Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response; a review
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CRD summary
The review found that vagus nerve stimulation was effective and relatively safe as an adjunctive therapy for individuals with refractory epilepsy not amenable to resection. In view of limitations in the review that included a suboptimal search, poor reporting, failure to assess study quality, heterogeneity between the studies and lack of randomised evidence, the authors’ conclusions may not be reliable.

Authors’ objectives
To evaluate the efficacy of vagus nerve stimulation for reducing the frequency of seizures in individuals with medically refractory epilepsy.

Searching
PubMed was searched up to November 2010 for studies published in English. Search terms were reported. Reference lists of selected articles were checked.

Study selection
Studies with a primary outcome of change in seizure frequency in individuals with medically refractory epilepsy before and after vagus nerve stimulation surgery were eligible for inclusion. Studies were required to have at least three months’ postoperative follow-up and to include at least five participants. Registry surveys were excluded. The primary review outcome was at least (≥) 50% decrease in seizure frequency from baseline.

Participants in the included studies were adults and children with medically refractory epilepsy. Aetiologies included encephalopathy, tuberous sclerosis, tumour, infection, ischaemia and idiopathy. Most of the prospective studies were conducted in single centres among participants with partial/focal or mixed seizures. No details of interventions or control conditions (where applicable) were reported in the review except for the five randomised controlled trials (RCTs). Three RCTs compared high- versus low-frequency stimulation and two compared different stimulation paradigms (no further details reported). Some studies stratified change in seizure frequency by Engel class (or equivalent). As well as decrease in seizure frequency, the review reported adverse events in selected studies only. Duration of study follow-up ranged from three months to five years (mean about 10 months).

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Prospective studies were graded by design as Class I (blinded randomised controlled trial), Class II (non-blinded RCT) and Class III (observational study). The authors did not state whether they assessed other aspects of validity or how many reviewers conducted the assessment.

Data extraction
For each study the reviewers extracted incidence rates (binary outcomes) and median or mean percentages (continuous outcomes). An odds ratio (OR) and 95% confidence interval (CI) was calculated for each intervention group, representing the likelihood of achieving (versus not achieving) 50% or more seizure reduction from baseline. Descriptive data on the findings of prospective studies were extracted.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Studies were combined to calculate pooled odds ratios and 95% CIs. A fixed-effect model was used unless there was heterogeneity and then a random-effects model was used. Individual studies were weighted by inverse variance. Subgroup analyses were conducted by seizure type, participant age and epilepsy aetiology. Various methods were used.
to analyse differences between groups. Heterogeneity between studies was assessed with the Q statistic, Freidman test and Kendal W test. Publication bias was assessed with funnel plots. The findings of prospective studies were reported in a narrative synthesis.

**Results of the review**

Seventy-four studies (77 articles) were included (3,321 participants). These included 15 prospective studies (955 participants, range 15 to 196), including three blinded RCTs (327 participants) and two unblinded RCTs (89 participants) and 10 observational studies (539 participants). Fifty-nine studies were retrospective (2,366 participants).

In the three blinded RCTS, at three months the proportion of participants in the intervention groups with a 50% or more reduction in seizure frequency from baseline was 23%, 31% and 57%. Two of these RCTs reported a greater reduction in seizure frequency in the high stimulation than in the sham stimulation group (25% versus 6% and 28% versus 15%).

In the two non-blinded RCTs across all stimulation paradigms 29% to 45% of participants had at least 50% fewer seizures than at baseline; mean seizure reduction ranged from 26% to 30%.

In the 10 prospective observational studies 21% to 50% of participants had at least 50% fewer seizures than at baseline and mean seizure reduction ranged from 17% to 55%.

When all 74 studies were pooled, the odds of achieving (versus not achieving) at least 50% fewer seizures significantly favoured vagus nerve stimulation (OR 1.83, 95% CI 1.80 to 1.86). Data on seizure frequency were available for 1,789 participants among whom seizures were reduced by a mean of 44.6% (standard error 0.5%). Seizure outcomes by Engel class were available for 2,634 participants among whom 50.6% achieved at least 50% fewer seizures after vagus nerve stimulation; fewer than 5% achieved complete seizure freedom and 25.4% had no benefit.

In subgroup analyses, more than one year’s follow-up, young age, generalised epilepsy, traumatic epilepsy and tuberous sclerosis were associated with significantly higher seizure reduction. Funnel tests did not suggest significant publication bias. Only three studies reported adverse events (hoarseness was the most common with 37% to 62%).

**Authors’ conclusions**

Vagus nerve stimulation was effective and relatively safe as an adjunctive therapy for refractory epilepsy not amenable to resection.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Only one database was searched and the search was limited by language and (apparently) publication status, so some studies may have been missed but there was no evidence of publication bias. It was unclear whether the inclusion criteria for sample size and registry studies were prespecified. Few aspects of study validity were assessed and it was unclear whether review tasks were undertaken in duplicate to limit potential reviewer bias and error. Few details were reported about the methodological and clinical characteristics of the included studies.

The meta-analysis utilised only before-and-after data and did not make use of randomised comparisons. The forest plot indicated marked heterogeneity, but no measures of statistical heterogeneity were reported. These factors made it impossible to determine the statistical or clinical implications of the review findings.

In view of limitations in the review that included a suboptimal search, poor reporting, failure to assess study quality, heterogeneity between the studies and lack of randomised evidence, the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that vagus nerve stimulation should be tried in individuals with epilepsy refractory to medical treatment in whom medical therapy had failed and who were unsuitable or unresponsive to resection.

**Research:** The authors stated that an RCT that examined long-term effects of vagus nerve stimulation in epilepsy would be useful.

**Funding**
Bibliographic details

PubMedID
21838505

DOI
10.3171/2011.7.JNS11977

Original Paper URL
http://thejns.org/doi/abs/10.3171/2011.7.JNS11977

Indexing Status
Subject indexing assigned by NLM

MeSH
Epilepsy /therapy; Humans; Predictive Value of Tests; Randomized Controlled Trials as Topic; Treatment Outcome; Vagus Nerve Stimulation /standards

AccessionNumber
12012000164

Date bibliographic record published
13/02/2012

Date abstract record published
28/05/2012

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.