

# **Clinical Practice Guidelines for Epilepsy 2018**

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## Publication of Clinical Practice Guidelines for Neurological Diseases

In 2001, the Executive Board of the Japanese Society of Neurology decided to develop clinical practice guidelines for the major neurological diseases, based on a proposal by the then President Nobuo Yanagisawa. In 2002, “Treatment Guidelines 2002” for six diseases comprising “chronic headache”, “Parkinson disease”, “epilepsy”, “amyotrophic lateral sclerosis”, “dementia”, and “cerebrovascular disease” were published.

Following the publication of “Treatment Guidelines 2002”, new knowledge was accumulated at an accelerated rate. In 2008, the Executive Board of the Japanese Society of Neurology (Past President, Shigeki Kuzuhara) decided to revise the guidelines. Six guideline development committees were organized to develop “Treatment Guidelines 2010” for “chronic headache” (published in 2013), “dementia” (published in 2010), “epilepsy” (published in 2010), “multiple sclerosis” (published in 2010), “Parkinson disease” (published in 2011), and cerebrovascular disease (published in 2009), as well as a guideline development committee for “genetic diagnosis of neurological disorders” (published in 2009).

On the occasion of the development of “Treatment Guidelines 2010”, the Japanese Society of Neurology established a consistent structure, the guideline development committee, and procedures for all the guidelines to be developed by the Society. Regarding conflicts of interest, the committee members involved in the development of these guidelines submitted to the President a “Japan Neurological Society Declaration of Conflict of Interest” and obtained an “Approval Regarding Conflict of Interest” from the Japanese Society of Neurology. With the exception of Parkinson’s disease, the revised guidelines for all other diseases were developed by joint committees with corroboration from other academic societies.

The guidelines published between 2009 and 2011 were those for representative neurological diseases. However, due to an increase in demand of guidelines for other neurological diseases, a decision was made at the Executive Board in 2011 to publish new clinical practice guidelines for six additional neurological disorders (Guillain-Barré syndrome/Fisher syndrome, chronic inflammatory demyelinating polyneuropathy/multifocal motor neuropathy, amyotrophic lateral sclerosis, bacterial meningitis, Duchenne muscular dystrophy, and myasthenia gravis). These guidelines were published in 2013–2014, and have been widely used clinically as “Guidelines 2013”.

For the present series of guideline revision/development, revision of the guidelines for “genetic diagnosis” (published in 2009), “epilepsy” (published in 2010), “dementia” (published in 2010), “multiple sclerosis” (published in 2010), and “Parkinson disease” (published in 2011) as well as development of guidelines for “herpes simplex encephalitis” and “dystonia” were approved at the Executive Board in 2013, while the development of “Clinical practice guideline for spinocerebella degeneration and multiple system atrophy” was approved at the Executive Board in 2014.

As with previous guidelines, revision or development of the above guidelines was based on the concept of evidence-based medicine (EBM) and guided by Minds Manual for Guideline Development 2007 edition, or 2014 edition for those guidelines that were able to utilize the 2014 edition (guidelines for multiple sclerosis/neuromyelitis optica, Parkinson’s disease, and epilepsy were developed according to the 2014 edition). The 2014 edition recommends introduction of the GRADE system, with the participation of both patients and medical staff in formulating the clinical questions. The GRADE system approach is also adopted as a part of the new guidelines.

Clinical practice guidelines are developed based on current medical knowledge with the purpose to assist clinicians in making clinical decisions to provide appropriate medical care. Clinical care provided for each patient should be decided individually by the attending doctor based on all the clinical data, and the clinical practice guidelines by no means restrict the clinical discretion of doctors. Clinical practice guidelines are not supposed to be applicable to all the patients; they are created as a reference for each treatment setting after the doctor has accurately grasped the patient’s condition.

Treatments for neurological diseases are advancing rapidly, and the clinical practice guidelines will need to be revised regularly in the future. We sincerely hope that the new clinical practice guidelines will help members of our Society in their routine medical practice, and we look forward to your evaluations and opinions to improve the clinical practice guidelines for the next revision.

May 2017

Hidehiro Mizusawa, Past President

Ryosuke Takahashi, Executive President

Gen Sobue, Past Chairman, Guideline Executive Committee

Satoshi Kamei, Chairman, Guideline Executive Committee

Japanese Society of Neurology



# Revision of the Clinical Practice Guidelines for Epilepsy

## Introduction

Epilepsy affects a large number of people, and many doctors other than epilepsy specialists are involved in providing treatment for these patients. For this reason, the Epilepsy Treatment Guideline Development Committee developed the Epilepsy Treatment Guideline 2010 as a guide for general practitioners who treat patients with epilepsy. Following publication of the guideline, new antiepileptic drugs were launched, and the British epilepsy guideline (NICE) was revised, so was epilepsy classification by the International League Against Epilepsy (ILAE). In this revision, descriptions of new antiepileptic drugs have been added. As the first attempt of the Society, systematic review was performed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for three clinical questions (CQ) to be described later. Anti-NMDA receptor antibody encephalitis, the treatment method of which has drawn attention in recent years, is also described in the revised guideline, together with a brief summary of the latest diagnosis, tests, treatments and prognosis of adult and childhood epilepsies.

Adopting the same approach as the previous edition, this revised guideline uses the format consisting of CQ (purpose) and its answer. The CQs that have been systematically reviewed are colored in green to distinguish them from other CQs, and the strength of recommendation and quality of evidence are described, followed by comment on the evidence. For the other CQs, “Summary” is used to describe the overall opinions of experts (colored in red), followed by comment.

This guideline was prepared by the Clinical Practice Guidelines for Epilepsy Development Committee (abbreviated as Guideline Development Committee hereinafter) of the Japanese Society of Neurology, and was developed in collaboration with the Japan Epilepsy Society, the Japan Neurosurgical Society, the Japan Society of Child Neurology, and the Japanese Society of Neurological Therapeutics. The Guideline Development Committee consists of neurologists, pediatricians, psychiatrists, and neurosurgeons who are members of the above-mentioned academic societies.

## 1. Funding Sources for the development of Clinical Practice Guidelines for Epilepsy and conflicts of Interest (COI) of committee members

Preparation of this guideline was funded by the Japanese Society of Neurology. The proceeds from sales of this guideline will be appropriated to cover the cost of preparation.

The chairman, vice-chairman, committee members, external members, collaborators, and evaluation/coordination committee members who are involved in the preparation of this guideline have submitted the “Declaration Form of Conflict of Interest for Preparation of the Japanese Society of Neurology Clinical Practice Guidelines” to the Executive President of the Japanese Society of Neurology, and obtained approval from the Japanese Society of Neurology for the disclosure of conflicts of interest.

The companies that have declared COI are shown below.

- ASKA Pharmaceutical Co. Ltd.
- Eisai Co., Ltd.
- Otsuka Pharmaceutical Co. Ltd.
- GlacoSmithKline K.K.
- Southern TOHOKU Hospital Group
- Daiichi Sankyo Co., Ltd.
- Sumitomo Dainippon Pharma Co., Ltd.
- Association of Radio Industries and Businesses
- MSD K.K.
- Nihon Kohden Corp.
- Novartis Pharma K.K.
- Medical Review Co., Ltd
- UCB Japan Co. Ltd.

## 2. On the use of this guideline

This clinical practice guideline provides recommendations to support the clinical decisions of healthcare professionals, and the recommendations have no enforcing power. The actual clinical decision should be made upon comprehensively considering not only this clinical practice guideline, but also the latest evidence, patient values, and environmental factors.

This clinical practice guideline does not promise to improve clinical outcomes. The Guideline Development Committee is not responsible for the results of medical treatments conducted using this clinical practice guideline.

This clinical practice guideline is not supposed to be used as evidence in a medical lawsuit. Since decision-making in actual clinical practice is based on comprehensive assessments including patients' values and environmental factors while referring to the recommendations in the clinical practice guidelines, providing medical treatment that deviates from the recommendations of the clinical practice guideline does not necessarily imply negligence. This Guideline Development Committee does not approve the use of this clinical practice guideline as evidence in a legal trial.

## 3. Outline of the method of systematic review (Part II)

In the present guideline, systematic review was conducted in three CQs described below, and the digest is summarized in Part II. Details are published on the website of Japanese Society of Neurology.

CQ9-2 Should temporal lobe resection be added to drug therapy in drug-resistant temporal lobe epilepsy?

CQ10-1 Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?

CQ10-2 When conducting vagus nerve stimulation for drug resistant epilepsy, which intensity of stimulation (high or low) should we use?

The recommendations were made according to the GRADE system, which is an international standard approach for guideline development. In the GRADE system, a systematic review is conducted for each outcome; then based on the results, a panel meeting is convened to formulate the recommendations.

### Formulating clinical question (CQ)

The CQ was decided by the Guideline Development Committee, as the clinical issue for which a recommendations can be expected to improve the quality of diagnosis and treatment for drug-resistant epilepsy.

CQ was formulated by the PICO format. PICO is the acronym for patient (P), intervention (I), comparison (C) and outcome (O). For each CQ, outcome was decided at the Guideline Development Committee meeting. The outcome was graded on a scale of 9 to 1 in descending order of importance. Eventually, outcomes graded as critical (scores 9 to 7) or important (scores 6 to 4) were selected for systematic review.

### Literature search

We requested a librarian who had a contract with Japanese Society of Neurology to construct literature search formulae and conduct literature search. MEDLINE and Cochrane CENTRAL were used in the search. From the articles yielded from the search, duplicates were excluded, the remaining papers were screened by title and abstract, then the full texts were evaluated, and sorted by outcome. Only literature of randomized controlled trials (RCTs) was adopted for systematic review.

The outline of literature search is shown in the flow diagram.

### Integrating evidence data

For each CQ, meta-analysis was conducted for each outcome, where possible. Meta-analysis was performed using the Cochrane standard application, Review Manager (RevMan) [Computer program] version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Fixed-effect models were used for integration of outcomes: Mantel-Haenszel method was used when the outcomes were binary variables, and inverse variance method was used when the outcomes were continuous variables.

Risk ratio and 95% confidence interval were calculated for outcomes that were binary variables, and mean difference and standard deviation were calculated for outcomes that were continuous variables, and presented as forest plots.

When the data was not adequate for performing meta-analysis, requests were made to the researchers to obtain more data.

### Evaluating quality of evidence

The quality of evidence was evaluated by the method proposed by the GRADE working group, and was graded as "high", "moderate", "low", and "very low". Since only RCTs were evaluated in this clinical practice guideline, the quality of evidence started from a score of "high". From there, the score might be downgraded depending on the result of evaluation of the

following: “risk of bias”, “inconsistency: variation of treatment estimates between studies”, “indirectness: dissociation between PICO of primary study and PICO of CQ”, “imprecision: low precision of the effect estimate due to small number of samples or events”, and “publication bias: influence by studies that are not published due to negative results”, according to the method defined by the GARDE working group.

After determining the final quality of evidence, the results of systematic review were tabulated in the Summary of Findings (SoF) table and GRADE Evidence Profile. GRADEproGDT (<https://gradepro.org/>) was used for tabulation.

### **Determination of overall quality of evidence for all outcomes**

For each CQ, we adopted the highest quality of evidence if the effects of all the important outcomes were in the same direction of either benefit or harm to the patient. On the other hand, we adopted the lowest quality of evidence if the effects of some outcomes were in the direction of benefit while others were in the direction of harm. This quality of evidence is synonymous with the “certainty of evidence” in the recommendation statement.

In the alphabetical notation of GRADE, “high” certainty of evidence is represented by “A”, “moderate” by “B”, “low” by “C”, and “very low” by “D”.

### **Formulating recommendation from evidence**

Recommendation was formulated using the SoF table and GRADE Evidence Profile.

Four factors determine recommendation: “overall quality of evidence for all outcomes”, “balance of benefit and harm”, “variation in values and preferences” and “resources (cost)”.

To determine recommendation at the panel meeting, the following were discussed: “priority of the issue”, “desirable effects”, “undesirable effects”, “certainty of evidence”, “uncertainty and diversity of values towards major outcomes”, “balance between desirable and undesired effects”, “costs and resources required”, “acceptability to stakeholders”, and “feasibility”. The results are described in the former half of the Evidence-to-Decision (EtD) table; “Evaluation table of recommendation judgment criteria”.

Then, based on the “Evaluation table of criteria for determining recommendation”, consensus was formed regarding the strength and direction of recommendation. The grade of recommendation was presented by a combination of the strength determined as “strong or weak” and the direction determined as “recommended or not recommended”. In GRADE numerical notation, strong recommendation is represented by “1” and weak recommendation by “2”. The rationale for the recommendation is shown in the latter part of the EtD table; “Recommendation decision table”.

### **Panel meeting**

Panelists participated in the panel meeting include epilepsy specialists (neurologists, pediatricians, psychiatrists and neurosurgeons) who are members of the Clinical Practice Guideline Developing Committee, as well as primary care physicians, representatives of patients’ families, lawyers, and all other stakeholders.

A panel meeting was held on October 23, 2016, in which CQ9-2, CQ10-1 and CQ10-2 were discussed from noon to evening. The panel meeting was moderated by Eishu Nango, an expert in clinical practice guideline development methods. After commenting on the GRADE system, participants discussed based on the SoF table, GRADE Evidence Profile, and draft recommendation statements.

For CQ10-1 and CQ10-2, the recommendations were unanimously agreed. Regarding CQ9-2, almost all the panelists expressed the opinion that the strength of recommendation was “strong”, but the certainty of evidence was “very low”. Therefore, “weak recommendation” was decided according to the GRADE rules.

### **Writing the clinical practice guidelines**

Based on the recommendations decided at the panel meeting, the draft of the guidelines was written, was externally evaluated, and then finalized.

#### 4. About the notation of antiepileptic drug

For all the drugs that are approved in Japan, the names are written in katakana in the text (Table 1). On the other hand, † is added to denote drugs that are not covered by insurance in Japan.

February 2018

“Clinical Practice Guidelines for Epilepsy” Development Committee

Chairman Yoshikazu Ugawa

Secretariat Yoshihiro Sugiura

**Table 1. Antiepileptic drugs approved in Japan.**

Generic name	Abbreviation	Major brand name
acetazolamide	AZM	Diamox
ethosuximide	ESM	Epileo pepti mal, Zaronin
oxcarbazepine <sup>1)</sup>	OXC	Ocnobel
gabapentin <sup>2)</sup>	GBP	Gabapen
carbamazepine	CBZ	Tegretol
clonazepam <sup>3)</sup>	CZP	Landsen, Rivotril,
clobazam	CLB	Mystan
diazepam	DZP	Cercine, Horizon, Diapp
potassium bromide	KBr	Potassium bromide
stiripentol <sup>4)</sup>	STP	Diacomit
sultiam	ST	Ospolot
zonisamide	ZNS	Excegran
topiramate <sup>5)</sup>	TPM	Topina
nitrazepam	NZP	Benzalin
valproate	VPA	Depakene, Selenica
vigabatrin <sup>6)</sup>	VGB	Sabril
phenytoin	PHT	Aleviatin, Hydantol
phenobarbital	PB	Phenobal
primidone	PRM	Primidone
perampanel <sup>7)</sup>	PER	Fycompa
lacosamide <sup>8)</sup>	LCM	Vimpat
lamotrigine <sup>9)</sup>	LTG	Lamictal
rufinamide <sup>10)</sup>	RFN	Inovelon
levetiracetam <sup>11)</sup>	LEV	E Keppra

- 1) Oxcarbazepine is approved as combination therapy for partial seizures in children aged 4 years or older, who do not respond adequately to other antiepileptic drugs.
- 2) Gabapentin is approved as combination therapy for partial seizures in patients aged 3 years or older, who do not respond adequately to other antiepileptic drugs.
- 3) Clobazam is approved as combination therapy for partial or generalized seizures not responding adequately to other antiepileptic drugs.
- 4) Stiripentol is approved as adjunctive therapy to valproic acid and clobazam for Dravet syndrome.
- 5) Topiramate is approved as combination therapy for partial seizures in patients aged 2 years or older, who do not respond adequately to other antiepileptic drugs.
- 6) Vigabatrin is approved for West syndrome.
- 7) Perampanel is approved as combination therapy for partial seizures and tonic-clonic seizures in patients aged 12 years or older, who do not respond adequately to other antiepileptic drugs.
- 8) Lacosamide is approved as combination therapy for partial seizures not responding adequately to other antiepileptic drugs.
- 9) Lamotrigine is approved as monotherapy for partial seizures, tonic-clonic seizures and typical absence seizures (aged 15 or older), and as combination therapy for partial seizures, tonic-clonic seizures and generalized seizures in Lennox-Gastaut syndrome not responding adequately to other antiepileptic drugs.
- 10) Rufinamide is approved as combination therapy for tonic seizures and atonic seizures in Lennox-Gastaut syndrome in patients aged 4 years or older, who do not respond adequately to other antiepileptic drugs.
- 11) Levetiracetam is approved as monotherapy for partial seizures in patients aged 4 years or older, and as combination therapy for tonic-clonic seizures.

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**Part I**  
**The Clinical Practice Guidelines**  
**for Epilepsy 2018**

# Chapter 1

## Diagnosis, Classification and Differential

### Diagnosis of Epilepsies (Including REM Sleep Behavior Disorder)

#### CQ 1-1

## What is epilepsy?

### Summary

**Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures. In other words, epilepsy is a chronic brain disease, in which abnormal hyperexcitable neurons in the brain cause recurrence of seizure symptoms. Seizures occur suddenly, manifesting physical symptoms different from the normal state, altered consciousness, and motor and sensory changes. The possibility of epilepsy is adequately high if accompanied by seizures.**

### Comment

Cerebral neurons generate regular rhythm electrically, while maintaining synchronous neuronal activity in the brain. Epilepsy is caused by a sudden disturbance of this activity accompanied by abnormal, disorderly discharges of the electrical activities of neurons in the brain (excessive excitation or synchronization). This may occur in an afebrile state, and the seizure symptoms are diverse depending on the region of the brain that is involved in the abnormal electrical activity<sup>1)</sup>. These symptoms include not only “convulsions and spasms” but also various symptoms such as “feeling black out”, “jerking of the body”, “moving around with loss of consciousness” (see CQ1-4 on page 10, and CQ1-5 on page 11). In addition, epilepsy is characterized by recurrence. Electroencephalography (EEG) has a central role in various examinations and is necessary to establish the diagnosis (see CQ1-6 on page 13).

Traditionally, epilepsy was defined as “two unprovoked seizures occurring at intervals of longer than 24 hours”. In 2014, a task force of the International League Against Epilepsy Organization (ILAE) recognized that epilepsy may be present in special circumstances that do not meet the criteria of “two unprovoked seizures”. In order to address this issue, the task force proposed to consider epilepsy as a disease of the brain defined by any of the following criteria<sup>2)</sup>: (1) at least two unprovoked (or reflex) seizures occurring at intervals of longer than 24 hours; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years (see Note below); and (3) diagnosis of an epilepsy syndrome.

The term “unprovoked seizure” is a term that describes spontaneous seizure as a chronic disease without a definitive trigger. In contrast, “provoked seizure” is also known as acute symptomatic seizure or situation-related seizure, which occurs secondary to acute brain disorders such as encephalitis, trauma, cerebrovascular disorders, and metabolic disorders<sup>3)</sup>.

Note: Number (2) in the second paragraph signifies that if there is one unprovoked seizure and the risk of recurrence can be proven to be over 60%, then patient care should be initiated assuming a diagnosis of epilepsy. Some specific examples include patients with a single seizure occurring at least one month after onset of stroke, and children with a single seizure simultaneous with a structural or indirect symptomatic etiology for the symptom and an epileptiform EEG. Another example is patients in whom a specific epilepsy syndrome associated with persistent threshold change can be detected after a single seizure. Even when the first seizure manifests as status epilepticus, this by itself does not imply epilepsy<sup>2)</sup>.

## ■ References

- 1) Inuma K, Fujiwara T, Ikeda A, et al. Japan Epilepsy Society, Task Force on Guideline Committee. Guideline for Diagnosis of Epilepsy. Tenkan Kenkyu. 2008; 26(1): 110-113 (in Japanese).
- 2) Fisher RS, Accvedo C, Arzimanoglou A, et al. ILAE Official Report. A practical clinical definition of epilepsy. Epilepsia. 2014; 55(4): 475-482.
- 3) Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010; 51(4): 671-675.

## ■ Search formula and secondary reference sources

PubMed search: September 12, 2008

epilepsy [Mesh] and (define\* OR definition\*) = 2,382

No references that could serve as evidence were found in Ichushi Web.

PubMed search: June 28, 2015

(((((epilepsy/classification [majr] OR epilepsy/diagnosis [majr])) AND ((define\* OR definite\*)))) AND (Humans [Mesh] AND (English [LA] OR Japanese [LA]))) AND ("2008" [Date-Publication]: "2015" [Date-Publication])) AND (("ILAE") OR ("NICE" OR "National Institute for Health and Care Excellence")) = 17

Ichushi search: June 25, 2015

((((Differential diagnosis/TH) and (((REM sleep behavior disorder/TH or REM sleep behavior abnormality/AL) or (epilepsy/MTH)) and (Japan Epilepsy Society/AL)))) and (DT = 2008:2015 and PT = excluding proceedings and CK = human) = 6

## What are the key clinical features to be included in history taking for epilepsy diagnosis?

### Summary

Accumulation of detailed information (medical history) and a witness of the actual seizure are most useful for the diagnosis of epilepsy. The chief complaint in most cases is a convulsive seizure (non-convulsive seizure in some cases). However, usually it is necessary to confirm the history of the seizure at least twice in order to diagnose epilepsy.

### Comment

Detailed history taking of clinical features 1 to 3 described below is important for making a diagnosis<sup>1, 2</sup>.

#### 1. It is important to obtain seizure information from the patient and a witness of the seizure.

- a. Frequency of seizure
- b. Situation and trigger of the seizure (such as photosensitivity)
- c. Symptoms before and during seizure (physical symptoms, psychological symptoms, and consciousness impairment)
- d. Duration of symptoms
- e. Symptoms after the seizure
- f. Presence or absence of injury, tongue bite and urinary incontinence
- g. Headache and muscle pain after seizure
- h. Age of the first seizure for a patient with multiple seizures
- i. Change and evolution of seizure and type of seizure
- j. The last seizure
- k. Relation between seizure and wake-sleep states

#### 2. It is important to include the following clinical features in history taking from a witness of seizure.

- a. Frequency of seizure
- b. Detailed situations observed before and during seizure (patient's response, arm and leg movements, open or closed eyes, eyeball displacement, making sound, facial pallor, respiration and pulse)
- c. Details of movements and behaviors after seizure
- d. Video recorded by family members

#### 3. When recording the medical history in the clinical record, it is important to include the following demographic characteristics.

- a. Age (many epilepsies are age-dependent)
- b. Sex
- c. Past history (including perinatal abnormalities, febrile convulsions, head trauma, and mental illness)
- d. Comorbid conditions (see **Table 1**)
- e. History of alcohol consumption, regular medications, and history of narcotic use
- f. Family history
- g. Social history

## ■ References

- 1) Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. A national clinical guideline, 2003, p.3-7.
- 2) Stokes T, Shaw EL, Juarez-Garcia A, et al. Clinical Guidelines and Evidence Review for the Epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners, 2004, p. 49-50, 85-95.

## ■ Search formula and secondary reference sources

PubMed search: October 30, 2008

((epileptic seizures or epilepsy) and diagnosis and (interview or (history taking)) and ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh] or meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb] = 58

No references that could serve as evidence were found in Ichushi Web.

PubMed search: June 28, 2015

((((((((epilepsy [majr]) AND medical history taking [mesh])) AND ("2008" [Date-Publication]: "2015" [Date-Publication])) AND (English [Language] OR Japanese [Language])))) AND Humans [Filter])) AND ("ILAE" OR "NICE") = 0

Ichushi search: June 25, 2015

(((((epilepsy/MTH)) and (SH = diagnosis)) and (history taking/MTH))) and (DT = 2008:2015 and PT = excluding proceedings) = 0

**Table 1. Main comorbid conditions of epilepsy.**

1. Birth asphyxia	8. Central nervous system infection
2. Brain malformation	9. Autoimmune encephalitis
3. Genetic abnormality	10. Cerebral hemorrhage
4. Chromosomal abnormality	11. Cerebral infarction
5. Developmental disorder	12. Brain tumor
6. Metabolic abnormality	13. Brain trauma
7. Hypoxia	14. Dementia

## How are epileptic seizure types, epilepsies, epilepsy syndromes, and related seizure disorders classified?

### Summary

Classification of epileptic seizures is indispensable for subsequent patient care, examinations, and choice of antiepileptic drugs. The ILAE classifications are widely used. Diagnosis of epilepsy for patients has important significance on physical, mental, social and economic status. Therefore, it is recommended that specialists conduct definitive clinical diagnosis of epilepsy.

### Comment

Currently, the following ILAE classifications are widely used in Japan: the classification of epileptic seizures of 1981<sup>1)</sup> and the classification of epilepsies, epileptic syndromes and related seizure disorders of 1989<sup>2)</sup>. However, the ILAE task force proposed a new disease classification in 2010<sup>3)</sup>. **Tables 1 and 2** show the corresponding classification categories in the new and old classifications of 1981, 1989 and 2010<sup>4)</sup>. This guideline follows the classification of seizure types of 1981, in which epileptic seizures are divided into partial and generalized seizures. “Partial” is used to indicate “focal” or “localization-related”.

The feature of the 1981 classification of seizure types is based on an accurate correspondence between seizure symptoms and EEG findings (left column of **Table 1**), and the scheme is based on “epileptic discharge” on EEG, which is the information with the highest sensitivity and specificity. On the other hand, the feature of the 1989 classification of epilepsies and epilepsy syndromes is based on a 2 × 2 classification table (left column of **Table 2**). With this classification, idiopathic epilepsies and syndromes are not necessary only generalized epilepsies but also include some partial epilepsies. Conversely, within symptomatic epilepsies and syndromes, partial epilepsies and generalized epilepsies are both clearly classified. Furthermore, among these four categories, apart from symptomatic partial epilepsies, all the others have in principle age-dependent onset and reflect the element of onset age at the same time.

1. Idiopathic partial epilepsies are benign, (1) with childhood onset, (2) manifest localization-related seizure symptoms and localized EEG findings, (3) show no abnormal neuroimaging findings, and (4) remit by adolescence. This category includes benign epilepsy with centrotemporal sharp waves and Panayiotopoulos type with focus in the occipital region.
2. Symptoms suggestive of symptomatic partial epilepsies include: (1) a history of disease that may constitute the etiology, (2) aura, (3) local motor or sensory signs at onset or during seizure, and (4) automatism. However, even with absence seizures, automatism may sometimes occur.
3. Idiopathic generalized epilepsies rarely have onset older than at 25 years of age and show no other neurological symptoms. The symptoms suggesting this category include: (1) childhood onset (before adolescence), (2) induced by sleep deprivation and alcohol, (3) tonic-clonic seizure or myoclonic seizure immediately after waking, (4) seizure type is absence, with no other neurologic symptoms (5) spontaneous photoreaction on EEG, including generalized 3-Hz spike-and-slow-wave complexes or multiple spike-and-slow-wave complexes.
4. Symptoms suggestive of symptomatic generalized epilepsies include: (1) very early onset (neonatal period, infancy: under 1 year of age), (2) frequent seizures, (3) mental retardation and neurological symptoms from before onset, (4) progression and regression of neurological symptoms, (5) diffuse EEG abnormalities, and (6) organic morphological abnormalities in the brain.

The basic concepts for the 2010 classifications are as follows.

#### 1. Modes of seizure manifestation and classification of seizures

The term partial seizure is eliminated, and is replaced by “focal seizures” (with or without impairment of consciousness) (right column of **Table 1**). “Generalized” and “focal” are redefined. Generalized seizures are seizures that occur within the network of bilateral cerebral hemispheres, and this network is rapidly involved in seizure. Focal seizures are seizures that occur within the network limited to unilateral cerebral hemisphere and is either discretely localized or more widely distributed within unilateral hemisphere.

#### 2. Classification of underlying causes

Instead of the traditional terms “idiopathic”, “symptomatic” and “cryptogenic”, the 2010 classification recommends modified concepts using the new terms “genetic”, “structural-metabolic” and “unknown”.

This chapter is based on the classifications reported up to the time of this writing (2016), and the classifications published thereafter are not addressed.

## ■ References

- 1) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1981; 22(4): 489-501.
- 2) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1989; 30(4): 389-399.
- 3) Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts of organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4): 676-685.
- 4) Tobimatsu S. Chapter 1. Epidemiology of Epilepsy. 2. Classification (comparison of 1981, 1989 and 2010). In: Guidebook for Epileptologists, Japan Epilepsy Society (Ed.) Shindan To Chiryousha, Tokyo. 2014, p. 5-10 (in Japanese).

## ■ Search formula and secondary reference sources

PubMed search: October 17, 2008

((epileptic seizures) or epilepsy) and diagnosis and (classification or categorization) and (“sensitivity and specificity” [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh] or meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR “meta analysis” OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb] = 273

No references that could serve as evidence were found in Ichushi Web.

PubMed search: June 28, 2015

(((((epilepsy/classification [majr]) AND classification [ti])) AND (“2008” [Date-Publication]: “2015” [Date-Publication])) AND (English [Language] OR Japanese [Language])) AND Humans [Filter])) AND (“ILAE” OR “NICE”) = 22

Ichushi search: June 25, 2015

((epilepsy/MTH) and (classification/TI))) and (DT = 2008:2015 and PT = excluding proceedings) = 0

**Table 1. International classifications of epileptic seizure types: corresponding categories for the 1981 classification and the 2010 revised classification.**

1981 classification of seizure type <sup>a</sup>	2010 revised classification of seizure type <sup>b</sup>
<b>Partial (focal, local) seizures</b>	<b>Focal seizures</b>
A. Simple partial seizures (consciousness not impaired) 1. With motor signs 2. With somatosensory or special sensory symptoms 3. With autonomic symptoms or signs 4. With psychiatric symptoms (most experienced as “complex partial seizures”)	A. Without impairment of consciousness With observable motor or autonomic components. This roughly corresponds to the concept of “simple partial seizure.” “Focal motor” and “autonomic” are terms that may adequately convey this concept depending on the seizure manifestations). Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary.
B. Complex partial seizures 1. Simple partial onset followed by impairment of consciousness a. With simple partial at onset b. With automatism at onset c. With impairment of consciousness at onset	B. With impairment of consciousness This roughly corresponds to the concept of complex partial seizure. “Dyscognitive” is a term that has been proposed for this concept.
C. Partial seizures evolving to secondarily generalized seizures 1. Simple partial seizures (A) evolving to generalized seizures 2. Complex partial seizures (B) evolving to generalized seizures 3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures	Evolving to a bilateral, convulsive seizure (involving tonic, clonic, or tonic-clonic components). This expression replaces the term “secondarily generalized seizure.
<b>Generalized seizures</b>	<b>Generalized seizures</b>
A. 1. Absence seizures a. Impairment of consciousness only b. With mild clonic components c. With atonic components d. With tonic components e. With automatisms f. With autonomic component (b-f may be alone or in combination)	A. Absence seizures 1. Typical absence seizure 3. Absence with special features Myoclonic absence Eyelid myoclonia
2. Atypical absence seizure a. Changes in tone more pronounced than A1 b. Onset/offset not abrupt	2. Atypical absence seizure
B. Myoclonic seizures	B. 1. Myoclonic seizures 2. Myoclonic atonic seizure 3. Myoclonic tonic seizure
C. Clonic seizures	C. Clonic seizure
D. Tonic seizures	D. Tonic seizure
E. Tonic-clonic seizures (no clearly corresponding entity)	E. Tonic-clonic seizure (in any combination)
F. Atonic seizures	F. Atonic seizure
<b>Unclassified epileptic seizures</b>	<b>Unclassified epileptic seizures</b>
Neonatal seizures	Epileptic spasms
Rhythmic eye movements	
Chewing	
Swimming movement	
	Seizures that cannot be clearly diagnosed into one of the above categories should be considered “unclassified” until additional information allows their accurate diagnosis. However, “unclassified” is not considered a classification category.

<sup>a</sup> Modified from: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1981; 22(4): 489-501.

<sup>b</sup> Modified from: Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts of organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4): 676-685.



**Table 2. International classification of epilepsy syndromes: 1989 classification and 2010 revised classification.**

1989 classification of epilepsy syndromes <sup>a</sup>	2010 revised classification of epileptic syndromes <sup>b</sup>
<p><b>1. Localization-related (focal, local, partial) epilepsies and syndromes</b></p> <p>1.1 Idiopathic (age-related onset)</p> <ul style="list-style-type: none"> <li>Benign childhood epilepsy with centrotemporal spikes</li> <li>Childhood epilepsy with occipital paroxysms</li> <li>Primary reading epilepsy</li> </ul> <p>1.2 Symptomatic</p> <ul style="list-style-type: none"> <li>Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)</li> <li>Syndromes characterized by seizures with specific modes of precipitation</li> <li>Temporal lobe epilepsies</li> <li>Frontal lobe epilepsies</li> <li>Parietal lobe epilepsies</li> <li>Occipital lobe epilepsies</li> </ul> <p>1.3 Cryptogenic</p> <p><b>2. Generalized epilepsies and syndromes</b></p> <p>2.1 Idiopathic (with age-related onset - arranged by age)</p> <ul style="list-style-type: none"> <li>Benign neonatal familial convulsions</li> <li>Benign neonatal convulsions</li> <li>Benign myoclonic epilepsy in infancy</li> <li>Childhood absence epilepsy (pyknolepsy)</li> <li>Juvenile absence epilepsy</li> <li>Juvenile myoclonic epilepsy (impulsive petit mal)</li> <li>Epilepsy with grand mal (GTCS) seizures on awakening</li> <li>Other generalized idiopathic epilepsies not defined above</li> <li>Epilepsies with seizures precipitated by specific modes of activation</li> </ul> <p>2.2 Cryptogenic or symptomatic (arranged by age)</p> <ul style="list-style-type: none"> <li>West syndrome (infantile spasm, nodding spasm)</li> <li>Lennox-Gastaut syndrome</li> <li>Epilepsy with myoclonic-astatic seizures</li> <li>Epilepsy with myoclonic absences</li> </ul> <p>2.3 Symptomatic</p> <p>2.3.1 Non-specific etiology</p> <ul style="list-style-type: none"> <li>Early myoclonic encephalopathy</li> <li>Early infantile epileptic encephalopathy with suppression burst</li> <li>Other symptomatic generalized epilepsies not defined above</li> </ul> <p>2.3.2 Specific syndromes</p> <p><b>3. Epilepsies and syndromes undetermined whether focal or generalized</b></p> <p>3.1 With both generalized and focal seizures</p> <ul style="list-style-type: none"> <li>Neonatal seizures</li> <li>Severe myoclonic epilepsy in infancy</li> <li>Epilepsy with continuous spike-waves during slow-wave sleep</li> <li>Acquired epileptic aphasia (Landau-Kleffner syndrome)</li> <li>Other undetermined epilepsies not defined above</li> </ul> <p>3.2 Without unequivocal generalized or focal features</p> <p><b>4. Special syndromes</b></p> <p>4.1 Situation-related seizures</p> <ul style="list-style-type: none"> <li>Febrile convulsions</li> <li>Isolated seizures or isolated status epilepticus</li> <li>Seizures occurring only when there is an acute metabolic or toxic event such as alcohol, drugs, eclampsia, nonketotic hyperglycemia, etc.</li> </ul>	<p><b>Electroclinical syndromes (arranged by age at onset)<sup>c</sup></b></p> <p>Neonatal period</p> <ul style="list-style-type: none"> <li>Benign familial neonatal epilepsy</li> <li>Early myoclonic encephalopathy</li> <li>Ohtahara syndrome</li> </ul> <p>Infancy</p> <ul style="list-style-type: none"> <li>Epilepsy of infancy with migrating focal seizures</li> <li>West syndrome</li> <li>Myoclonic epilepsy in infancy</li> <li>Benign infantile epilepsy</li> <li>Benign familial infantile epilepsy</li> <li>Dravet syndrome</li> <li>Myoclonic encephalopathy in nonprogressive disorders</li> </ul> <p>Childhood</p> <ul style="list-style-type: none"> <li>Febrile seizures plus (have infancy onset)</li> <li>Early onset benign childhood occipital epilepsy syndrome (Panayiotopoulos syndrome)</li> <li>Epilepsy with myoclonic atonic (previously astatic) seizures</li> <li>Benign epilepsy with centrotemporal spikes</li> <li>Autosomal-dominant nocturnal frontal lobe epilepsy Late onset childhood occipital epilepsy (Gastaut type)</li> <li>Epilepsy with myoclonic absences</li> <li>Lennox-Gastaut syndrome</li> <li>Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)<sup>d</sup></li> <li>Landau-Kleffner syndrome</li> <li>Childhood absence epilepsy</li> </ul> <p>Adolescence-Adult</p> <ul style="list-style-type: none"> <li>Juvenile absence epilepsy</li> <li>Juvenile myoclonic epilepsy</li> <li>Epilepsy with generalized tonic-clonic seizures alone</li> <li>Progressive myoclonus epilepsies</li> <li>Autosomal dominant epilepsy with auditory features</li> <li>Other familial temporal lobe epilepsies</li> </ul> <p>Less specific age relationship</p> <ul style="list-style-type: none"> <li>Familial focal epilepsy with variable foci (childhood to adult)</li> <li>Reflex epilepsies</li> </ul> <p><b>Distinctive constellations</b></p> <ul style="list-style-type: none"> <li>Mesial temporal lobe epilepsy with hippocampal sclerosis</li> <li>Rasmussen syndrome</li> <li>Gelastic seizures with hypothalamic hamartoma</li> <li>Hemicconvulsion-hemiplegia-epilepsy</li> </ul> <p>Epilepsy not belonging to these diagnostic categories are distinguished based on first, presence or absence of structural-metabolic disease (presumed cause), and second, mode of seizure onset (generalized vs. focal)</p> <p><b>Epilepsies attributed to and organized by structural-metabolic causes (arranged by etiology)</b></p> <ul style="list-style-type: none"> <li>Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)</li> <li>Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)</li> <li>Tumor</li> <li>Infection</li> <li>Trauma</li> </ul> <p><b>Angioma</b></p> <ul style="list-style-type: none"> <li>Perinatal insults</li> <li>Stroke</li> <li>Others</li> </ul> <p><b>Epilepsies of unknown cause</b></p> <p><b>Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se.</b></p> <ul style="list-style-type: none"> <li>Benign neonatal seizures</li> <li>Febrile seizures</li> </ul>

<sup>a</sup> Modified from: Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*.1989; 30(4): 389-399.

<sup>b</sup> Modified from: Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts of organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4): 676-685.

<sup>c</sup> Classification of electroclinical syndromes does not reflect the etiology.

<sup>d</sup> Sometimes also called "electrical status epilepticus during slow sleep (ESES).

# Which diseases should be differentiated from epilepsy in adults?

## Summary

The conditions that may be misdiagnosed as epilepsy are as follows.

- (1) Syncope (vasovagal, cardiac, etc.)
- (2) Psychogenic nonepileptic seizures
- (3) Hyperventilation or panic disorder
- (4) Stroke (cerebral infarction, cerebral hemorrhage), transient ischemic attack
- (5) Parasomnia (REM sleep behavior disorders, non-REM parasomnia)
- (6) Acute intoxication (drugs, alcohol), drug withdrawal, alcohol withdrawal
- (7) Acute metabolic disorders (hypoglycemia, tetany, etc.)
- (8) Acute renal failure
- (9) Head injury (within one week)
- (10) Involuntary movements (tic, tremor, myoclonus, paroxysmal dyskinesia, etc.)
- (11) Episodic ataxia

## Comment

Among patients visiting the emergency room with acute onset of loss of consciousness, the most common causes are vasovagal syncope or psychogenic nonepileptic seizure (40%), followed by epilepsy (29%) and cardiac syncope (8%)<sup>1)</sup>. In the diagnosis of epilepsy, we should exclude or consider an associated cardiovascular factor<sup>2)</sup>. A syncope attack is characterized by no change in consciousness level, fatigue, and malaise after an attack<sup>3,4)</sup>. Patients who develop acute convulsion within 1 week after head injury have an overall risk of approximately 25% for developing epilepsy in the future<sup>3)</sup>. Alcohol withdrawal may also cause a convulsive attack<sup>3,4)</sup>.

## ■ References

- 1) Day SC, Cook EF, Funkenstein H, et al. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med.* 1982; 73(1): 15-23.
- 2) Zaidi A, Clough P, Cooper P, et al. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol.* 2000; 36(1): 181-184.
- 3) Japanese Society of Neurology Ad Hoc Committee of Treatment Guidelines. Guideline for Treatment of Epilepsy 2002. *Rinsho Shinkeigaku.* 2002; 42(6): 549-597 (in Japanese).
- 4) Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. A national clinical guideline, 2003. p.3-5.

## ■ Search formula and secondary reference sources

PubMed search: October 30, 2008

((epileptic seizures) or epilepsy) and diagnosis and (distinguish or differentiate or "Diagnosis, Differential" [Mesh]) and ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) and (meta-analysis [mh] OR meta analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 32

No references that could serve as evidence were found in Ichushi Web.

PubMed search: June 28, 2015

((("Epilepsy" [Major Mesh]) AND "diagnosis, differential" [MeSH Terms]) AND (English [Language] OR Japanese [Language])) AND ("2008"[Date-Publication]: "2015" [Date-Publication])) AND adult [MeSH]) AND ("ILAE" OR "NICE") = 4

Ichushi search: June 25, 2015

((((epilepsy/MTH)) and (SH = diagnosis)) and (differential diagnosis/TH))) and (DT = 2008:2015 and PT = excluding proceedings and CK = adult (19-44), middle-aged (45-64), elderly (65-), elderly (80-)) = 3

## Which diseases should be differentiated from epilepsy in children?

### Summary

Confirm that there are no features suggestive of the following pathological conditions. Especially, take history carefully about the situation before and after the attack. In the case of children, check for fever, crying, diarrhea, sleep-wake rhythm, and whether the child is hungry.

- (1) Febrile convulsion
- (2) Breath-holding spells
- (3) Benign convulsions with mild gastroenteritis
- (4) Convulsion during sleep/sleep myoclonus
- (5) Non-REM parasomnia (night terror/sleepwalking)
- (6) Tic
- (7) Syncope (vasovagal, cardiac, etc.)
- (8) Psychogenic nonepileptic seizures
- (9) Masturbation
- (10) Acute metabolic disorders (hypoglycemia, tetany, etc.)

### Comment

In children, some diseases or conditions with paroxysmal symptoms are often misdiagnosed as epileptic seizures. The symptoms and the diseases/conditions that may show these symptoms are as follows: (1) generalized tonic convulsions and tonic-clonic convulsion: febrile convulsions, benign convulsions with mild gastroenteritis, some psychogenic seizures, acute metabolic disorders, and prolonged cyanotic breath-holding attacks; (2) loss of consciousness and atonic attack: breath-holding spells, vasovagal syncope, some psychogenic seizures, some acute metabolic disorders, and some febrile convulsions; (3) muscle jerks: sleep myoclonus and some psychogenic reactions; (4) strange behaviors such as fear and wandering: night terror, sleepwalking, and psychogenic reactions. Medical history, symptoms, and onset age help differentiate these diseases from epilepsy, and EEG examination is sometimes needed<sup>1,2)</sup>. Note that some febrile convulsions (especially in children over 3 years of age) or some of the acute metabolic disorders may show epileptic discharges (epileptiform EEG) (Table 1).

### ■ References

- 1) Iinuma K, Fujiwara T, Ikeda A, et al. Japan Epilepsy Society. Task Force on Guideline Committee. Guideline for Diagnosis of Epilepsy. Tenkan Kenkyu 2008; 26(1): 110-113 (in Japanese).
- 2) Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. A national clinical guideline, 2003.

### ■ Search formula and secondary reference sources

PubMed search: October 30, 2008

((epileptic seizures) or epilepsy) and diagnosis and (distinguish or differentiate or "Diagnosis, Differential" [Mesh]) and ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) and (meta-analysis [mh] OR meta analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 32

No references that could serve as evidence were found in Ichushi Web.

PubMed search: June 28, 2015

(((((("Epilepsy" [Major Mesh]) AND diagnosis, differential [MeSH Terms])) AND (English [Language] OR Japanese [Language])) AND ("2008" [Date-Publication]: "2015" [Date-Publication])) AND "child" [Filter])) AND ("ILAE" OR "NICE") = 1

Ichushi search: June 25, 2015

(((((epilepsy/MTH)) and (SH = diagnosis)) and (differential diagnosis/TH))) and (DT = 2008:2015 and PT = excluding proceedings and CK= infancy (2-5), children (6-12), young adult (13-18))) and (Japan Epilepsy Society/AL) = 1

**Table 1. Diseases that have to be differentiated from epilepsy in children – benign convulsions and related disorders.**

Benign convulsion		Seizure symptoms	EEG abnormality	Diagnosis
Febrile convulsion		Generalized tonic convulsion accompanied by fever of over 38°C; tonic-clonic convulsions. From medical history and clinical examinations, convulsion seems not attributed to central nervous system infection, metabolic abnormalities, or other obvious causes. Atonic febrile convulsions such as atonia, staring, and upward rolling of eyeballs 5%; familial onset 20-30%. EEG may show epileptiform waves.	+/-	Convulsions occurring only during fever. No symptoms suggestive of other disorders.
Breath-holding spells	cyanotic	Child cries uncontrollably due to pain, anger, or bad mood. Suddenly stops breathing resulting in cyanosis. Loses consciousness, becomes limp. If prolonged, whole body becomes tonic.	-	Medical history. If anxious, perform EEG
	pallid	Suddenly loses consciousness without crying, due to sudden pain, surprise, or fear. Becomes limp, face turns pale.	-	
Benign convulsions with mild gastroenteritis		Generalized afebrile tonic-clonic convulsions caused by diarrhea or vomiting for 2 to 5 days with mild or no dehydration. Convulsions may be caused by vomiting alone before diarrhea occurs. If no abnormalities found in EEG and electrolyte tests, the possibility is high. Commonly seen in rotavirus infection. 80% of patients show cluster of 2 or more spasms, lasting 2-3 days in 20%.	-	Medical history, rotavirus antigen in feces (other viruses too), (EEG)
Convulsion during sleep / sleep myoclonus		Convulsion during sleep: brief and minor convulsions occurring at the beginning of sleep; single or repetitive. Although commonly left-right asymmetric affecting lower limbs, may be seen in upper limbs and head muscle. Sleep myoclonus: can occur in all sleep stages, not only asynchronously but also left-right symmetrically; not only in distal muscles but also in proximal muscles and trunk.		Symptoms, time of occurrence. If anxious, perform EEG
Non-REM parasomnia (night terror/sleepwalking)		Night terror: strong fear that happens suddenly during sleep; showing screams, crying, excitement, tachycardia, etc.; lasting 1 to 10 minutes. One-half of patients also show sleepwalking. Sleepwalking: suddenly rising during sleep, walking or running around, etc., lasting 1 to 40 minutes. Both occur during the first one-third of sleep at night, and are common among 4-12 year-old children. Do not wake up even when someone tries to wake them. Patient does not remember the episode. There may be a family history.	-	Symptoms, time of occurrence. If anxious, perform EEG and polysomnography
Tic		Abrupt movements noticeable in the face, neck, shoulders, upper limbs, etc., which repeat regularly and constantly. Also occurs in eyeballs. Increase with mental tension. Does not disturb other movements while the tic occurs. Does not bother the patient. Does not occur during sleep.	-	Symptoms
Vasovagal syncope		Suddenly loses consciousness and collapses; becomes atonic. May be postural dysregulation occurring during postural change or standing; vagal reflex due to fear and pain; or reflex due to cough, urination, or swallowing. The duration of consciousness loss is short.	-	Medical history and symptoms
Psychogenic nonepileptic seizures		Diverse seizure symptoms, difficult to diagnose from symptoms alone. Tends to occur under the same situation. Usually does not occur where nobody is watching. In the case of only psychogenic reaction, the reaction may be concomitant with epilepsy. Ictal EEG is necessary for a reliable diagnosis. See the section of "Psychogenic nonepileptic seizure" (CQ14-1 on page 123).	-	Symptoms Ictal EEG
Masturbation		Repeated motion of extending lower limbs with force over a long time. Conscious. When looking closely, the thighs and pelvis are rubbing against the bed or something. Symptoms are interrupted when the thighs are separated. Sometimes red face can be seen.	-	Observe motions carefully
Acute metabolic disorders (hypoglycemia, tetany, etc.)		Hypoglycemia may cause loss of consciousness and tonic-clonic convulsion. Hypocalcemia may cause tonic convulsion or tonic-clonic convulsion. Hyponatremia may cause tonic-clonic convulsion. Hyperammonemia may cause loss of consciousness and tonic-clonic convulsion.	-/+	Blood glucose, serum calcium, serum sodium, blood ammonia, etc.

# What are the practical procedures for the diagnosis of epilepsy?

## Summary

The main procedures of diagnosis of epilepsy are summarized in Figure 1<sup>1)</sup>. It is recommended that a neurology specialist should make a definitive clinical diagnosis of epilepsy.

## Comment

In patients presenting with the first unprovoked seizures, EEG recording (including photic stimulation, hyperventilation, and sleep) is recommended<sup>1, 2)</sup>. Sleep-deprived EEG increases the detection rate of epileptic discharges<sup>2)</sup>. Neuroimaging study<sup>1)</sup> and video-EEG monitoring are necessary.

## References

- 1) Krumholz A, Wiebe S, Gronseth G, et al. Practice Parameter: Evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2007; 69(21): 1996-2007.
- 2) van Donselaar CA, Schimsheimer R-J, Geerts A, et al. Value of the electroencephalogram in adult patients with untreated idiopathic first seizures. *Arch Neurol*. 1992; 49(3): 231-237.

## Search formula and secondary reference sources

PubMed search: October 30, 2008

((epileptic seizures) or epilepsy) and diagnosis and (distinguish or differentiate or "Diagnosis, Differential" [Mesh]) and ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) and (meta-analysis [mh] OR meta analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 32

No references that could serve as evidence were found in Ichushi Web.

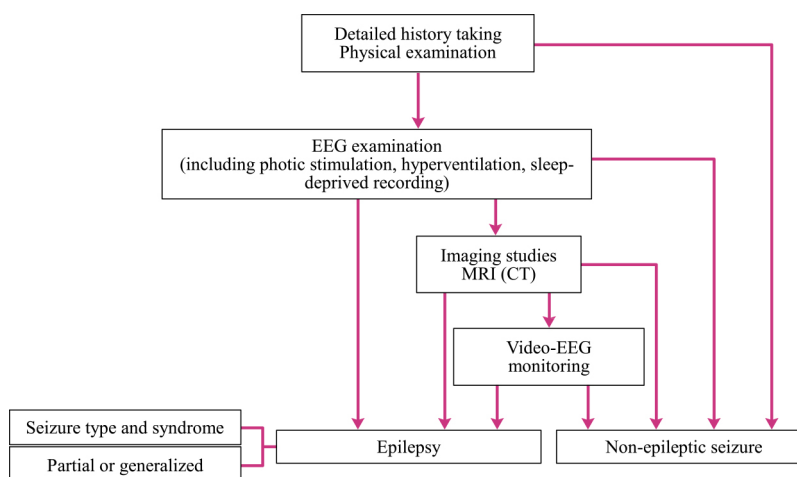
PubMed search: June 28, 2015

(((((epilepsy/diagnosis [majr]) AND diagnosis/methods [majr]) AND ((procedure\* OR protocol\*)))) AND ("2008" [Date-Publication]: "2015" [Date-Publication])) AND (English [Language] OR Japanese [Language]) = 116

Ichushi search: June 25, 2015

(((((epilepsy/MTH)) and (SH = diagnosis))) and (DT = 2008:2015 and PT = review)) and (Japan Epilepsy Society/AL) = 2

**Figure 1. Procedures for the diagnosis of epilepsy.**



# Chapter 2

## Examinations for Clinical Practice of Epilepsy

### CQ 2-1

## How useful is EEG for the diagnosis of epilepsy?

### Summary

Electroencephalography (EEG) is the most useful clinical examination for the diagnosis of epilepsy. In a considerable number of patients, however, epileptic discharges cannot be detected by only a single routine EEG examination, and multiple EEG recordings including sleep or sleep-deprived EEG are required.

### Comment

Diagnosis of epilepsy is conducted in accordance with the International League Against Epilepsy (ILAE) classification of epileptic seizure types (1981) as well as classification of epilepsies, epileptic syndromes and related seizure disorders (1989). Thus, EEG findings are essential in addition to clinical seizure types and neurological symptoms. Regarding the EEG recording methods, it is desirable to follow the guidelines of the Japanese Society of Clinical Neurophysiology <sup>1)</sup>.

However, in a considerable number of patients, seizure discharges cannot be detected by a single routine EEG examination. In a systematic review of 12 articles with evidence levels of classes I and II [as defined by the American Academy of Neurology (AAN)] comprising 1,766 adult patients, approximately 50% of the patients with epilepsy had normal EEG <sup>2)</sup>. Regarding the question of how many EEG examinations are needed to exclude a diagnosis of epilepsy, there is no solid evidence-based answer. However, some reports indicate that the more EEG examinations are repeated, the higher is the epileptic discharges detection rate on EEG <sup>3)</sup>.

In addition, the diagnostic value of sleep EEG is high. In patients in whom no epileptic discharges are detected in awake recordings, epileptic discharges are often detected by sleep EEG <sup>3)</sup>. Especially, it has been reported that during sleep, the epileptic discharges detection rate is higher in children than in adults, and higher for partial epilepsy than for generalized epilepsy.

However, even if epileptic discharges are recorded in EEG, unless the discharges can explain the seizure symptom, this finding alone does not necessarily lead to a diagnosis of epilepsy. Abnormal EEG activity is also seen in some normal persons, and one paper reported that epileptiform discharges were recorded in 0.5% (69/13,658) of normal persons <sup>3)</sup>.

A recent systematic review of 15 articles with a total of 1,799 patients presenting with a first unprovoked seizure analyzed the (1) sensitivity (percentage of patients with epileptiform discharges on routine EEG among those who had repeated seizures during one-year follow-up and hence were diagnosed with epilepsy) and (2) specificity (percentage of patients finally diagnosed with epilepsy among those who were found to have epileptiform discharges on routine EEG) separately in children and adults <sup>4)</sup>. In adults, (1) sensitivity was 17.3% and (2) specificity was 94.7%. In children, (1) sensitivity was 58.7% and (2) specificity was 69.6%.

### ■ References

- 1) Japanese Society of Clinical Neurophysiology, Clinical Electroencephalography Examination Standards Revision Committee. Revised clinical electroencephalography examination standards, 2002. Japanese Journal of Clinical Neurophysiology. 2003; 31(2): 221-242 (in Japanese). <http://jcn.umin.ac.jp/files/guideline/ClinicalEEGtest.pdf> (in Japanese).
- 2) Krumholz A, Wiebe S, Gronseth G, et al. Practice Parameter: Evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007; 69(21): 1996-2007.
- 3) National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004, p.1-397.
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## ■ Search formula and secondary reference sources

PubMed search: November 8, 2008

epilepsy [majr] AND (electroencephalography [majr] OR "brain wave" OR "brain waves") AND classification AND ("sensitivity and specificity" [mh] OR diagnostic errors [mh] OR sensitivity [tiab] OR specificity [tiab] OR predictive value\* OR likelihood ratio\* OR false negative\* OR false positive\* OR controlled clinical trial [pt] OR randomized controlled trial [pt] OR double blind method [mh] OR single blind method [mh] OR practice guideline [pt] OR diagnosis, differential [mh] OR consensus development conference [pt] OR random\* [tiab] OR random allocation [mh] OR single blind\* [tiab] OR double blind\* [tiab] OR triple blind\* [tiab] OR likelihood functions [mh] OR area under curve [mh] OR reproducibility of results [mh] OR meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 150

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 1, 2015

(epilepsy/diagnosis [MeSH Major Topic]) AND Electroencephalography [MeSH] Filters: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 85

No references that could serve as evidence were found in Ichushi Web.



# What is the significance of EEG examination in the treatment of epilepsy?

## Summary

Generally, EEG examination is useful for the evaluation of therapeutic effect and prognosis of epilepsy.

## Comment

Many reports have shown that EEG examination is generally useful for the evaluation of the therapeutic effect and the prognosis of epilepsy. In the treatment of epilepsy patients, it is important to follow the pattern of appearance of epileptic discharges and their frequency over time<sup>1,2)</sup>. In particular, in patients with absence seizure, since the occurrence rate of 3-Hz spike-and-wave complex on EEG reflects the disease severity, it is useful to do follow-up EEG in order to monitor the therapeutic effect<sup>3)</sup>. Also, the type of epilepsy may change, and EEG examination is useful to capture this change<sup>3)</sup>. However, there is a lack of clear evidence on these issues, and epilepsy patients do not always show abnormal findings in EEG examinations. On the other hand, even if epileptiform discharges are detected, if they are interictal abnormalities and the patient is clinically seizure-free, we do not always need to increase the drug dose or add a new antiepileptic drug. Hence, we should interpret EEG findings during the treatment process taking into account the clinical course and other findings. Furthermore, regarding the question of how often EEG examination should be done during epilepsy treatment, there is no solid evidence.

## ■ References

- 1) Fowle AJ, Binnie CD. Uses and abuses of the EEG in epilepsy. *Epilepsia*. 2000; 41(Suppl 3): S10-18.
- 2) Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2007; 69(21): 1996-2007.
- 3) Binnie CD, Stefan H. Modern electroencephalography: its role in epilepsy management. *Clin Neurophysiol*. 1999; 110(10): 1671-1697.

## ■ Search formula and secondary reference sources

PubMed search: October 30, 2008

(epileptic seizures OR epilepsy) AND diagnosis AND "electroencephalography" [MeSH Terms] AND ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) AND (meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 125

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015

((epilepsy [MeSH Major Topic]) AND Electroencephalography [MeSH Major Topic] AND (Monitoring, Physiologic [Mesh] OR monitor\*)) Filters: Guideline; Meta-Analysis; Randomized Controlled Trial; Clinical Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; Japanese; English = 27

No references that could serve as evidence were found in Ichushi Web.



## What is the significance of long-term video-EEG monitoring in clinical practice of epilepsy?

### Summary

**Long-term video-electroencephalography (VEEG) monitoring is a useful examination for making a definitive diagnosis of epilepsy, diagnosis of seizure type, and localization of epileptogenic zone.**

### Comment

Long-term video-electroencephalography (VEEG) monitoring examination simultaneously records video and EEG throughout 24 hours of a day, usually for several days<sup>1)</sup>. The main purpose of this examination is to record “habitual seizures”. While seizures are recorded at a rate of 2.5–7% in routine EEG examinations, reports have shown that seizures are recorded in 70–85% of the patients when VEEG is performed for 3.5–6 days<sup>1, 2)</sup>.

By analyzing the video (seizure symptoms) and EEG (ictal EEG findings), the following can be achieved: (1) differentiation of epileptic seizure from non-epileptic seizure; (2) in the case of epileptic seizure, differentiation of generalized seizure from partial seizure; (3) in the case of focal seizure, localization of epileptogenic zone<sup>3)</sup>. Recordings for long duration sometimes reveal seizures not accompanied by clinical symptoms and interictal abnormalities not usually captured by routine EEG. The results of the VEEG study may greatly advance the diagnosis and treatment strategy or change them considerably. According to previous reports, the diagnosis and therapeutic strategy were altered in 55–60% of the patients who underwent VEEG<sup>1-3)</sup>. Patients suspected of being refractory to drug therapy should undergo VEEG examination in a specialized facility<sup>4)</sup>. VEEG is not only important in localization of the epileptogenic zone for epilepsy surgery, but is also useful for making a definitive diagnosis of epilepsy and defining the disease type.

### ■ References

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### ■ Search formula and secondary reference sources

PubMed search: July 2, 2015

(“epilepsy/diagnosis” [MeSH Major Topic]) AND (“video recording” [MeSH Terms]) OR ((Monitoring, Physiologic [Mesh] OR monitor\*))  
Filters: Clinical Trial; Guideline; Randomized Controlled Trial; Meta-Analysis; Publication date from 2000/01/01 to 2015/12/31; Humans; English; Japanese = 77

No references that could serve as evidence were found in Ichushi Web.

# What are the essential neuroimaging studies for clinical practice of epilepsy?

## Summary

**In the diagnosis of epilepsy, it is necessary to perform magnetic resonance imaging (MRI) or computed tomography (CT). MRI is especially useful in the diagnosis of partial epilepsy.**

## Comment

MRI or CT examination is essential for the diagnosis of epilepsy<sup>1-3</sup>). However, this does not apply to idiopathic generalized epilepsy or idiopathic partial epilepsy, because organic lesions are rarely found in these epilepsies. Although there is no class I and II evidence based on direct comparison between MRI and CT, MRI is considered to have higher diagnostic utility than CT, and is the first choice among several imaging studies<sup>1</sup>). Especially when making a diagnosis of partial epilepsy, MRI is a requisite. However, CT is preferable in the case of emergency, when the patient has a contraindication for MRI, or when a calcified lesion is suspected<sup>4</sup>).

Specifically, the “practical clinical definition of epilepsy” reported by ILAE in 2014 recommends making a diagnosis of epilepsy in patients presenting with a first unprovoked seizure in whom MRI or CT examination shows organic lesions suggesting stroke, central nervous system infection, and traumatic brain injury, even though they have experienced only one seizure episode<sup>2</sup>), because these patients have a high risk of seizure recurrence.

Regarding MRI imaging methods, fluid attenuated inversion recovery (FLAIR) images are useful in addition to the conventional T1-weighted and T2-weighted images. FLAIR images have been reported to enhance the diagnostic sensitivity for epileptogenic lesions such as hippocampal sclerosis and cortical dysplasia. For detecting hippocampal sclerosis, cross-sectional images perpendicular and parallel to the long axis of the hippocampus are needed<sup>5</sup>). Also, 3 Tesla MRI is useful when evaluating the indication for epilepsy surgery<sup>6</sup>). It is reported that 3 Tesla MRI depicts some lesions, such as hippocampal sclerosis, cortical dysplasia, and dysembryoplastic neuroepithelial tumor (DNT), which are not detected by 1.5 Tesla MRI<sup>6</sup>).

## ■ References

- 1) Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: Evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2007; 69(21): 1996-2007.
- 2) Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014; 55(4): 475-482.
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- 5) Morioka T, Nishio T, Mihara F, et al. Efficacy of the fluid attenuated inversion recovery (FLAIR) sequence of MRI as a preoperative diagnosis of hippocampal sclerosis. *Neurol Surg*. 1998; 26(2): 143-150. (in Japanese with English abstract)
- 6) Winston GP, Micallef C, Kendell BE, et al. The value of repeat neuroimaging for epilepsy at a tertiary referral centre: 16 years of experience. *Epilepsy Res*. 2013; 105(3): 349-355.

## ■ Search formula and secondary reference sources

PubMed search: October 30, 2008

((epileptic seizures OR epilepsy) AND (“Magnetic Resonance Imaging” [Mesh] OR “Tomography, X-Ray Computed” [Mesh])) AND (“sensitivity and specificity” [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh] AND meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR “meta analysis” OR multicenter study [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb]) = 126

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015

(“epilepsy/diagnosis” [MeSH Major Topic]) AND (“magnetic resonance imaging” [MeSH Terms] OR “ultrasonography” [MeSH Terms])) Filters: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 48

No references that could serve as evidence were found in Ichushi Web.

## What are the useful functional neuroimaging studies for presurgical evaluation of epilepsy?

### Summary

Nuclear medicine imaging techniques [interictal glucose metabolism fluorodeoxyglucose-positron emission tomography (FDG-PET), cerebral blood flow single photon emission computed tomography (SPECT), and iomazenil SPECT, as well as ictal cerebral blood flow SPECT] and magnetoencephalography (MEG) may be useful as presurgical evaluation tools for partial epilepsy by providing localization of MRI-negative epileptogenic zones.

### Comment

In the presurgical evaluation of surgical indication for patients with partial epilepsy, nuclear medicine neuroimaging studies as well as magnetoencephalography (MEG) are used to localize the epileptogenic zones. Although the usefulness of these modalities in preoperative diagnosis is yet to be established <sup>1)</sup>, they may be useful in localizing MRI-negative epileptogenic zones. Even for MRI-positive lesions (with MRI structural lesions), additional information may be obtained.

Nuclear medicine imaging techniques include positron emission tomography (PET) and single photon emission computed tomography (SPECT). In general, epileptogenic zones exhibit reduced metabolism or blood flow during the interictal period, and increased metabolism or blood flow during the ictal period. The above examinations are conducted to image these changes in an attempt to identify the epileptogenic zone. PET methods include FDG-PET using [<sup>18</sup>F] fluorodeoxyglucose (FDG) to observe glucose metabolism, and SPECT methods include cerebral blood flow SPECT using N-isopropyl-<sup>123</sup>I-p-iodoamphetamine (IMP) or <sup>99m</sup>Tc-ethyl-cysteinate dimer (ECD) to measure cerebral blood flow.

The spatial resolution of FDG-PET is higher than that of SPECT, and the detection power of epileptogenic zone is also higher. Hence, FDG-PET may be useful for the detection of MRI-negative epileptogenic zone <sup>2)</sup>. Especially, coregistering FDG-PET image to MRI enables us to know the accurate distribution of the regions with reduced metabolism. On the other hand, while many reports have indicated that ictal SPECT, which captures the high blood flow region at the time of seizure, is the most powerful method to detect the responsible focus, there is no clear evidence to support it <sup>2)</sup>. Another powerful method is the subtraction ictal SPECT coregistered to MRI (SISCOM). In this method, the regions of statistically increased blood flow obtained by subtracting the interictal SPECT image from the ictal SPECT image are superimposed on MRI. This method is useful for detecting the epileptogenic zone in extra-temporal lobe epilepsy or MRI-negative partial epilepsy <sup>3, 4)</sup>.

Iomazenil SPECT using <sup>123</sup>I-iomazenil depicts the distribution of central benzodiazepine receptors (BZR). Central BZR couples with the GABA<sub>A</sub> receptor (the primary inhibitory neurotransmitters) to form the chloride channel. These inhibitory neurotransmitters are presumably decreased in the epileptogenic zone. Thus, iomazenil SPECT was anticipated to be capable of directly depicting their distribution. However, there is no clear evidence for its usefulness <sup>5)</sup>.

MEG is a neuromagnetic technique that measures the magnetic field generated by electrical activity of neurons. This method estimates the location of electrical source of interictal epileptic discharges. Magnetic source imaging is the technique of superimposing this electrical source on anatomical MRI. This method is a useful tool for noninvasive presurgical evaluation of epilepsy surgery <sup>6)</sup>. When all noninvasive presurgical examinations fail to pinpoint the location of the epileptogenic zone, we should perform invasive EEG recording using subdural electrodes. In that case, magnetic source imaging provides useful information for deciding the sites of electrode placement. Use of magnetic source imaging in presurgical epilepsy evaluation has been found to correlate significantly with postoperative seizure-free outcome <sup>7, 8)</sup>.

## ■ References

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- 6) Lau M, Yam D, Burneo JG. A systemic review on MEG and its use in the presurgical evaluation of localization-related epilepsy. *Epilepsy Res*. 2008; 79(2-3): 97-104.
- 7) Knowlton RC, Razdan SN, Limdi N, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. *Ann Neurol*. 2009; 65(6): 716-723.
- 8) De Tiège X, Carrette E, Legros B, et al. Clinical added value of magnetic source imaging in the presurgical evaluation of refractory focal epilepsy. *J Neurol Neurosurg Psychiatry*. 2012; 83(4): 417-423.

## ■ Search formula and secondary reference sources

PubMed search: October 9, 2008

- #1 ((epilepsy [majr] AND electroencephalography [majr] OR “brain wave” OR “brain waves” AND Magnetoencephalography [majr])) AND (meta-analysis [mh] OR meta-analysis [pt] OR metaanaly\* [tiab] OR “meta analysis” OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review\* OR systematic [sb] OR “sensitivity and specificity” [mh] OR diagnostic errors [mh] OR sensitivity [tiab] OR specificity [tiab] OR predictive value\* OR likelihood ratio\* OR false negative\* OR false positive\* OR controlled clinical trial [pt] OR randomized controlled trial [pt] OR double blind method [mh] OR single blind method [mh] OR practice guideline [pt] OR diagnosis, differential [mh] OR consensus development conference [pt] OR random\* [tiab] OR random allocation [mh] OR single blind\* [tiab] OR double blind\* [tiab] OR triple blind\* [tiab] OR likelihood functions [mh] OR area under curve [mh] OR reproducibility of results [mh]) = 25
- #2 (epilepsy AND FDG-PET) AND (“sensitivity and specificity” [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) = 117
- #3 (epilepsy AND (“tomography, emission-computed, single-photon” [MeSH Terms] OR (“tomography” [All Fields] AND “emission-computed” [All Fields] AND “single-photon” [All Fields]) OR “single-photon emission-computed tomography” [All Fields] OR “spect” [All Fields] OR “SPECT” [All Fields])) AND (“sensitivity and specificity” [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio\* OR practice guideline [pt] OR likelihood functions [mh]) = 153

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015

(“epilepsy/diagnosis” [MeSH Major Topic]) AND (((((Magnetoencephalography [MH]) OR “FDG-PET”) OR (“SPECT” OR “Tomography, Emission-Computed, Single-Photon” [MeSH])))) OR (“PET” OR “Positron-Emission Tomography”)) Filters: Clinical Trial; Meta-Analysis; Randomized Controlled Trial; Guideline; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 26

No references that could serve as evidence were found in Ichushi Web.

# 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<sup>1, 2)</sup>.

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 treatment<sup>3-5)</sup>.

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 seizure<sup>6)</sup>.

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 significant<sup>4)</sup>. 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%)

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## What are the recommended drugs for new-onset partial epilepsy?

### Summary<sup>1-7)</sup>

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.

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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 <sub>A</sub> 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 <sub>A</sub> -mediated inhibition, inhibition of glutamate-mediated excitability	Thrombocytopenia, obesity, alopecia, tremor, diuresis, fibrinogen decrease, liver dysfunction, acute pancreatitis
Phenobarbital	PB	GABA <sub>A</sub> -Cl <sup>-</sup> benzodiazepine receptor, Na/Ca channel inhibition, glutamate receptor blockade	Drowsiness, sedation, restlessness, excitability, hyperactivity, ataxia, rash, liver dysfunction, cytopenia
Clobazam	CLB	Enhancement of GABA <sub>A</sub> -mediated inhibition	Drowsiness, salivation, ataxia, abnormal behavior, airway hypersecretion, rash
Clonazepam	CZP	Enhancement of GABA <sub>A</sub> -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?

### Summary<sup>1-11)</sup>

- (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 ages<sup>9-11)</sup>. During pregnancy, valproate should be avoided when possible, and if valproate is used, a dose of 600 mg per day or lower is preferable.

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## Which antiepileptic drugs should be avoided for generalized epilepsies?

### Summary <sup>1)</sup>

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 <sup>2)</sup>. Phenytoin is recommended not to be used for the treatment of PME, because it induces marked cerebellar ataxia or deteriorates cerebellar ataxia.

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**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 overlooked<sup>1)</sup>. Antiepileptic drugs such as ethosuximide, zonisamide, primidone, high-dose phenytoin, topiramate, and levetiracetam may cause acute psychosis<sup>1,2)</sup>. 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<sup>1, 2)</sup>. Levetiracetam has been reported to increase aggressiveness, and lamotrigine to cause insomnia, anxiety and irritation<sup>2)</sup>.

- The risk of concomitant psychiatric symptoms is high in patients with intractable epilepsy, limbic seizures, and a past history or family history of psychosis<sup>3)</sup>.
- For patients with depressive disorder, phenobarbital, zonisamide, topiramate, or levetiracetam should not be used, and use of lamotrigine may be considered<sup>2)</sup>.
- For patients with bipolar disorder, use of phenytoin, carbamazepine, lamotrigine, or oxcarbazepine may be considered<sup>2)</sup>.
- For patients with anxiety disorder, lamotrigine or levetiracetam should not be used, and use of benzodiazepines or gabapentin may be considered<sup>2)</sup>.
- For patients with psychiatric disorder, phenytoin, ethosuximide, zonisamide, topiramate, or levetiracetam should not be used<sup>2)</sup>.
- 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<sup>1, 4)</sup>.

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- 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).
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((("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.**

	<b>Depressive disorder</b>	<b>Bipolar disorder</b>	<b>Anxiety disorder</b>	<b>Psychiatric disorder</b>
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?

### Summary<sup>1-4)</sup>

- (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 <sup>1)</sup>. A subsequent study reported that there was no difference in seizure control rate between levetiracetam and lamotrigine <sup>2)</sup>.

### ■ References

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## 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)<sup>1-3)</sup>.
- (2) Caution is required regarding the drug interaction effects on blood concentration by induction or inhibition of hepatic metabolizing enzymes (Figure 1)<sup>4)</sup>.

### 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.

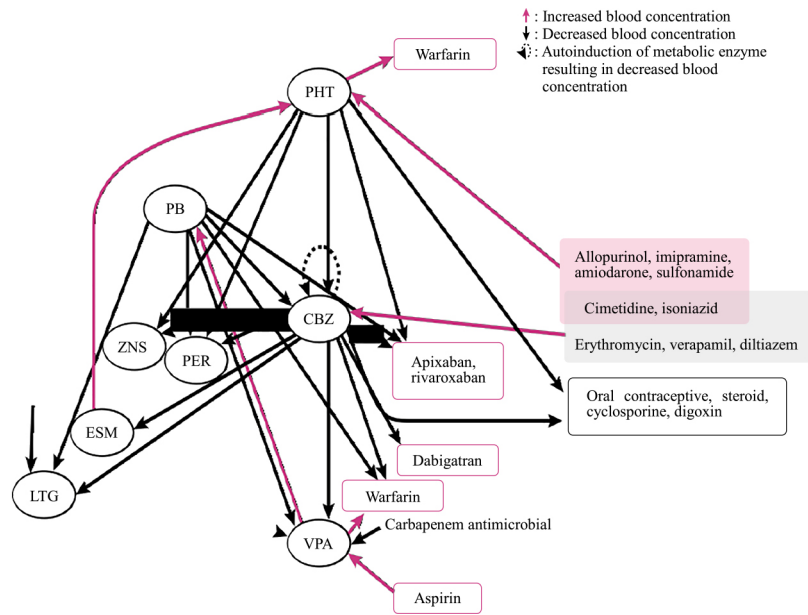
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**Table 1. Drugs that lower the threshold of epileptic seizure.**

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 <sup>1, 2)</sup>.

### 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 <sup>1, 2)</sup>.

### ■ 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)
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# Chapter 4

## Epilepsies in Children and Adolescents and Their Treatment

### CQ 4-1

### Which epilepsy syndromes with childhood or adolescent onset have high prevalence?

#### Summary

According to epidemiological studies, partial epilepsy syndrome constitutes 60–70% of all childhood epilepsies, generalized epilepsy syndrome 20–30%, and undetermined epilepsy around 1–10%. In childhood epilepsies, many epilepsy syndromes have good prognosis, such as childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes. Childhood epilepsy covers the onset age range of one month after birth to around 18 years of age.

#### Comment

In a prospective community-based study, Berg et al.<sup>1)</sup> attempted to classify 613 patients with childhood epilepsy into epilepsies, epilepsy syndromes and related seizure disorders. They found partial epilepsy in 58.6% of the cases, generalized epilepsy in 29.0%, and undetermined epilepsy in 12.4%. Regarding the proportions of epilepsy syndromes, they reported 74 cases (12.1%) of childhood absence epilepsy, 59 cases (9.6%) of benign childhood epilepsy with centrotemporal spikes, 15 cases (2.4%) of juvenile absence epilepsy, 12 cases (2.0%) of juvenile myoclonic epilepsy, 24 cases (3.9%) of West syndrome, 10 cases (1.6%) of Doose syndrome, and 4 cases (0.7%) of Lennox-Gastaut syndrome. In an epidemiological study conducted in Japan, Oka et al.<sup>2)</sup> analyzed 1,337 patients younger than 13 years with strictly defined epilepsies (excluding those with a first unprovoked convulsion or febrile seizure), and classified 907 (75.8%) patients as partial epilepsy, 268 (22.4%) patients as generalized epilepsy, 21 (1.8%) patients as undetermined epilepsy, with the remaining 141 (10.5%) patients as unclassifiable. In addition, Wirrell et al.<sup>3)</sup> studied all 359 patients diagnosed with new-onset childhood epilepsy (0–17 years of age) in Olmsted County, Minnesota in 1980–2004, and classified the epilepsy of each patient based on the 2010 ILAE classification (see Chapter 1, CQ1-3 on page 6). As for the classification of seizure type, focal seizure accounted for 68%, generalized or bilateral seizures 23%, spasms 3%, and undetermined 5%. For the classification of epilepsy syndrome, 105 cases (29.2%) could be classified, and they comprised benign childhood epilepsy with centrotemporal spikes in 26 cases (7.2%), childhood absence epilepsy in 17 cases (4.7%), juvenile absence epilepsy in 11 cases (3.1%), juvenile myoclonic epilepsy in 11 cases (3%), West syndrome in 9 cases (2.5%), Doose syndrome in 2 cases (0.6%), Lennox-Gastaut syndrome in 1 case (0.3%), and mesial temporal lobe epilepsy with hippocampal sclerosis in 8 cases (2.2%).

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## ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

((epilepsy/TH or epilepsy syndrome/AL) and ((epidemiology/TH or epidemiology/AL) or (prevalence/TH or prevalence/AL) or (incidence/TH or incidence/AL) or (classification/TH or classification/AL)))) and (DT = 2008:2015 and (PT = excluding case report) and (PT= excluding proceedings) and CK= neonatal, infancy (1–23 months), early childhood (2–5), childhood (6–12), adolescence (13–18)) = 271

Ichushi search: December 31, 2015

#1 epilepsy/TH or epilepsy syndrome/AL 46,973

#2 epidemiology/TH or epidemiology/AL 249,524

#3 prevalence/TH or prevalence/AL 13,162

#4 incidence/TH or incidence/AL 37,381

#5 classification/TH or classification/AL 126,662

#6 #2 or #3 or #4 or #5 399,286

#7 #1 and #6 2,059

#8 (#7) and (DT = 2008:2015 (PT= excluding case report) AND (PT = excluding proceedings) CK = neonatal, infancy (1–23 months), early childhood (2–5), childhood (6–12), adolescence (13–18)) = 271

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## What examinations are recommended for the first unprovoked seizure in children and adolescents?

### Summary

The examinations are basically the same as those in adults (see also Chapter 2 “Examinations for Clinical Practice of Epilepsy”). They include electroencephalogram (EEG), neuroimaging studies, and routine blood tests. Of these, EEG can detect epileptiform activities at a higher rate than in adults, and it is the most useful examination. MRI is recommended among the neuroimaging modalities.

### Comment

#### 1. EEG

Previous studies reported that epileptiform EEG abnormalities are detected in 18–56% of children after new-onset seizures (compared with 13–35% in adults<sup>1)</sup>). In addition, an epidemiological study including children and adults shows that we rarely detect an epileptiform abnormality after the third negative EEG examination<sup>2)</sup>. The patients with epileptiform discharges have epilepsy approximately two times more frequently than those with normal EEGs<sup>1)</sup>. In a prospective study in children with a first unprovoked seizure conducted by Shinnar et al.<sup>3)</sup>, EEG abnormalities were found in 135 (42%) of 321 children studied. The EEG abnormalities comprised focal spikes in 77 cases, generalized spike-and-wave complexes in 28 cases, slowing in 43 cases, and nonspecific abnormalities in 7 cases. The detection rate was higher in partial seizures than in generalized seizures, higher in children aged 3 years or older than in younger children, and higher in symptomatic epilepsies than in idiopathic epilepsies. In the symptomatic epilepsy group, seizure recurrence was observed in 54% of 103 cases with EEG abnormalities, but in only 25% of 165 cases without any EEG abnormalities. EEG abnormalities, especially epileptiform discharges and localized slow waves, are useful for predicting seizure recurrence. When used in combination with other clinical findings, EEG may play an important role in the diagnosis of epilepsy syndrome even in patients with only a single seizure. For example, when a child with a convulsion attack during sleep for the first time shows spikes in the centrottemporal region, a diagnosis of childhood benign epilepsy with centrottemporal spike is strongly suggested, and the prognosis can be predicted.

#### 2. Neuroimaging examinations

There is no sufficient evidence on whether neuroimaging examination should be performed routinely after the first unprovoked seizure in children. If symptomatic epilepsy is suggested, neuroimaging studies are recommended, especially MRI. Shinnar et al.<sup>4)</sup> performed imaging examinations in 411 children with a first unprovoked seizure, and found brain tumor and neurocysticercosis in two children each. They enrolled the remaining 407 children in a prospective study. Among them, 58 children underwent MRI examination, and abnormalities were found in 19 children (33%), including cortical dysplasia in six children with normal imaging findings at the initial examination. In a prospective study conducted by Tanabe et al.<sup>5)</sup> in Japan, MRI examination was performed in children having a first seizure, and abnormal findings were detected in 10 of 41 children (24.4%), including cortical dysplasia in 4 children. Even with these results, the clinical significance of the lesions shown by imaging studies should be evaluated carefully, especially for their epileptogenicity.

#### 3. Routine blood tests

In children, routine blood tests have clinical significance because the first seizure may also occur under conditions of hypoglycemia or electrolyte abnormalities.

## ■ References

- 1) Wirrell EC. Prognostic significance of interictal epileptiform discharges in newly diagnosed seizure disorders. *J Clin Neurophysiol.* 2010; 27(4): 239-248.
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## ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

((unprovoked) AND ((first AND diagnosis [sh]))) AND ((seizures [mesh] OR seizure)) Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese

#1 seizures [mesh] OR seizure 111,023

#2 first AND diagnosis [sh] 403,484

#3 unprovoked 1,332

#4 #1 AND #2 AND #3 149

#5 #4 AND Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese = 51

Ichushi search: December 31, 2015

(((((epilepsy/TH or epilepsy/AL))) and (SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) and (onset/AL))) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1-23 months), early childhood(2-5), childhood (6-12), adolescence (13-18) and SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) = 15

(((((epilepsy/TH or epilepsy/AL))) and (SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) and (onset/AL))) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1-23 months), early childhood (2-5), childhood (6-12), adolescence (13-18) and SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) and (Japan Epilepsy Society/AL) = 1

## For unprovoked seizures in children and adolescents, is the long-term prognosis worse if treatment would start after the second seizure?

### Summary

**For unprovoked seizures in children and adolescents, the long-term seizure outcome is not affected even if treatment is started after the second seizure, as in the case of adults (see CQ3-1 on page 21).**

### Comment

There have been debates on whether there is any difference in the long-term outcome between patients who start antiepileptic drug therapy promptly after the first epileptic seizure and those who start later. According to a large-scale, prospective, randomized, controlled trial reported from the UK, immediate treatment after onset was superior to delayed treatment in terms of prompt seizure control, but there was no significant difference in the long-term outcome (remission)<sup>1)</sup>. There was also no significant difference in QOL such as employment status. The natural courses of the epilepsies were not affected by the number of epileptic seizures. Apart from controlling seizures, it is an unsolved issue in clinical epileptology of whether antiepileptic drug treatment also changes the natural course of epilepsy. To date, there is no clear evidence that antiepileptic drugs affect the natural course of epilepsy.

On the other hand, there is evidence that even when patients with unprovoked seizures are followed without any treatment, seizures do not recur in one-half of them. Therefore, if treatment is started after the first seizure, one-half of the patients would be treated unnecessarily. Most clinicians start treatment with antiepileptic drugs when seizures are repeated three or four times, but there are only a few studies on the short-term and long-term outcome of this policy.

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### ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

(seizures [mesh] OR seizure) AND (first AND prognosis [MeSH]) AND unprovoked Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years

#1 seizures [mesh] OR seizure 111,023

#2 first AND prognosis [MeSH] 151,190

#3 unprovoked 1,332

#4 #1 AND #2 AND #3 149

#5 #4 AND Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese = 51

Ichushi search: December 31, 2015

((((epilepsy/TH or epilepsy/AL) and (seizure/AL)) and (outcome/TH))) and (DT = 2008:2015 and (PT = excluding case report) and (PT = excluding proceedings) and CK = neonate, infancy (1-23 months), early childhood (2-5), childhood (6-12), adolescence (13-18) and SH = treatment) = 8

((((epilepsy/TH or epilepsy/AL) and (seizure/AL)) and (outcome /TH))) and (DT = 2008:2015 and (PT = excluding case report) and (PT = excluding proceedings) and CK = neonate, infancy (1-23 months), early childhood (2-5), childhood (6-12), adolescence (13-18) and SH = treatment)) and

(Japan Epilepsy Society/AL) = 0

# How to make a diagnosis of juvenile myoclonic epilepsy?

## Summary

**Juvenile myoclonic epilepsy is a disease with major symptoms of myoclonic seizures and generalized tonic-clonic seizures. Medical history, onset age, triggers of seizures, and electroencephalographic findings are important for diagnosis.**

## Comment

Myoclonic seizures are sudden, brief, shock-like muscle jerks affecting muscles of the face, trunk and extremities. The jerks occur in a single muscle or several muscles together<sup>1)</sup>. Usually, no loss of consciousness is associated with the seizures. Although the seizures may occur alone, they may also develop into generalized tonic-clonic seizures. Myoclonic seizures are readily induced by external stimuli, especially by photic stimuli.

Juvenile myoclonic epilepsy (JME) accounts for 26% of idiopathic generalized epilepsy and 5–10% of all epilepsies<sup>2)</sup>. Symptoms suggestive of this epilepsy are (1) childhood to adolescent onset, (2) induced by sleep deprivation and alcohol, (3) tonic-clonic seizure or myoclonic seizure in the early morning, (4) brief absence seizure, (5) photoparoxysmal EEG response with generalized 3-Hz spike-and-wave complexes or polyspike-and-wave complexes<sup>3)</sup>.

## ■ References

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## ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

Myoclonic Epilepsy, Juvenile/diagnosis [majr] Filters: Publication date from 2000/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years

#1 Myoclonic Epilepsy, Juvenile/diagnosis [majr] 119

#2 AND Filters: Publication date from 2000/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years = 57

Ichushi search: December 31, 2015

((epilepsy-myoclonus-juvenile/TH) or (epilepsy-myoclonus-juvenile/AL))) and (PT = excluding proceedings and SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) = 33

((epilepsy-myoclonus-juvenile/TH) or (epilepsy-myoclonus-juvenile/AL))) and (PT = excluding proceedings and SH = diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, nucleotide diagnosis, ultrasound diagnosis) and (Japan Epilepsy Society/AL) = 0

## What are the first-line drugs for childhood- or adolescence-onset epilepsy with undetermined seizure type (partial or generalized)?

### Summary

Valproate, carbamazepine, zonisamide, levetiracetam, and lamotrigine are the candidate drugs, and physicians should select one of them taking into consideration various factors including the antiepileptic spectrum, age, sex, and adverse effect profile. Carbamazepine has been reported to exacerbate generalized seizures other than generalized tonic-clonic seizure. For lamotrigine, physicians should strictly follow the package insert for the dosage and administration, and it therefore takes a long time to up-titrate to the effective dosage. For child-bearing aged women, see Chapter 13 (page 113).

### Comment

When 260 children with newly diagnosed idiopathic generalized epilepsy and partial epilepsy were randomly allocated to treatment with valproate or carbamazepine, the efficacy did not differ significantly between the two drugs<sup>1)</sup>. Valproate was more effective than carbamazepine for generalized seizures (all ages)<sup>2)</sup>. Carbamazepine may exacerbate idiopathic and symptomatic generalized epilepsies manifesting absence and myoclonic seizures<sup>3)</sup>. Zonisamide is effective for partial seizures and secondarily generalized seizures, but physicians should pay attention to some adverse effects including hypohidrosis and impaired cognitive function in children<sup>4)</sup>. Levetiracetam is also effective for partial seizures and secondarily generalized seizures, with only few adverse effects including teratogenicity. Lamotrigine has broad spectrum antiepileptic activities for partial seizures, generalized seizures, and absence seizures, with generally few adverse effects including teratogenicity; but note that the prescribed dosage and administration processes have to be strictly followed.

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### ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

(epilepsy/drug therapy AND carbamazepine/therapeutic use) Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years

#1 epilepsy/drug therapy AND carbamazepine/therapeutic use 2,944

#2 Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years = 207

Ichushi search: December 31, 2015

(epilepsy/TH) or (epilepsy/AL)) and ((“Valproic Acid”/TH) or (Carbamazepine/TH) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1-23 months), early childhood (2-5), childhood (6-12), adolescence (13-18)))) and (SH = therapeutic use, pharmacotherapy) = 296  
(epilepsy/TH) or (epilepsy/AL)) and ((“Valproic Acid”/TH) or (Carbamazepine/TH))) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1-23 months), early childhood (2-5), childhood (6-12), adolescence (13-18)))) and (SH = therapeutic use, pharmacotherapy)) and (Japan Epilepsy Society/AL) = 17

**If seizures recur in those treated with valproate for childhood/adolescent generalized seizure or carbamazepine for childhood/adolescent partial seizures, even when their drug concentrations are in the therapeutic ranges, which drugs should be the next candidates?**

### Summary

#### 1. In the case of recurrence when valproate is used for generalized seizures

##### a. Generalized tonic-clonic seizure (GTCS)

Select lamotrigine, carbamazepine, oxcarbazepine<sup>†</sup>, clobazam, levetiracetam, or topiramate<sup>†</sup>, considering their adverse effect profiles. However, when absence seizures and myoclonic seizures coexist, we should consider the fact that carbamazepine and oxcarbazepine<sup>†</sup> have a risk of aggravating these seizures.

##### b. Absence seizures

Ethosuximide is recommended. If ethosuximide cannot be used, lamotrigine is recommended, although it is considered less effective than ethosuximide.

##### c. Myoclonic seizure

For juvenile myoclonic epilepsy, levetiracetam<sup>†</sup>, lamotrigine and topiramate<sup>†</sup> are recommended. For myoclonic seizure complicating other epilepsies, clonazepam and clobazam are selected although the evidence is low.

#### 2. In the case of recurrence when carbamazepine is used for partial seizures

Select zonisamide, lamotrigine, levetiracetam, clobazam, topiramate, valproate, or gabapentin, considering their adverse effect profiles.

### Comment

- 1) There was no significant difference in effectiveness between valproate and carbamazepine in children with new-onset generalized tonic-clonic seizures or partial seizures<sup>1)</sup>. In children with new-onset generalized tonic-clonic seizures and partial seizures, there were also no significant differences in efficacy among phenobarbital, phenytoin, carbamazepine, and valproate<sup>2)</sup>. In adults and children with generalized epilepsy or unclassified epilepsy randomly allocated to treatment with valproate, lamotrigine or topiramate, valproate was the best in both tolerability and efficacy. As the initial treatment for generalized tonic-clonic seizures, NICE guideline 2012 recommends valproate followed by lamotrigine, and then carbamazepine and oxcarbazepine<sup>†</sup>, or adjunctive therapy using clobazam, levetiracetam or topiramate<sup>† 3)</sup>.
- 2) In randomized controlled trials comparing valproate, ethosuximide, and lamotrigine for childhood absence epilepsy, valproate and ethosuximide were superior in efficacy to lamotrigine, but there was no difference between the two former drugs<sup>4, 5)</sup>. However, since ethosuximide has less adverse effects compared to valproate, ethosuximide is recommended as the first-line drug for childhood absence epilepsy.
- 3) In a study comparing valproate and lamotrigine for juvenile myoclonic epilepsy, no significant difference in seizure control rate was observed between the two drugs, while the rate of discontinuation due to adverse effects was lower with lamotrigine<sup>6)</sup>. In an randomized controlled trial (RCT) for idiopathic generalized epilepsy with myoclonic seizures, levetiracetam reduced myoclonic seizures at a significantly higher rate compared to placebo<sup>7)</sup>. In addition, expert consensus studies recommended the following drugs for myoclonic seizure, in the order of: valproate, clonazepam, and clobazam in one paper, and valproate and lamotrigine in another paper<sup>8, 9)</sup>. Based on all these studies, valproate followed by levetiracetam, lamotrigine, clonazepam, and clobazam are recommended. However, it should be noted that lamotrigine has a risk of deteriorating myoclonic seizures in patients with Dravet syndrome (severe myoclonic epilepsy in infancy) and in some patients with juvenile myoclonic epilepsy.



- 4) In children aged 2–16 years with partial epilepsy and in some children with generalized epilepsy, there was no significant difference in efficacy among clobazam, carbamazepine and phenytoin when used as monotherapy<sup>10</sup>. However, in Japan, clobazam is currently not approved for monotherapy.
  - 5) Lamotrigine and carbamazepine were equivalent in efficacy for partial seizures with or without generalized tonic-clonic seizures<sup>11</sup>. When the effects and efficacy of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate were compared in 1,721 adults and children with partial epilepsy, lamotrigine was more useful than carbamazepine, gabapentin or topiramate in terms of lower discontinuation rate and fewer adverse effects, and was not significantly different from oxcarbazepine.
  - 6) NICE guideline 2012 recommends adjunctive use of clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate or topiramate<sup>12</sup>.
- \*For the use of perampanel in patients aged 12 years and above, and lacosamide in patients aged 16 years and above, see Chapter 3 “Drug Therapy for Adult Epilepsy”.

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## ■ Search formula and secondary reference sources

PubMed search: December 31, 2015

(epilepsy/drug therapy AND carbamazepine/therapeutic use) Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years

#1 epilepsy/drug therapy AND carbamazepine/therapeutic use 2,944

#2 Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese; Child: birth-18 years = 207

Ichushi search: December 31, 2015

((epilepsy/TH) or (epilepsy/AL)) and ((“Valproic Acid”/TH) or (Carbamazepine/TH)) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1–23 months), early childhood (2–5), childhood (6–12), adolescence (13–18))) and (SH = therapeutic use, pharmacotherapy) = 296  
 (((epilepsy/TH) or (epilepsy/AL)) and ((“Valproic Acid”/TH) or (Carbamazepine/TH))) and (DT = 2008:2015 and PT = excluding proceedings and CK = infancy (1–23 months), early childhood (2–5), childhood (6–12), adolescence (13–18))) and (SH = therapeutic use, pharmacotherapy) and (Japan Epilepsy Society/AL) = 17

**Table 1. Drug options by seizure type in revised NICE guideline (2012).**

Seizure type	First-line drugs	Adjunctive drugs	Other drugs that may be considered	Do not offer drugs
Generalized tonic–clonic seizure	oxcarbazepine <sup>†</sup> carbamazepine valproate lamotrigine	clobazam topiramate <sup>†</sup> valproate lamotrigine levetiracetam		oxcarbazepine <sup>†a</sup> carbamazepine <sup>a</sup> gabapentin <sup>†a</sup> vigabatrin <sup>†a</sup> phenytoin <sup>a</sup>
Tonic seizure or atonic seizure	valproate	lamotrigine	topiramate <sup>†</sup> rufinamide	oxcarbazepine <sup>†</sup> carbamazepine gabapentin <sup>†</sup> vigabatrin <sup>†</sup>
Absence seizure	ethosuximide valproate lamotrigine	ethosuximide valproate lamotrigine	clobazam clonazepam <sup>†</sup> zonisamide topiramate <sup>†</sup> levetiracetam <sup>†</sup>	oxcarbazepine <sup>†</sup> carbamazepine gabapentin <sup>†</sup> phenytoin vigabatrin <sup>†</sup>
Myoclonic seizure	topiramate <sup>†</sup> valproate levetiracetam <sup>†</sup>	topiramate <sup>†</sup> valproate levetiracetam <sup>†</sup>	clobazam clonazepam zonisamide piracetam	oxcarbazepine <sup>†</sup> carbamazepine gabapentin <sup>†</sup> phenytoin vigabatrin <sup>†</sup>
Partial seizure (including secondarily generalized)	oxcarbazepine <sup>†</sup> carbamazepine valproate lamotrigine levetiracetam	oxcarbazepine carbamazepine gabapentin clobazam topiramate valproate lamotrigine levetiracetam	zonisamide vigabatrin <sup>†</sup> phenobarbital phenytoin lacosamide	

<sup>a</sup>: in the case of complication by absence seizure or myoclonic seizure, in the case of juvenile myoclonic epilepsy

<sup>†</sup>: not covered by medical insurance in Japan (as of December 6, 2017)

(Modified from NICE guideline 2012)

**Table 2. Drug options by epileptic syndrome in revised NICE guideline (2012).**

Epilepsy syndrome	First-line drugs	Adjunctive drugs	Other drugs that may be considered	Do not offer drugs
<b>Idiopathic epilepsy</b>				
Childhood absence epilepsy Juvenile absence epilepsy	ethosuximide valproate lamotrigine	ethosuximide valproate lamotrigine	clonazepam clobazam† zonisamide topiramate† levetiracetam†	oxcarbazepine† carbamazepine gabapentin† vigabatrin† phenytoin
Juvenile myoclonic epilepsy	topiramate† valproate lamotrigine levetiracetam	topiramate† valproate lamotrigine levetiracetam	clonazepam clobazam zonisamide	oxcarbazepine† carbamazepine gabapentin† vigabatrin† phenytoin
Epilepsy with generalized tonic–clonic seizures alone (grand mal epilepsy on awakening)	oxcarbazepine† carbamazepine valproate lamotrigine	clobazam topiramate† valproate lamotrigine levetiracetam		
Idiopathic generalized epilepsy	topiramate† valproate lamotrigine	topiramate† valproate lamotrigine levetiracetam	clonazepam clobazam zonisamide	oxcarbazepine† carbamazepine gabapentin vigabatrin phenytoin
Benign epilepsy with centrotemporal spikes Panayiotopoulos syndrome Late-onset childhood occipital epilepsy (Gastaut type)	oxcarbazepine† carbamazepine valproate lamotrigine levetiracetam	oxcarbazepine carbamazepine gabapentin clobazam topiramate valproate lamotrigine levetiracetam	zonisamide vigabatrin† phenobarbital phenytoin lacosamide	
<b>Epileptic encephalopathy</b>				
Infantile spasm (West syndrome) not due to tuberous sclerosis	Discuss with or refer to specialist facility			
Infantile spasm (West syndrome) due to tuberous sclerosis	ACTH steroid vigabatrin			
Dravet syndrome (severe myoclonic epilepsy in infancy)	Discuss with or refer to specialist facility  topiramate valproate	clobazam stiripentol		oxcarbazepine† gabapentin carbamazepine vigabatrin phenytoin lamotrigine
Epilepsy with continuous spike and wave during slow sleep	Discuss with or refer to specialist facility			
Lennox–Gastaut syndrome	Discuss with or refer to specialist facility  valproate	lamotrigine	topiramate rufinamide	oxcarbazepine† gabapentin carbamazepine vigabatrin†
Landau–Kleffner syndrome	Discuss with or refer to specialist facility			
Myoclonic-astatic epilepsy	Discuss with or refer to specialist facility			

Only those drugs that are available for use in Japan

†: not covered by medical insurance in Japan (as of December 6, 2017)

(Modified from NICE guideline 2012)

# Chapter 5

## Drug-Resistant Epilepsy

### CQ 5-1

## What is the definition of drug-resistant epilepsy?

### Summary

Clinically, drug-resistant epilepsy is defined as the epilepsy which cannot be controlled for a certain period (at least 1 year or 3 times the longest interval between seizures) by using two appropriately selected antiepileptic drugs (whether as monotherapy or combination therapy), with sufficiently high blood concentrations but without adverse events.

### Comment

Since not all the epilepsies that cannot be controlled by antiepileptic drugs are intractable epilepsies (only some are intractable), “intractable epilepsy” that was used in the previous edition is replaced by “drug-resistant epilepsy” in the 2018 edition. Some subtle seizures that do not impede daily life and recur several times a year are drug resistant, but not intractable. Even when antiepileptic drugs fail to control seizures, if the seizure frequency is 1–2 times a year, the patient is not indicated for surgery. However, if seizure frequency is 1–2 times a month, the patient has an intractable epilepsy in whom surgical treatment should be considered.

The definition of drug-resistant epilepsy depends on the use situation and we have no universal definition. The ILAE proposed the above definition so that it can be applied to various situations<sup>1)</sup>. This definition is intended not only for clinical settings but also for purposes such as designing clinical trials, clinical research, and facilitating referral of the patients to specialized facilities. Referral to specialized facilities is recommended if seizures are not controlled by two appropriately selected drugs at adequately high doses.

The evidence for two drug regimens was provided by a study of 1,098 adolescent or adult patients with untreated epilepsy. The seizure-free rate was 50% after the first drug regimen, 13% after the second regimen of monotherapy or combination therapy, but only 5% after the third to ninth regimen of monotherapy or combination therapy. Since there is very low possibility of achieving seizure-free status by continued drug therapy after failure of 2 regimens of antiepileptic drugs as monotherapy or combination therapy, epilepsy uncontrollable by 2 appropriate drugs as monotherapy or combination therapy can be regarded as drug resistant<sup>2)</sup>.

The evidence of at least one year is based on community-based studies showing that one or more seizures in the past two years have various impact such as psychological symptoms or disadvantages in daily life. In addition, being seizure-free for at least one year is a requirement for acquiring a driver's license in many countries. However, in a long-term follow-up (2–22 years, median 6.1 years) study of 780 adolescent-adult patients with untreated epilepsies, out of 462 patients whose seizures were controlled for more than 1 year at the time of the final observation, 74% had seizures controlled within one year, and 11% within two years after the treatment started. In another definition, drug resistance was defined as seizures persisting after at least two years of treatment, in addition to control failure with two drugs. This is because the possibility of drug resistance is high if seizures are not controlled after two years of treatment<sup>3)</sup>.

However, these definitions do not always apply to children, and there are many pediatric patients in whom seizures are well controlled by three or more drug regimens. In a cohort of 613 children with epilepsy prospectively followed for 13 years at the longest (median 9.7 years), 128 children who did not respond favorably to two drugs were treated with the third or more drugs (median 3 drugs). After treatment for 1–14 (median 10.1) years, seizures were controlled for at least 1 year during this period in 57% of the patients, and seizures were controlled for more than 1 year at the final observation in 38%<sup>4)</sup>. Therefore, for children, drug resistance must not be defined only by seizures not controlled by two drug regimens, or not controlled after 1–2 years of treatment.

According to the guideline of the Japan Epilepsy Society for the purpose of considering surgical indication, the criterion

of drug-resistant epilepsy is seizures not controlled after more than 2 years of treatment even with 2–3 kinds of appropriate drugs<sup>5)</sup>.

It should be noted that there are many patients with pseudo-drug-resistant epilepsy due to misdiagnosis (see CQ5-3 on page 47).

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((((refractory/AL and (epilepsy/TH or epilepsy/AL)) and (definition/AL or classification/TH or classification/AL)))) and (DT = 2008:2015 and PT = excluding proceedings) = 27

No references that could serve as evidence were found in Ichushi Web.

# What are the true drug-resistant epilepsies in adults?

## Summary

Drug-resistant epilepsies in adults include symptomatic partial epilepsies with intracranial lesions (including cerebrovascular disorder, cerebral dysplasia, brain tumor, hippocampal sclerosis, encephalitis or encephalopathy, and systemic diseases) on MRI and other imaging studies; cryptogenic partial epilepsies including temporal lobe epilepsy; symptomatic generalized epilepsies with degenerative disorders such as dentatorubral pallidoluysian atrophy (DRPLA) or metabolic disorders; various childhood onset epilepsies uncontrolled even in adulthood such as Lennox-Gastaut syndrome; and epilepsies associated with autoimmune encephalitis.

## Comment

In one study, out of a total of 2,200 outpatients (partial epilepsy 1,369 cases, generalized epilepsy 473 cases, and undetermined epilepsy 358 cases) aged 16 years and above, 1,696 patients were treated and followed for 1–7 years. Among them, 45% were seizure-free for one year or longer. By epilepsy classification, the seizure-free rate was 27% in symptomatic (with a definitive cause of epilepsy) or cryptogenic (cause of epilepsy suspected but not definite) generalized epilepsy, 82% in idiopathic generalized epilepsy, 35% in symptomatic partial epilepsy, 45% in cryptogenic partial epilepsy, and 11% in partial epilepsy with hippocampal sclerosis. Among the partial epilepsies, seizure-free rate was 20% in temporal lobe epilepsy and 36% in non-temporal lobe epilepsy. For temporal lobe epilepsy, the seizure-free rate was 10% when accompanied by hippocampal sclerosis, and was 31% when not accompanied by hippocampal sclerosis. There was no difference in the seizure-free rate between temporal lobe epilepsy without hippocampal sclerosis and non-temporal lobe epilepsy. The seizure-free rate was markedly low in hippocampal sclerosis, dual pathology (hippocampal sclerosis + other lesions), and cerebral dysgenesis (11%, 3% and 24%, respectively)<sup>1</sup>.

In a prospective study of 550 adolescent and adult patients with partial epilepsy treated with antiepileptic drugs, 312 (57%) patients were seizure-free for at least 1 year at the last follow-up. The seizure-free rate was 42% in patients with mesial temporal sclerosis, 78% with cerebral arteriovenous malformation, 67% with cerebral infarction, 63% with brain tumor, 57% with gliosis, 55% with cerebral atrophy, and 54% with cortical dysplasia. Patients with mesial temporal sclerosis were the most intractable. There was no difference in seizure-free rate between patients with symptomatic partial epilepsy and those with cryptogenic partial epilepsy<sup>2</sup>. In patients with Lennox-Gastaut syndrome (mean age 28.6 years) observed for an average of 16 years, seizures were controlled in only 5% of the patients<sup>3</sup>.

Among 780 adolescent and adult patients newly diagnosed with epilepsy and followed long-term after treatment initiation (2–22 years, median 6.1 years), 318 (41%) patients did not achieve seizure control at least for the last 12 months of follow-up. These patients frequently had (1) symptomatic or cryptogenic epilepsy; (2) more than 10 seizures before treatment initiation; (3) a family history of epilepsy, previous febrile convulsion, and traumatic brain injury; (4) nonadherence or irregular use of antiepileptic drugs; and (5) prior or current psychiatric comorbidity (especially depression)<sup>4</sup>. The presence of these factors may predict a high possibility of drug-resistant epilepsy.

Some autoimmune encephalitis-related epilepsies such as autoimmune limbic encephalitis and anti-NMDA receptor encephalitis are highly drug-resistant and require immunotherapy<sup>5</sup>. Furthermore, although not an epilepsy, psychogenic nonepileptic seizure is also highly drug resistant and is difficult to diagnose and treat.

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## What are the drug-resistant epilepsies in children?

### Summary

Drug-resistant epilepsies in children include epileptic encephalopathies with infant and early childhood onset, such as West syndrome; cerebral dysplasia; chromosomal abnormalities such as 4p minus syndrome; neurocutaneous syndromes including tuberous sclerosis; post-encephalitis/encephalopathy; post-hypoxic ischemic encephalopathies such as severe neonatal asphyxia; epilepsy associated with cerebral degenerative/metabolic disorders; and autoimmune encephalitis-related epilepsy.

### Comment

#### 1. Causes of drug resistance

In one 2-year follow-up study of 381 children with newly diagnosed epilepsy, 75 patients (19.7%) were found to have drug-resistant epilepsy. Neuroimaging abnormalities, some abnormalities found in clinical neurological examination, and focal seizures were associated with drug resistance. Despite treatment of these patients with appropriate drugs for an average of 11.7 years, 49% remained drug resistant, and the resistance was mostly associated with neuroimaging abnormalities<sup>1)</sup>. In another study, among 459 patients with childhood epilepsy treated for 2–14 years (mean 7.5 years), 87 patients (19%) were drug resistant. The factors associated with the drug resistance were age younger than 4 years, developmental delay or motor deficit, brain structural abnormality, and specific epileptic syndromes<sup>2)</sup>.

#### 2. Relation of drug resistance with epilepsy syndromes or underlying diseases<sup>3)</sup>

In children, there are drug-resistant epilepsies specific to age of onset<sup>4, 5)</sup>. Infantile epileptic encephalopathies (including early-stage myoclonic encephalopathy, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, West syndrome, and Dravet syndrome) and early childhood onset epileptic encephalopathies (Lennox-Gastaut syndrome, myoclonic encephalopathy in non-progressive diseases, and myoclonic absence seizure) are extremely drug resistant. In these epilepsies, seizure control is almost impossible except for West syndrome, in which seizures could be controlled in approximately 50% of the cases.

As in adults, seizures caused by localized cortical dysplasia in children are drug resistant, but some childhood-specific epilepsies such as epilepsies associated with unilateral megalencephaly, lissencephaly, and holoprosencephaly are markedly severe and seizures cannot be controlled by antiepileptic drugs.

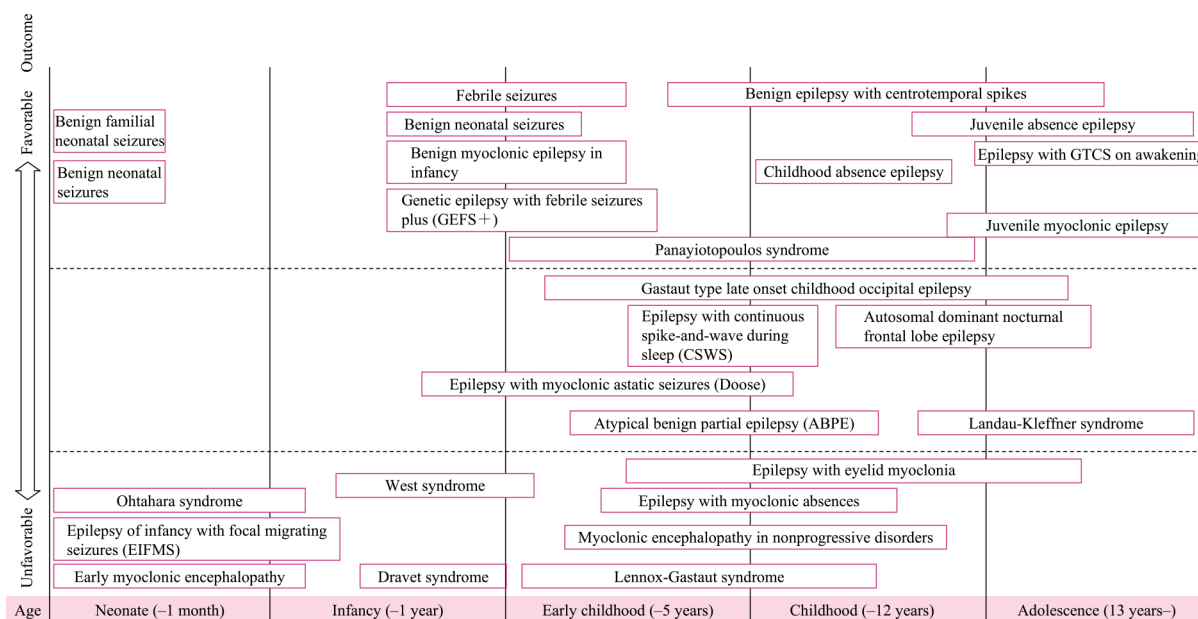
Among chromosomal abnormalities, seizures associated with ring chromosome 20 syndrome are intractable, and seizures associated with 4p minus syndrome (Wolf-Hirschhorn syndrome) are also highly drug resistant.

Among neurocutaneous syndromes, seizures associated with Sturge-Weber syndrome and linear nevus syndrome are not controlled by drugs. Tuberous sclerosis is accompanied by epileptic seizures at a very high rate (approximately 85%), and most cases are West syndrome. West syndrome caused by tuberous sclerosis responds well to vigabatrin, but rarely responds to other antiepileptic drugs.

Epileptic seizures associated with destructive lesions in the brain caused by hypoxic ischemic encephalopathies such as encephalitis/encephalopathy, meningitis, and severe neonate asphyxia; as well as seizures associated with neurodegenerations in the brain such as metabolic neurological diseases and neurodegenerative diseases (including DRPLA, Krabbe disease, neuronal ceroid lipofuscinosis, and GLUT-1 deficiency) are drug resistant, and seizures related to autoimmune encephalitis are also drug resistant in children.

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**Figure 1. Ages of children and specific epilepsy syndromes.**

(Modified from: Bureau M, Genton P, Dravet C, et al. eds. *Epileptic syndromes in infancy, childhood and adolescence*. Montrouge: John Libbey Eurotext, 2012./ Duchowny M, Cross JH, Arzimanoglou A eds. *Pediatric Epilepsy*. New York, McGraw Hill, 2013.)



## What is pseudo-drug-resistant epilepsy?

### Summary

Pseudo-drug-resistant epilepsy arises when appropriate antiepileptic drugs are not used at adequate doses, which may be due to misdiagnosis of the epilepsy or seizure type, wrong choice of antiepileptic drugs, wrong dosage, or poor adherence.

### Comment

When epilepsy is found to be drug resistant, it may be truly drug resistant; that is, not responding to appropriately selected antiepileptic drugs at adequate doses, or it may be pseudo-resistant because appropriate drugs are not used at appropriate doses.

#### 1. In the case of inappropriate choice of drugs

(1) The most common cause is misdiagnosis of non-epileptic seizures as epilepsy, such as psychogenic non-epileptic seizures (PNES), syncope, and arrhythmia. (2) Inappropriate drugs are selected due to wrong diagnosis of epilepsy syndrome or seizure type. (3) The antiepileptic drugs are inappropriate for the correct diagnosis of seizure type or epilepsy syndrome, such as using carbamazepine for myoclonic seizure leading to exacerbation<sup>1)</sup>.

In one study in which 1,590 patients underwent simultaneous EEG-video monitoring, 32.3% were found to have psychogenic seizures<sup>2)</sup>. In another study, 46 (25%) of 184 patients treated for epilepsy did not have epilepsy, and 12 (13%) of 94 patients who were regarded as having intractable epilepsy did not have epilepsy<sup>3)</sup>.

#### 2. In the case of drug resistance despite using appropriate drugs

The cause may be due to pharmacokinetics, such as (1) the blood concentration may be low because the dose is inadequate, or may not be much enough because not titrating the dose to the maximum tolerable level paying too much attention to the therapeutic range of blood concentration; (2) inappropriate multidrug therapy including a combination of drugs showing interactions (see **Table 1** of CQ 12-4 on page 109) that lower the blood concentration; and (3) occurrence of drug tolerance (including benzodiazepines and acetazolamide).

#### 3. In the case of drug resistance despite prescription of appropriate antiepileptic drugs at adequate doses

The causes may include (1) poor adherence due to a lack of understanding and motivation of epilepsy treatment by the patient or the family, or excessive anxiety over antiepileptic drugs; (2) induction of seizures by alcohol or drug abuse, and poor adherence; (3) inappropriate time of drug taking or irregular time of drug taking due to irregular life rhythm such as night shift; and (4) lifestyle problem such as shift work causing disturbed circadian rhythm, sleep deprivation, and fatigue<sup>1)</sup>.

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## How to manage drug-resistant epilepsies?

### Summary

The first step to manage drug-resistant epilepsy is finding the cause. After reviewing the seizure symptoms, epilepsy diagnosis and etiology of epilepsy, assess whether the case is truly drug resistant or pseudo-resistant. In the case of pseudo-resistance, remove the causative factors (see CQ 5-4 on page 50). In the case of true resistance, review the drug therapy (diagnosis, choice of drugs, dose, use of antiepileptic drugs based on pharmacokinetics, rational use of multidrug combinations, etc.) and consider other treatment options such as surgery and immunotherapy.

### Comment

#### 1. Are the choices of drug and dose appropriate?

Confirm the seizure symptoms, medical history, situations when seizures occur, interictal EEG (sleep EEG essential), and brain MRI. Examine the underlying disease (family history, past history, present illness, general physical findings, and neurological findings). Based on the above, determine whether the case is truly epilepsy or not, and diagnose the seizure type and epilepsy syndrome, and investigate the etiology of epilepsy. Next, examine the type of antiepileptic drug and dose, and blood concentration. Interview, gesture mimicking seizure symptoms, and video recording by family members are useful to confirm seizure symptoms.

#### 2. Identification of pseudo-drug resistance and management

##### a. Differentiation between epilepsy and confounding seizure symptoms (see CQ1-4 on page 10, and CQ1-5 on page 11)

Confirmation of seizure symptoms (from home video if possible), interview (especially the situation of seizure occurrence), interictal sleep EEG, and video-EEG monitoring are useful.

##### b. Review diagnosis of epilepsy, epilepsy syndrome and related seizure disorders, as well as seizure type

The procedures are similar to those described above (a). Juvenile myoclonic epilepsy is sometimes misdiagnosed as partial epilepsy and treated with carbamazepine or phenytoin, which may exacerbate the seizures<sup>1)</sup>.

##### c. Review the choice of drug and the dose

Examine whether the drug is appropriate for the epilepsy syndrome and seizure type (see **Table 1** in CQ4-6 on page 42 and **Table 1** in Chapter 6 on page 54), whether the drug is used sufficiently (dose and blood concentration), and whether tolerance occurs. In the case of multidrug therapy, examine whether each drug is appropriate for the seizure type, whether there is drug interaction that lowers blood concentration, and whether drugs with the same mechanism of action are used in combination.

From the above information, switch to the appropriate drug, up-titrate until the maximum tolerated dose with blood concentration exceeding the therapeutic range, and confirm the effect. Conduct rational multidrug therapy by selecting drugs appropriate for each seizure type, increase or decrease the doses considering drug interactions, and use drugs with different mechanisms of action in the combination.

##### d. When poor adherence is suspected

Confirm the situation of drug taking (time of drug taking, missed doses), lifestyle and rhythm, as well as time and situation at which seizures often occur. Monitoring blood concentration is useful for detecting habitual poor adherence.

To prevent lowered adherence, explain to the patient and the family about the following: (1) the nature of epilepsy from the viewpoint of epilepsy syndrome and the prognosis, (2) the necessity of treatment, (3) caution in daily life, and (4) properties of the drugs being taken (half-life, interaction with other drugs or foods, possible adverse effects and their frequency and severity). Also, adjust the time of drug taking considering the patient's lifestyle such as night shift.

### 3. True drug-resistant epilepsy

- (1) If MRI detects an intracranial lesion, evaluate for epilepsy surgery soon.
- (2) Select first-line or second-line drug that is deemed appropriate, and increase the dose up to the maximum tolerated dose. As long as adverse effects are not induced, up-titrate to blood concentrations exceeding the therapeutic range. When adverse effect appears, reduce the dose.

Despite the above procedures, if seizures remain uncontrolled, conduct rational multidrug therapy considering interactions of antiepileptic drugs (see **Table 1** of CQ12-4 on page 109) and the mechanisms of action. Add a drug that has different mechanism of action from the drug currently being used or a drug with multiple mechanisms of actions<sup>2)</sup>. An effective combination is to use a Na<sup>+</sup> channel blocker and a GABAergic inhibition enhancer. Although the therapeutic effect is increased by combining two drugs that both enhance GABAergic inhibition, or combining two glutamate receptor inhibitors (such as AMPA antagonist and NMDA antagonist), tolerability is often reduced. Combination of two Na<sup>+</sup> channel blockers not only has limited effectiveness, but also causes adverse effects such as exacerbating dizziness<sup>3)</sup>.

- (3) Consider referral to or consultation with epilepsy specialists, measurement of autoimmune antibodies, and immunotherapies (including intravenous immunoglobulin, steroids, and immunosuppressants), and consider surgical indication even though MRI shows no intracranial lesions.

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((intractable [TIAB] OR refractory [TIAB]) AND “Epilepsy/therapy” [majr]) AND “treatment outcome” [mh] Filters: Review; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 112

## What are the intellectual prognosis and social prognosis of drug-resistant epilepsy?

### Summary

Both intellectual and social prognoses are poorer than people without epilepsy, and there are major disadvantages in academic, employment, and marriage aspects. These two outcomes are especially poor when seizures are not controlled. The rate of sudden death is also higher among people with epilepsy than the general population.

### Comment

#### 1. Socioeconomic situation

For people with drug-resistant epilepsy, even when they have no intellectual problems and are in general employment, their work contents are sometimes restricted. In addition, if seizure occurs at work, they often lose their jobs. They also often have difficulty in marriage. In the United States, the total household annual income of people with epilepsy is 93% of the average annual income of the whole population, their unemployment rate is 25%, the high school graduation rate of those aged 25 years and above is 64% (82% in the United States in general), and the marriage rate of those aged 19 years and above is 51% for men and 48% for women (63% and 59%, respectively, in the United States in general)<sup>1)</sup>. This data is for all epilepsies including treatable epilepsies, and these figures would be even worse in people with drug-resistant epilepsy.

#### 2. Intellectual prognosis

In a study of 136 adults with various epilepsies who had uncontrolled seizures, WAIS-R was performed twice with an interval of 10 years or longer. The mean verbal IQ decreased from 90.3 to 82.3, performance IQ decreased from 91.0 to 84.5, and full scale IQ decreased from 91.0 to 84.5, and the frequency of generalized tonic-clonic seizure was most strongly related to the cognitive decline<sup>2)</sup>.

#### 3. Social prognosis

Among 102 patients (mean age 28.6, range 15–60 years) with Lennox-Gastaut syndrome followed long-term for 10–20 (mean 16.3) years, 12 patients worked normally, 36 worked part-time or at a sheltered workshop, and the remaining 54 were under home care or institutionalization<sup>3)</sup>. Most of the 12 patients in normal employment were seizure-free for at least 1 year or had only tonic seizures during sleep.

Ninety-nine patients with uncomplicated childhood epilepsy (onset age younger than 16 years) followed for 27–31 years were compared with controls matched for sex, age, and birthplace. The relative risk of completing primary education only was 2.1-fold, not married was 3.5-fold, no children was 3.0-fold, and unemployed was 3.8-fold<sup>4)</sup>.

#### 4. Sudden unexpected death in epilepsy (SUDEP)

SUDEP refers to death for which no cause can be found besides suffering from epilepsy.

Patients with epilepsy have high mortality rate and high SUDEP rate. The standardized mortality rate for SUDEP was 24-fold compared to the general population, accounting for 2–17% of all-cause deaths in epilepsy patients<sup>5)</sup>.

The mortality rate of 2,689 patients with chronic epilepsy who had been followed for 20 years was 2.05 times the mortality rate of the general population in Scotland matched for sex and age<sup>6)</sup>. The incidence of SUDEP per 1,000 person-years was 0.35–1.5 cases in a population-based incidence cohort of epilepsy, but increased to 1.2–3.8 cases in persons with chronic epilepsy and further to 3.5–9.3 cases in persons with intractable epilepsy. Seizure frequency is the strongest risk factor for SUDEP, and other risk factors are onset at an early age and long duration of disease<sup>7)</sup>. The risk of SUDEP increases if generalized tonic-clonic seizures are not controlled.

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# Chapter 6

## Treatment Guide by Epilepsy Syndrome

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

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

\*: 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 life-time. 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<sup>1)</sup>.

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<sup>2, 3)</sup>. Among them, carbamazepine, valproate, levetiracetam are considered to be first-line drugs in consideration of their seizure control effect and adverse effects<sup>2, 4)</sup>.

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<sup>5)</sup>. For BECTS, RCTs were conducted for sultiame and levetiracetam<sup>6)</sup> as well as for oxcarbazepine and levetiracetam<sup>7)</sup>. 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.

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### ■ 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] Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 55件

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

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Care Excellence.

<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<sup>1)</sup>. 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%)<sup>2)</sup>. 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<sup>3)</sup>, carbamazepine<sup>4, 5)</sup>, and phenytoin<sup>5)</sup> have been reported to exacerbate absence seizures.

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## ■ 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

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Care Excellence.

<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<sup>1)</sup>.

Expert opinion recommends valproate as the first-line drug, followed by topiramate and lamotrigine as other first-line drugs<sup>2)</sup>.

The efficacy of lamotrigine<sup>3)</sup>, topiramate<sup>4)</sup>, and rufinamide<sup>5)</sup> 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%)<sup>3)</sup>, 33% for topiramate (placebo 8%)<sup>4)</sup>, and 32.7% for rufinamide (placebo 11.7%)<sup>5)</sup>. A cohort study of zonisamide was conducted, and the effective rate (50% seizure reduction rate) when used as adjunctive therapy was 51.6%<sup>6)</sup>.

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%<sup>7)</sup>. 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<sup>8)</sup>.

A report has shown that gabapentin and carbamazepine increase seizure frequency in LGS<sup>9)</sup>.

### ■ References

- 1) Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol.* 2009; 8(1): 82-93.
- 2) Wheless JW, Clarke DF, Arzimanoglou A, et al. Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord.* 2007; 9(4): 353-412.
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## ■ 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

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Care Excellence.

<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<sup>1)</sup>. 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<sup>2)</sup>. Since valproate has been reported to be teratogenic<sup>3)</sup> and affect cognitive ability of babies<sup>4)</sup>, treatment with drugs other than valproate should be given priority in child-bearing women.

In studies on JME, levetiracetam (seizure control rate 80%)<sup>5)</sup>, lamotrigine (seizure control rate 81.9%)<sup>6)</sup>, zonisamide (seizure control rate 38.5–69.5%)<sup>7)</sup>, and topiramate (seizure control rate 67%)<sup>8)</sup> have been shown to be effective as monotherapy. Among these drugs, lamotrigine should be used carefully because it often exacerbates myoclonic seizure<sup>9)</sup>. Clonazepam can be effective for myoclonic seizure<sup>10)</sup>.

A report has shown that gabapentin and carbamazepine exacerbate absence seizures and myoclonic seizures, while phenytoin exacerbates absence seizures<sup>11)</sup>. On the other hand, in a certain number of patients, a combination of carbamazepine and valproate is needed to control generalized tonic-clonic seizures<sup>12)</sup>.

### References

- 1) Wheless JW, Clarke DF, Arzimanoglou A, et al. Treatment of pediatric epilepsy: European expert opinion, 2007. *Epileptic Disord.* 2007; 9(4): 353-412.
- 2) Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet.* 2007; 369(9566): 1016-1026.
- 3) Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs; an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol.* 2011; 10(7): 609-617.
- 4) Meador K, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013; 12(3): 244-252.
- 5) Sharpe DV, Patel AD, Abou-Khalil B, et al. Levetiracetam monotherapy in juvenile myoclonic epilepsy. *Seizure.* 2008; 17(1): 64-68.
- 6) Machado RA, Garcia VF, Astencio AG, et al. Efficacy and tolerability of lamotrigine in juvenile myoclonic epilepsy in adults: a prospective, unblinded randomized controlled trial. *Seizure.* 2013; 22(10): 846-855.
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## ■ 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

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Care Excellence.

<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 syndromes<sup>1)</sup>.

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 phenytoin<sup>2)</sup>. Since valproate has been reported to be teratogenic<sup>3)</sup> and affect cognitive ability of babies<sup>4)</sup>, treatment with drugs other than valproate should be given priority in child-bearing aged women.

Zonisamide (seizure control rate 42.6%)<sup>5)</sup>, lamotrigine (seizure control rates 30–37% at one year or 40 weeks after starting treatment)<sup>6–8)</sup>, levetiracetam (seizure control rate 34.2%)<sup>9)</sup>, and topiramate (seizure control rate 39–49%)<sup>8, 10)</sup> 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%)<sup>11)</sup>.

### ■ References

- 1) Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4): 676-685.
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- 3) Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs; an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011; 10(7): 609-617.
- 4) Meador K, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013; 12(3): 244-252.
- 5) Yamauchi T, Aikawa H. Efficacy of zonisamide: our experience. *Seizure*. 2004; 13(Suppl 1): S41-48.
- 6) Steiner TJ, Dellaportas CI, Findley LJ, et al. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia*. 1999; 40(5): 601-607.
- 7) Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet*. 1995; 345(8948): 476-479.
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- 10) Privitera MD, Brodie MJ, Mattson RH, et al. Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. *Acta Neurol Scand*. 2003; 107(3): 165-175.
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## ■ 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件

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

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. National Institute for Health and Care Excellence.

<http://www.nice.org.uk/guidance/cg137>

# Chapter 7

## Adverse Effects of Antiepileptic Drugs

### CQ 7-1

## What are the adverse effects of antiepileptic drugs?

### Summary

Adverse effects of antiepileptic drugs comprise idiosyncratic drug reactions, dose-dependent adverse effects, and adverse effects after long-term usage.

### Comment

Adverse effects of antiepileptic drugs are roughly divided into acute early idiosyncratic reactions to drugs associated with allergic mechanisms, dose-dependent inhibitory action on the nervous system, and chronic phase adverse effects seen after long-term usage.

For idiosyncratic reactions to drugs, skin rash is a representative adverse effect occurring at a relatively high frequency. Rare but serious adverse effects include Stevens-Johnson syndrome (SJS), drug-induced hypersensitivity syndrome (DIHS), and toxic epidermal necrolysis (TEN). When these conditions are suspected, the suspected drug should be discontinued, and a dermatologist should be consulted. Pancytopenia, myelosuppression, and hepatic dysfunction may also be observed as adverse effects with allergic mechanisms. Most of the adverse effects due to these idiosyncratic reactions occur from 1–2 weeks to 2–3 months after the start of treatment. Therefore, attention should be given during the early stage of administration.

Adverse effects due to suppression of the nervous system (neurotoxic side effects) include many adverse effects such as dizziness, nystagmus, diplopia, drowsiness, nausea, anorexia, cerebellar ataxia, and psychiatric symptoms. Many of these adverse effects are dose-dependent.

Some adverse effects are accompanied by long-term use of antiepileptic drugs, such as weight gain, hypertrichosis or hair loss, urolithiasis, cerebellar atrophy, and gingival hyperplasia. Enzyme inducers (phenytoin, carbamazepine, phenobarbital, and primidone) and valproate are risk factors of osteoporosis.

To identify adverse effects of antiepileptic drugs, systematic adverse effect screening has been reported to be useful<sup>1)</sup>. Representative adverse effects of major antiepileptic drugs are summarized in **Table 1**.

### ■ References

- 1) Gilliam FG, Fessler AJ, Baker G, et al. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. *Neurology*. 2004; 62(1): 23-27.

### ■ Search formula and secondary reference sources

PubMed search: June 26, 2015

((("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 = 119

Ichushi search: June 29, 2015

(((((epilepsy/TH or epilepsy/AL)) and (SH = drug therapy)) and (adverse effects/AB or adverse effects/TI)) and (DT = 2008:2015 and PT = excluding proceedings))) and (PT = Comment, review) = 94

**Table 1. Typical adverse effects of major antiepileptic drugs.**

<b>Drug</b>	<b>Idiosyncratic adverse effects</b>	<b>Dose-dependent adverse effects</b>	<b>Adverse effects after long-term use</b>
Carbamazepine	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	diplopia, nystagmus, dizziness, ataxia, drowsiness, nausea, hyponatremia, cardiac conduction disturbance or cardiac failure, reduced cognitive function, hearing abnormality	osteoporosis
Clobazam	rare	drowsiness, ataxia, behavioral disorder, salvation	
Clonazepam	rare	drowsiness, ataxia, behavioral disorder, salvation	
Ethosuximide	rash, pancytopenia	drowsiness, abnormal behavior	
Gabapentin	rare	dizziness, ataxia, drowsiness, myoclonus	weight gain
Lamotrigine	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	drowsiness, dizziness, diplopia, excitability	
Levetiracetam	rare	drowsiness, abnormal behavior, bad mood	
Phenobarbital	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	dizziness, ataxia, drowsiness, reduced cognitive function	osteoporosis
Phenytoin	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	diplopia, nystagmus, dizziness, ataxia, drowsiness, peripheral neuropathy, cardiac conduction disturbance or cardiac failure, asterixis	cerebellar atrophy, hypertrichosis, gingival hyperplasia, osteoporosis
Primidone	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	dizziness, ataxia, drowsiness	osteoporosis
Valproate	pancreatitis, liver injury	thrombocytopenia, tremor, hyponatremia, increased ammonia, Parkinson syndrome	weight gain, hair loss, osteoporosis
Topiramate	rare	anorexia, psychotic symptom, drowsiness, speech symptom, metabolic acidosis, hypohidrosis	urolithiasis, weight loss
Zonisamide	rare	anorexia, psychotic symptom, drowsiness, speech symptom, metabolic acidosis, hypohidrosis, reduced cognitive function	urolithiasis
Rufinamide	drug-induced hypersensitivity syndrome, SJS, status epilepticus, aggressiveness, QT interval shortening	anorexia, drowsiness	
Stiripentol	attention deficit, hyperactivity disorder, talkativeness, sleeping disorder, aggressiveness, prolonged QT	somnolence, insomnia, anorexia, ataxia	
Sultiame	rash, leukocytopenia, tachypnea, paresthesia	anorexia, drowsiness	

SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis, DIHS: drug-induced hypersensitivity syndrome  
 [Before prescription, read the package inserts of individual drugs]



# Chapter 8

## Status Epilepticus

### CQ 8-1

## What is the definition of status epilepticus?

### Summary

Status epilepticus (SE) was defined as “a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur” (International League Against Epilepsy: ILAE, 1981)<sup>1)</sup>. Regarding the length of seizure, if convulsive seizure persists for 5 minutes or longer, treatment should be started, and if persists for 30 minutes or longer, there is a risk of long-term consequences (ILAE 2015)<sup>2)</sup>.

### Comment

In 2015, ILAE proposed a new definition for SE as follows: “Status epilepticus is a condition resulting either from the failure of the mechanisms for seizure termination or from the initiation of mechanisms provoking abnormally prolonged seizures (after time point  $t_1$ ). It is a condition, which can have long-term consequences (after time point  $t_2$ ), including neuronal cell death, neuronal cell abnormality, and alteration of neuronal networks, depending on the type and duration of seizures”<sup>2)</sup>.

Although the traditional definition did not define the seizure duration, epileptic seizures usually terminate in 1 to 2 minutes in most cases. It has become clear that a prolonged seizure duration is associated with drug resistance. For this reason, it is recommended that if the convulsive seizure lasts more than 5 minutes ( $t_1$ )<sup>2, 3)</sup>, the diagnosis of SE should be made and treatment should be started. In addition, animal experiments have shown that brain damage occurs if the epileptic discharges continue for 30–45 minutes or more. If seizure persists for more than 30 minutes ( $t_2$ ), there is a risk of serious long-term consequences<sup>2)</sup>.

### ■ References

- 1) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1981; 22(4): 489-501.
- 2) Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015; 56(10): 1515-1523.
- 3) Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001; 345(9): 631-637.

### ■ Search formula and secondary reference sources

PubMed search: September 12, 2008

Status Epilepticus AND (define\* OR definition\*) = 136

Additional PubMed search: December 8, 2015

“Status Epilepticus/classification” [Majr] OR “Status Epilepticus/etiology” [Majr] = 24

No references that could serve as evidence were found in Ichushi Web.

# Which drugs are used for convulsive status epilepticus?

## Summary

Figure 1 shows the treatment flowchart for convulsive status epilepticus.

## Comment

Early status epilepticus (stage 1) is defined as convulsive seizures persisting for more than 5 minutes. Established status epilepticus (stage 2) is defined as seizures persisting for over 30 minutes without cessation after treatment with benzodiazepines. Refractory status epilepticus (stage 3) is defined as seizures persisting for more than 60–120 minutes despite treatment with intravenous infusion or intravenous injection of antiepileptic drugs<sup>1)</sup>. Treatment strategy depends on the disease stage<sup>1-5)</sup>. When seizures are not controlled even by general anesthesia and persist for more than 24 hours, the condition is called super-refractory status epilepticus (stage 4), for which no standard treatment strategy has been established<sup>1)</sup>. Non-convulsive status epilepticus treatment generally follows those for convulsive status epilepticus, but the usefulness of general anesthesia is undetermined.

## ■ References

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- 5) Ohsawa M. Treatment for status epilepticus. *No To Hattatsu*. 2007; 39(3): 185-192. (in Japanese)

## ■ Search formula and secondary reference sources

PubMed search: September 9, 2008

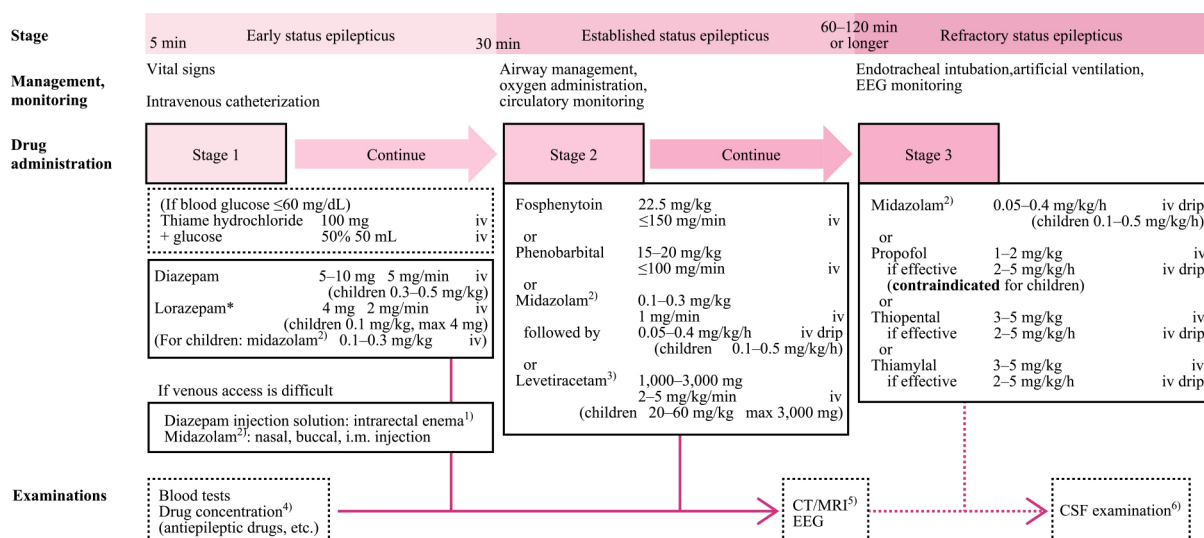
Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49

Additional PubMed search: June 26, 2015

((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr]) OR ((Status Epilepticus/drug therapy [Majr]) AND ((first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

**Figure 1. Treatment flowchart for status epilepticus (constructed from references 1–5).**



<sup>1)</sup> The dose of diazepam injection solution administered as enema is 10–30 mg (for children 0.2–0.5 mg/kg) (not covered by medical insurance)

<sup>2)</sup> When midazolam is administered nasally, buccally, and intramuscularly, use 0.5% injection solution at 10 mg (for children 0.3 mg/kg) (not covered by medical insurance). When administered as intravenous injection or continuous intravenous drip, use of 0.1% injection solution is covered by medical insurance. In the package insert for midazolam 0.1% injection solution, the dose is 0.15 mg/kg for intravenous injection and 0.1–0.4 mg/kg/h for drip. In general anesthesia, adjust dose as appropriate.

<sup>3)</sup> Not covered by medical insurance for status epilepticus.

<sup>4)</sup> If treated with antiepileptic drugs, check blood concentrations of the antiepileptic drugs being taken. If overdose of convulsion-inducing drugs (including theophylline) is suspected, check those blood levels if possible.

<sup>5)</sup> Perform brain MRI or CT as necessary to investigate the cause of seizures. Start treatment as for acute symptomatic seizure if necessary. If possible, continuous EEG monitoring must be done ideally to differentiate psychogenic seizures and evaluate the course of treatment, and even if not possible, it is desirable to record EEGs after treatment to confirm the cessation.

<sup>6)</sup> In cases suspected of meningitis or encephalitis, perform CSF examination. In addition to general CSF examination, bacterial culture and microscopic examination, it is desirable to freeze a portion of the sample for investigation of anti-neuronal antibodies in the future.

\*: Lorazepam is not marketed in Japan as of December 2017.

# What treatment should be given when intravenous line has not yet been established?

## Summary

**Intrarectal administration of diazepam injection solution is effective. In children, nasal / buccal administration and intramuscular injection of midazolam are effective (not covered by medical insurance).**

## Comment

A small-scale prospective open study<sup>1)</sup> and a small-scale retrospective study<sup>2)</sup> have demonstrated the efficacy of intrarectal administration of diazepam injection solution. The incidence of adverse effects including respiratory depression is low, and is safer compared to intravenous injection.

When diazepam is administered intrarectally, the beneficial effect appears within 10 minutes in most cases<sup>1, 2)</sup>. However, to be effective for status epilepticus, rather than suppository, gel enema preparation (not available in Japan) or injection solution should be used. Diazepam suppository lacks fast-acting effect, and is usually not effective in controlling on-going convulsions<sup>3)</sup>.

In addition, diazepam intramuscular injection is not recommended due to the delayed onset of effect and large variability of time course of effects<sup>1)</sup>.

The use of 10 mg (for children 0.3 mg/kg) of midazolam 0.5% injection solution (note: not 0.1% injection) is effective. In a meta-analysis of a total of 774 children and young adults, non-intravenous midazolam was more effective than intravenous diazepam. In an analysis of 628 patients, buccal midazolam was more effective than rectal diazepam<sup>4)</sup>. In a randomized double-blind trial of 893 patients, intramuscular midazolam (73.4%) had equivalent efficacy as intravenous lorazepam (63.4%)<sup>5)</sup>. Another report suggests that intrarectal and intranasal lorazepam may also be effective<sup>6)</sup> (not available in Japan).

## ■ References

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## ■ Search formula and secondary reference sources

PubMed search: September 9, 2008

Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49

Additional PubMed search: June 26, 2015

((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr]) OR ((Status Epilepticus/drug therapy [Majr]) AND (first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

## What are the drugs for stage 1 status epilepticus?

### Summary

The therapeutic drug for stage 1 is intravenous diazepam or lorazepam; both drugs are benzodiazepines. However, lorazepam for injection is not available in Japan.

### Comment

A prospective, randomized, double-blind study showed that intravenous injection of diazepam 10 mg controlled seizures in 76% of the patients<sup>1)</sup>. Diazepam has to be administered intravenously, not intramuscularly. Diazepam should be injected undiluted, because it becomes turbid when diluted with normal saline or glucose. If the first injection is ineffective, additional injection can be given after 5–10 minutes. Pay attention to respiratory depression when giving additional injection. An intravenous injection of diazepam usually has an anti-convulsion effect for 20 minutes<sup>2)</sup>.

A prospective randomized double-blind trial in 273 children found no difference in efficacy and adverse effects between diazepam and lorazepam<sup>3)</sup>, but a meta-analysis by Cochrane review of 289 cases showed that lorazepam had a lower rate of ineffectiveness (32/130 cases for lorazepam versus 51/134 cases for diazepam, hazard ratio 0.64, 95% confidence interval 0.45–0.9)<sup>4)</sup>. Intravenous preparation of lorazepam is not available in Japan.

As an alternative to intravenous diazepam, midazolam 0.1% injection may be given, and is often used for stage 1 treatment in children.

If the benzodiazepines are ineffective, proceed to stage 2 treatment.

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### ■ Search formula and secondary reference sources

PubMed search: September 9, 2008

Status Epilepticus/drug therapy" AND (first-line OR first choice) = 49

Additional PubMed search: June 26, 2015

((Anticonvulsants/therapeutic use [Majr]) AND Status Epilepticus/drug therapy [Majr]) OR ((Status Epilepticus/drug therapy [Majr]) AND ((first-line) OR first-choice)) = 242

No references that could serve as evidence were found in Ichushi Web.

# How effective is intravenous fosphenytoin for status epilepticus?

## Summary

**Fosphenytoin or phenytoin is used for the treatment of stage 2 status epilepticus.**

## Comment

Phenytoin has been used for a long time and fosphenytoin was developed to overcome the adverse effects associated with phenytoin. Therefore, fosphenytoin is easy to use in clinical practice.

While intravenous phenytoin should be injected slowly, fosphenytoin can be injected at an usual speed and reaches effective blood concentration more rapidly. In addition, phenytoin is strongly alkaline, causing vascular pain and vascular disorder, and its extravasation induces tissue necrosis. On the other hand, fosphenytoin is almost neutral, and rarely produces the above adverse effects<sup>1)</sup>.

The effective rate of fosphenytoin is reported to be 44–97%, and a randomized study of 256 emergency patients showed no difference in efficacy between phenytoin and fosphenytoin<sup>1)</sup>.

Phenytoin is effective for many types of status epilepticus, except absence seizure status epilepticus and myoclonic seizure status epilepticus<sup>2)</sup>. In a meta-analysis of 8 studies with 294 patients in total, the effective rate of phenytoin was 50.2% (95% confidence interval 43.2–66.1%)<sup>3)</sup>. Phenytoin should be injected intravenously immediately after injection of the fast-acting diazepam, because phenytoin begins to exert its effect approximately 20 minutes after administration<sup>4, 5)</sup>.

We should follow the instructions shown below when using phenytoin. Inject undiluted phenytoin into a relatively large blood vessel. Since there is a risk of heart failure due to cardiovascular disturbance (mainly hypotension and arrhythmia), inject the drug slowly while monitoring blood pressure, pulse and electrocardiogram. In addition, phenytoin causes vascular pain and purple glove syndrome due to vascular disorder at an incidence rate of 5.9%<sup>1)</sup>, and may cause tissue necrosis due to extravasation. Care should be taken, especially for children.

## ■ References

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## ■ Search formula and secondary reference sources

PubMed search: September 21, 2008

Status Epilepticus AND ("Diazepam" OR "Phenytoin" OR "Midazolam" OR "Propofol") = 357

Additional PubMed search: June 26, 2015

("Status Epilepticus" [Mesh]) AND "Phenytoin/therapeutic use" [Mesh] = 56

No references that could serve as evidence were found in Ichushi Web.

## How effective is intravenous phenobarbital for status epilepticus?

### Summary

**Intravenous phenobarbital is used for the treatment of stage 2 status epilepticus.**

### Comment

In a prospective randomized controlled trial comparing a combination of diazepam and phenytoin versus phenobarbital, the latter was slightly better in shortening both the duration of convulsion and the time of effect onset (average 5.5 minutes), although there was no difference in adverse effects<sup>1)</sup>. In another double-blind comparative study, there was no significant difference in seizure control between diazepam plus phenytoin and phenobarbital<sup>2)</sup>. In a meta-analysis of two studies with a total of 43 seizures, the rate of benefit of phenobarbital was 73.6% (95% confidence interval 58.3–84.8%)<sup>3)</sup>. Inject phenobarbital intravenously after intravenous diazepam injection<sup>4)</sup>, or use phenobarbital when a combination of diazepam and phenytoin fails to control seizures<sup>5)</sup>. Note that when using phenobarbital after diazepam, the frequency of respiratory depression increases.

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### ■ Search formula and secondary reference sources

PubMed search: September 21, 2008

Status Epilepticus AND ("Diazepam" OR "Phenytoin" OR "Midazolam" OR "Propofol") = 357

Additional PubMed search: June 26, 2015

("Status Epilepticus" [Mesh]) AND "Phenobarbital/therapeutic use" [Mesh] = 18

No references that could serve as evidence were found in Ichushi Web.

## How effective is midazolam for status epilepticus?

### Summary

**Midazolam is used for treating stage 1 and stage 2 status epilepticus, or as a general anesthetic agent.**

### Comment

Midazolam can be used as a therapeutic agent for stage 1 and stage 2 status epilepticus or as a general anesthetic agent<sup>1, 2)</sup>. Midazolam belongs to the benzodiazepines. It is a fast-acting agent and a potent anticonvulsant. When vein access cannot be secured, intranasal, buccal or intramuscular midazolam can be administered<sup>3)</sup>. As an alternative to intravenous diazepam, intravenous injection or continuous infusion of midazolam is an option<sup>1)</sup>. Midazolam can be infused intravenously, and it has a low risk of respiratory depression or cardiovascular disturbances. Moreover, because of its short half-life, midazolam can be switched to other drugs (such as general anesthesia with barbiturates) when it is ineffective, without wasting time.

In a meta-analysis by Cochrane review, there were no significant differences in efficacy and adverse effects between intravenous midazolam and intravenous diazepam<sup>4)</sup>. In the pediatric clinical practice in Japan, midazolam has been used as a therapeutic agent for stage 1 status epilepticus<sup>5)</sup>. In addition, midazolam has been reported to be effective for non-convulsive status epilepticus uncontrolled by diazepam and phenytoin<sup>6)</sup>.

### ■ References

- 1) Singhi S, Murthy A, Singhi P, et al. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. *J Child Neurol.* 2002; 17(2): 106-110.
- 2) Claassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory Status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia.* 2002; 43(2): 146-153.
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### ■ Search formula and secondary reference sources

PubMed search: September 21, 2008

Status Epilepticus AND ("Diazepam" OR "Phenytoin" OR "Midazolam" OR "Propofol") = 357

Additional PubMed search: June 26, 2015

("Status Epilepticus" [Mesh]) AND "Midazolam/therapeutic use" [Mesh] = 41

No references that could serve as evidence were found in Ichushi Web.



## How effective is intravenous levetiracetam for status epilepticus?

### Summary

**Intravenous levetiracetam is effective as a therapeutic agent for stage 2 status epilepticus. However, this drug is not covered by medical insurance in Japan.**

### Comment

Levetiracetam has a mechanism of action different from those of other antiepileptic drugs<sup>1)</sup>. This drug is fast-acting, with few adverse effects including respiratory depression and cardiovascular disturbances<sup>1-3)</sup>, and interaction with other drugs is also uncommon<sup>1)</sup>.

Comparative studies of levetiracetam with intravenous phenytoin<sup>4)</sup> and intravenous lorazepam<sup>5)</sup> have reported equivalent efficacy among them. In a systematic review of 7 retrospective studies with a total of 141 cases, the effective rate was 52–94%. In another systemic review of 3 prospective studies with 100 cases, the effective rate was 44–75%<sup>2)</sup>. In a meta-analysis of 8 studies with 204 cases, the effective rate was 68.5%<sup>3)</sup>.

### ■ References

- 1) Deshpande LS, Delorenzo RJ. Mechanisms of levetiracetam in the control of status epilepticus and epilepsy. *Front Neurol.* 2014; 5: 11.
- 2) Zelano J, Kumlien E. Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: a systematic review. *Seizure.* 2012; 21(4): 233-236.
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### ■ Search formula and secondary reference sources

PubMed search: December 14, 2015

("Status Epilepticus" [Mesh]) AND "levetiracetam/therapeutic use" [Mesh] = 193

No references that could serve as evidence were found in Ichushi Web.

## How effective is general anesthesia for refractory status epilepticus?

### Summary

**Administer general anesthesia as early as possible for refractory status epilepticus. As general anesthetic agent, midazolam, propofol, thiopental or thiamylal can be used.**

### Comment

Refractory status epilepticus is defined as status epilepticus that is not controlled by stage 1 (such as diazepam) and stage 2 therapeutic drugs (such as fosphenytoin).

Refractory status epilepticus develops in 31–43% of patients with status epilepticus<sup>1)</sup>. When seizures are not controlled by stage 1 and stage 2 therapeutic agents, we should administer general anesthetic agent immediately. When convulsive status epilepticus persists for more than 30 minutes, irreversible changes occur in the brain. Based on this result, it is reasonable to use general anesthesia when seizures persist for approximately 30 minutes. However, there is no high quality evidence for the timing to start anesthesia, which general anesthetic agent to use, the depth of anesthesia, or the duration of anesthesia. There are no clear recommendation standards for the above issues<sup>2)</sup>.

For general anesthesia, midazolam (see CQ 8-2-(5) on page 72), propofol or barbiturate is used.

Propofol has a potent antiepileptic effect and is effective in many patients. Moreover, it is fast-acting with a short half-life, and there is no waste of time when switching to other anesthetics. Its lethal adverse effects have been reported, but the risk is low when used at doses not exceeding 5 mg/kg/hour<sup>3)</sup> and terminated within 48 hours<sup>2)</sup>. However, general anesthesia with propofol is contraindicated for children.

Thiopental and thiamylal belong to the barbiturates. Thiopental<sup>4)</sup> is fast-acting, but takes a long time to arouse after its cessation. The frequency of adverse effects (including hypotension and infections) during anesthesia is high. Thiamylal has a similar profile as thiopental.

In terms of controlling convulsive seizures, thiopental is superior to propofol and midazolam, but there is no association between these anesthetics and prognosis of disease<sup>4)</sup>. In a meta-analysis by Cochrane review of only one single-blind trial of 24 cases, there was no clear difference in efficacy between thiopental and propofol<sup>5)</sup>.

### ■ References

- 1) Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol.* 2005; 62(11): 1698-1702.
- 2) Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia.* 2007; 48(Suppl 8): 52-55.
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- 5) Prabhakar H, Kalaivani M. Propofol versus thiopental sodium for the treatment of refractory status epilepticus. *Cochrane Database Syst Rev.* 2015; (6): CD009202.

### ■ Search formula and secondary reference sources

PubMed search: September 9, 2008

Status Epilepticus AND (general anesthesia) = 48

Additional PubMed search: June 26, 2015

("Status Epilepticus" [Mesh]) AND (("Anesthesia, General" [Mesh]) OR "general anesthesia" [TIAB]) = 9

No references that could serve as evidence were found in Ichushi Web.

## Does EEG monitoring during status epilepticus have clinical significance?

### Summary

**Electroencephalographic monitoring during status epilepticus is useful.**

### Comment

When seeing patients with suspected status epilepticus, record EEG in parallel with treatment. The EEG examination is useful in (1) exclusion of non-epileptic seizures such as psychogenic nonepileptic seizures (PNES), (2) differentiation between generalized seizures and partial seizures, (3) diagnosis of nonconvulsive status epilepticus (NCSE), (4) evaluation of brain function, and (5) prediction of prognosis.

PNES is not a malingering disorder, and it may cause not only incontinence or self-injury, but also any other symptoms, and some patients with PNES require mechanical ventilator<sup>1,2</sup>. EEG recording during or immediately after seizure is useful for a definitive diagnosis. When examining patients with suspected PNES, record EEG as far as possible concurrent with treatment (see Chapter 14 on page 123).

For evaluation of treatment, we should confirm not only the clinical improvements but also reduction of epileptic discharges on EEG. A report demonstrated that after anesthesia was stopped, 48% of the clinically controlled patients still had subtle convulsion or electrical status on EEG<sup>3</sup>.

Many reports have shown that in status epilepticus, maintaining flat EEG<sup>3,4</sup> or burst suppression pattern<sup>5</sup> with deep anesthesia using general anesthetic agents improves the final outcome.

Continuous EEG monitoring is useful for the diagnosis of NCSE<sup>6,7</sup>. EEG monitoring for over 6 hours can detect abnormal findings in 82% of NCSE<sup>8</sup> (not covered by medical insurance). In addition, the occipitally dominant background EEG activity has been reported to be related to clinical outcome<sup>9</sup>.

### ■ References

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### ■ Search formula and secondary reference sources

PubMed search: September 7, 2008

Status Epilepticus AND "Electroencephalography" = 178

Additional PubMed search: June 29, 2015

((Status Epilepticus [majr]) AND "Electroencephalography" [Mesh]) AND (("Monitoring, Physiologic" [Mesh]) OR monitor\*) = 89

No references that could serve as evidence were found in Ichushi Web.

# Chapter 9

## Surgical Treatment for Epilepsy

### CQ 9-1

## Which kinds of epilepsies (syndromes) are indications for surgical treatment?

### Summary

The following five epilepsies (syndromes) can be treated with surgery: (1) mesial temporal lobe epilepsy, (2) partial epilepsy with responsible organic lesions detected, (3) partial epilepsy without detectable organic lesions, (4) partial epilepsy due to extensive lesions within one hemisphere, and (5) intractable epilepsy with atonic seizures.

### Comment

We consider that patients with epilepsy are candidates for surgical treatment when the epileptogenic zone can be determined by examinations, and resection of the epileptogenic zone is expected to result in no or acceptable sequelae. The above five epilepsy syndromes are treatable by surgery (surgically remediable syndromes)<sup>1)</sup>. (1) Mesial temporal lobe epilepsy (MTLE), especially MTLE with hippocampal sclerosis (HS) (MTLE-HS), is considered to be the best indication for surgical treatment as an independent syndrome, and significant seizure control is predicted<sup>2-4)</sup>. (2) For partial epilepsy, when a lesion is detected by diagnostic imaging and is resectable, we consider surgical treatment. Thermocoagulation surgery is effective for gelastic seizures induced by hypothalamic hamartoma<sup>5)</sup>. (3) Even when no lesion is depicted on MRI, surgical treatment may be indicated if the epileptogenic zone can be detected by EEG and functional neuroimaging. (4) Partial epilepsy caused by extensive lesions in unilateral hemisphere is included as a candidate for surgical treatment. Since the arrest or regression of psychomotor development is often induced in patients who have intractable epilepsy with infancy or early childhood onset, early surgical treatment is recommended<sup>6)</sup>. (5) Corpus callosotomy is effective for atonic seizures.

### ■ References

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## Is temporal lobe resection effective for drug-resistant temporal lobe epilepsy?

### Summary

The effectiveness and safety of temporal lobe resection have been established for drug-resistant temporal lobe epilepsy, and it is a treatment that should be considered for complex partial seizures that impede daily living. This treatment is particularly effective when localized temporal lobe lesions are depicted on MRI.

### Comment

The results of surgical treatment for temporal lobe epilepsy have been accumulated from major epilepsy centers around the world since the 1990's<sup>1)</sup>. In 2001, the superiority of surgical treatment to drug treatment was demonstrated by a randomized controlled trial (RCT)<sup>2)</sup>. In 2003, the American Academy of Neurology together with the American Epilepsy Society and the American Association of Neurological Surgeons published guidelines stating that "Patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center"<sup>3)</sup>.

The rate of freedom from seizures that impede daily living in patients who underwent surgery was 60–80% if MRI detected localized temporal lesions related to seizures, and the rate was approximately 50% if MRI detected no lesions<sup>4)</sup>. Apart from hippocampal sclerosis, localized lesions responsible for epilepsy include benign tumors such as ganglioglioma, dysembryoplastic neuroepithelial tumor and diffuse astrocytoma; cavernous malformations; and cerebral cortical dysplasia.

Postoperative complications such as speech disturbance, memory impairment, hemiparesis, and visual field defect may occur, but the incidence is low<sup>5)</sup>. Memory impairment after medial temporal lobe resection may involve various degrees of verbal memory loss if there is no hippocampal atrophy on the language dominant side, but in patients with hippocampal atrophy and below average preoperative memory, there is no change in verbal memory after surgery<sup>3)</sup>.

Temporal lobe resection has been shown to be highly effective and safe in patients with drug-resistant temporal lobe epilepsy, and is an established therapy. However, it takes more than 10 years on average from diagnosis to surgery. To address this issue, epileptologists in the United States performed a randomized controlled trial (RCT) and recommended that when two trials with appropriate antiepileptic drugs failed, surgery should be conducted at an early stage without waiting for years<sup>6)</sup>.

Comparison between surgical and medical treatments involves an inherent limitation of the low level of evidence. The evaluation bias always occurs because blinding of medical and surgical treatments is impossible (see Systematic Review Digest on page 148). If surgical treatment is believed to be clearly effective, randomization becomes an ethical concern. Furthermore, we often have further difficulty in accomplishing a clinical trial since subject recruitment is challenging. This is shown by the fact that the randomized trial of Engel et al.<sup>6)</sup> was terminated prematurely. No comparative trials have been reported, probably because long-term comparative studies are especially difficult to complete. In a case series report, the rate of seizure recurrence after surgery was several percent per year, and the seizure-free rate was approximately 50% after 10 years<sup>7)</sup>.

Regarding the surgical methods, in addition to the classical standard anterior temporal lobe resection, various approaches to the medial temporal lobe have been proposed. Anterior temporal lobectomy is superior to selective amygdalohippocampectomy in seizure outcome<sup>8), 9)</sup>. The superiority of selective resection for postoperative cognitive function has not been shown so far. For patients with high risk of postoperative memory impairment, new therapies such as multiple hippocampus transection, laser ablation and hippocampal electrical stimulation therapy have been proposed, and evaluation of these methods is awaited.

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## What are the indications for chronic intracranial EEG (long-term intracranial EEG) in presurgical evaluation?

### Summary

There is no clear criterion for the indication of chronic intracranial EEG as a presurgical evaluation for epilepsy surgery. The current consensus is described below, but it may be changed by the advances and widespread use of other presurgical examinations.

### Comment

Although there is no clear criterion for the indication of chronic intracranial EEG, this examination has been regarded as a gold standard for determining the epileptogenic zone and the extent of resection area since over 50 years ago<sup>1)</sup>.

The consensus to date for the indications includes: (1) patients with partial epilepsy diagnosed by seizure symptoms and other noninvasive examinations (including positron emission tomography and magnetoencephalography) even without any localized lesion detected by MRI; (2) patients with localized lesions demonstrated by MRI, which are inconsistent with the epileptogenic zones localized by other noninvasive examinations, or in whom multiple epileptogenic zones are suggested by noninvasive examinations; (3) regardless of the presence or absence of localized lesions on MRI, patients with epileptogenic lesions near the functional area, in whom high-resolution focus localization and brain function mapping are required<sup>1, 2)</sup>.

Chronic subdural EEG recording is often omitted when noninvasive examination results are consistent with anatomical findings in patients with mesial temporal lobe epilepsy associated with unilateral hippocampal sclerosis or partial epilepsy with localized neocortical lesions. Also, this examination is often omitted in a standard extensive resection (including callosotomy) (especially in children). Furthermore, this examination is usually not done before corpus callosotomy for generalized seizures.

There are two types of intracranial electrodes: subdural electrodes that are placed on the brain surface and depth electrodes placed inside the brain. In the former case, electrodes are placed by craniotomy; and in the latter, electrodes are stereotactically implanted. We have no conclusion about their superiority, and both are used when necessary<sup>3)</sup>.

Even though the required recording period has not been established, the recording is done for usually 1–4 weeks in many institutions. While it usually takes more than two weeks to perform an adequate examination, the incidence of wound infection or intracranial infection increases as the placement period increases. Complications of chronic intracranial EEG recording include infection, cerebrospinal fluid leak, and focal neurologic symptoms. The incidence rate is 8.3% (7.7% cured within 3 months, 0.6% prolonged)<sup>4)</sup>.

In EEG analyses, in addition to conventional visual inspection, new analytical methods are available using signal processing for a broader frequency range. For functional brain mapping, in addition to the classical electrical stimulation method, new method is available to identify the high-frequency oscillations during a task. However, the superiority of these new analytical methods has not been established<sup>5, 6)</sup>.

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## How to determine the timing of considering surgical treatment?

### Summary

When seizures have continued even after two or more regimens of appropriately selected antiepileptic drugs given as monotherapy or combination therapy, classify such epilepsy with uncontrolled seizures for a certain period as drug-resistant epilepsy, and consider surgical treatment. The “certain period” of persistent seizures is considered to be one year or longer (or a period at least three times the pre-treatment interval between seizures). Earlier surgery should be considered in children.

### Comment

The ILAE<sup>1)</sup> defines drug-resistant epilepsy as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom for an adequate period”. An adequate period without seizures may be considered as at least one year (or a minimum of three times the pre-treatment inter-seizure interval) without seizure recurrence. For adults, surgical treatment should be considered promptly when epilepsy is judged to be drug resistant. For childhood, early surgery is desirable considering functional and survival outcomes. The ILAE Commission on Neurosurgery<sup>2)</sup> also recommends early surgery. The goal of surgical treatment is not only to eliminate seizures but also to improve quality of life. Intellectual impairment and psychiatric disorder are not exclusion criteria for surgical indication. In children, it is known that psychomotor development improves when seizures are controlled after surgical treatment (treatable epileptic encephalopathy)<sup>3)</sup>.

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## Is surgical treatment effective even for drug-resistant epilepsies in children?

### Summary

The surgical treatment is widely used for children with drug-resistant epilepsy and is recommended as a treatment by international experts despite no high-grade evidence supporting its efficacy. Epilepsy syndromes in children are diverse, and poorly controlled epileptic seizures may affect cognitive and behavioral developments. Therefore, presurgical evaluation should be performed at an appropriate timing in a specialized hospital or center.

### Comment

The outcome of surgical treatment for drug-resistant epilepsy in children is better than that in adults, especially when a lesion is confirmed pathologically or by MRI<sup>1)</sup>. However, there is no high-grade evidence for it, and the ILAE recommends the treatment based on expert consensus<sup>2)</sup>.

The conspicuous features of epilepsy surgery in children include a high proportion of multilobar resection and hemispherectomy (including callosotomy), and cerebral cortical dysplasia as a common etiology. Surgical resection of localized cortical dysplasia results in a high rate of seizure-free outcome<sup>3, 4)</sup>.

Children are affected by diverse epilepsy syndromes, and poor control of epileptic seizures has a risk of worsening cognitive and behavioral developments. Therefore, presurgical evaluation should be performed at an appropriate timing in a specialized hospital or center<sup>3)</sup>. Good seizure control by surgery sometimes improves developmental outcomes, especially in the case of infants treated with hemispherectomy<sup>4)</sup>.

In children with severe epilepsy showing localized lesions or hemispheric lesions, good outcome may be obtained even when EEG demonstrates extensive bilateral epileptic abnormalities.

### ■ References

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## What is the risk of psychiatric symptoms after epilepsy surgery?

### Summary

- (1) The risk of psychiatric symptoms after epilepsy surgery is high in patients with a past history or a family history of psychiatric symptoms (including anxiety, depression, and psychosis) before epilepsy surgery, and in those in whom seizures persist after surgery.
- (2) Explain to patients before surgery the possibility of psychiatric symptoms after epilepsy surgery.
- (3) For early detection and early treatment of psychiatric symptoms, we should follow the patients carefully for approximately 6 months to 1 year.

### Comment

It is desirable that all patients treated with epilepsy surgery should receive psychiatric evaluation before surgery<sup>1)</sup>. A past history of psychiatric disease is not a contraindication for surgery under the condition that psychiatric intervention is given. The frequency of de novo postsurgical psychiatric symptoms such as anxiety, depression and psychosis, including mild conditions such as adaptation disorder, is 1.1–18.2%<sup>2)</sup>. Presurgical psychiatric complications frequently exacerbate or recur up to one year after surgery. Regular close psychiatric follow-up after surgery leads to good outcome.

Risk factors for psychiatric symptoms such as anxiety, depression, and psychosis after epilepsy surgery are residual seizures after surgery and presence of a family history or past history of psychiatric condition before surgery. In surgically treated patients with temporal lobe epilepsy, the rate of de novo depression after surgery is 4–18%, occurring 3–12 months after surgery and lasting for 1 to 11 months. The rate of de novo anxiety disorder occurring after surgery is 3–26%, showing a peak in the first month after surgery. The rate of de novo psychiatric disorders developing after surgery is 1.1%, and the occurrence of psychiatric disorders is not related to the postsurgical seizure control or laterality of the resected hemisphere<sup>3)</sup>.

In patients with favorable seizure outcome (seizure-free) after surgery, the outcome of psychiatric symptoms is also favorable, but in rare cases adaptation disorder may occur. A hypothesis of “burden of normality” has been proposed to explain this phenomenon. It may be a kind of reaction of cured epilepsy patients to their new situation, that they should take on various social obligations that have been neglected while they were affected by epilepsy<sup>4)</sup>.

Treatment is basically the same as the usual treatment for psychiatric symptoms. In patients who did not receive any explanation about the risk of postsurgical psychiatric symptoms before surgery, the patients and families often react to or resist the involvement of psychiatrists after surgery. Therefore, participation of a psychiatrist in the treatment team before surgery is desirable.

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### ■ Search formula and secondary reference sources

Search formula

epilepsy [majr] AND mental disorders [majr] AND therapy [sh] Filters: Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Publication

PubMed = 86

# Should temporal lobe resection be added to drug therapy in drug-resistant temporal lobe epilepsy?

## Recommendation

We recommend temporal lobectomy in addition to drug therapies in patients with drug-resistant epilepsy (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note:** In the GRADE system, when the evidence level is “very low”, in principle it is not possible to grade “strong recommendation”. Since temporal lobe resection is highly effective with a low incidence of adverse effects, almost all the panelists supported “strong recommendation”, but due to the constraint of the GRADE system, the final grading was “weak recommendation”.

## 1. Background, priority of the problem

For drug-resistant epilepsy, adding further new drugs has limited effect. The temporal lobe resection is expected to achieve seizure-free condition despite its invasiveness.

## 2. Comment

### Evidence summary

There were 2 randomized controlled trials (RCTs) (total 118 patients) on the effectiveness of temporal lobe resection versus medical therapy for drug-resistant epilepsy<sup>1, 2</sup>. With regard seizure outcome, the relative risk was 20.57 (95% confidence interval 4.24–99.85) and the number needed to treat (NNT: indicating the number of persons needed to treat to achieve the outcome for one person) was 4, showing superiority of temporal lobe resection. Neither of the two RCTs mentioned decrease of antiepileptic drugs after surgery. Death rate did not differ between two groups.

The relative risk of surgical complications was 12.33 (95% confidence interval 1.67–90.89), and was higher in the temporal lobe resection group. Death, memory impairment, and psychiatric symptoms were not significantly different between the two groups. Quality of life (QOL) improvement was superior in the temporal lobe resection group.

## 3. Panel meeting

### 3-1. What is the overall quality of evidence across outcomes?

Since it was not possible to mask the intervention, the risk of bias was high overall in the collected studies. Bias for death was considered not serious, while that for the other outcomes was considered serious and was downgraded one rank. Inconsistency and non-directness of the results were without question and considered not serious. For imprecision, confidence intervals crossed the clinical decision threshold in many items, and was downgraded one or two ranks. Publication bias could not be judged because of the small number of studies. Consequently, the level of evidence for the outcomes was as follows: “low” for seizure freedom, death, surgical complications, and quality of life improvement; and “very low” for memory impairment and psychiatric symptoms. The overall level of evidence was “D (very low)”.

\* For surgical therapy, since blinding of the control group is difficult, the level of evidence is generally low.

### 3-2. How is the balance between benefits and harms?

Temporal lobe resection can be expected to control seizures. As a result, antiepileptic drugs are possibly reduced although it is not shown in RCT. The incidence of serious adverse effects was low. Therefore, the risk of temporal lobe resection is considered to be smaller as compared to its benefit.

### 3-3. What about patients’ values and preference?

Some patients may feel resistance in to receive invasive surgical therapy, but the beneficial effect of seizure-free produced by the surgery outweighs the resistance to the invasive procedure. There is perhaps no significant uncertainty or variability in value among the patients.

### **3-4. What is the balance between net benefit and cost or resources?**

The medical insurance fee scale for epilepsy surgery using a microscope (including temporal lobe resection) is 131,630 points (as of January 11, 2018). The surgery is conducted under general anesthesia and requires neurosurgeons.

However, through reducing antiepileptic drugs, decreasing hospitalization duration accompanying reduced seizures, and enabling more active social activities, epilepsy surgery is expected to lead to saving in the long term. For this reason, the cost can be considered negligible.

### **3-5. Recommendation grading**

During the discussions at the panel meeting, temporal lobe resection was expected to eliminate seizures, and overall the cost of the surgery could be considered negligible. Even taking the adverse effects into account, the surgery was supported by panelists.

At the panel meeting, many panelists supported a recommendation grade of “strong recommendation”. However, in the GRADE system, when the evidence level is “very low”, in general we are not able to grade “strong recommendation”. For this reason, the final grading was “weak recommendation”.

## **4. Descriptions in other related guidelines**

In Japan, the Japan Epilepsy Society published the “Guideline on indications for epilepsy surgery”<sup>3)</sup> in 2008, and “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy”<sup>4)</sup> in 2010.

The “Guideline on indications for epilepsy surgery” recommends surgical treatment for mesial temporal lobe epilepsy at a suitable timing, stating that “since surgical results are superior in cases of mesial temporal lobe epilepsy with a localized organic lesion or with extensive lesions in unilateral hemisphere, consider surgical treatment from an early stage and do not miss the timing of surgery”. The “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy” also follows the above recommendation, stating that “patients should be selected in accordance with the guideline on indications for epilepsy surgery”.

In overseas countries, the Quality Standards Subcommittee of the American Academy of Neurology, the American Epilepsy Society, and the American Association of Neurological Surgeons published a guideline<sup>5)</sup> in 2003. The guideline states that “drug-resistant epilepsy should be considered for referral to an epilepsy surgery center” and that “patients who meet established criteria for an anteromesial temporal lobe resection and who accept the risks and benefits of this procedure should be offered surgical treatment”.

## **5. Treatment monitoring and evaluation**

Monitoring and evaluation during the perioperative period of treatment are generally performed by a neurosurgeon. After this period, although a neurosurgeon is not necessarily required to monitor and evaluate the patients, follow-up and support for the patients should be provided.

## **6. Possibility of future research**

Some memory-preserving or minimally invasive surgery may be developed in the future. In addition, we would like to know the surgical outcomes and adverse events over a longer follow-up period because the observation periods of the two RCTs were 1 year<sup>1)</sup> and 2 years<sup>2)</sup>.

## **7. RCT reports reviewed for this CQ**

Wiebe 2001<sup>1)</sup>, Engel 2012<sup>2)</sup>

## **8. List of appendices (to be shown later)**

Appendix CQ9-2-01. Flow diagram and literature search formula

Appendix CQ9-2-02. Risk of bias summary

Appendix CQ9-2-03. Risk of bias graph

Appendix CQ9-2-04. Forest plot

Appendix CQ9-2-05. Summary of findings (SoF) table

Appendix CQ9-2-06. Evidence-to-decision table

## ■ References

- 1) Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001; 345(5): 311-318.
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# Chapter 10

## Stimulation Therapy for Epilepsy

### CQ 10-1

## Is vagus nerve stimulation therapy effective for drug-resistant epilepsy?

### Summary

**Vagus nerve stimulation (VNS) is one of the non-pharmacological, accommodative therapies for epilepsy, in which an implantable electrical stimulator activates the left cervical vagal nerve intermittently to reduce or attenuate drug-resistant epileptic seizures. This method is covered by medical insurance, but implementation of the treatment requires certification.**

### Comment

Vagus nerve stimulation (VNS) is used as an adjunctive accommodative treatment for patients with drug-resistant epileptic seizure, who are not indicated for epileptic surgery with craniotomy, or who do not respond adequately to the surgical treatment.

The first evidence for the efficacy of VNS was based on two randomized controlled trials (RCTs) conducted in the United States in the 1990s<sup>1, 2)</sup>. In RCTs of therapies that require surgical treatment and implantation procedure, we usually have difficulties in including an appropriate control group. However, in these two RCTs, efficacy was compared with a sham stimulation (low level stimulation) control group. In the sham stimulation group, an implantation procedure was performed in the same manner as in the treatment group, but the stimulation intensity was so low that it almost had no effect (active control group) even though the patients feel something (**Table 1**). In patients aged 12 years or above with drug-resistant partial seizures, the mean seizure reduction rate 3 months after surgery was 25–28% in the high-level stimulation group and 6–15% in the low-level stimulation group (see Systematic Review Digest on page 162). Furthermore, as a more clinically oriented comparative study, an RCT was conducted to compare best medical therapy (BMT) alone with a combination of BMT and VNS (BMT + VNS), and significantly greater improvement of health-related QOL was achieved by a combination of VNS and BMT<sup>3)</sup>.

Although the effectiveness of VNS increases on long-term continued administration<sup>4, 5)</sup>, RCT for long-term treatment is difficult to establish because of the ethical issue, and only a limited number of patients can be recruited. The study by Ryvlin et al.<sup>3)</sup> was initially planned for a two-year follow-up period, but the study was terminated prematurely due to difficulties in patient recruitment. We should take this limitation into consideration when evaluating the outcome assessment in systematic review. Regarding the long-term effect, many reports have indicated that seizure reduction rate by VNS for 2 years is approximately 50%, and the responder rate (seizure reduction  $\geq$  50%) is mostly reported to be approximately 50%.

In addition to RCT, many investigations such as registry research and case series have demonstrated the seizure reduction effect of VNS<sup>5, 6)</sup>, and the VNS has been established as an accommodative treatment for drug-resistant epilepsy. This treatment has been covered by medical insurance from 2010 in Japan, although it was delayed as compared with other countries.

Some studies have reported the effectiveness of VNS in children or for generalized seizures<sup>7, 8)</sup>. In Japan, there are no restrictions regarding seizure type and age for the use of VNS. However, since RCT has not been performed, indications have to be decided cautiously when used in children or for generalized seizures. Adverse effects associated with VNS include cough, hoarseness, throat discomfort, and swallowing disturbance, but the occurrence rate decreases during continuation of VNS<sup>2, 3)</sup>.

In addition to the accommodative effects on epileptic seizures, VNS was reported to be efficacious against concomitant symptoms such as cognitive dysfunction and affective disorder seen in patients with epilepsy<sup>9–11)</sup>. However, it should be noted that the primary end point of those studies was the effect of VNS on epileptic seizures, and the effect on concomitant symptoms was not the main objective.

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**Table 1. Stimulation conditions used in RCTs of VNS.**

	High-level stimulation		Low-level stimulation	
	Reference 1995	Reference 1998	Reference 1995	Reference 1998
Current (milliamperes)*	0.25–3.0	1.3**	0.25–2.75	1.2**
Frequency (Hz)	20–50	30	1 or 2	1
Pulse width (microseconds)	500	500	130	130
ON time (seconds)	30–90	30	30	30
OFF time (minutes)	5–10	5	60–180	180
Magnet mode	used	used	not used	used***

\*: At high-level stimulation, current was set at the highest tolerable level for each patient. At low-level stimulation, current was set at the lowest level that could be sensed by the patient.

\*\*: Mean value of final current

\*\*\*: Current at magnet mode was set at 0.

(Data excerpted from: A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology*. 1995; 45(2): 224-230. / Handforth A., DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998; 51(1): 48-55.

# Is intracranial electrical stimulation therapy with implanted electrodes effective for epilepsy?

## Summary

**Shot-term (1–3 months) efficacy of stimulation of the anterior nucleus of thalamus and responsive stimulation of the seizure onset zone has been shown for partial seizures. Although a limited number of reports have also indicated the long-term efficacy of these methods and the effectiveness of other intracranial stimulation methods (hippocampus, paracentral thalamic nucleus, and cerebellum), evidence is not sufficient and further verification is required.**

## Comment

Many patients do not achieve freedom from seizure even with appropriate drug therapies and surgical treatments. In recent years, intracranial electrical stimulation therapy with implanted electrodes has attracted attention as a treatment for these patients. However, as of December 2017, intracranial electrical stimulation therapy with implanted electrodes has not been approved in Japan.

Stimulation of the anterior nucleus of thalamus is performed by stimulating bilateral anterior nuclei of the thalamus intermittently using an implanted stimulator. For partial seizures in adults, the median seizure reduction rate is 40% after three months of treatment<sup>1)</sup>. The effect may last for 5 years<sup>2)</sup>. Adverse events include subjective depressive symptoms and memory impairment.

Responsive stimulation of the seizure onset zone is performed by implanting deep or subdural electrodes at 1–2 epileptogenic zones, which automatically detect seizure onset and initiate stimulation. For partial seizures in adults, the mean seizure reduction rate is 38% after 3 months of treatment<sup>3)</sup>. The effect may last for 5 years<sup>4)</sup>. Adverse events include intracranial hemorrhage and wound infection.

Multiple institutes have reported the efficacy of hippocampal stimulation for temporal lobe epilepsy, but the number of cases is limited<sup>5–9)</sup>.

## ■ References

- 1) Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010; 51(5): 899-908.
- 2) Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015; 84(10): 1017-1025.
- 3) Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011; 77(13): 1295-1304.
- 4) Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*. 2015; 84(8): 810-817.
- 5) Boon P, Vonck K, De Herdt V, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia*. 2007; 48(8): 1551-1560.
- 6) Velasco AL, Velasco F, Velasco M, et al. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia*. 2007; 48(10): 1895-1903.
- 7) McLachlan RS, Pigott S, Tellez-Zenteno JF, et al. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. *Epilepsia*. 2010; 51(2): 304-307.
- 8) Bondallaz P, Boëx C, Rossetti AO, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. *Seizure*. 2013; 22(5): 390-395.
- 9) Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. *Seizure*. 2014; 23(1): 6-9.

## ■ Search formula and secondary reference sources

PubMed search: December 11, 2014

epilepsy AND treatment AND brain stimulation AND clinical trial = 184

Sprengrers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy (Review). *The Cochrane Library* 2014, Issue 6.



# Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?

## Recommendation

We suggest to add vagus nerve stimulation to drug therapies (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note:** In principle, vagus nerve stimulation is considered for patients with no indication for curative surgery. Implantation of the vagus nerve stimulation device involves surgery under general anesthesia in an experienced hospital. After implantation, the patients need to be followed in the hospital where the operation was performed or other facilities by experts with experience in stimulator control.

## 1. Background, priority of the problem

In patients with drug-resistant epilepsy in whom seizures are not controlled even after trials of two appropriate antiepileptic drugs, further addition of drugs has only limited effect. Vagus nerve stimulation added to antiepileptic drug therapy is expected to provide additive effect of seizure frequency reduction. Because vagus nerve stimulation is less invasive and has lower seizure control effect as compared with brain surgery with craniotomy, it may be selected as a treatment option in patients with no indication for curative neurosurgery.

## 2. Comment

### Evidence summary

Only one randomized controlled trial (RCT) examined the effectiveness of vagus nerve stimulation adjunct to best medical practice (BMP) (intervention group) versus BMP alone (control group) for drug-resistant epilepsy<sup>1)</sup>. We therefore considered also to use observational studies. However, because the outcomes of those studies, such as reduced seizure frequency and mood change, are susceptible to placebo effect, we determined to use the single RCT.

Regarding efficacy, the relative risk for 50% seizure frequency reduction was 1.34 (95% confidence interval 0.59–3.04), and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 25. As for mood changes, there were no significant differences between the intervention group and control group in the scores for several scales: QOLIE-89 (89-item Quality of Life in Epilepsy Inventory), CES-D (Center for Epidemiologic studies Depression scale), and NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale). Regarding mood changes, the only scale showing a statistically significant difference was the 7-point evaluation scale CGI-I (Clinical Global Impression of Impression Important Scale), but the difference was only 0.5 (95% confidence interval 0.99–0.01), showing a small effect. For serious adverse events, vocal cord paralysis and brief respiratory arrest occurred only in the intervention group, but were transient with no sequelae. There was no significant difference in the adverse event of dysphonia between the intervention group and the control group.

It should be noted that the selected RCT was prematurely terminated by the sponsor due to a low recruitment rate, because many study candidates did not accept randomization of the treatment. Therefore, the study may be underpowered for detection of the outcome.

## 3. Panel meeting

### 3-1. What is the overall quality of evidence across outcomes?

In the study reviewed, the risk of bias was high overall, which was judged as serious for all the outcomes, and was downgraded by one rank. The inconsistency of results was not downgraded because of only one study used. The indirectness was judged as not serious and without any problems. As for imprecision, the confidence intervals in many analyses crossed the clinical decision threshold, and it was hence downgraded by one or two ranks. As for publishing bias, there was only one study, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: “very low” for seizure frequency  $\leq$  50%, serious adverse events, and dysphonia; and “low” for the other outcomes. The overall level of evidence was “very low”.

### **3-2. What is the balance between benefits and harms?**

Since there was only one RCT, the certainty of the effect estimate was low, and it was difficult to consider the balance between benefits and harms.

### **3-3. What about patients' values and preferences?**

The importance of outcomes has great inter-individual differences, and it should be diverse. It should be noted that some patients place importance on the reduction of seizure frequency, while others regard the risk of adverse effects to be more important.

### **3-4. What is the balance between net benefit and cost or resources?**

The electrode implantation for VNS surgery is conducted under general anesthesia. Vagus nerve stimulation is covered by medical insurance, and the medical insurance fee scale for implantation is 24,350 points, and that for exchange is 4,800 points (as of January 11, 2018). The reoperation should be done once every few years for replacement of the power generator because of degradation of the condenser. Considering the effectiveness for refractory epilepsy and the above-mentioned factors, the cost was judged to be moderate.

### **3-5. Recommendation grading**

During the discussions at the panel meeting, considering the moderate burden and cost, and the few alternative treatment options available, the panelists concluded that it was reasonable to use this treatment method despite a certain amount of harm, burden and cost. The unanimous decision was “to propose implementing vagus nerve stimulation for drug-resistant epilepsy”. As an additional consideration, the patients' families at the panel meeting expressed the following opinion: “We desire to overcome social constraints. If there is any method to solve this, please include it as one of the options.”

## **4. Descriptions in other related guidelines**

In Japan, the “Practice guideline of vagus nerve stimulation therapy for epilepsy”<sup>2)</sup> was published by the Japan Epilepsy Society in 2012, which states that “VNS has accommodative effect on drug-resistant epileptic seizures [recommendation grade A]”. Also, the American Academy of Neurology released a guideline update entitled “Vagus nerve stimulation for the treatment of epilepsy” in 2013. This guideline update describes the possibilities of the effectiveness of vagus nerve stimulation appearing several years after VNS operation, the effectiveness in children [rate of > 50% seizure reduction: 55% (95% confidence interval 50–59%)], and an increased risk of infection in children compared to adults [odds ratio 3.4 (95% confidence interval 1.0–11.2)].

According to the guidelines in Japan and overseas and the recommendation from the ILEA, the indication for vagus nerve stimulation is, in principle, patients who have no indication for curative neurosurgery<sup>2-4)</sup>.

## **5. Treatment monitoring and evaluation**

Vagus nerve stimulation treatment requires adjustment of the stimulation conditions, management of complications, and solving equipment troubles. Epilepsy specialists or doctors trained by the specialists should perform monitoring and evaluation after the operation based on expert knowledge.

## **6. Possibility of future research**

The RCT reviewed for this CQ had high risk of bias. Therefore, it is desirable to have more RCTs with better quality. In addition, further research focusing on how to identify good responders and the effects on status epilepticus is needed in the future.

## **7. RCT reports reviewed for this CQ**

Ryvlin 2014<sup>1)</sup>

## 8. List of appendices (to be shown later)

- Appendix CQ10-1-01. Flow diagram and search formula for references
- Appendix CQ10-1-02. Risk of bias summary
- Appendix CQ10-1-03. Risk of bias graph
- Appendix CQ10-1-04. Forest plot
- Appendix CQ10-1-05. Summary of findings (SoF) table
- Appendix CQ10-1-06. Evidence-to-decision table

## ■ References

- 1) Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. 2014; 55(6): 893-900.
- 2) Kawai K, Sugai K, Akamatsu N, et al. Guideline on implementation of vagus nerve stimulation therapy for epilepsy. *Tenkan Kenkyu*. 2012; 30(1): 68-72 (in Japanese).
- 3) Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; 81(16): 1453-1459.
- 4) Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia*. 2006; 47(6): 952-959.

## When conducting vagus nerve stimulation for drug-resistant epilepsy, which intensity of stimulation (high or low) should we use?

### Recommendation

When conducting vagus nerve stimulation (VNS) for drug-resistant epilepsy, we suggest to use high intensity stimulation rather than low intensity stimulation (GRADE 1C) (strong recommendation, low level of evidence).

- **Supplementary note:** Adjustment of stimulation conditions should be conducted in the hospital where the electrode implantation was performed or in a hospital/institution where VNS specialist is present.

### 1. Background, priority of this issue

The efficacy of vagus nerve stimulation is known to depend on the stimulation conditions. The intensity of stimulation should be adjusted while monitoring its therapeutic effect and adverse effects. Therefore, it is necessary to clarify whether high intensity stimulation or low intensity stimulation is superior when conducting VNS.

In addition, as mentioned in CQ 10-1 “Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?”, we have difficulty in performing comparison between real VNS and sham VNS (with no stimulation). Therefore, there is an increase in randomized controlled trials (RCTs) using low intensity stimulation as sham stimulation (placebo stimulation or pseudo-stimulation) to compare with high intensity stimulation.

There is one Cochrane Review<sup>1)</sup> on a similar clinical question. This review shows that high intensity stimulation has superior therapeutic effect, while treatment withdrawal is rare both when using high and low intensity stimulation.

### 2. Comment

#### Evidence summary

There were 4 RCTs that examined the efficacy of vagus nerve stimulation therapy for drug-resistant epilepsy<sup>2-5)</sup>.

For efficacy, the relative risk for seizure frequency  $\leq 50\%$  was 1.74 (95% confidence interval 1.14–2.65) and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 10. For adverse events, low level stimulation was significantly superior in dysphonia and hoarseness (relative risk 2.06, 95% confidence interval 1.34–3.17) and dyspnea (relative risk 2.43, 95% confidence interval 1.29–4.57). Treatment withdrawal, cough, and pain did not differ significantly between high level and low level stimulations.

### 3. Panel meeting

#### 3-1. What is the quality of evidence about the overall outcomes?

In all the studies collected, the risk of bias was low overall, and the level was not downgraded for all the outcomes. For inconsistency of the results,  $I_2$  was 32% for only dysphonia / hoarseness. Since the effect estimate differed between studies, heterogeneity was considered high. Inconsistency was thus considered serious and was downgraded one rank. There was no problem with indirectness, and was judged not serious. As for imprecision, the confidence intervals in many analyses crossed the clinical decision thresholds, and hence was downgraded by one or two ranks. Regarding publication bias, there were only four studies, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: “moderate” for seizure frequency  $\leq 50\%$ , cough, and dyspnea; “low” for treatment withdrawal, dysphonia / hoarseness, and pain. The overall level of evidence was “low”.

### **3-2. What is the balance between benefits and harms?**

High level stimulation was superior to low level stimulation for the outcome of seizure frequency  $\leq 50\%$ . Among the adverse events, dysphonia/hoarseness and dyspnea showed lower rates in low level stimulation, but since there was no significant difference in treatment withdrawal between two groups, there must be few adverse events serious enough to cause treatment withdrawal. According to expert opinion, many adverse events are reversible and can be controlled by adjusting the stimulation current intensity. Taken together, we decided that high level stimulation is probably superior in terms of the balance between benefits and harms.

### **3-3. What about patients' values and preferences?**

We concluded that there is probably no significant uncertainty and variability in patient's values and preferences because high level stimulation is more effective than low level stimulation, and although adverse events are more prevalent in high level stimulation, they are reversible and can be controlled by adjusting the stimulation current.

### **3-4. What is the balance between net benefit and cost or resources?**

Adjustment of stimulation intensity can be done by placing the programming wand over the subcutaneously implanted generator; thus resources and costs are negligible. However, reoperation is needed every few years to replace the generator when the battery runs out of power. Battery consumption is higher for high level stimulation than for low level stimulation. Based on these, it was decided that high level stimulation costs moderately more as compared to low level stimulation.

### **3-5. Recommendation grading**

In the discussions at the panel meeting, high level stimulation was considered superior in efficacy, and adverse effects were acceptable because most of them were presumably at a level that would not cause treatment withdrawal. As for burden and cost, high level stimulation was expected to consume more battery power, requiring more frequent generator exchange. Based on the above arguments, despite considerable adverse events that did not cause treatment withdrawal as well as the increased burden and cost, we finally unanimously recommended using high level stimulation, considering the highly anticipated seizure control effect.

## **4. Descriptions in other related guidelines**

In Japan, the "Guideline on implementation of vagus nerve stimulation therapy for epilepsy"<sup>6)</sup> was published by the Japan Epilepsy Society in 2012, which states that "In principle, initiate VNS two weeks after implantation. Start with low stimulation intensity and then gradually increase the intensity while monitoring the adverse effects [recommendation grade C]".

In 2013, the American Academy of Neurology released a guideline update entitled "Vagus nerve stimulation for the treatment of epilepsy"<sup>7)</sup>. There is no recommendation for high level or low level stimulation in that guideline. However, it states that whether stimulation at a higher frequency is more likely to reduce seizures than usual stimulation remains unknown.

## **5. Treatment monitoring and evaluation**

For adjusting stimulation intensity, we need a system which is capable of managing complications and coping with equipment troubles.

## **6. Future research issues**

Further research on the optimal intensity of stimulation is needed. In addition, other than stimulus intensity, there is no RCT on supplementary techniques such as magnet stimulation, which will be a future research subject. It is also desirable to elucidate the mechanisms underlying the subgroup with high response and develop evaluation methods to identify these subjects.

## **7. RCT reports reviewed for this CQ**

Michael 1993<sup>2)</sup>, VNS study Group 1995<sup>3)</sup>, Handforth 1998<sup>4)</sup>, Klinkenberg 2012<sup>5)</sup>

## 8. List of appendices (to be shown later)

- Appendix CQ10-2-01. Flow diagram and search formula for references
- Appendix CQ10-2-02. Risk of bias summary
- Appendix CQ10-2-03. Risk of bias graph
- Appendix CQ10-2-04. Forest plot
- Appendix CQ10-2-05. Summary of findings (SoF) table
- Appendix CQ10-2-06. Evidence-to-decision table

## ■ References

- 1) Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev*. 2015; (4): CD002896.
- 2) Michael JE, Wegener K, Barnes. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs*. 1993; 25(6): 362-366.
- 3) The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*. 1995; 45(2): 224-230.
- 4) Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998; 51(1): 48-55.
- 5) Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. 2012; 54(9): 855-861.
- 6) Kawai K, Sugai K, Akamatsu N, et al. Guideline on implementation of vagus nerve stimulation therapy for epilepsy. *Tenkan Kenkyu*. 2012; 30(1): 68-72 (in Japanese).
- 7) Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; 81(16): 1453-1459.

# Chapter 11

## Termination of Epilepsy Treatment

### CQ 11-1

## How many years after seizure remission should treatment termination be considered?

### Summary

**In children, consider treatment termination after seizures have remitted for at least 2 years.**

**In adults, more cautious consideration should be given, but in the case of a desire of child-bearing, actively consider dose reduction and termination.**

### Comment

Termination of epilepsy treatment is one of the most difficult clinical decisions. Although much evidence has been accumulated, there is no clear consensus on the timing of treatment termination.

In children, some epilepsy syndromes have good prognosis (= idiopathic partial epilepsy). To avoid adverse effects of long-term treatment with antiepileptic drugs on cognitive and behavioral development, the benefits of treatment termination are great. In adults, such subgroup with good prognosis has not been reported, and the risk of seizure recurrence by drug termination is higher than in the case of childhood-onset epilepsy<sup>1)</sup>. Because social factors such as employment and driving license have great impact on the decision in adults, more careful consideration is required. In women whose seizures are in remission, a desire of child-bearing is a good opportunity to consider treatment termination. If seizure recurs in the process of treatment withdrawal, the seizure is controlled by restarting therapy in most cases, although the seizure control may be difficult in some patients<sup>2)</sup>. We should make a final decision on treatment termination individually by comprehensively considering various conditions of each patient (in particular, the presence or absence of a poor prognostic factor) together with respect for the intentions of the patients and their families.

As for the timing of treatment termination in children, there is a Cochrane review that compared an early treatment withdrawal group (seizure remission for less than 2 years) and a late treatment withdrawal group (seizure remission for more than 2 years)<sup>3)</sup>. In this analysis, the early treatment withdrawal group had a higher risk of seizure relapse than the late treatment withdrawal group, with a relative risk of 1.32 (1.02–1.70). Particularly, in patients with partial seizure or EEG abnormality, the risk of relapse was even higher; the relative risk of early withdrawal was 1.52 (0.95–2.41), and that of late withdrawal was 1.67 (0.95–3.00). There is no reliable evidence on generalized seizures. In children, there is little risk of relapse if treatment is terminated after 2 years or longer of seizure remission.

In adults, there is no evidence that compares early and late treatment termination. According to the results of a randomized controlled trial of 1,013 adult epilepsy patients who had seizure remission for more than 2 years, the complete remission rate was 78% in the patients who continued treatment, and 59% in those who withdrew treatment after 2 years of follow-up<sup>4)</sup>. The most important factor influencing seizure relapse was the duration of seizure remission.

### ■ References

- 1) Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994; 44(4): 601-608.
- 2) Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand*. 2005; 111(5): 291-300.
- 3) Sirven J, Sperling MR, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev*. 2015; (2): CD001902.
- 4) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet*. 1991; 337(8751): 1175-1180.

## ■ Search formula and secondary reference sources

PubMed search: December 13, 2015

((“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields])) AND termination [All Fields] = 383. Finally the above references were included.



# Does the risk of seizure recurrence differ depending on seizure type, epilepsy type, or epilepsy syndrome?

## Summary

**The risk of seizure recurrence differs depending on epilepsy syndrome.**

## Comment

According to a prospective study on treatment termination in 264 children with epilepsy by Shinnar et al.<sup>1)</sup>, seizures recurred in 95 children (36%) during the follow-up period (average 58 months). In this study, among the epilepsy syndromes, no recurrences occurred in 14 children with idiopathic partial epilepsy (benign childhood epilepsy with centrotemporal spikes, benign Roland epilepsy), while seizures recurred in all 4 children with juvenile myoclonic epilepsy (JME)<sup>2)</sup>. Meanwhile, in a long-term follow-up (median 44.6 years) study of 66 patients with JME, 39 patients (59.1% of all patients) remained seizure-free for over 5 years ( $22.9 \pm 10.9$  years), 11 of whom (16.7% of all patients) had no antiepileptic drugs for over 5 years<sup>3)</sup>. Thus, the results are inconsistent among reports.

The above findings suggest that the diagnosis of epilepsy syndrome is critical when considering termination of treatment. However, there are few epilepsy syndromes in which a definite prognosis can be predicted. For the other epilepsy syndromes, the risk of seizure relapse is relative, and evidence is poor. In addition, many patients cannot be classified under one specific epilepsy syndrome. At least, the recurrence rate is higher in symptomatic epilepsy than in idiopathic epilepsy [relative risk 1.81 (1.21–2.70)]<sup>1)</sup>.

There is not enough evidence on the risk of seizure recurrence for each of the seizure types. According to a study from Japan that analyzed the recurrence and clinical features of 556 patients with childhood-onset epilepsy who discontinued antiepileptic drug therapy, 80 patients (14.4%) had recurrence, and the rate was especially high in those who stopped drugs after adolescence<sup>2)</sup>. By epilepsy type, the rates were high in adolescent- or adult-onset idiopathic generalized epilepsy (31.3%), symptomatic localization-related epilepsy (25.2%), and cryptogenic or symptomatic generalized epilepsy (19.2%).

## References

- 1) Shinnar S, Berg AT, Moshé SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol*. 1994; 35(5): 534-545.
- 2) Yamatani M, Konishi T, Matsuzawa J, et al. Relapse of seizure after withdrawal of antiepileptic drug treatment in childhood epilepsy: age-dependent factors. *No To Hattatsu*. 2000; 32(1): 15-20 (in Japanese with English abstract).
- 3) Senf P, Schmitz B, Holtkamp M, et al. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. *Neurology*. 2013; 81(24): 2128-2133.

## Search formula and secondary reference sources

PubMed search: December 13, 2015

((("epilepsy" [MeSH Terms] OR "epilepsy" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields])) AND ("recurrence" [MeSH Terms] OR "recurrence" [All Fields])) OR ("recurrence" [MeSH Terms] OR "recurrence" [All Fields] OR "relapse" [All Fields])) AND (("risk factors" [MeSH Terms] OR ("risk" [All Fields] AND "factors" [All Fields]) OR "risk factors" [All Fields] OR ("risk" [All Fields] AND "factor" [All Fields]) OR "risk factor" [All Fields]) AND type [All Fields] AND ("syndrome" [MeSH Terms] OR "syndrome" [All Fields])) = 349. Finally the above references were included.

## Is there an optimal dose reduction speed of antiepileptic drugs?

### Summary

**There is no reliable evidence for recommendation of the optimal speed for dose reduction of antiepileptic drugs for both children and adults.**

### Comment

According to a Cochrane review<sup>1)</sup> that verified the risk of seizure relapse in a rapid withdrawal group that terminated treatment within a tapering period of 3 months and a slow withdrawal group with a longer tapering period, there was no such study in adults. There were several studies in children. However, no conclusion could be derived because of issues such as deficient methodology and insufficient sample size. Even in children, there is no evidence that can be reflected in guideline.

In principle, we should taper the dose gradually. Abrupt cessation of the antiepileptic drugs has the risk of causing unexpected rebound seizure or status epilepticus. Especially, phenobarbital and clonazepam should be tapered carefully.

### ■ References

- 1) Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. Cochrane Database Syst Rev. 2006; (2): CD005003.

### ■ Search formula and secondary reference sources

PubMed search: December 13, 2015

("epilepsy" [MeSH Terms] OR "epilepsy" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("anticonvulsants" [Pharmacological Action] OR "anticonvulsants" [MeSH Terms] OR "anticonvulsants" [All Fields] OR "anticonvulsant" [All Fields]) AND ("appointments and schedules" [MeSH Terms] OR ("appointments" [All Fields] AND "schedules" [All Fields]) OR "appointments and schedules" [All Fields] OR "schedule" [All Fields]) AND withdrawal [All Fields] AND discontinuation [All Fields] = 27. Finally the above reference was included.

## What are the poor prognostic factors in treatment termination?

### Summary

The risk of seizure recurrence is high in patients with adolescent-onset epilepsy, symptomatic epilepsy, and EEG abnormalities.

In adult-onset epilepsy, the following factors increase the risk of recurrence: (1) taking two or more drugs at the onset of dose reduction, (2) a history of tonic-clonic seizure, (3) a history of myoclonic seizure, and (4) neurological abnormalities.

### Comment

Berg and Shinnar<sup>1)</sup> conducted a detailed meta-analysis on the predictors of poor prognosis related to treatment withdrawal in childhood and adult epilepsy. The risk of recurrence in the first year after tapering of antiepileptic drug was 0.25 (0.21–0.30) and the risk of recurrence in the second year was 0.29 (0.24–0.34). The risk factors were as follows. Adolescent onset epilepsy had a higher recurrent risk compared to childhood onset epilepsy [relative risk 1.79 (1.46–1.81)]. Adult onset epilepsies had a higher recurrent risk compared to childhood onset epilepsies [relative risk 1.34 (1.00–1.81)]. Symptomatic epilepsy had a higher recurrent risk compared to idiopathic epilepsy [relative risk 1.55 (1.21–1.98)]. Especially, symptomatic epilepsy with motor symptoms had a higher risk of recurrence compared to idiopathic epilepsy [relative risk 1.79 (1.13–2.83)]. Patients with abnormal EEGs had a relative risk of 1.45 (95% CI, 1.18 to 1.79) compared to those with normal EEGs. There was no adequate evidence regarding the degree of abnormalities in EEG.

In a randomized controlled trial (RCT) of 1,013 adult epilepsy patients who had been seizure-free for more than 2 years, the risk of recurrence was higher in patients who took two or more drugs or those with a history of tonic-clonic seizure<sup>2)</sup>. Based on this study, a prognostic index for recurrence of seizures after remission of epilepsy was developed<sup>3)</sup>. A study on the consequences of treatment termination in adult epilepsy pointed out that recurrence rate was higher in patients with neurological signs<sup>4)</sup>.

According to a review on recurrence after treatment termination in adults and children<sup>5)</sup>, seizures remitted again in most of the patients by restarting the drugs, but in 19% of the patients (mean of 14 studies, 95% CI: 15–24%), remission was not obtained by resuming the drugs, and 23% of them became refractory. The factors inducing intractable recurrence included symptomatic etiology, partial epilepsy, and cognitive impairment.

### ■ References

- 1) Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994; 44(4): 601-608.
- 2) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet*. 1991; 337(8751): 1175-1180.
- 3) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizures after remission of epilepsy. *BMJ*. 1993; 306(6889): 1374-1378.
- 4) Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study). *Epilepsia*. 2008; 49(3): 455-463.
- 5) Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand*. 2005; 111(5): 291-300.

### ■ Search formula and secondary reference sources

PubMed search: December 13, 2015

("epilepsy" [MeSH Terms] OR "epilepsy" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "treatment" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("prognosis" [MeSH Terms] OR "prognosis" [All Fields]) AND outcome [All Fields] AND termination [All Fields] = 83. Finally the above references were included.

# Should driving be avoided during dose reduction of antiepileptic drugs?

## Summary

The Road Traffic Act revised in 2013 and later contains no regulation concerning driving motor vehicles during dose reduction of antiepileptic drugs.

The “Guidelines for assessing fitness of driving for people with epilepsy”<sup>1)</sup> produced by the Japan Epilepsy Society Legal Issue Committee in 2001 claimed the following: When antiepileptic drugs are being reduced or stopped following the instructions of a doctor, the patients are prohibited from driving a motor vehicle during the period of dose reduction and for three months after the end of dose reduction. Thereafter, the “Proposal for Epilepsy and Driving”<sup>2)</sup> also produced by the same Committee proposed no driving and observation for 6 months after the end of dose reduction or termination of treatment, except when there is sufficient evidence that there is no risk of recurrence (long seizure-free period, small total number of attacks, epilepsy syndrome with low risk of recurrence, patients with good prognosis after epilepsy surgery).

## ■ References

- 1) Japan Epilepsy Society Legal Issue Committee. Guidelines for assessing fitness of driving for people with epilepsy. Tenkan Kenkyu. 2001; 19(2): 140-141 (in Japanese).
- 2) Japan Epilepsy Society Legal Issue Committee. “Proposal for epilepsy and driving” (2014) <http://square.umin.ac.jp/jes/images/jes-image/driveteigen2.pdf> (in Japanese).

## ■ Search formula and secondary reference sources

PubMed search: December 13, 2015

(“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“automobile driving” [MeSH Terms] OR (“automobile” [All Fields] AND “driving” [All Fields]) OR “automobile driving” [All Fields]) AND (“jurisprudence” [MeSH Terms] OR “jurisprudence” [All Fields] OR “law” [All Fields]) = 93. Finally the above references were included.

# Chapter 12

## Drug Concentration Monitoring

### CQ 12-1

## When should serum concentrations of antiepileptic drugs be monitored?

### Summary

Measurement of serum concentrations of antiepileptic drugs is useful for the following purposes: (1) to establish individual therapeutic ranges when the desired seizure control is obtained; (2) to diagnose adverse effects; (3) to evaluate adherence at the time of poor seizure control or breakthrough seizure; (4) to adjust doses in situations of pharmacokinetic changes (such as in children, elderly patients, comorbid disorders, and change in dosage form); (5) to adjust doses when change in pharmacokinetics is predicted (such as during pregnancy and addition or removal of drugs having interactions); and (6) to adjust doses of drugs having dose-dependent pharmacokinetics (particularly phenytoin).

### Comment

Monitoring serum concentrations of antiepileptic drugs is useful in deciding patient's medication regimen, if monitoring is done for a clear purpose and the results are interpreted properly along with other clinical factors. Serum concentrations of antiepileptic drugs should not be monitored routinely without intended purposes. However, they should be measured when there are clinical needs (**Table 1**)<sup>1)</sup>.

The reference range of serum concentrations of a certain drug is not the same as its therapeutic range. The lower limit of the reference range of serum concentrations is the concentration being more likely to produce an insufficient therapeutic effect, and the upper limit is the concentration being more often associated with adverse effects. That is, the serum concentrations of antiepileptic drugs within the reference range (so-called effective serum concentrations) indicate that they are expected to be effective with fewer adverse effects in most of the patients<sup>1)</sup>.

The therapeutic range of serum concentrations for a certain patient is the range within which that patient has the best seizure control. In most of the patients, the therapeutic range is within or overlaps with the reference range. However, treatment may be effective even when the serum concentration is lower than the reference range in some cases, or conversely may be effective only when the concentration is higher than the reference range in other cases, because of large inter-individual variability of the therapeutic range. Therefore, it is important to know the therapeutic range for each patient. The dose should not be increased if the patient remains seizure-free at serum concentration lower than the reference range. On the other hand, the dose might be increased to above the reference range if the patient has residual seizures without any adverse effects. The reference range of serum concentration differs depending on age, epilepsy syndrome, and seizure type<sup>1, 2)</sup>.

The reference range is determined based on the lowest serum concentration (the trough value, which is measured before drug taking in the morning). However, it is difficult to measure the trough value in outpatient clinic, and serum concentration measured at our clinics is usually higher than the trough. Therefore, it is not a concern if the measured value exceeds the upper limit of the therapeutic range. We should interpret the blood concentration considering the blood sampling time, the drug taking time, and the time of maximum concentration ( $T_{max}$ ) of each drug (**Table 1** in CQ 12-2 on page 104).

Antiepileptic drug exists in two forms in the blood: a protein-bound form and a free form. In patients with hypoproteinemia, pregnancy, hepatic disorders or renal disorders, the amount of drug in the free form is larger than that in healthy subjects even when the measured serum concentration is the same, and the efficacy and adverse effects are not the same as in normal controls. Although the free form possesses antiepileptic effect, measurement of free form is not covered by medical insurance. In general, the total serum concentrations of antiepileptic drugs, including both protein-bound form and free form, are measured and recorded.

## ■ References

- 1) Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the Subcommission on Therapeutic Drug Monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008; 49(7): 1239-1276.
- 2) Johannessen SI, Patsalos PN. Individual approach to laboratory monitoring of antiepileptic drugs. In: Wyllie E, Gidal BE, Goodkin HP, et al eds. *Willie's Treatment of Epilepsy: Principles and Practice*, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.568-573.

**Table 1. General indications for monitoring blood concentrations of antiepileptic drugs.**

1. After initiation of treatment or after dose adjustment, when the clinician decides to aim at a target concentration for that patient.
2. Once the desired seizure control state has been achieved, to establish the “individual therapeutic range.”
3. To determine the magnitude of a dose increase, particularly with antiepileptic drugs showing dose-dependent pharmacokinetics (most notably, phenytoin).
4. When there are uncertainties in the differential diagnosis of signs or symptoms suggesting drug-related adverse reaction, or when adverse effect is difficult to assess clinically (young children, patients with mental disability).
5. When seizures persist despite an adequate dosage.
6. When change in pharmacokinetics (consequently, required dose also change) is suspected, due to age, pregnancy, comorbidity, or drug interaction.
7. To assess changes in steady state drug concentration when a change in drug formulation or change to generic formulation is made.
8. When there is an unexpected change in clinical response.
9. To conform adherence when poor compliance is suspected.

(Modified from: Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the Subcommission on Therapeutic Drug Monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008; 49(7); 1239: 1276.)

## Serum concentration monitoring is useful for which drugs?

### Summary

The reference ranges of serum concentrations have been established for carbamazepine, phenytoin, phenobarbital, primidone, valproate, and ethosuximide. Serum concentration monitoring is useful for these drugs. However, for some other drugs, the serum concentration monitoring is not very useful because the reference ranges have not determined for them or they show remarkable fluctuations in serum concentration (Tables 1 and 2)<sup>1-5</sup>.

### Comment

Because there are large interindividual variabilities in epileptogenesis and response to a given antiepileptic drug, it is difficult to find a general therapeutic range of serum concentrations applicable to all patients. However, it is known that there exists a range of serum concentrations at which seizures are controlled and dose-dependent adverse effects are rarely seen in most of the patients. This range is called the “reference range” (so-called effective blood concentration).

Even for drugs with no established general reference ranges, serum concentration measurement is useful for comparisons within an individual patient. Benzodiazepines play a role as an anti-convulsant by binding with benzodiazepine receptors in the brain. Because the number of benzodiazepine receptors varies from person to person, it is difficult to determine the reference blood concentration range for all persons. The reference ranges for clobazam, nitrazepam and diazepam have not been reported. However, repetitive serum concentration measurements in one patient are useful for monitoring adverse effects such as drowsiness in that patient.

Phenytoin is a drug showing big fluctuations in serum concentration, which requires attention. Because of the non-linear relationship between dosage and serum concentration and the narrow therapeutic window, measurement of serum concentration is critical for setting the optimal dosage. Especially, a rapid rise in serum concentration occurs at high doses<sup>1</sup>. The serum concentration of lamotrigine decreases drastically when used concomitantly with enzyme-inducing drugs (phenytoin, carbamazepine, phenobarbital, and primidone), increases greatly when used in combination with valproate, and declines significantly during pregnancy. Serum level of carbamazepine decreases within 1–3 months after start of treatment, due to enzyme self-induction. Therefore, serum concentration has to be monitored shortly after treatment initiation.

### ■ References

- 1) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.376-700.
- 2) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015, p.593-768.
- 3) Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.
- 4) Drugs in Japan Forum, ed. Drugs in Japan: Ethical Drugs 2016 Edition. Tokyo: Jiho Inc., 2015 (in Japanese).
- 5) Johannessen SI, Johannessen-Landmark C, Perucca E. Pharmacokinetic optimization of therapy. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.124-138.

**Table 1. Therapeutic ranges of blood levels and pharmacokinetics of major antiepileptic drugs.**

Generic name (abbreviation)		Maintenance dose <sup>a</sup>		Dose increase range		Blood conc. reference range <sup>b</sup> (µg/mL)	T <sub>1/2</sub> <sup>c</sup> : elimination half-life <sup>c</sup> (h)			T <sub>max</sub> <sup>c</sup> : peak time <sup>c</sup> (h)	
		Adult (mg)	Child (mg/kg)	Adult (mg)	Child (mg/kg)		Adult		Child	Adult	Child
							mono-therapy	with enzyme inducer <sup>d</sup>			
Phenobarbital	PB							almost unchanged			
Primidone	PRM										
Carbamazepine	CBZ						10–26 <sup>e</sup>				
Phenytoin <sup>f</sup>	PHT							almost unchanged			
Valproate	VPA										
sustained release	VPA-R									7.5–16 <sup>g</sup>	
Ethosuximide	ESM										
Clonazepam	CZP										
Nitrazepam	NZP										
Clobazam	CLB										
N-desmethyl	CLB <sup>h</sup>										
Acetazolamide	AZM										
Potassium bromide	KBr						10–13 days		5–8 days		
Gabapentin	GBP										
Topiramate	TPM										
Lamotrigine <sup>i</sup> (1) with VPA (2) with enzyme inducer <sup>d</sup> (3) with (1) and (2)	LTG										
Levetiracetam <sup>j</sup>	LEV										
Rufinamide	RFN <sup>k</sup>	by weight	by weight								
Stiripentol	STP										
Vigabatrin	VGB										
Perampanel	PER <sup>l</sup>		8–12 <sup>l</sup>								
Lacosamide <sup>m</sup>	LCM		200–400 <sup>m</sup>								

a: In children, the younger the age, the higher the dose per kg body weight is required to obtain a given blood concentration, the maintenance dose is higher, and half-life and peak time are shorter. In adolescents, pharmacokinetics are almost the same as adults.

b: If effective, blood concentration can stay low, or can be increased to higher than the therapeutic range as long as there is no adverse effect.

c: This is the time for the concentration to decrease by half from the peak. The time until blood concentration decreases by one-half after administration is peak time + half-life. Half-life and peak time are in principle determined for monotherapy with drug taking after meal. In combination therapy, half-life is shortened when the combination lowers blood level through interaction, and is prolonged when the combination increases blood concentration (see “Interaction” in CQ 12-4 on page 109). Peak time is shortened significantly with drug is taken when fasting.

d: Enzyme-inducing drugs: PB, PRM, CBZ and PHT. Increase drug metabolism in the liver, concomitant use shortens half-life of original drug.

e: Value at the time when self-induction is completed (3–4 weeks after starting)

f: For PHT, the higher the blood level, the longer is the half-life. L: low dose (blood level around 5 µg/mL), H: high dose (blood level 10 µg/mL or above)

g: Peak time of VPA sustained release preparation varies depending on the dosage form: 5 to 10 h for Selenica® R fine granule, 7.5 to 10 h for Depakene® R tablet, and 13 to 16 h for Selenica® R tablet.

h: N-DMCLB is a metabolite of CLB. N-DMCLB has anticonvulsive action of approximately 1/4 strength of that of CLB. When classified by CLB:N-DMCLB concentration ratio into three groups of approximately 1:2–3 (10% of the subjects), around 1:10 (80%), and around 1:50–100 (10%), drowsiness occurs at a higher rate as the CLB:NDMCLB concentration ratio increases.

i: In Japan, monotherapy use is approved only for partial seizure (including secondarily generalized seizures) and tonic clonic seizure in 16 year-old and above. To prevent rash (especially Stevens–Johnson syndrome), follow the instructions in the package insert concerning the initial dose, the dose increase range and the maximum dose of LTG.

j: Monotherapy use only for 4 year-old and above with partial seizure.



- k: Covered by insurance for 4 year-old and above. Starting dose to maximum dose is as follows: 15 to < 30 kg in weight: 200–1,000 mg, 30 to < 50 kg: 400–1,800 mg, 50 to < 70 kg: 400–2,400 mg, ≥ 70 kg: 400–3,200 mg. Dose increase range is: 15 to < 30 kg: ≤ 200 mg, and ≥ 30 kg: ≤ 400 mg. Official abbreviation is undecided and RUF is also commonly used.
- l: Covered by insurance for 12 year-old and above. Official abbreviation is undecided and PRP is also commonly used.
- m: Covered by insurance for 6 year-old and above.

(Compiled from: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds.: Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015, p.593–768. / Patsalos PN, Bourgeois BFD: The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010. / Drugs in Japan Forum, ed. Drugs in Japan: Ethical Drugs 2016 edition. Tokyo: Jiho Inc., 2015.)

**Table 2. Usefulness of measuring blood concentration.**

Usefulness	Antiepileptic drugs
Very useful	Phenytoin, lamotrigine
Useful	Carbamazepine, phenobarbital, valproate, rufinamide, perampanel
Useful to certain extent	Primidone, ethosuximide, zonisamide, topiramate
Limited or undetermined	Clonazepam, clobazam, diazepam, nitrazepam, acetazolamide, gabapentin, levetiracetam, potassium bromide, stiripentol, vigabatrin, lacosamide

(Compiled from: Johannessen SI, Johannessen-Landmark C, Perucca E. Pharmacokinetic optimization of therapy. In: Shorvon S, Perucca E, Engel J Jr, eds. The treatment of epilepsy, 4th ed. Chichester: Wiley Blackwell, 2015, p.124–138.)

## Is serum concentration monitoring a requisite in the treatment of patients with hepatic or renal dysfunction?

### Summary

Since the pharmacokinetics of antiepileptic drugs may alter in patients with hepatic or renal dysfunction, conduct treatment based on serum concentrations of drugs. Dialysis reduces serum drug concentrations.

### Comment

Antiepileptic drugs are mainly metabolized by the liver and excreted by the kidney. But the ratio of hepatic metabolism and renal excretion varies depending on the drug. In patients with liver or kidney disorders, pay attention to the increase in serum concentrations of antiepileptic drugs, bearing in mind the metabolism and excretion routes and the ratio of hepatic metabolism and renal excretion for each drug. Then, the doses should be reduced if necessary. For drugs that are metabolized by the liver, serum concentrations do not change markedly in acute hepatitis since metabolic enzymes do not decrease, but serum concentrations rise in cirrhosis because metabolic enzyme and hepatic blood flow are both reduced. In patients treated with hemodialysis, the blood levels of some drugs decrease, therefore consider dose increment<sup>1)</sup> (**Table 1**)<sup>2-4)</sup>.

### ■ References

- 1) Singh G. Management of medical comorbidity associated with epilepsy. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015, p.245-258.
- 2) Spina E, Italiano D. Drug interactions. In: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2016. p.344-359.
- 3) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700.
- 4) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768.

**Table 1. Metabolic and excretion routes of major antiepileptic drugs, and dose adjustment of antiepileptic drugs in the case of hepatic and renal impairment.**

	<b>Hepatic metabolism (%)</b>	<b>Renal excretion (%)</b>	<b>Adjustment during liver impairment</b>	<b>Adjustment during kidney impairment</b>
Phenytoin	90	< 2	Dose reduction	No need
Carbamazepine	90	< 1	Dose reduction	No need
Valproate	85	< 5	Dose reduction	No need
Phenobarbital	55	25	Slight dose reduction–No need	Slight dose reduction
Primidone	45–60	20–25	Slight dose reduction–No need	Slight dose reduction
Clobazam	> 90	< 1	Dose reduction	No need e
Clonazepam	> 90	< 1	Dose reduction	No need
Zonisamide	70	< 30	Dose reduction	Slight dose reduction
Ethosuximide	70	20	Dose reduction	No need
Potassium bromide	0	100	No need	Dose reduction
Gabapentin	0	100	No need	Dose reduction
Topiramate	< 25	75	No need	Dose reduction
Lamotrigine	90	10	Dose reduction	No need
Levetiracetam	< 3	70	No need	Dose reduction
Rufinamide	85	2	Dose reduction	No need
Stiripentol	75	25	Dose reduction	No need
Vigabatrin	10	90	No need e	Dose reduction
Perampanel	70	30	Dose reduction	No need
Lacosamide	30	40	Dose reduction	Slight dose reduction

(Compiled from: Spina E, Italiano D. Drug interactions. In: Shorvon S, Perucca E, Engel J Jr. eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2016. p.344–359. / Shorvon S, Perucca E, Engel J Jr. eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768.)

## What are the drugs that interact with antiepileptic drugs?

### Summary<sup>1-5)</sup>

When addition or removal of a given non-antiepileptic drug results in an increase in seizures or adverse effects, suspect drug interaction with the antiepileptic drugs being used and consider measurement of serum concentrations of the antiepileptic drugs. Conversely, when an antiepileptic drug is being added or removed, pay attention to the possibility that the therapeutic effects of other drugs may alter, which may result in some changes in comorbid symptoms.

### Comment

Drug interactions include interactions between antiepileptic drugs (**Table 1**)<sup>1-3)</sup>, interactions between antiepileptic drugs and psychotropic drugs (**Tables 2 and 3**)<sup>1-5)</sup>, and interactions between antiepileptic drugs and general drugs other than psychotropic drugs (**Tables 4 and 5**)<sup>1-5)</sup>. Pay special attention when patients are complicated with psychiatric disease or developmental disorder, or elderly people taking various drugs because of comorbidities.

Among antibiotics, clarithromycin and erythromycin inhibit the metabolism of carbamazepine, resulting in a large increase in serum concentration of carbamazepine, causing dizziness, vertigo, and severe drowsiness. Carbapenem antibiotics (panipenem–betamipron, meropen, imipenem–cilastatin, doripenem, biapenem, tebipenem) are contraindicated when taking valproate, as they significantly lower the serum concentration of valproate.

For antithrombotic drugs, warfarin used with phenytoin mutually increase the serum concentrations of each other, and the blood level of rivaroxaban is lowered by carbamazepine, phenytoin or phenobarbital (see CQ 3-8 on page 30).

### ■ References

- 1) Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700.
- 2) Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768.
- 3) Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.
- 4) Drugs in Japan Forum, ed. Drugs in Japan: Ethical Drugs 2016 edition. Tokyo: Jiho Inc., 2015 (in Japanese).
- 5) Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika (Japanese Journal of Pediatric Medicine) 2014; 46(9): 1242-1247 (in Japanese).

**Table 1. Interactions between epileptic drugs.**

Added drug	Blood concentration of the original antiepileptic drug																	
	VPA	PB	CBZ	PHT	ZNS	CZP	CLB	ESM	AZM	GBP	TPM	LTG	LEV	RFN	STP	VGB	PER	LCM
VPA		↑↑	↓ <sup>a</sup>	↓ <sup>b</sup>	↓		↓	↑		→	↓	↑↑	→	↑↑				
PB	↓		↓	→↓	↓	↓	↓	↓		→	↓↓	↓↓	↓	↓↓	↓↓			↓
CBZ	↓↓	↑↓→		↑	↓	↓	↓	↓↓		→	↓↓	↓↓	↓	↓	↓↓	→	↓↓	↓
PHT	↓↓	↑↓	↓↓		↓↓	↓	↓	↓↓		→	↓↓	↓↓	↓	↓↓	↓↓	→	↓↓	↓
ZNS		→	→ <sup>c</sup>	→						→		↑						
CZP		→	↓	→						→		→						
CLB	↑↑	↑	↑ <sup>d</sup>	↑↑						→		→			↑			
ESM	↓	→	→	↑						→		→						
AZM			↑	↑														
GBP	→	→	→	→	→	→	→	→			→	→	→					
TPM	↓	→	→	↑						→		→		→				
LTG	↓	→	→	→	→	↓	→			→	→		→	→				
LEV	→	→	→	→		→	→			→		→						
RFN	→	↑	↓	↑							→	↓						
STP	↑	↑	↑↑	↑↑			↑↑											
VGB	→	→	→	↓														
PER	→	↓	→	→	→	→	→				→	→	→					
LCM	→		→	→	→					→	→	→	→					

Blood level: ↑ increase, ↑↑ marked increase, ↓ decrease, ↓↓ marked decrease, → unchanged.

In the case of marked increase or marked decrease, consider decrease or increase dose of the original antiepileptic drug.

<sup>a</sup>: Although total concentration decreases, CBZ-epoxide increases and the effect is augmented, no need to increase dose.

<sup>b</sup>: Although total concentration decreases, free drug increases and the effect is augmented, no need to increase dose.

<sup>c</sup>: CBZ-epoxide increases.

<sup>d</sup>: Both CBZ and CBZ-epoxide increase

PRM is metabolized to PB and is the same as PB, therefore is omitted.

(Compiled from: Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010)

**Table 2. Effects of psychotropic drugs on antiepileptic drugs (AED).**

AED	Blood concentration of AED	Psychotropic drugs that influence AED
PB	↑	Tricyclic antidepressant, zotepine, methylphenidate, tetracyclic antidepressant
PRM	↑	Tricyclic antidepressant, zotepine, phenothiazines, methylphenidate
CBZ	↑	Quetiapine, chlorpromazine, paroxetine, haloperidol, fluvoxamine, risperidone
PHT	↑	Tricyclic antidepressant, trazodone, fluvoxamine, methylphenidate, tetracyclic antidepressant
VPA	↑	Chlorpromazine, tricyclic antidepressant, sertraline
CLB	↑	Haloperidol, phenothiazines, fluvoxamine
NZP	↑	Phenothiazines
ZNS	↑	Adverse effects increased by tricyclic antidepressant
	↓	Risperidone
KBr	↑	Phenothiazines (drowsiness, attention, concentration, reduced reflex movement worsened)
LTG	↑	Sertraline
	↓	Olanzapine, risperidone (somnolence enhanced)
TPM	↑	Amitriptyline, lithium

\*: Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, and amoxapine. Tetracyclic antidepressants: maprotiline and mianserin. Phenothiazines: chlorpromazine, levomepromazine, fluphenazine, and prochlorperazine.

\*\*: CZP, AZM, ESM, GBP, LEV, RFN, STP, VGB, LCM: no description.

(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

**Table 3. Effects of antiepileptic drugs (AED) on psychotropic drugs.**

AED	Blood concentration of psychotropic drugs	Psychotropic drugs that are influenced by AED
PB	↑	Tricyclic antidepressant, zotepine, phenothiazines, tetracyclic antidepressant
	↓	Olanzapine, chlorpromazine, tricyclic antidepressant, paroxetine, haloperidol, tetracyclic antidepressant, risperidone
PRM	↑	Tricyclic antidepressant, zotepine, phenothiazines
CBZ	↑	Lithium
	↓	Aripiprazole, alprazolam, tricyclic antidepressant, sertraline, trazodone, paliperidone, paroxetine, haloperidol, phenothiazines, tetracyclic antidepressant, risperidone
PHT	↑	Tricyclic antidepressant, trazodone, fluvoxamine, tetracyclic antidepressant
	↓	Quetiapine, tricyclic antidepressant, trazodone, paroxetine, tetracyclic antidepressant
VPA	↑	Aripiprazole, chlorpromazine, tricyclic antidepressant, paroxetine
CZP	↑	Effect of phenothiazines enhanced
CLB	↑	Haloperidol, phenothiazines
NZP	↑	Phenothiazines
ZNS	↑	Adverse effects of tricyclic antidepressant increased
KBr	↑	Phenothiazines (drowsiness, attention, concentration, reduced reflex movement worsened <sup>†</sup> )
TPM	↑	Amitriptyline, haloperidol, lithium
	↓	Risperidone
RFN	↓	Triazolam

\*: Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, and amoxapine. Tetracyclic antidepressants: maprotiline and mianserin. Phenothiazines: chlorpromazine, levomepromazine, fluphenazine, and prochlorperazine

\*\*: AZM, ESM, GBP, LTG, LEV, STP, VGB, LCM: no description.

(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

**Table 4. Effects of general drugs other than psychotropic drugs on antiepileptic drugs (AED).**

AED	Blood concentration of AED	General drugs other than psychotropic agents that influence AED
PB	↑	Chloramphenicol, antihistamines (hydroxyzine, diphenhydramine ), selegiline
	↓	Antacid
	contraindicated	In the case of PB elixir: <u>cyanamide, disulfiram (enhance alcohol reaction)</u>
PRM	↑	Selegiline, antihistamines
CBZ	↑	Azole antifungals (including miconazole, fluconazole, and itraconazole), isoniazid, omeprazole, Ca channel blockers (including verapamil, amlodipine, nifedipine, and benidipine), quinupristin/dalfopristin, chloramphenicol, salicylic acid, ciprofloxacin, cimetidine, diltiazem, sulfamethoxazole-trimethoprim, selegiline, danazol, darunavir , telaprevir, bicalutamide, verapamil, macrolide antibiotics (including erythromycin, clarithromycin, and josamycin), ritonavir
	↓	Aminophylline, efavirenz, antacid, theophylline, rifampicin
PHT	↑	Azole antifungals (including miconazole, fluconazole, itraconazole, and voriconazole), amiodarone, aminophylline, allopurinol, isoniazid, omeprazole, chloramphenicol, cyclosporine, disulfiram, cimetidine, diltiazem, sulfamethoxazole-trimethoprim, tacrolimus, ticlopidine, theophylline, nelfinavir, para-amino-salicylic acid, fluorouracil-based preparations (including tegafur preparations and doxifluridine), fosfluconazole, warfarin
	↓	Aminophylline, salicylic acid, diazoxide, cisplatin, theophylline, nelfinavir, pyridoxine, vinca alkaloids (including vincristine), rifampicin
VPA	↑	Isoniazid, salicylates (including aspirin), cimetidine, macrolide antibiotics (including erythromycin, clarithromycin, and josamycin)
	↓	<u>Carbapenem antibiotics (panipenem-betamipron, meropen, imipenem-cilastatin, doripenem, biapenem, tebipenem)</u> , cholestyramine, cisplatin, naproxen, methotrexate, rifampicin
ESM	↑	Isoniazid
	↓	Rifampicin
CZP	↑	Selegiline
CLB	↑	Cimetidine, drugs metabolized by CYP3A4 (including rifampicin), CYP3A4 inhibitors (including ritonavir, corticosteroid preparations, and macrolide antibiotics), selegiline
NZP	↑	Cimetidine, selegiline
AZM	↑	High-dose aspirin
	↓	Ammonium chloride
GBP	↑	Cimetidine, naproxen, morphine
	↓	Antacid (aluminum hydroxide, magnesium hydroxide)
TPM	↑	Hydrochlorothiazide
LTG	↓	Acetaminophen, atazanavir, oral contraceptives (including ethinylestradiol and norethisterone), ritonavir, rifampicin, lopinavir-ritonavir combination
PER	↑	Ketoconazole

\*: ZNS, KBr, LEV, RFN, STP, VGB, LCM: no description.

\*\* : Underlined parts denote concomitant use contraindicated.

(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376–700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593–768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)

**Table 5. Effects of antiepileptic drugs (AED) on general drugs other than psychotropic drugs.**

AED	Blood concentration of general drugs	General drugs other than psychotropic agents that are influenced by AED
PB	↑	Including thiazide hypotensive diuretics (orthostatic hypotension↑), selegiline, antihistamines (hydroxyzine, diphenhydramine)
	↓	Azelnidipine, aminophylline, imatinib, irinotecan, HIV protease inhibitors (including indinavir, saquinavir, nelfinavir, and lopinavir), chloramphenicol, cyclosporine, tacrolimus, theophylline, doxycycline, PDE5 inhibitors (sildenafil, <u>tadalafil</u> , vardenafil), felodipine, corticosteroids (including dexamethasone), flecainide, verapamil, <u>voriconazole</u> , montelukast etc., estrogen-progestogen preparations (including norgestrel and ethinylestradiol), rivaroxaban, warfarin
PRM	↑	Antihistamines, thiazide hypotensive diuretics (including trichlormethiazide) (orthostatic hypotension↑), selegiline
	↓	Doxycycline
CBZ	↑	Isoniazid (enhance hepatotoxicity), cyclophosphamide, selegiline
	↓	Acetaminophen, aprepitant, aminophylline, albendazole, alprazolam, itraconazole, HIV protease inhibitors (including saquinavir, indinavir, nelfinavir, and lopinavir), etravirine, efavirenz, eplerenone, eletriptan, ondansetron, caspofungin, anticancer drugs (axitinib, irinotecan, imatinib, gefitinib, sunitinib, sorafenib, dasatinib, tamibarotene, temsirolimus, toremifene, nilotinib, lapatinib), dienogest, digoxin, dihydropyridine calcium antagonists (including nifedipine, felodipine, and nilvadipine), sildenafil, solifenacin, <u>tadalafil</u> , dabigatran etexilate, theophylline, telaprevir, doxycycline, donepezil, tramadol, nondepolarizing muscle relaxant (including vecuronium), corticosteroids (including prednisolone and dexamethasone), buprenorphine, praziquantel, flecainide, fosaprepitant, <u>voriconazole</u> , maraviroc, mirabegron, meglumine, immunosuppressants (cyclosporine, tacrolimus, everolimus), estrogen-progestogen preparations, rivaroxaban, <u>rilpivirine</u> , warfarin
PHT	↑	Warfarin
	↓	Azelnidipine, aminophylline, itraconazole, imatinib, irinotecan, indinavir, ondansetron, quinidine, hypoglycemic agents (insulin, oral hypoglycemic agents), thyroid hormone preparations (including levothyroxine), saquinavir, cyclosporine, disopyramide, tacrolimus, <u>tadalafil</u> , theophylline, deferasirox, doxycycline, nisoldipine, nifedipine, nelfinavir, nondepolarizing muscle relaxant (including vecuronium and pancuronium), PDE5 inhibitors (tadalafil, sildenafil, vardenafil), felodipine, corticosteroids (including dexamethasone), praziquantel, flecainide, verapamil, voriconazole, mexiletine, estrogen / gestagen preparations (including norgestrel and ethinylestradiol), rivaroxaban, warfarin
VPA	↑	Warfarin
CZP	↑	Selegiline
CLB	↑	Drugs metabolized by CYP3A4 (including rifampicin), selegiline
NZP	↑	Selegiline
AZM	↑	ACTH, antihypertensive drugs, digitalis preparations (digoxin)
TPM	↑	Metformin
	↓	Oral contraceptives (including ethinylestradiol and norethisterone), digoxin, pioglitazone
LTG	↑	Oral contraceptives (including ethinylestradiol and norethisterone)
	↓	Oral contraceptives (including ethinylestradiol and norethisterone)
RFN	↓	Oral contraceptives (including ethinylestradiol and norethisterone)
PER	↓	Oral contraceptives (including ethinylestradiol, and norethisterone)

\*: ZNS, ESM, KBr, LEV, STP, VGB, LCM: no description. However, STP has potent inhibitory effect on drug metabolic enzymes in the liver, and may increase the blood concentrations of various drugs.

\*\* : Underlined parts denote concomitant use contraindicated.

(Supplemented and modified from: Sugai K: Interactions between antiepileptic drugs and other drugs and food. Shoni Naika. 2014; 46(9): 1242-1247. / Shorvon S, Perucca E, Engel J Jr eds. The treatment of epilepsy, 4th edition. Chichester: Wiley Blackwell, 2015. p.376-700. / Wyllie E, Gidal BE, Goodkin HP, et al eds. Wyllie's Treatment of Epilepsy: Principles and Practice, 6th edition. Philadelphia: Wolters Kluwer, 2015. p.593-768. / Patsalos PN, Bourgeois BFD. The Epilepsy Prescriber's Guide to Antiepileptic Drugs. Cambridge: Cambridge University Press, 2010.)



# Chapter 13

## Epilepsy and Women

### CQ 13-1

## What kind of advice and information should be provided regarding pregnancy and childbirth for women with epilepsy?

### Summary

For women with epilepsy, comprehensive counseling including guidance about pregnancy and childbirth should be provided in consideration of women's life cycle. Specifically, encourage adolescents to understand the basic and practical knowledge regarding pregnancy and childbirth as well as the knowledge about epilepsy including daily life and importance of treatment. Also, recommend planned pregnancy and childbirth to make these life events possible with the lowest risk. In patients who need to continue antiepileptic medication, it is desirable to select a drug with lower teratogenic risk and conduct appropriate dose adjustment to control seizures before pregnancy.

### Comment

For women of childbearing age, it is desirable for the attending doctor to comprehensively assess the patient's capability of daily living based on the severity of epilepsy, environmental factors, and presence or absence of coexisting disability, and discuss with the family members, pediatrician and other health personnel to make a reasonable decision about the possibility of pregnancy and childbirth and to develop a plan for medication adherence<sup>1-3</sup>). Specifically, health professionals should provide advice and guidance to all women with childbearing potential starting from adolescence (junior high school students), at the timings appropriate to women's life cycle such as marriage and pregnancy, and recommend planned pregnancy and childbirth with strengthened cooperation from the family.

Regarding antiepileptic drugs (AEDs) during pregnancy and childbirth, we should be careful with the following points: (1) prescribe monotherapy in principle, (2) use the lowest required dose, (3) select AED with as low teratogenicity as possible, and (4) watch out for fluctuation in blood concentration of AED during pregnancy<sup>2,3</sup>). Pay attention to the change in seizure frequency at each stage of pregnancy and childbirth, and aim at optimal AED therapy considering the balance between seizure control and reduction of risk to pregnancy and childbirth. In addition, give detailed explanations in advance on general precautions concerning pregnancy and childbirth, effects of AED on fetus and neonate, the course after childbirth, genetic inheritance of epilepsy, and development of the child. **Table 1** summarizes the measures to be taken concerning pregnancy and childbirth.

Although there is no clear difference in the rate of infants with congenital malformations between women with epilepsy not taking AEDs and the general population<sup>4,5</sup>), the frequency of congenital malformations in infants born from women taking AEDs during pregnancy is 4–10%, which is roughly 2–3 times higher than the frequency of 2–5% in the general population. The teratogenic risk varies depending on the AED being taken<sup>2,5,6</sup>). On the other hand, AEDs taken when not pregnant or AEDs taken by male patients have little effect on the fetus<sup>2</sup>).

The types of congenital malformation are similar to those found in the general population, with high frequencies of cleft lip, cleft palate and cardiac anomalies. There are no clear differences among AEDs for minor anomalies, with one exception of spina bifida which is more often induced by valproate and carbamazepine<sup>2</sup>).

When using oral contraceptives for planned pregnancy, explain their interactions with AEDs (phenobarbital, phenytoin, carbamazepine, and lamotrigine reduce the effect of contraceptives). We should recommend the patients to consult with an obstetrician or gynecologist for proper guidance about pills containing estrogen of 50 µg or more and other contraceptive methods<sup>2,7</sup>).

Furthermore, the experience of pregnancy and childbirth has great significance for women (and their families) in their lifetime. Therefore, we should follow the patients always considering psychological features.

In clinical practice, we may use charts such as that shown in Figure 1 to highlight points that require special attention at each stage of pregnancy, and also the drug adjustment plan.

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## ■ Search formula and secondary reference sources

Search for the previous version of CQ13-1

PubMed search: June 28, 2015

epilepsy [mesh] AND (pregnancy [mesh] OR pregnant) AND "patient education" = 34

Ichushi search: June 28, 2015

((epilepsy/MTH) and ((pregnancy/TH or pregnancy/AL)) and ((patient education/TH or patient education/AL))) and (PT = excluding proceedings) = 12

PubMed search: June 28, 2015

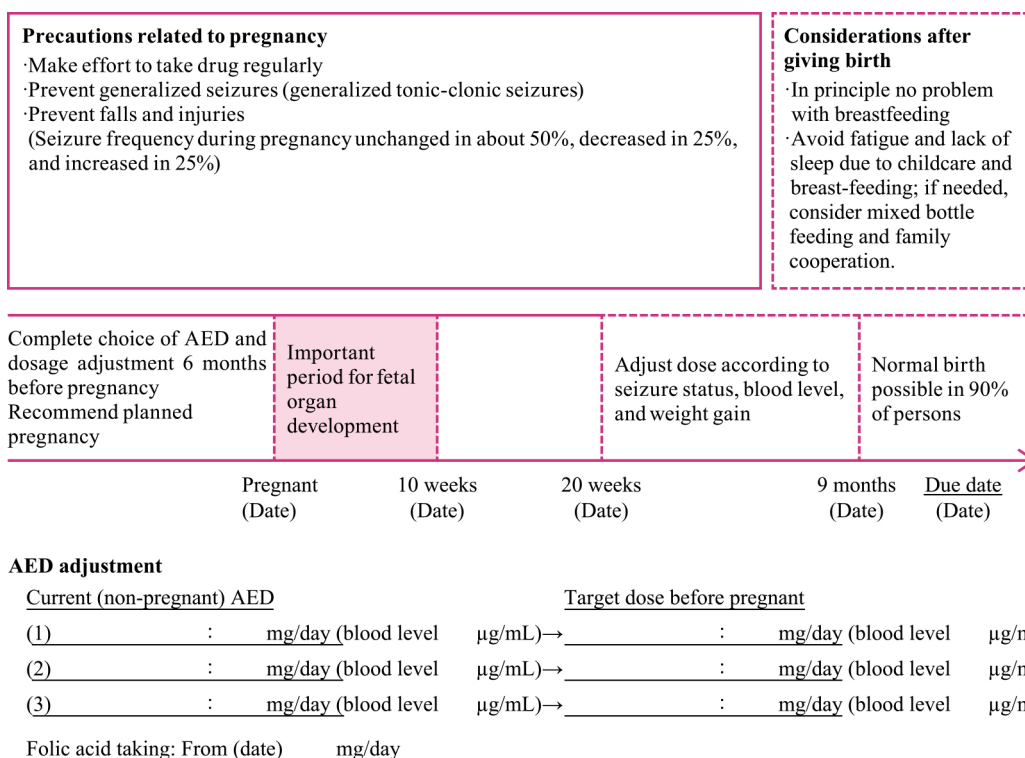
epilepsy [majr] AND (pregnancy [majr] OR Delivery, Obstetric [mesh] OR lactation [mesh]) Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 96

Ichushi search: June 28, 2015

((epilepsy/MTH) and ((pregnancy/TH or pregnancy/AL) or (childbirth/TH or childbirth/AL) or (breastfeeding/TH or breastfeeding /AL))) and (DT = 2008:2015 and PT = excluding proceedings) = 136

**Table 1. Major measures for epilepsy patients of childbearing potential.**

Before pregnancy	During pregnancy
<p>(1) Adherence building with patient/family Conduct detailed counseling from before pregnancy Counseling items:</p> <ul style="list-style-type: none"> <li>· Basic knowledge of childbirth and pregnancy for women with epilepsy</li> <li>· Daily life and medication guidance</li> <li>· Recommendation of planned pregnancy and childbirth</li> <li>· Whether pregnancy and childbirth are realistic: explain importance of family cooperation</li> <li>· If necessary, also consider specialized psychological support</li> </ul> <p>(2) Doctor's judgement after consultation with patient</p> <ul style="list-style-type: none"> <li>· Possibility of dose reduction, adjustment or discontinuation of antiepileptic drugs (AED)</li> <li>· If drug taking is continued, use monotherapy at the lowest required dose possible</li> <li>· If using multiple drugs, pay attention to the combination Combination to be avoided: valproate + carbamazepine or phenytoin + primidone + phenobarbital Valproate should be avoided if possible; if must be given, use sustained release formulation aiming at a dose of 600 mg/day or less.</li> <li>· Folic acid supplement from before pregnancy (approx. 0.4 mg/day)</li> <li>· Collaboration with obstetrics/gynecology and pediatrics departments (cooperation from before pregnancy to after delivery preferable)</li> </ul>	<p>Regular visits and medication</p> <ul style="list-style-type: none"> <li>· Increase AED dose only when symptoms worsen despite regular drug taking</li> <li>· Measure <math>\alpha</math> fetoprotein and folic acid levels at least once before pregnancy and as appropriate thereafter</li> <li>· <math>\alpha</math> fetoprotein measurement at around 16 weeks' gestation</li> <li>· Perform fetal monitoring such as ultrasound at 18 weeks' gestation</li> <li>· In patients with generalized tonic-clonic seizures, pay attention to premature labor</li> </ul> <p><b>At birth and puerperium</b></p> <ul style="list-style-type: none"> <li>· In general, natural birth is possible</li> <li>· Pay attention to seizure worsening due to irregular drug taking before and after parturition</li> </ul> <p><b>After birth</b></p> <ul style="list-style-type: none"> <li>· Adjust AED dose if blood level fluctuates after childbirth</li> <li>· Breastfeeding is possible in principle (consider both mother and child factors comprehensively)</li> </ul>



**Figure 1. Points that require attention for pregnancy and childbirth**

(Translated and modified from original figure of Ikeda A. Department of Epilepsy, Movement Disorders and Physiology, Kyoto University School of Medicine)

## What is to be noted for antiepileptic medication in women at childbearing age?

### Summary

When pregnancy is expected, try to control seizures with antiepileptic monotherapy if possible. Also, select drugs with careful consideration for the risk of teratogenicity and cognitive impairment in children as well as the efficacy for seizure control. Also pay attention to dose adjustment.

### Comment

In antiepileptic drug treatment, multidrug therapy has higher risk for teratogenicity than monotherapy, and the rates and types of malformation also vary depending on the types of drugs used in combination<sup>1-3</sup>). When antiepileptic medication is needed during pregnancy, aim at monotherapy as far as possible from before pregnancy and select drugs with low teratogenicity risk. The risk of major malformations for various antiepileptic drug are shown in **Table 1**<sup>3</sup>). Levetiracetam and lamotrigine have a low incidence of congenital malformation when used as monotherapy<sup>3-5</sup>). Carbamazepine also has a relatively low induction rate of malformation. Phenytoin, phenobarbital, and topiramate have slightly higher malformation induction rates<sup>4</sup>). Valproate has a higher malformation induction rate than the other drugs.

We should take note of the following point: even for antiepileptic drugs with low teratogenic risk when used alone, when these drugs are used in combination, the teratogenic risk increases depending on the combination<sup>2, 4, 6</sup>). For polytherapy, valproate, phenytoin, and phenobarbital are known to be drugs that increase the risk of teratogenicity when used in combination<sup>2, 6</sup>). Study has also shown that the teratogenic risk is increased when phenytoin or carbamazepine is used in combination with certain drugs including barbiturates (such as valproate + carbamazepine, and phenytoin + primidone + phenobarbital)<sup>2</sup>).

In children born from a mother taking valproate during pregnancy, decrease of IQ (full scale IQ, especially verbal IQ) was found in a dose-dependent manner (especially at high doses of 1,000 mg/day or higher)<sup>7</sup>). The incidence of autism spectrum disorders also increased by prenatal exposure to valproate<sup>8</sup>). When using valproate, in addition to the high teratogenic risk, the risk of cognitive dysfunction and behavioral disorder in children should also be noted. When valproate needs to be taken unavoidably, we should prescribe it at a dose of 600 mg/day or lower as much as possible<sup>7, 9</sup>). Use of a sustained release formulation is desirable aiming to stabilize blood concentration<sup>2</sup>). International guidance also recommends that caution should be taken in the decision to prescribe valproate to pregnant women<sup>9</sup>).

Regarding perampanel and lacosamide that have been launched on the market recently in Japan, there is currently insufficient data concerning human pregnancy and childbirth.

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**Table 1. The prevalence of major congenital malformations caused by taking antiepileptic drugs.**

	VPA	CBZ	LTG	PB	PHT	LEV	OXC	TPM
EURAP	9.7% (98/1,010)	5.6% (79/1,402)	2.9% (37/1,280)	7.4% (16/217)	5.8% (6/103)	1.6% (2/126)	3.3% (6/184)	6.8% (5/73)
NAAPR	9.3% (30/323)	3.0% (31/1,033)	1.9% (31/1,562)	5.5% (11/199)	2.9% (12/416)	2.4% (11/450)	2.2% (4/182)	4.2% (15/359)
UKIre	6.7% (82/1,220)	2.6% (43/1,657)	2.3% (49/2,098)		3.7% (3/82)	0.7% (2/304)		4.3% (3/70)
AUS	13.8% (35/253)	5.5% (19/346)	4.6% (14/307)		2.4% (1/41)	2.4% (2/84)	5.9% (1/17)	2.4% (1/42)
NMBR	6.3% (21/333)	2.9% (20/685)	3.4% (28/833)	7.4% (2/27)		1.7% (2/118)	1.8% (1/57)	4.2% (2/48)
SMBR	4.7% (29/619)	2.7% (38/1,430)	2.9% (32/1,100)		6.7% (8/119)	(0/61)	3.7% (1/27)	7.7% (4/52)

(Abbreviations: VPA: valproate, CBZ: carbamazepine, LTG: lamotrigine, PB: phenobarbital, PHT: phenytoin, LEV: levetiracetam, OXC: oxcarbazepine (not approved in Japan as of January 2018), TPM: topiramate)

EURAP: European and International Registry of Antiepileptic Drugs in Pregnancy, NAAPR: North American Antiepileptic Drugs and Pregnancy Registry, UKIre: UK and Irish Epilepsy and Pregnancy Registry, AUS: Australian Register of Antiepileptic Drugs in Pregnancy), NMBR: Medical Birth Registry of Norway, SMBR: Swedish Medical Birth Register

(Modified from: Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. *Seizure*. 2015;28:46-50.)

## Is folic acid supplementation needed?

### Summary

**Folic acid supplementation is useful to prevent the occurrence of neural tube defect.**

### Comment

Some antiepileptic drugs are known to lower blood folic acid levels<sup>1-3)</sup>. In particular, when valproate or carbamazepine is administered, supplementation of folic acid at an appropriate dose (0.4–0.6 mg/day)<sup>3, 4)</sup> is desirable to reduce the risk of neural tube closure defect. It has also been reported that folic acid mitigates the adverse effect of antiepileptic drugs on IQ of children<sup>5)</sup>.

For administration, use of ready-made folic acid preparations or multivitamin preparations containing folic acid may be considered<sup>1, 3)</sup>.

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## Is it useful to monitor serum concentrations of antiepileptic drugs during pregnancy?

### Summary

Since serum concentrations of antiepileptic drugs may change from the pre-pregnant values during pregnancy, it is desirable to conduct therapeutic drug monitoring (TDM) as necessary.

### Comment

Serum concentrations of antiepileptic drugs may change during pregnancy. For example, serum concentration of lamotrigine may decrease to approximately 40% of the pre-pregnant level<sup>1, 2)</sup>. Even though levetiracetam has a low serum protein binding rate, its serum concentration may decrease by 50% or more during pregnancy<sup>3, 4)</sup>. Therefore, it is necessary to prevent the attenuation of seizure control effect of drugs by adjusting the doses appropriately based on serum concentrations measured at various appropriate times during pregnancy and at childbirth, using the optimal concentrations of antiepileptic drugs before pregnancy as the baseline level. On the other hand, it is important to prevent the adverse effects due to increase in serum concentrations after childbirth.

Attention should be paid to the interpretation of serum concentrations of protein-bound drugs such as phenytoin and valproate, because even when the total blood concentration shows a low value, the concentration of free drug may be increased due to decreased serum protein during pregnancy. Since the therapeutic effect of antiepileptic drug is mainly provided by the free drug, dosage should not be increased unnecessarily even when the total serum concentration decreases. If a reduction of free drug concentration is confirmed and seizures worsen despite good medication adherence, then consider increasing the dose of the drug<sup>5)</sup>.

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## Are women with epilepsy more likely to have complications during pregnancy?

### Summary

Although the rate of complications is almost unchanged, some complications are increased slightly.

### Comment

Injury caused by falls during seizure as well as intracranial hemorrhage, venous thrombosis, sinus thrombosis, and ischemic stroke attack could occur during pregnancy. Their frequencies are low and statistical figures are unknown<sup>1-3</sup>). There are few reports on premature rupture of membrane and umbilical cord abnormalities as complications at delivery. Over 90% of mothers affected by epilepsy have normal pregnancy and delivery.

According to a recent systematic review, the rates of complications including spontaneous abortion, preterm labor, perinatal hypertension, and postpartum hemorrhage, as well as the proportion requiring caesarean section were slightly higher in mothers with epilepsy than control mothers, but the incidence of events requiring intensive care was not different between these two groups<sup>4</sup>).

### ■ References

- 1) Kaplan PW, Norwitz ER, Ben-Menachem E, et al. Obstetric risks for women with epilepsy during pregnancy. *Epilepsy Behav.* 2007; 11(3): 283-291.
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## Can women with epilepsy have a natural delivery?

### How are seizures treated during delivery?

#### Summary

In general, women with epilepsy can have a natural delivery. Seizures during delivery can be treated by the general strategy for epilepsy.

#### Comment

In most cases the patient gives birth by normal delivery<sup>1-4</sup>. In general, there is no indication for caesarean section, but caesarean section may be conducted depending on concomitant symptoms<sup>3</sup>. Vacuum-assisted delivery should be avoided<sup>3</sup>.

Guide patients to continue regular drug taking as far as possible until birth<sup>1-4</sup>. If seizures occur during labor, they can be managed by the general strategy for seizures, but if necessary, administration of benzodiazepines is recommended.

We should pay attention to the withdrawal seizures in neonates because it sometimes occurs in neonates<sup>3</sup>.

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## Can women taking antiepileptic drugs breastfeed a baby?

### Summary

They can breastfeed a baby.

### Comment

Breastfeeding is in principle possible even when taking antiepileptic drugs. However, pay attention to the fact that antiepileptic drugs are transferred from maternal blood to breast milk at different rates<sup>1-3)</sup>.

When breastfeeding, observe symptoms in neonates such as withdrawal seizures, somnolence, hypotonia, and poor suckling, considering the transfer rate of the antiepileptic drug to breast milk and the half-life of the antiepileptic drug in the infant<sup>3)</sup>. When these symptoms appear, manage in a flexible manner such as refraining from breastfeeding and measuring the serum concentration in the neonate<sup>3)</sup>. **Table 1** shows the breast milk transfer rates of various antiepileptic drugs.

In any case, make realistic decision about breastfeeding based on a comprehensive assessment giving priorities to the child's mental and physical growth and the mother's wish. In addition, during the breastfeeding period, provide adequate care and guidance on daily life, including sleep deprivation and fatigue due to childcare.

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**Table 1. Breast milk transfer rates of various AEDs and half-life of AEDs in neonates.**

AED	Transplacental transfer rate of AED	Breast milk transfer rate of AED	Half-life of AED in neonate (hours)
CBZ	0.69–0.78	0.36–0.41	8–36
CLB0.	1.7–7.5	13–0.36	17–31
CZP	0.59	1.0–3.0	13–33
DZP	1.2–2.0	0.5	31
ESM	0.97	0.86–1.36	32–38
GBP	1.74 (1.3–2.1)	0.7–1.3	14
LEV	1.14 (0.56–2.0)	1.0–3.09	16–18
LTG	0.9 (0.6–1.3)	0.61 (0.5–0.77)	24
OXC	0.92–1.0	0.5–0.65 1	7–22
PB	0.7–1.0	0.36–0.46	100–500
PHT	0.86–1.0	0.06–0.19	15–105
PRM	0.88–0.99	0.72	7–60
TPM	0.95 (0.85–1.06)	0.67–1.1	24
VPA	1.59–1.71	0.01–0.1	30–60
ZNS	0.92	0.41–0.93	61–109

Transplacental transfer rate = AED concentration in umbilical cord blood/AED concentration in maternal blood

Breast milk transfer rate = AED concentration in breast milk/AED concentration in maternal blood

(Modified from: Kikuchi T, Yoshida S. Effect of child exposure to antiepileptic drugs via transfer of drugs to breast milk. In: Kaneko S, ed. *The Course on Epilepsy*, 3<sup>rd</sup> revised edition. Tokyo: Shinkoh Igaku Shuppansha Co., Ltd. 2012. p.215-218.)

# Chapter 14

## Diagnosis of psychogenic nonepileptic seizures

### CQ 14-1

## How are psychogenic nonepileptic seizures differentiated from epileptic seizures?

### Summary

- (1) Even in the presence of clinical symptoms suggesting psychogenic nonepileptic seizures (PNES), PNES cannot be diagnosed based on those symptoms alone.
- (2) A diagnosis of PNES can be made by an experienced doctor, who confirms typical PNES semiology without any EEG abnormal findings immediately before, during, and immediately after the seizure in an ictal video-EEG recording.
- (3) However, ictal video-EEG recording may not provide decisive findings for the diagnosis of simple partial seizures and seizures arising from supplementary motor area, orbital frontal cortex, or cingulate gyrus.
- (4) Even if a definite diagnosis of PNES has been established for one of the seizure types in a patient, we should avoid a hasty conclusion that all other seizures are PNES in the same patient.

### Comment

Psychogenic non-epileptic seizures (PNES) are paroxysmal psychosomatic symptoms resembling epileptic seizures, which is not explainable by already accepted pathophysiological mechanisms. PNES are found in 5–20% of patients who first visit a hospital for suspected epilepsy, and in 15–30% of patients diagnosed with intractable epilepsy with an indication for surgery<sup>1)</sup>. The male to female ratio varies depending on the subject population; PNES are female-dominant in patients with neither concomitant mental retardation (intellectual disability) nor epilepsy, but show no definite gender difference in patients with concomitant mental retardation or epilepsy. The frequencies of concomitant mental retardation vary from 17 to 37% depending on report. In PNES with concomitant epileptic seizures or mental retardation, direct inducing factors are often present. Therefore, we should take detailed history of the patient's living conditions and focus on any changes in lifestyle just before the onset of PNES. On the other hand, in PNES with neither concomitant epilepsy nor mental retardation, we should seek advice from psychiatrists and clinical psychologists because the life history such as family relationship is often critical in those patients.

Typical seizure semiology suggesting PNES includes (1) long duration of seizure, (2) fluctuating symptoms during seizure, (3) asynchronous (left-right) body movements, (4) pelvic thrusting, (5) side-to-side swinging of the head and body, (6) closed eyes during seizure, (7) crying during seizure, (8) memory recall of seizure event, (9) no postictal confusion, and (10) seizures appear to occur during sleeping, but EEG findings show an arousal state<sup>2)</sup>.

However, no symptoms can lead to a definite diagnosis on their own, and the above symptoms should be considered as reference findings.

In the case of suspected PNES, we should confirm the diagnosis over time while following the clinical symptoms as well as performing environmental adjustment and psychotherapy.

Urinary incontinence and tongue biting have been reported during seizures in patients with PNES, although the incidence is low<sup>3)</sup>. Therefore, incontinence and tongue biting do not exclude a diagnosis of PNES<sup>4)</sup>.

Abnormally high prolactin concentration within 10–20 minutes after the attack indicates the unlikelihood of PNES<sup>5)</sup>.

There are four levels of certainty for a diagnosis of PNES, ranging from possible to documented. **Table 1** shows the criteria for the four levels<sup>5)</sup>. Descriptions from a witness of seizure or a video of the actual seizure with routine EEG finding lead to a “possible”, “probable” or “clinically established” diagnosis, while a “documented” diagnosis requires visit to a specialized hospital equipped with simultaneous ictal video-EEG recording.

The main purpose of admission for making a definite diagnosis is to record ictal video-EEG. Moreover, the hospitalization also provides medical staff a chance to observe the actual seizures.

In the case of dose reduction or cessation of antiepileptic drugs at the hospital, we should pay attention to the following risks: manifestation of epileptic seizures that have been controlled until the reduction of drugs, withdrawal seizures in patients treated with phenobarbital and benzodiazepines for a certain period, and induction of status epilepticus.

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## ■ Search formula and secondary reference sources

((((psychogenic AND (nonepileptic OR non-epileptic)) OR PNES) AND (therapy [sh] OR psychotherapy [mh])) Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese

PubMed = 92

psychogenic seizures

Cochrane = 3

**Table 1. Levels of certainty for diagnosis of PNES.**

Diagnostic Level	Source of information	EEG
Possible	By witness or self-reported descriptions	No epileptic activities on routine or sleep-deprived interictal EEG
Probable	Clinician-confirmed semiology typical of PNES by reviewing a video recording or seeing actual attack	As above
Clinically established	Clinician having much experience with epilepsy patients confirmed semiology typical of PNES by reviewing a video recording or seeing actual attack, but not on ictal EEG	No epileptic activities on routine or Holter EEG recorded at the attack with semiology resembling epileptic seizures (epileptic EEG activities would be expected in case of true epileptic seizure)
Documented	Confirmed by clinician having much experience with epilepsy patients on ictal video-EEG	No epileptic activities on video-EEG recorded immediately before, during or immediately after the attack with typical PNES symptoms

(Modified from: LaFrance WC Jr, Baker GA, Duncan R, et al. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures : a staged approach : a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia*. 2013; 54(11): 2005-2018.)

## How are psychogenic nonepileptic seizures treated?

### Summary

- (1) The management of psychogenic nonepileptic seizures (PNES) includes: (1) clearly disclose the diagnosis to the patient as a good news, without nuance of condemnation, (2) explain no need for antiepileptic drug, (3) list up the factors that induce seizure and the factors that perpetuate symptoms, (4) offer psychiatric evaluation, (5) implement individual psychotherapy and family psychotherapy, and (6) consider the use of psychotropic drugs in patients with mood disorder, anxiety disorder, and somatization disorder.
- (2) In principle, antiepileptic drugs are tapered and stopped, but this involves risks such as transient deterioration of the psychological state or manifestation of epileptic seizures masked by antiepileptic drugs.
- (3) When associated with mental retardation (intellectual disability), disclose the diagnosis to the patient and the family, and at the same time adjust the social and psychological environments.
- (4) When PNES coexist with true epileptic seizures, explain in detail to the patients and their family which type of seizure is PNES and which type is epileptic seizure.

### Comment

- (1) Even in patients with PNES confirmed by ictal video-EEG, all the seizures are not necessarily PNES. Considering this point, we should initially explain it to the patients as follows, “Attacks due to emotional problems, not real epilepsy, may coexist with attacks due to epilepsy”<sup>1)</sup>.

In an RCT recruiting patients (IQ 70 or above) without coexisting epileptic seizures who had PNES attacks more than twice a month, cognitive behavioral therapy (CBT) for 4 months significantly reduced the seizure frequency with a moderate or greater effect size, and the odds ratio of seizure control for at least 3 months was 3.125<sup>2)</sup>.

In patients who have taken antiepileptic drugs for long periods of time, some feel that epilepsy is their major problem in life because they believe “they cannot get a job due to epilepsy” and “they cannot have children because of epilepsy”. These patients may have severe psychological disturbance due to loss of identity. Negating the diagnosis of epilepsy needs to go hand in hand with formation of new identity.

Showing the data of ictal video-EEG recorded during seizure to the patient and family is often educational and effective. However, care has to be taken not to convey a value judgment that PNES are false seizures. Most of the PNES are not malingering disorders, but are seizures caused by endogenous conflict.

When referring a patient to a psychiatrist, the message to the patient and family has to be carefully worded so as not to be perceived as sending them away from one’s care, such as, “To exclude all possible disorders and to try all possible treatments, let’s also ask the psychiatrist to give us some advice.” It is desirable to follow the patient by both departments for at least a certain period of time.

- (2) In principle, antiepileptic drugs are reduced in dose and stopped<sup>3)</sup>. Particularly at the cessation of drugs, it is necessary to explain in advance to the patient and family about the possibility of emergence of epilepsy seizures controlled by medications so far or appearance of withdrawal syndrome<sup>1)</sup>.

When the patient and family are very anxious about seizure relapse during dose reduction or cessation of antiepileptic drugs, or when the family has difficulties in coping with urgent situations such as emergency hospital visit, then short-term inpatient treatment is indicated.

If the patient and family request inpatient treatment because they worry about frequent seizures, explain to them that he/she will be hospitalized as a part of psychotherapy in collaboration with the psychiatrist. We should try to prevent long-term hospitalization.

- (3) When the patient has coexisting mental retardation (intellectual disability), explain and disclose the diagnosis to the patient and family and at the same time adjust the psychological and social environments. Full-fledged psychotherapy accompanied by introspection is often difficult to conduct. Listen carefully to the situations leading to PNES, such as loss of parents who protected the patient, big changes in workplace, and human relation at work<sup>1)</sup>.

Maintain an environment that does not encourage gain from illness, such as getting help from many staff members when seizures occur or admission to a hospital when the patient shows PNES. We should adjust the environment so that the patient can receive appropriate attention and protection even without showing PNES.

Disclosure of PNES coexisting with epileptic seizures is more easily accepted by the patient and family, because the presence of PNES does not entail changes in the basic treatment framework such as transfer to another department and cessation of medications.

- (4) When PNES coexist with true epileptic seizures, explain in detail to the patient and family which type of seizure is PNES and which type is epileptic seizure. For the antiepileptic drugs, reduce the doses and change to monotherapy if possible.

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## ■ Search formula and secondary reference sources

((psychogenic AND (nonepileptic OR non-epileptic)) OR PNES) AND (therapy [sh] OR psychotherapy [mh]) Filters: Publication date from 2008/01/01 to 2015/12/31; English; Japanese

PubMed = 92

psychogenic seizures

Cochrane = 3

# Chapter 15

## Psychotic Symptoms of Epilepsy

### CQ 15-1

## What kinds of psychosis accompany epilepsy and what are their treatments?

### Summary

- (1) The majority of psychoses associated with epilepsy are interictal psychoses including alternative psychosis and postictal psychosis.
- (2) For treatment of psychosis, use antipsychotic drugs according to symptoms as for schizophrenia, and if some antiepileptic drugs are suspected to be the cause, consider dose reduction and discontinuation.
- (3) After remission of psychotic symptoms, taper the antipsychotic agents carefully. In patients with a long duration of psychotic symptoms, taper gradually from 1–2 months after complete remission.
- (4) For postictal psychosis, administer benzodiazepine or a sedating antipsychotic drug to induce sleep during the lucid interval after seizure clustering or during the manic state just before emergence of psychotic symptoms.

### Comment

- (1) Psychosis (psychotic disorder or psychiatric symptoms) is a state of obviously abnormal behaviors such as delusions, pronounced hallucinations with lack of insight, or disorganized languages, disorganized behavior, and catatonic behavior. In a meta-analysis<sup>1)</sup>, the frequency of psychosis associated with epilepsy was 5.6% (95% CI: 4.8–6.4%, odds ratio 7.8) among all patients with epilepsy, and 7% (95% CI: 4.9–9.1%) among patients with temporal lobe epilepsy. The frequency of interictal psychosis was 5.2% (95% CI: 3.3–7.2%) and that of postictal psychosis was 2% (95% CI: 1.2–2.8%). Preictal psychosis and ictal psychosis are rare.

Interictal psychosis<sup>2)</sup> is delusional psychosis with strong emotional change, sometimes accompanied by first-rank symptoms typical of schizophrenia such as feeling of being manipulated, but unlike schizophrenia, emotions are preserved.

Alternative psychosis<sup>2)</sup> is a subtype of interictal psychosis with various emotional symptoms and delusions occurring when seizures are controlled. The EEG often shows forced normalization (paradoxical normalization), but EEG examination is not a requisite for the diagnosis. Alternative psychosis sometimes occurs when seizures disappear following epilepsy surgery<sup>3)</sup>.

Postictal psychosis<sup>2)</sup> occurs after seizure clustering (rarely after a single seizure). After a lucid interval of 24 to 48 hours, visual hallucination, auditory hallucination, or delusion occurs within one week. Various hallucination-delusion states accompanied by emotional changes last from a few days to a few weeks (usually 1–2 weeks).

- (2) For the treatment of psychosis, antipsychotic agents are used as for schizophrenia<sup>4)</sup>. Many antiepileptic drugs induce hepatic metabolic enzymes and attenuate the effects of antipsychotic agents. Therefore, high-dose antipsychotics may be needed<sup>5)</sup>. If antiepileptic drugs are suspected to have induced psychotic symptoms, consider dose reduction and discontinuation of the antiepileptic drugs<sup>4, 5)</sup>.
- (3) After remission of psychotic symptoms, reduce the doses of antipsychotic agents carefully. In patients with prolonged psychotic symptoms, reduce doses gradually from 1–2 months after complete remission<sup>5)</sup>.
- (4) During the lucid interval after seizure clustering or during the manic state, administration of benzodiazepine or a sedating antipsychotic drug to induce sleep may prevent the postictal psychosis or mitigate psychotic symptoms<sup>4)</sup>.

## ■ References

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## ■ Search formula and secondary reference sources

epilepsy [majr] AND mental disorders [majr] AND therapy [sh] Filters: Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Publication

PubMed = 86



## How to manage depression and suicide-related behaviors associated with epilepsy?

### Summary

- (1) Treat epilepsy-associated depression with individualized psychotherapy and antidepressants.
- (2) The first-line antidepressants are new antidepressants such as SSRI and SNRI.
- (3) After recovery from the first episode of depression, carefully taper and discontinue antidepressant. After recovery from the second or subsequent depression episode, continue antidepressant even after recovery.
- (4) For patients with a history of depression, when tapering antiepileptic drugs which also have mood-stabilizing effect, carefully taper those drugs.
- (5) Antiepileptic drugs may increase suicide-related behaviors. Provide information to patients and their families regarding the negative psychotropic effects of antiepileptic drugs. Consult with experts in mental health for high risk patients.

### Comment

- (1) In a meta-analysis of epilepsy and depression<sup>1)</sup>, the overall prevalence of active (current or in the past year) depression was 23.1% (95% CI: 20.6–28.3%), with an odds ratio of 2.77 (95% CI: 2.09–3.67). The lifetime prevalence was 13.0% (95% CI: 5.1–33.1%) with an odds ratio of 2.20 (95% CI: 1.07–4.51).

Treatments include individualized supportive psychotherapy, psychoeducation, cognitive behavioral therapy (CBT), and antidepressants<sup>2)</sup>. According to systematic reviews<sup>3, 4)</sup>, antidepressants and CBT are effective. Especially, CBT tailored to individual patient is useful.

- (2) The first-line antidepressants are new antidepressant that are less likely to exacerbate seizures, such as a selective serotonin reuptake inhibitor (SSRI) and serotonin–noradrenaline reuptake inhibitor (SNRI). Start with a low dose to reduce adverse effects and increase until the therapeutic effect appears.

Among SSRIs, enzyme inhibitors such as fluvoxamine may increase serum concentrations of antiepileptic drugs.

When lithium carbonate is used in combination with antiepileptic drugs, adverse effects such as seizure exacerbation and neurotoxicity may occur. Pay special attention to encephalopathy when combined with carbamazepine.

- (3) For the first depression episode, continue antidepressants for around 6 months even after recovery. From the second or subsequent depression episode, continue antidepressants for around 2 years after recovery.
- (4) In patients with a history of mood disorder, carefully taper antiepileptic drugs with mood-stabilizing effect (carbamazepine, oxcarbazepine, valproate, and lamotrigine) when tapering those drugs.
- (5) Provide information to patients and families regarding the negative psychotropic effect of antiepileptic drugs. Especially, pay attention to suicidal ideation in patients with a history of mental disorders.

In patients with a history of suicidal ideation, avoid antiepileptic drugs that induce depression. In patients with a history of episodic behavioral disorders, pay attention to the manifestation of depression in association with a seizure-free state, and consult a mental health expert for patients at high risk of these symptoms<sup>2)</sup>.

A systematic review reported no sufficient evidence for a significant association between antiepileptic drugs and suicide-related behaviors<sup>5)</sup>. However, expert consensus from the ILEA Task Force on Therapeutic Strategies proposed the followings.<sup>6)</sup> (1) Although some antiepileptic drugs may induce psychiatric symptoms and lead to suicidal tendency, its rate is very low and the actual suicidal risk is yet to be established. (2) Suicide in epilepsy is multifactorial. Even in patients with some suicide risk factors, treatment should not be withdrawn. (3) When starting or switching antiepileptic drugs, we (attending doctors) should tell patients to report any mode changes and suicidal ideation when they appear. (4). In clinical trials, information on psychiatric adverse effects caused by antiepileptic drugs should be collected, including family and past history of psychiatric disorders, past history of suicidal behaviors, and screening result using a suicide scale.

## ■ References

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## ■ Search formula and secondary reference sources

epilepsy AND (mental disorders OR depression OR mood OR suicide) Cochrane = 303

epilepsy [majr] AND (depress\* OR suicide) Filters: Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; English; Japanese

PubMed = 104

# Chapter 16

## Acute Symptomatic Seizures

### CQ 16-1

## What is the definition of acute symptomatic seizure?

### Summary

**Acute symptomatic seizures are seizures that occur in close temporal association with acute central nervous system disorders, which include metabolic, toxic, structural, infectious, or inflammatory disorders.**

### Comment

The Commission on Epidemiology and Prognosis of the ILAE defined acute symptomatic seizures as “seizures occurring in close temporal association with an acute systemic, metabolic, or toxic encephalopathy or in association with an acute central nervous system disorder (infection, stroke, head injury, or acute alcohol intoxication or withdrawal)”<sup>1)</sup>. This definition was also adopted by Beghi et al.<sup>2)</sup>.

Among acute symptomatic seizures, convulsive seizures mostly occur only once, but may be repeated or even develop to status epilepticus. Convulsive seizures may recur when the above disorders relapse.

Acute symptomatic seizure is clearly distinguished from epileptic seizure unprovoked by organic disorders (see CQ 1-1 on page 2).

### ■ References

- 1) Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. *Epilepsia*. 1993; 34(4): 592-596.
- 2) Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*. 2010; 51(4): 671-675.

### ■ Search formula and secondary reference sources

PubMed search: November 28, 2008

Acute symptomatic seizure = 222

Additional PubMed search: May 7, 2015

Acute symptomatic seizure (Filters: Clinical Trial; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; Meta-Analysis;)  
= 28

No references that could serve as evidence were found in Ichushi Web.

## What are the causes of acute symptomatic seizures?

### Summary

The etiologies of acute symptomatic seizures include cerebrovascular disease, central nervous system infection, acute immune-mediated encephalopathies, head injury, metabolic or systemic disease, intoxication, withdrawal, post-neurosurgical operation, demyelinating disease, post-radiation therapy, and overlap of several etiologies.

### Comment

The major etiologies for acute symptomatic seizures are shown in **Table 1**<sup>1-4</sup>.

Acute symptomatic seizures differ from epilepsy in having clearly identifiable etiologies, having high mortality rates due to the acute diseases, and requiring short-term treatment with antiepileptic drugs<sup>4,5</sup>. Acute symptomatic seizures often occur in the neonates and the elderly, similarly to epilepsy.

### References

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### Search formula and secondary reference sources

PubMed search: November 28, 2008

Acute symptomatic seizure = 222

Additional PubMed search: May 7, 2015

Acute symptomatic seizure (Filters: Clinical Trial; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; Meta-Analysis;) = 28

No references that could serve as evidence were found in Ichushi Web.

**Table 1. Major acute symptomatic seizures.**

Cerebrovascular disease	Seizure occurring within 7 days of cerebrovascular attack
CNS infection	Seizure occurring in the acute phase of CNS infection
Immune-mediated encephalopathies	See CQ16-6 (page 161)
Head injury	Seizure occurring within 7 days of head trauma
Metabolic or systemic disorders	Seizure occurring in association with systemic diseases including electrolyte imbalance, hypoglycemia, non-ketotic hyperglycemia, uremia, hypoxic encephalopathy, hepatic encephalopathy, hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy syndrome (PRES), systemic lupus erythematosus (SLE), and mitochondrial encephalopathy
Intoxication	Seizure occurring when taking narcotics (such as cocaine), prescribed drugs (such as aminophylline and imipramine), dangerous drugs, drug overdose, environmental pollution (such as carbon monoxide, lead, camphor, and organophosphorus), and alcohol (such as acute alcohol intoxication).
Withdrawal	Seizure occurring within 1-3 days after discontinuation of alcohol and drugs (such as barbiturate and benzodiazepines) in patients who are addicted to those agents
Post-neurosurgical operation	Seizure occurring immediately after intracranial surgery
Demyelinating disease	Seizure occurring in the acute phase of acute disseminated encephalomyelitis or multiple sclerosis
Post-radiotherapy	Seizures occurring within 24 hours after radiation exposure
Multiple etiologies	Seizure related to several concomitant conditions

## How to manage patients with acute symptomatic seizures?

### Summary

**In patients with acute symptomatic seizures, we promptly measure vital signs including consciousness level, take history, perform general and neurological examinations, and continue to perform these procedures.**

### Comment

**Figures 1 and 2** show the flow chart of clinical investigation of patients suspected of acute symptomatic seizures.

In patients with convulsion, we first perform procedures to prevent injury or aspiration. Check vital signs and consciousness level, and perform respiratory and circulatory management if needed. Suspect inflammatory disease if the patient has a fever; and consider hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES), or eclampsia if the patient has severe hypertension. In the case of status epilepticus, start treatment for status epilepticus (see Chapter 8).

For history taking, we should obtain information about symptoms at seizure attack, history of trauma, diseases under treatment (for example, hypoglycemia if receiving insulin injection for diabetes), current medications (for example, drug intoxication if taking massive dose of drug), alcohol drinking history (alcohol dependence, acute alcohol intoxication or withdrawal), and possibility of pregnancy.

For general physical examination, check for injury, incontinence, bite wound, skin conditions (color, rash, cyanosis, etc.), breath odor, and tachypnea. If arrhythmia, cardiac murmur, or cyanosis is present, consider the possibility of syncope, cerebral embolism or heart failure<sup>1)</sup>.

For neurological examinations, first check the level of consciousness, then suspect meningitis or encephalitis if meningeal irritation signs are present, brain tumor or cerebrovascular disease if focal neurological signs are present, and hypocalcemia if Trousseau signs or Chvostek signs are present.

### ■ References

- 1) National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004.

### ■ Search formula and secondary reference sources

PubMed search: November 28, 2008

Acute symptomatic seizure = 222

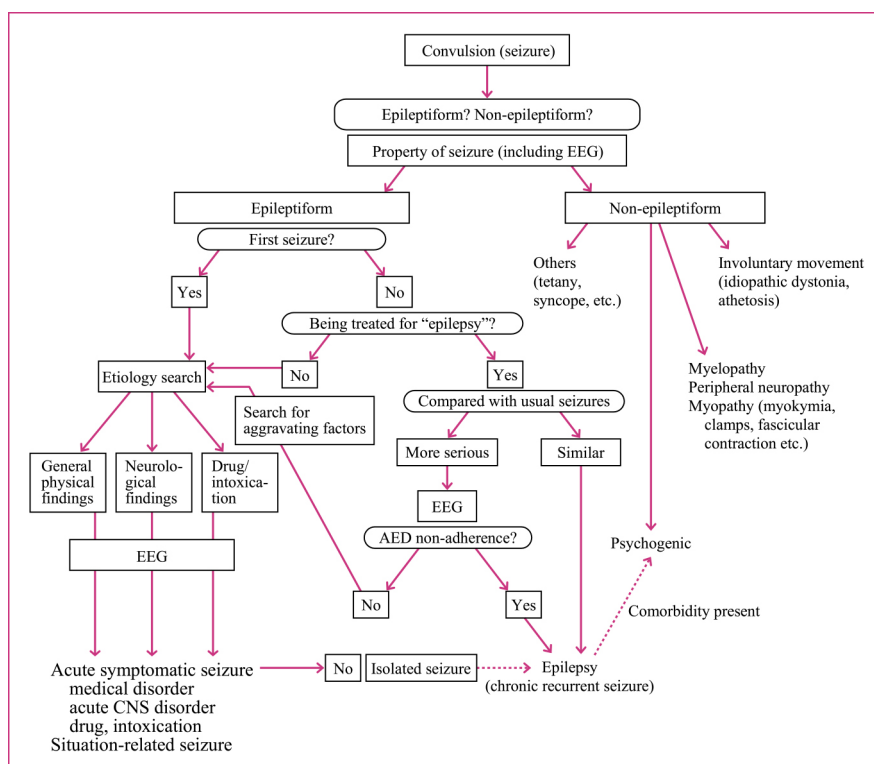
Additional PubMed search: May 7, 2015

Acute symptomatic seizure (Filters: Clinical Trial; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; Meta-Analysis;)  
= 28

No references that could serve as evidence were found in Ichushi Web.

**Figure 1. Procedures of investigation for patients suspected of acute symptomatic seizures, and examples.**

Convulsive seizure, seizure with loss of consciousness	
↓	
Vital sign (conscious state) evaluation	Respiratory and circulatory management as necessary, treatment for status epilepticus
↓	
Medical history	Situation of seizure, past history including trauma, diseases being treated, drugs being used, drinking history, pregnancy, etc.
↓	
General physical examination	Injury, incontinence, bite, skin color, breath odor, tachypnea, etc. Arrhythmia, heart murmur, cyanosis
↓	
Neurological examinations	Level of impaired consciousness, meningeal irritation sign, focal neurological signs, Trousseau signs, Chvostek signs
↓	
Other examinations	Blood tests, head CT or MRI, EEG, ECG, chest X ray, etc. If necessary, cerebrospinal fluid examination
↓	
Treatment	Treatment of underlying disease Antiepileptic drugs in case of high probability of relapse



**Figure 2. Flowchart for diagnosis of acute symptomatic seizures.**

Situation-related seizure: seizure induced only in the presence of inducing factor.

Isolated seizure: unprovoked seizure occurring once in the lifetime.

Broken line in figure suggests the possibility of transition in some cases.

Note: "Epileptiform" in the figure signifies symptoms caused by a state of excessive activation in the brain, and does not necessarily mean seizure symptoms of epilepsy as a chronic disease. (Modified from: Ikeda A, Shibasaki H. Convulsion; differentiation between syncope and epilepsy. In: Sugimoto T, Omata M (ed.) Differential Diagnosis in Internal Medicine, 2<sup>nd</sup> edition. Tokyo: Asakura Publishing Co. Ltd. 2003. p.87–96)

## What kinds of examination are needed for acute symptomatic seizures?

### Summary

Conduct blood test, brain CT or MRI, EEG, electrocardiogram, and chest X-ray, and perform cerebrospinal fluid examination if necessary.

### Comment

Check for hypoglycemia, hypocalcemia, hyponatremia, high creatinine (uremic encephalopathy), high ammonia (hepatic encephalopathy), antinuclear antibody [systemic lupus erythematosus (SLE) and vasculitis], and antibodies of immune-mediated encephalopathies<sup>1)</sup>. Brain CT or MRI is critical for the diagnosis of brain tumor, brain abscess, brain granuloma, and cerebrovascular disease<sup>2, 3)</sup>. Perform cerebrospinal fluid examination if meningitis or encephalitis is suspected in febrile patients with headache or impaired consciousness.

### ■ References

- 1) National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004.
- 2) Harden CL, Huff JS, Schwartz TH, et al. Reassessment: neuroimaging in the emergency patient presenting with seizure (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2007; 69(18): 1772-1780.
- 3) Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2007; 69(21): 1966-2007.

### ■ Search formula and secondary reference sources

PubMed search: November 28, 2008

Acute symptomatic seizure = 222

Additional PubMed search: May 7, 2015

Acute symptomatic seizure (Filters: Clinical Trial; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; Meta-Analysis)  
= 28

No references that could serve as evidence were found in Ichushi Web.

## How to treat acute symptomatic seizures?

### Summary

**For acute symptomatic seizures, treat the underlying disease and start antiepileptic drugs if there is a high probability of seizure recurrence.**

### Comment

If seizure persists, treat as for status epilepticus (see Chapter 8). In the case of a highly probable seizure recurrence in the acute phase, intravenous injection of fosphenytoin, phenytoin, levetiracetam or phenobarbital is useful for patients who have difficulties in taking oral antiepileptic drugs<sup>1, 2)</sup>. Conventional oral antiepileptic drugs are useful for patients capable of oral intake<sup>3-5)</sup>.

Avoid chronic prophylactic use of antiepileptic drugs and stop their administration after a short period, because continuous administration does not prevent transition to epilepsy<sup>2)</sup>.

### ■ References

- 1) Minicucci F, Muscas G, Perucca E, et al. Treatment of status epilepticus in adults: guidelines of the Italian League against Epilepsy. *Epilepsia*. 2006; 47(Suppl 5): 9-15.
- 2) Koppel BS. Treatment of acute and remote symptomatic seizures. *Curr Treat Options Neurol*. 2009; 11(4): 231-241.
- 3) Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia*. 2001; 42(4): 515-524.
- 4) Marson AG, Williamson PR, Clough H, et al. Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis. *Epilepsia*. 2002; 43(5): 505-513.
- 5) Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2006; 47(7): 1094-1120.

### ■ Search formula and secondary reference sources

PubMed search: November 28, 2008

Acute symptomatic seizure = 222

Additional PubMed search: May 7, 2015

Acute symptomatic seizure (Filters: Clinical Trial; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; Meta-Analysis;) = 28

No references that could serve as evidence were found in Ichushi Web.



## How to diagnose and treat anti-NMDA receptor encephalitis?

### Summary

- (1) If acute symptomatic seizures are suspected to be caused by anti-NMDA receptor encephalitis, perform brain MRI and cerebrospinal fluid examination and consider to measure anti-NMDA receptor antibody. Perform a systemic search for the presence of neoplastic disorders including ovarian teratoma.
- (2) After starting appropriate circulatory and respiratory management, consider surgical resection of the tumor in the early stage if paraneoplastic syndrome is suspected. Also consider steroid pulse therapy, high-dose intravenous immunoglobulin therapy, plasmapheresis, and immunosuppressants (currently not covered by medical insurance).

### Comment

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is more prevalent in young women. It initially manifests diverse psychiatric symptoms such as emotional disorder, memory impairment, hallucination, and delusion; and later shows convulsive seizures and involuntary movements such as dyskinesia, respiratory failure, and autonomic nervous system symptoms<sup>1, 2)</sup>. Convulsive seizures may be the initial symptom<sup>3)</sup>.

Brain MRI shows high signal intensity regions in mesial temporal lobe, cerebral cortex, and cerebellum on T2-weighted images. Cells and proteins increase in cerebrospinal fluid. However, these abnormal findings are absent in some cases<sup>1, 2)</sup>. Measurement of autoantibodies including anti-NMDA receptor antibody in blood and cerebrospinal fluid specimens is requisite for the diagnosis<sup>1, 2)</sup>. However, these tests can be done only in a limited number of facilities. Systemic search for malignancies is recommended because tumors such as ovarian teratoma may be involved in the pathophysiology<sup>1, 2, 4)</sup>.

We should consider early surgical resection of a tumor when its involvement is suspected<sup>1, 2)</sup>. When acute anti-NMDA receptor antibody encephalitis is strongly suspected, consider steroid pulse therapy, high-dose immunoglobulin therapy, plasmapheresis, and immunosuppressants<sup>1, 3, 4)</sup>. There is no high level evidence for the choice of treatment method.

### ■ References

- 1) Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* 2008; 7(12): 1091-1098.
- 2) Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol.* 2013; 12(2): 157-165.
- 3) Viacoz A, Desestret V, Ducray F, et al. Clinical specificities of adult male patients with NMDA receptor antibodies encephalitis. *Neurology.* 2014; 82(7): 556-63.
- 4) Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology.* 2008; 70(7): 504-511.

### ■ Search formula and secondary reference sources

PubMed search: December 11, 2014

“anti-n-methyl-d-aspartate receptor encephalitis” [MeSH Terms] OR (“anti-n-methyl-d-aspartate” [All Fields] AND “receptor” [All Fields] AND “encephalitis” [All Fields]) OR “anti-n-methyl-d-aspartate receptor encephalitis” [All Fields] OR (“anti” [All Fields] AND “nmdar” [All Fields] AND “encephalitis” [All Fields]) OR “anti nmdar encephalitis” [All Fields] = 399 Among the 399 papers, the above references were reviewed.

No references that could serve as evidence were found in Ichushi Web.

# Chapter 17

## Epilepsy and Genetics

### CQ 17-1

## Relation between epilepsy and genetics

### Summary

When a parent has epilepsy, the frequency of the patient's children developing epilepsy is 4–6%, which is 2–3 times higher than that in the general population. However, the frequency varies depending on the cause of epilepsy. There is no clear pattern of inheritance for epilepsy in general.

### Comment

The genetic factor plays a small role in the pathogenesis of epilepsy in general<sup>1)</sup>. Therefore, we should take care not to give excessive anxiety to patients and their families and not to lead them to misunderstand the negative impact of the genetic factor.

In some patients, family history reveals definite inheritance patterns (epilepsy syndrome) such as autosomal dominant and recessive inheritance, or sex-linked inheritance. However, the inheritance pattern is undetermined in most of the patients with epilepsy. The familial prevalence and the rate of EEG abnormalities differ even for the same epilepsy syndrome, suggesting multifactorial inheritance pattern involving many overlapping factors. The incidence rate of epilepsy in descendants of the patients is 6%, which is clearly higher than the incidence for people aged up to 20 years in the general population (1–2%). When the mother has epilepsy or when one of the parents has absence seizures, the incidence rate is further increased to 8–9%<sup>2)</sup>. In addition, epilepsy occurs relatively frequently in siblings of patients with epilepsy. In the case that the onset age of the proband is under 15 years, the incidence rate of epilepsy in siblings by 20 years of age is 3–5%<sup>2)</sup>. Moreover, the incidence rate increases to 5–15% in the proband's siblings when the EEG of the proband shows generalized spike-and-wave complex, or when the proband's parent is (or both parents are) affected by epilepsy<sup>2)</sup>.

Regarding febrile convulsion, while the prevalence in children is 7–11% (4% in other countries), the prevalence increases to 20–25% in siblings of patients with febrile convulsion. Also, children with febrile convulsion will eventually have non-febrile convulsion (epilepsy) at a higher rate when their parents are affected by epilepsy<sup>3, 4)</sup>.

### ■ References

- 1) Genetics Commission of International League Against Epilepsy. Things you want to know. <https://www.ilae.org/files/dmfile/GeneticsPamphlet-2013.pdf>
- 2) Hauser WA, Hesdorffer DC. Facts about epilepsy. New York: Demos press, 1999. p.1-16.
- 3) Granstrom ML, Gaily E, Beck-Mannagetta G. Febrile convulsions, epileptic seizures and EEG abnormalities in offspring of epileptic mothers. In: Beck-Mannagetta G, Anderson VE, Doose H, Janz D eds. Genetics of epilepsies, Berlin: Springer-Verlag, 1989. p.137-141.
- 4) Clinical Practice Guideline for Febrile Convulsion Development Committee (ed.), The Japanese Society of Child Neurology (supervision). Clinical Practice Guideline for Febrile Convulsion 2015. Tokyo: Shindan To Chiryō Sha, Inc. 2015 (in Japanese).

### ■ Search formula and secondary sources for reference

PubMed search: June 28, 2015

No. of references 63 “epilepsy/genetics [majr] AND heredity [mesh] Sort by: Relevance Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese”

Ichushi search: June 28, 2015

No. of references 100, ((epilepsy/MTH) and ((genetic test/TH or genetic test/AL))) and (PT = excluding proceedings)

# Current situation of genetic research and genetic testing for epilepsy

## Summary

Various mutations have been identified in many epilepsy syndromes. However, genetic diagnosis has clinical significance in only a few epilepsy syndromes. Identification of gene abnormalities leads to a definite diagnosis only for progressive myoclonic epilepsy, Angelman syndrome, Rett syndrome, and Dravet syndrome.

## Comment

The causative genetic abnormalities for various epilepsy syndromes are shown in **Table 1**<sup>1, 2)</sup>, and those for progressive myoclonic epilepsy (PME) are shown in **Table 2**<sup>3)</sup>. When Dravet syndrome is suspected, gene testing is useful because the findings from the SCN1A genetic test may help us determine the treatment strategy and provide genetic counseling at an earlier stage than when diagnosis is obtained from only clinical symptoms<sup>4)</sup>.

On the other hand, based on the current knowledge about genetic research on epilepsy, genetic results cannot accurately predict the prognosis (for example, patients with the same SCN1A mutation may have different phenotypes). Moreover, even when the genetic test result is negative, it does not exclude the possibility of having an unknown causative gene or a gene unidentifiable by conventional sequence analyses such as copy-number polymorphisms. It should be noted that genetic tests have only limited usefulness for exclusion diagnosis.

Furthermore, many genetic tests are not covered by medical insurance at present, making it difficult to be used as a routine test in the clinical practice.

## ■ References

- 1) Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. *Epilepsia*. 2010; 51(4): 655-670.
- 2) Ishii A. Molecular genetics of Dravet syndrome and GEFS+ : The spectrum of epilepsies caused by mutations of SCN1A and other genes. *Igaku No Ayumi*. 2015; 253(7); 561-567 (in Japanese).
- 3) Nakayama T. Molecular genetics of progressive myoclonic epilepsy. *Igaku No Ayumi*. 2015; 253(7); 584-588 (in Japanese).
- 4) Hirose S, Scheffer IE, Marini C, et al. Genetics Commission of the International League Against Epilepsy. SCN1A testing for epilepsy: application in clinical practice. *Epilepsia*. 2013; 54(5): 946-952.

## ■ Search formula and secondary sources for reference

PubMed search: June 28, 2015

No. of references: 21, “epilepsy/genetics [majr] AND genes [mesh] Filters: Review; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese”

Ichushi search: June 28, 2015

No. of references: 27, ((epilepsy/MTH) and ((gene/TH or gene/AL))) and (PT = review)

**Table 1. Causative genes identified in various epilepsy syndromes.**

<b>Epilepsy syndrome</b>	<b>Locus</b>	<b>Gene</b>	<b>Product</b>
Benign familial neonatal seizures	20q13.3 8q24	<i>KCNQ2</i> <i>KCNQ3</i>	K <sub>v</sub> 7.2(K <sup>+</sup> channel) K <sub>v</sub> 7.3(K <sup>+</sup> channel)
Benign familial neonatal-infantile seizures	2q23-q24.3	<i>SCN2A</i>	Na <sup>+</sup> channel $\alpha_2$ subunit
Benign infantile epilepsy	16p11.2	<i>PRRT2</i>	Proline-rich transmembrane protein 2
Ohtahara syndrome	9q34.1 Xp22.13	<i>STXBP1</i> <i>ARX</i>	Syntaxin binding protein 1 Aristaless related homeobox
Infantile spasms (atypical Rett syndrome / West syndrome)	Xp22	<i>STK9/CDKL5</i>	Cyclin-dependent kinase-like 5
X-linked infantile spasms	Xp22.13	<i>ARX</i>	Aristaless related homeobox
Severe myoclonic epilepsy of infancy (Dravet syndrome)	2q24 2q24.3 5q34-q35 9q34.1	<i>SCN1A</i> <i>GABRG2</i> <i>GABRA1</i> <i>CHD2</i> <i>STXBP1</i>	Na <sup>+</sup> channel $\alpha_1$ subunit GABA <sub>A</sub> receptor $\gamma_2$ subunit GABA <sub>A</sub> receptor $\alpha_1$ subunit Chromodomain helicase DNA binding protein 2 Syntaxin binding protein 1
Genetic epilepsy with febrile seizures plus (GEFS+)	2q24 19q13.1 5q34	<i>SCN1A</i> <i>SCN1B</i> <i>GABRG2</i> <i>GABRD</i> <i>SCN9A</i> <i>STX1B</i>	Na <sub>v</sub> 1.1(Na <sup>+</sup> channel) Na <sup>+</sup> channel $\beta_1$ subunit GABA <sub>A</sub> receptor $\gamma_2$ subunit GABA <sub>A</sub> receptor $\delta$ subunit Na <sup>+</sup> channel $\alpha_9$ subunit Syntaxin 1B
Childhood absence epilepsy (with febrile seizures plus)	5q34	<i>GABRG2</i>	GABA <sub>A</sub> receptor $\gamma_2$ subunit
<i>PCDH19</i> -related epilepsy limited to females	Xq22	<i>PCDH19</i>	Protocadherin 19
Early-onset absence epilepsy (glucose transporter-1 deficiency syndrome)	1p35-p31.1	<i>SLC2A1</i>	GLUT1
Juvenile myoclonic epilepsy	5q34-q35 6p12-p11	<i>GABRA1</i> <i>EFHC1</i>	GABA <sub>A</sub> receptor $\alpha_1$ subunit EF-hand domain-containing protein 1
Autosomal dominant nocturnal frontal lobe epilepsy	20q13.2-q13.3 1q21 8p21	<i>CHRNA4</i> <i>CHRNA2</i> <i>CHRNA2</i>	nACh receptor $\alpha_4$ subunit nACh receptor $\beta_2$ subunit nACh receptor $\alpha_2$ subunit
Autosomal dominant lateral temporal epilepsy (autosomal dominant epilepsy with auditory features)	10q24	<i>LGII</i>	Leucine rich glioma inactivated 1
Generalized epilepsy and paroxysmal dyskinesia	10q22	<i>KCNMA1</i>	K <sub>Ca</sub> 1.1(K <sup>+</sup> channel)
Absence epilepsy and episodic ataxia type 2	19p13	<i>CACNA1A</i>	Ca <sub>v</sub> 2.1(Ca <sup>2+</sup> channel)
Focal epilepsy and episodic ataxia type 1	12p13	<i>KCNA1</i>	K <sub>v</sub> 1.1(K <sup>+</sup> channel)
Familial hemiplegic migraine and epilepsy	1p21-23	<i>ATP1A2</i>	Sodium-potassium ATPase
Angelman syndrome	15q11-13	Loss including <i>UBE3A</i>	(UBE3A)
Rett syndrome	Xp28 14q12	<i>MECP2</i> <i>FOXG1</i>	Methyl-CpG-binding protein-2 Forkhead box protein G1

(Partially modified from: Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. *Epilepsia*. 2010; 51(4): 655-670.)

**Table 2. Causative genes in progressive myoclonic epilepsy (PME).**

Name of disease	Onset age (years)	Clinical symptoms	Locus	Gene
Neuronal ceroid lipofuscinosis (NCL)*				
Infantile NCL	0.5–2	Vision loss, microcephaly, epilepsy, regression	1p34.2	<i>CNL1</i>
			11p15.4	<i>CNL2</i>
			16p11.2	<i>CNL3</i>
Late Infantile NCL)	2–4	Vision loss, epilepsy, myoclonus	20q13.33	<i>CNL4</i>
			13q22.3	<i>CNL5</i>
			15q23	<i>CNL6</i>
Juvenile NCL	4–10	Vision loss, epilepsy	4q28.2	<i>CNL7</i>
			8p23.3	<i>CNL8</i>
Adult NCL	12–50	Epilepsy, ataxia, dementia	Not Mapped	<i>CNL9</i>
			11p15.5	<i>CNL10</i>
			17q21.31	<i>CNL11</i>
			11q13.2	<i>CNL13</i>
			7q11.21	<i>CNL14</i>
Dentatorubral-pallidoluysian atrophy (DRPLA)	All ages	Myoclonus, cerebella ataxia, epilepsy	12p13.31	<i>ATNI</i>
Mitochondrial encephalomyopathy (MERRF)	5–42 (mostly in childhood)	Short stature, hearing loss, cardiomyopathy	mtDNA	<i>MT-TK</i>
			mtDNA	<i>MT-TL1</i>
			mtDNA	<i>MT-TF</i>
			mtDNA	<i>MT-T1</i>
			13q34	<i>CARS2</i>
Unverricht-Lundborg disease (ULD)	6–16	Myoclonus, epilepsy, no or mild intellectual disability	21q22.3	<i>CSTB</i>
			12q12	<i>PRICKL</i>
			4q21.1	<i>E1</i>
			17q21.32	<i>SCARB2</i>
				<i>GOSR2</i>
PME with K <sup>+</sup> channel abnormality	6–14	Resembling Unverricht-Lundborg disease	11p15.1	<i>KCNK1</i>
Lafora disease	9.5–18	Epilepsy, myoclonus, regression	6q24.3	<i>EPM2A</i>
			6p22.3	<i>EPM2B</i>

\* The loci and responsible genes for NCL are identified from all NCL, and does not correspond to each clinical subcategory.  
(Partially modified from: Nakayama T. Molecular genetics of progressive myoclonic epilepsy. Igaku No Ayumi. 2015: 253(7); 584-588.)

# Chapter 18

## Advice and Information for Patients

### CQ 18-1

## What kinds of advice should be given to patients?

### Summary

Provide the following information to patients with epilepsy (and their families), or inform them of the methods to obtain such information.

- (1) General knowledge about epilepsy
- (2) Caution in daily life
- (3) Types of epileptic seizures
- (4) Effects and adverse effects of antiepileptic drugs, and method of drug taking
- (5) How to cope with epileptic seizures and risk of seizures
- (6) Psychological problems about epilepsy
- (7) Support system and organizations for epilepsy
- (8) Legal knowledge on driver's license
- (9) Matters concerning education and employment
- (10) Pregnancy and childbirth

### Comment

Regarding advice to patients, explain the above contents depending on the situation of individual patients<sup>1)</sup>.

### ■ Reference

- 1) Couldridge L, Kendall S, March A. A systematic overview—"a decade of research". The information and counselling needs of people with epilepsy. *Seizure*. 2001; 10(8): 605-614.

## How to give advice on driver's license?

### Summary

- (1) It is desirable to explain matters about driving when a person is newly diagnosed with epilepsy or at the first visit.
- (2) Provide information about epilepsy written in the Road Traffic Act and the Act on Punishment of Acts Inflicting Death or Injury on Others by Driving a Motor Vehicle.
- (3) Give advice on whether or not to drive a car following the domestic law on driving.

### Comment

It is desirable to explain matters about driving a motor vehicle to patients with epilepsy when they are newly diagnosed with the disease or at their first visit.

We should give the patients information about an outline of the items related to epilepsy in the Road Traffic Act and the Act on Punishment of Acts Inflicting Death or Injury on Others by Driving a Motor Vehicle, as shown below.

- (1) Do not drive a vehicle when the patients are under the condition in which they may not be able to drive normally, such as due to overwork, illness, medication, or other reasons (Road Traffic Act Article 66, with penalty).
- (2) The Public Safety Commission will not issue a driving licenses to persons with epilepsy (Road Traffic Act Article 90). However, this restriction does not apply when there is no risk of seizure that will hinder driving. The required criterion is that seizure that impairs consciousness or movement during the awake state has not occurred for a period of 2 years (operation standards for issuing license by the Public Safety Commission, **Table 1**).
- (3) A patient should declare the disease condition accurately when obtaining or renewing the driver's license (partially revised law of Road Traffic Act, with penalty).
- (4) If the driver's license was revoked due to illness but later the patient recovers to a state capable of re-acquiring the license, the written test and the practical test will be exempted (partially revised law of Road Traffic Act).
- (5) For epilepsy with a risk of recurrence of seizures that impair consciousness or movement, if a patient, despite being under influence of the above condition (with a risk of hindering normal driving) and consequently not able to drive normally, drives a motor vehicle and causes death or injury, a penalty will be imposed which is heavier than that for professional negligence resulting in death (Act on Punishment of Acts Inflicting Death or Injury on Others by Driving a Motor Vehicle).

In giving advice on whether or not to drive a car, in principle provide guidance in accordance with domestic laws (**Table 1**). For items without legal provisions, provide appropriate medical guidance, such as the following.

- (1) "There is no risk of seizure" in the Act is usually interpreted as "the risk is considerably low" rather than "the risk of seizure is zero".
- (2) Even after seizures has not occurred for 2 years, instruct the patient not to drive during periods when the risk of seizure relapse is judged medically to be high, such as after changing antiepileptic drugs, under poor physical condition, or lack of sleep.
- (3) When epilepsy is newly diagnosed or when seizure relapses after a certain seizure-free period, even if the patient still retains the driver's license, he/she is in "a state of not able to drive normally". Therefore, advise the patient not to drive for 2 years.
- (4) At the first attack which is not diagnosed as epilepsy, instruct the patient not to drive for a certain period (for example, 6 months).

### For reference

According to the revised Road Traffic Law and operation standards enforced on June 1, 2014, a driver's license is permitted if a patient with epilepsy meets the prescribed conditions. Whether a license is issued is determined by the Public Safety Commission based on a doctor's medical report or a special fitness screening. Regarding epilepsy and driver's license, there is a detailed comment in the Q&A regarding the revised Road Traffic Act on the website of the Japan Epilepsy Society<sup>1)</sup>. If there is any question, contact the "Inquiry Desk for Fitness of Driving" installed in prefectural driver's license centers, or

recommend patients to consult the driver's license center.

From 2014, when a patient is diagnosed to be in a state subject to denial of driver's license provided by the Operation Standards of the Road Traffic Act, and the patient is found to possess a driver's license and is actually driving, it is possible to report the case to the Public Safety Commission on a voluntary basis. Regarding notification, the Japan Epilepsy Society (Table 2) and the Japan Medical Association have published notification guidelines<sup>2, 3)</sup>.

## ■ References

- 1) Japan Epilepsy Society Legal Issue Committee. Q&A on the revised Road Traffic Act. (2014) [http://square.umin.ac.jp/jes/images/jes-image/140912\\_RoadTrafficLaw.pdf](http://square.umin.ac.jp/jes/images/jes-image/140912_RoadTrafficLaw.pdf) (in Japanese)
- 2) Japan Epilepsy Society Legal Issue Committee. Guideline on doctor's notification for epilepsy. [http://square.umin.ac.jp/jes/images/jes-image/140910JES\\_GL.pdf](http://square.umin.ac.jp/jes/images/jes-image/140910JES_GL.pdf) (in Japanese)
- 3) Japan Medical Association. Guideline on voluntary notification from doctors who diagnosed the diseases manifesting given symptoms based on the Road Traffic Act. (2014) [http://dl.med.or.jp/dl-med/teireikaiken/20140910\\_1.pdf](http://dl.med.or.jp/dl-med/teireikaiken/20140910_1.pdf) (in Japanese)

**Table 1. Criteria for permission or denial of license related to specific diseases.**

<p>(1) License is not denied in the following cases.</p> <p>A. If no seizure has occurred within the past 5 years, and a doctor has made a diagnosis to the effect that “there is no risk of seizure occurring in the future”</p> <p>B. If no seizure has occurred within the past 2 years, and a doctor has made a diagnosis to the effect that “there is no risk of seizure occurring in the next x years”</p> <p>C. If, after 1-year follow-up, a doctor has made a diagnosis to the effect that “seizure is limited to simple partial seizure without impaired consciousness or movement, and there is no risk of worsening of symptoms in the future.”</p> <p>D. If, after 2-year follow-up, a doctor has made a diagnosis to the effect that “seizure only occurs during sleep, and there is no risk of worsening of symptoms in the future.”</p> <p>(2) In the case that a doctor has made a diagnosis to the effect that “it is expected that a diagnosis corresponding to (1) above can be made within 6 months,” license shall be withheld or suspended for 6 months. (Based on the diagnosis of a doctor, if it is recognized that a withholding or suspension period shorter than 6 months is sufficient, that period shall be set as the withholding or suspension period)</p> <p>During the period of withholding or suspension, issue order to take fitness screening or submit medical report.</p> <p>① When the result of fitness screening or the medical report is consistent with (1) above, license is not denied.</p> <p>② If the content is “Eventually, a diagnosis corresponding to (1) above cannot be made, but because there was a special circumstance of ○ ○ during the period, it is expected that a diagnosis corresponding to (1) above can be made within another 6 months”, then the license shall be withheld or suspended for another 6 months. (Based on the diagnosis of a doctor, if it is recognized that a withholding or suspension period shorter than 6 months is sufficient, that period shall be set as the withholding or suspension period).</p> <p>③ For other cases, the license shall be denied or cancelled.</p> <p>(3) For other cases, the license shall be denied or cancelled.</p> <p>(4) For cases corresponding to item (1) (A) above, a special fitness screening test shall be conducted after a certain period (x year).</p> <p>(5) The Japan Epilepsy Society currently expresses the opinion that at this point in time, except those who have had no seizures related to epilepsy without medication for the past 5 years and no risk of relapse in the future, usually persons with epilepsy do not have the fitness for the licenses to drive mid-sized vehicles [except mid-sized vehicles (limited to 8 t)] and large vehicles, and for class II license. When persons corresponding to this category apply for these licenses or apply for renewal, even they are not subject to ruling as in (2) and (3) above, they should be given explanation of the opinion and recommended to reconsider the license application or renewal application for the time being, and to utilize the application revocation system.</p>
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**Table 2. Japan Epilepsy Society Legal Issue Committee. Guideline on doctor's notification for epilepsy**

<p>(1) If a patient is diagnosed as in a state subject to denial of a driver's license shown in the Operation Standards of the Road Traffic Act, and if the patient is found to possess a driver's license and is actually driving, try to persuade the patient not to drive.</p> <p>(2) Explain to the patient the possibility that when applying or renewing a driver's license, if the patient is diagnosed as in a state subject to denial of a driver's license shown in the Operation Standards, the Public Safety Commission will refuse, cancel, withhold or suspend the license. Also, recommend the patient to report the symptoms accurately to the Public Safety Commission. Explain that if he/she intentionally conceal symptoms that interfere with driving or acquires/renews the license by making a false declaration, it is possible that he/she will be penalized for violation of the Road Traffic Act (penal provision: imprisonment up to 1 year or a fine of up to 300,000 yen).</p> <p>(3) In the case that the risk of traffic accident caused by a patient is judged to be extremely high (for example, the risk is considered high if, in addition to the number of seizures, there is a history of traffic accidents or irregular drug taking), and the patient is found to be actually driving despite sufficient persuasion to stop driving, assess the situation comprehensively and consider notification to the Public Safety Commission. However, when submitting a notification, pay close attention to avoid damaging the doctor-patient relationship, with the result that the patient avoids reporting his/her medical condition accurately or receiving proper medical care.</p> <p>(4) Refer to the guidelines of the Japan Medical Association for specific notification procedures to the Public Safety Committee.</p>
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# Part II

## Systematic Review Digest

# CQ 9-2 Digest Edition

## CQ 9-2

### Should temporal lobe resection be added to drug therapy in drug-resistant temporal lobe epilepsy?

#### Recommendation

We recommend temporal lobectomy in addition to drug therapies in patients with drug-resistant epilepsy (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note:** In the GRADE system, when the evidence level is “very low”, in principle it is not possible to grade “strong recommendation”. Since temporal lobe resection is highly effective with low incidence of adverse effects, almost all the panelists supported “strong recommendation”, but due to the constraint of the GRADE system, the final grading was “weak recommendation”.

#### 1. Background, priority of the problem

For drug-resistant epilepsy, adding further new drugs has limited effect. The temporal lobe resection is expected to achieve seizure-free condition despite its invasiveness.

#### 2. Comment

##### Evidence summary

There were 2 randomized controlled trials (RCT) (total 118 patients) on the effectiveness of temporal lobe resection for drug-resistant epilepsy<sup>1, 2</sup>. With regard seizure outcome, the relative risk was 20.57 (95% confidence interval 4.24–99.85) and the number needed to treat (NNT: indicating the number of persons needed to treat to achieve the outcome for one person) was 4, showing superiority of temporal lobe resection. Neither of the two RCTs mentioned decrease of antiepileptic drugs after surgery. Death rate did not differ between two groups.

The relative risk of surgical complications was 12.33 (95% confidence interval 1.67–90.89), and was higher in the temporal lobe resection group. Death, memory impairment, and psychiatric symptoms were not significantly different between the two groups. Quality of life (QOL) improvement was superior in the temporal lobe resection group.

#### 3. Panel meeting

##### 3-1. What is the overall quality of evidence across outcomes?

Since we were not able to mask the intervention, the risk of bias was high overall in the collected studies. Bias for death was considered not serious, while that for the other outcomes was considered serious and was downgraded one rank. Inconsistency and non-directness of the results were without question and considered not serious. For imprecision, confidence intervals crossed the clinical decision threshold in many items, and was downgraded one or two ranks. Publication bias could not be judged because of the small number of studies. Consequently, the level of evidence for the outcomes was as follows: “low” for seizure freedom, death, surgical complications, and quality of life improvement; and “very low” for memory impairment and psychiatric symptoms. The overall level of evidence was “D (very low)”.

\* For surgical therapy, since blinding of the control group is difficult, the level of evidence is generally low.

##### 3-2. How is the balance between benefits and harms?

Temporal lobe resection can be expected to control seizures. As a result, antiepileptic drugs are possibly reduced although it is not shown in RCT. The incidence of serious adverse effects was low. Therefore, the risk of temporal lobe resection is considered to be smaller compared to its benefit.

### **3-3. What about patients' values and preference?**

Some patients may feel resistant to receive invasive surgical therapy, but the beneficial effect of seizure-free produced by the surgery outweighs the resistance to the invasive procedure. There is perhaps no significant uncertainty or variability in value among the patients.

### **3-4. What is the balance between net benefit and cost or resources?**

The health insurance fee scale for epilepsy surgery using a microscope (including temporal lobe resection) is 131,630 points (as of January 11, 2018). The surgery is conducted under general anesthesia and requires neurosurgeons.

However, through reducing antiepileptic drugs, decreasing hospitalization duration accompanying reduced seizures, and enabling more active social activities, epilepsy surgery is expected to lead to saving in the long term. For this reason, the cost can be considered negligible.

### **3-5. Recommendation grading**

During the discussions at the panel meeting, temporal lobe resection was expected to eliminate seizures, and overall the cost of the surgery could be considered negligible. Even taking the adverse effects into account, the surgery was supported by panelists.

At the panel meeting, many panelists supported a recommendation grade of “strong recommendation”. However, in the GRADE system, when the evidence level is “very low”, in general we are not able to grade “strong recommendation”. For this reason, the final grading was “weak recommendation”.

## **4. Descriptions in other related guidelines**

In Japan, the Japan Epilepsy Society published the “Guideline on indications for epilepsy surgery”<sup>3)</sup> in 2008, and “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy”<sup>4)</sup> in 2010.

The “Guideline on indications for epilepsy surgery” recommends surgical treatment for mesial temporal lobe epilepsy at a suitable timing, stating that “since surgical results are superior in cases of mesial temporal lobe epilepsy with a localized organic lesion or with extensive lesions in unilateral hemisphere, consider surgical treatment from an early stage and do not miss the timing of surgery”. The “Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy” also follows the above recommendation, stating that “patients should be selected in accordance with the guideline on indications for epilepsy surgery”.

In overseas countries, the Quality Standards Subcommittee of the American Academy of Neurology, the American Epilepsy Society, and the American Association of Neurological Surgeons published a guideline<sup>5)</sup> in 2003. The guideline states that “drug-resistant epilepsy should be considered for referral to an epilepsy surgery center” and that “patients who meet established criteria for an anteromesial temporal lobe resection and who accept the risks and benefits of this procedure should be offered surgical treatment”.

## **5. Treatment monitoring and evaluation**

Monitoring and evaluation during the perioperative period of treatment are generally performed by a neurosurgeon. After this period, although a neurosurgeon is not necessarily required to monitor and evaluate, follow-up and support should be provided to the patients.

## **6. Possibility of future research**

Some memory-preserving or minimally invasive surgery may be developed in the future. In addition, we would like to know the surgical outcomes and adverse events over a longer follow-up period because the observation periods of the two RCT were 1 year<sup>1)</sup> and 2 years<sup>2)</sup>.

## **7. RCT reports reviewed for this CQ**

Wiebe 2001<sup>1)</sup>, Engel 2012<sup>2)</sup>

## 8. List of appendices (to be shown later)

- Appendix CQ9-2-01. Flow diagram and literature search formula
- Appendix CQ9-2-02. Risk of bias summary
- Appendix CQ9-2-03. Risk of bias graph
- Appendix CQ9-2-04. Forest plot
- Appendix CQ9-2-05. Summary of Findings (SoF) table
- Appendix CQ9-2-06. Evidence-to-Decision table

## ■ References

- 1) Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001; 345(5): 311-318.
- 2) Engel J Jr, McDermott MP, Wiebe, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA*. 2012; 307(9): 922-930.
- 3) Mihara T, Fujiwara T, Ikeda A, et al. Guideline on indications for epilepsy surgery. *Tenkan Kenkyu*. 2008; 26(1): 114-118 (in Japanese).
- 4) Watanabe E, Fujiwara T, Ikeda A, et al. Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy. *Tenkan Kenkyu*. 2006; 27(3): 412-416 (in Japanese).
- 5) Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology*. 2003; 60(4): 538-547.

## Literature search

### PICO

P: Patients with drug-resistant epilepsy

I: Temporal lobe resection added to drug therapy

C: Compared with drug therapy alone

O: Are seizures eliminated or reduced?

Are antiepileptic drugs reduced or discontinued?

Is there increase in death related to surgery?

Are there increases in complications (medical/neurological) related to surgery?

Is memory (IQ, memory) lowered?

Is QOL (including psychiatric symptoms) improved?

## ■ Search formula

PubMed search: September 28, 2016

#1 Search (("drug resistant epilepsy" [mesh] OR ((epilepsy OR seizures OR convulsions) AND (intractable OR refractory OR resistant)))

#2 Search ("anterior temporal lobectomy" OR (temporal lobe AND surgery [sh]))

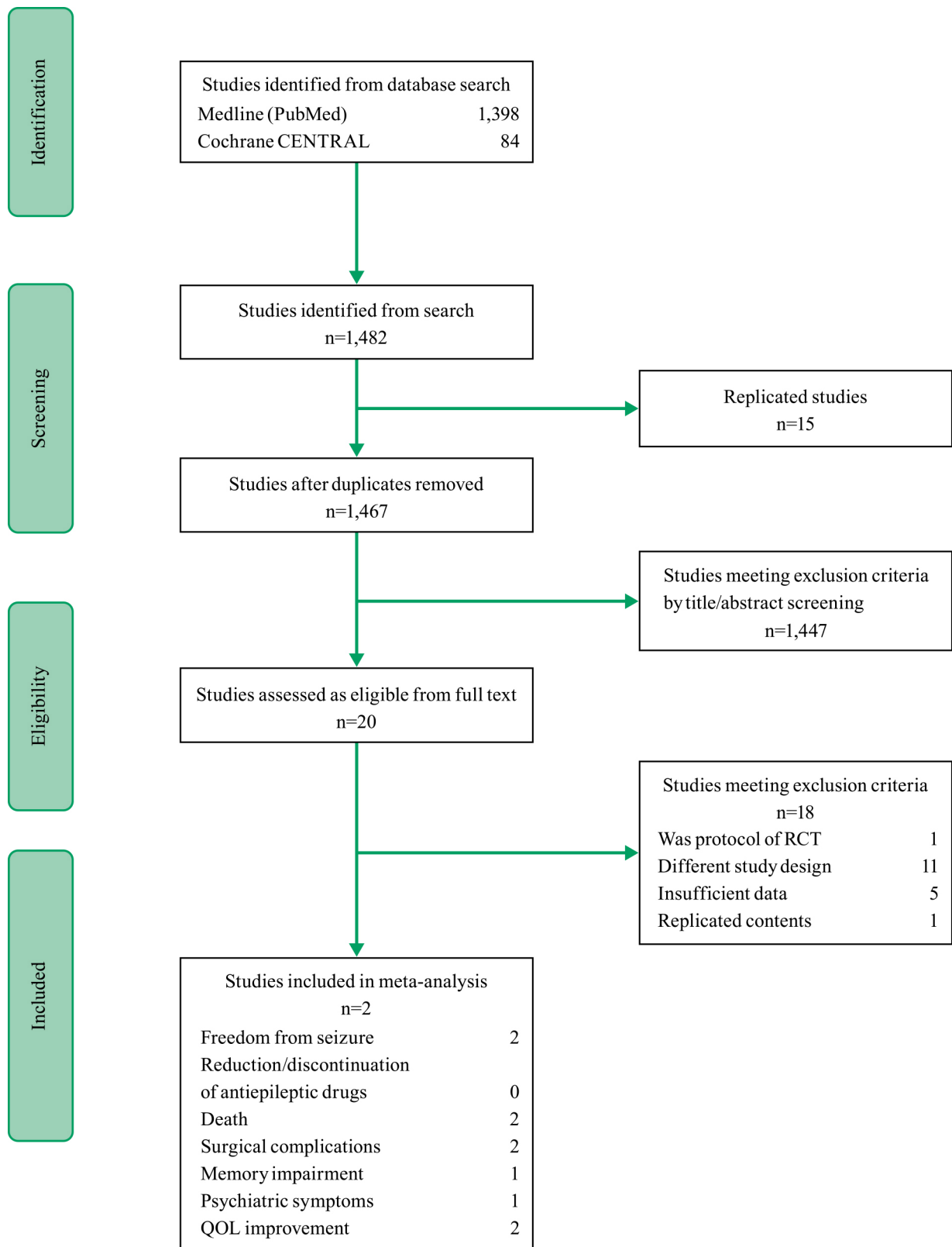
#3 Search (randomized controlled trial[pt] OR meta-analysis[pt] OR randomized OR blind OR observation\* OR cohort OR "follow-up" OR cross OR case OR series OR prospective OR retrospective OR placebo OR trial)

#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

(epilepsy OR seizures) AND "temporal lobe" AND surgery

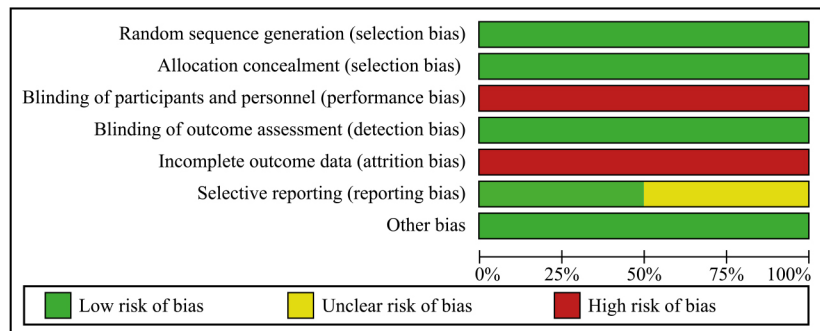
## CQ9-2. Flow diagram of literature search (modified PRISMA 2009)





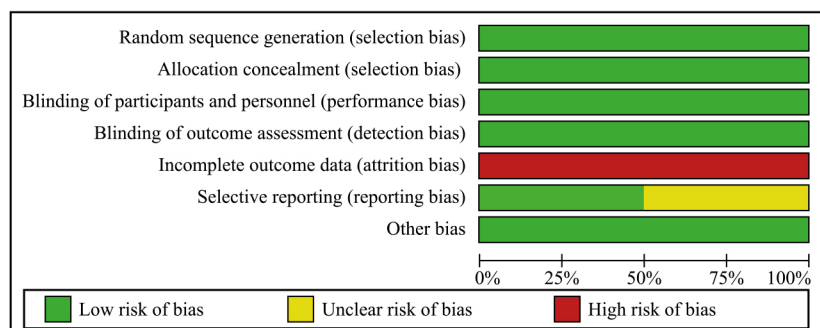
## Seizure freedom

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Engel 2012	+	+	-	+	-	+	+
Wiebe 2001	+	+	-	+	-	?	+

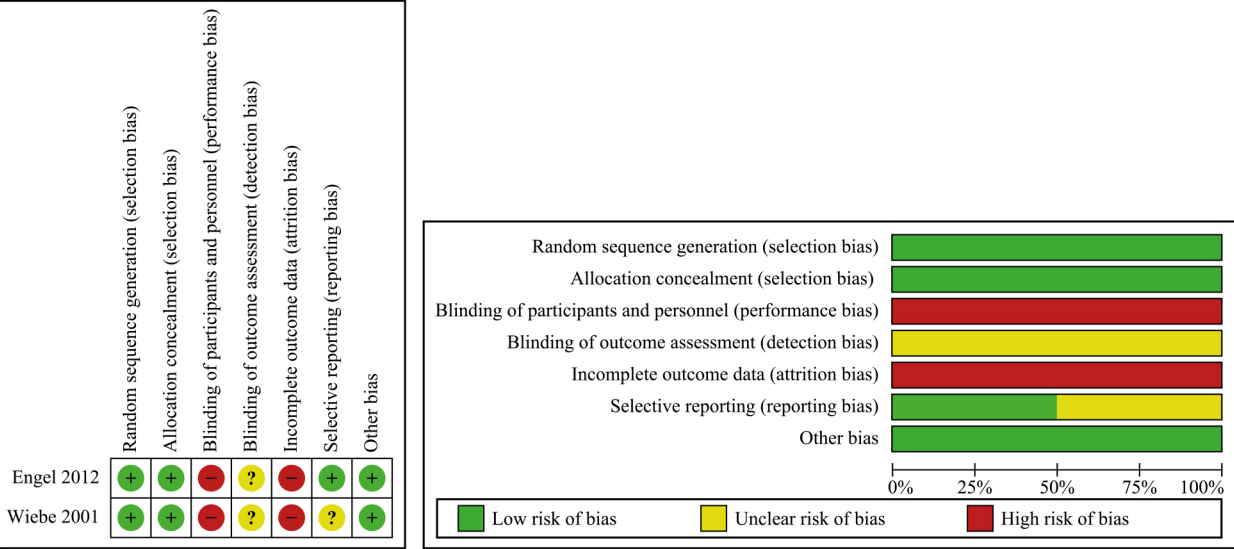


## Death

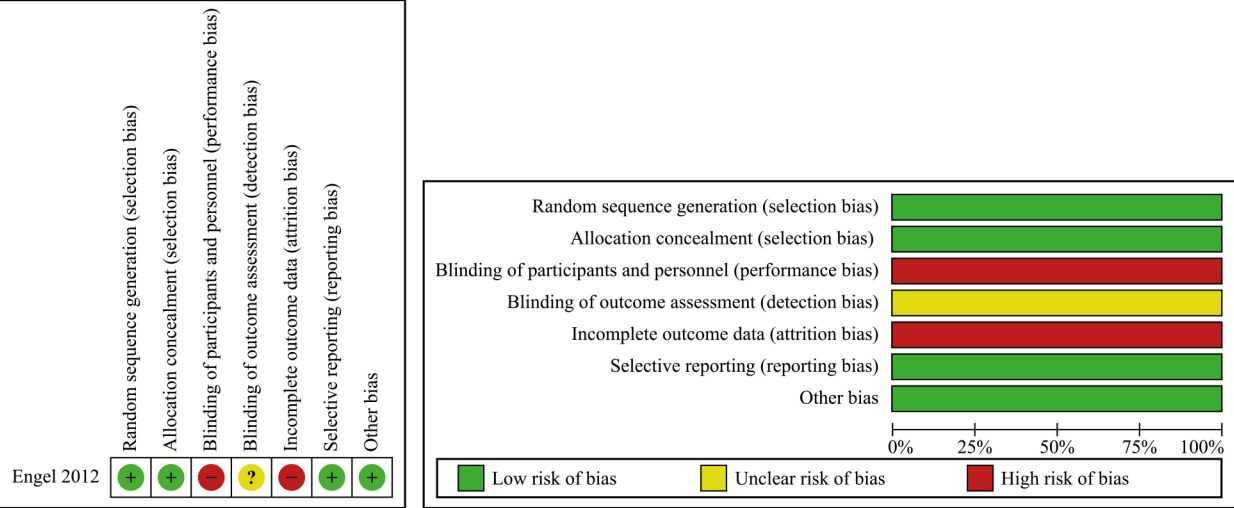
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Engel 2012	+	+	+	+	-	+	+
Wiebe 2001	+	+	+	+	-	?	+



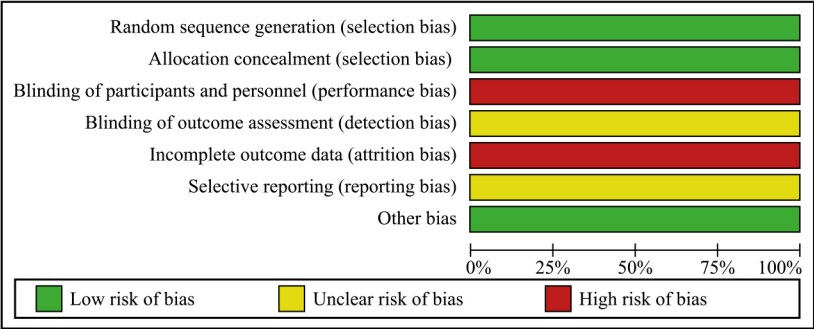
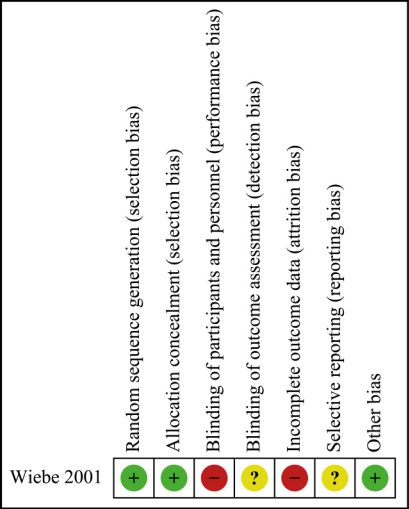
Surgical complications



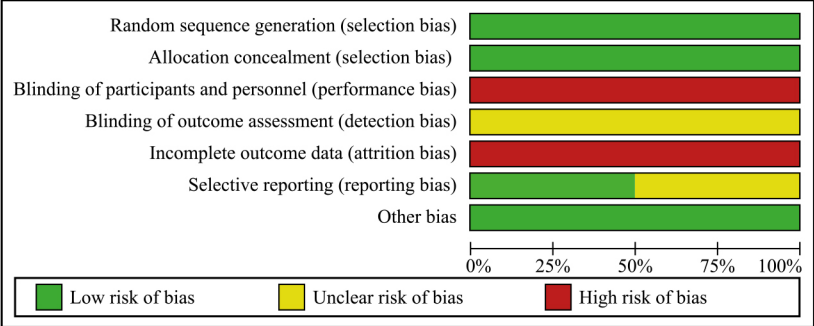
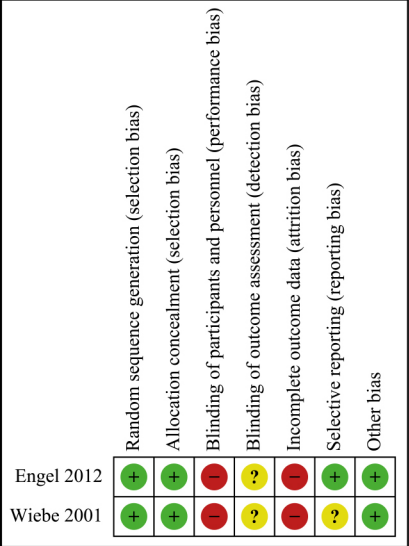
Memory impairment



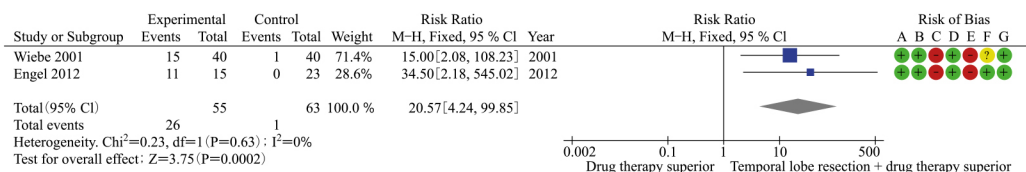
Psychiatric symptoms



QOL improvement



## Outcome 9-2-1: Seizure freedom



## Risk of bias legend

- (A) Random sequence generation (selection bias)  
 (B) Allocation concealment (selection bias)  
 (C) Blinding of participants and personnel (performance bias)  
 (D) Blinding of outcome assessment (detection bias)  
 (E) Incomplete outcome data (attrition bias)  
 (F) Selective reporting (reporting bias)  
 (G) Other bias

## Outcome 9-2-2: Reduction/discontinuation of antiepileptic drugs

No primary study found

## Outcome 9-2-3: Death



## Outcome 9-2-4: Surgical complications



### Outcome 9-2-5: Memory impairment



#### Risk of bias legend

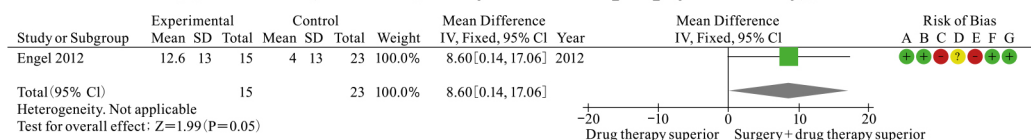
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

### Outcome 9-2-6: Psychiatric symptoms



### Outcome 9-2-7: Improvement of QOL

#### [QOLIE-89 (89-item Quality of Life in Epilepsy Inventory)]



Patients: Patients with drug resistant epilepsy

Intervention: Temporal lobe resection + drug therapy

Comparison: Drug therapy

Outcome	Expected absolute effect* (95% confidence interval)		Relative effect: risk ratio(RR) (95% confidence interval)	No. of patients (No. of studies)	Quality of evidence (GRADE)	Comment
	Risk of drug therapy	Risk of vagus nerve stimulation + drug therapy				
Seizure freedom	16 (per 1,000)	327 (per 1,000) (67–1,000)	RR 20.57 (4.24–9.85)	118 (2 RCTs)	⊕⊕○○ Low <sup>a,b</sup>	
Reduction/discontinuation of antiepileptic drugs	0 (per 1,000)	0 (per 1,000) (0–0)	Not estimable	(0 RCTs)	–	
Death	16 (per 1,000)	5 (per 1,000) (0–126)	RR 0.33 (0.01–7.95)	118 (2 RCTs)	⊕⊕○○ Low <sup>c</sup>	
Surgical complications	0 (per 1,000)	0 (per 1,000) (0–0)	RR 12.33 (1.67–90.89)	118 (2 RCTs)	⊕⊕○○ Low <sup>a,b</sup>	
Memory impairment	0 (per 1,000)	0 (per 1,000) (0–0)	RR 12.00 (0.71–202.18)	26 (1 RCT)	⊕○○○ Very low <sup>a,c</sup>	
Psychiatric symptoms	225 (per 1,000)	200 (per 1,000) (86–466)	RR 0.89 (0.38–2.07)	80 (1 RCT)	⊕○○○ Very low <sup>a,b</sup>	
QOL improvement: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score (range of QOLIE-89: 0–100)	Mean QOL improvement (change in QILIE-89) was 0	QOL improvement by temporal lobe resection + drug therapy was 8.6 times higher (0.14–17.06 higher) than drug therapy group	–	38 (1 RCT)	⊕⊕○○ Low <sup>a,d</sup>	

\*Risk (and 95% confidence interval) in the intervention group was estimated based on the risk in the control group and the effect due to intervention (and 95% confidence intervals).

Grades of quality of evidence according to the GRADE Working Group:

High: High certainty of the effect estimate. True effect is near the effect estimate.

Moderate: Moderate certainty of the effect estimate. The effect estimate is considered to be near the true effect, but further research may change the effect estimate.

Low: There is limitation in the certainty of the effect estimate. Although the effect estimate may be near the true effect, further research is very likely to change the effect estimate.

Very low: Very low certainty of the effect estimate. The true effect is very likely to be different from the effect estimate.

<sup>a</sup>: because masking was not done, which affected the outcomes

<sup>b</sup>: because although confidence interval of effect estimate does not cross the clinical decision threshold of appreciable benefit or that of appreciable harm, it does not satisfy the criteria for optimal information size (OIS).

<sup>c</sup>: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm

<sup>d</sup>: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable benefit, but not the clinical decision threshold of appreciable harm

## Evaluation table of recommendation decision criteria

Study population: Patients with drug-resistant temporal lobe epilepsy																																													
Intervention: Temporal lobe resection (added to drug therapy)																																													
CRITERIA		JUDGEMENTS	RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS																																							
PROBLEM	Is there a priority problem? More serious problems and more urgent problems have higher priority	- No - Probably no - Probably yes - Yes - Varies - Don't know	For drug resistant epilepsy, the effect of further adding new drugs is limited. Temporal lobe resection is a treatment that can be expected to achieve seizure freedom.																																										
	DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?  - Trivial - Small - Moderate - Large - Varies - Don't know	The relative importance or values of the main outcomes of interest:																																										
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?  - Large - Moderate - Small - Trivial - Varies - Don't know		Outcome	Relative importance	Certainty of the evidence (GRADE)	It depends on patient. Memory impairment can be predicted to some extent. One RCT (Wiebe 2001) reported transient asymptomatic visual defect in 22 of 40 patients.																																							
	CERTAINTY OF THE EVIDENCE		What is the overall certainty of this evidence?  - Very low - Low - Moderate - High - No included studies	Seizure freedom	CRITICAL		⊕⊕○○ LOW	Surgery generally has evidence with low certainty due to difficulties with blinding.																																					
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?		Reduction/discontinuation of antiepileptic drugs	CRITICAL																																									
			Death	CRITICAL	⊕⊕○○ LOW																																								
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?		Surgical complications	CRITICAL	⊕⊕○○ LOW																																								
			Memory impairment	CRITICAL	⊕○○○ VERY LOW																																								
			Psychiatric symptoms	CRITICAL	⊕○○○ VERY LOW																																								
			QOL improvement	CRITICAL	⊕⊕○○ LOW																																								
Summary of findings																																													
<table><tr><th>Outcome</th><th>No temporal lobe resection</th><th>Temporal lobe resection</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr><tr><td>Seizure freedom</td><td>1.6%</td><td>32.7% (6.7 to 100.0)</td><td>31.1% more (5.1 more to 156.9 more)</td><td>RR 20.57 (4.24 to 99.85)</td></tr><tr><td>Reduction/ discontinuation of antiepileptic drugs</td><td></td><td></td><td></td><td></td></tr><tr><td>Death</td><td>1.6%</td><td>0.5% (0.0 to 12.6)</td><td>1.1% fewer (1.6 fewer to 11 more)</td><td>RR 0.33 (0.01 to 7.95)</td></tr><tr><td>Surgical complications</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>0.0% fewer (0 fewer to 0 fewer)</td><td>RR 12.33 (1.67 to 90.89)</td></tr><tr><td>Memory impairment</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>0.0% fewer (0 fewer to 0 fewer)</td><td>RR 12.00 (0.71 to 202.18)</td></tr><tr><td>Psychiatric symptoms</td><td>22.5%</td><td>20.0% (8.6 to 46.6)</td><td>2.5% fewer (14 fewer to 24.1 more)</td><td>RR 0.89 (0.38 to 2.07)</td></tr><tr><td>QOL improvement</td><td>Mean QOL improvement was 0</td><td>-</td><td>MD 8.6 higher (0.14 higher to 17.06 higher)</td><td>-</td></tr></table>						Outcome	No temporal lobe resection	Temporal lobe resection	Difference (95% CI)	Relative effect (RR) (95% CI)	Seizure freedom	1.6%	32.7% (6.7 to 100.0)	31.1% more (5.1 more to 156.9 more)	RR 20.57 (4.24 to 99.85)	Reduction/ discontinuation of antiepileptic drugs					Death	1.6%	0.5% (0.0 to 12.6)	1.1% fewer (1.6 fewer to 11 more)	RR 0.33 (0.01 to 7.95)	Surgical complications	0.0%	0.0% (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	RR 12.33 (1.67 to 90.89)	Memory impairment	0.0%	0.0% (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	RR 12.00 (0.71 to 202.18)	Psychiatric symptoms	22.5%	20.0% (8.6 to 46.6)	2.5% fewer (14 fewer to 24.1 more)	RR 0.89 (0.38 to 2.07)	QOL improvement	Mean QOL improvement was 0	-	MD 8.6 higher (0.14 higher to 17.06 higher)	-
Outcome	No temporal lobe resection	Temporal lobe resection	Difference (95% CI)	Relative effect (RR) (95% CI)																																									
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QOL improvement	Mean QOL improvement was 0	-	MD 8.6 higher (0.14 higher to 17.06 higher)	-																																									

			Summary: With regard seizure outcome, relative risk was 20.57 (95% confidence interval 4.24–99.85) and NNT was 4. No study on the outcome of antiepileptic drug reduction was found. There was no significant increase in death due to surgery. Surgical complications was increased with relative risk of 12.33 (95% confidence interval 1.67–90.89), and included stroke and infection. Other than these, Wiebe et al, reported transient visual defect in approximately one-half of patients in surgery group. Memory impairment tended to increase when temporal lobe resection was added to drug therapy but there was no significant difference. The main psychiatric symptom was depression, but there was no significant difference between with and without temporal lobe resection. Quality of life (QOL) was superior in the group with add-on temporal lobe resection.	
<b>COST AND RESOURCE</b>	How large are the required resources (cost)?	<ul style="list-style-type: none"> <li>- High cost</li> <li>- Moderate cost</li> <li>- Negligible</li> <li>- Moderate saving</li> <li>- Large saving</li> <li>- Varies</li> <li>- Don't know</li> </ul>	The health insurance fee scale for epilepsy surgery using a microscope (including temporal lobe resection) is 131,630 points (as of January 11, 2018). The surgery is conducted under general anesthesia and requires a neurosurgeon. However, through reducing antiepileptic drugs, hospitalization decreases accompanying reduced seizures, and more active social activities are possible. these are expected to lead to saving in the long term.	
<b>ACCEPTABILITY</b>	Is the option acceptable to key stakeholders?	<ul style="list-style-type: none"> <li>- No</li> <li>- Probably no</li> <li>- Probably yes</li> <li>- Yes</li> <li>- Varies</li> <li>- Don't know</li> </ul>	Access to facility capable of surgery is required, but is possible.	
<b>FEASIBILITY</b>	Is the option feasible to implement?	<ul style="list-style-type: none"> <li>- No</li> <li>- Probably no</li> <li>- Probably yes</li> <li>- Yes</li> <li>- Varies</li> <li>- Don't know</li> </ul>	Feasible in specialized facilities. To find hospitals capable of surgery, consult the following websites: 1. The Japan Neurosurgical Society <a href="http://jns.umin.ac.jp/">http://jns.umin.ac.jp/</a> 2. Epilepsy Surgery Society of Japan <a href="http://plaza.umin.ac.jp/~jess/">http://plaza.umin.ac.jp/~jess/</a> 3. The Japan Epilepsy Society <a href="http://square.umin.ac.jp/jes/">http://square.umin.ac.jp/jes/</a>	



## Recommendation decision table

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Judgment	○	○	○	●	○
Recommendation	<b>Addition of temporal lobe resection to drug therapy is recommended for drug-resistant temporal lobe epilepsy. (GRADE 2D, strength of recommendation “weak recommendation” / certainty of evidence “very low”)</b>				
Justification	<p><b>Question (CQ):</b> Should temporal lobe resection be added to drug therapy for drug resistant temporal lobe epilepsy?</p> <p><b>Patients (P):</b> Patients with drug resistant epilepsy</p> <p><b>Intervention (I):</b> Temporal lobe resection (added to drug therapy)</p> <p><b>Comparison (C):</b> Continued drug therapy only</p> <p><b>Outcome (O):</b> Seizure freedom, death, surgical complications</p> <p><b>Summary of evidence:</b> Systematic review identified 2 RCTs (118 subjects). Relative risk of freedom from seizure due to temporal lobe resection was 20.57 (95% confidence interval 4.24–99.85) and NNT was 4. No studies investigating the outcome of antiepileptic drug reduction was found. There was no significant increase in death due to surgery. Complications related to surgery were increased with relative risk of 12.33 (95% confidence interval 1.67–90.89), and included stroke and infection. Other than these, Wiebe et al, reported transient visual defect in approximately one-half of patients in surgery group. Memory impairment tended to increase when temporal lobe resection was added to drug therapy, but there was no significant difference. The main psychiatric symptom was depression, but there was no significant difference between with and without temporal lobe resection. Quality of life (QOL) was superior in the group with add-on temporal lobe resection.</p> <p><b>Certainty of evidence:</b> Since masking of the intervention was impossible, the risk of bias in the studies collected was high overall. Bias for death was considered not serious, while that for other outcomes was considered serious and downgraded one rank. Inconsistency and non-directness of the results were without question, and not serious. For imprecision, confidence intervals crossed the clinical decision threshold in many cases, and was downgraded one or two ranks. Publication bias could not be judged because of the small number of studies. Consequently, the certainty of evidence for the outcomes was as follows: “low” for seizure freedom, death, surgical complications, and QOL improvement; and “very low” for memory impairment and psychiatric symptoms. The overall certainty of evidence was “D (very low)”.</p> <p><b>Judgment of benefits and harms, burden, and cost:</b></p> <p>Surgical invasiveness is high. However, the merit of freedom from seizure in patients with drug resistant epilepsy is great, and the efficacy is also high.</p> <p><b>Recommendation:</b></p> <p>Addition of temporal lobe resection to drug therapy is proposed for drug resistant temporal lobe epilepsy. (strength of recommendation “weak recommendation” / certainty of evidence “very low”)</p> <p><b>Additional considerations:</b></p> <p>According to GRADE, when the certainty of evidence is “very low”, in principle it is not possible to rank “strong recommendation”. Since temporal lobe resection is expected to be highly effective with low incidence of adverse effects, the opinion of almost all of the panelists was “strong recommendation” at the panel meeting, but due to the constraint of the GRADE system, the final grade was “weak recommendation”.</p>				
<b>Subgroup considerations.</b> Consider how to set criteria for patient population or intervention, which may change the recommendation statement	No RCTs comparing surgical methods were identified.				
<b>Implementation considerations.</b> In clinical practice, problems such as feasibility and tolerability may arise.	Selection of the optimal surgical method depending on the cause is necessary. Follow-up and support after surgery are necessary.				
<b>Monitoring and evaluation.</b> What kind of monitoring is necessary during implementation? Is evaluation necessary before or after publication?					
<b>Research possibilities.</b> What are the unclear points in judgment that require future research?	There is room for further research on the development of memory-preserving, minimally invasive surgery. In addition, the observation periods of the two RCT were 1 year and 2 years, and there is accumulating interest on the data of surgical outcomes and adverse events over a longer period of follow-up.				

# CQ 10-1 Digest Edition

## CQ 10-1

### Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?

#### Recommendation

We suggest to add vagus nerve stimulation to drug therapies (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note:** In principle, vagus nerve stimulation is considered for patients with no indication for curative surgery. Implantation of the vagus nerve stimulation device involves surgery under general anesthesia in an experienced hospital. After implantation, the patients need to be followed in the hospital where operation was performed or other facilities, by experts with experience in stimulator control.

#### 1. Background, priority of the problem

In patients with drug-resistant epilepsy in whom seizures are not controlled even after trials of two appropriate antiepileptic drugs, further addition of drugs has only limited effect. Vagus nerve stimulation added to antiepileptic drug therapy is expected to provide additive effect of seizure frequency reduction. Because vagus nerve stimulation is less invasive and has lower seizure control effect compared to brain surgery with craniotomy, it may be selected as a treatment option in patients with no indication for curative neurosurgery.

#### 2. Comment

##### Evidence summary

Only one randomized controlled trial (RCT) examined the effectiveness of vagus nerve stimulation for drug-resistant epilepsy<sup>1)</sup>. We therefore considered to use observational studies together. However, because outcomes of those studies, such as reduced seizure frequency and mood change, are susceptible to placebo effect, we determined to use a single RCT.

Regarding efficacy, the relative risk for 50% seizure frequency reduction was 1.34 (95% confidence interval 0.59–3.04), and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 25. As for mood changes, there were no significant differences between the intervention group and control group in the scores for several scales: QOLIE-89 (89-item Quality of Life in Epilepsy Inventory), CES-D (Center for Epidemiologic studies Depression scale), and NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale). Regarding mood changes, the only scale showing a statistically significant difference was the 7-point evaluation scale CGI-I (Clinical Global Impression of Impression Important Scale), but the difference was only 0.5 (95% confidence interval 0.99–0.01), showing a small effect. For serious adverse events, vocal cord paralysis and brief respiratory arrest occurred only in the intervention group, but were transient with no sequelae. There was no significant difference in the adverse event of dysphonia between the intervention group and the control group.

It should be noted that the selected RCT was prematurely terminated by the sponsor due to a low recruitment rate, because many study candidates did not accept randomization of the treatment. Therefore, the study may be underpowered for detection of the outcome.

### 3. Panel meeting

#### 3-1. What is the overall quality of evidence across outcomes?

In the study reviewed, the risk of bias was high overall, which was judged as serious for all the outcomes, and was downgraded by one rank. The inconsistency of results was not downgraded because of only one study used. The indirectness was judged as not serious and without any problems. As for imprecision, the confidence intervals in many analyses crossed the clinical decision threshold, and it was hence downgraded by one or two ranks. As for publishing bias, there was only one study, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: “very low” for seizure frequency  $\leq 50\%$ , serious adverse events, and dysphonia; and “low” for the other outcomes. The overall level of evidence was “very low”.

#### 3-2. What is the balance between benefits and harms?

Since there was only one RCT, the certainty of the effect estimate was low, and it was difficult to consider the balance between benefits and harms.

#### 3-3. What about patients’ values and preferences?

The importance of outcomes has great inter-individual differences, and it should be diverse. It should be noted that some patients place importance on the reduction of seizure frequency, while others regard the risk of adverse effects to be more important.

#### 3-4. What is the balance between net benefit and cost or resources?

The electrode implantation for VNS surgery is conducted under general anesthesia. Vagus nerve stimulation is covered by health insurance, and the health insurance fee scale for implantation is 24,350 points, and that for exchange is 4,800 points (as of January 11, 2018). The reoperation should be done once every few years for replacement of the power generator because of degradation of the condenser. Considering the effectiveness for refractory epilepsy and the above-mentioned factors, the cost was judged to be moderate.

#### 3-5. Recommendation grading

During the discussions at the panel meeting, considering the moderate burden and cost, and the few alternative treatment options available, the panelists concluded that it was reasonable to use this treatment method despite a certain amount of harm, burden and cost. The unanimous decision was “to propose implementing vagus nerve stimulation for drug-resistant epilepsy”. As an additional consideration, the patients’ families at the panel meeting expressed the following opinion: “We desire to overcome social constraints. If there is any method at all, please include it as one of the options.”

### 4. Descriptions in other related guidelines

In Japan, the “Practice guideline of vagus nerve stimulation therapy for epilepsy”<sup>2)</sup> was published by the Japan Epilepsy Society in 2012, which states that “VNS has accommodative effect on drug-resistant epileptic seizures [recommendation grade A]”. Also, the American Academy of Neurology released a guideline update entitled “Vagus nerve stimulation for the treatment of epilepsy” in 2013. This guideline update describes the possibilities of the effectiveness of vagus nerve stimulation appearing several years after VNS operation, the effectiveness in children [rate of  $> 50\%$  seizure reduction: 55% (95% confidence interval 50–59%)], and an increased risk of infection in children compared to adults [odds ratio 3.4 (95% confidence interval 1.0–11.2)].

According to the guidelines in Japan and overseas and the recommendation from the ILEA, the indication for vagus nerve stimulation is in principle patients who have no indication for curative neurosurgery<sup>2-4)</sup>.

### 5. Treatment monitoring and evaluation

Vagus nerve stimulation treatment requires adjustment of the stimulation conditions, management of complications, and solving equipment troubles. Epilepsy specialists or doctors trained by the specialists should perform monitoring and evaluation after the operation based on specialist knowledge.

### 6. Possibility of future research

The RCT reviewed for this CQ had high risk of bias. Therefore, it is desirable to have more RCTS with better quality. In addition, research focusing on how to identify good responders and the effects on status epilepticus is needed in the future.

## 7. RCT report reviewed for this CQ

Ryvlin 2014<sup>1)</sup>

## 8. List of appendices (to be shown later)

Appendix CQ10-1-01. Flow diagram and literature search formula

Appendix CQ10-1-02. Risk of bias summary

Appendix CQ10-1-03. Risk of bias graph

Appendix CQ10-1-04. Forest plot

Appendix CQ10-1-05. Summary of Findings (SoF) table

Appendix CQ10-1-06. Evidence-to-Decision table

## ■ References

- 1) Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. 2014; 55(6): 893-900.
- 2) Kawai K, Sugai K, Akamatsu N, et al. Guideline on implementation of vagus nerve stimulation therapy for epilepsy. *Tenkan Kenkyu*. 2012; 30(1): 68-72 (in Japanese).
- 3) Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; 81(16): 1453-1459.
- 4) Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia*. 2006; 47(6): 952-959.

**CQ 10-1 Literature search**

## PICO

P: Patients with drug resistant epilepsy (children as subgroup)

I: Vagus nerve stimulation added to drug therapy

C: Compared with drug therapy alone

O: Are seizures controlled (25, 50, 75%)?

Is there a decrease in treatment continuation rate?

Is there an increase in dysphonia/hoarseness?

Is there an increase in coughing?

Is there an increase in pain?

Is mood improved (= mood change)?

**■ Search formula**

PubMed search: September 28, 2016

#1 Search (("drug resistant epilepsy" [mesh] OR ((epilepsy OR seizures OR convulsions) AND (intractable OR refractory))))

#2 Search ("vagus nerve stimulation" [mesh] OR ("vagal nerve" AND stimulation) OR ("vagus nerve" AND "electric stimulation therapy"))

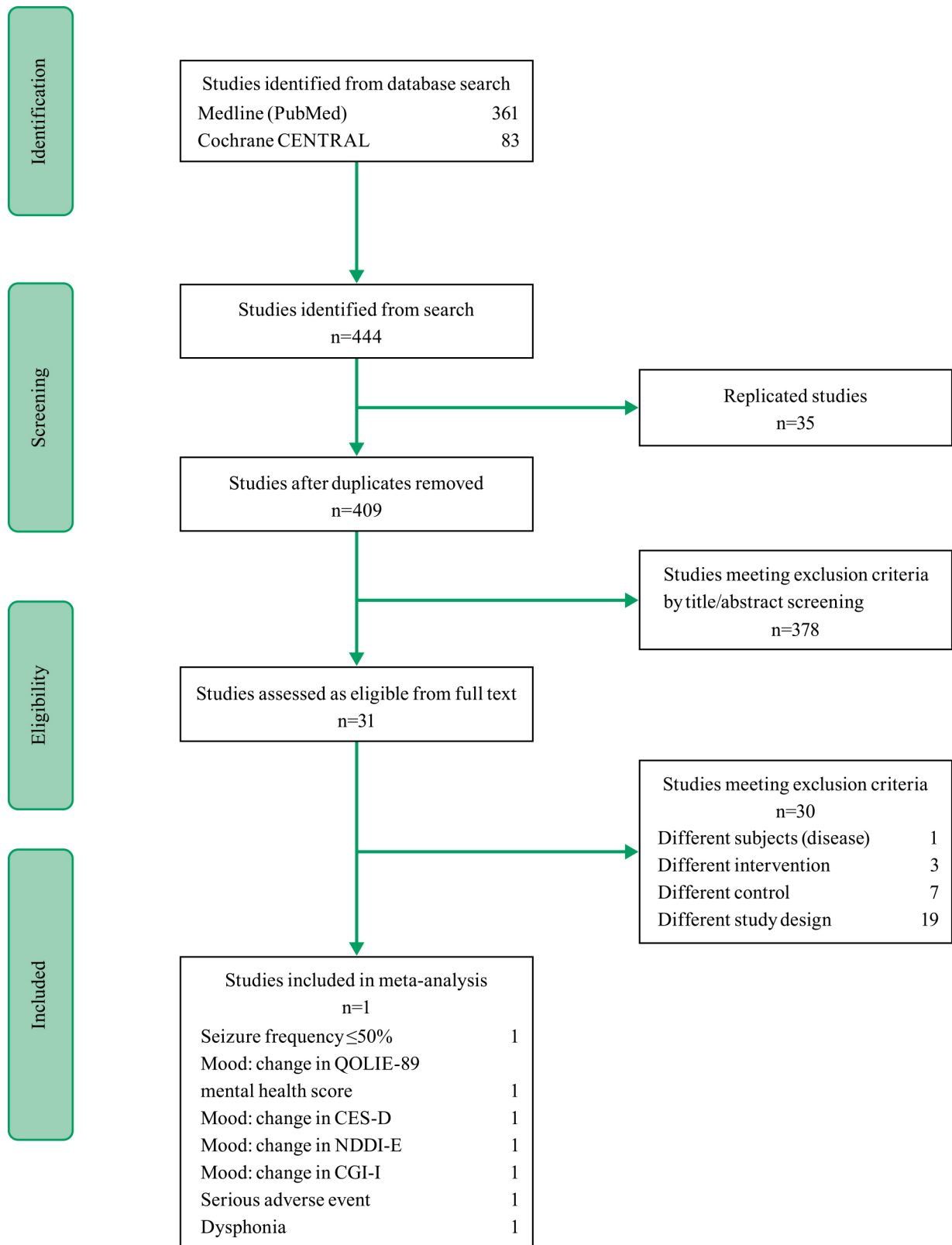
#3 Search (randomized controlled trial [pt] OR meta-analysis [pt] OR randomized OR blind OR observation\* OR cohort OR "follow-up" OR cross  
OR case OR series OR prospective OR retrospective OR placebo OR trial)

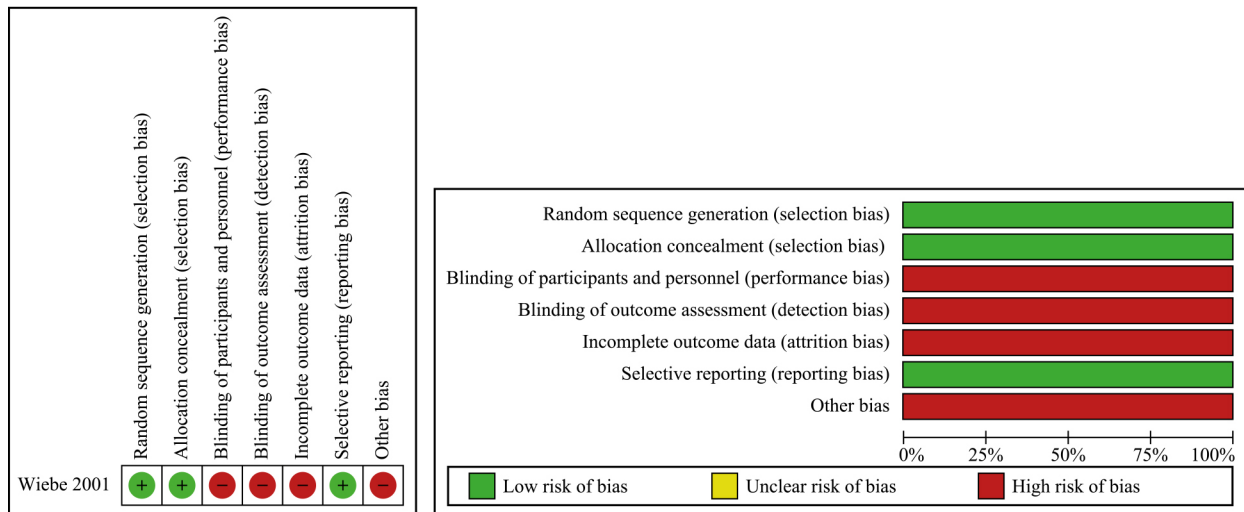
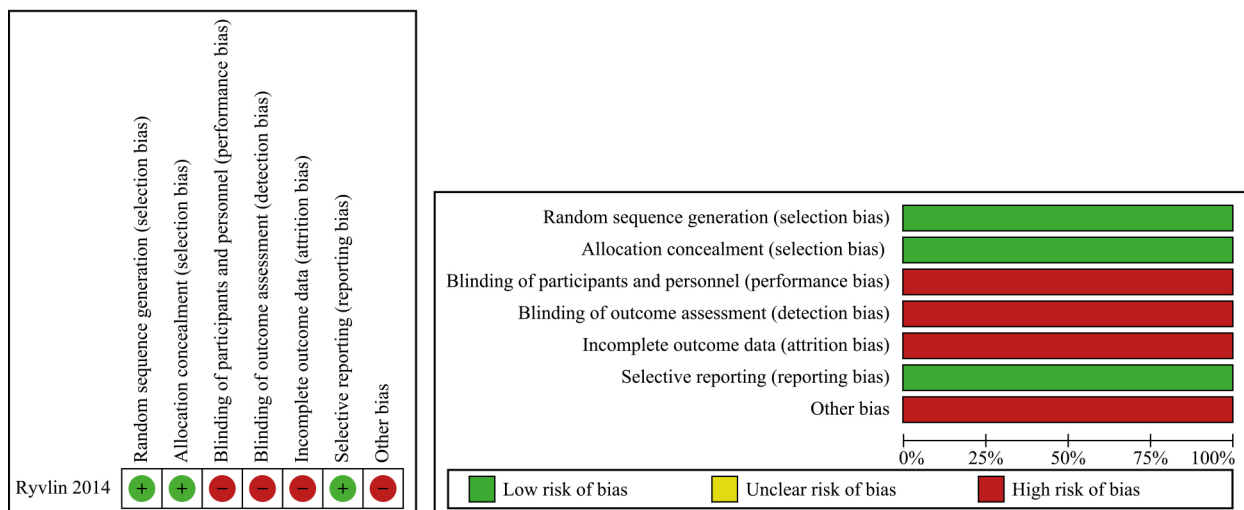
#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

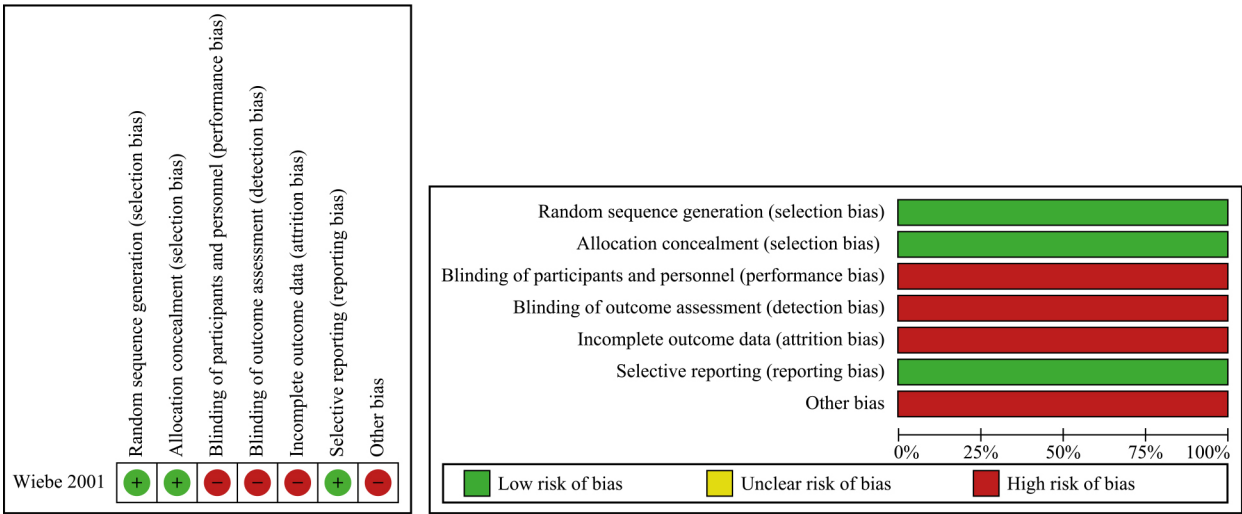
(epilepsy OR seizures) AND vagus nerve stimulation

# CQ10-1. Flow diagram of literature search (modified PRISMA 2009)

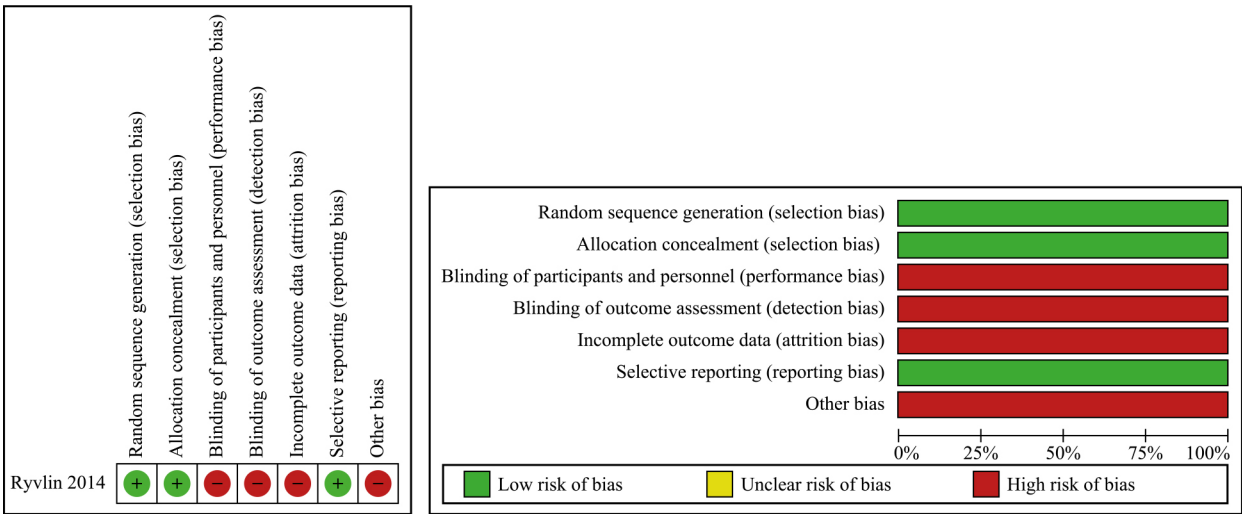


**12-month 50% seizure reduction****Mood after 12 months: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score**

### Mood after 12 months: change in CES-D (Centre for Epidemiologic studies Depression scale) score

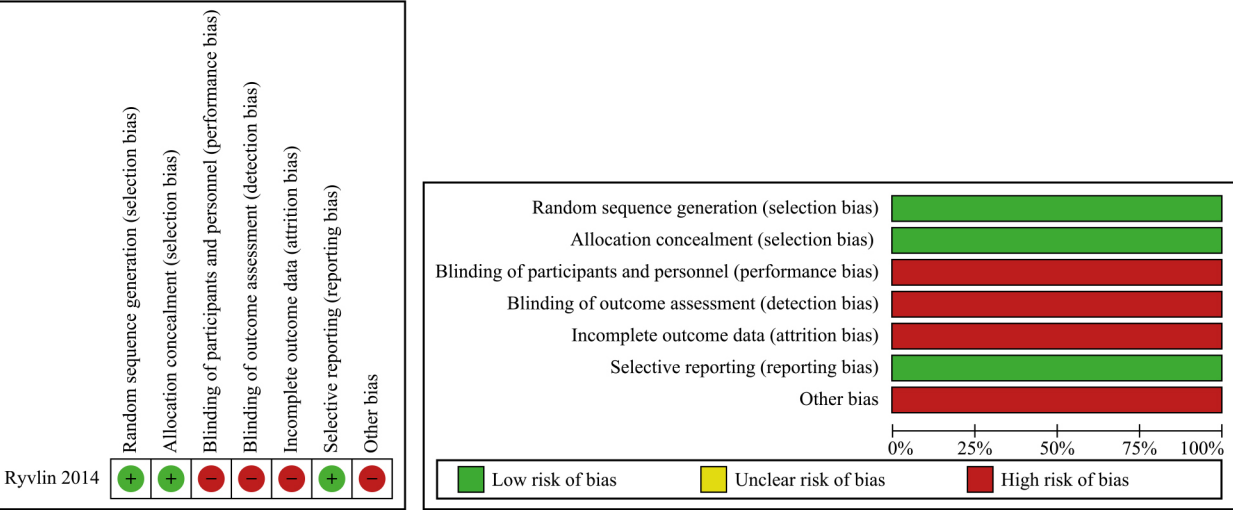


### Mood after 12 months: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale) score

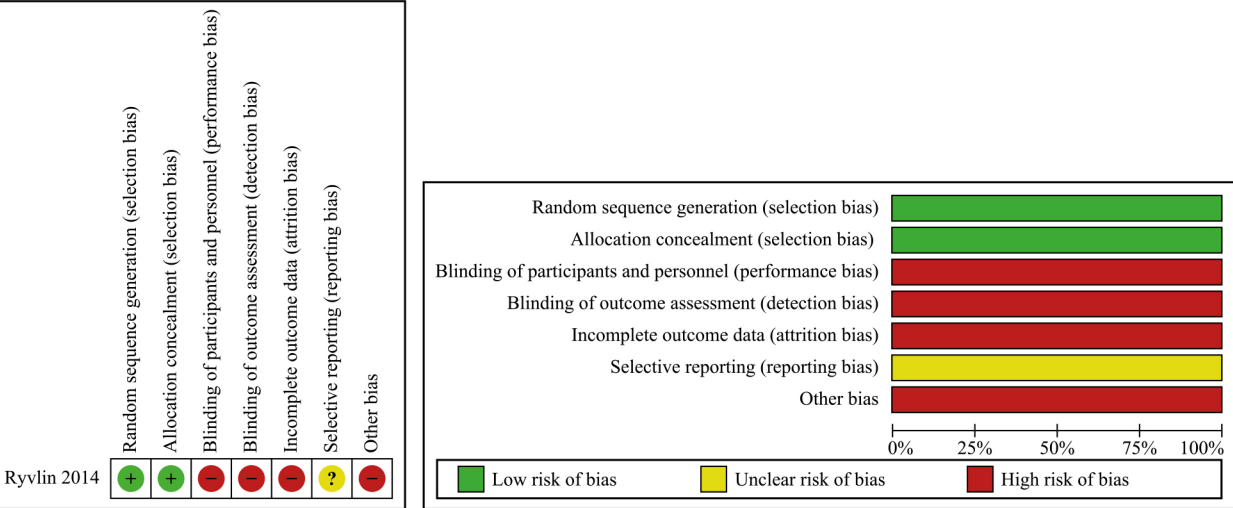




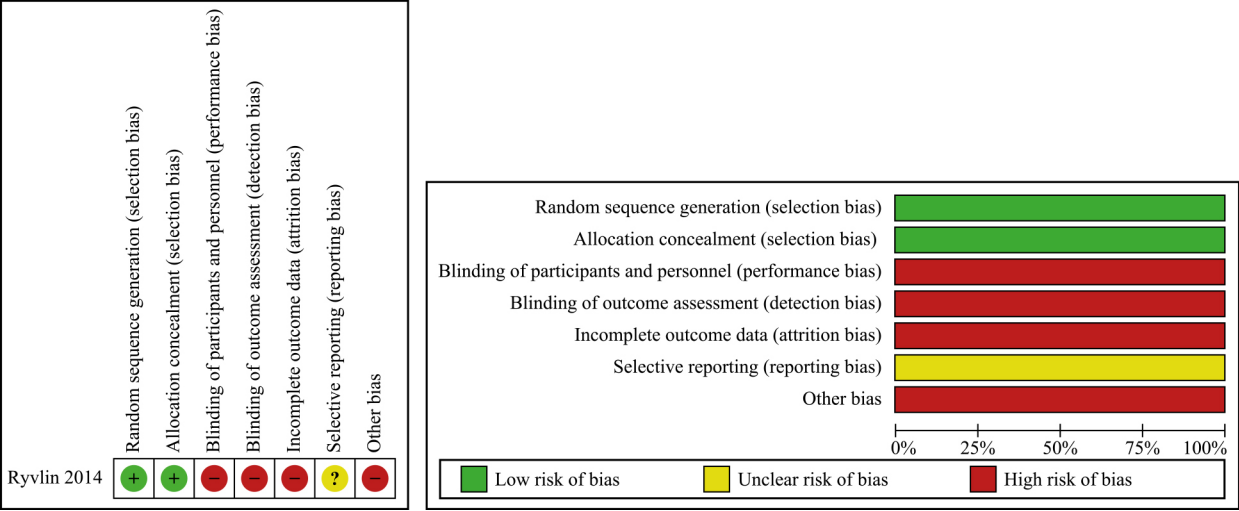
# Mood after 12 months: change in CGI-I (Clinical Global Impression of Improvement scale) score

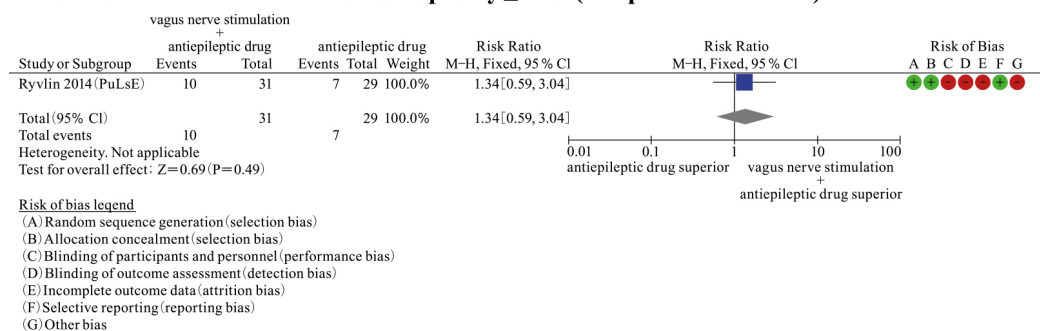
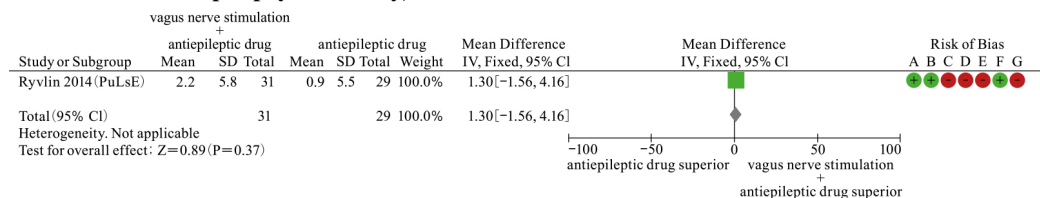
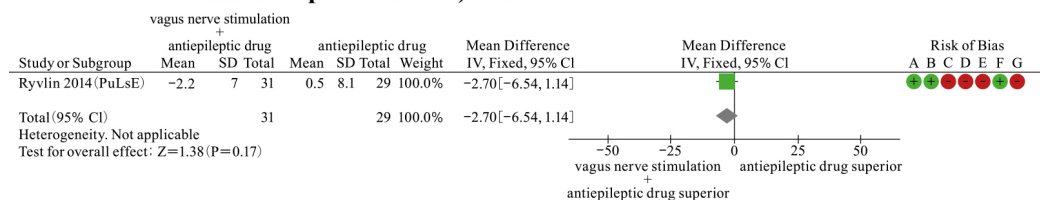
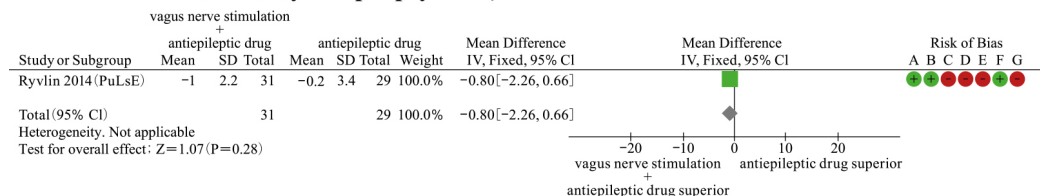


## Serious adverse events

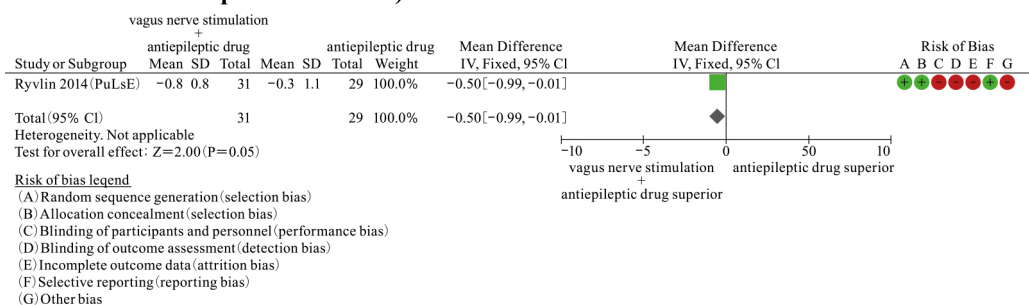


Dysphonia

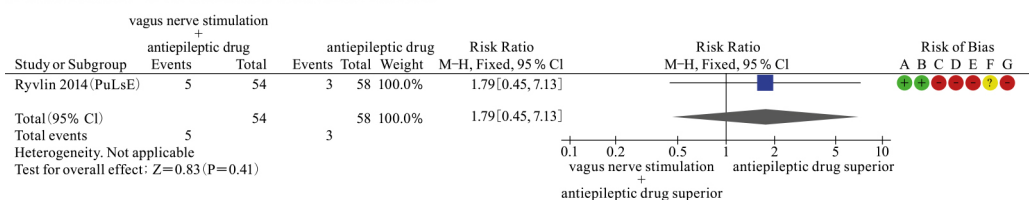


**Outcome 10-1-1: 12-month seizure frequency  $\leq 50\%$  (compared to baseline)****Outcome 10-1-2: Mood after 12 months: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score****Outcome 10-1-3: Mood after 12 months: change in CES-D (Centre for Epidemiologic studies Depression scale) score****Outcome 10-1-4: Mood after 12 months: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale) score**

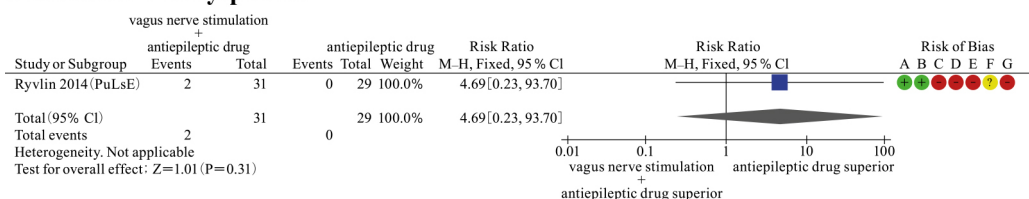
### Outcome 10-1-5: 12 Mood after 12 months: change in CGI-I (Clinical Global Impression of Improvement scale) score



### Outcome 10-1-6: Serious adverse events



### Outcome 10-1-7: Dysphonia



Patients: Patients with drug-resistant epilepsy

Intervention: Vagus nerve stimulation (VNS) + drug therapy

Comparison: Drug therapy

Outcome	Expected absolute effect* (95% confidence interval)		Relative effect: risk ratio (RR) (95% confidence interval)	No. of patients (No. of studies)	Quality of evidence (GRADE)	Comment
	Risk of drug therapy	Risk of vagus nerve stimulation + drug therapy				
12-month seizure frequency ≤50%	Study subject population		RR 1.34 (0.59–3.04)	60 (1 RCT)	⊕○○○ Very low <sup>a,b</sup>	
	241 (per 1,000)	323 (per 1,000) (142–734)				
	Low risk population					
	120 (per 1,000)	161 (per 1,000) (71–365)				
	High risk population					
	480 (per 1,000)	643 (per 1,000) (283–1,000)				
Mood after 12 months: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score (range of QOLIE-89: 0–100)	Mood change (QOLIE-89): 0	Mean mood change (QOLIE-89) in vagus nerve stimulation + drug therapy group was 1.3 higher (1.56–4.16) than drug therapy group	–	60 (1 RCT)	⊕⊕○○ Low <sup>a,c</sup>	
Mood after 12 months: change in CES-D (Centre for Epidemiologic Studies Depression scale) score (range of CED-D: 0–60)	Mood change (CES-D): 0	Mean mood change (CES-D score) in vagus nerve stimulation + drug therapy group was 2.7 lower (6.54–1.14) than drug therapy group	–	60 (1 RCT)	⊕⊕○○ Low <sup>a,d</sup>	
Mood after 12 months: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale) score (range of NDDI-E: 6–24)	Mood change (NDDI-E): 0	Mean mood change (NDDI-E score) in vagus nerve stimulation + drug therapy group was 0.8 lower (2.26–0.66) than drug therapy group	–	60 (1 RCT)	⊕⊕○○ Low <sup>a,c</sup>	
Mood after 12 months: change in CGI-I (Clinical Global Impression of Improvement scale) score (range of CGI-I: 1–7)	Mood change (CHI-I): 0	Mean mood change (CHI-I score) in vagus nerve stimulation + drug therapy group was 0.5 lower (0.99–0.01) than drug therapy group	–	60 (1 RCT)	⊕⊕○○ Low <sup>a,c</sup>	
Serious adverse events	Study subject population		RR 1.79 (0.45–7.13)	112 (1 RCT)	⊕○○○ Very low <sup>a,b</sup>	
	52 (per 1,000)	93 (per 1,000) (23–369)				
	Low risk population					
	25 (per 1,000)	45 (per 1,000) (11–178)				
	High risk population					
	100 (per 1,000)	179 (per 1,000) (45–713)				
Dysphonia	0 per 1,000	0 per 1,000 (0 to 0)	RR 4.69 0.23–93.70)	60 (1 RCT)	⊕○○○ Very low <sup>a,b</sup>	

\*Risk (95% confidence interval) in the intervention group was estimated based on the risk in the control group and the effect due to intervention (and 95% confidence intervals).

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Grades of quality of evidence according to the GRADE Working Group:

High: High certainty of the effect estimate. True effect is near the effect estimate.

Moderate: Moderate certainty of the effect estimate. The effect estimate is considered to be near the true effect, but further research may change the effect estimate.

Low: There is limitation in the certainty of the effect estimate. Although the effect estimate may be near the true effect, further research is very likely to change the effect estimate.

Very low: Very low certainty of the effect estimate. The true effect is very likely to be different from the effect estimate.

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<sup>a</sup>: because masking was not done, which affected the outcome.

<sup>b</sup>: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm.

<sup>c</sup>: because although confidence interval of effect estimate does not cross the clinical decision threshold of appreciable benefit or that of appreciable harm, it does not satisfy the criteria for optimal information size (OIS).

<sup>d</sup>: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable benefit, but does not cross the clinical decision threshold of appreciable harm.

## Evaluation table of recommendation decision criteria

Study population: Patients with drug resistant temporal lobe epilepsy								
Intervention: vagus nerve stimulation								
CRITERIA		JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
PROBLEM	Is there a priority problem? More serious problems and more urgent problems have higher priority	- No - Probably no - Probably yes - Yes - Varies - Don't know	For drug-resistant epilepsy in which seizures cannot be controlled even with two regimens of appropriate antiepileptic drugs, the effect of adding further drugs is limited. By adding vagus nerve stimulation (VNS) to antiepileptic drugs, the effect of lowering the seizure frequency is expected. Compared with brain surgery by craniotomy, VNS is minimally invasive and may be selected as one of the treatment options.					
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?	- Trivial - Small - Moderate - Large - Varies - Don't know	The relative importance or values of the main outcomes of interest:		Relative risk for seizure frequency ≤ 50% by intervention was 1.34 (0.59–3.04), and NNT was 25. For mood change, the effect was small for all the scales.			
			Outcome Relative	Relative importance		Certainty of the evidence (GRADE)		
			Seizure frequency ≤50%	CRITICAL		⊕○○○ VERY LOW		
			Mood: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score	CRITICAL		⊕⊕○○ LOW		
			Mood: change in CES-D (Centre for Epidemiologic Studies Depression scale)	CRITICAL		⊕⊕○○ LOW		
			Mood: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale)	CRITICAL		⊕⊕○○ LOW		
			Mood: change in CGI-I (Clinical Global Impression of Improvement scale)	CRITICAL		⊕⊕○○ LOW		
			Serious adverse events	CRITICAL		⊕○○○ VERY LOW		
Dysphonia	CRITICAL	⊕○○○ VERY LOW						
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?	- Large - Moderate - Small - Trivial - Varies - Don't know	Summary of findings		In the intervention group (31 patients), serious adverse events occurred in 5 patients, 2 (40%) of whom had vocal cord paralysis and 1 had brief respiratory arrest, but all recovered completely. Therefore, from RCT, the relative risk of significant undesirable effects occurring in clinical practice is estimated to be smaller than 1.79 (0.45–7.13).			
			Outcome	Drug therapy		Vagus nerve stimulation (VNS) + drug therapy	Difference (95% CI)	Relative effect (RR) (95% CI)
			Seizure frequency ≤ 50%	241 per 1,000		323 per 1,000 (142 to 734)	82 more per 1,000 (from 99 fewer to 492 more)	RR 1.34 (0.59 to 3.04)
				120 per 1,000		161 per 1,000 (71 to 365)	41 more per 1,000 (from 49 fewer to 245 more)	
CERTAINTY OF THE EVIDENCE	What is the overall certainty of the evidence of effects?	- Very low - Low - Moderate - High - No included studies	480 per 1,000	643 per 1,000 (283 to 1,000)	163 more per 1,000 (from 197 fewer to 979 more)			
			Mood: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score				MD 1.3 higher (1.56 lower to 4.16 higher)	-

VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?	<ul style="list-style-type: none"><li>- Important uncertainty or variability</li><li>- Probably important uncertainty or variability</li><li>- Probably no important uncertainty or variability</li><li>- No important uncertainty and variability</li></ul>	Mood: change in CES-D (Centre for Epidemiologic Studies Depression scale)			MD 2.7 lower (6.54 lower to 1.14 higher)		Individuals differ in the way they attach importance to outcomes. Some patients place importance on the reduction of seizure frequency, while others regard the risk of adverse effects to be more important.
			Mood: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale)			MD 0.8 lower (2.26 lower to 0.66 higher)		
			Mood: change in CGI-I (Clinical Global Impression of Improvement scale)			MD 0.5 lower (0.99 lower to 0.01 lower)		
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	<ul style="list-style-type: none"><li>- Control is superior</li><li>- Control is probably superior</li><li>- Control and intervention are equivalent</li><li>- Intervention is probably superior</li><li>- Intervention is superior</li><li>- It depends</li><li>- Don't know</li></ul>	Serious adverse event	52 per 1,000	93 per 1,000 (23 to 369)	41 more per 1,000 (from 28 fewer to 317 more)	RR 1.79 (0.45 to 7.13)	
				25 per 1,000	45 per 1,000 (11 to 178)	20 more per 1,000 (from 14 fewer to 153 more)		
				100 per 1,000	179 per 1,000 (45 to 713)	79 more per 1,000 (from 55 fewer to 613 more)		
			Dysphonia	0 per 1,000	0 per 1,000 (0 to 0)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	RR 4.69 (0.23 to 93.70)	
<p>Summary: Only one RCT was extracted from the literature search, and this RCT was prematurely terminated by the sponsor due to a low enrollment rate, which resulted primarily from the strong views expressed by candidates toward randomization. Therefore, there is a possibility that the study was underpowered for detecting the outcome. The relative risk for reduction of seizure frequency to <math>\leq 50\%</math> was 1.34 (0.59–3.04).</p> <p>The relative risk for mood change was 1.3 (–1.56–4.16) for QOLIE-89, –2.7 (–6.54–1.14) for CES-D, –0.8 (–2.26–0.66) for NDDI-E, and –0.5 (–0.99–0.01) for CGI-I.</p> <p>The relative risk for serious adverse events was 1.79 (0.45–7.13). Although there was no significant difference, the result suggests a possibility of increase in risk. However, vocal cord paralysis and brief respiratory arrest seen only in the intervention group were transient.</p>								
COST AND RESOURCE	How large are the resource requirement (cost)?	<ul style="list-style-type: none"><li>- High cost</li><li>- Moderate cost</li><li>- Negligible</li><li>- Moderate saving</li><li>- Large saving</li><li>- Varies</li><li>- Don't know</li></ul>	The implantation surgery is conducted under general anesthesia. Vagus nerve stimulation is covered by health insurance, and the health insurance fee scale for implantation is 24,350 points, and that for exchange is 4,800 points (as of January 11, 2018). Also, it is necessary to replace the generator once every few years when the battery runs out, which requires reoperation. The cost of exchange is approximately ¥2,000,000 (covered by health insurance).					
ACCEPTABILITY	Is the option acceptable to key stakeholders?	<ul style="list-style-type: none"><li>- No</li><li>- Probably no</li><li>- Probably yes</li><li>- Yes</li><li>- Varies</li><li>- Don't know</li></ul>						
FEASIBILITY	Is the option feasible to implement?	<ul style="list-style-type: none"><li>- No</li><li>- Probably no</li><li>- Probably yes</li><li>- Yes</li><li>- Varies</li><li>- Don't know</li></ul>	In the past, there were several prefectures that did not have vagus nerve stimulation device implantation facility or guidance/management facility, and access to treatment was poor in some regions. However, currently the criteria for adjusting doctor have been relaxed and access has improved. If the environment of access to device implantation facility and guidance/management facility continues to improve, adjustment of stimulation condition is feasible.					A list of facilities that can provide this therapy is posted on the Society website.



## Recommendation decision table

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<b>Judgment</b>	○	○	○	●	○
<b>Recommendation</b>	Addition of vagus nerve stimulation on drug therapy is proposed for drug resistant epilepsy. (GRADE 2D, strength of recommendation “weak recommendation” / certainty of evidence “very low”)				
<b>Justification</b>	<p><b>Question (CQ):</b> Should vagus nerve stimulation be used for drug resistant epilepsy?</p> <p><b>Patient (P):</b> Drug resistant epilepsy</p> <p><b>Intervention (I):</b> Vagus nerve stimulation (added to drug therapy)</p> <p><b>Comparison (C):</b> Drug therapy</p> <p><b>Outcome:</b> Seizure frequency <math>\leq 50\%</math>, mood improvement (QOLIE-8, CES-D, NDDI-E, CGI-I), serious adverse events, dysphonia</p> <p><b>Summary of evidence:</b> Systematic review identified 1 RCT (96 subjects). When seizure frequency <math>\leq 50\%</math> is the outcome, relative risk due to intervention was 1.34 (95% confidence interval 0.59–3.04). For mood change, the result differed depending on the evaluation scale, but the effect was small.</p> <p>Certainty of evidence: The study collected had a high overall bias risk which was judged as serious for all the outcomes, and was downgraded by 1 rank. For inconsistency of results, there was only one study, and therefore was not downgraded. There was no problem with indirectness and was judged not serious. As for imprecision, the confidence intervals in many analyses crossed the clinical decision threshold; hence was downgraded by one or two ranks. As for publishing bias, there was only one study, and therefore was not downgraded. Consequently, the certainty of evidence for the outcomes was as follows: “very low” for seizure frequency <math>\leq 50\%</math>, serious adverse events, and dysphonia; and “low” for the other outcomes. The overall certainty of evidence was “very low”.</p> <p><b>Judgment of benefits and harms, burden and cost:</b></p> <p>Since there was only 1 RCT, the certainty of effect estimate was low, and it was difficult to judge the balance between benefits and harms. Among the serious adverse events, vocal cord paralysis and brief respiratory arrest that occurred only in the intervention group were transient with no sequelae. Burden and cost are moderate. Considering that there are not many treatment options, it is appropriate to implement the therapy with expectation of the effectiveness even at the expense of harms, burden and cost.</p> <p><b>Recommendation:</b></p> <p>Addition of vagus nerve stimulation on drug therapy is proposed for drug resistant epilepsy. (strength of recommendation “weak recommendation” / certainty of evidence “very low”.)</p> <p><b>Additional considerations:</b></p> <p>At the panel meeting, the patient’s families expressed the following opinion: “There is desire to overcome social constraints. If there is any method at all, please include it as one of the options.”</p>				
<b>Subgroup considerations.</b> Consider how to set criteria for patient population or intervention, which may change the recommendation statement	In children, no RCT comparing with and without vagus nerve stimulation was found. In addition, the 2013 guideline update of the American Academy of Neurology [Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. 2013; 81(16): 1453-1459.] analyzed 14 non-RCT studies (481 subjects). The rate of $\geq 50\%$ seizure reduction was 55% (95% confidence interval 51–59%) and the seizure-free rate was 7% (95% confidence interval 5–10%). However, the heterogeneity between studies was very large. The same guideline update suggests that the risk of infection is higher in children (odds ratio 3.4, 95% confidence interval 1.0–11.2) than in adults.				
<b>Implementation considerations.</b> In clinical practice, problems such as feasibility and tolerability may arise.	To initiate therapy, access to vagus nerve stimulation device implantation facility and guidance/management facility becomes an issue. Patient should be given explanation that surgery is necessary before therapy can be initiated, and that it is not possible to predict beforehand whether it will be effective for any patient. Indication judgment and stimulation device implantation are performed by or under the guidance of a doctor specializing in epilepsy surgery, who is both a Japan Epilepsy Society board-certified specialist and a Japanese Neurosurgical Society board-certified specialist. Adjustment of the stimulation conditions after therapy initiation as well as follow-up of therapeutic effect and adverse events are conducted by or under the guidance of a Japan Epilepsy Society board-certified specialist, or a board-certified specialist of the Japanese Society of Child Neurology, Japanese Society of Neurology, Japanese Society of Psychiatry, or Japanese Neurosurgical Society [Japan Epilepsy Society Criteria for VNS Qualification (enforced on January 8, 2010, revised on July 1, 2014 and June 26, 2016)].				
<b>Monitoring and evaluation.</b> What monitoring is necessary during implementation? Is evaluation of effect necessary before or after publication?	Implementation of vagus nerve stimulation requires a system that allows adjustment of the stimulation conditions, interventions for complications, and correction of equipment troubles. Monitoring and evaluation are conducted by specialists or physicians who have received guidance from the specialists.				
<b>Research possibilities.</b> What are the unclear points in judgment that require future research?	RCT with better quality is desirable. In addition, research focusing on identifying good responders and the effects on status epilepticus is needed in the future.				

# CQ 10-2 Digest Edition

## CQ 10-2

### When conducting vagus nerve stimulation for drug resistant epilepsy, which intensity of stimulation (high or low) should we use?

#### Recommendation

When conducting vagus nerve stimulation for drug-resistant epilepsy, we suggest to use high intensity stimulation rather than low intensity stimulation (GRADE 1C) (strong recommendation, low level of evidence).

- **Supplementary note:** Adjustment of stimulation conditions should be conducted in the hospital where the electrode implantation was performed or in a hospital/institution where VNS specialist is present.

#### 1. Background, priority of this issue

The efficacy of vagus nerve stimulation is known to depend on the stimulation conditions. The intensity of stimulation should be adjusted while monitoring its therapeutic effect and adverse effects. Therefore, it is necessary to clarify whether high intensity stimulation or low intensity stimulation is superior when conducting VNS.

In addition, as mentioned in CQ 10-1 “Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?”, we have difficulty in performing comparison between real VNS and sham VNS (with no stimulation). Therefore, there is an increase in randomized controlled trials (RCTs) using low intensity stimulation as sham stimulation (placebo stimulation or pseudo-stimulation) to compare with high intensity stimulation.

There is one Cochrane Review<sup>1)</sup> on a similar clinical question. This review shows that high intensity stimulation has superior therapeutic effect, while treatment withdrawal is rare both when using high and low intensity stimulation.

#### 2. Comment

##### Evidence summary

There were 4 RCTs that examined the efficacy of vagus nerve stimulation therapy for drug-resistant epilepsy<sup>2-5)</sup>.

For efficacy, the relative risk of seizure frequency  $\leq 50\%$  was 1.74 (95% confidence interval 1.14–2.65) and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 10. For adverse events, low level stimulation was significantly superior in dysphonia and hoarseness (relative risk 2.06, 95% confidence interval 1.34–3.17) and dyspnea (relative risk 2.43, 95% confidence interval 1.29–4.57). Treatment withdrawal, cough, and pain did not differ significantly between high level and low level stimulations.

#### 3. Panel meeting

##### 3-1. What is the quality of evidence about the overall outcomes?

In all the studies collected, the risk of bias was low overall, and the level was not downgraded for all the outcomes. For inconsistency of the results,  $I_2$  was 32% for only dysphonia / hoarseness. Since the effect estimate differed between studies, heterogeneity was considered high. Inconsistency was thus considered serious and was downgraded one rank. There was no problem with indirectness, and was judged not serious. As for imprecision, the confidence intervals in many analyses crossed the clinical decision thresholds, and hence was downgraded by one or two ranks. Regarding publication bias, there were only four studies, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: “moderate” for seizure frequency  $\leq 50\%$ , cough, and dyspnea; “low” for treatment withdrawal, dysphonia/ hoarseness, and pain. The overall level of evidence was “low”.

### **3-2. What is the balance between benefits and harms?**

High level stimulation was superior to low level stimulation for the outcome of seizure frequency  $\leq 50\%$ . Among the adverse events, dysphonia/hoarseness and dyspnea showed lower rates in low level stimulation, but since there was no significant difference in treatment withdrawal between two groups, there must be few adverse events serious enough to cause treatment withdrawal. According to expert opinion, many adverse events are reversible and can be controlled by adjusting the stimulation current intensity. Taken together, we decided that high level stimulation is probably superior in terms of the balance between benefits and harms.

### **3-3. What about patients' values and preferences?**

We concluded that there is probably no significant uncertainty and variability in patient's values and preferences because high level stimulation is more effective than low level stimulation, and although adverse events are more prevalent in high level stimulation, they are reversible and can be controlled by adjusting the stimulation current.

### **3-4. What is the balance between net benefit and cost or resources?**

Adjustment of stimulation intensity can be done by placing the programming wand over the subcutaneously implanted generator; thus resources and costs are negligible. However, reoperation is needed to replace the generator every few years when the battery runs out. Battery consumption is higher for high level stimulation than for low level stimulation. Based on these, it was decided that high level stimulation costs moderately more as compared to low level stimulation.

### **3-5. Recommendation grading**

In the discussions at the panel meeting, high level stimulation was considered superior in efficacy, and adverse effects were acceptable because most of them were presumably at a level that would not cause treatment withdrawal. As for burden and cost, high level stimulation was expected to consume more battery power, requiring more frequent generator exchange. Based on the above arguments, despite considerable adverse events that did not cause treatment withdrawal as well as the increased burden and cost, we finally unanimously recommended using high level stimulation, considering the highly anticipated seizure control effect.

## **4. Descriptions in other related guidelines**

In Japan, the "Guideline on implementation of vagus nerve stimulation therapy for epilepsy"<sup>6)</sup> was published by the Japan Epilepsy Society in 2012, which states that "In principle, initiate VNS two weeks after implantation. Start with low stimulation intensity and then gradually increase the intensity while monitoring the adverse effects [recommendation grade C]".

In 2013, the American Academy of Neurology released a guideline update entitled "Vagus nerve stimulation for the treatment of epilepsy". There is no recommendation for high level or low level stimulation in that guideline. However, it states that whether stimulation at a higher frequency is more likely to reduce seizures than usual stimulation remains unknown.

## **5. Treatment monitoring and evaluation**

For adjusting stimulation intensity, we need a system which is capable of managing complications and coping with equipment troubles.

## **6. Future research issues**

Further research on the optimal intensity of stimulation is needed. In addition, other than stimulus intensity, there is no RCT on supplementary techniques such as magnet stimulation, which will be a future research subject. It is also desirable to elucidate the mechanisms underlying the subgroup with high response and develop evaluation methods to identify these subjects.

## **7. RCT reports reviewed for this CQ**

Michael 1993<sup>2)</sup>, VNS study Group 1995<sup>3)</sup>, Handforth 1998<sup>4)</sup>, Klinkenberg 2012<sup>5)</sup>

## 8. List of appendices (to be shown later)

- Appendix CQ10-2-01. Flow diagram and search formula for references
- Appendix CQ10-2-02. Risk of bias summary
- Appendix CQ10-2-03. Risk of bias graph
- Appendix CQ10-2-04. Forest plot
- Appendix CQ10-2-05. Summary of Findings (SoF) table
- Appendix CQ10-2-06. Evidence-to-Decision table

## ■ References

- 1) Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev*. 2015; (4): CD002896.
- 2) Michael JE, Wegener K, Barnes. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs*. 1993; 25(6): 362-366.
- 3) The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*. 1995; 45(2): 224-230.
- 4) Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. 1998; 51(1): 48-55.
- 5) Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. 2012; 54(9): 855-861.
- 6) Kawai K, Sugai K, Akamatsu N, et al. Guideline on implementation of vagus nerve stimulation therapy for epilepsy. *Tenkan Kenkyu*. 2012; 30(1): 68-72 (in Japanese).
- 7) Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; 81(16): 1453-1459.

**CQ 10-2 Literature search**

PICO

P: Patients with drug-resistant epilepsy (children as subgroup)

I: Vagus nerve stimulation at high level stimulation

C: Compared with vagus nerve stimulation at low level stimulation

O: Are seizures controlled (25, 50, 75%)?

Is there a decrease in treatment continuation rate?

Is there an increase in dysphonia/hoarseness? / and cough?

Is there an increase in dyspnea?

Is there an increase in pain?

**■ Search formula**

PubMed search: September 28, 2016

#1 Search (("drug resistant epilepsy" [mesh] OR ((epilepsy OR seizures OR convulsions) AND (intractable OR refractory))))

#2 Search ("vagus nerve stimulation" [mesh] OR ("vagal nerve" AND stimulation) OR ("vagus nerve" AND "electric stimulation therapy"))

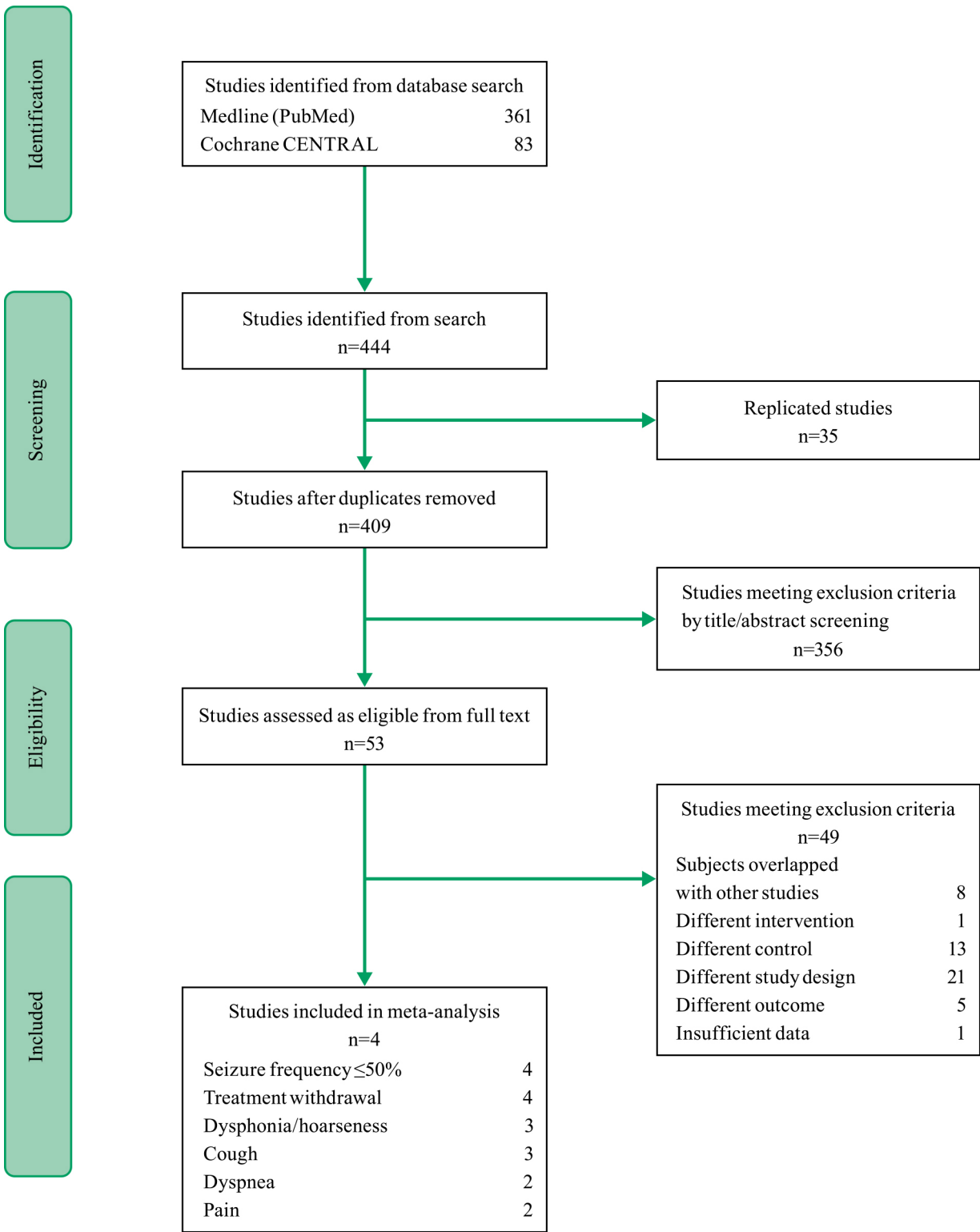
#3 Search (randomized controlled trial [pt] OR meta-analysis [pt] OR randomized OR blind OR observation\* OR cohort OR "follow-up" OR cross OR case OR series OR prospective OR retrospective OR placebo OR trial)

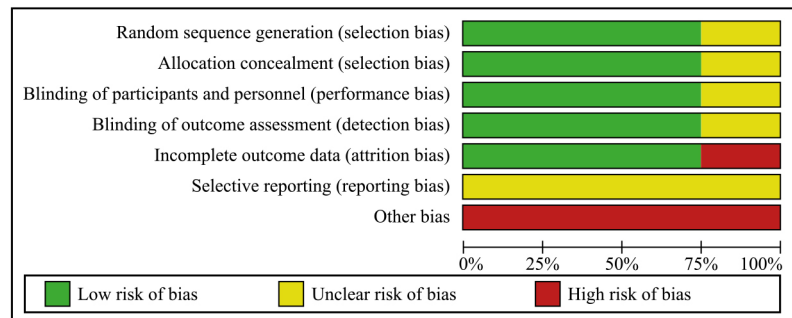
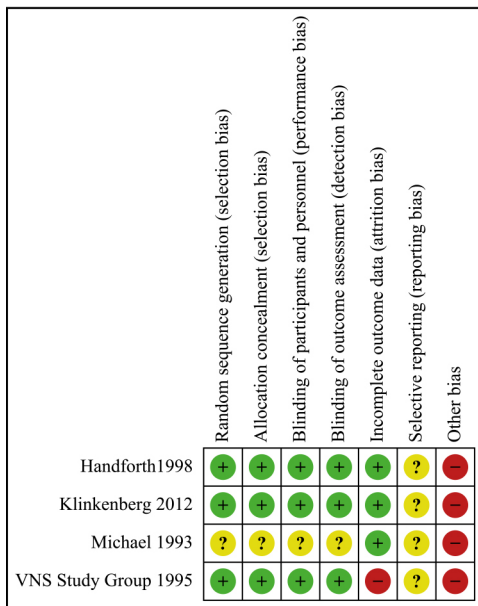
#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

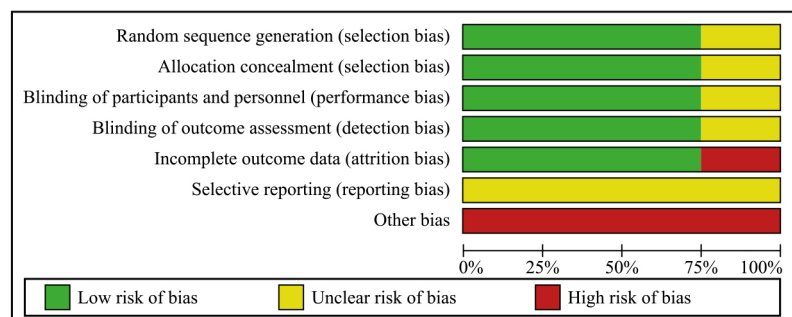
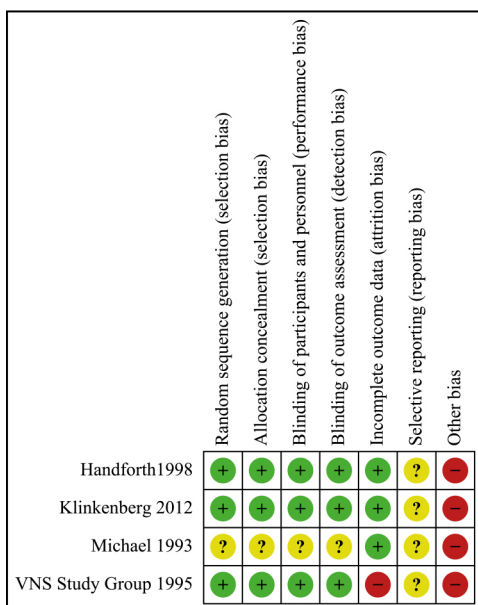
(epilepsy OR seizures) AND vagus nerve stimulation

**CQ10-2. Flow diagram of literature search (modified PRISMA 2009)**

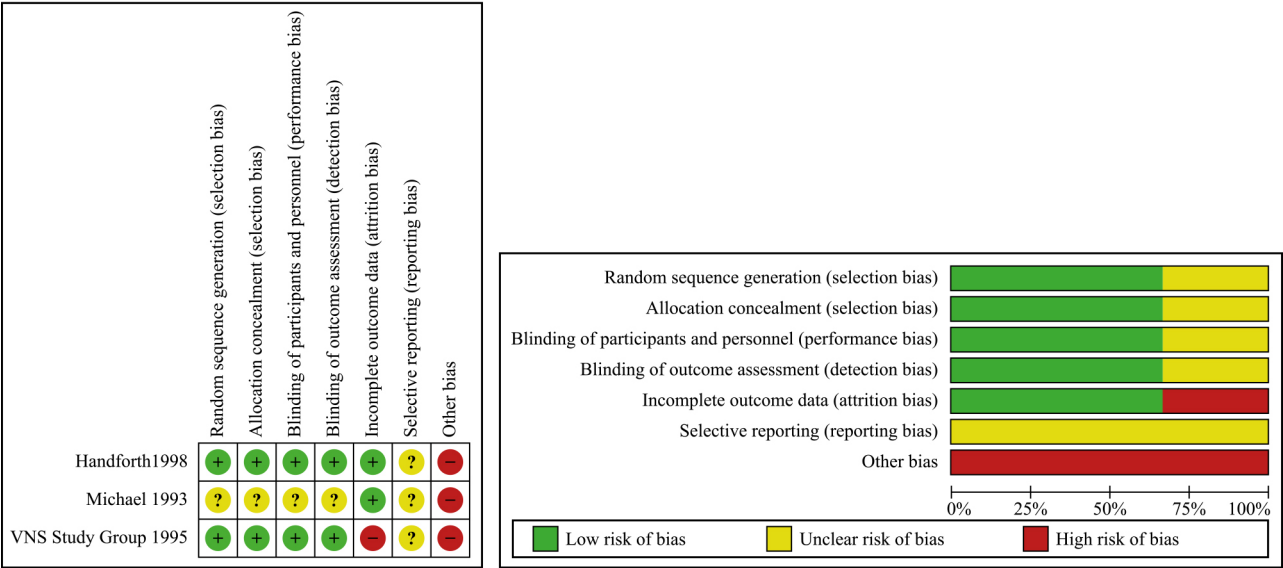


Seizure reduction  $\leq 50\%$ 

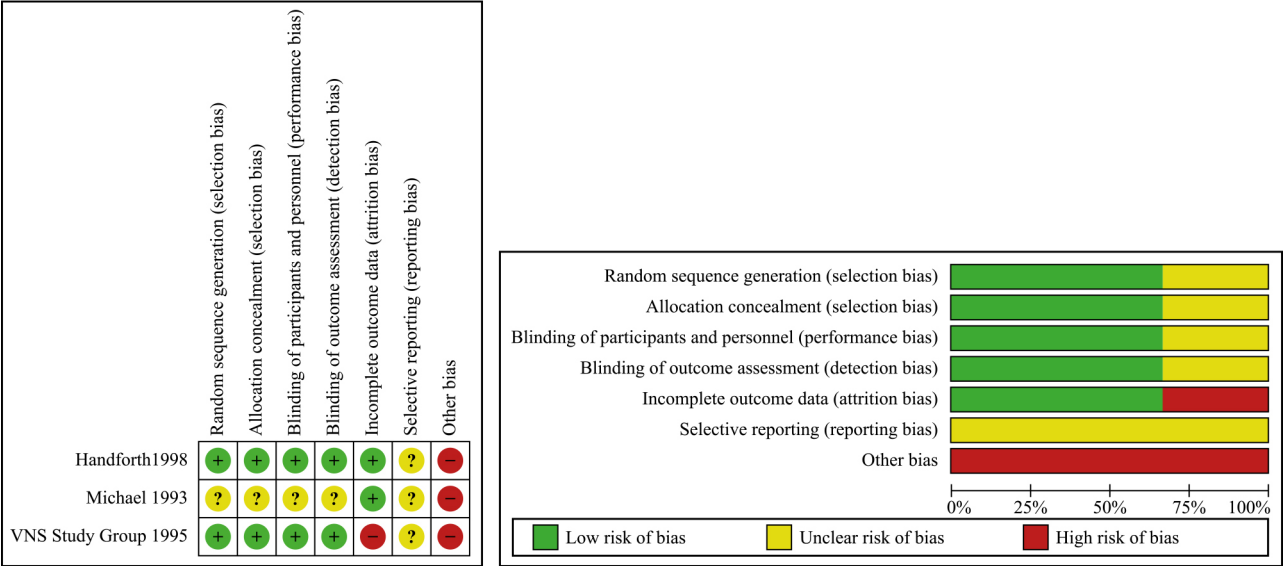
## Treatment withdrawal



Dysphonia/hoarseness

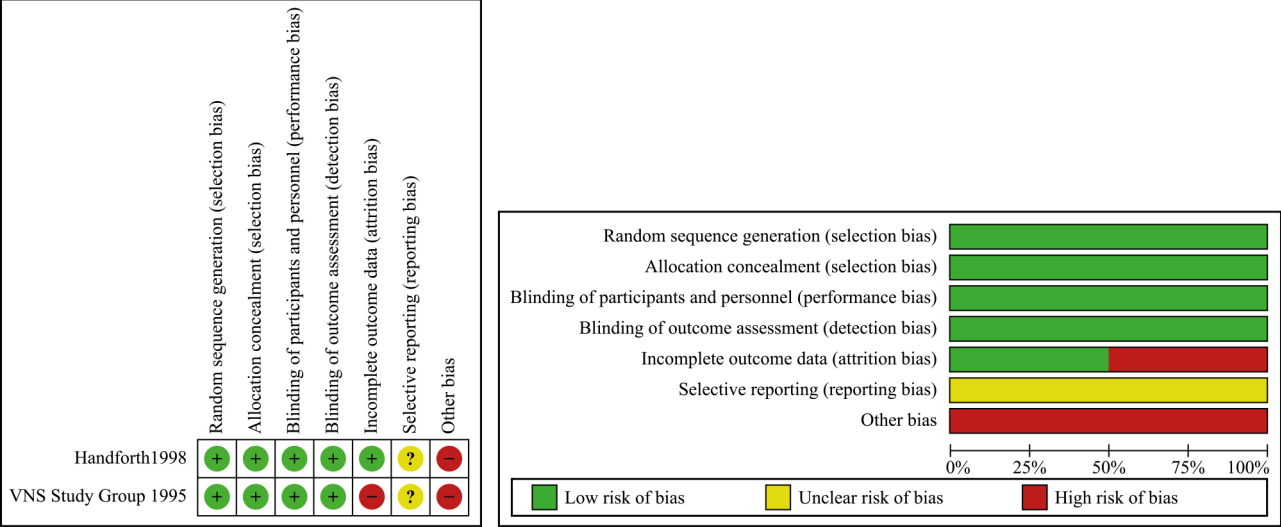


Cough

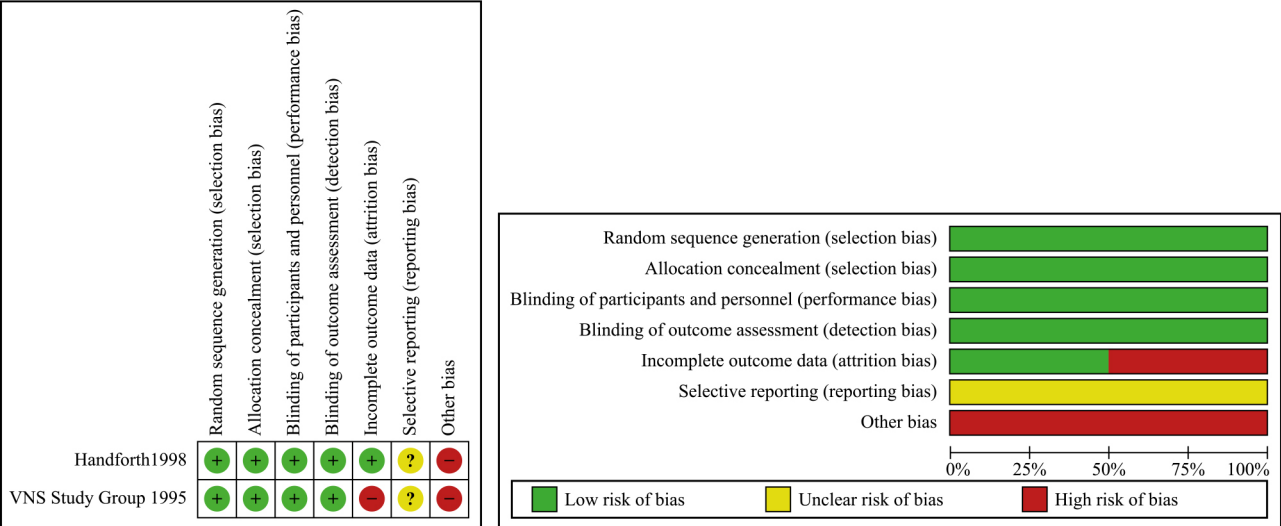


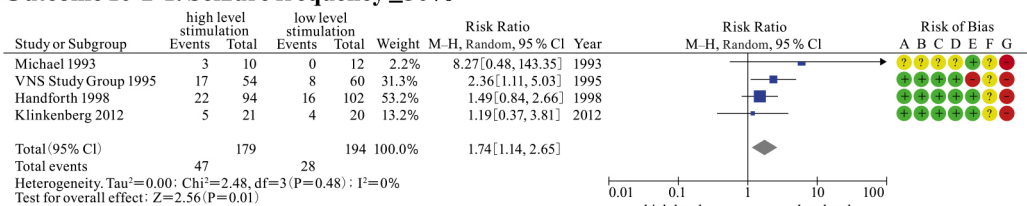


Dyspnea



Pain

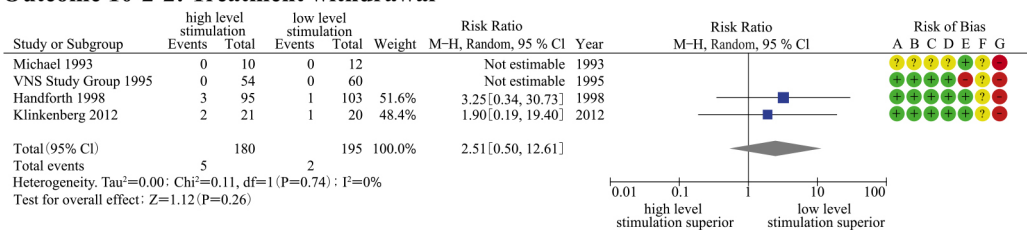


Outcome 10-2-1: Seizure frequency  $\leq 50\%$ 

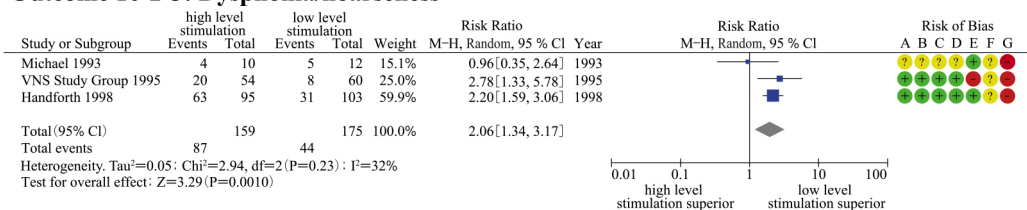
## Risk of bias legend

- (A) Random sequence generation (selection bias)  
 (B) Allocation concealment (selection bias)  
 (C) Blinding of participants and personnel (performance bias)  
 (D) Blinding of outcome assessment (detection bias)  
 (E) Incomplete outcome data (attrition bias)  
 (F) Selective reporting (reporting bias)  
 (G) Other bias

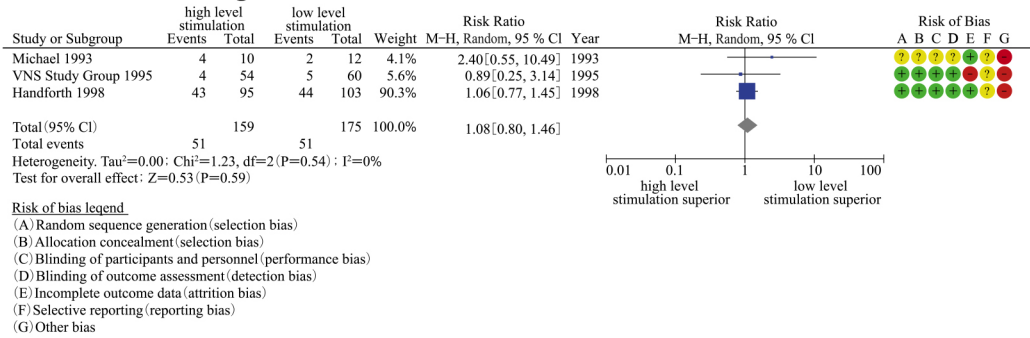
## Outcome 10-2-2: Treatment withdrawal



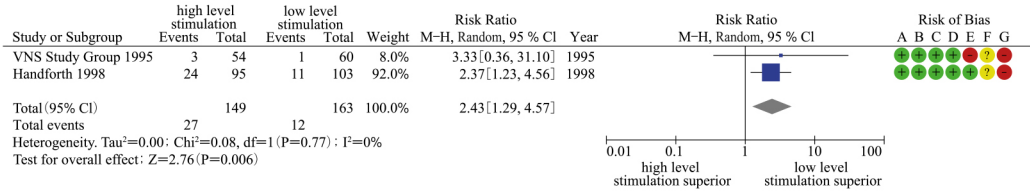
## Outcome 10-2-3: Dysphonia/hoarseness



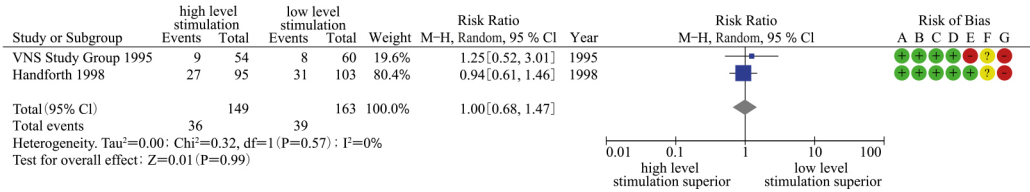
Outcome 10-2-4: Cough



Outcome 10-2-5: Dyspnea



Outcome 10-2-6: Pain



Patients: Patients with drug-resistant epilepsy

Intervention: High level stimulation

Comparison: Low level stimulation

Outcome	Expected absolute effect* (95% confidence interval)		Relative effect: risk ratio (RR) (95% confidence interval)	No. of patients (No. of studies)	Quality of evidence (GRADE)	Comment
	Risk of low level stimulation	Risk of high level stimulation				
Seizure frequency $\leq$ 50%	144 (per 1,000)	251 (per 1,000) (165–382)	RR 1.74 (1.14–2.65)	373 (4 RCTs)	⊕⊕⊕○ Moderate <sup>a</sup>	
Treatment withdrawal	10 (per 1,000)	26 (per 1,000) (5–129)	RR 2.51 (0.50–12.61)	375 (4 RCTs)	⊕⊕○○ Low <sup>b</sup>	
Dysphonia/hoarseness	251 (per 1,000)	518 (per 1,000) (337–797)	RR 2.06 (1.34–3.17)	334 (3 RCTs)	⊕⊕○○ Low <sup>c,d</sup>	
Cough	291 (1,000)	315 (per 1,000) (233–425)	RR 1.08 (0.80–1.46)	334 (3 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>	
Dyspnea	74 (1,000)	179 (per 1,000) (95–336)	RR 1.08 (0.80–1.46)	312 (2 RCTs)	⊕⊕⊕○ Moderate <sup>d</sup>	
Pain	239 (1,000)	239 (per 1,000) (163–352)	RR 1.00 (0.68–1.47)	312 (2 RCTs)	⊕⊕○○ Low <sup>b</sup>	

\*Risk (95% confidence interval) in the intervention group was estimated based on the risk in the control group and the effect due to intervention (and 95% confidence intervals).

Grades of quality of evidence according to the GRADE Working Group:

High: High certainty of the effect estimate. True effect is near the effect estimate.

Moderate: Moderate certainty of the effect estimate. The effect estimate is considered to be near the true effect, but further research may change the effect estimate.

Low: There is limitation in the certainty of the effect estimate. Although the effect estimate may be near the true effect, further research is very likely to change the effect estimate.

Very low: Very low certainty of the effect estimate. The true effect is very likely to be different from the effect estimate.

<sup>a</sup>: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable benefit

<sup>b</sup>: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm.

<sup>c</sup>: because  $I^2 = 32\%$ ; effect estimates differ among studies, heterogeneity is probably high

<sup>d</sup>: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable harm

## Evaluation table of recommendation decision criteria

Study population: Patients with drug-resistant temporal lobe epilepsy																																							
Intervention: vagus nerve stimulation																																							
CRITERIA		JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																			
PROBLEM	Is there a priority problem? More serious problems and more urgent problems have higher priority	- No - Probably no - Probably yes - Yes - Varies - Don't know	Vagus nerve stimulation is known to have different effects depending on the stimulation conditions. The intensity of stimulation should be adjusted while monitoring the therapeutic effect and adverse effects.	Comparison between high and low level stimulation was examined, because research comparing with vs. without vagus stimulation is difficult to implement due to issues in research execution																																			
	DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?  - Trivial - Small - Moderate - Large - Varies - Don't know	<b>The relative importance or values of the main outcomes of interest:</b> <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Seizure frequency ≤ 50%</td><td>CRITICAL</td><td>⊕⊕⊕○ MODERATE</td></tr><tr><td>Treatment withdrawal</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr><tr><td>Dysphonia, hoarseness</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr><tr><td>Cough</td><td>CRITICAL</td><td>⊕⊕⊕○ MODERATE</td></tr><tr><td>Dyspnea</td><td>CRITICAL</td><td>⊕⊕⊕○ MODERATE</td></tr><tr><td>Pain</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr></table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	Seizure frequency ≤ 50%	CRITICAL	⊕⊕⊕○ MODERATE	Treatment withdrawal	CRITICAL	⊕⊕○○ LOW	Dysphonia, hoarseness	CRITICAL	⊕⊕○○ LOW	Cough	CRITICAL	⊕⊕⊕○ MODERATE	Dyspnea	CRITICAL	⊕⊕⊕○ MODERATE	Pain	CRITICAL	⊕⊕○○ LOW	The relative risk of seizure frequency ≤50% for high level stimulation was 1.74 (1.14–2.65), and was significantly superior to low level.														
Outcome	Relative importance	Certainty of the evidence (GRADE)																																					
Seizure frequency ≤ 50%	CRITICAL	⊕⊕⊕○ MODERATE																																					
Treatment withdrawal	CRITICAL	⊕⊕○○ LOW																																					
Dysphonia, hoarseness	CRITICAL	⊕⊕○○ LOW																																					
Cough	CRITICAL	⊕⊕⊕○ MODERATE																																					
Dyspnea	CRITICAL	⊕⊕⊕○ MODERATE																																					
Pain	CRITICAL	⊕⊕○○ LOW																																					
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?  - Large - Moderate - Small - Trivial - Varies - Don't know		<b>Summary of findings</b> <table><tr><th>Outcome</th><th>Low level stimulation</th><th>High level stimulation</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr><tr><td>Seizure frequency ≤ 50%</td><td>144 per 1,000</td><td>251 per 1,000 (165 to 382)</td><td>107 more per 1,000 (from 20 more to 238 more)</td><td>RR 1.74 (1.14 to 2.65)</td></tr><tr><td>Treatment withdrawal</td><td>10 per 1,000</td><td>26 per 1,000 (5 to 129)</td><td>15 more per 1,000 (from 5 fewer to 119 more)</td><td>RR 2.51 (0.50 to 12.61)</td></tr><tr><td>Dysphonia/ hoarseness</td><td>251 per 1,000</td><td>518 per 1,000 (337 to 797)</td><td>267 more per 1,000 (from 85 more to 466 more)</td><td>RR 2.06 (1.34 to 3.17)</td></tr><tr><td>Cough</td><td>291 per 1,000</td><td>315 per 1,000 (233 to 425)</td><td>23 more per 1,000 (from 58 fewer to 134 more)</td><td>RR 1.08 (0.80 to 1.46)</td></tr><tr><td>Dyspnea</td><td>74 per 1,000</td><td>179 per 1,000 (95 to 336)</td><td>105 more per 1,000 (from 21 more to 263 more)</td><td>RR 2.43 (1.29 to 4.57)</td></tr><tr><td>Pain</td><td>239 per 1,000</td><td>239 per 1,000 (163 to 352)</td><td>0 fewer per 1,000 (from 77 fewer to 112 more)</td><td>RR 1.00 (0.68 to 1.47)</td></tr></table>	Outcome	Low level stimulation	High level stimulation	Difference (95% CI)	Relative effect (RR) (95% CI)	Seizure frequency ≤ 50%	144 per 1,000	251 per 1,000 (165 to 382)	107 more per 1,000 (from 20 more to 238 more)	RR 1.74 (1.14 to 2.65)	Treatment withdrawal	10 per 1,000	26 per 1,000 (5 to 129)	15 more per 1,000 (from 5 fewer to 119 more)	RR 2.51 (0.50 to 12.61)	Dysphonia/ hoarseness	251 per 1,000	518 per 1,000 (337 to 797)	267 more per 1,000 (from 85 more to 466 more)	RR 2.06 (1.34 to 3.17)	Cough	291 per 1,000	315 per 1,000 (233 to 425)	23 more per 1,000 (from 58 fewer to 134 more)	RR 1.08 (0.80 to 1.46)	Dyspnea	74 per 1,000	179 per 1,000 (95 to 336)	105 more per 1,000 (from 21 more to 263 more)	RR 2.43 (1.29 to 4.57)	Pain	239 per 1,000	239 per 1,000 (163 to 352)	0 fewer per 1,000 (from 77 fewer to 112 more)	RR 1.00 (0.68 to 1.47)	Significant differences between high level and low level stimulation were observed for dysphonia/ hoarseness (relative risk 2.06, 1.34 to 3.17) and dyspnea (relative risk 2.43, 1.29 to 4.57). However, the relative risk of treatment withdrawal was 2.51 (0.50 to 12.61), with no significant difference between high level and low level stimulation. It can be inferred that there are few adverse events serious enough to cause treatment discontinuation. Adverse effects are reversible and can be controlled by adjusting electric current.
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CERTAINTY OF THE EVIDENCE	What is the overall certainty of the evidence of effects?  - Very low - Low - Moderate - High - No included studies																																						
	VALUES	Is there important uncertainty about or variability in how much people value the main outcomes?  - Important uncertainty or variability - Probably important uncertainty or variability - Probably no important uncertainty or variability - No important uncertainty and variability																																					

<b>BALANCE OF EFFECTS</b>	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	<ul style="list-style-type: none"> <li>- Control is superior</li> <li>- Control is probably superior</li> <li>- Control and intervention are equivalent</li> <li>- Intervention is probably superior</li> <li>- Intervention is superior</li> <li>- It depends</li> <li>- Don't know</li> </ul>	Summary: High frequency stimulation is significantly superior for the outcome of seizure frequency $\leq 50\%$ (relative risk 1.74, 1.14–2.65). For adverse events, low level stimulation was significantly superior for dysphonia/hoarseness (relative risk 2.06, 1.34–3.17) and dyspnea (relative risk 2.43, 1.29–4.57). Treatment withdrawal, cough, and pain did not differ significantly between two groups.	
<b>COST AND RESOURCE</b>	How large are the resource requirement (cost)?	<ul style="list-style-type: none"> <li>- High cost</li> <li>- Moderate cost</li> <li>- Negligible</li> <li>- Moderate saving</li> <li>- Large saving</li> <li>- Varies</li> <li>- Don't know</li> </ul>	Stimulation intensity can be adjusted by manipulating the programming wand located above the subcutaneously implanted generator, and resources and costs are negligible. However, it is necessary to replace the generator once every few years when the battery runs out, requiring exchange with a cost of about ¥2,000,000 (covered by health insurance). Battery consumption is higher for high level stimulation than for low level stimulation.	
<b>ACCEPTABILITY</b>	Is the option acceptable to key stakeholders?	<ul style="list-style-type: none"> <li>- No</li> <li>- Probably no</li> <li>- Probably yes</li> <li>- Yes</li> <li>- Varies</li> <li>- Don't know</li> </ul>		
<b>FEASIBILITY</b>	Is the option feasible to implement?	<ul style="list-style-type: none"> <li>- No</li> <li>- Probably no</li> <li>- Probably yes</li> <li>- Yes</li> <li>- Varies</li> <li>- Don't know</li> </ul>	In the past, there were several prefectures that did not have vagus nerve stimulation device implantation facility or guidance/management facility, and access to treatment was poor in some regions. However, currently the criteria for adjusting doctor have been relaxed and access has improved. If the environment of access to device implantation facility and guidance/management facility continues to improve, adjustment of stimulation condition is feasible.	A list of facilities that can provide this therapy is posted on the Society website.

## Recommendation decision table

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
Judgment	○	○	○	○	●
Recommendation	When conducting vagus nerve stimulation for drug resistant epilepsy, high level stimulation rather than low level stimulation is recommended (GRADE 1C, strength of recommendation “strong recommendation”/certainty of evidence “low”).				
Justification	<p><b>Question (CQ):</b> When conducting vagus nerve stimulation for drug resistant epilepsy, should high-level stimulation or low-level stimulation be used?</p> <p><b>Patients (P):</b> Patients with drug-resistant epilepsy who were implanted a vagal nerve stimulating device.</p> <p><b>Intervention (I):</b> High level stimulation</p> <p><b>Comparison (C):</b> Low level stimulation</p> <p><b>Outcomes (O):</b> Seizure frequency ≤50%, treatment withdrawal, dysphonia/hoarseness, cough, dyspnea, pain</p> <p><b>Summary of evidence:</b> Systematic review identified four RCTs (375 patients). For seizure frequency ≤50%, high level stimulation was significantly superior (relative risk 1.74, 1.14–2.65) [NNT 10]. Among adverse events, significant differences were observed for dysphonia/ hoarseness (relative risk 2.06, 1.34–3.17) and dyspnea (relative risk 2.43, 1.29–4.57). The relative risk of treatment withdrawal was 2.51 (0.50–12.61), with no significant difference between high level stimulation and low level stimulation groups.</p> <p><b>Certainty of evidence:</b> In all the studies collected, the risk of bias was low overall, and was not downgraded for all the outcomes. For inconsistency of the results, <math>I_2</math> was 32% for only dysphonia and hoarseness. Since the effect estimate differed between studies, heterogeneity was considered high. Inconsistency was thus considered serious and was downgraded one rank. There was no problem with indirectness, which was not serious. As for imprecision, the confidence intervals in many analyses crossed the clinical decision thresholds, and hence was downgraded by one or two ranks. Regarding publication bias, there were only four studies, and therefore was not downgraded. Consequently, the certainty of evidence for the outcomes was as follows: “moderate” for seizure frequency ≤50% cough, and dyspnea; and “low” for treatment withdrawal, dysphonia/ hoarseness, and pain. The overall certainty of evidence was “low”.</p> <p><b>Judgment of benefits and harms, burden and cost:</b></p> <p>In 4 RCTs, high level stimulation was significantly superior for the outcome of seizure frequency ≤50% outcome. Among the adverse events, dysphonia/ hoarseness (relative risk 2.06, 1.34–3.17) and dyspnea (relative risk 2.43, 1.29– 4.57) were significantly more frequent in high level stimulation, but both were transient. There was no significant difference in treatment withdrawal between two groups (relative risk 2.51, 0.50–12.61). As for the burden and cost, it is expected that high level stimulation consumes more battery power and requires a higher frequency of generator exchange. Taking the above into consideration, despite adverse events that do not lead to treatment withdrawal and the possibility of increases in burden and cost, it is worth trying high level stimulation in anticipation of seizure control.</p> <p><b>Recommendation:</b></p> <p>When conducting vagus nerve stimulation for drug resistant epilepsy, high level stimulation rather than low level stimulation is recommended (strength of recommendation “strong recommendation”/certainty of evidence “low”).</p> <p><b>Additional considerations:</b></p> <p>Due to the problems with research execution, it is difficult to realize comparative study of vagus nerve stimulation versus no stimulation. Therefore, there is an increase in RCT comparing high level stimulation versus low level stimulation. Low level stimulation is generally treated as sham stimulation (placebo group). On the other hand, theoretically there exists an argument: the fact that low level stimulation is harmful may account for the therapeutic effect observed when compared with high level stimulation.</p>				
<b>Subgroup considerations.</b> Consider how to set criteria for patient population or intervention, which may change the recommendation statement	There was one RCT in children (Klinkenberg 2012). The relative risk of 50% reduction of seizure frequency for high level stimulation was 1.19 (0.94–1.44), with no significant difference compared to low level stimulus. On the other hand, the relative risk of treatment withdrawal was 1.90 (1.75–2.06) and was significantly higher. However, since the observation period in this RCT was only 20 weeks, and therapeutic effect can be expected with prolonged treatment, this finding alone cannot be used as evidence for withholding treatment.				
<b>Implementation considerations.</b> In clinical practice, problems such as feasibility and tolerability may arise.	High level stimulation usually refers to the intensity of stimulation used in treatment. On the other hand, low level stimulation refers to control stimulation (so-called sham stimulation) in which the stimulation frequency, pulse width, and stimulation frequency are set at low levels.  There may be a problem in the case of poor access to vagus nerve stimulation device implantation facility and guidance/ management facility due to changing residence and other reasons.				
<b>Monitoring and evaluation.</b> What monitoring is necessary for implementation? Is evaluation of effect necessary before or after publication?	For adjustment of stimulation intensity, a system has to be in place to respond to complications and to cope with equipment troubles. The frequency of hospital visit is about once a month after implantation surgery, and once every 3 months when the condition is stabilized.				
<b>Research possibilities.</b> What are the unclear points in judgment that require future research?	Further studies are needed to examine the optimal intensity of stimulation, elucidate the characteristics of subgroup demonstrating high efficacy, and develop methods to identify the high responders. Also, apart from adjusting stimulation intensity, there are no RCTs on other supplementary techniques such as magnet stimulation, which is a topic of future research.				