Tables e-1 through e-3

Table e-1: Efficacy

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Alexopoulos, 2006[3]	N=46 Ages 2–18 years; median 12.1	Partial, generalized, and LG seizures included	Patient and family seizure diaries; median follow-up 2 years	As compared with baseline, median seizure frequency reduction in the setting of declining numbers was 56% at 3 months (n=46), 50% at 6 months (n=45), 63% at 12 months (n=39), 83% at 24 months (n=23), and 74% at 36 months (n=16); median follow-up was 2 years; no change in number of AEDs used before and after VNS	5	6
Benifla, 2006[4]	N=40 Ages 3–19 years; mean age 13	Partial epilepsy and LG seizures	Parental report; median follow-up 31 months	15 (41%) reported a >90% seizure frequency reduction, 3 more reported at least a 50% seizure frequency reduction for a total of 18 (45%); an additional 3 patients had a more than 25% but less than 50% seizure frequency reduction. However, 20 patients had no significant	Not reported	2

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
				seizure frequency change.		
Hallböök, 2005[5]	N=15 Ages 4–17 years, median 11	Partial with and without secondary generalization, generalized tonic-clonic, atonic, and atypical absence	Seizure diaries; AEDs stable during study period. Duration 9 months: VNS settings stable for the last 8 months of the study.	The seizure frequency decreased 50% or more in 6/15 children; seizure frequency decreased between 25% and 50% in 2 and decreased less than 25% in 4. Seizure frequency increased in 2 patients and was unchanged in 1. Median seizure frequency reduction was 65% (p = 0.02) at 3 months and 63% (p = 0.04) at 9 months.	1	None
Kang, 2006[6]	N=16 Ages 2 years 5 months to 17 years, 11 months; mean age 9 years 3 months	Partial epilepsy, secondary generalized, and 11 with LG seizures	Seizure diaries; duration of follow-up at least 12 months	>50% frequency reduction in 50% (8/16) of children; 5/16 had 90% seizure frequency reduction at last follow-up	2	None
Parain, 2001[17]	N=10 Ages 54-	Complex partial and generalized	Seizure diaries; meds could be	1 no change, 9 >50% seizure frequency reduction, 5/9 >90%;	None	None

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
	20; mean age 13, median age 15	tonic-clonic seizures associated with tuberous sclerosis	changed as needed during the study	follow-up was 6 months		
Rossignol, 2009[7]	N=28 Ages 3.5–21 years; no mean or median age available	Multiple seizure types; most very severe	Seizure diaries; AEDs unchanged for the first 6 months	75% (21/28) had >50% seizure frequency reduction at 6 months. 68% (19/28) had ≥50% reduction in seizure frequency, including 14% (4/28) who became seizure-free at 24 months follow-up.	4 at 24 months after implant; 1 patient with childhood absence, 1 patient with partial seizures of the frontal lobe, 1 patient with LGS, and 1 patient with Doose syndrome	None, but did not improve seizures in 2 patients

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Colicchio, 2010[11]	18 children implanted at ages 0–6 years, 32 at ages 7–12 years, 31 at ages 13–18 years, and 54 adults	Multiple seizure types, including severe multifocal epilepsy, LG seizures, and partial epilepsy	Seizure diaries; follow-up ranged from 6–36 months, with 121 patients at 12 months, 99 patients at 18 months, 87 patients at 24 months, and 78 patients at 36 months	3 months postimplantation overall seizure reduction of 38.2%, and the 50% responder rates at 3, 6, 12, 18, 24 and 36 months were 27.5%, 26.6%, 36.7%, 42.6%, 41.6%, and 49.2%, respectively. There was a statistically significant increase between 6 and 12 months (McNemar test p=0.04). The rate of seizure-free patients tended to increase over time: 2.4% at 12 months, 4.5% at 24 months, and 5.1% at 36 months.	2	None

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Majkowska-Zwolińska, 2012[12]	57 adolescents with epilepsy (mean age 11.4 ± 3.85 years; all were less than 18 years and 34 were less than 12 years)	Most with partial epilepsy	Seizure diaries; 2-year follow-up in 54 patients; AEDs were held stable in this study	52% seizure frequency reduction at 12 months and a 50% responder rate of 55% at 2 years	9.3% seizure free at 2 years	None

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Wheeler, 2011[13]	189 patients with mainly partial epilepsies (of which 45 were ≤ 20 years old)	Most with partial epilepsies	Seizure diaries used; at least 12 months of follow-up with a mean of 41 months; the results were evaluated in terms of Engel classifications	Of the 45 predominantly pediatric cases, 6 (13%) had a Class I or II outcome (no or rare disabling seizures), 17 (38%) had a Class III outcome (worthwhile improvement), and 22 (49%) had a Class IV outcome (no worthwhile improvement)	Not reported	Not reported

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Shahwan, 2009[8]	N=26 Age range 5–16 years, median age 11.8	Multiple seizure types	Seizure diaries	54% of patients responded to VNS with ≥50% seizure frequency reduction. Patients with LGS and tonic seizures had a higher responder rate; 78% (7 of 9 patients) ($p <$ 0.01). Follow-up minimum 18 months (up to 8.5 years; median 3 years).	None	4, 2 of whom also had adverse effects (aggravation of behavioral problems and side effects)
Zamponi, 2011[9]	N=39 Mean age 13 years,	Drop attacks in all patients, LGS in 14	Seizure diaries followed for 3 years; AEDs	17 had ≥50% frequency reduction at 1 year and 9 were unchanged. Two patients were	2	3

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
	range 2–51 years; including 3 patients over 18 years: ages 20, 30 and 51 years		unchanged	seizure free. The average reduction was 41% at 6 months, 50% at 12 months, and 54% at 36 months. Frequency of 50% responders was significantly greater in the non-LGS group (52%) compared to the LGS group (21%) (p=0.01).		
Sherman, 2008[10]	N=34 Mean age 12.3, range 3–18	16 partial, 17 generalized. 5 with LG	Seizure diaries; followed for 1 year	14 patients had >50% seizure frequency reduction and 1 was seizure free	1	Not reported
Elliott, 2011[14]	N=141 Mean age 11.1, age range 1–18; 86 patients under 12; 55 patients 12 or older	39% with multifocal partial epilepsy, 29% with symptomatic generalized epilepsy, 13.5% with idiopathic generalized epilepsy	Seizure logs; followed for mean of 5.2 years (range 25 days to 11.4 years)	Of the 128 patients who had follow-up data, 64.8% had >50% seizure frequency reduction	10 or 7.8% seizure free for at least 6 months at last follow-up	8
Pastrana, 2011[15]	N=13 Mean age 12, range	Various seizure types, however most patients had	Seizure diaries; followed for a minimum of 9	54% (7/13) had a 50% or greater reduction in seizure frequency; 3 patients had no	1	None

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
	6–18 years	generalized tonic-clonic and complex partial seizures	months	benefit		
Majoie, 2005[19]	N=19 Mean age 10.8 years, range 5.9–18.8	LG seizures	Patient report; AEDs unchanged in the first 12 months	21% (4/19) had seizure reduction of ≥50%, 20.6% reduction in seizure frequency at 12 months	1	None
Kostov, 2009[20]	N=30 Mean age 13 years, range 4–52; 18 were under 18 years	LG seizures	Patient report	Seizure frequency reduction rates for atonic seizures were 80.2% (8/12) and for tonic seizures were 73.3% (8/13) during a mean follow-up of 52 months. The frequency of disabling seizures fell from 77.5 monthly to 22.5 monthly. For generalized tonic-clonic seizures, 11/20 or 57.4% were responders. Numbers of AEDs used were significantly reduced during the study.	1	4
You, 2008[21]	N=10 Ages not provided	LG seizures	Seizure diaries; duration of follow-up 1–7 years	7/10 had >50% seizure frequency reduction; 2/10 had >75% seizure frequency reduction	None	None reported

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
Cersósimo, 2011[22]	N=20 Mean age 12.5, range 5–19 years	LGS	Seizure diaries; follow-up for 36 months	16/20 had at least a 50% seizure frequency reduction	None	None
Zamponi, 2011[18]	N=8 Mean age 10.28 years, range 5–25	Dravet syndrome	Seizure diaries used; 12-month follow-up	Mean seizure rate reduction of 12% at 3 months, 6% at 6 months, and 31% at 12 months	None	None reported
Zamponi, 2010[16]	N=11 Age range 2–35 years, median age 14; 2 subjects older than 19 years (ages 27 and 35)	Tuberous sclerosis	Seizure diaries used; 12-month follow-up	Mean seizure rate reduction of 43% at 3 months (median 40%), 52% at 9 months (median 50%), and 58% at 12 months (median 50%)	None	None reported
Elger, 2000[23]	N=11	Adult patients with complex partial epilepsy	Patients used self-rated scales; 3 and 6 months follow-up	Most scales and subscales at the 3-month follow-up improved ($p<0.05$). Mood improvements were sustained at the 6-month follow-up (9/11 subjects).		
Harden, 2000[24]	N=20	Adults with	Patients used	*t* tests for change in subject-		

Author, year	Population	Seizure types	Outcome assessment and study characteristics (including duration of study)	Seizure change	Seizure free	Number turned off and/or explanted due to lack of efficacy
		epilepsy	self-rated scales; 3-month follow-up	rated scales: Cornell Dysthymia Rating Scale improved (p = 0.001), Beck Depression Index improved (p = 0.045)		
Morris, 1999[25]	N=440	Adults with partial epilepsy	From phase III clinical trials; seizure diaries used	A ≥50% seizure reduction postimplantation occurred in 36.8% of patients at 1 year, in 43.2% at 2 years, and in 42.7% at 3 years. Median seizure reductions compared with baseline were 35% at 1 year, 44.3% at 2 years, and 44.1% at 3 years.		
Kuba, 2009[26]	N=90 Ages 13–64 years	Multiple seizure types	Patient diaries	>50% seizure frequency reduction in 41% at 1 year, in 53.2% of 87 patients at 2 years, and in 48.9% at 5 years		

AEDs = antiepileptic drugs; LG = Lennox-Gastaut; LGS = Lennox-Gastaut syndrome; VNS = vagus nerve stimulation.

Table e-2: Adverse effects in children

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
Alexopoulous, 2006[3]	N=46 Ages 2–18 years; median 12.1	Standardized forms to document reason for treatment withdrawal	5/4	56% experienced mild and transient symptoms such as hoarseness, throat pain, drooling, or cough that did not require device removal. These symptoms limited changes of the generator's stimulation settings in 3/46 patients (6.5%).	None
Benifla, 2006[4]	N=40 Ages 3–19 years; mean age 13	Chart review and parent report	2/1	13 patients reported voice change or cough and 1 reported pain. 1 patient had sleep problems and 3 had worsening behavior. Most were managed with adjusting VNS settings.	2 had the device removed due to adverse effects; 1 due to voice change and 1 due to pain
Hallböök, 2005[5]	N=15 Ages 4–17 years,	Families were specifically	None	4 with coughing and hoarseness, 1 with persistent pain in	Patient with persistent pain had VNS turned

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
	median 11	queried for adverse effects		neck, 1 with weight loss	off after study completion
Kang, 2006[6]	N=16 Ages 2 years 5 months to 17 years, 11 months; mean age 9 years 3 months	Not stated	1/none	1 with hoarseness and wound infection that required revision of the wound site, 1 with excessive salivation, 1 with dyspnea during sleep	1 patient had device explanted due to generator malfunction
Parain, 2001[17]	N=10 Ages 54-20; mean age 13, median age 15	Not stated	None/none	Coughing occurred in unspecified number of patients; 1 patient had temporary exacerbation of psychotic behavior shortly after implantation	None
Rossignol, 2009[7]	N=28 Ages 3.5–21 years; no mean or median age available	Not stated	2/2, but VNS was reimplanted within several months	68% (19/28) reported adverse effects, mostly throat pain, voice change, chest discomfort, local thoracic pain at site of VNS battery, dyspnea, coughing or mild dysphagia; 1	3; 2 for pain at site (both had VNS reimplanted within several months) and 1 patient with severe dysphagia

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
				severely disabled patient died from upper airway obstruction while eating unattended 2 months after VNS placement	
Colicchio, 2010[11]	18 children implanted at ages 0–6 years, 32 at ages 7–12 years, 31 at ages 13–18 years, and 54 adults		None reported	None reported	None reported
Majkowska-Zwolińska, 2012[12]	57 adolescents with epilepsy (mean age 11.4 ± 3.85 years; all were less than 18 years and 34 were less than 12 years)		None	Adverse effects included intermittent hoarseness of voice in 14 (25.0%), persistent hoarseness in 2 (3.6%), intermittent cough in 10 (17.9%), local pain and intermittent paresthesia in 9 (16.1%), intermittent	None

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
				dyspnea in 1 (1.8%), aggressive behavior in 2 (3.6%), and vomiting and dysphagia in 1 (1.8%)	
Wheeler, 2011[13]	189 patients with mainly partial epilepsies (of which 45 were ≤ 20 years old)		Not reported	Not reported	Not reported
Shahwan, 2009[8]	N=26 Age range 5–16 years, median age 11.8	Data collected on a diary	None/none	Throat discomfort in 3 patients, weight loss in 3 patients, and dyspnea in 1 patient. Transient left vocal cord paresis also occurred; however, the number of patients who experienced this was not reported. Behavioral problems occurred in 6 patients, 4 of whom became seizure free.	2 were explanted due to lack of efficacy but 1 also had behavioral problems and the other had weight loss

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
Zamponi, 2011[9]	N=39 Mean age 13 years, range 2–51 years; including 3 patients over 18 years: ages 20, 30 and 51 years	None stated	None/none	Mild transient "chronic side effect stimulation" occurred in an unspecified number of patients	1 who also had lack of efficacy
Zamponi, 2010[16]	N=11 Age range 2–35 years, median age 14; 2 subjects older than 19 years (ages 27 and 35)		None	1 patient had transient cough and vomiting during the first 3 months after the implant	None
Sherman, 2008[10]	N=34 Mean age 12.3, range 3–18	None stated	Not reported	Not reported	Not reported
Elliott, 2011[14]	N=141 Mean age 11.1, age range 1–18; 86 patients under 12; 55		4/1	85 patients were under age 12; 55 patients were age 12 or older. The adverse effects were presented in terms of this age	None

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
	patients 12 or older			cut-off. 2 patients below age 12 had neurologic complications (hoarseness and cough in 1 each); hoarseness was present in 1 child older than 12. No child under 12 had neck pain, but 1 child older than 12 had neck pain. 1 superficial infection treated with antibiotics occurred in both age groups, and 1 deep infection requiring removal occurred in the under 12 group. 1 seroma/hematoma and 1 pneumothorax occurred in the older than 12 group.	
Pastrana, 2011[15]	N=13 Mean age 12, range 6–18		1 surgical complication (a partial wound	None reported	None

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
	years		dehiscence treated with IV antibiotics and debridement)		
Majoie, 2005[19]	N=19 Mean age 10.8 years, range 5.9–18.8		None/none	Coughing in 4, tingling sensation in 2	None
Kostov, 2009[20]	N=30 Mean age 13 years, range 4–52; 18 were under 18 years		1/1	Drooling and voice alteration were the most frequent adverse effects (6/30); a single patient reported enuresis, light sensitivity, and fever	1 case of vocal cord paralysis occurred, with recovery after VNS was turned off, but eventually was explanted due to this effect
You, 2008[21]	N=10 Ages not provided		None/none	1 patient with dyspnea while sleeping and 1 with drooling	None
Cersósimo, 2011[22]	N=20 Mean age 12.5, range 5–19 years		2/1	Transient hoarseness in the majority	None
Smyth, 2003[e13]	N=74 Mean age 8.8		6/3 Infectious	2 with electrode fracture, 1 with	4 (5.4%) were removed for

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
	years, range 11 months–18 years with a minimum follow-up of 1 year and a mean follow-up of 2.2 years		surgical complications occurred in 6/74 or 7.1% overall, including deep infection in 3 (3.6%) which required explantation. 2 with superficial infection were treated with oral antibiotics and 1 was treated with IV antibiotics and surgical debridement.	ipsilateral vocal cord paralysis. 1 patient each reported hoarseness, cough, involuntary arm movement, inappropriate laughter, drooling, torticollis, and urinary retention. 1 of the 2 electrode fractures was thought to result from the child pulling at the surgical sites.	lack of efficacy and device intolerance, including symptomatic tachycardia, fever of unknown origin (1 each) and 2 with discomfort at the site
Kirse, 2002[e14]	102 patients (mean age 12 years 3 months, range 21 months–40 years with only 12 patients over age 18)		4/3 4 patients (4%) had wound infections (1 treated with IV antibiotics (no explantation); 1 treated with IV antibiotics eventually	1 patient had wound dehiscence from wrestling 9 days after implantation and was treated with IV then oral antibiotics. 5 patients (5%) had lead fracture. 4 of 46 patients who responded to a	None

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
			requiring explantation even after changing generator, 6 weeks later VNS was reimplanted successfully; 1 patient treated with antibiotics but eventually needed explantation and was reimplanted 2 months later; 1 patient treated with IV antibiotics, abscess eventually found thought to be due to patient scratching wound, device explanted and	follow-up questionnaire reported difficulty swallowing while the device was stimulating.	

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
			reimplanted 6 weeks later		
Kabir, 2009[e15]	N=69 Mean age 10.7 years, range 3–16 years		3/3 2 were implanted again later. 2 had fluid collections around the VNS treated with aspiration and antibiotics although the aspirates did not grow organisms. 1 of these required lead revision.	2 other cases had lead fracture. 1 patient died due to unrelated causes.	1 patient had difficulty swallowing and 1 had the VNS turned off due to persistent neck pain
Handforth, 1998[e16]	N=254 adult patients with refractory partial epilepsy (mean age 32, range 13–60 years)		3/3 (1.2%) 1 was reimplanted later in the study (time frame not specified)	The frequency of other adverse events was “dose” related, greater at the highest-tolerated stimulation intensity vs the lowest-perceptible stimulation intensity: voice alteration 47.4% vs. 9.7%, dyspnea 11.6% vs.	2

Author, year	Population	Method of obtaining adverse effects	No. wound infections/no. explanted due to wound infections	Other adverse effects	Explanted or turned off due to adverse effects
				1.0%, pharyngitis 15.8% vs. 3.9%	

VNS = vagus nerve stimulation.

Table e-3: Findings of case reports of complications from VNS use

Author, year	Complication	Description
Amark, 2007[32] **Iriarte, 2009**[33] **Borusiak, 2009**[34]	Late-onset bradycardia	2.4, 6, and 9 years post-implant, resolved with VNS discontinuation
Ali, 2004[35] **Asconape, 1999**[36] **Schuurman, 2009**[37] **Tatum, 1999**[38] **Ardesch, 2007**[39]	Intraoperative bradycardia and asystole during implantation and initiation	Patients with intraoperative asystole. only 1 continued VNS therapy; VNS later activated in both of the patients with intraoperative bradycardia
Sheck, 2011[40]	Episodic monocular blindness	Theorized as vasospasm of left common carotid artery; treated successfully by decreasing the VNS stimulus intensity
Cukiert, 2009[e1]	Extrapyramidal signs	Child with "double-cortex syndrome" treated for epilepsy. Reversed with VNS turned off and resumed when it was turned on; VNS effect on the basal ganglia theorized
St Louis, 2010[e2]	Sleep-related stridor	Young woman with epilepsy. Resolved with reduction of current intensity
Hajnšek, 2010[e3]	VNS-induced bronchospasm	
El Tahry, 2010[e4]	SUDEP	62-year-old woman 6 months post–VNS implant
Gerson, 2011[e5]	Mania	19-year-old woman with JME and a history of unipolar depression. Resolved with temporary VNS discontinuation; VNS resumed without mania exacerbation
Murr, 2011[e6]	New, disabling seizure type	51-year-old man with refractory partial epilepsy. After VNS discontinuation and medication changes, the new, recurrent seizures stopped
Spitz, 2010[e7]	Discontinuity in the silicone insulation over a VNS electrode	Current leak to the phrenic nerve caused diaphragmatic dysfunction, inability to vocalize, and severe radiating pain into the jaw and upper

Author, year	Complication	Description
		incisor for the duration of each stimulation. Device explanted; symptomatic relief; new device implanted
Marzec, 2003[e8] **Ebben, 2008[e9]**	Increase in AHI	16 patients, the average baseline AHI was 1.9, which increased to 4.2 after VNS activation[e8]; CPAP titration in a patient with obstructive sleep apnea could not be achieved in the presence of the patient's standard VNS on/off cycling mode[e9]
Chayasirisobhon, 2003[30] **Amar, 1999[e10]** **Kawai, 2002[e11]**	Other AEs	164 adult patients with partial epilepsy. At 21 months: Lead fracture (1.8%), transient voice alterations during stimulation (56%), unspecified pain (20%), headache (16%) (headache having not been reported previously at this rate[30]); headache rate of 4.5% found in a 3-year follow-up study[e10] 13 adults with partial epilepsy receiving long-term therapy. One patient found dead in the early morning of day 6 of therapy with no sign of seizure[e11]

AE = adverse effect; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; JME = juvenile myoclonic epilepsy; SUDEP = sudden unexpected death in epilepsy; VNS = vagus nerve stimulation.