

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, Zaronitin
oxcarbazepine ¹⁾	OXC	Ocnobel
gabapentin ²⁾	GBP	Gabapen
carbamazepine	CBZ	Tegretol
clonazepam ³⁾	CZP	Landsen, Rivotril,
clobazam	CLB	Mystan
diazepam	DZP	Cercine, Horizon, Diapp
potassium bromide	KBr	Potassium bromide
stiripentol ⁴⁾	STP	Diacomit
sultiam	ST	Ospolot
zonisamide	ZNS	Excegran
topiramate ⁵⁾	TPM	Topina
nitrazepam	NZP	Benzalin
valproate	VPA	Depakene, Selenica
vigabatrin ⁶⁾	VGB	Sabril
phenytoin	PHT	Aleviatin, Hydantol
phenobarbital	PB	Phenobal
primidone	PRM	Primidone
perampanel ⁷⁾	PER	Fycompa
lacosamide ⁸⁾	LCM	Vimpat
lamotrigine ⁹⁾	LTG	Lamictal
rufinamide ¹⁰⁾	RFN	Inovelon
levetiracetam ¹¹⁾	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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