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[1, 2]. 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"[3] in 2008, and "Guideline on diagnosis and surgical indications of mesial temporal lobe epilepsy"[4] 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[5] 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[1] and 2 years[2].

7. RCT reports reviewed for this CQ

Wiebe 2001[1], Engel 2012[2]

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.

Appendix CQ 9-2-01. Flow diagram and literature search formula

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]))

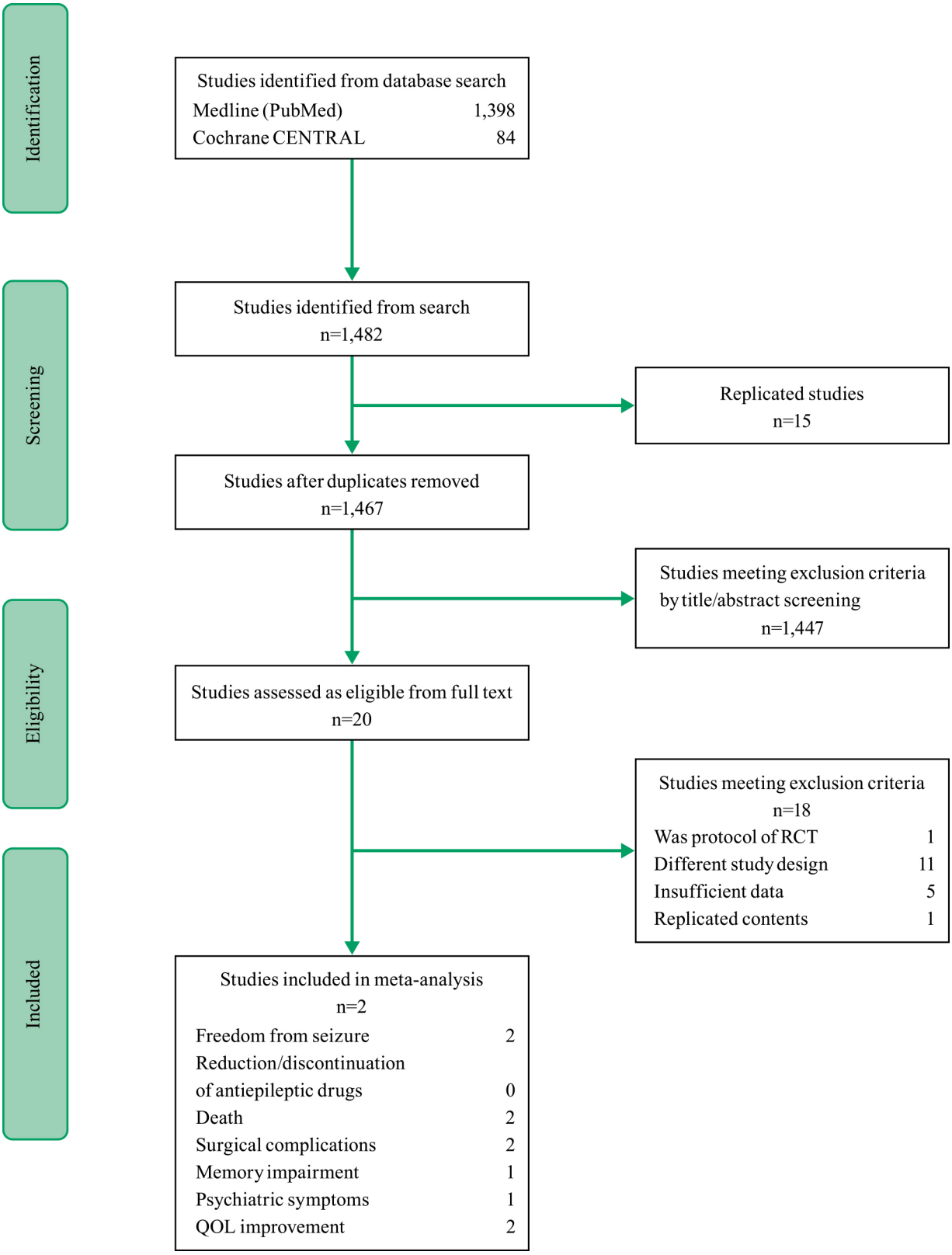
#3 Search (randomized controlled trial[pt] OR meta-analysis[pt] OR randomized OR blind OR observation* OR cohort OR "follow-up" OR cross OR case OR series OR prospective OR retrospective OR placebo OR trial)

#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

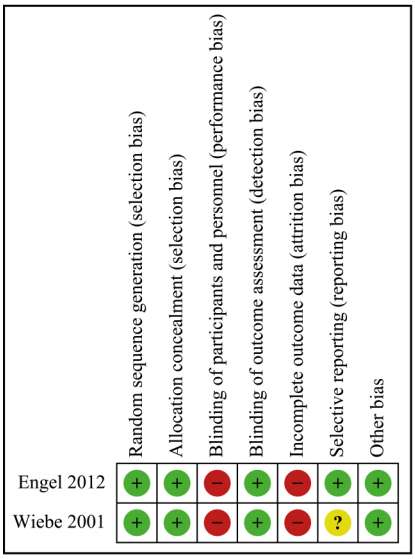
(epilepsy OR seizures) AND "temporal lobe" AND surgery

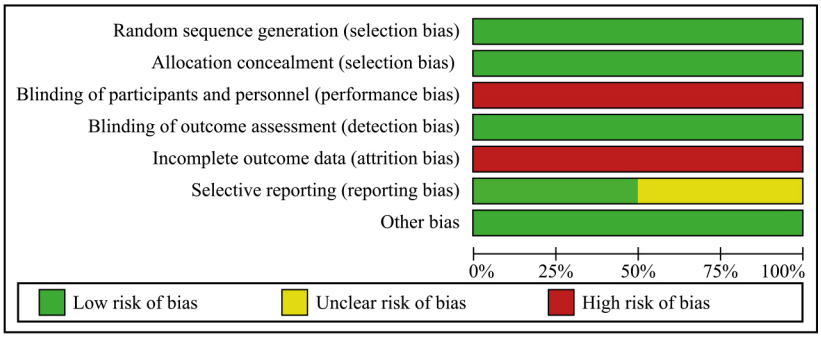
CQ9-2. Flow diagram of literature search (modified PRISMA 2009)



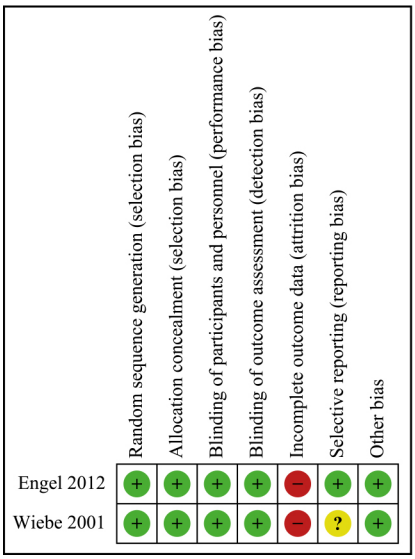
Appendix CQ9-2-02 and -03. **Risk of bias summary**
Risk of bias graphs

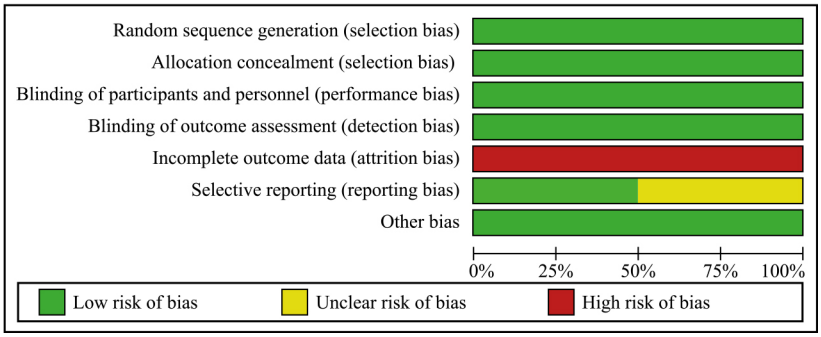
Seizure freedom



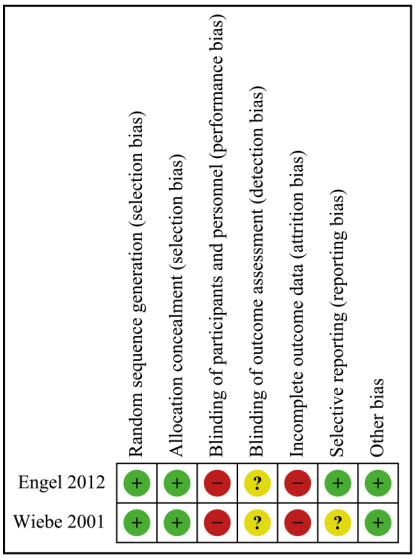


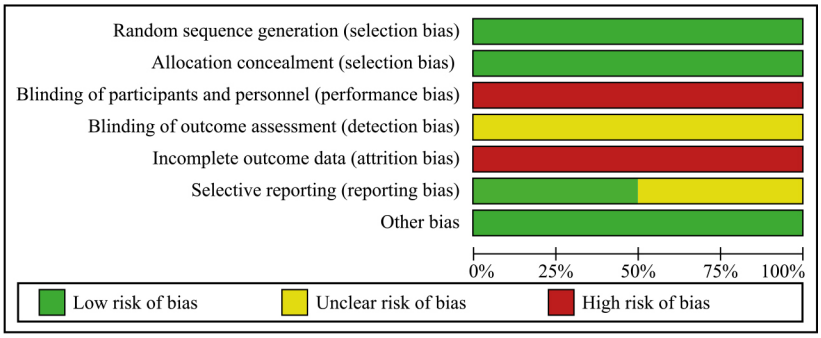
Death



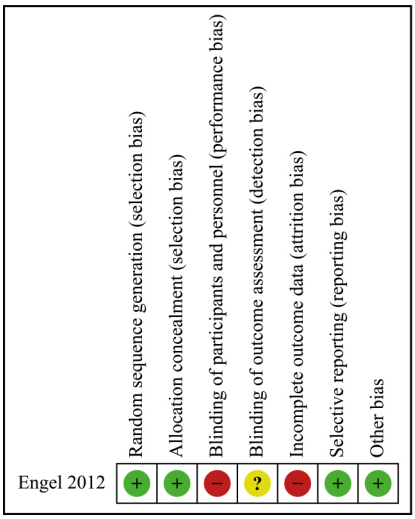


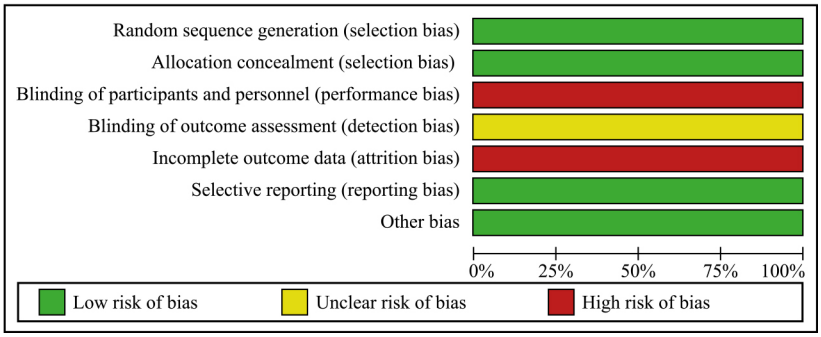
Surgical complications



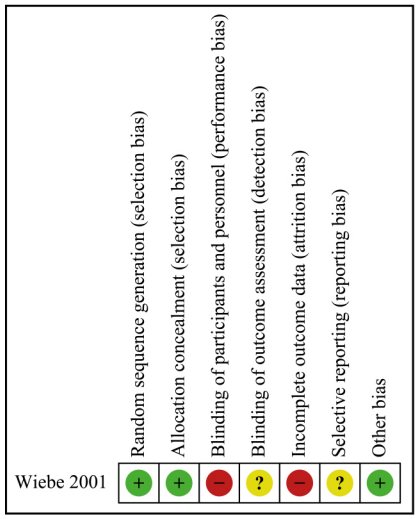


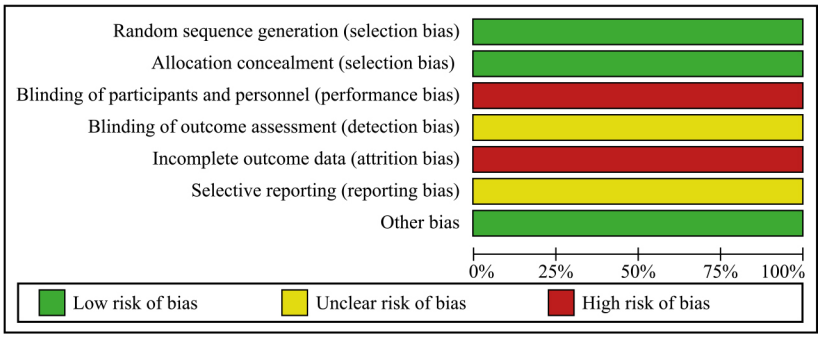
Memory impairment



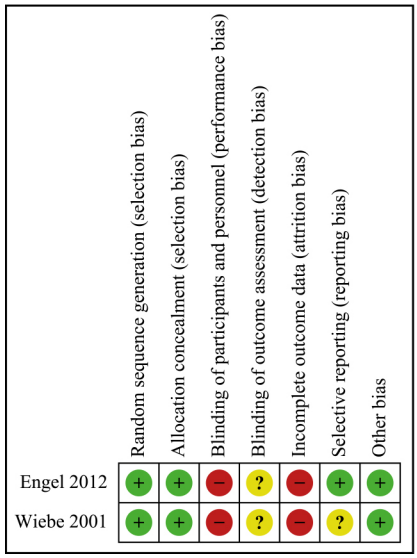


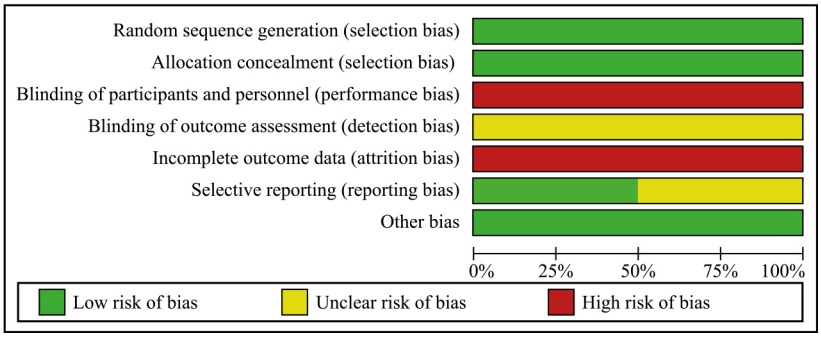
Psychiatric symptoms





QOL improvement



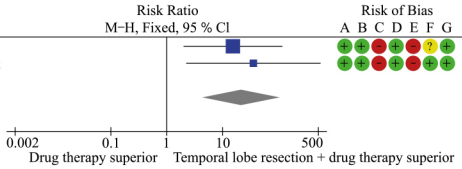


Appendix CQ9-2-04. Forest plot

Outcome 9-2-1: Seizure freedom

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95 % CI	Year
Wiebe 2001	15	40	1	40	71.4%	15.00[2.08, 108.23]	2001
Engel 2012	11	15	0	23	28.6%	34.50[2.18, 545.02]	2012
Total(95% CI)		55		63	100.0 %	20.57[4.24, 99.85]	
Total events	26		1				

Heterogeneity. Chi^2=0.23, df=1(P=0.63); I^2=0%
Test for overall effect: Z=3.75(P=0.0002)



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

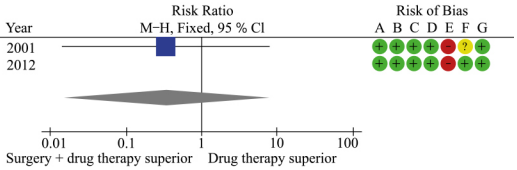
Outcome 9-2-2: Reduction/discontinuation of antiepileptic drugs

No primary study found

Outcome 9-2-3: Death

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95 % CI	Year
Wiebe 2001	0	40	1	40	100.0%	0.33[0.01, 7.95]	2001
Engel 2012	0	15	0	23		Not estimable	2012
Total(95% CI)		55		63	100.0%	0.33[0.01, 7.95]	
Total events	0		1				

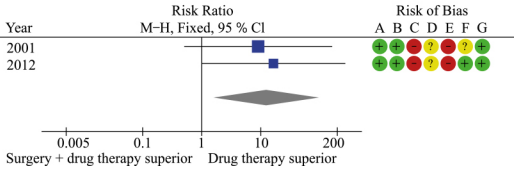
Heterogeneity. Not applicable
Test for overall effect: Z=0.68(P=0.50)



Outcome 9-2-4: Surgical complications

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95 % CI	Year
Wiebe 2001	4	40	0	40	55.6%	9.00[0.50, 161.86]	2001
Engel 2012	5	15	0	23	44.4%	16.50[0.98, 278.23]	2012
Total(95% CI)		55		63	100.0%	12.33[1.67, 90.89]	
Total events	9		0				

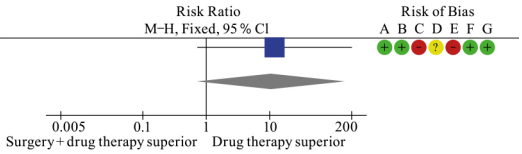
Heterogeneity. Chi^2=0.09, df=1(P=0.77); I^2=0%
Test for overall effect: Z=2.47(P=0.01)



Outcome 9-2-5: Memory impairment

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95 % CI
Engel 2012	4	11	0	15	100.0%	12.00[0.71, 202.18]
Total(95% CI)		11		15	100.0%	12.00[0.71, 202.18]
Total events	4		0			

Heterogeneity. Not applicable
Test for overall effect: Z=1.72(P=0.08)

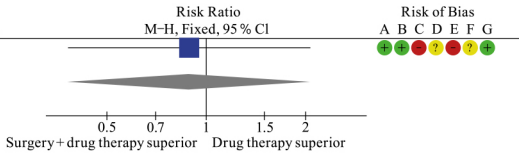


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Outcome 9-2-6: Psychiatric symptoms

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95 % CI
Wiebe 2001	8	40	9	40	100.0%	0.89[0.38, 2.07]
Total(95% CI)		40		40	100.0%	0.89[0.38, 2.07]
Total events	8		9			

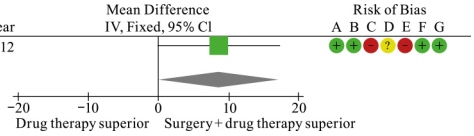
Heterogeneity. Not applicable
Test for overall effect: Z=0.27(P=0.78)



Outcome 9-2-7: Improvement of QOL [QOLIE-89 (89-item Quality of Life in Epilepsy Inventory)]

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Engel 2012	12.6	13	15	4	13	23	100.0%	8.60[0.14, 17.06]	2012
Total(95% CI)			15			23	100.0%	8.60[0.14, 17.06]	

Heterogeneity. Not applicable
Test for overall effect: Z=1.99(P=0.05)



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

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[a,b]	
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[c]	
Surgical complications	0 (per 1,000)	0 (per 1,000) (0–0)	RR 12.33 (1.67–90.89)	118 (2 RCTs)	⊕⊕◯◯ Low[a,b]	
Memory impairment	0 (per 1,000)	0 (per 1,000) (0–0)	RR 12.00 (0.71–202.18)	26 (1 RCT)	⊕◯◯◯ Very low[a,c]	
Psychiatric symptoms	225 (per 1,000)	200 (per 1,000) (86–466)	RR 0.89 (0.38–2.07)	80 (1 RCT)	⊕◯◯◯ Very low[a,b]	
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[a,d]	

*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.

[a]: because masking was not done, which affected the outcomes
[b]: 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).
[c]: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm
[d]: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable benefit, but not the clinical decision threshold of appreciable harm

Appendix CQ 9-2-06. Evidence-to-Decision table

Evaluation table of recommendation decision criteria

Study population: Patients with drug-resistant temporal lobe epilepsy

Intervention: Temporal lobe resection (added to drug therapy)

<table>
<tr><th colspan="2">CRITERIA</th><th>JUDGEMENTS</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is there a priority problem?
More serious problems and more urgent problems have higher priority</td><td>- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know</td><td>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.</td><td></td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?</td><td>- Trivial
- Small
- Moderate
- Large
- Varies
- Don't know</td><td rowspan="3">The relative importance or values of the main outcomes of interest:
<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Seizure freedom</td><td>CRITICAL</td><td>⊕⊕◯◯
LOW</td></tr><tr><td>Reduction/discontinuation of antiepileptic drugs</td><td>CRITICAL</td><td></td></tr><tr><td>Death</td><td>CRITICAL</td><td>⊕⊕◯◯
LOW</td></tr><tr><td>Surgical complications</td><td>CRITICAL</td><td>⊕⊕◯◯
LOW</td></tr><tr><td>Memory impairment</td><td>CRITICAL</td><td>⊕◯◯◯
VERY LOW</td></tr><tr><td>Psychiatric symptoms</td><td>CRITICAL</td><td>⊕◯◯◯
VERY LOW</td></tr><tr><td>QOL improvement</td><td>CRITICAL</td><td>⊕⊕◯◯
LOW</td></tr></table></td><td></td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?</td><td>- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know</td><td>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.</td></tr>
<tr><td>CERTAINTY OF THE EVIDENCE</td><td>What is the overall certainty of this evidence?</td><td>- Very low
- Low
- Moderate
- High
- No included studies</td><td>Surgery generally has evidence with low certainty due to difficulties with blinding.</td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?</td><td>- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty and variability</td><td rowspan="2">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></td><td></td></tr>
<tr><td>BALANCE OF EFFECTS</td><td>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</td><td>- Control is superior
- Control is probably superior
- Control and intervention are equivalent
- Intervention is probably superior
- Intervention is superior
- It depends
- Don't know</td><td></td></tr>
</table>

			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.	
COST AND RESOURCE	How large are the required resources (cost)?	- High cost - Moderate cost - Negligible - Moderate saving - Large saving - Varies - Don't know	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.	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	- No - Probably no - Probably yes - Yes - Varies - Don't know	Access to facility capable of surgery is required, but is possible.	
FEASIBILITY	Is the option feasible to implement?	- No - Probably no - Probably yes - Yes - Varies - Don't know	Feasible in specialized facilities. To find hospitals capable of surgery, consult the following websites: 1. The Japan Neurosurgical Society http://jns.umin.ac.jp/ 2. Epilepsy Surgery Society of Japan http://plaza.umin.ac.jp/~jess/ 3. The Japan Epilepsy Society http://square.umin.ac.jp/jes/	

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	**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")**				
Justification	**Question (CQ)**: Should temporal lobe resection be added to drug therapy for drug resistant temporal lobe epilepsy? **Patients (P):** Patients with drug resistant epilepsy **Intervention (I):** Temporal lobe resection (added to drug therapy) **Comparison (C):** Continued drug therapy only **Outcome (O):** Seizure freedom, death, surgical complications **Summary of evidence:** 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. **Certainty of evidence:** 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)". **Judgment of benefits and harms, burden, and cost:** 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. **Recommendation:** 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") **Additional considerations:** 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".				
Subgroup considerations. Consider how to set criteria for patient population or intervention, which may change the recommendation statement	No RCTs comparing surgical methods were identified.				
Implementation considerations. 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.				
Monitoring and evaluation. What kind of monitoring is necessary during implementation? Is evaluation necessary before or after publication?					
Research possibilities. 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[1]. 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 ≤ 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"[2] 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[2-4].

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[1)]

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.

Appendix CQ 10-1-01. **Flow diagram and literature search formula**

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"))

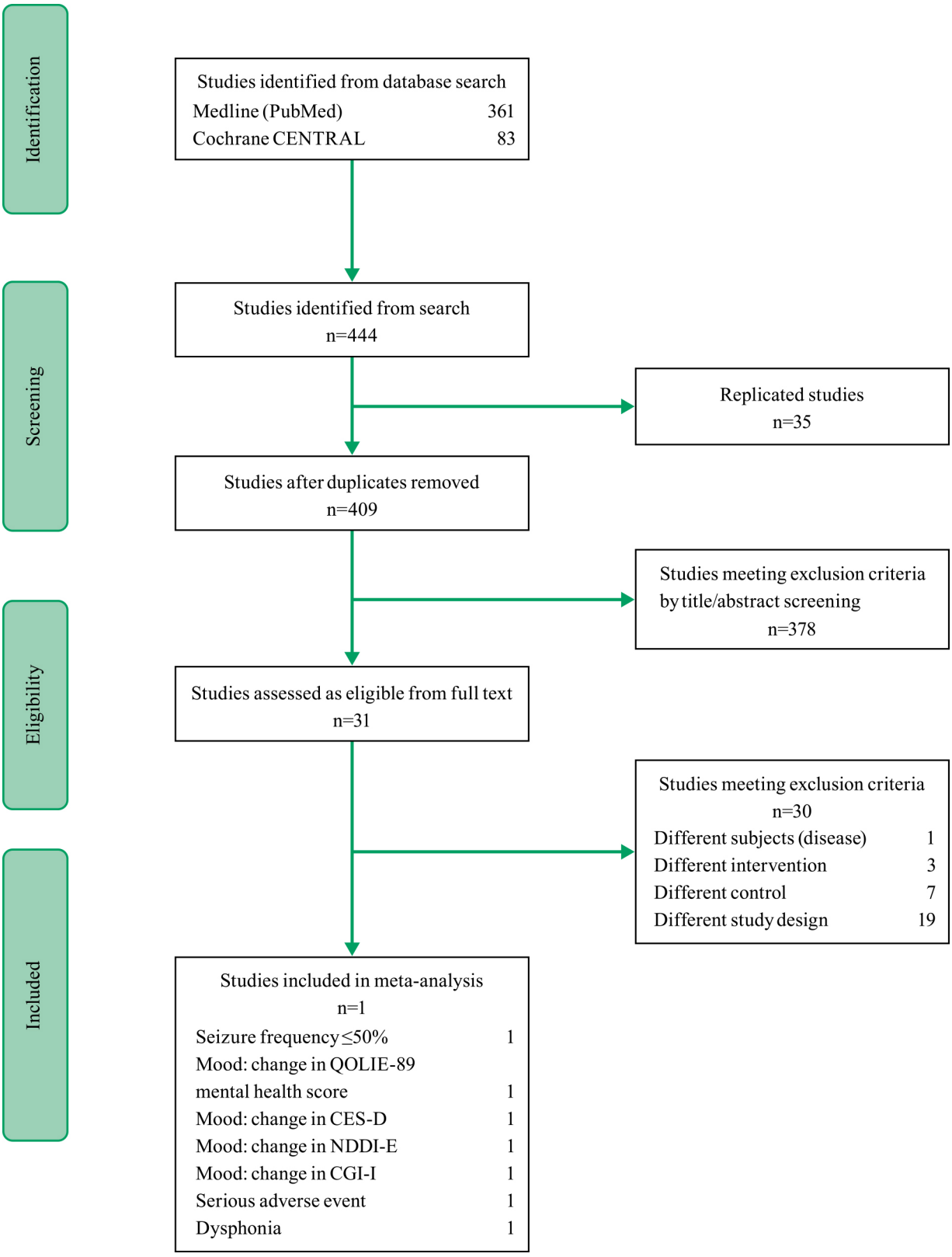
#3 Search (randomized controlled trial [pt] OR meta-analysis [pt] OR randomized OR blind OR observation* OR cohort OR "follow-up" OR cross OR case OR series OR prospective OR retrospective OR placebo OR trial)

#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

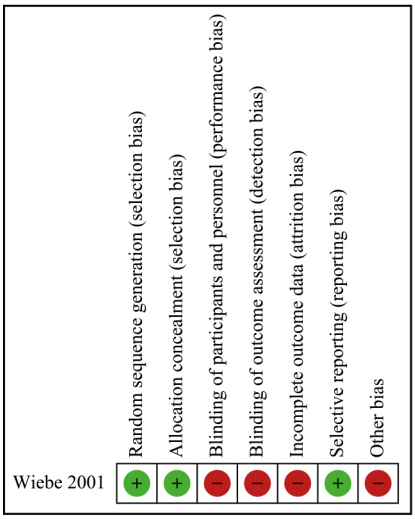
(epilepsy OR seizures) AND vagus nerve stimulation

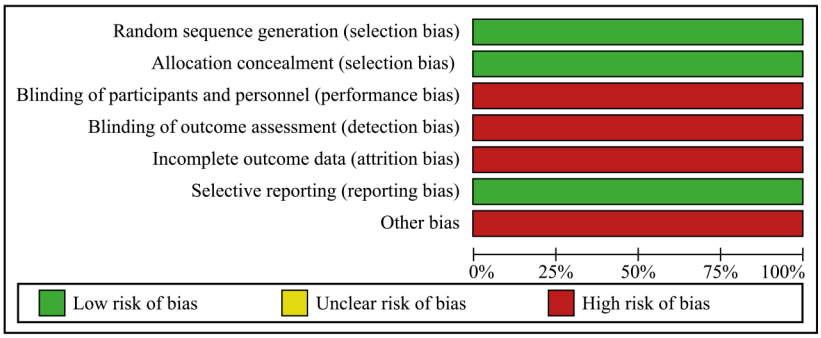
CQ10-1. Flow diagram of literature search (modified PRISMA 2009)



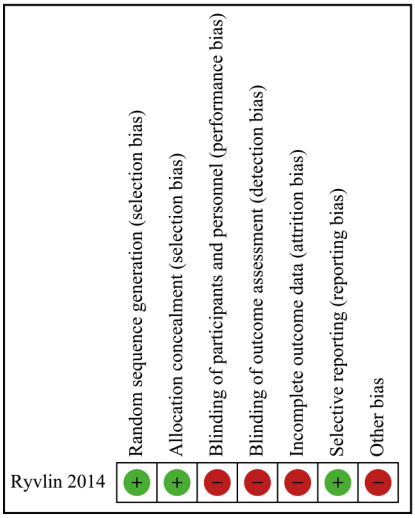
Appendix CQ10-1-02 and -03. **Risk of bias summary**
Risk of bias graphs

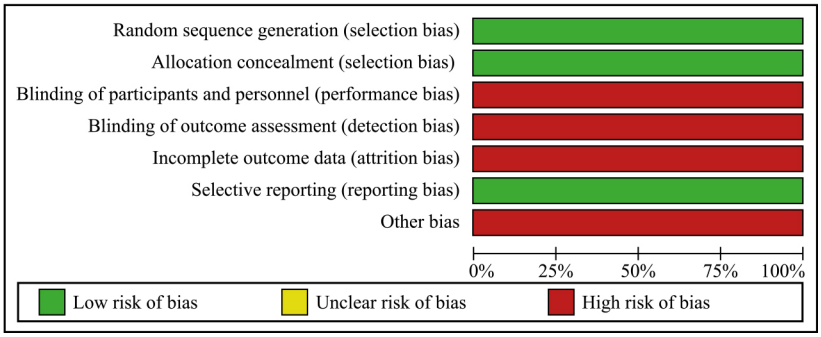
12-month 50% seizure reduction



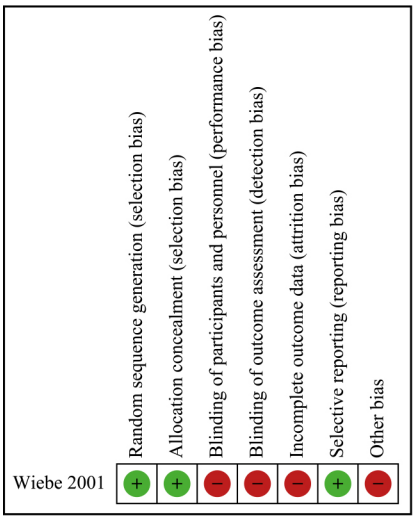


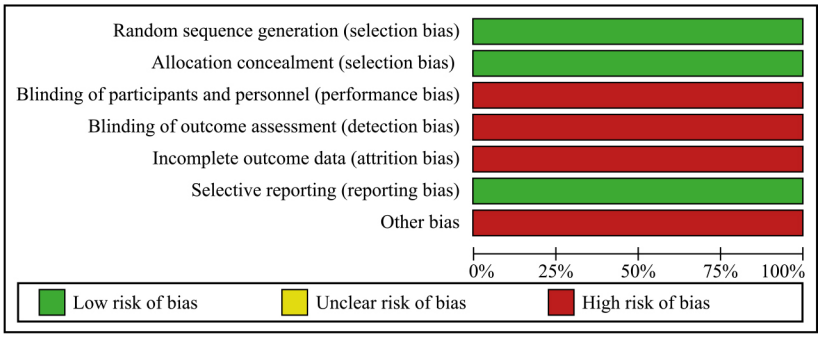
Mood after 12 months: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score



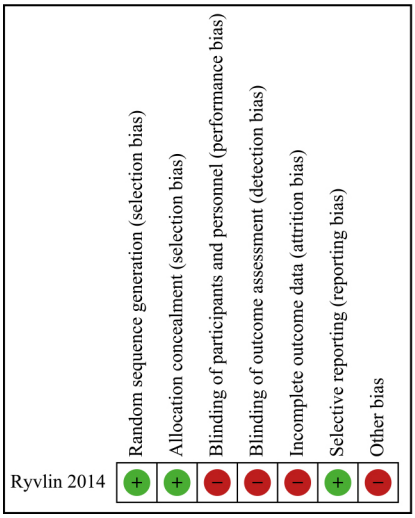


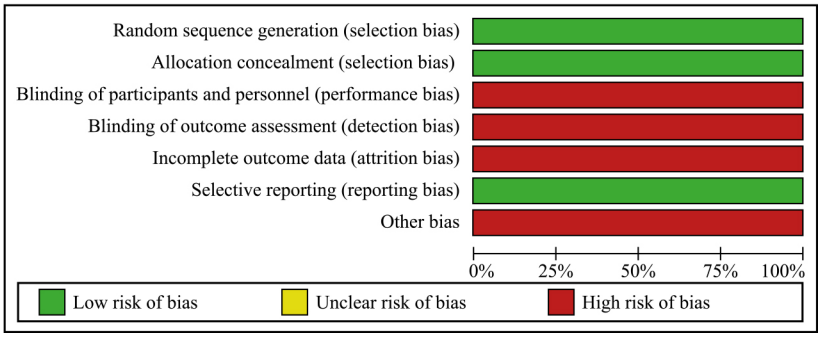
Mood after 12 months: change in CES-D (Centre for Epidemiologic studies Depression scale) score



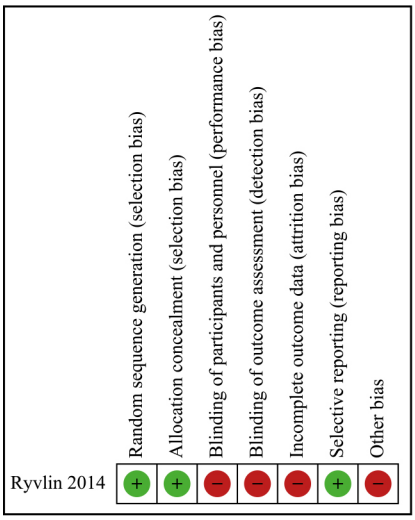


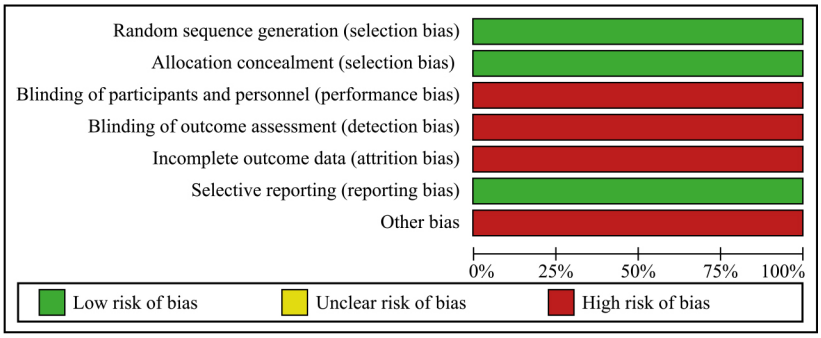
Mood after 12 months: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale) score



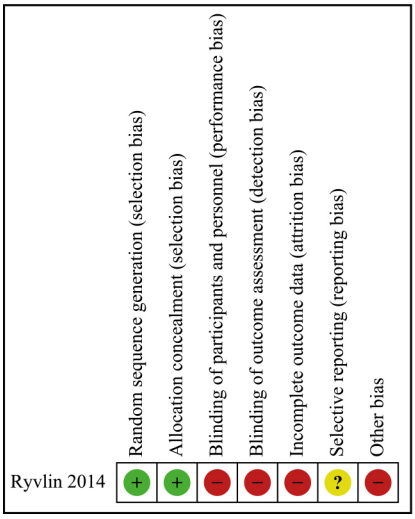


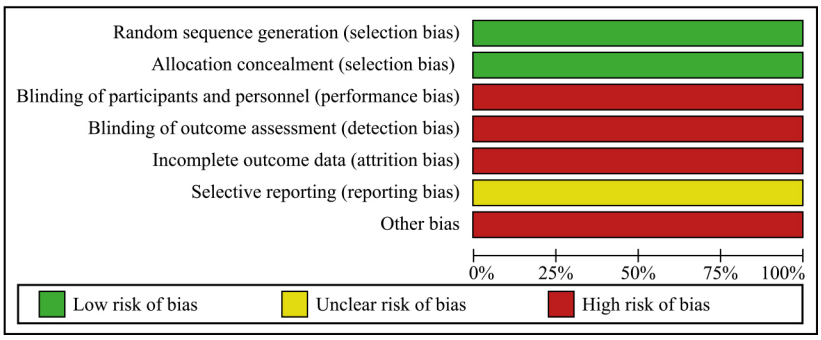
Mood after 12 months: change in CGI-I (Clinical Global Impression of Improvement scale) score



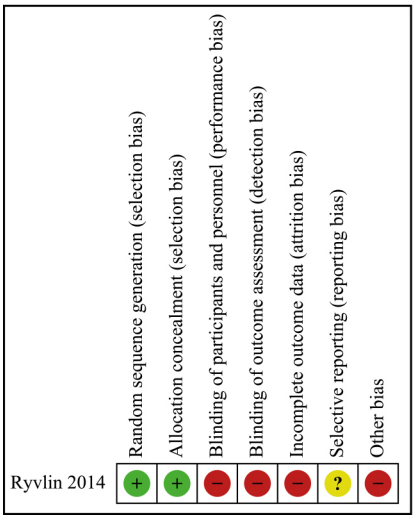


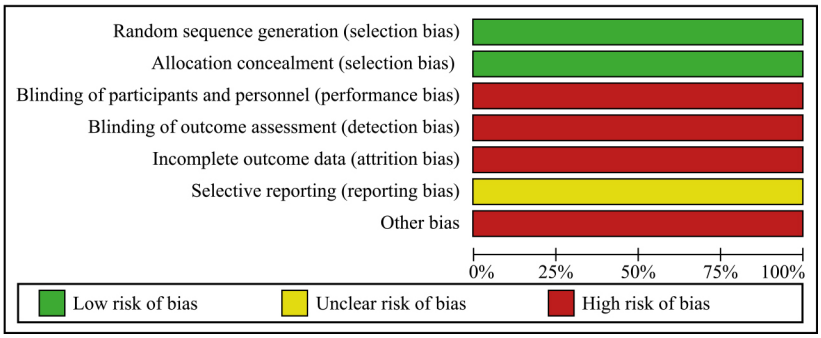
Serious adverse events





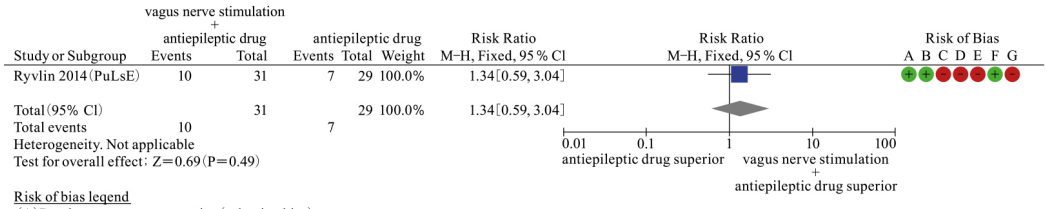
Dysphonia


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
Ryvlin 2014


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
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

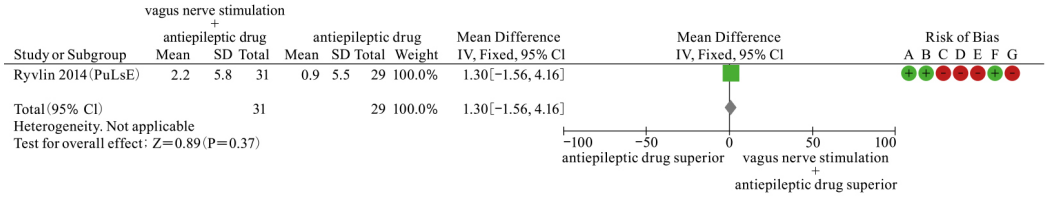
Appendix CQ10-1-04. Forest plot

Outcome 10-1-1: 12-month seizure frequency ≤50% (compared to baseline)

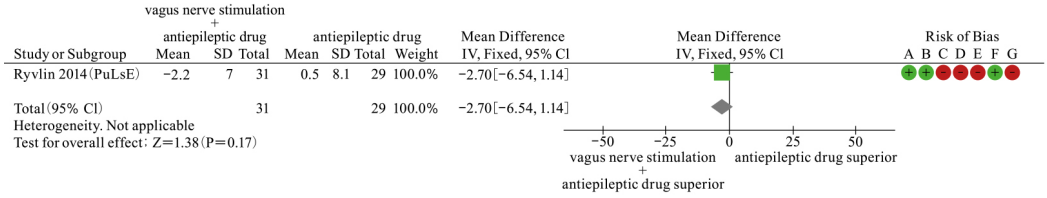


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

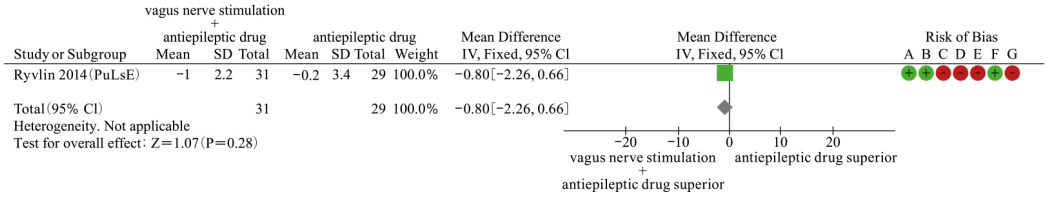
Outcome 10-1-2: Mood after 12 months: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score



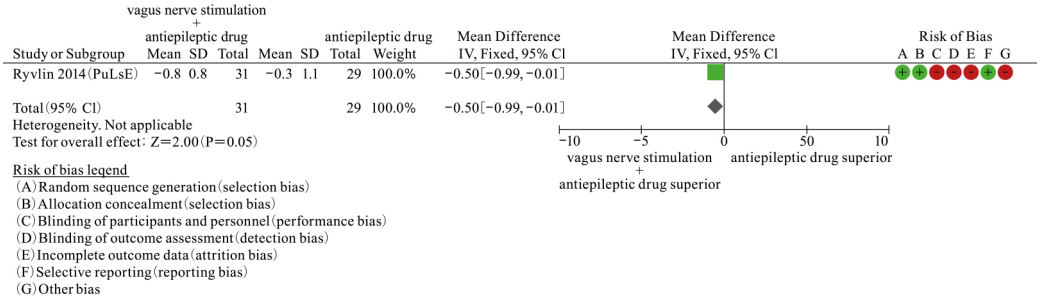
Outcome 10-1-3: Mood after 12 months: change in CES-D (Centre for Epidemiologic studies Depression scale) score



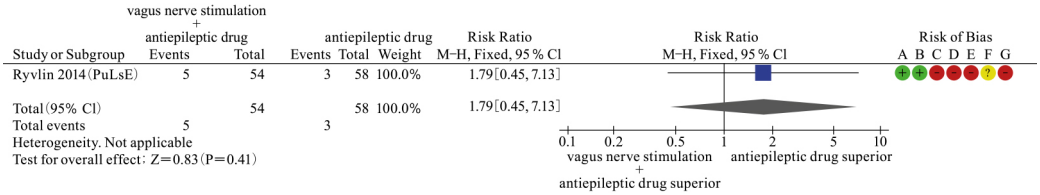
Outcome 10-1-4: Mood after 12 months: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale) score



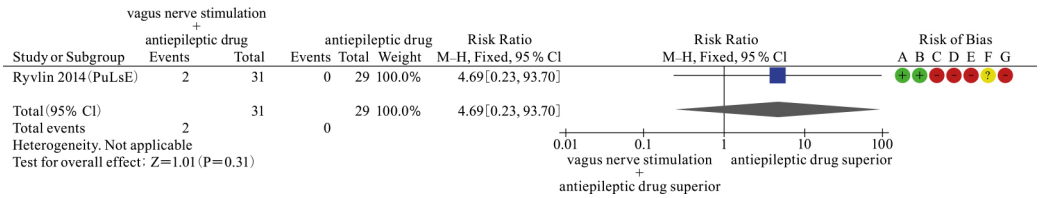
Outcome 10-1-5: 12 Mood after 12 months: change in CGI-I (Clinical Global Impression of Improvement scale) score



Outcome 10-1-6: Serious adverse events



Outcome 10-1-7: Dysphonia



Appendix CQ10-1-05. Summary of Findings (SoF) table

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 [a,b]	
	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 [a,c]	
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 [a,d]	
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 [a,c]	
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 [a,c]	
Serious adverse events	Study subject population		RR 1.79 (0.45–7.13)	112 (1 RCT)	⊕◯◯◯ Very low [a,b]	
	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 [a,b]	

*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.

[a]: because masking was not done, which affected the outcome.
[b]: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm.
[c]: 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).
[d]: 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.

Appendix CQ 10-1-06. Evidence-to-Decision table

Evaluation table of recommendation decision criteria

Study population: Patients with drug resistant temporal lobe epilepsy

Intervention: vagus nerve stimulation

<table>
<tr><th colspan="2">CRITERIA</th><th>JUDGEMENTS</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is there a priority problem?
More serious problems and more urgent problems have higher priority</td><td>- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know</td><td>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.</td><td></td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?</td><td>- Trivial
- Small
- Moderate
- Large
- Varies
- Don't know</td><td>The relative importance or values of the main outcomes of interest:
<table><tr><th>Outcome Relative</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Seizure frequency ≤50%</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW</td></tr><tr><td>Mood: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score</td><td>CRITICAL</td><td>⨁⨁◯◯
LOW</td></tr><tr><td>Mood: change in CES-D (Centre for Epidemiologic Studies Depression scale)</td><td>CRITICAL</td><td>⨁⨁◯◯
LOW</td></tr><tr><td>Mood: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale)</td><td>CRITICAL</td><td>⨁⨁◯◯
LOW</td></tr><tr><td>Mood: change in CGI-I (Clinical Global Impression of Improvement scale)</td><td>CRITICAL</td><td>⨁⨁◯◯
LOW</td></tr><tr><td>Serious adverse events</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW</td></tr><tr><td>Dysphonia</td><td>CRITICAL</td><td>⨁◯◯◯
VERY LOW</td></tr></table></td><td>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.</td></tr>
<tr><td>UNDESIRABLE EFFCETS</td><td>How substantial are the undesirable anticipated effects?</td><td>- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know</td><td>Summary of findings
<table><tr><th>Outcome</th><th>Drug therapy</th><th>Vagus nerve stimulation (VNS) + drug therapy</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr><tr><td rowspan="3">Seizure frequency ≤ 50%</td><td>241 per 1,000</td><td>323 per 1,000 (142 to 734)</td><td>82 more per 1,000 (from 99 fewer to 492 more)</td><td rowspan="3">RR 1.34 (0.59 to 3.04)</td></tr><tr><td>120 per 1,000</td><td>161 per 1,000 (71 to 365)</td><td>41 more per 1,000 (from 49 fewer to 245 more)</td></tr><tr><td>480 per 1,000</td><td>643 per 1,000 (283 to 1,000)</td><td>163 more per 1,000 (from 197 fewer to 979 more)</td></tr><tr><td>Mood: change in QOLIE-89 (89-item Quality of Life in Epilepsy Inventory) mental health score</td><td></td><td></td><td>MD 1.3 higher (1.56 lower to 4.16 higher)</td><td>-</td></tr></table></td><td>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).</td></tr>
<tr><td>CERTAINTY OF THE EVIDENCE</td><td>What is the overall certainty of the evidence of effects?</td><td>- Very low
- Low
- Moderate
- High
- No included studies</td><td></td><td></td></tr>
</table>

<table>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?</td><td>- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty and variability</td><td colspan="5"><table>
<tr><td>Mood: change in CES-D (Centre for Epidemiologic Studies Depression scale)</td><td></td><td></td><td>MD 2.7 lower (6.54 lower to 1.14 higher)</td><td></td></tr>
<tr><td>Mood: change in NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale)</td><td></td><td></td><td>MD 0.8 lower (2.26 lower to 0.66 higher)</td><td></td></tr>
<tr><td>Mood: change in CGI-I (Clinical Global Impression of Improvement scale)</td><td></td><td></td><td>MD 0.5 lower (0.99 lower to 0.01 lower)</td><td></td></tr>
</table></td><td>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.</td></tr>
<tr><td>BALANCE OF EFFECTS</td><td>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</td><td>- Control is superior
- Control is probably superior
- Control and intervention are equivalent
- Intervention is probably superior
- Intervention is superior
- It depends
- Don’t know</td><td colspan="5"><table>
<tr><td>Serious adverse event</td><td>52 per 1,000</td><td>93 per 1,000 (23 to 369)</td><td>41 more per 1,000 (from 28 fewer to 317 more)</td><td>RR 1.79 (0.45 to 7.13)</td></tr>
<tr><td></td><td>25 per 1,000</td><td>45 per 1,000 (11 to 178)</td><td>20 more per 1,000 (from 14 fewer to 153 more)</td><td></td></tr>
<tr><td></td><td>100 per 1,000</td><td>179 per 1,000 (45 to 713)</td><td>79 more per 1,000 (from 55 fewer to 613 more)</td><td></td></tr>
<tr><td>Dysphonia</td><td>0 per 1,000</td><td>0 per 1,000 (0 to 0)</td><td>0 fewer per 1,000 (from 0 fewer to 0 fewer)</td><td>RR 4.69 (0.23 to 93.70)</td></tr>
</table>
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 ≤ 50% was 1.34 (0.59–3.04).
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.
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.</td><td></td></tr>
<tr><td>COST AND RESOURCE</td><td>How large are the resource requirement (cost)?</td><td>- High cost
- Moderate cost
- Negligible
- Moderate saving
- Large saving
- Varies
- Don’t know</td><td colspan="5">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).</td><td></td></tr>
<tr><td>ACCEPTABILITY</td><td>Is the option acceptable to key stakeholders?</td><td>- No
- Probably no
- Probably yes
- Yes
- Varies
- Don’t know</td><td colspan="5"></td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the option feasible to implement?</td><td>- No
- Probably no
- Probably yes
- Yes
- Varies
- Don’t know</td><td colspan="5">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.</td><td>A list of facilities that can provide this therapy is posted on the Society website.</td></tr>
</table>

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	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")				
Justification	**Question (CQ):** Should vagus nerve stimulation be used for drug resistant epilepsy? **Patient (P):** Drug resistant epilepsy **Intervention (I):** Vagus nerve stimulation (added to drug therapy) **Comparison (C):** Drug therapy **Outcome:** Seizure frequency ≤ 50%, mood improvement (QOLIE-8, CES-D, NDDI-E, CGI-I), serious adverse events, dysphonia **Summary of evidence:** Systematic review identified 1 RCT (96 subjects). When seizure frequency ≤ 50% 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. 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 ≤ 50%, serious adverse events, and dysphonia; and "low" for the other outcomes. The overall certainty of evidence was "very low". **Judgment of benefits and harms, burden and cost:** 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. **Recommendation:** Addition of vagus nerve stimulation on drug therapy is proposed for drug resistant epilepsy. (strength of recommendation "weak recommendation" / certainty of evidence "very low". **Additional considerations:** 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."				
Subgroup considerations. 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 guidelines 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 ≥ 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.				
Implementation considerations. 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)].				
Monitoring and evaluation. 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.				
Research possibilities. 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[1] 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[2–5].

For efficacy, the relative risk of seizure frequency ≤ 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 ≤ 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 ≤ 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"[6] 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[2], VNS study Group 1995[3], Handforth 1998[4], Klinkenberg 2012[5]

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.

Appendix CQ10-2-01. **Flow diagram and literature search formula**

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"))

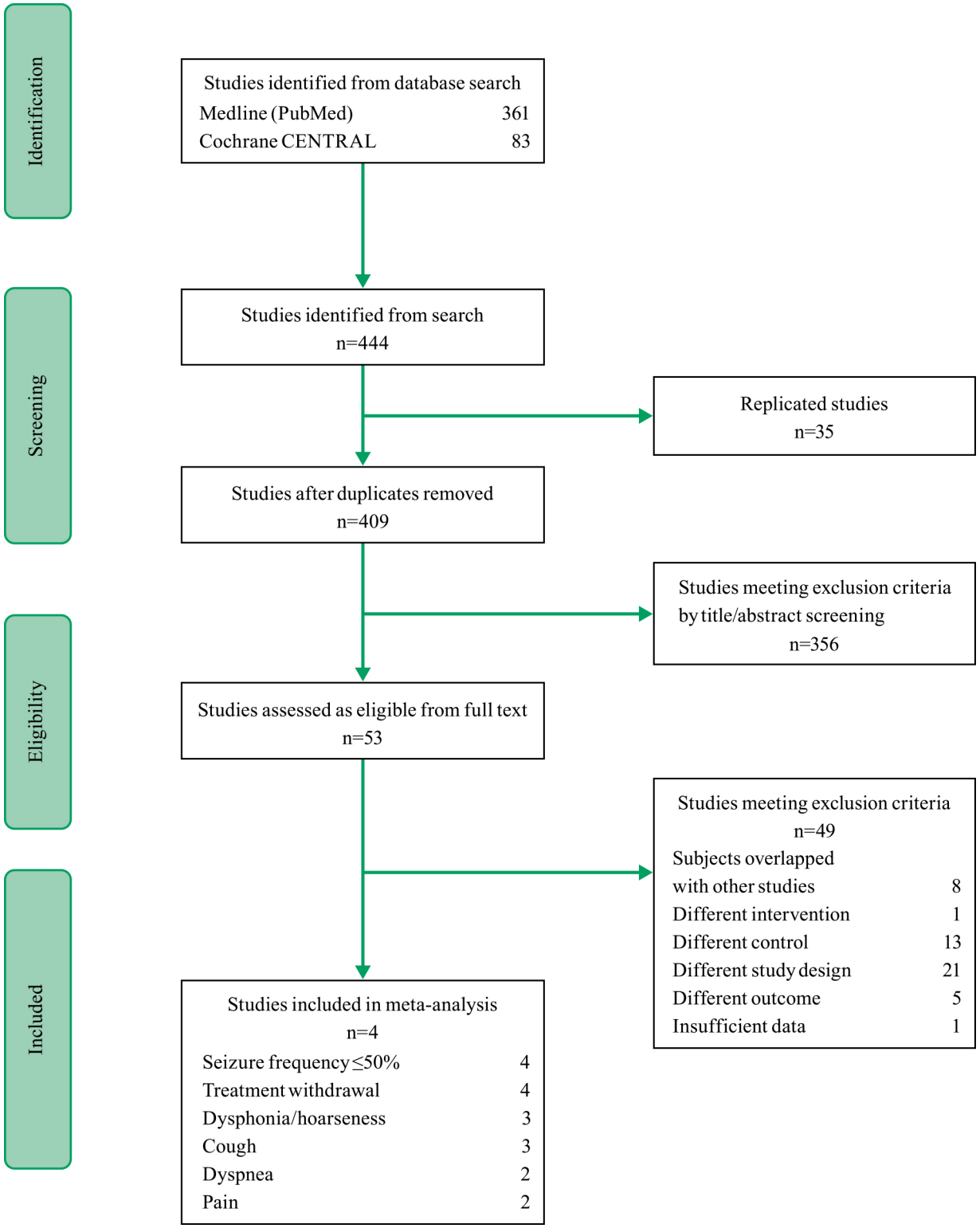
#3 Search (randomized controlled trial [pt] OR meta-analysis [pt] OR randomized OR blind OR observation* OR cohort OR "follow-up" OR cross OR case OR series OR prospective OR retrospective OR placebo OR trial)

#4 (#1 AND #2 AND #3)

Cochrane CENTRAL search: September 28, 2016

(epilepsy OR seizures) AND vagus nerve stimulation

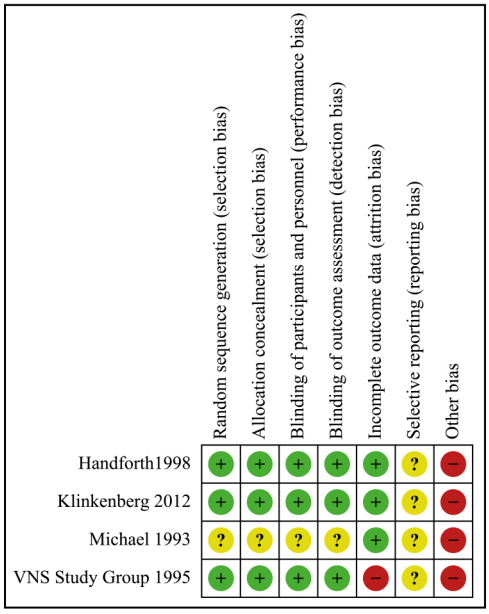
CQ10-2. Flow diagram of literature search (modified PRISMA 2009)

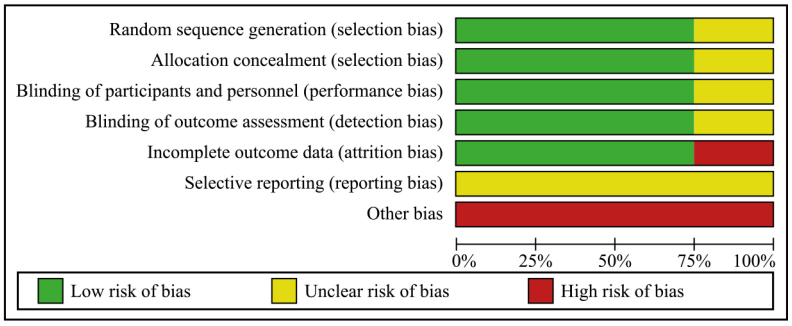


Appendix CQ10-2-02 and -03.

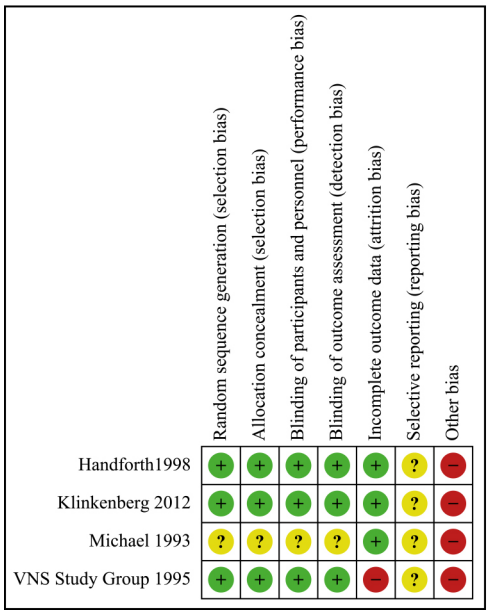
Risk of bias summary
Risk of bias graphs

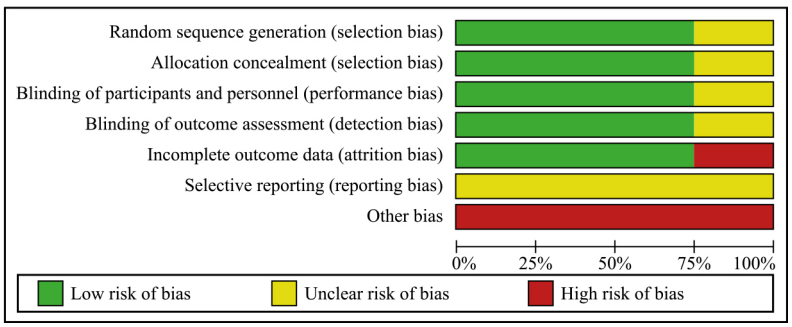
Seizure reduction ≤50%



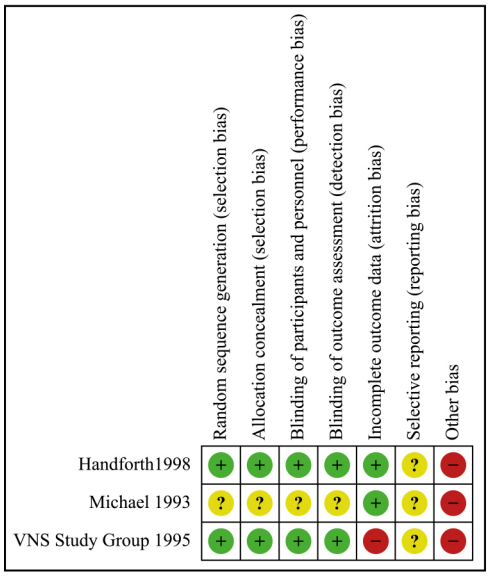


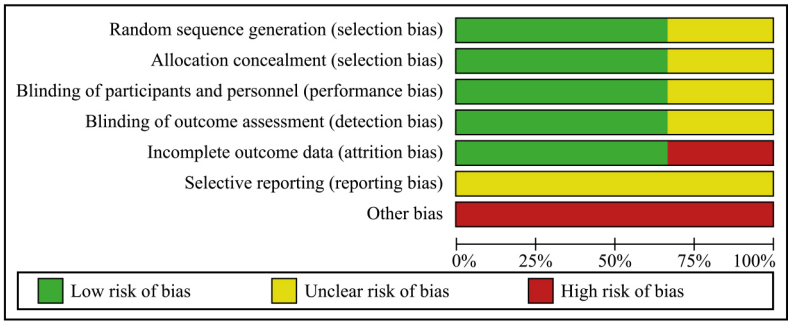
Treatment withdrawal



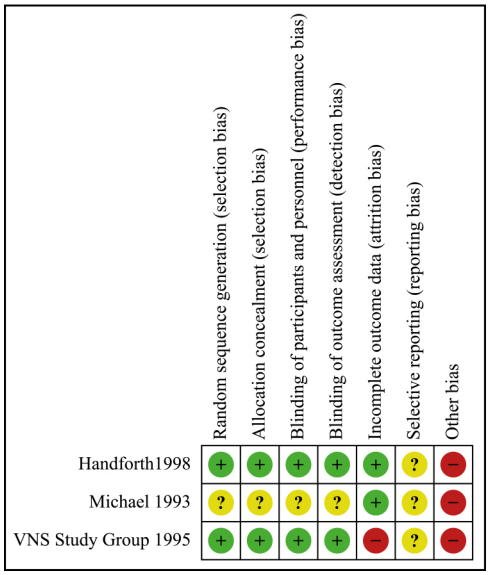


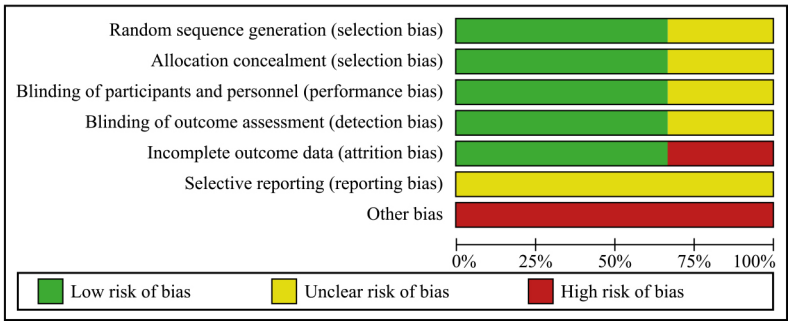
Dysphonia/hoarseness



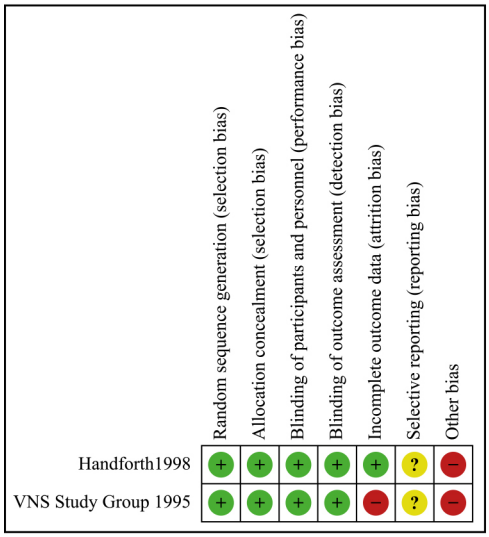


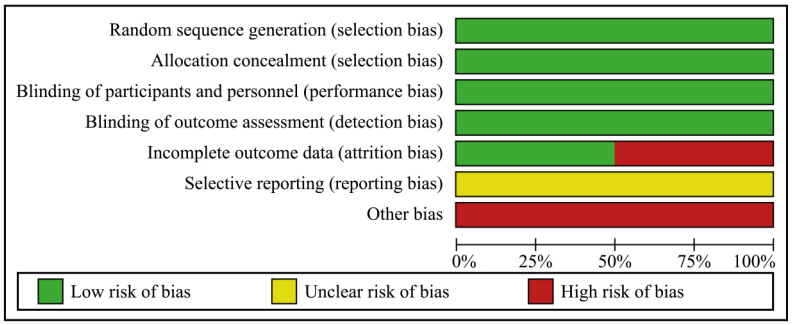
Cough



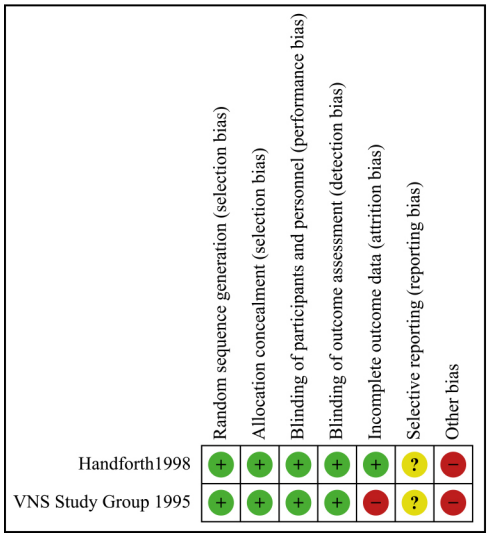


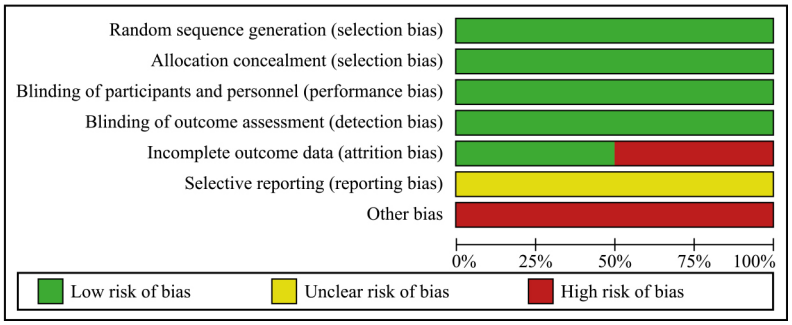
Dyspnea





Pain



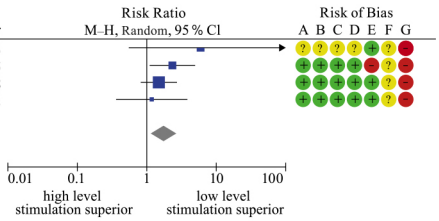


Appendix CQ10-2-04. Forest plot

Outcome 10-2-1: Seizure frequency ≤50%

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
Michael 1993	3	10	0	12	2.2%	8.27[0.48, 143.35]	1993
VNS Study Group 1995	17	54	8	60	31.3%	2.36[1.11, 5.03]	1995
Handforth 1998	22	94	16	102	53.2%	1.49[0.84, 2.66]	1998
Klinkenberg 2012	5	21	4	20	13.2%	1.19[0.37, 3.81]	2012
Total (95% CI)		179		194	100.0%	1.74[1.14, 2.65]	
Total events	47		28				

Heterogeneity. Tau²=0.00; Chi²=2.48, df=3 (P=0.48); I²=0%
Test for overall effect: Z=2.56 (P=0.01)

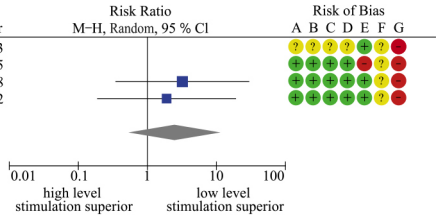


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Outcome 10-2-2: Treatment withdrawal

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
Michael 1993	0	10	0	12		Not estimable	1993
VNS Study Group 1995	0	54	0	60		Not estimable	1995
Handforth 1998	3	95	1	103	51.6%	3.25[0.34, 30.73]	1998
Klinkenberg 2012	2	21	1	20	48.4%	1.90[0.19, 19.40]	2012
Total (95% CI)		180		195	100.0%	2.51[0.50, 12.61]	
Total events	5		2				

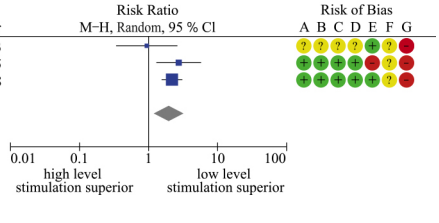
Heterogeneity. Tau²=0.00; Chi²=0.11, df=1 (P=0.74); I²=0%
Test for overall effect: Z=1.12 (P=0.26)



Outcome 10-2-3: Dysphonia/hoarseness

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
Michael 1993	4	10	5	12	15.1%	0.96[0.35, 2.64]	1993
VNS Study Group 1995	20	54	8	60	25.0%	2.78[1.33, 5.78]	1995
Handforth 1998	63	95	31	103	59.9%	2.20[1.59, 3.06]	1998
Total (95% CI)		159		175	100.0%	2.06[1.34, 3.17]	
Total events	87		44				

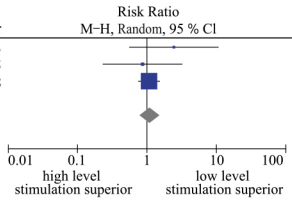
Heterogeneity. Tau²=0.05; Chi²=2.94, df=2 (P=0.23); I²=32%
Test for overall effect: Z=3.29 (P=0.0010)



Outcome 10-2-4: Cough

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
Michael 1993	4	10	2	12	4.1%	2.40[0.55, 10.49]	1993
VNS Study Group 1995	4	54	5	60	5.6%	0.89[0.25, 3.14]	1995
Handforth 1998	43	95	44	103	90.3%	1.06[0.77, 1.45]	1998
Total (95% CI)		159		175	100.0%	1.08[0.80, 1.46]	
Total events	51		51				

Heterogeneity. Tau²=0.00; Chi²=1.23, df=2 (P=0.54); I²=0%
Test for overall effect: Z=0.53 (P=0.59)

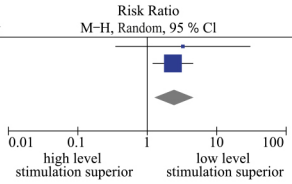


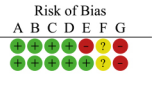
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Outcome 10-2-5: Dyspnea

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
VNS Study Group 1995	3	54	1	60	8.0%	3.33[0.36, 31.10]	1995
Handforth 1998	24	95	11	103	92.0%	2.37[1.23, 4.56]	1998
Total (95% CI)		149		163	100.0%	2.43[1.29, 4.57]	
Total events	27		12				

Heterogeneity. Tau²=0.00; Chi²=0.08, df=1 (P=0.77); I²=0%
Test for overall effect: Z=2.76 (P=0.006)

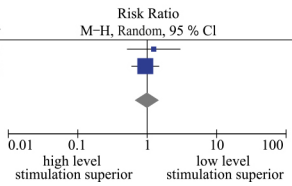




Outcome 10-2-6: Pain

Study or Subgroup	high level stimulation Events	Total	low level stimulation Events	Total	Weight	Risk Ratio M-H, Random, 95 % CI	Year
VNS Study Group 1995	9	54	8	60	19.6%	1.25[0.52, 3.01]	1995
Handforth 1998	27	95	31	103	80.4%	0.94[0.61, 1.46]	1998
Total (95% CI)		149		163	100.0%	1.00[0.68, 1.47]	
Total events	36		39				

Heterogeneity. Tau²=0.00; Chi²=0.32, df=1 (P=0.57); I²=0%
Test for overall effect: Z=0.01 (P=0.99)



Appendix CQ10-2-05. Summary of Findings (SoF) table

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 ≤ 50%	144 (per 1,000)	251 (per 1,000) (165–382)	RR 1.74 (1.14–2.65)	373 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	
Treatment withdrawal	10 (per 1,000)	26 (per 1,000) (5–129)	RR 2.51 (0.50–12.61)	375 (4 RCTs)	⊕⊕◯◯ Low[b]	
Dysphonia/hoarseness	251 (per 1,000)	518 (per 1,000) (337–797)	RR 2.06 (1.34–3.17)	334 (3 RCTs)	⊕⊕◯◯ Low[c,d]	
Cough	291 (1,000)	315 (per 1,000) (233–425)	RR 1.08 (0.80–1.46)	334 (3 RCTs)	⊕⊕⊕◯ Moderate[d]	
Dyspnea	74 (1,000)	179 (per 1,000) (95–336)	RR 1.08 (0.80–1.46)	312 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	
Pain	239 (1,000)	239 (per 1,000) (163–352)	RR 1.00 (0.68–1.47)	312 (2 RCTs)	⊕⊕◯◯ Low[b]	

*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.

[a]: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable benefit
[b]: because confidence interval of effect estimate crosses the clinical decision thresholds of both appreciable benefit and appreciable harm.
[c]: because I_2 = 32%; effect estimates differ among studies, heterogeneity is probably high
[d]: because confidence interval of effect estimate crosses the clinical decision threshold of appreciable harm

Appendix CQ 10-2-06. Evidence-to-Decision table

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 EFECTS	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:**	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.
UNDESIRABLE EFFCETS	How substantial are the undesirable anticipated effects?	- Large - Moderate - Small - Trivial - Varies - Don't know	**Summary of findings**	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.
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		

The relative importance or values of the main outcomes of interest:

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

Summary of findings

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 46 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 ewer 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)

BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	- Control is superior - Control is probably superior - Control and intervention are equivalent - Intervention is probably superior - Intervention is superior - It depends - Don't know	Summary: High frequency stimulation is significantly superior for the outcome of seizure frequency ≤ 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.	
COST AND RESOURCE	How large are the resource requirement (cost)?	- High cost - Moderate cost - Negligible - Moderate saving - Large saving - Varies - Don't know	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 or about ¥2,000,000 (covered by health insurance). Battery consumption is higher for high level stimulation than for low level stimulation.	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	- No - Probably no - Probably yes - Yes - Varies - Don't know		
FEASIBILITY	Is the option feasible to implement?	- No - Probably no - Probably yes - Yes - Varies - Don't know	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	**Question (CQ):** When conducting vagus nerve stimulation for drug resistant epilepsy, should high-level stimulation or low-level stimulation be used? **Patients (P)**: Patients with drug-resistant epilepsy who were implanted a vagal nerve stimulating device. **Intervention (I)**: High level stimulation **Comparison (C)**: Low level stimulation **Outcomes (O)**: Seizure frequency ≤50%, treatment withdrawal, dysphonia/hoarseness, cough, dyspnea, pain **Summary of evidence:** 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. **Certainty of evidence:** 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, I_2 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". **Judgment of benefits and harms, burden and cost:** 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. **Recommendation:** 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"). **Additional considerations:** 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.				
Subgroup considerations. 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.				
Implementation considerations. 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.				
Monitoring and evaluation. 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.				
Research possibilities. 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.				