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Vagus nerve stimulation for focal seizures (Review)

Panebianco M, Rigby A, Marson AG

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[Intervention Review]

Vagus nerve stimulation for focal seizures

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ABSTRACT

Background

This is an updated version of the Cochrane Review published in 2015.

Epilepsy is a chronic neurological disorder, characterised by recurring, unprovoked seizures. Vagus nerve stimulation (VNS) is a neuromodulatory treatment that is used as an adjunctive therapy for treating people with drug-resistant epilepsy. VNS consists of chronic, intermittent electrical stimulation of the vagus nerve, delivered by a programmable pulse generator.

Objectives

To evaluate the efficacy and tolerability of VNS when used as add-on treatment for people with drug-resistant focal epilepsy.

Search methods

For this update, we searched the Cochrane Register of Studies (CRS), and MEDLINE Ovid on 3 March 2022. We imposed no language restrictions. CRS Web includes randomised or quasi-randomised controlled trials from the Specialised Registers of Cochrane Review Groups, including Epilepsy, CENTRAL, PubMed, Embase, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform.

Selection criteria

We considered parallel or cross-over, randomised, double-blind, controlled trials of VNS as add-on treatment, which compared high- and low-level stimulation (including three different stimulation paradigms: rapid, mild, and slow duty-cycle), and VNS stimulation versus no stimulation, or a different intervention. We considered adults or children with drug-resistant focal seizures who were either not eligible for surgery, or who had failed surgery.

Data collection and analysis

We followed standard Cochrane methods, assessing the following outcomes:

1. 50% or greater reduction in seizure frequency
2. Treatment withdrawal (any reason)
3. Adverse effects
4. Quality of life (QoL)
5. Cognition
6. Mood

Main results

We did not identify any new studies for this update, therefore, the conclusions are unchanged.

We included the five randomised controlled trials (RCT) from the last update, with a total of 439 participants. The baseline phase ranged from 4 to 12 weeks, and double-blind treatment phases from 12 to 20 weeks. We rated two studies at an overall low risk of bias, and three at an overall unclear risk of bias, due to lack of reported information about study design. Effective blinding of studies of VNS is difficult, due to the frequency of stimulation-related side effects, such as voice alteration.

The risk ratio (RR) for 50% or greater reduction in seizure frequency was 1.73 (95% confidence interval (CI) 1.13 to 2.64; 4 RCTs, 373 participants; moderate-certainty evidence), showing that high frequency VNS was over one and a half times more effective than low frequency VNS.

The RR for treatment withdrawal was 2.56 (95% CI 0.51 to 12.71; 4 RCTs, 375 participants; low-certainty evidence). Results for the top five reported adverse events were: hoarseness RR 2.17 (99% CI 1.49 to 3.17; 3 RCTs, 330 participants; moderate-certainty evidence); cough RR 1.09 (99% CI 0.74 to 1.62; 3 RCTs, 334 participants; moderate-certainty evidence); dyspnoea RR 2.45 (99% CI 1.07 to 5.60; 3 RCTs, 312 participants; low-certainty evidence); pain RR 1.01 (99% CI 0.60 to 1.68; 2 RCTs; 312 participants; moderate-certainty evidence); paraesthesia 0.78 (99% CI 0.39 to 1.53; 2 RCTs, 312 participants; moderate-certainty evidence).

Results from two studies (312 participants) showed that a small number of favourable QOL effects were associated with VNS stimulation, but results were inconclusive between high- and low-level stimulation groups. One study (198 participants) found inconclusive results between high- and low-level stimulation for cognition on all measures used. One study (114 participants) found the majority of participants showed an improvement in mood on the Montgomery–Åsberg Depression Rating Scale compared to baseline, but results between high- and low-level stimulation were inconclusive.

We found no important heterogeneity between studies for any of the outcomes.

Authors' conclusions

VNS for focal seizures appears to be an effective and well-tolerated treatment. Results of the overall efficacy analysis show that high-level stimulation reduced the frequency of seizures better than low-level stimulation. There were very few withdrawals, which suggests that VNS is well tolerated.

Adverse effects associated with implantation and stimulation were primarily hoarseness, cough, dyspnoea, pain, paraesthesia, nausea, and headache, with hoarseness and dyspnoea more likely to occur with high-level stimulation than low-level stimulation.

However, the evidence for these outcomes is limited, and of moderate to low certainty.

Further high-quality research is needed to fully evaluate the efficacy and tolerability of VNS for drug-resistant focal seizures.

PLAIN LANGUAGE SUMMARY

Vagus nerve stimulation for focal seizures

What did we want to find out?
The aim of this review was to find the current evidence on how effective vagus nerve stimulation is in reducing the frequency of epileptic seizures, and any side effects associated with the treatment.

What is epilepsy and how is it treated?
Epilepsy is a disorder in which unexpected electrical discharges from the brain cause seizures. Most seizures can be controlled by a single antiepileptic drug, but sometimes, seizures do not respond to drugs. Some people need more than one antiepileptic drug to control their seizures, especially if they originate from one area of the brain (focal epilepsy), instead of involving the whole brain.

The vagus nerve runs down the side of the neck, from the brain to the large intestines, and controls body systems, like the heart and digestion. The vagus nerve stimulator (VNS) is a device that is used as an add-on treatment for epilepsy, if it does not respond well to drugs, and only affects one part of the brain. The device is connected to the vagus nerve, and sends mild electrical impulses to it. This is particularly important for treating people whose epilepsy did not respond well to drugs, who are not eligible for epilepsy surgery, or for whom surgery was not successful in reducing the frequency of their seizures.

What did we do?
We did not identify any new studies for this update. We included five multicentre, randomised controlled trials (RCTs) from the last update, which recruited a total of 439 participants, and compared different types of VNS therapy. Three compared high-level stimulation to low-level stimulation in participants from 12 to 60 years old. One trial examined high frequency stimulation versus low frequency stimulation in children. One trial examined three different stimulation frequencies.

What did we find?

Since we did not identify any new studies, the conclusions remain unchanged.

VNS seems to be an effective treatment for people with intractable focal epilepsy. High-level stimulation seems to reduce the number of seizures people had compared to low-level stimulation.

Common side effects were voice alteration and hoarseness, pain, shortness of breath, cough, feeling sickly, tingling sensation, headache, or infection at the site of the operation. Shortness of breath, voice alteration and hoarseness were more common in people receiving high-level stimulation compared to people receiving low-level stimulation.

What are the limitations of the evidence?

The evidence for the effectiveness and side effects of VNS therapy was limited and imprecise. There were a small number of studies and participants included in the review, and details about the design and conduct of the trials was sometimes lacking. We rated the evidence as moderate or low certainty. This means that further research is likely, or very likely, to have an important impact on our confidence in the estimate of the effect, and may change the estimate.

How up to date is this evidence?

The evidence is current to 3 March 2022.

Summary of findings 1. High versus low stimulation for focal seizures

High versus low stimulation for focal seizures						
Patient or population: people with focal seizures **Settings:** outpatients **Intervention:** high stimulation **Comparison**: low stimulation						
Outcomes	**Illustrative comparative risks* (95% CI)** **For adverse effects (99% CI)**		**Relative effect (95% CI)** **For individual adverse effects** **(99% CI)**	**No of Participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Low stimulation	**High stimulation**				
50% reduction in seizure frequency (responders)	144 per 1000	249 per 1000 (163 to 380)	RR 1.73 (1.13 to 2.64)	373 (4 studies)	⊕⊕⊕⊖ moderate[a]	RR > 1 indicates outcome is more likely with high stimulation
Withdrawals	10 per 1000	26 per 1000 (5 to 130)	RR 2.56 (0.51 to 12.71)	375 (4 studies)	⊕⊕⊖⊖ low[a,b]	RR > 1 indicates outcome is more likely with high stimulation
Voice alteration or hoarseness	251 per 1000	545 per 1000 (374 to 796)	RR 2.17 (1.49 to 3.17)	330 (3 studies)	⊕⊕⊕⊖ moderate[a]	RR > 1 indicates outcome is more likely with high stimulation
Cough	291 per 1000	317 per 1000 (215 to 471)	RR 1.09 (0.74 to 1.62)	334 (3 studies)	⊕⊕⊕⊖ moderate[a]	RR > 1 indicates outcome is more likely on high stimulation
Dyspnoea	74 per 1000	181 per 1000 (79 to 414)	RR 2.45 (1.07 to 5.60)	312 (2 studies)	⊕⊕⊖⊖ low[a,c]	RR > 1 indicates outcome is more likely on high stimulation
Pain	239 per 1000	241 per 1000 (143 to 402)	RR 1.01 (0.60 to 1.68)	312 (2 studies)	⊕⊕⊕⊖ moderate[a]	RR > 1 indicates outcome is more likely on high stimulation
Paraesthesias	172 per 1000	134 per 1000 (67 to 263)	RR 0.78 (0.39 to 1.53)	312 (2 studies)	⊕⊕⊕⊖ moderate[a]	RR > 1 indicates outcome is more likely on high stimulation

*The basis for the **assumed risk** is provided in footnote [d]. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty evidence: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty evidence: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty evidence: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty evidence: we are very uncertain about the estimate.

[a]One study that contributed to this outcome was judged to be at high risk of bias, as it had incomplete outcome data, which could not be analysed by an intention-to-treat approach.
[b]Wide, imprecise confidence interval of the pooled effect estimate due to low withdrawal rates in the included studies
[c]Wide, imprecise confidence interval of the pooled effect estimate due to low event rates in the included studies
[d]Assumed Risk: the event rate in the low-level stimulation group multiplied by 1000. The event rate is the proportion of the total in which the event occurred.

BACKGROUND

This is an updated version of the Cochrane review published in 2015 (Panebianco 2015).

Description of the condition

Epilepsy is a condition characterised by a tendency for recurrent seizures, unprovoked by any known proximate insult. Epileptiform (relates to seizure patterns) discharges involve either a localised area of the brain resulting in a focal seizure, or the entire brain resulting in a generalised seizure. The prevalence of epilepsy is estimated to be five to eight per 1000 population in developed countries; in adults, the most common type is focal epilepsy (Forsgren 2005; Hauser 1975). The majority of people given a diagnosis of epilepsy have a good prognosis, and their seizures will be controlled by treatment with a single antiepileptic drug (AED). However, 20% (reported in population-based studies) to 30% (reported in clinical (non-population-based) series) will develop drug-resistant epilepsy, often requiring treatment with combinations of AEDs (Cockerell 1995; Kwan 2000). People in this population tend to have frequent, disabling seizures that limit their ability to work and participate in activities. Many of them also suffer from the chronic effects of long-term, high-dose AED polytherapy (treatment that uses more than one medication), while anxiety and depressive disorders are common in people with epilepsy. Therefore, the development of effective new therapies for the treatment of drug-resistant seizures is of considerable importance.

Description of the intervention

Vagus nerve stimulation (VNS) is a neuromodulatory treatment (neuromodulation is the process by which nervous activity is regulated, by controlling the physiological levels of neurotransmitters), used as an adjunctive therapy for people with drug-resistant epilepsy who are not eligible for epilepsy surgery, or for whom surgery has failed. In this procedure, a pacemaker-like device (the Neuro-Cybernetic Prosthesis (NCP)) is implanted under the skin of the chest. The stimulating electrodes of the NCP carry electrical signals from the generator to the left vagus nerve. By programming the device, the frequency, intensity, and duration of stimulation can be varied (the stimulation paradigm). In the initial trials, the vagus nerve was stimulated for 30 seconds, every five minutes (Sackeim 2001). During each 30-second stimulation, the device delivered 500 microsecond pulses, at 30 Hz frequency. For each individual, the intensity of the current was set to the highest level they could tolerate, or to low-level stimulation, depending on the allocated treatment group. Also, in an attempt to further abort seizures, participants could activate the device by placing a magnet over it when a seizure had occurred, or was about to occur. Participants enrolled in the initial randomised controlled trials of VNS had drug-resistant focal epilepsy, and experienced a 24% to 28% median reduction in seizure frequency over a three-month treatment period (Selway 1987).

How the intervention might work

Left VNS is a promising, relatively new treatment for epilepsy. In 1997, VNS was approved in the United States as an adjunctive treatment for drug-resistant focal-onset seizures in adults and adolescents. For some people with focal-onset seizures, the adverse effects of AEDs are intolerable; for others, no single AED or combination of anticonvulsant agents is effective. Cerebral resective surgery (a procedure during which the brain tissue is resected to remove the seizure focus) is an alternative to pharmacotherapy in some cases, but many people with focal-onset seizures are not optimal candidates for intracranial (within the cranium) surgery (Schachter 1998).

The mechanism of action of VNS is not fully understood, but can be reasonably assumed to involve brainstem nuclei. The nucleus of the solitary tract, the main terminus for vagal afferents (fibres specialised to detect stimuli associated with physiological activity of visceral endings), has direct or indirect projections to the locus coeruleus, raphe nucleus, reticular formation, and other brainstem nuclei. These nuclei have been shown to influence cerebral seizure susceptibility, hence vagal modulation of one or more of these nuclei could plausibly represent the mechanism for seizure suppression (Krahl 2012). In this context, the immunomodulatory function (modulation of the immune system) of the vagus nerve is of particular interest. When inflamed, afferent signals can activate the so-called cholinergic (receptors or synapses that use acetylcholine as neurotransmitter) anti-inflammatory pathway. Through this pathway, efferent (motor) vagus nerve fibres inhibit the release of pro-inflammatory cytokines (small secreted proteins with a specific effect on the interactions and communications between cells), and in this way, reduce inflammation. In recent years, inflammation has been strongly implicated in the development of seizures and epilepsy, and therefore, the activation of the anti-inflammatory pathway by VNS could decrease the inflammatory response, and thereby, explain its clinical effects. In addition to anticonvulsive effects, VNS might have positive effects on behaviour, mood, and cognition (Panebianco 2016; Vonck 2014).

Why it is important to do this review

In this review, we summarised evidence from randomised controlled trials that investigated the efficacy and tolerability of VNS for people with drug-resistant focal epilepsy, in order to aid clinical decision-making.

OBJECTIVES

To evaluate the efficacy and tolerability of vagus nerve stimulation (VNS) when used as add-on treatment for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

Trials had to meet all the following criteria:

1. Randomised controlled trials;
2. Double-blind trials;
3. Placebo-controlled, with active control (low stimulation) or other intervention control groups; and
4. Parallel group or cross-over studies.

Types of participants

Individuals of any age with focal epilepsy (i.e. experiencing simple focal, complex focal, or secondarily generalised tonic-clonic seizures) who had failed to respond to at least one antiepileptic

drug (AED), who were not eligible for surgery, or for whom surgery had previously failed.

Types of interventions

1. Vagus nerve stimulation (VNS) using high-level stimulation (therapeutic) versus low-level stimulation (presumed sub-therapeutic)
2. VNS stimulation versus different stimulation of the VNS
3. VNS stimulation versus no stimulation
4. VNS stimulation versus a different intervention

Types of outcome measures

Primary outcomes

50% or greater reduction in seizure frequency

The proportion of participants with a 50% or greater reduction in seizure frequency during the treatment period, compared to the pre-randomisation baseline period

Secondary outcomes

Treatment withdrawal

The proportion of participants having their allocated VNS paradigm stopped or altered during the course of the trial, for whatever reason was used as a measure of 'global effectiveness'. Treatment is likely to be withdrawn due to adverse effects, lack of efficacy, or a combination of both, and this was an outcome to which the individual made a direct contribution.

Adverse effects

We reported the incidence of adverse events in all VNS-implanted participants, and according to randomised group. We chose to investigate the following adverse effects, which were the most common and important.

1. Infection at implantation site
2. Haemorrhage at implantation site
3. Voice alteration or hoarseness
4. Pain
5. Dyspnoea
6. Cough
7. Ataxia
8. Dizziness
9. Paraesthesias
10. Fatigue
11. Nausea
12. Somnolence
13. Headache

In addition, we reported the five most common adverse effects (if different from those stated above).

Quality of life

The difference between intervention and control group(s) means on quality of life measures used in the individual studies

Cognition

The difference between intervention and control group(s) means on cognitive assessments used in the individual studies

Mood

The difference between intervention and control group(s) means on mood assessments used in the individual studies

Search methods for identification of studies

Electronic searches

Searches were run for the original review in 2000. Subsequent searches were run in 2005, July 2007, January 2010, July 2012, September 2013, February 2015, December 2016, and May 2019. For the latest update, we searched the following databases on 3 March 2022.

1. The Cochrane Register of Studies (CRS Web), using the strategy outlined in Appendix 1. CRS Web includes randomised or quasi-randomised, controlled trials from the Specialised Registers of Cochrane Review Groups, including Epilepsy, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform (ICTRP).
2. MEDLINE Ovid (1946 to March 02, 2022), using the strategy outlined in Appendix 2. In MEDLINE Ovid, the coverage end date always lags a few days behind the search date.

We imposed no language restrictions.

Searching other resources

We checked reference lists of included studies to search for additional reports of relevant studies, and performed citation searches on key articles, as we did in Panebianco 2015. We contacted experts in the field for ongoing trials, and the manufacturer of VNS (Cyberonics) for additional information.

Data collection and analysis

Selection of studies

For this update, two review authors (MP and AR) independently assessed trials for inclusion. Any disagreements were resolved by discussion with a third author (AM). For the original version of this review, three review authors (MP, AR, and JW) extracted data and assessed the risk of bias; again, disagreements were resolved by discussion.

See Figure 1 for the flow-chart of study identification and selection.

Figure 1. Study flow diagram (reflecting results of the search carried out on 3 March 2022)

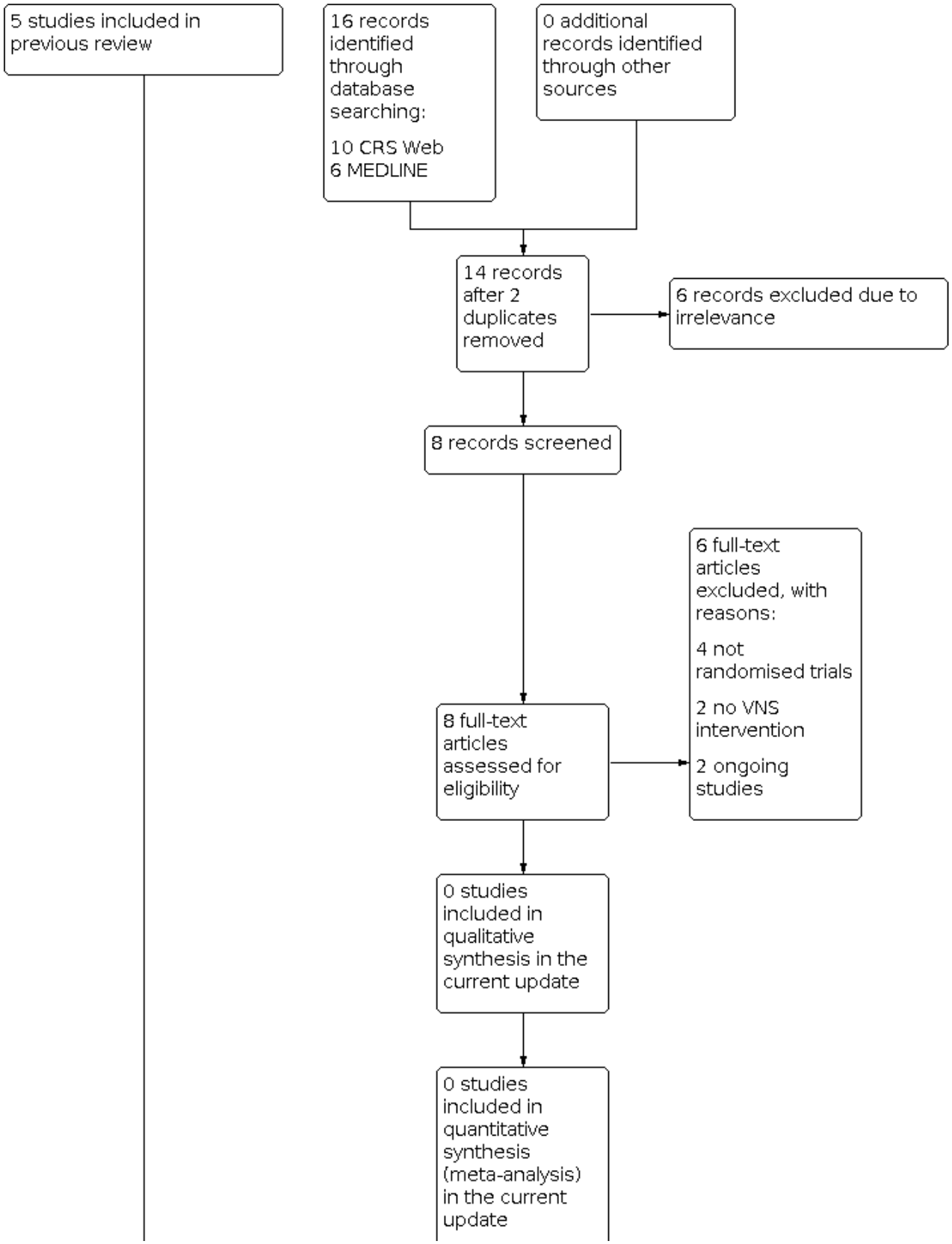
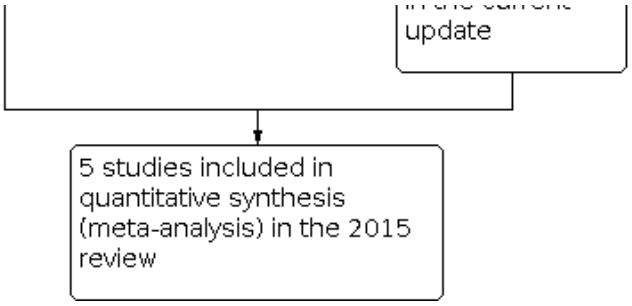


Figure 1. (Continued)



Data extraction and management

The following data were extracted for each trial, using a data extraction form.

Methodological/trial design

1. Method of randomisation
2. Method of allocation concealment
3. Method of double-blinding
4. Whether any participants were excluded from reported analyses
5. Duration of baseline period
6. Duration of treatment period
7. Frequency of VNS tested
8. Information on sponsorship/funding

Participant/demographic information

1. Total number of participants allocated to each treatment group
2. Age/sex
3. Number with focal/generalised epilepsy
4. Seizure types
5. Seizure frequency during the baseline period
6. Number of background drugs

Outcomes

We recorded the number of participants experiencing each outcome (see Types of outcome measures) per randomised group, and contacted authors of trials for any missing information.

Assessment of risk of bias in included studies

MP and AR independently assessed the risk of bias for each trial, using the Cochrane RoB 1 tool, described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were discussed and resolved. We rated all included studies as having a low, high, or unclear risk of bias on six domains applicable to randomised controlled trials: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

We analysed the primary outcome of seizure reduction as a binary outcome, and presented it as a risk ratio. We also analysed secondary outcomes, including adverse effects and treatment withdrawal, as binary outcomes, and presented risk ratios. We planned to analyse quality of life and cognition as continuous outcomes, using the standardised mean difference, but this was not possible, due to limited information from single studies for cognition outcomes, and heterogenous measurement scales for quality of life outcomes. Therefore, these outcomes were discussed narratively.

Unit of analysis issues

We did not encounter any unit of analysis issues, as we did not find any cross-over studies; we analysed all outcomes using risk ratios, as planned, or discussed them narratively.

Dealing with missing data

We sought missing data by contacting the study authors. We carried out intention-to-treat (ITT), best-case, and worst-case analyses on the primary outcome, to account for any missing data (see Data synthesis). We presented all analyses in the main report.

Assessment of heterogeneity

We assessed clinical heterogeneity, by comparing the distribution of important individual participant factors among trials (for example age, seizure type, duration of epilepsy, number of AEDs taken at the time of randomisation), and trial factors (for example randomisation concealment, blinding, losses to follow-up). We evaluated statistical heterogeneity among trials using the Chi^2 test with significance set at 0.1, along with the I^2 statistic. For the Chi^2 test, $P > 0.1$ indicated no significant statistical heterogeneity; $P \leq 0.1$ indicated heterogeneity, according to percentage ranges of the I^2 statistic (Deeks 2011).

Assessment of reporting biases

We requested protocols from study authors for all included studies, to enable a comparison of outcomes of interest. If we suspected outcome reporting bias for any included study, we planned to further investigate, using the ORBIT matrix system (Kirkham 2010). We planned to exam asymmetry in funnel plots to assess the likelihood of publication bias, but we were unable to complete this assessment, due to the small number of studies included in the review.

Data synthesis

We used a fixed-effect model in the meta-analysis. We planned to stratify each comparison by the type of control group, that is level of stimulation (if any), and study characteristics, to ensure the appropriate combination of study data. Our preferred estimator for all binary outcomes was the Mantel-Haenzsel risk ratio (RR). For the outcomes, 50% or greater reduction in seizure frequency, and treatment withdrawal, we used 95% confidence intervals (CIs). For

individual adverse effects, we used 99% CIs, to make an allowance for multiple testing. Our analyses included all participants in the treatment groups to which they had been allocated following implantation of VNS. For the efficacy outcome (50% or greater reduction in seizure frequency), we undertook three analyses.

1. **Primary (ITT) analysis**. Participants not completing follow-up, or with inadequate seizure data were assumed to be non-responders. We analysed by ITT when this was reported by the included studies.To test the effect of this assumption, we undertook sensitivity analyses.
2. **Worst-case analysis.** Participants not completing follow-up, or with inadequate seizure data were assumed to be non-responders in the high-level stimulation group, and responders in the low-level stimulation group.
3. **Best-case analysis.** Participants not completing follow-up, or with inadequate seizure data were assumed to be responders in the high-level stimulation group, and non-responders in the low-level stimulation group.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis for adverse effects. We intended to investigate heterogeneity using sensitivity analysis, if deemed appropriate.

Sensitivity analysis

We planned to conduct the following sensitivity analyses to test the robustness of the meta-analysis, where possible.

1. Repeating the analysis excluding unpublished studies.
2. Repeating the analysis excluding studies published only as abstracts.

These sensitivity analyses was not required, as all the included studies were published journal articles.

Summary of findings and assessment of the certainty of the evidence

We created Summary of findings 1, using the GRADE approach to assess the certainty of the evidence. We downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, or high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious, and by two levels if very serious.

We included the primary outcome, 50% or greater reduction in seizure frequency, the secondary outcome, treatment withdrawal, and the five most commonly reported adverse events in the table.

RESULTS

Description of studies

Results of the search

The latest search (carried out 3 March 2022) identified 16 records. We screened 14 records after duplicates were removed. We excluded six at this point, and requested eight full-text articles to assess for eligibility. We contacted authors of these trials when their contact details were available, for more information. Following this, we excluded six studies. Two studies were ongoing. Thus, we did not include any new studies in this review.

Included studies

We did not find any new studies for this update.

The previous version of this review included five randomised controlled trials, which recruited a total of 439 participants (DeGiorgio 2005; Handforth 1998; Klinkenberg 2012; Michael 1993; VNS Study Group 1995). Trial characteristics are summarised below. For further information on each trial, please see Characteristics of included studies.

Three trials compared high-level stimulation to low-level stimulation, in participants aged 12 to 60 years (Handforth 1998; Michael 1993; VNS Study Group 1995), and another trial examined high-level stimulation versus low-level stimulation in children (Klinkenberg 2012). One trial examined three different stimulation paradigms (DeGiorgio 2005). We did not find any studies with different comparisons (different stimulation, no stimulation, different intervention).

One multicentre, parallel trial from the USA randomised 64 participants, older than 12 years, to one of three treatment arms, corresponding to rapid, medium, and slow duty-cycles: group A, seven seconds on and 18 seconds off (N = 19); group B, 30 seconds on and 30 seconds off (N = 19); group C, 30 seconds on and three minutes off (N = 23). The baseline was four weeks long, with a treatment period of three months (DeGiorgio 2005). Another multicentre, parallel trial from the USA included 198 participants, aged 13 to 60 years, and had two treatment arms: intervention, high-level stimulation (N = 95) and active control group (low stimulation; N = 103). This trial had a baseline period of 12 to 16 weeks, and a treatment period of 16 weeks (Handforth 1998). Dodrill 2000 and Amar 1998 are linked to this study.

A recent multicentre, parallel trial from the Netherlands investigated children only, and consisted of two treatment arms, including high-level stimulation (N = 21) and low-level stimulation (N = 20). The baseline period was 12 weeks long, followed by a treatment period of 20 weeks (Klinkenberg 2012). After the blinded phase, all participants underwent a non-controlled follow-up, in which they received high-level stimulation (add-on phase). Aalbers 2012 and Klinkenberg 2014 are linked to this study.

One multicentre, parallel trial from the USA and Europe had a pre-randomisation period of 12 weeks, and a treatment period of 14 weeks, during which 22 adults were randomised to one of two treatment arms: high-level stimulation, therapeutic (N = 10) or low-level stimulation, sub-therapeutic (N = 12). All participants completed the acute phase of the study and entered the extension phase (Michael 1993).

Another multicentre, parallel trial from the USA, Sweden, and Germany randomised 114 participants to one of two treatment arms: high-level stimulation (N = 54) and low-level stimulation (N = 60). This trial had a baseline period of 12 weeks, and a treatment period of 14 weeks. Participants exiting the study were offered indefinite extension treatment in an open trial (VNS Study Group 1995). Ben-Menachem 1994, Ben-Menachem 1995, Elger 2000, Ramsay 1994, Holder 1992, and Lötvall 1994 are linked to this study.

Excluded studies

In this update, we excluded six studies for the following reasons: four studies were not randomised trials; two studies assessed different interventions. For further information on each trial, please see Characteristics of excluded studies.

Ongoing studies

We identified two ongoing studies (please see Characteristics of ongoing studies).

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of the risk of bias in each included study. We allocated an overall rating for risk of bias of low, high, or unclear for each study. See below for specific domain ratings.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

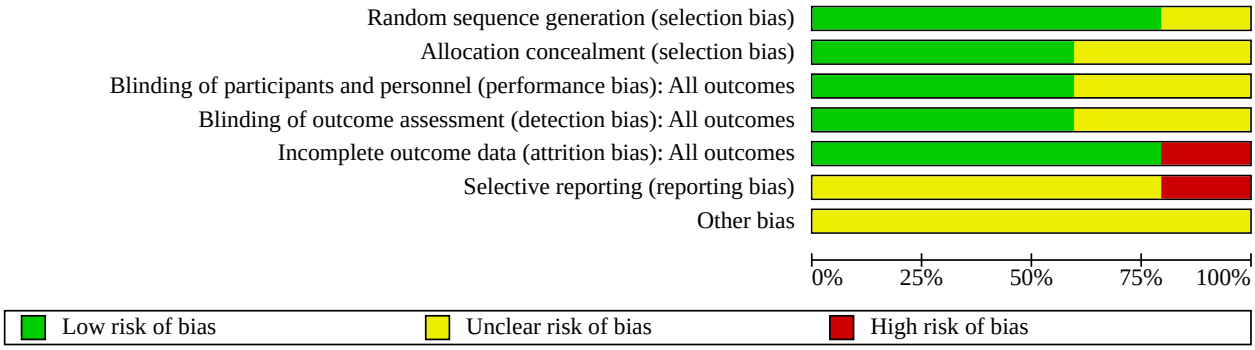
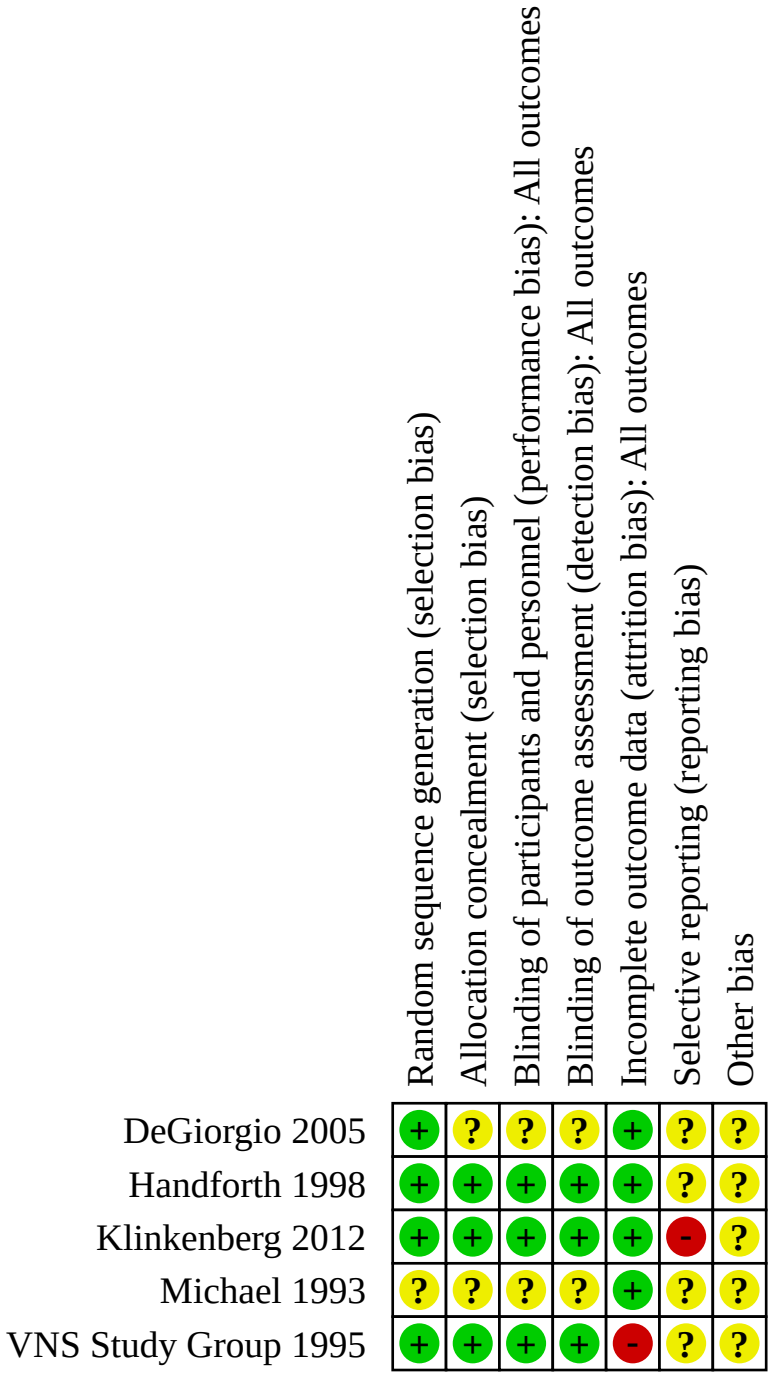


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We rated four studies at low risk of bias for sequence generation, because they reported using a computer-generated randomisation schedule, random number tables, or random permuted blocks (DeGiorgio 2005; Handforth 1998; Klinkenberg 2012; VNS Study

Group 1995). We rated one study as unclear due to a lack of details on the methods used (Michael 1993).

We rated the method by which allocation was concealed at low risk of bias In three trials (Handforth 1998; Klinkenberg 2012; VNS Study Group 1995). Two trials did not provide clear methods, and we rated them as unclear risk of bias (DeGiorgio 2005;Michael 1993).

Blinding

All of the studies achieved blinding by using identical implants in the different groups.

We judged blinding of participants as unclear in two papers, as they provided no details of the method of blinding (DeGiorgio 2005; Michael 1993). We rated the other three studies at low risk of bias for this particular domain, because to assure blinding, at each treatment-phase visit, the device was temporarily turned off while the participant was assessed by the blinded interviewer (Handforth 1998;Klinkenberg 2012; VNS Study Group 1995).

An important issue in blinded trials on VNS is the difficulty of effectively blinding the participants, given the frequency of stimulation-related side effects, such as voice alteration. This could limit the validity of the observed treatment effects.

Incomplete outcome data

We rated three studies at low risk of bias for incomplete outcome data, as intention-to-treat analysis was used, and there were no concerns of missing data having an effect on the overall outcome estimate (Handforth 1998; Klinkenberg 2012; Michael 1993). We rated the DeGiorgio 2005 study as unclear risk of bias, as three participants out of 64 exited early from the study, and an intention-to-treat analysis was not used; however, it was unclear if this approach influenced the results of the study. We rated the VNS Study Group 1995 at high risk of bias because 57 participants were randomised to low-level stimulation; however, three participants allocated to high-level stimulation had their stimulator programmed for low-level stimulation, in error. These participants were analysed in the low-level stimulation group rather than in the high-level stimulation group, to which they were randomised, therefore, this was not an intention-to-treat analysis.

Selective reporting

None of the protocols for the included studies were available, therefore, we were unable to compare a priori methods and outcomes for the published reports. Because of this, we rated all but one study as unclear risk of bias (Klinkenberg 2012). However, It should be noted that based on the information contained in the publications, there was no suspicion of reporting bias. Klinkenberg 2012 described the outcome of IQ in the methods section, but did not report it in the results, thus, we assessed this study at high risk of reporting bias.

Other potential sources of bias

All studies were sponsored by Cyberonics, Inc, Webster (TX), the manufacturers of the device, and therefore, we rated them as unclear risk of bias for this domain.

Effects of interventions

See: **Summary of findings 1** High versus low stimulation for focal seizures

See: Summary of findings 1.

High-level versus low-level vagus nerve stimulation (VNS)

Primary outcomes

50% or greater reduction in seizure frequency

Data from four studies contributed to this outcome.

Intention-to-treat analysis

Results of a Chi^2 test showed no significant heterogeneity between trials for a response to VNS (Chi^2 = 3.67, df = 3, P = 0.30, I^2 = 18%). The overall risk ratio (RR) for a response to high-level stimulation compared to low-level stimulation, using the fixed-effect model, was 1.73 (95% CI 1.13 to 2.64; P = 0.01; 4 trials, 373 participants; moderate-certainty evidence; Analysis 1.1), showing that participants receiving high-level stimulation were more likely to show a 50% or greater reduction in seizure frequency.

Best- and worst-case scenarios

No significant heterogeneity was found for these outcomes. The overall worst-case response to VNS was RR 1.61 (95% CI 1.07 to 2.43; P = 0.02; Chi^2 = 4.94; df = 3; P = 0.18; I^2 = 0%; Analysis 1.2); the best-case response was RR 1.91 (95% CI 1.27 to 2.89; P = 0.002; Chi^2 = 2.13; df = 3; P = 0.55; I^2 = 39%; Analysis 1.3).

All three analyses showed that high-level stimulation was more likely to reduce the frequency of seizures by 50% or more than low-level stimulation.

Secondary outcomes

Treatment withdrawal

Data from four studies contributed to this outcome. Five participants withdrew from high-level stimulation and three participants withdrew from low-level stimulation in Handforth 1998 and Klinkenberg 2012 combined. No participants withdrew from either stimulation paradigm in Michael 1993 and VNS Study Group 1995. A Chi^2 test revealed no significant statistical heterogeneity (Chi^2 = 0.11, df = 1, P = 0.74). The overall risk ratio (RR) for withdrawal for any reason was 2.56 (95% CI 0.51 to 12.71; P = 0.2; 4 studies, 375 participants; low-certainty evidence; Analysis 1.4). None of the four analyses showed a difference in withdrawal between high- and low-level stimulation.

Adverse effects

Four studies reported adverse effects. The risk ratios (RR) were as follows.

1. *Voice alteration and hoarseness:* more likely to be reported in the high-level stimulation group (RR 2.17, 99% CI 1.49 to 3.17; 3 studies, 334 participants; moderate-certainty evidence; Analysis 1.5; (Handforth 1998; Michael 1993; VNS Study Group 1995)).
2. *Cough*: the results between the two groups were inconclusive (RR 1.09; 99% CI 0.74 to 1.62; 3 studies, 334 participants; moderate-certainty evidence; Analysis 1.6; (Handforth 1998; Michael 1993; VNS Study Group 1995)).
3. *Dyspnoea*: more likely to be reported in the high-level stimulation group (RR 2.45, 99% CI 1.07 to 5.60; 2 studies, 312 participants; Analysis 1.7; (Handforth 1998; VNS Study Group 1995)).

4. *Pain*: the results between the two groups were inconclusive (RR 1.01, 99% CI 0.60 to 1.68; 2 studies, 312 participants; Analysis 1.8; (Handforth 1998; VNS Study Group 1995)).
5. *Paraesthesia:* more likely to be reported in the low-level stimulation group (RR 0.78; 99% CI 0.39 to 1.53; 2 studies, 312 participants; Analysis 1.9; (Handforth 1998; VNS Study Group 1995)).
6. *Nausea*: the results between the two groups were inconclusive (RR 0.89, 99% CI 0.42 to 1.90; 2 studies, 312 participants; Analysis 1.10; (Handforth 1998; Michael 1993)).
7. *Headache*: more likely to be reported in the low-level stimulation group (RR 0.90, 99% CI 0.48 to 1.69; 2 studies, 220 participants; Analysis 1.11; (Handforth 1998; VNS Study Group 1995)).

Overall, this showed that high-level stimulation led to voice alteration and hoarseness, and dyspnoea. None of the studies reported on haemorrhage at implantation site, ataxia, dizziness, fatigue, or somnolence.

Quality of life (QoL)

Two studies reported data on QoL. We were unable to pool the data because of heterogeneous measurement scales, so reported the results narratively (Handforth 1998; VNS Study Group 1995).

Using the Short-Form Health Survey (SF-36), high-level stimulation led to better physical function and social function, but the results were inconclusive for the other domains. Using the Washington Psychosocial Seizure Inventory, high-level stimulation led to improved financial status. Participants, investigators, and companions reported improved QoL compared to baseline for both groups using Global Rating Scales. However, the results were inconclusive when they compared the results between raters. Participants who had at least 50% seizure reduction exhibited signs of slight improvement in QoL compared to those who did not demonstrate this degree of seizure reduction. The results were inconclusive between groups when measured with the Quality of Life in Epilepsy-31 scale, the Medical Outcomes Study, and Health-Related Hardiness Scale. Overall, a small number of favourable QoL effects were associated with low-levels stimulation that are now typically used clinically. On the Washington Psychosocial Seizure Inventory, only financial status was reported to be significantly different between groups.

Cognition

Data from one study contributed to this outcome (Handforth 1998). The study authors reported no statistically significant differences in interaction effects between groups for all four measures used: Wonderlic Personnel Test, Digit Cancellation, Stroop Test, and Symbol Digit Modalities.

Mood

Data from one study contributed to this outcome (VNS Study Group 1995). Mood was measured according to the Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline, three months, and six months. A MADRS total score of between 10 and 20 (maximum score 20) indicates mild depressive mood disorder.

In the low-level stimulation group (N = 5), three participants at baseline, two at three months, and one participant at six months had MADRS scores higher than 10. In the high-level stimulation group (N = 6), four participants at baseline, two at three months, and one participant at six months had MADRS scores higher than 10. Overall, four of five participants in the low-level stimulation group, and five of six participants in the high-level stimulation group showed decreases in MADRS scores over the study, but the difference between groups was inconclusive (Mann-Whitney's test $P < 0.10$).

Rapid versus medium versus slow duty-cycle VNS

Primary outcomes

50% or greater reduction in seizure frequency

Data from one study contributed to this comparison (DeGiorgio 2005).

The reduction in seizure frequency was 22% for rapid-cycle ($P = 0.0078$), 26% for medium-cycle ($P = 0.0270$), and 29% for slow-cycle VNS ($P = 0.0004$). When all three groups were combined, the reduction in seizure frequency was 40%. Study authors reported that between-group comparisons found no statistically significant differences in seizure frequency (Kruskal Wallis test, P value was not reported).

A responder rate > 50% was the same for all three groups (six participants in each group achieved 50% or greater reduction in seizure frequency).

Secondary outcomes

Treatment withdrawal

Three participants withdrew during the study: one developed a device infection, one was lost to follow-up, and one could not tolerate stimulation (rapid cycle). The randomisation assignments of the first two participants were unknown; presumably, the study authors deemed this to be irrelevant to the conclusion.

Adverse effects

The combined adverse effects from all three groups were: postoperative pain at the generator 21.3%, throat pain and pharyngitis 9.8%, cough 9.8%, voice alteration 4.9%, vocal cord paralysis 1.6%, abdominal pain and diarrhoea 1.6%. Cough and voice alteration were more common during rapid-cycle stimulation (26%), versus 5% during medium-cycle, and 9% during slow-cycle. The study authors did not list the other adverse effects by treatment groups.

DISCUSSION

Summary of main results

We found no new studies that met the selection criteria during this update.

We included five randomised controlled trials, which recruited 439 participants, from the previous version of the review (Panebianco 2015). All trials were sponsored by Cyberonics, Inc., Webster, TX, USA.

Results of the overall efficacy analysis showed that participants who received high-level vagus nerve stimulation (VNS) were 1.73 times more likely to have at least a 50% reduction in seizures compared to those who received low-level stimulation (moderate-certainty evidence). This effect did not vary substantially for either

the best- or worst-case scenarios, which accounted for missing outcome data in one study.

One study compared three different duty-cycle paradigms (rapid versus mild versus slow), and did not find that one duty cycle reduced seizure frequency more or less than the others.

The total withdrawal rate was 4.7%, which suggests the treatment was well tolerated. The most common adverse events were voice alteration and hoarseness, cough, dyspnoea, pain, paraesthesias, nausea, and headache. Voice alteration, hoarseness, and dyspnoea were more than twice as likely to be reported in participants who received high-level VNS. However, there was some uncertainty and imprecision in reported differences for the other adverse events between groups; there were often wide confidence intervals, making it difficult to draw conclusions.

A small number of favourable quality of life effects resulted from VNS stimulation, but the results between high- and low-level stimulation were inconclusive. The results were also inconclusive between groups for cognition and mood, although the majority of participants reported improvement in their mood.

Overall completeness and applicability of evidence

Currently, there are only five studies that examined the effects of VNS for focal seizures, with fewer than 500 participants in total. The addition of further evidence from future studies may change the results and conclusions of this review. This review focused on the use of VNS in drug-resistant focal seizures. The results cannot be extrapolated to other populations, such as those with generalised epilepsy. The results of this review suggest that VNS is an effective add-on treatment for drug-resistant seizures, but we cannot state how VNS compares to other antiepileptic treatments, because it was tested in an active control situation, whereas antiepileptic drugs are tested against placebo. Head-to-head trials are needed to assess the relative efficacy and tolerability of antiepileptic treatments.

Quality of the evidence

Out of the five included studies, we rated two studies at an overall low risk of bias; the other three studies as unclear risk of bias, due to lack of methodological detail concerning study design. We used the GRADE approach to rate the level of certainty of the evidence for each outcome (see Summary of findings 1).

We rated the certainty of the evidence as moderate for the main outcome of 50% reduction in seizure frequency, due to incomplete outcome data from one study contributing to the analysis. We rated tolerability outcomes (withdrawal and adverse effects) as moderate to low-certainty evidence, due to the imprecision of pooled results and incomplete outcome data from one study contributing to the analysis.

Potential biases in the review process

Although we requested all trial protocols from the study authors, the time frame in which the majority of the studies were conducted made retrieval of all of these difficult. This could lead to potential bias through omitted information to which we did not have access.

Agreements and disagreements with other studies or reviews

The studies included in this review were essentially active control trials, thus results may be difficult to compare against other meta-analyses of antiepileptic drugs that were compared against placebo. The magnitude of the risk ratio for high-level VNS compared to control would tend to be reduced by any anti-seizure effect of the low-level stimulation. A higher risk ratio may have been found if high-level VNS was compared against no stimulation, while with low-level stimulation participants were less likely to guess which treatment they were receiving. Another review on VNS supported our conclusions regarding a positive outcome with VNS (Morris 2013). This review also described an association between VNS and mood in adult participants, and included children-specific analyses.

AUTHORS' CONCLUSIONS

Implications for practice

Vagus nerve stimulation (VNS) appears to be an effective treatment for people with drug-resistant focal epilepsy, as an add-on treatment. High-level VNS reduced seizure frequency better than low-level VNS. Both high- and low-level VNS seemed to be well tolerated and withdrawals were rare; however, limited withdrawal information was available for this review, so important differences between high- and low-level stimulation cannot be excluded. Adverse effects associated with implantation and stimulation were primarily hoarseness, cough, dyspnoea, pain, paraesthesia, nausea, and headache; voice alteration and dyspnoea were more likely to occur with high-level stimulation than low-level stimulation. The adverse effect profile was substantially different from the adverse effect profile associated with antiepileptic drugs, making VNS a potential alternative for people who have difficulty tolerating antiepileptic drug adverse effects.

Implications for research

Identifying the adverse effect profile of VNS was rather complex, because treatment involves both the implantation of the device and intermittent stimulation, each with slightly different adverse effects. In addition, these studies were essentially active control trials.

Further research is needed to determine:

1. the mode of action of VNS;
2. the long-term effects of VNS;
3. the details of effective stimulation paradigms and protocols;
4. the effectiveness of VNS compared to antiepileptic drugs currently available.

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- Managing Editor (provided editorial guidance to authors, edited the update, conducted editorial policy checks): Rachael Kelly
- Copy Editor (copy-editing and production): Victoria Pennick

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

DeGiorgio 2005

Study characteristics	
Methods	Randomised, prospective, active-control study Pre-randomisation baseline period: 4 weeks Duration of treatment: 3 months. This period included month 1, month 2, and month 3 time points.
Participants	A multicentre trial (USA) 64 people randomised Group A (rapid cycle): 19 participants; mean output current at completion of study 0.87 mA Group B (mild cycle): 19 participants; mean output current at completion of study 0.80 mA Group C (low cycle): 23 participants; mean output current at completion of study 0.93 mA
Interventions	Randomised comparison of three distinct duty-cycles in treatment of refractory focal seizures: Group A: on/off time 7 s/18 s, duty-cycle 28%, frequency 20 Hz, pulse width 500 sec rapid cycle; Group B: on/off time 30 s/30 s, duty-cycle 50%, frequency 20 Hz, pulse width 250 seconds mild cycle; Group C: on/off time 30 s/3 min, duty-cycle 14%, frequency 30 Hz, pulse width 500 seconds slow cycle. All participants had an identical implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics).
Outcomes	Primary outcome:

DeGiorgio 2005 *(Continued)*

	Seizure frequency (50% and 75% reduction of seizures) Secondary outcomes: 1. Treatment withdrawal 2. Adverse events
Notes	Supported by a grant from Cyberonics, Inc., Webster, TX

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred in blocks of six (2 for each group), with a unique predetermined randomisation schedule for each site.
Allocation concealment (selection bias)	Unclear risk	No details of concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Identical implants used, but no details of method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 out 64 participants exited early: one developed a device infection, so the device had to be removed; one could not tolerate rapid cycle stimulation, so was converted to a standard duty-cycle and removed from the study; and one participant was lost to follow-up. No intention-to-treat analysis was performed.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable, but it appeared all expected and prespecified outcomes were reported.
Other bias	Unclear risk	All studies were sponsored by Cyberonics, the manufacturer of the device.

Handforth 1998

Study characteristics

Methods	Randomised, prospective, double-blind, active-control study Pre-randomisation baseline period: 12 to 16 weeks Duration of treatment: 16 weeks. This period included 2, 12, and 16-week time points.
Participants	A multicentre trial (USA) 198 people randomised High stimulation group: 95 participants; mean age 32.1 years; 51.6% male and 48.4% female; mean seizures/day 1.59; mean duration of epilepsy 22.1 years Low stimulation group: 103 participants; mean age 34.2 years; 42.7% male and 57.3% female; mean seizures/day 0.97; mean duration of epilepsy 23.7 years

Handforth 1998 *(Continued)*

Interventions	Comparison of high (on/off cycles of 30 seconds every 5 minutes, each 'on' period consisting of 500 µs duration pulses at 30 Hz frequency) and low stimulation (on/off cycles of 30 seconds every 3 hours, each 'on' cycle of 130 µs duration pulse at 1 Hz frequency) in treatment of refractory focal seizures All participants had an identical implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics).
Outcomes	Primary outcome: Seizure frequency (50% reduction of seizures) Secondary outcomes: 1. Treatment withdrawal 2. Adverse events 3. Cognitive impact 4. Quality of life (QOL) impact
Notes	Supported by a grant from Cyberonics, Inc., Webster, TX

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule was generated by a statistical consultant before study initiation.
Allocation concealment (selection bias)	Low risk	Telephone communication to obtain randomised treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel and participants were blinded. Identical implants used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study data were analysed by a blinded interviewer. Identical implants used
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants withdrew, but the reasons for exclusion were reported.
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the methods section of the paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Unclear risk	All studies were sponsored by Cyberonics, the manufacturer of the device.

Klinkenberg 2012

Study characteristics

Methods	Randomised, double-blinded add-on, active-control study in children with refractory focal seizures Pre-randomisation baseline period: 12 weeks

Klinkenberg 2012 *(Continued)*

	Duration of treatment phase: 20 weeks
Participants	A multicentre trial (the Netherlands) 41 people randomised High-output stimulation group: 21 participants; mean age at onset 2:10 (y:mo); median age at onset 1:2 (y:mo); mean age at implantation 10:11 (y:mo); 11/10 male/female; median seizures/day 2.1; localisation-related 90% (symptomatic 71%, cryptogenic 19%); generalised 10% (Idiopathic 0, symptomatic 10%) Low-output stimulation group: 20 participants; mean age at onset 1:8 (y:mo); median age at onset 1:2 (y:mo); mean age at implantation 11:6 (y:mo);12/8 male/female; median seizures/day 0.9; localisation-related 80% (symptomatic 50%, cryptogenic 30%); generalised 20% (Idiopathic 10%, symptomatic 10%) A small sample (6 participants) had generalised epilepsy (2 idiopathic and 2 symptomatic).
Interventions	Comparison of high (output current 0.25 mA, duty-cycle on/off 30 s/5 min, frequency 30 Hz, pulse width 0.5 ms) and low (output current 0.25 mA, duty-cycle on/off 14 s/60 min, frequency 1 Hz, pulse width 0.1 ms) stimulation frequency in treatment of refractory focal seizures. In the treatment group, the current was increased stepwise at 2-week intervals to the maximally tolerated output current (maximum 1.75 mA). All participants had an identical implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics).
Outcomes	Primary outcomes: Seizure frequency (50% reduction of seizures) Secondary outcomes: 1. Treatment withdrawal 2. Adverse events 3. Intelligence quotient (IQ) assessment described in the methods section of the study
Notes	Supported by Cyberonics, Inc., Webster, TX

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation method used
Allocation concealment (selection bias)	Low risk	Participants were allocated to a treatment condition by one trial nurse, using a computer program.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neurologist, participants, and parents were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded. Identical implants used
Incomplete outcome data (attrition bias)	Low risk	3 participants withdrew, but the reasons for exclusion were reported.

Klinkenberg 2012 *(Continued)*

All outcomes

Selective reporting (reporting bias)	High risk	The secondary outcome of IQ, described in the methods, was not reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Unclear risk	All studies were sponsored by Cyberonics, the manufacturer of the device.

Michael 1993

Study characteristics	
Methods	Randomised, controlled, double-blind, active-control study of participant with refractory focal seizures Pre-randomisation baseline period: 12 weeks Duration of treatment: 14 weeks. Efficacy was determined at the end of the acute phase. At the end of the 14-week double-blind phase, participants entered an extension phase, in which low stimulation participants were switched to high stimulation.
Participants	A multicentre trial (USA) 22 people randomised High stimulation group: 10 participants Low stimulation group: 12 participants Mean age 32 years (range 15 to 56); seizure frequency 2 per day; mean duration of epilepsy 19 years (range 5 to 32)
Interventions	Comparison of high (output current 1.0 to 3.0 mA, on/off time 30 s/5 min, frequency 30 Hz, pulse width 500 µs) and low (output current 0.25 to 0.5 mA, on/off time 30 s/60 to 90 min, frequency 1 Hz, pulse width 130 µs) stimulation in treatment of refractory focal seizures All participants had an identical implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics).
Outcomes	Primary outcome: seizure frequency (mean seizure frequency percent reduction) Secondary outcomes: 1. Treatment withdrawal 2. Adverse events
Notes	Supported by Cyberonics, Inc., Webster, TX

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided

Michael 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided. Identical implants used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable, but it appeared all expected and prespecified outcomes were reported.
Other bias	Unclear risk	All studies were sponsored by Cyberonics, the manufacturer of the device.

VNS Study Group 1995

Study characteristics	
Methods	Randomised, prospective, double-blind, active-control study Pre-randomisation baseline period: 12 weeks Duration of treatment: 14 weeks. Efficacy was determined at the 12-week time point. At the end of the 14 week double-blind phase, participants entered an extension phase in an open trial.
Participants	A multicentre trial (USA, Canada, Sweden, and Germany) 114 people randomised High stimulation group: 54 participants; mean age 33.1 years; 61% male and 39% female; mean seizures/day 1.49; median seizures/day 0.73; mean duration of epilepsy 23.1 years; simple focal seizures 24 participants; complex focal seizures 50 participants; secondarily generalised seizures 38 participants Low stimulation group: 60 participants; mean age 33.5 years; 63% male and 37% female; mean seizures/day 1.71; median seizures/day 0.82; mean duration of epilepsy 20.0 years; simple focal seizures 25 participants; complex focal seizures 58 participants; secondarily generalised seizures 33 participants
Interventions	Comparison of high (output current 0.25 to 3.0 mA, on/off time 30 to 90 s/5 to 10 min, frequency 20 to 50 Hz, pulse width 500 µs) and low (output current 0.25 to 1.75 mA, on/off time 30 s/60 to 180 min, frequency 1 to 2 Hz, pulse width 130 µs) stimulation in treatment of refractory focal seizures All participants had an identical implantation of the vagus nerve stimulation device (NeuroCybernetic Prosthesis, Cyberonics).
Outcomes	Primary outcome: Seizure frequency (50% and 75% reduction of seizures) Secondary outcomes: 1. Treatment withdrawal

VNS Study Group 1995 *(Continued)*

2. Adverse events
3. Quality of life
4. Mood changes

Notes	Supported by a grant from Cyberonics, Inc., Webster, TX

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation tables were developed by an independent statistician with assignments, based on the participant's identification code.
Allocation concealment (selection bias)	Low risk	Assignments were made automatically by a look-up table in the computer software used to program the generator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded and one investigator for each site was unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The interviewer remained blinded to treatment group. Identical implants used.
Incomplete outcome data (attrition bias) All outcomes	High risk	57 participants were randomised to low stimulation. 3 participants allocated to high stimulation had their stimulator programmed for low stimulation in error. These participants were analysed in the low stimulation group according to the treatment they received rather than the treatment they were randomised to. This was not an intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	All outcomes stated in the methods section of the paper were reported in the results. There was no protocol available to check a priori outcomes.
Other bias	Unclear risk	All studies were sponsored by Cyberonics, the manufacturer of the device.

µs: microseconds
Hz: hertz
IQ: intelligent quotient
mA: milliampere
min: minutes
mo: month
ms: milliseconds
QOL: quality of life
s: seconds
VNS = vagus nerve stimulation
y: year

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bauer 2016	Different intervention (transcutaneous vagus nerve stimulation: a noninvasive technique to stimulate the left auricular branch of the vagus nerve at the ear conch)

Study	Reason for exclusion
Boon 2015	Different outcomes (this study evaluated the performance of a CBSDA incorporated into a closed-loop VNS device)
Brodtkorb 2019	Not a randomised controlled trial
Clarke 1997	Not a randomised controlled trial
Colicchio 2010	No comparison group
Cramer 2001	Not a randomised controlled trial
Cukiert 2013	Ineligible population (participants with Lennox-Gastaut Syndrome)
Cukiert 2015	Not a randomised controlled trial
DeGiorgio 2000	Not a randomised controlled trial
Dibue-Adjei 2019	Not a randomised controlled trial
Dumoulin 2018	Different intervention (transcutaneous auricular vagus nerve stimulation)
Ernst 2019	Different intervention (RNS System)
Fisher 2016	Not a randomised controlled trial
Galbarriatu 2015	Not a randomised controlled trial
Garcia-Navarrete 2013	Not a randomised controlled trial
Geller 2017	Different intervention (brain-responsive neurostimulation)
George 1994	Not a randomised controlled trial
Ghani 2015	Not a randomised controlled trial
He 2015	Different intervention (transcutaneous auricular vagus nerve stimulation (tVNS))
Ho 2016	No comparison group
Hornig 1997	Not a randomised controlled trial
Jobst 2017	Different intervention (brain-responsive neurostimulation (RNS))
Lee 2013	Not a randomised controlled trial
Liu 2017	Not a randomised controlled trial
Madaan 2021	Not a randomised controlled trial
Marras 2013	Not a randomised controlled trial
Marrosu 2003	Not a randomised controlled trial
Marrosu 2005	Not a randomised controlled trial

Study	Reason for exclusion
Morris 1999	Not a randomised controlled trial
Muller 2010	Ineligible population (participants with Lennox-Gastaut Syndrome)
NCT00215215	This study was terminated, and no data were available.
NCT01118455	This study was terminated, and no data were available (insufficient enrolment).
NCT01178437	This study was terminated, and no data were available.
NCT01910129	This study was terminated, and no data were available.
NCT02385526	Not a randomised controlled trial
NCT02465970	Different intervention (transcranial direct current stimulation (TDCS))
NCT02603991	Not a randomised controlled trial
Pelot 2018	Ineligible population (no epilepsy)
Perez-Carbonell 2020	Not a randomised controlled trial
Robinson 2013	Not a randomised controlled trial
Ronkainem 2006	Not a randomised controlled trial
Rossignol 2009	Not a randomised controlled trial
Salanova 2021	Different intervention (stimulation of the anterior nucleus of the thalamus)
Salinsky 1996	Not a randomised controlled trial
Scherrrmann 2001	Not a randomised controlled trial
Shimizu 1995	Not a randomised controlled trial
Sirven 2000	Not a randomised controlled trial
Tormasiova 2014	Not a randomised controlled trial
Uthman 1993	Not a randomised controlled trial
Wang 2004	Not a randomised controlled trial
Wang 2009	Not a randomised controlled trial
Zambrelli 2016	Not a randomised controlled trial

CBSDA: cardiac-based seizure detection algorithm
TDCS: transcranial direct current stimulation
VNS: vagus nerve stimulation

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2018-003464-32-HU

Study name	Effect of mirtazapine on seizure frequency in epileptic patients with vagal nerve stimulation device
Methods	Clinical randomised trial
Participants	The study population consisted of adults participants with refractory epilepsy
Interventions	VNS therapy
Outcomes	1) Seizure frequency 2) Quality of life (QOLIE-89) 3) Depression (HAM-D; BDI)
Starting date	May 2019
Contact information	No details
Notes	

Ji 2019

Study name	Vagus nerve stimulation for paediatric patients with intractable epilepsy between 3 and 6 years of age: study protocol for a double-blind, randomised control trial
Methods	Prospective randomised trial
Participants	The study population consisted of paediatric participants with intractable epilepsy
Interventions	VNS therapy
Outcomes	1) Seizure frequency 2) Side effects
Starting date	February 2017
Contact information	No details
Notes	

NCT00782249

Study name	Trial comparing different stimulation paradigms in patients treated with vagus nerve stimulation for refractory epilepsy
Methods	Prospective randomised trial
Participants	People with refractory epilepsy
Interventions	Comparison of three different paradigms in participants treated with VNS therapy
Outcomes	1) Seizure frequency 2) Side effects

NCT00782249 *(Continued)*	
	3) Quality of life
Starting date	October 2005
Contact information	Veerle De Herdt, veerle.deherdt@ugent.be
Notes	

NCT01281293	
Study name	Vagus nerve stimulation clinical outcomes measured prospectively in patients stimulated (V-COM-PAS)
Methods	Long-term, prospective, observational, multi-site outcome study to follow the clinical course and seizure reduction of people with refractory seizures who are being treated with adjunctive VNS therapy
Participants	The study population consisted of participants with a diagnosis of refractory seizures who were treated with adjunctive VNS therapy.
Interventions	VNS therapy
Outcomes	1) Efficacy 2) Safety and tolerability
Starting date	January 2011
Contact information	Mark Bunker, PharmD mark.bunker@cyberonics.com
Notes	

NCT01378611	
Study name	Does VNS interact with the serotonergic and immune system in children with intractable epilepsy?
Methods	Clinical randomised controlled observer-blinded add-on design
Participants	The study population consisted of children (age 4 to 18 years) with intractable epilepsy who were not eligible for resective surgery.
Interventions	VNS therapy
Outcomes	Seizure frequency
Starting date	March 2006
Contact information	No details
Notes	

NCT02089243

Study name	Controlled randomised vagus nerve stimulation (VNS) therapy versus resection (CoRaVNStiR)
Methods	A randomised, single-blind, parallel study
Participants	The study population consist of subjects (child and adults) 12 to 60 years with pharmacoresistant focal seizures.
Interventions	VNS therapy
Outcomes	1) Seizure frequency 2) Neuropsychological examination 3) Responder rates 4) Mean seizure-free interval 5) Seizure severity 6) Quality of life 7) Complications
Starting date	June 2014
Contact information	Yanchun YC Deng, China, +86 29 84773994 yanchund@fmmu.edu.cn
Notes	

NCT02378792

Study name	Clinical trial of vagus nerve stimulation for treatment of refractory epilepsy (VNSRE)
Methods	A randomised, double-blind, parallel study
Participants	The study population consisted of subjects (child and adults) 6 to 60 years with refractory epilepsy.
Interventions	VNS therapy
Outcomes	1) Changes in seizure frequency from baseline to the seizure count evaluation period at 6 months 2) Changes in seizure frequency from baseline to 4, 8, 12, 16, 20, and 24 months 3) Overall Quality of Life in Epilepsy-31 (QOLIE-31) score in participants with baseline and at least one post-baseline QOLIE assessment 4) Changes in the number of antiepileptic drugs in participants with less then a 50% reduction in seizures 5) Changes from baseline in the Engel and McHugh description 6) Changes from baseline in 24-hour ECG description
Starting date	August 2014
Contact information	Jia Fumin, China, +86 010-59361265 pins_medical@163.com
Notes	

NCT05180916	
Study name	Priming the epileptic brain: tVNS to improve efficacy of add-on AED in patients with focal epilepsy
Methods	Randomised controlled trial
Participants	The study population consisted of adults with refractory focal epilepsy
Interventions	VNS therapy
Outcomes	1) Seizure reduction 2) Improvement of cognition 3) Improvement of quality of life
Starting date	January 2022
Contact information	Angelique A Stuurman, Netherlands, +31 0402279777 prep@tue.nl
Notes	

AED: antiepileptic drug
ECG: electrocardiogram
QOLIE-31: Overall Quality of Life in Epilepsy-31
tVNS: transcutaneous vagus nerve stimulation
VNS: vagal nerve stimulation

DATA AND ANALYSES

Comparison 1. High versus low stimulation

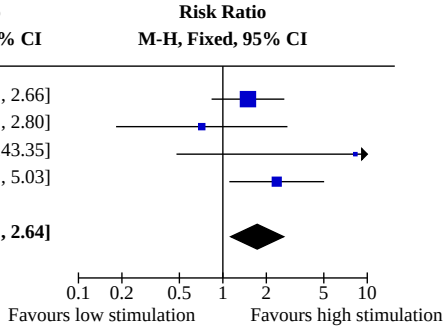
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 50% responders	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.13, 2.64]
1.2 50% responders – worst-case scenario	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.07, 2.43]
1.3 50% responders – best-case scenario	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.27, 2.89]
1.4 Withdrawals	4	375	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.51, 12.71]
1.5 Voice alteration or hoarseness	3	334	Risk Ratio (M-H, Fixed, 99% CI)	2.17 [1.49, 3.17]
1.6 Cough	3	334	Risk Ratio (M-H, Fixed, 99% CI)	1.09 [0.74, 1.62]
1.7 Dyspnoea	2	312	Risk Ratio (M-H, Fixed, 99% CI)	2.45 [1.07, 5.60]
1.8 Pain	2	312	Risk Ratio (M-H, Fixed, 99% CI)	1.01 [0.60, 1.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Paraesthesias	2	312	Risk Ratio (M-H, Fixed, 99% CI)	0.78 [0.39, 1.53]
1.10 Nausea	2	220	Risk Ratio (M-H, Fixed, 99% CI)	0.89 [0.42, 1.90]
1.11 Headache	2	312	Risk Ratio (M-H, Fixed, 99% CI)	0.90 [0.48, 1.69]

Analysis 1.1. Comparison 1: High versus low stimulation, Outcome 1: 50% responders

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Handforth 1998	22	94	16	102	55.8%	1.49 [0.84 , 2.66]
Klinkenberg 2012	3	21	4	20	14.9%	0.71 [0.18 , 2.80]
Michael 1993	3	10	0	12	1.7%	8.27 [0.48 , 143.35]
VNS Study Group 1995	17	54	8	60	27.6%	2.36 [1.11 , 5.03]
Total (95% CI)		**179**		**194**	**100.0%**	**1.73 [1.13 , 2.64]**
Total events:	45		28			

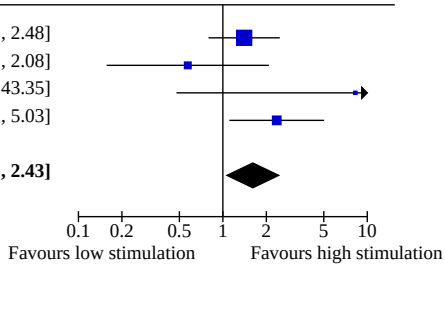
Heterogeneity: Chi² = 3.67, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: High versus low stimulation, Outcome 2: 50% responders – worst-case scenario

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Handforth 1998	22	94	17	102	55.3%	1.40 [0.80 , 2.48]
Klinkenberg 2012	3	21	5	20	17.4%	0.57 [0.16 , 2.08]
Michael 1993	3	10	0	12	1.6%	8.27 [0.48 , 143.35]
VNS Study Group 1995	17	54	8	60	25.7%	2.36 [1.11 , 5.03]
Total (95% CI)		**179**		**194**	**100.0%**	**1.61 [1.07 , 2.43]**
Total events:	45		30			

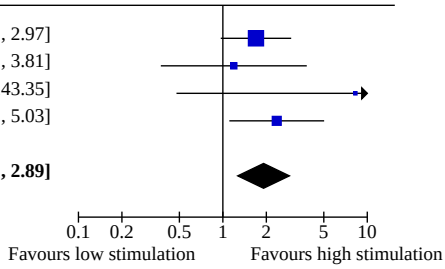
Heterogeneity: Chi² = 4.94, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 2.28 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: High versus low stimulation, Outcome 3: 50% responders – best-case scenario

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Handforth 1998	25	94	16	102	55.8%	1.70 [0.97 , 2.97]
Klinkenberg 2012	5	21	4	20	14.9%	1.19 [0.37 , 3.81]
Michael 1993	3	10	0	12	1.7%	8.27 [0.48 , 143.35]
VNS Study Group 1995	17	54	8	60	27.6%	2.36 [1.11 , 5.03]
Total (95% CI)		**179**		**194**	**100.0%**	**1.91 [1.27 , 2.89]**
Total events:	50		28			

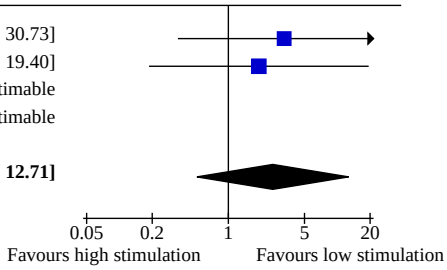
Heterogeneity: Chi² = 2.13, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: High versus low stimulation, Outcome 4: Withdrawals

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Handforth 1998	3	95	1	103	48.4%	3.25 [0.34 , 30.73]
Klinkenberg 2012	2	21	1	20	51.6%	1.90 [0.19 , 19.40]
Michael 1993	0	10	0	12		Not estimable
VNS Study Group 1995	0	54	0	60		Not estimable
Total (95% CI)		**180**		**195**	**100.0%**	**2.56 [0.51 , 12.71]**
Total events:	5		2			

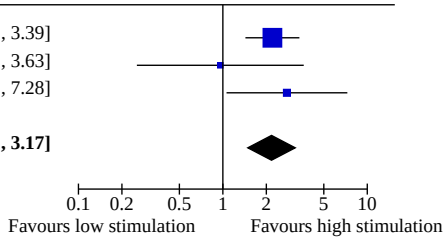
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: High versus low stimulation, Outcome 5: Voice alteration or hoarseness

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	63	95	31	103	71.0%	2.20 [1.43 , 3.39]
Michael 1993	4	10	5	12	10.9%	0.96 [0.25 , 3.63]
VNS Study Group 1995	20	54	8	60	18.1%	2.78 [1.06 , 7.28]
Total (99% CI)		**159**		**175**	**100.0%**	**2.17 [1.49 , 3.17]**
Total events:	87		44			

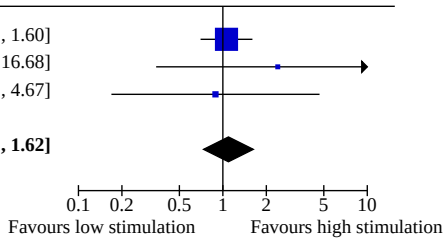
Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 5.29 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: High versus low stimulation, Outcome 6: Cough

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	43	95	44	103	86.6%	1.06 [0.70 , 1.60]
Michael 1993	4	10	2	12	3.7%	2.40 [0.35 , 16.68]
VNS Study Group 1995	4	54	5	60	9.7%	0.89 [0.17 , 4.67]
Total (99% CI)		**159**		**175**	**100.0%**	**1.09 [0.74 , 1.62]**
Total events:	51		51			

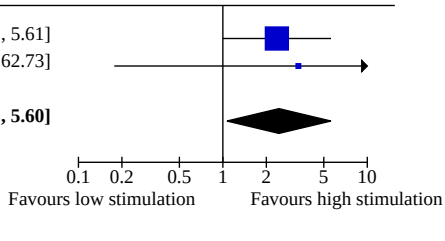
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: High versus low stimulation, Outcome 7: Dyspnoea

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	24	95	11	103	91.8%	2.37 [1.00 , 5.61]
VNS Study Group 1995	3	54	1	60	8.2%	3.33 [0.18 , 62.73]
Total (99% CI)		**149**		**163**	**100.0%**	**2.45 [1.07 , 5.60]**
Total events:	27		12			

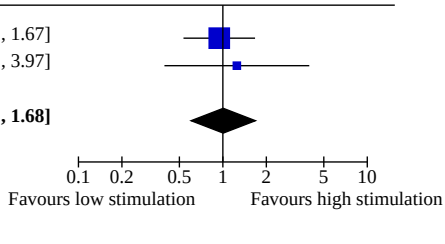
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: High versus low stimulation, Outcome 8: Pain

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	27	95	31	103	79.7%	0.94 [0.53 , 1.67]
VNS Study Group 1995	9	54	8	60	20.3%	1.25 [0.39 , 3.97]
Total (99% CI)		**149**		**163**	**100.0%**	**1.01 [0.60 , 1.68]**
Total events:	36		39			

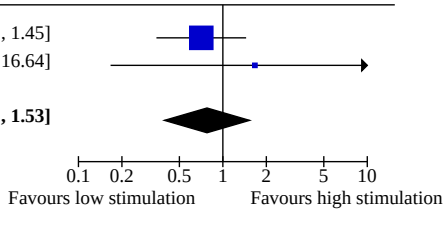
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: High versus low stimulation, Outcome 9: Paraesthesias

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	17	95	26	103	92.9%	0.71 [0.35 , 1.45]
VNS Study Group 1995	3	54	2	60	7.1%	1.67 [0.17 , 16.64]
Total (99% CI)		**149**		**163**	**100.0%**	**0.78 [0.39 , 1.53]**
Total events:	20		28			

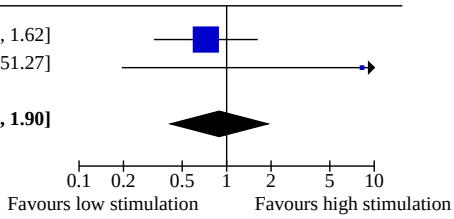
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: High versus low stimulation, Outcome 10: Nausea

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	14	95	21	103	97.8%	0.72 [0.32 , 1.62]
Michael 1993	3	10	0	12	2.2%	8.27 [0.19 , 351.27]
Total (99% CI)		**105**		**115**	**100.0%**	**0.89 [0.42 , 1.90]**
Total events:	17		21			

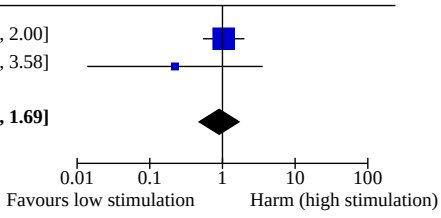
Heterogeneity: Chi² = 2.79, df = 1 (P = 0.10); I² = 64%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: High versus low stimulation, Outcome 11: Headache

Study or Subgroup	High stimulation Events	Total	Low stimulation Events	Total	Weight	Risk Ratio M-H, Fixed, 99% CI
Handforth 1998	23	95	24	103	82.9%	1.04 [0.54 , 2.00]
VNS Study Group 1995	1	54	5	60	17.1%	0.22 [0.01 , 3.58]
Total (99% CI)		**149**		**163**	**100.0%**	**0.90 [0.48 , 1.69]**
Total events:	24		29			

Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CRS Web search strategy

1. MeSH DESCRIPTOR Vagus Nerve Explode All AND CENTRAL:TARGET

2. (vagus or vagal) NEAR3 stimul* AND CENTRAL:TARGET

3. #1 OR #2

4. MESH DESCRIPTOR Epilepsies, Partial EXPLODE ALL AND CENTRAL:TARGET

5. ((partial or focal) and (seizure* or epilep*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

6. (secondar* and (generalized or generalised) and seizure*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

7. #4 OR #5 OR #6

8. #3 AND #7

Appendix 2. MEDLINE search strategy

This strategy includes a modification of the Cochrane Highly sensitive search strategy for identifying randomised trials (Lefebvre 2019).

1. exp Vagus Nerve/

2. ((vagus or vagal) adj3 stimul$).mp.

3. 1 or 2

4. exp Epilepsies, Partial/

5. ((partial or focal) and (seizure$ or epilep$)).mp.

6. (secondar$ and generali?ed and seizure$).mp.

7. 4 or 5 or 6

8. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

9. clinical trials as topic.sh.

10. trial.ti.

11. 8 or 9 or 10

12. exp animals/ not humans.sh.

13. 11 not 12

14. 3 and 7 and 13

15. remove duplicates from 14

FEEDBACK

Query regarding analysis 01.01, May 2006

Summary

The following comment was made on 21 May 2006 regarding Analysis 01.01. Comparison 01: High stimulation versus low stimulation, Outcome 01: 50% responders.

The two groups in the VNS Study Group consists of 54 people and 60 people and NOT 2 x 57 people. This mistake is shown in many of the analyses.

Reply

Whilst there may be a discrepancy between the data presented in this review and the original published report by the VNS Study Group, the authors have not made a mistake in the preparation of this review.

In the VNS study group trial, 57 patients were randomised to high stimulation and 57 were randomised to low stimulation. However, three patients allocated to high stimulation had their stimulator programmed for low stimulation in error. For the paper published in Neurology, these three participants were analysed in the low stimulation group rather than in the group to which they had been allocated. The authors of this Cochrane Review preferred to use the more conservative intention-to-treat analysis, in which participants are analysed in the treatment group to which they were allocated.

Reply made by Dr Tony Marson (Co-ordinating Editor, Cochrane Epilepsy Group) on behalf of the review authors (06 August 2008).

Update 2014. Following re-review of the data extracted from the VNS study Group manuscripts, most of the data used in the analyses in this review are presented for the high stimulation group of 54 people, and the low stimulation group of 60 people; in other words, groups according to the treatment received rather than treatment allocated. In the analysis of the previous version of the review, the event rates reported for the groups of 54 and 60 patients respectively were used in the analysis, but with group totals assigned as 57 participants per group, as an intention-to-treat analysis.

However, following consideration for this update, given that separate data for the three participants randomised to high stimulation, but who received low stimulation are not presented; and assuming that event rates in the treatment-received groups would be the same as in the treatment-allocated groups may not necessarily be correct; for this reason, the authors of the updated review presented results in terms of the treatment-received groups. They acknowledge that this is not an intention-to-treat approach, and reflected this in the risk of bias table for the VNS Study Group 1995 study.

Contributors

Comment made by Dr Jesper Erdal

WHAT'S NEW

Date	Event	Description
21 March 2022	New citation required but conclusions have not changed	Conclusions are unchanged.
3 March 2022	New search has been performed	Searches updated 3 March 2022; no new relevant studies were identified.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 1, 2002

Date	Event	Description
2 May 2019	New search has been performed	Searches updated 02 May 2019; no new studies added. The term 'partial' has been replaced by 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).
2 May 2019	New citation required but conclusions have not changed	Conclusions are unchanged.
20 December 2016	New search has been performed	Searches updated 20 December 2016; no new studies added.
20 December 2016	New citation required but conclusions have not changed	Conclusions remain unchanged.
23 February 2015	New search has been performed	The searches were updated on 23 February 2015.
23 February 2015	New citation required but conclusions have not changed	Three new studies have been included (identified from a search carried out in September 2013); however the conclusions remain unchanged. A pre-publication search carried out on 23rd February 2015 identified two potentially relevant studies (Klinkenberg 2014a; NCT02089243). These will be addressed at the next update.
7 August 2009	Amended	Copyedits made at editorial base.
24 October 2008	Amended	Search strategy amended to comply with RevMan 5.
11 August 2008	Feedback has been incorporated	A response has now been made to the feedback originally left on 21 May 2006.
31 July 2008	Amended	Converted to new review format.
19 July 2007	New search has been performed	Searches updated 6 July 2007; no new studies identified.

CONTRIBUTIONS OF AUTHORS

Mariangela Panebianco was primarily responsible for the writing of this update, and completed data extraction and risk of bias assessments. Alexandra Rigby assessed studies for eligibility, extracted data, and assessed risk of bias. Anthony G Marson provided guidance and manuscript feedback during the update process.

DECLARATIONS OF INTEREST

MP: none known
AR: none known
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SOURCES OF SUPPORT

Internal sources

- no internal support, Other

  no internal support

External sources

- National Institute for Health and Care Research, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The previous version of this review changed the inclusion criteria slightly to include active controlled trials (Panebianco 2015).

We replaced the term 'partial' with 'focal', in accordance with the most recent classification of epilepsies of the International League Against Epilepsy (Scheffer 2017).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [therapeutic use]; Cough; *Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination; Dyspnea [drug therapy]; Hoarseness [chemically induced] [drug therapy]; Pain [drug therapy]; Paresthesia [chemically induced]; Seizures [drug therapy]; *Vagus Nerve Stimulation [adverse effects]

MeSH check words

Adult; Child; Humans