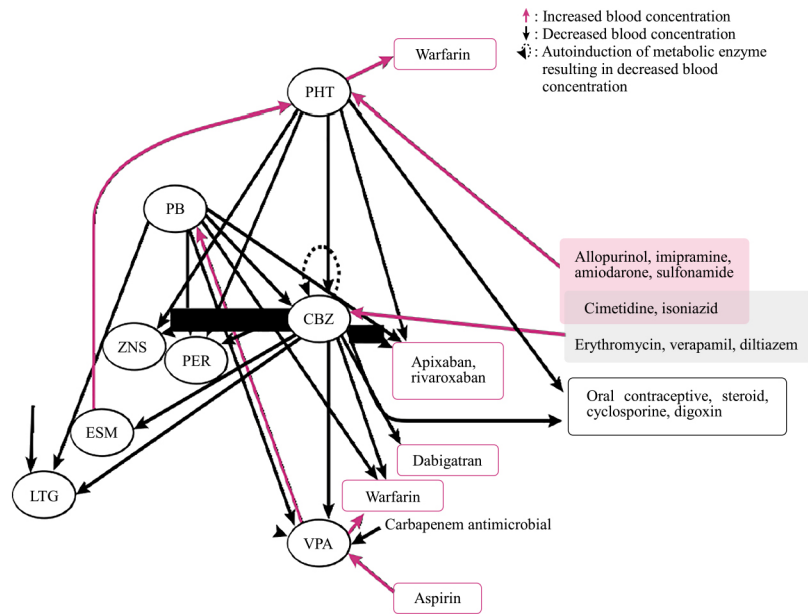


Figure 1. Interactions among major antiepileptic drugs and other drugs

PHT: phenytoin, PB: phenobarbital, CBZ: carbamazepine, ZNS: zonisamide, ESM: ethosuximide, LTG: lamotrigine, VPA: valproate, PER: perampanel

Note: The upper and lower positions between all pairs of drugs show the influence on blood concentration or effect. Upper position denotes increase in effect and lower position denotes decrease in effect.

(Modified from: Sato T, Ikeda A, Shibasaki H. Other symptoms and treatment: epilepsy. In: Treatment Guide for Neurosurgery. Tokyo: Chugai Igakusha. 2002, p. 29, Figures 1-12)

What are the precautions when switching from the original antiepileptic drugs to generic drugs?

Summary

Patients whose seizures are well controlled are recommended not to switch from the original antiepileptic drugs to generic drugs. When switching from original drugs to generic drugs or between generic drugs, informed consent from the medical staffs and the patients is indispensable ^{1, 2)}.

Comment

There is no high-quality evidence that validates the therapeutic equivalence between original antiepileptic drugs and generic drugs. However, seizure recurrence, seizure exacerbation, and adverse effects have been reported in some patients upon switching from original drugs to generic drugs ^{1, 2)}.

■ References

- 1) The Japanese Society of Child Neurology Pharmaceutical Affairs Committee and Executive Board. Proposal from The Japanese Society of Child Neurology: Switching from the original antiepileptic drugs to generic drugs. <http://www.childneuro.jp/uploads/files/about/20080325.pdf> (in Japanese)
- 2) The Japan Epilepsy Society. Proposal from The Japan Epilepsy Society: The use of generic drugs as antiepileptic drugs. <http://square.umin.ac.jp/jes/pdf/generic.pdf> (in Japanese)