## Table 1. Drug options for various epilepsy syndromes.

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>First-line drugs</th>
<th>Second-line drugs</th>
<th>Combination therapy, other</th>
<th>Drugs to avoid if possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic partial epilepsy</td>
<td>carbamazepine valproate, levetiracetam</td>
<td>lamotrigine, oxcarbazepine*, topiramate*, gabapentin*, clobazam*</td>
<td>sulthiame (BECTS)</td>
<td></td>
</tr>
<tr>
<td>Childhood absence epilepsy</td>
<td>valproate ethosuximide</td>
<td>lamotrigine</td>
<td></td>
<td>gabapentin, carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>valproate (for women of child-bearing potential, see Chapter 13)</td>
<td>lamotrigine*, zonisamide, topiramate*, rufinamide*</td>
<td>clobazam (drop seizure)*, ethosuximide (atypical absence seizure), levetiracetam</td>
<td>gabapentin, carbamazepine</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>valproate (for women of child-bearing potential, see Chapter 13)</td>
<td>levetiracetam*, lamotrigine, zonisamide, topiramate*</td>
<td>clonazepam (myoclonic seizure)</td>
<td>gabapentin, carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Epilepsy with generalized tonic-clonic seizures alone</td>
<td>valproate (for women of child-bearing potential, see Chapter 13)</td>
<td>zonisamide, lamotrigine, levetiracetam*, topiramate*</td>
<td>clobazam*</td>
<td></td>
</tr>
</tbody>
</table>

*: covered by medical insurance in Japan.
- topiramate and gabapentin are covered by medical insurance as adjunctive therapy for partial seizures.
- clobazam is covered by medical insurance as adjunctive therapy for partial seizure and generalized seizures.
- lamotrigine is covered by medical insurance as monotherapy for partial seizures, tonic-clonic seizures and absence seizures, and also as adjunctive therapy for Lennox-Gastaut syndrome.
- rufinamide is covered by medical insurance as adjunctive therapy for tonic seizures and atonic seizures in Lennox-Gastaut syndrome.
- levetiracetam is covered by medical insurance as monotherapy for partial seizures, and also as adjunctive therapy for tonic-clonic seizures.
What are the drug options for idiopathic partial epilepsy?

Summary

(1) Because some patients with idiopathic partial epilepsy may not require therapeutic intervention, the expected beneficial effect and the adverse effect from treatment should be considered carefully.

(2) First-line drugs for idiopathic partial epilepsy are carbamazepine, valproate, and levetiracetam.

(3) Second-line drugs are lamotrigine, oxcarbazepine, topiramate, gabapentin, and clobazam.

(4) Sultiame is also used as a second-line drug for benign childhood epilepsy with centrotemporal spikes (BECTS).

Comment

Basically, idiopathic partial epilepsy has good prognosis, and in some patients, seizure may occur only once in a lifetime. Therefore, therapeutic intervention is sometimes unnecessary. For this reason, it is necessary to explain to the family (and the patient him/herself) about the therapeutic effects and the adverse effects of treatment with antiepileptic drugs, and to consider the whole treatment policy.

No randomized controlled trial (RCT) of drug therapy for idiopathic partial epilepsy has been conducted, and general antiepileptic drugs (carbamazepine, valproate, levetiracetam, lamotrigine, oxcarbazepine, topiramate, gabapentin, and clobazam) are used. Among them, carbamazepine, valproate, levetiracetam are considered to be first-line drugs in consideration of their seizure control effect and adverse effects.

In an RCT of sultiame for benign childhood epilepsy with centrotemporal spikes (BECTS), which is the main idiopathic partial epilepsy, the seizure control rate was 40% in the control group compared with 87.1% in the sultiame group, indicating the effectiveness of sultiame. For BECTS, RCTs were conducted for sultiame and levetiracetam as well as for oxcarbazepine and levetiracetam. In these two trials, the seizure control rates were 90.9% for sultiame versus 81.0% for levetiracetam, and 72.2% for oxcarbazepine versus 90.5% for levetiracetam, both reported high seizure control effect.

References


Search formula and secondary reference sources

PubMed search: June 25, 2015

(((“Epilepsies, Partial” [Mesh]) AND ((idiopathy) OR idiopathic)) AND Anticonvulsants/therapeutic use [Mesh])) OR “Epilepsy, Rolandic/drug therapy” [Mesh]

Ichushi search: June 15, 2015

(((anti-epileptic drug/TH or antiepileptic drug/AL)) and ((idiopathic partial epilepsy/AL) or (((epilepsy-focus/TH or partial epilepsy/AL)) and (idiopathic/AL)))) and (PT = excluding proceedings)) = 41

Secondary reference source


http://www.nice.org.uk/guidance/cg137
What are the drug options for childhood absence epilepsy?

Summary
(1) The first-line drugs are valproate and ethosuximide.
(2) The second-line drug is lamotrigine.
(3) Do not use gabapentin, carbamazepine or phenytoin.

Comment
Traditionally, valproate, ethosuximide, and lamotrigine have been used for the treatment of childhood absence epilepsy\(^1\). In a randomized control trial (RCT), valproate and ethosuximide showed equivalent seizure control effect (16-week seizure control rates of 58% and 53%, respectively), and both were more effective than lamotrigine (29%)\(^2\). Although ethosuximide is superior to valproate from the viewpoint of adverse effects, valproate is superior in being easy to take. On the other hand, valproate is used rather than ethosuximide when complicated by generalized tonic-clonic seizures.

Gabapentin\(^3\), carbamazepine\(^4, 5\), and phenytoin\(^5\) have been reported to exacerbate absence seizures.

References

Search formula and secondary reference sources
PubMed search: June 25, 2015
"Epilepsy, Absence/drug therapy" [Mesh] Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 91
Ichushi search: June 15, 2015
(((epilepsy-absence/TH or absence epilepsy/AL) or ((epilepsy-absence /TH or absence seizures/AL))) and (PT = excluding proceedings and SH = drug therapy)) = 88

Secondary reference source
http://www.nice.org.uk/guidance/cg137
What are the drug options for Lennox-Gastaut syndrome?

Summary
(1) Lennox-Gastaut syndrome (LGS) is often drug resistant, and correct clinical evaluation and consideration of treatment goal are needed when planning treatment.
(2) The first-line drug is valproate, but for child-bearing aged women, priority is given to drugs other than valproate.
(3) In the case that valproate cannot be used, or valproate is not adequately effective, lamotrigine, zonisamide, topiramate, rufinamide or levetiracetam is used.
(4) Clobazam is used for drop seizures, while ethosuximide is used for atypical absence seizures.
(5) Do not use gabapentin or carbamazepine.
(6) When treatment is difficult, refer to epilepsy specialists.

Comment
Lennox-Gastaut syndrome (LGS) manifests many types of seizures such as tonic seizures, atypical absences, atonic seizures, and myoclonic seizures. These seizures are drug resistant and may further be complicated by mental retardation or other features. Too high doses of antiepileptic drugs for controlling resistant seizures may impair quality of life (QOL), and drugs used to control some seizures may exacerbate other types of seizures. Therefore, it is necessary to set appropriate treatment goals while reevaluating the QOL and the QOL-impairing factors.

Expert opinion recommends valproate as the first-line drug, followed by topiramate and lamotrigine as other first-line drugs.

The efficacy of lamotrigine, topiramate, and rufinamide for LGS has been studied in randomized control trials (RCTs). The effective rates (50% seizure reduction rates) of these drugs when used as adjunctive therapy were 33% for lamotrigine (placebo 16%), 33% for topiramate (placebo 8%), and 32.7% for rufinamide (placebo 11.7%). A cohort study of zonisamide was conducted, and the effective rate (50% seizure reduction rate) when used as adjunctive therapy was 51.6%.

The effectiveness of clobazam for drop attacks in LGS was studied in a RCT. The effective rate (50% seizure reduction rate) when used at doses of 0.2–1 mg/kg/day was 77.6%. Ethosuximide has been reported to be effective for atypical absence seizures and myoclonic seizures with few adverse effects, and is therefore recommended as a drug for these seizures.

A report has shown that gabapentin and carbamazepine increase seizure frequency in LGS.

References
Search formula and secondary reference sources

PubMed search: June 25, 2015
(((“Lennox Gastaut Syndrome” [Mesh]) OR “Lennox Gastaut Syndrome” [TIAB])) AND “drug therapy” [Subheading] Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 122

Ichushi search: June 29, 2015
((((((Lennox-Gastaut syndrome/TH or Lennox-Gastaut syndrome/AL))) and (SH = drug therapy))) and (PT = excluding proceedings)) = 89

Secondary reference source
http://www.nice.org.uk/guidance/cg137
What are the drug options for juvenile myoclonic epilepsy?

Summary
(1) The first-line drug is valproate, but for child-bearing aged women, priority is given to drugs other than valproate.
(2) In the case that valproate cannot be used, or valproate is not adequately effective, monotherapy with levetiracetam, lamotrigine, zonisamide or topiramate is used.
(3) Clonazepam is used as adjunctive therapy for myoclonic seizure.
(4) Do not use gabapentin, carbamazepine or phenytoin.

Comment
Juvenile myoclonic epilepsy (JME) mainly manifests myoclonic seizure and generalized tonic-clonic seizure. Both seizure types are treatment targets, but generalized tonic-clonic seizure is often the main treatment target because of its high impact on QOL.

Expert opinion for JME recommends valproate as the first-line drug. There is no randomized control trial (RCT) of valproate for JME alone, but RCT have demonstrated the efficacy of valproate for generalized epilepsies (seizure control rate 92%), and its effect is superior to those of topiramate and lamotrigine. Since valproate has been reported to be teratogenic and affect cognitive ability of babies, treatment with drugs other than valproate should be given priority in child-bearing women.

In studies on JME, levetiracetam (seizure control rate 80%), lamotrigine (seizure control rate 81.9%), zonisamide (seizure control rate 38.5–69.5%), and topiramate (seizure control rate 67%) have been shown to be effective as monotherapy. Among these drugs, lamotrigine should be used carefully because it often exacerbates myoclonic seizure. Clonazepam can be effective for myoclonic seizure.

A report has shown that gabapentin and carbamazepine exacerbate absence seizures and myoclonic seizures, while phenytoin exacerbates absence seizures. On the other hand, in a certain number of patients, a combination of carbamazepine and valproate is needed to control generalized tonic-clonic seizures.

References
8) Levisohn PM, Holland KD. Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison. Epilepsy Behav. 2007; 10(4): 547-552.
Search formula and secondary reference sources

PubMed search: June 25, 2015
"Myoclonic Epilepsy, Juvenile/drug therapy" [Mesh] Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 63

Ichushi search: June 29, 2015
(((Juvenile myoclonic epilepsy/AL) or (epilepsy-myoclonus-juvenile/TH))) and (PT = excluding proceedings and SH = drug therapy)) = 35

Secondary reference source
http://www.nice.org.uk/guidance/cg137
What are the drug options for epilepsy with generalized tonic-clonic seizures alone (epilepsy with grand mal on awakening)?

Summary
(1) The first-line drug is valproate, but for child-bearing aged women, priority is given to drugs other than valproate.
(2) In the case that valproate cannot be used, or valproate is not adequately effective, zonisamide, lamotrigine, levetiracetam or topiramate is used.
(3) In the case that the above drugs cannot be used, or when these drugs are not completely effective, adjunctive therapy with clobazam is used.

Comment
The epilepsy traditionally called “epilepsy with grand mal on awakening” was changed to “epilepsy with generalized tonic-clonic seizures alone” in the 2010 International League Against Epilepsy (ILAE) classification of epilepsy syndromes1).

There is no randomized controlled trial (RCT) exclusively on epilepsy with generalized tonic-clonic seizures alone, but a meta-analysis on generalized tonic-clonic seizures has demonstrated the efficacy of valproate and phenytoin2). Since valproate has been reported to be teratogenic3) and affect cognitive ability of babies4), treatment with drugs other than valproate should be given priority in child-bearing aged women.

Zonisamide (seizure control rate 42.6%)5), lamotrigine (seizure control rates 30–37% at one year or 40 weeks after starting treatment)6–8), levetiracetam (seizure control rate 34.2%)9), and topiramate (seizure control rate 39–49%)8, 10) have been reported to be effective in controlling generalized tonic-clonic seizures. The efficacy of phenytoin and phenobarbital has also been reported, but they are not used as first-line drugs because of the adverse effect profile. As adjunctive therapy, clobazam also exhibits seizure control effect (seizure control rate 10–30%)11).

References
Search formula and secondary reference sources

PubMed search: June 26, 2015

(((“Epilepsy, Tonic-Clonic” [Mesh]) OR (((“Epilepsy” [Mesh]) AND awaking [TIAB]) AND “Grand mal” [TIAB]))) AND ("Drug Therapy" [Mesh]) OR "drug therapy" [Subheading]) Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 169

Ichushi search: June 29, 2015

(((epilepsy with GTCS on awakening/AL) or (awakening/AL and seizure/AL and (epilepsy/TH or epilepsy/AL)))) and (PT = excluding proceedings and SH = drug therapy)) = 35

Secondary reference source