Transforming Healthcare with Evidence

Update Literature Search,

2009 WA HTA on Vagus Nerve Stimulation for Depression and Epilepsy

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OVERVIEW

This update literature search provides a basis for deciding whether to update the report on *Vagus Nerve Stimulation for Depression and Epilepsy* prepared for the Washington HTA Program by Hayes, Inc. in 2009.

The following objectives reflect methods guidance for systematic review updates published by the Agency for Healthcare Research and Quality (AHRQ) (Tsertsvadze et al., 2011)[1]. They are accompanied by key findings.

Objectives

- **Estimate the volume of new literature published since 2009, relative to each Key Question, and using the same general inclusion criteria that were specified for the 2009 report.**

  Findings:

  - 7 new systematic reviews, including one by AHRQ, and 1 randomized trial addressed effectiveness of VNS.
  - 13 new observational studies providing evidence on the safety of VNS and treatment success predictors.

- **Identify any new harms that have been reported since 2009.**

  Findings: One case series of 436 patients reported permanent injury to the vagus nerve in 2.8% of the patients.

- **Assess whether new evidence fills gaps in the evidence available as of 2009.**

  Findings: Accumulating evidence regarding adverse event rates and differential effectiveness/safety but the new evidence is not likely to change previous conclusions.

- **Assess whether vagus nerve stimulation (VNS) has been studied in subpopulations or in comparison with specific alternative treatments that were not addressed as of 2009.**

  Findings:

  - No comparisons with alternative treatments that were not addressed in the 2009 report.
  - A new meta-analysis of VNS in patients with Lennox-Gastaut syndrome.

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[1] Tsertsvadze A, Maglione M, Chou R, et al. Updating comparative effectiveness reviews: Current efforts in AHRQ's Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1208-1215.

- **Assess whether new evidence allows stronger conclusions or is likely to modify conclusions, including estimates of the magnitude of benefit.**

Findings:

- New evidence of VNS for epilepsy and depression is limited and will have little impact on conclusions.
- The safety profile of VNS remains largely unchanged although one large case series noted a 2.8% incidence of permanent nerve damage, which had not been reported in previous published studies.
- Although there are several new large case series, evidence regarding differential effectiveness/safety according to patient characteristics remains sparse and indirect.

Other Comments

- Only 1 new randomized trial was identified, which compared 3 different doses of VNS for the treatment of depression. No new comparative or controlled studies were identified.
- No in-depth search for new harms data, e.g. review of FDA Maude reports or recently published narrative reviews, was made.

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Changes in CMS Policy

There are no changes in CMS policy regarding VNS use for epilepsy or depression.

New Indications or Devices Approved by the FDA

There are no new indications or VNS devices since the 2009 report.

*See **Table 1** and **Table 2** on the following pages for more detail and commentary by Key Question.*

Table 1. Summary of New Literature, Epilepsy

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
Key Question #1. Is the use of vagus nerve stimulators plus antiepileptic medication effective, compared with medication alone, in reducing the frequency or severity of clinical seizures or in improving quality of life?			
Adults High-quality evidence, VNS reduces seizure rates in some patients older than 12 years of age with medically refractory partial-onset seizures who are not suitable candidates for surgery or in whom surgical treatment has failed.	**Connor 2012** (>10 patients; medically-refractory epilepsy; 20 studies including 2 Class I, 7 Class II, and 11 Class III evidence; searched to 2010) **Positive:** Majority of evidence supports VNS usage in adults and children with refractory epilepsy. **Englot 2011** (Patients with intractable epilepsy; 74 clinical studies identified including 3 RCTs, 10 prospective studies, and numerous retrospective studies) **Positive:** Adults and children with generalized epilepsy, posttraumatic epilepsy, and tuberous sclerosis had significant benefit from VNS.		The new evidence will probably have a minimal impact on the conclusions of the 2009 report. Conclusions are consistent with the conclusions of the 2009 report. The search dates for the 2 systematic reviews are relatively close to the search date used in the 2009 report, so it is not expected that they would provide a significant body of new evidence.
Adults Low-quality evidence, VNS may improve QOL	---	---	----
Children Low quality evidence of efficacy	---	---	----

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
Key Question #2: Are vagus nerve stimulators safe?			
Overall, with few exceptions, complication rates were similar for sham VNS and active VNS.	---	*Pubmed search:* **Horowitz 2013** (Case series; n=100; mean follow-up 25±22 months) Most common complication was local infection in 6% of patients; 4 devices removed because of infection and 2 devices removed because of loss of clinical effect. **Elliott 2011a** (Case series; n=436 patients; >3 months follow-up) Permanent injury to the vagus nerve occurred in 2.8% of patients. **Elliott 2011b** (Case series; n=141; ≥1 year follow-up) Complications occurred in 6% of patients and included: deep infection requiring device removal, pneumothorax, superficial infections, hematoma, persistent cough, neck pain, and hoarseness. **Kabir 2009** (Case series; n=69 children) Complications included: infection, lead fracture, fluid	New evidence is available; extent to which it will change conclusions is unclear. Of note is a finding of 2.8% incidence of permanent nerve damage.

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
		collection around the stimulator, neck pain, and dysphagia.	
Key Question #3: Does effectiveness vary by age group, response to antiepileptics, or other patient characteristics?			
Not possible to discern which patient subgroups were most likely to benefit from VNS treatment.	**Lancman 2013** (Prospective or retrospective studies with at least one patient with Lennox-Gastaut syndrome; 17 VNS and 9 corpus callostomy studies) **Atonic seizure type:** Results favored **corpus callostomy**. **Nonatonic seizure types: No difference**.	*Pubmed search:* **Colicchio 2012** (Case series; n=53; 1 year follow-up) Factors associated with better outcome include: lesional etiology epilepsy, short duration of epilepsy, VNS implantation <18 years of age. **Englot 2012** (Case series; sample size not reported; 1 year follow-up) Patients with post-traumatic epilepsy had a greater reduction in seizure frequency than patients with non-post-traumatic epilepsy. **Wheeler 2011** (Case series; n=189 patients; ≥1 year follow-up) Patients with normal mental functioning had a significantly better outcome. **Ghaemi 2010** (Case series; n=144 patients; 2-year follow-up) Patients with unilateral interictal epileptiform	New evidence showing an association between improvement following VNS implantation and certain patient factors is available from case series. However, no particular factor is supported by a substantial volume of evidence. A new meta-analysis suggested that in Lennox-Gastaut syndrome VNS is inferior to corpus callostomy, but only in patients with atonic seizure.

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
		discharges and earlier implantation achieved the most benefit from VNS. **Colicchio 2010** (Case series; n=135 patients) Young lesional epileptic patients have the best response to VNS.	

Table 2. Summary of New Literature, Depression

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
Key Question #1. Is the use of vagus nerve stimulators with or without antidepressant medication effective, compared with medication alone, in reducing the severity of depression, or in improving function or quality of life?			
The currently available evidence is of low overall quality and does not support the use of VNS as an adjunct therapy in adult patients with treatment-resistant MDD and bipolar disorders	**AHRQ** (Gaynes 2011) (Nonpharmacologic interventions for treatment resistant depression; RCTs only; 1 RCT of VNS versus sham; search end November 2010) **Negative:** No significant differences in severity of depression or response rate between VNS and sham. **Hayes 2009** (1 RCT of VNS versus sham, 1 prospective case control study, and a few uncontrolled studies; search end September 2009) **Negative:** No differences in outcome between VNS and sham in RCT. **Positive:** Moderate treatment effect in uncontrolled studies **Berry 2013** (Treatment resistant depression; 2 RCTs, 1 cohort, 2 case series, 1 dosimetric study, and 1 unpublished ongoing study) **Positive:** VNS plus treatment as usual leads to a greater response and	*Pubmed search:* **Aaronson 2013** (Randomized comparison of varying doses of VNS; n=331; 22 weeks follow-up) positive findings	Limited new evidence is available; extent to which it will change conclusions is unclear. Although a new meta-analysis had a positive conclusion, this study was supported by the manufacturer and selected only studies sponsored by the manufacturer (methods and clinical relevance of findings have not been reviewed in detail).

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
	remission rate than treatment as usual alone. **Martin 2012** (14 studies including 1 RCT and several uncontrolled studies) **Negative:** No significant differences between VNS and sham group in the RCT. **Positive:** Meta-analysis of uncontrolled studies revealed a significant reduction in depression scores.		
Key Question #2: Are vagus nerve stimulators safe?			
Safety is not proven May increase depression and suicide ideation but 1 nonrandomized controlled study suggested no increase.		*Pubmed search:* **Spuck 2010** (Case series; n=105 patients including 84 children and adolescents) 19% of patients had technical problems or complications; 6% of complications were caused by the surgery. Complications included: electrode fractures, early and late onset of deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator. The major complication in younger patients is electrode fracture.	The new evidence will probably have a minimal impact on the conclusions of the 2009 report.

Conclusions, 2009 Report*	New Systematic Reviews/Technology Assessments	Controlled/comparative studies or large case series w/ safety or predictor data; June 2009 or later	Potential Impact of New Evidence
		Olin 2012 (Case series; n=636 patients treated with VNS or standard therapies) Reduced risk of suicidal ideation. **Bajbouj 2010** (Case series; n=74; 2-year follow-up) Most frequently reported complications were voice alteration, cough, and pain.	
Key Question #3: Does effectiveness vary by age, response to antidepressants, or other patient characteristics?			
No conclusions	---	---	No new evidence.

METHODS

Relevant reports and studies have been added to Tables 1 and 2. See Appendix I for abstracts.

Systematic Search #1 (Key Systematic Reviews and Technology Assessments)

The following databases were searched on July 29, 2013 (depression) and again on August 9, 2013 (epilepsy), for reports published June 2009 or later:

a. PubMed, using filters for systematic review, meta-analysis, practice guideline
b. Hayes Knowledge Center
c. Centre for Reviews and Dissemination (CRD)
d. AHRQ

Yield: 7 potentially relevant systematic reviews.

Systematic Search #2 (PubMed)

PubMed searches were conducted to identify literature published June 2009 or later. No language or study type limits were used.

Epilepsy

Repeated search strategy from 2009 report on August 9, 2013: *vagus nerve stimulation, vagal stimulation, or VNS*, combined with *epilepsy or seizure*

Yield: 9 studies relevant to Key Questions, added to Table 1.

Depression

Conducted searches on August 1-4 in the context of the 2013 WA report on *Nonpharmacologic Treatment for Treatment-Resistant Depression* and on August 9 to compare results of those searches with a search according to the precise search strategy used in the 2009 WA report on *Vagus Nerve Stimulation.*

Yield: 4 studies relevant to Key Questions 1-3, added to Table 2.

APPENDIX I. Bibliography

SYSTEMATIC REVIEWS
(listed in reverse chronological and then alphabetical order)

Berry SM, Broglio K, Bunker M, et al.
A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression.
***Med Devices (Auckl)*. 2013;6:17-35.**
OBJECTIVE: To compare response and remission rates in depressed patients with chronic treatment-resistant depression (TRD) **treated with vagus nerve stimulation (VNS) Therapy(®) plus treatment as usual (VNS + TAU) or TAU alone** in a meta-analysis using Bayesian hierarchical models.DATA SOURCES AND STUDY SELECTION: Six outpatient, multicenter, clinical trials that have evaluated VNS + TAU or TAU in TRD, including two single-arm studies of VNS + TAU (n = 60 and n = 74), a randomized study of VNS + TAU versus TAU (n = 235), a randomized study of VNS + TAU comparing different VNS stimulation intensities (n = 331), a nonrandomized registry of VNS + TAU versus TAU (n = 636), and a single-arm study of TAU (n = 124) to provide longer-term, control data for comparison with VNS-treated patients.DATA EXTRACTION: A systematic review of individual patient-level data based on the intent-to-treat principle, including all patients who contributed more than one post-baseline visit. Response was based on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I), as these were the two clinician-rated measures common across all or most studies. Remission was based on the MADRS.RESULTS: Outcomes were compared from baseline up to 96 weeks of treatment with VNS + TAU (n = 1035) versus TAU (n = 425). The MADRS response rate for VNS + TAU at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% versus 4%, 7%, 12%, and 14% for TAU. The MADRS remission rate for VNS + TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14% versus 1%, 1%, 2%, and 4%, for TAU. Adjunctive VNS Therapy was associated with a greater likelihood of response (odds ratio [OR] = 3.19, 95% confidence interval [CI]: 2.12, 4.66) and remission (OR = 4.99, CI: 2.93, 7.76), compared with TAU. For patients who had responded to VNS + TAU at 24 weeks, sustained response was more likely at 48 weeks (OR = 1.98, CI: 1.34, 3.01) and at 96 weeks (OR = 3.42, CI: 1.78, 7.31). Similar results were observed for CGI-I response.CONCLUSION: For patients with chronic TRD, VNS + TAU has greater response and remission rates that are more likely to persist than TAU.

Lancman G, Virk M, Shao H, et al.
Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis.
***Seizure*. 2013;22(1):3-8.**
PURPOSE: Lennox-Gastaut syndrome (LGS) is an epileptogenic disorder that arises in childhood and is typically characterized by multiple seizure types, slow spike-and-wave complexes on EEG and cognitive impairment. If medical treatment fails, patients can proceed to one of two palliative surgeries, vagus nerve stimulation (VNS) or corpus callosotomy (CC). Their relative seizure control rates in LGS have not been well studied. The purpose of this paper is to compare seizure reduction rates between VNS and CC in LGS using meta-analyses of published data.METHODS: A systematic search of Pubmed, Ovidsp, and Cochrane was performed to find articles that met the following criteria: **(1) prospective or retrospective study, (2) at least one**

patient diagnosed with Lennox-Gastaut syndrome, and (3) well-defined measure of seizure frequency reduction. Seizure reduction rates were divided into seizure subtypes, as well as total seizures, and categorized as 100%, >75%, and >50%. Patient groups were compared using chi-square tests for categorical variables and t-test for continuous measures. Pooled proportions with 95% confidence interval (95% CI) of seizure outcomes were estimated for total seizures and seizure subtypes using random effects methods.RESULTS: 17 VNS and 9 CC studies met the criteria for inclusion. CC had a significantly better outcome than VNS for >50% atonic seizure reduction (80.0% [67.0-90.0%] vs. 54.1% [32.1-75.4%], p<0.05) and for >75% atonic seizure reduction (70.0% [48.05-87.0%] vs. 26.3% [5.8-54.7%], p<0.05). All other seizure types, as well as total number of seizures, showed no statistically significant difference between VNS and CC.CONCLUSIONS: CC may be more beneficial for LGS patients whose predominant disabling seizure type is atonic. For all other seizure types, VNS offers comparable rates to CC.

Connor DE Jr, Nixon M, Nanda A, Guthikonda B.
Vagal nerve stimulation for the treatment of medically refractory epilepsy: a review of the current literature.
***Neurosurg Focus*. 2012;32(3):E12.**
OBJECT: The authors conducted a study to evaluate the published results of vagal nerve stimulation (VNS) for medically refractory seizures according to evidence-based criteria.METHODS: The authors performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included **more than 10 patients evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation**. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology.RESULTS: A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence. The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%-27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations.CONCLUSIONS: Vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management.

Martin JLR, Martín-Sánchez E.
Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs.
***Eur. Psychiatry*. 2012;27(3):147-155.**
PURPOSE: To determine the efficacy of vagus nerve stimulation (VNS) for treatment of depression.METHODS: We conducted a **systematic review and meta-analysis of analytical studies**. Efficacy was evaluated according to severity of illness and percentage of responders.RESULTS: We identified 687 references. Of these, 14 met the selection criteria and were included in the review. The meta-analysis of efficacy for uncontrolled studies showed a significant reduction in scores at the Hamilton Depression Rating Scale endpoint, and the percentage of responders was 31.8% ([23.2% to 41.8%], P<0.001). However, the randomised control trial which covered a sample of 235 patients with depression, reported no statistically significant differences between the active intervention and placebo groups (OR=1.61 [95%CI

0.72 to 3.62]; P=0.25). To study the cause of this heterogeneity, a meta-regression was performed. The adjusted coefficient of determination (R2(Adj)) was 0.84, which implies that an 84% variation in effect size across the studies was explained by baseline severity of depression (P<0.0001).CONCLUSION: Currently, insufficient data are available to describe VNS as effective in the treatment of depression. In addition, it cannot be ruled out that the positive results observed in the uncontrolled studies might have been mainly due to a placebo effect.

Englot DJ, Chang EF, Auguste KI.
Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response.
***J. Neurosurg.* 2011;115(6):1248-1255.**
Vagus nerve stimulation (VNS) was approved by the US FDA in 1997 as an adjunctive treatment for medically refractory epilepsy. It is considered for use in patients who are poor candidates for resection or those in whom resection has failed. However, disagreement regarding the utility of VNS in epilepsy continues because of the variability in benefit reported across clinical studies. Moreover, although VNS was approved only for adults and adolescents with partial epilepsy, its efficacy in children and in patients with generalized epilepsy remains unclear. The authors performed the first meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 patients suffering from intractable epilepsy. These studies included 3 blinded, randomized controlled trials (Class I evidence); 2 nonblinded, randomized controlled trials (Class II evidence); 10 prospective studies (Class III evidence); and numerous retrospective studies. After VNS, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after > 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the patients, and VNS predicted a ≥ 50% reduction in seizures with a main effects OR of 1.83 (95% CI 1.80-1.86). Patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Furthermore, posttraumatic epilepsy and tuberous sclerosis were positive predictors of a favorable outcome. In conclusion, VNS is an effective and relatively safe adjunctive therapy in patients with medically refractory epilepsy not amenable to resection. However, it is important to recognize that complete seizure freedom is rarely achieved using VNS and that a quarter of patients do not receive any benefit from therapy.

Gaynes BN, Lux LJ, Lloyd SW, et al.
Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults.
2011.
(AHRQ report)
This review from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (EPC) provides a comprehensive summary of the available data addressing the **comparative effectiveness of four nonpharmacologic treatments as therapies for patients with treatment-resistant depression** (TRD): electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT). The core patient population of interest was patients with major depressive disorder (MDD) who met our definition of TRD: failure to respond following two or more adequate antidepressant treatments. We also included TRD studies in which the patient population could include a “mix” of up to 20 percent of patients with bipolar disorder (i.e., 80 percent or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations.
Hayes 2009
Vagus Nerve Stimulation for Depression.

Hayes ratings: C – For VNS as an adjunctive treatment in adults with severe major depression and bipolar disorder I and II when symptoms associated with a major depressive episode are refractory to multiple regimens of standard medication and other therapies, including electroconvulsive therapy and psychotherapy; D – For VNS as an adjunctive treatment in adults with severe, treatment-resistant rapid-cycling bipolar disorder (insufficient evidence); and D – For VNS in patients with other types of depression and in patients with major depression or bipolar disorder who respond to medical treatment, psychotherapy, and/or electroconvulsive therapy (insufficient evidence).

Update search, October 2012: No anticipated impact on Hayes ratings.

LARGE OBSERVATIONAL STUDIES WITH SAFETY DATA
(listed in reverse chronological and then alphabetical order)

Horowitz G, Amit M, Fried I, et al.
Vagal nerve stimulation for refractory epilepsy: the surgical procedure and complications in 100 implantations by a single medical center.
***Eur Arch Otorhinolaryngol*. 2013;270(1):355-358.**
In 1997, the US Food and Drug Administration approved the use of intermittent stimulation of the left vagal nerve as adjunctive therapy for seizure control. Vagal nerve stimulation (VNS) has since been considered a safe and effective treatment for medically intractable seizures. The objective of this study is to present our experience with the surgical procedure and outcomes after VNS insertion in the first 100 consecutive patients treated at the Tel-Aviv "Sourasky" Medical Center (TASMC). All patients who underwent VNS device implantation by the authors at TASMC between 2005 and 2011 were studied. The collected data included age at onset of epilepsy, seizure type, duration of epilepsy, age at VNS device implantation, seizure reduction, surgical complications, and adverse effects of VNS over time. Fifty-three males and 47 females, age 21.2 ± 11.1 years, underwent VNS implantation. Indications for surgery were medically refractory epilepsy. The most common seizure type was focal (55 patients, 55 %). Seizure duration until implantation was 14.4 ± 9 years. Mean follow-up time after device insertion was 24.5 ± 22 months. Complications were encountered in 12 patients. The most common complication was local infection (6 patients, 6 %). Six devices were removed-four due to infection and two due to loss of clinical effect. Currently, 63 patients remain in active long-term follow-up; of these, 35 patients have >50 % reduction in frequency of attacks.VNS is a well-tolerated and effective therapeutic alternative in the management of medically refractory epilepsy. The surgical procedure is safe and has a low complication rate.

Colicchio G, Montano N, Fuggetta F, et al.
Vagus nerve stimulation in drug-resistant epilepsies. Analysis of potential prognostic factors in a cohort of patients with long-term follow-up.
***Acta Neurochir (Wien)*. 2012;154(12):2237-2240.**
BACKGROUND: The results of vagus nerve stimulation (VNS) for the treatment of drug-resistant epilepsies are highly variable due to the lack of defined patient's selection criteria and a follow-up of published studies being generally too short. Here we report the outcome of VNS in a series with long-term follow-up and try to identify subgroups of patients who could be better candidates for this procedure.METHOD: We studied 53 patients (33 male, 20 female) with a

prospectively recorded follow-up (mean, 55.96 ± 43.53 months). The monthly average seizure frequency for each patient at baseline, 3, 6, 12 months, and each year until the latest follow-up after implant was measured and the percentage of "responders" and response time (RT) were calculated. We investigated the following potential prognostic role of these factors: age of onset of epilepsy, pre-implant epilepsy duration, etiology, and age at implant.RESULTS: Globally, 40 % of patients responded to VNS (mean RT, 14.85 ± 16.85 months). Lesional etiology (p = 0.0179, logrank test), particularly ischemia (p = 0.011, Fisher exact test) and tuberous sclerosis (p = 0.0229, Fisher exact test), and age at implant <18 years (p = 0.0242, logrank test) were associated to better response to VNS. In the lesional subgroup the best results were observed in patients with a pre-implant epilepsy duration <15 years (p = 0.0204, logrank test) and an age at implant <18 years (p = 0.0187 logrank test).CONCLUSIONS: The best candidate to VNS seems to be a patient with lesional etiology epilepsy (particularly post-ischemic and tuberous sclerosis) and a short duration of epilepsy who undergo VNS younger than 18 years.

Englot DJ, Rolston JD, Wang DD, et al.
Efficacy of vagus nerve stimulation in posttraumatic versus nontraumatic epilepsy.
***J. Neurosurg.* 2012;117(5):970-977.**
OBJECT: In the US, approximately 500,000 individuals are hospitalized yearly for traumatic brain injury (TBI), and posttraumatic epilepsy (PTE) is a common sequela of TBI. Improved treatment strategies for PTE are critically needed, as patients with the disorder are often resistant to antiepileptic medications and are poor candidates for definitive resection. Vagus nerve stimulation (VNS) is an adjunctive treatment for medically refractory epilepsy that results in a ≥ 50% reduction in seizure frequency in approximately 50% of patients after 1 year of therapy. The role of VNS in PTE has been poorly studied. The aim of this study was to determine whether patients with PTE attain more favorable seizure outcomes than individuals with nontraumatic epilepsy etiologies.METHODS: Using a case-control study design, the authors retrospectively compared seizure outcomes after VNS therapy in patients with PTE versus those with nontraumatic epilepsy (non-PTE) who were part of a large prospectively collected patient registry.RESULTS: After VNS therapy, patients with PTE demonstrated a greater reduction in seizure frequency (50% fewer seizures at the 3-month follow-up; 73% fewer seizures at 24 months) than patients with non-PTE (46% fewer seizures at 3 months; 57% fewer seizures at 24 months). Overall, patients with PTE had a 78% rate of clinical response to VNS therapy at 24 months (that is, ≥ 50% reduction in seizure frequency) as compared with a 61% response rate among patients with non-PTE (OR 1.32, 95% CI 1.07-1.61), leading to improved outcomes according to the Engel classification (p < 0.0001, Cochran-Mantel-Haenszel statistic).CONCLUSIONS: Vagus nerve stimulation should be considered in patients with medically refractory PTE who are not good candidates for resection. A controlled prospective trial is necessary to further examine seizure outcomes as well as neuropsychological outcomes after VNS therapy in patients with intractable PTE.

Olin B, Jayewardene AK, Bunker M, Moreno F.
Mortality and suicide risk in treatment-resistant depression: an observational study of the long-term impact of intervention.
***PLoS ONE*. 2012;7(10):e48002.**
Major depressive disorder is a common global disease that causes a significant societal burden. Most interventional studies of depression provide a limited assessment of the interventions on mortality and suicide risks. This study utilizes data from an observational registry of patients with major depressive disorder to determine the impact of intervention (vagus nerve

stimulation or standard pharmacological/non-pharmacological therapy) and a latent factor, patient trajectory toward response, on mortality, suicide and suicidal ideation. A total of 636 patients were available for an intent-to-treat analysis of all-cause mortality, suicide and suicidal ideation. Patients treated with vagus nerve stimulation in addition to standard therapies experienced lower, but not statistically significant, all-cause mortality (vagus nerve stimulation 4.93 per 1,000 person-years vs. 10.02 per 1,000 patient years for treatment as usual) and suicide rates (vagus nerve stimulation 0.88 per 1,000 person-years vs. 1.61 per 1,000 patient years for treatment as usual). Treatment with vagus nerve stimulation produced a statistically lower relative risk of suicidal ideation 0.80, 95% confidence interval (0.68,0.95). Further, patients that responded to either treatment saw a 51% reduction in relative risk of suicidal behavior; relative risk and 95% confidence interval of 0.49 (0.41,0.58). In summary, we find that treatment with adjunctive vagus nerve stimulation can potentially lower the risk of all-cause mortality, suicide and suicide attempts.

Elliott RE, Morsi A, Kalhorn SP, et al.
Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response.
***Epilepsy Behav*. 2011a;20(1):57-63.**
OBJECTIVE: The goal of this study was to assess the efficacy and safety of vagus nerve stimulation in a consecutive series of adults and children with treatment-resistant epilepsy (TRE).METHODS: In this retrospective review of a prospectively created database of 436 consecutive patients who underwent vagus nerve stimulator implantation for TRE between November 1997 and April 2008, there were 220 (50.5%) females and 216 (49.5%) males ranging in age from 1 to 76 years at the time of implantation (mean: 29.0 ± 16.5). Thirty-three patients (7.6%) in the primary implantation group had inadequate follow-up (<3 months from implantation) and three patients had early device removal because of infection and were excluded from seizure control outcome analyses.RESULTS: Duration of vagus nerve stimulation treatment varied from 10 days to 11 years (mean: 4.94 years). Mean seizure frequency significantly improved following implantation (mean reduction: 55.8%, P<0.0001). Seizure control ≥ 90% was achieved in 90 patients (22.5%), ≥ 75% seizure control in 162 patients (40.5%), ≥ 50% improvement in 255 patients (63.75%), and <50% improvement in 145 patients (36.25%). Permanent injury to the vagus nerve occurred in 2.8% of patients.CONCLUSION: Vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used in conjunction with a multidisciplinary and multimodality treatment regimen including aggressive antiepileptic drug regimens and epilepsy surgery when appropriate, more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden. Good results were seen in patients with non-U.S. Food and Drug Administration-approved indications. Prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment.

Elliott RE, Rodgers SD, Bassani L, et al.
Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases.
***J Neurosurg Pediatr*. 2011b;7(5):491-500.**
OBJECT: The authors undertook this study to analyze the efficacy of vagus nerve stimulation (VNS) in a large consecutive series of children 18 years of age and younger with treatment-resistant epilepsy and compare the safety and efficacy in children under 12 years of age with the

outcomes in older children.METHODS: The authors retrospectively reviewed 141 consecutive cases involving children (75 girls and 66 boys) with treatment-resistant epilepsy in whom primary VNS implantation was performed by the senior author between November 1997 and April 2008 and who had at least 1 year of follow-up since implantation. The patients' mean age at vagus nerve stimulator insertion was 11.1 years (range 1-18 years). Eighty-six children (61.0%) were younger than 12 years at time of VNS insertion (which constitutes off-label usage of this device).RESULTS: Follow-up was complete for 91.8% of patients and the mean duration of VNS therapy in these patients was 5.2 years (range 25 days-11.4 years). Seizure frequency significantly improved with VNS therapy (mean reduction 58.9%, $p < 0.0001$) without a significant reduction in antiepileptic medication burden (median number of antiepileptic drugs taken 3, unchanged). Reduction in seizure frequency of at least 50% occurred in 64.8% of patients and 41.4% of patients experienced at least a 75% reduction. Major (3) and minor (6) complications occurred in 9 patients (6.4%) and included 1 deep infection requiring device removal, 1 pneumothorax, 2 superficial infections treated with antibiotics, 1 seroma/hematoma treated with aspiration, persistent cough in 1 patient, severe but transient neck pain in 1 patient, and hoarseness in 2 patients. There was no difference in efficacy or complications between children 12 years of age and older (FDA-approved indication) and those younger than 12 years of age (off-label usage). Linear regression analyses did not identify any demographic and clinical variables that predicted response to VNS.CONCLUSIONS: Vagus nerve stimulation is a safe and effective treatment for treatment-resistant epilepsy in young adults and children. Over 50% of patients experienced at least 50% reduction in seizure burden. Children younger than 12 years had a response similar to that of older children with no increase in complications. Given the efficacy of this device and the devastating effects of persistent epilepsy during critical developmental epochs, randomized trials are needed to potentially expand the indications for VNS to include younger children.

Wheeler M, De Herdt V, Vonck K, et al.
Efficacy of vagus nerve stimulation for refractory epilepsy among patient subgroups: a re-analysis using the Engel classification.
***Seizure*. 2011;20(4):331-335.**
Optimal candidates for VNS as a treatment for refractory epilepsy have not been identified. In this retrospective two-center study, we used the Engel classification for evaluating seizure outcome, and tried to identify predictive factors for outcome by means of subgroup analysis. The medical records of patients who have been treated with VNS for at least one year at Dartmouth-Hitchcock Medical Center and Ghent University Hospital were evaluated. Seizure frequency outcome was assessed using the Engel classification for the study population as a whole, and for patient subgroups with regard to mental functioning, seizure type, predisposing factors for developing epilepsy, age at time of VNS implantation and epilepsy duration. 189 patients (102M/87F) were included in the study (mean FU: 41 months). 6% had a class I outcome (seizure-free), 13% a class II outcome (almost seizure-free), 49% a class III outcome (worthwhile improvement) and 32% had a class IV outcome (no improvement). When patients were divided into specific subgroups, a statistically significant better outcome was found patients with normal mental functioning ($p=0.029$). In our series, results for VNS are clearly inferior to resective surgery, but comparable to other treatment modalities for refractory epilepsy. With combined class I and II outcomes around 20%, and another 50% of patients having worthwhile improvement, VNS is a viable alternative when resective surgery is not feasible.

Bajbouj M, Merkl A, Schlaepfer TE, et al.
Two-year outcome of vagus nerve stimulation in treatment-resistant depression.
***J Clin Psychopharmacol*. 2010;30(3):273-281.**
One of the major goals of antidepressant treatment is a sustained response and remission of depressive symptoms. Some of the previous studies of vagus nerve stimulation (VNS) have suggested antidepressant effects. Our naturalistic study assessed the efficacy and the safety of VNS in 74 European patients with therapy-resistant major depressive disorder. Psychometric measures were obtained after 3, 12, and 24 months of VNS. Mixed-model repeated-measures analysis of variance revealed a significant reduction (P < or = 0.05) at all the 3 time points in the 28-item Hamilton Rating Scale for Depression (HRSD28) score, the primary outcome measure. After 2 years, 53.1% (26/49) of the patients fulfilled the response criteria (> or =50% reduction in the HRSD28 scores from baseline) and 38.9% (19/49) fulfilled the remission criteria (HRSD28 scores < or = 10). The proportion of patients who fulfilled the remission criteria remained constant as the duration of VNS treatment increased. Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study; no other deaths were reported. No statistically significant differences were seen in the number of concomitant antidepressant medications. The results of this 2-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with treatment-resistant depression.

Colicchio G, Policicchio D, Barbati G, et al.
Vagal nerve stimulation for drug-resistant epilepsies in different age, aetiology and duration.
***Childs Nerv Syst*. 2010;26(6):811-819.**
PURPOSE: The aim of the study was to compare the outcome with respect to age of implant, aetiology and duration of epilepsy.METHODS: One hundred thirty-five drug-resistant epileptic patients, excluded from ablative surgery, were submitted to vagal nerve stimulation (1995-2007). Aetiology was cryptogenic in 57 and symptomatic in 78 patients. Ages of implant were 0.5-6 years (18 patients), 7-12 years (32 patients), 13-18 years (31 patients) and more than 18 years (54 patients). Epilepsy types were Lennox-Gastaut (18 patients), severe multifocal epilepsy (33 patients) and partial (84 patients). Duration of epilepsy is 3 months to 57 years. Clinical outcome was determined by comparing the seizure frequency after stimulation at 3-6-12-18-24-36 months with the previous 3 months. “Responders” were the patients experiencing a seizure frequency reduction of 50% or more during follow-up. In statistical analysis, Wilcoxon and McNemar tests, general linear model for repeated measures, logistic regression and survival analysis were used.RESULTS: The seizure frequency reduction was significant in the group as a whole between baseline and the first follow-up (Wilcoxon test). The percentage of responder increases with time (McNemar test p = 0.04). Univariate analysis showed a significant effect of the age of implant on seizure frequency reduction: Adult patient had worst clinical outcome than children (p < 0.001) and adolescents (p = 0.08). Patients with severe multifocal epilepsy had better percentage seizure reduction compared with Lennox-Gastaut and partial (p = 0.03). Lesser duration of epilepsy had positive influence on outcome. Multivariate analysis confirmed age of implant to be the strongest factor influencing prognosis. Furthermore, positive is the association between lesional aetiology and young age.CONCLUSIONS: The best responder could be a young lesional epileptic patient; after 3 years of follow-up, the percentage of responders is still in progress.

Ghaemi K, Elsharkawy AE, Schulz R, et al.

Vagus nerve stimulation: outcome and predictors of seizure freedom in long-term follow-up.
***Seizure*. 2010;19(5):264-268.**
OBJECTIVES: To present long-term outcome and to identify predictors of seizure freedom after vagus nerve stimulation (VNS).METHODS: All patients who had undergone VNS implantation in the Epilepsy Centre Bethel were retrospectively reviewed. There were 144 patients who had undergone complete presurgical evaluation, including detailed clinical history, magnetic resonance imaging, and long-term video-EEG with ictal and interictal recordings. After implantation, all patients were examined at regular intervals of 4 weeks for 6-9 months. During this period the antiepileptic medication remained constant. All patients included in this study were followed up for a minimum of 2 years.RESULT: Ten patients remained seizure-free for more than 1 year after VNS implantation (6.9%). Seizures improved in 89 patients (61.8%) but no changes were observed in 45 patients (31.3%). The following factors were significant in the univariate analysis: age at implantation, multifocal interictal epileptiform discharges, unilateral interictal epileptiform discharge, cortical dysgenesis, and psychomotor seizure. Stepwise multivariate analysis showed that unilateral interictal epileptiform discharges (IEDs), P=0.014, HR=0.112 (95% CIs, 0.019-0.642), cortical dysgenesis P=0.007, HR=0.065 (95% CIs, 0.009-0.481) and younger age at implantation P=0.026, HR=7.533 (95% CIs 1.28-44.50) were independent predictors of seizure freedom in the long-term follow-up.CONCLUSION: VNS implantation may render patients with some forms of cortical dysgenesis (parietooccipital polymicrogyria, macrogyria) seizure-free. Patients with unilateral IEDs and earlier implantation achieved the most benefit from VNS.

Spuck S, Tronnier V, Orosz I, et al.
Operative and technical complications of vagus nerve stimulator implantation.
***Neurosurgery*. 2010;67(2 Suppl Operative):489-494.**
BACKGROUND: The treatment of refractory epilepsy by vagus nerve stimulation (VNS) is a well-established therapy option for patients not suitable for epilepsy surgery and therapy refractory depressions.OBJECTIVE: To analyze surgical and technical complications after implantation of left-sided VNS in patients with therapy-refractory epilepsy and depression.METHODS: One hundred five patients receiving a VNS or VNS-related operations (n = 118) from 1999 to 2008 were investigated retrospectively.RESULTS: At the time of operation, 84 patients were younger than 18 years, with a mean age of 10.5 years. Twenty (19%) patients had technical problems or complications. In 6 (5.7%) patients these problems were caused by the operation. The device was removed in 8 cases. The range of surgically and technically induced complications included electrode fractures, early and late onset of deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator.CONCLUSION: VNS therapy is combined with a wide spread of possible complications. Technical problems are to be expected, including electrode fracture, dislocation, and generator malfunction. The major complication in younger patients is the electrode fracture, which might be induced by growth during adolescence. Surgically induced complications of VNS implantation are comparably low. Cardiac symptoms and recurrent nerve palsy need to be taken into consideration.

Kabir SMR, Rajaraman C, Rittey C, et al.
Vagus nerve stimulation in children with intractable epilepsy: indications, complications and outcome.
***Childs Nerv Syst*. 2009;25(9):1097-1100.**

PURPOSE: To analyze the indication, complications and outcome of vagus nerve stimulation in intractable childhood epilepsy.MATERIALS AND METHODS: We retrospectively reviewed the data of 69 children who had insertion of vagal nerve stimulator (VNS) between June 1995 and August 2006 for medically intractable epilepsy. Outcome was based on the Engel's classification. Statistical analysis of the data was also done to see if any of the parameters significantly influenced the outcome.RESULT: Thirty-eight patients (55.08 %) had a satisfactory outcome (Engel class I, II or III), and in 31 patients (44.92 %), there was no worthwhile improvement of seizures (Engel class IV). There was no statistical significance between the type of seizure and outcome (Fisher's exact test, $p = 0.351$). Statistical analysis also showed that the following parameters did not significantly influence the outcome ($p > 0.05$): age at insertion of VNS, age of first fit, duration between first fit and insertion of VNS and the length of follow-up. Complications included infection, lead fracture, fluid collection around the stimulator, neck pain and difficulty swallowing.CONCLUSION: Vagus nerve stimulation is a relatively safe and potentially effective treatment for children with medically intractable epilepsy.

NEW RCTs (reverse chronological and then alphabetical order)

Aaronson ST, Carpenter LL, Conway CR, et al.
Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects.
***Brain Stimul*. 2013;6(4):631-640.**
BACKGROUND: Major depressive disorder is a prevalent, disabling, and often chronic or recurrent psychiatric condition. About 35% of patients fail to respond to conventional treatment approaches and are considered to have treatment-resistant depression (TRD).OBJECTIVE: We compared the safety and effectiveness of different stimulation levels of adjunctive vagus nerve stimulation (VNS) therapy for the treatment of TRD.METHODS: In a multicenter, double blind study, 331 patients with TRD were randomized to one of three dose groups: LOW (0.25 mA current, 130 µs pulse width), MEDIUM (0.5-1.0 mA, 250 µs), or HIGH (1.25-1.5 mA, 250 µs). A highly treatment-resistant population (>97% had failed to respond to ≥6 previous treatments) was enrolled. Response and adverse effects were assessed for 22 weeks (end of acute phase), after which output current could be increased, if clinically warranted. Assessments then continued until Week 50 (end of long-term phase).RESULTS: VNS therapy was well tolerated. During the acute phase, all groups showed statistically significant improvement on the primary efficacy endpoint (change in Inventory of Depressive Symptomatology-Clinician Administered Version [IDS-C]), but not for any between-treatment group comparisons. In the long-term phase, mean change in IDS-C scores showed continued improvement. Post-hoc analyses demonstrated a statistically significant correlation between total charge delivered per day and decreasing depressive symptoms; and analysis of acute phase responders demonstrated significantly greater durability of response at MEDIUM and HIGH doses than at the LOW dose.CONCLUSIONS: TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. Higher electrical dose parameters were associated with response durability.