

Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies

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ABSTRACT – *Aim.* We discuss the effectiveness, tolerability, and safety of vagus nerve stimulation (VNS) as adjunctive therapy in 64 paediatric patients with refractory epilepsies. *Materials and methods.* Sixty-four patients (34 male and 30 female) implanted with VNS for refractory epilepsy were analysed. Electroclinical features were compatible with Lennox-Gastaut syndrome in 46 patients, focal epilepsies in 10 patients, Dravet syndrome in three patients, epilepsy with myoclonic-astatic seizures in three patients, and West syndrome in two. The NeuroCybernetic Prosthesis (NCP) system (Cyberonics, Webster, TX, USA) was employed and the following stimulation parameters were used: output current of 1 to 2.5mA, signal frequency of 30Hz, signal pulse width of 500µs, and signal "on" and "off" times of 30 seconds and 5 minutes, respectively. *Results.* Of 46 patients with LGS, 30 cases showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. Ten patients with focal epilepsy, three patients with myoclonic-astatic seizures, two patients with Dravet, and two patients with West showed a significant improvement in seizure control, with a reduction in seizure frequency of at least 50%. A good clinical response was evident early and efficacy progressively improved with the duration of treatment up to 36 months. In a significant number of patients, reduced seizure severity and shorter recovery time and hospital stay were also observed. VNS was well tolerated in all patients. *Conclusion.* VNS is an effective and well-tolerated treatment for paediatric patients with refractory epilepsies, improving quality of life and neuropsychological performance.

Key words: epileptic encephalopathy, pediatrics, focal epilepsy, treatment, vagus nerve stimulation

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Vagus nerve stimulation (VNS) is an adjunctive therapy approved for use in adult and paediatric patients with drug-resistant epilepsy (Labar *et al.*, 1999; Rossignol *et al.*, 2009; Kabir *et al.*, 2009; Colicchio *et al.*, 2010; Coykendall *et al.*, 2010; Abd-El-Barr *et al.*, 2010; Elliott *et al.*, 2011a; Elliott *et al.*, 2011b). VNS has been also used for very young children (Zamponi *et al.*, 2008). The majority of adult patients treated with VNS have focal epilepsy, however, in children VNS is more often used in patients with symptomatic generalised epilepsy, including epileptic encephalopathies. A number of open case reports and uncontrolled studies of VNS have been published, suggesting possible benefits for patients with medically refractory seizures, including Lennox-Gastaut syndrome (LGS), and developmentally disabled or mentally retarded patients with epilepsy (Lundgren *et al.*, 1998; Parker *et al.*, 1999; Murphy *et al.*, 2000; Hosain *et al.*, 2000; Majoie *et al.*, 2001; Frost *et al.*, 2001; Helmers *et al.*, 2001; Benifla *et al.*, 2006; Buoni *et al.*, 2004).

Studies to date describe effects of VNS in terms of reduction of seizure frequency, diminished antiepileptic drug (AED) requirement, and improvement in overall quality of life (Schmidt and Bourgeois, 2000; Tatum *et al.*, 2001; Cramer *et al.*, 2001; McLachlan *et al.*, 2003; Sherman *et al.*, 2008; Mikati *et al.*, 2009). However, the therapeutic effects of VNS are in fact more significant and the benefits reported by patients are related to effects on seizure severity, postictal recovery, and termination of seizures (Shahwan *et al.*, 2009). Experience also suggests improved seizure control over time (Uthman *et al.*, 2004; Cersósimo *et al.*, 2011). Here, we discuss the effectiveness in terms of seizure frequency, seizure severity, recovery time, tolerability, and safety of VNS as adjunctive therapy in 64 paediatric patients with refractory epilepsy using a new classification for outcome (McHugh *et al.*, 2007).

Materials and methods

In this retrospective study, 64 patients implanted with VNS, as a result of refractory epilepsy, were analysed. The epileptic syndromes recognised were LGS in 46 patients, focal epilepsies in 10, Dravet syndrome (DS) in three, epilepsy with myoclonic-astatic seizures (EMAS) in three, and West syndrome (WS) in two patients. Twenty-six patients have been published previously (Cersósimo *et al.*, 2011).

The VNS device was implanted subcutaneously in the upper left side of the chest under general anaesthesia in sixty-two patients. Because the right vagus nerve has efferent projections to the sinoatrial node, the left vagus nerve is used for stimulation. The vagus nerve stimulator was implanted in the right

side in two patients due to a shunt for hydrocephalus implanted in the left hemisphere in one and severe infection of the device implanted in the left side in the other. The NeuroCybernetic Prosthesis (NCP) system (Cyberonics, Webster, TX, USA) was employed and the following stimulation parameters were used:

- output current:	1 to 2.5mA;
- signal frequency:	30Hz;
- signal pulse width:	500µs;
- signal "on" and "off" time:	30 seconds "on", 5 minutes "off";

The patients included in this study met the following criteria:

1. Refractory epilepsies including epileptic encephalopathy (Engel, 2001, 2006);
2. Epilepsy history of more than five years with seizures refractory to AEDs. In some cases, seizures were also refractory to the ketogenic diet and callosotomy;
3. Absence of progressive or systemic diseases.

Patients with severe swallowing difficulties, severe self-mutilating behaviour, congenital heart defects, or with poor parental collaboration were not included.

A three-month baseline frequency of seizures established before implantation was used for comparison with seizure frequency after implantation. Implantation included both a cervical incision for implanting the electrode and a subclavicular incision for implanting the stimulating unit.

Information was collected regarding each patient's pre-implantation history, seizures, implant, quality of life (QOL), and adverse events. Approval for the chart review was obtained as required at the institution.

QOL was assessed using the Quality-of-Life in Childhood Epilepsy Questionnaire (QOLCE) of the Child Epilepsy Questionnaire Parental Form (CEQ-P [III]) (Sabaz *et al.*, 2000). The QOL questionnaire responses were measured at baseline and after six months of VNS therapy.

Given the retrospective nature of the study, extensive chart review provided information on seizure frequency. Frequency of the seizures according to type was recorded as reported by the patient, parent, or guardian using a seizure diary and then combined to calculate each patient's average rate. After data collection, seizure records were carefully analysed across all patient visits to corroborate correct interpretation of the seizure counts. For the outcome measurement after VNS therapy, we used a classification system modelled on the Engel classification by McHugh *et al.* (2007).

Seizures were encoded according to the International League against Epilepsy classification (Commission, 1981). The antiepileptic therapy was not changed during the first six months after surgery, with the exception of one patient who had a status epilepticus.

Mental age was assessed using one of two different cognitive tests: the WISC III or the Terman-Merrill scales.

Aetiology of the type of epilepsy and epileptic syndrome were also considered. The aetiologies of the symptomatic cases were: perinatal injury in 20, malformations of cortical development in 12, sequelae of encephalitis in 12, hypothalamic hamartoma in one, and Aicardi's syndrome in one.

Interictal and ictal EEG findings were analysed in all patients. Video-EEG recordings were performed in 60 patients, however, video-EEG monitoring was not routinely performed at various stages of the trial. The video-EEG data were only used to accurately classify the type of epilepsy.

All patients had been treated with at least two AEDs in different combinations with unsuccessful results before VNS placement.

The follow-up visits took place every two months to assess the degree of tolerance and clinical efficacy of VNS.

The intensity of stimulation, beginning at 0.50mA, was increased by steps of 0.50mA until the stimulation parameters reached 2mA at a frequency of 30 c/s, with an "off" period of five minutes alternating with an "on" period of 30 seconds (standard stimulation setting). In 16 patients, the standard stimulation setting was switched to an intermediate stimulation pattern ("on" period of 30 seconds and "off" period of three minutes) after six months following an initial unsatisfactory clinical response. The intensity of magnetic stimulation, beginning at 0.50mA, was increased by steps of 0.25mA until the stimulation parameters reached 2mA.

Lennox-Gastaut syndrome

Forty-six patients, 26 male and 20 female, showed the typical electroclinical pattern of the syndrome. Twelve of these patients had had epileptic spasms in the first year of life.

All but one patient had multiple seizures. Overall, mean seizure frequency was always very high. All patients presented with mental retardation, which was severe in 17 and moderate in three. A focal motor deficit was found in eight patients. Seven patients had previously had palliative surgery (callosotomy) without good results.

Mean age at implant operation was 13 years (range: 5-19.5 years), with a mean epilepsy duration of 10.5 years. The mean follow-up time was 30 months (range: 12-108 months).

Focal epilepsies

Ten patients, six female and four male, had focal epilepsies, which were symptomatic in nine. Mean age at

implant operation was 17 years (range: 13-19 years), with a mean epilepsy duration of 12.5 years. The mean time of follow-up was 30 months (range: 12-60 months).

Dravet syndrome

Three patients, two male and one female, had characteristic electroclinical features of DS. All three patients had multiple and daily seizures, severe mental retardation, and behavioural disturbances. VNS was implanted at 13, 14, and 16 years of age and the mean time of follow-up was 23, 26, and 30 months, respectively.

Epilepsy with myoclonic-astatic seizures

Two male and one female patient had electroclinical features compatible with EMAS. Two patients had daily seizures and one had weekly seizures. All three patients presented with severe mental retardation and behavioural disturbances. VNS was implanted at 13.5, 15, and 17 years of age and the mean time of follow-up was 28, 34, and 40 months, respectively.

West syndrome

Two female patients had electroclinical features compatible with WS. Both patients had daily seizures and presented with severe mental retardation and behavioural disturbances. VNS was implanted at 5.5 and 6 years of age and the mean time of follow-up was 20 and 24 months, respectively. These two patients had epileptic spasms in clusters associated with modified hypsarrhythmia when the VNS device was implanted.

Results

Thirty-six males and 32 females implanted with VNS were included in the study. Mean age at implant operation was 14 years (range: 5-19.5 years) with a mean epilepsy duration of 9.5 years. The mean follow-up time was 32 months (range: 12-108 months).

Effectiveness

The children were discharged 48-72 hours after implant surgery. On post-operative day 14, the VNS device was switched on and the patients were periodically controlled as outpatients.

Data were available for all patients and patients were analysed according to their type of epileptic syndrome. As the study was retrospective, it was not possible to compare the percentage change in seizure frequency

between baseline and after treatment for the level of stimulation. In patients with LGS and EMAS who responded well to VNS, drop-attack seizures decreased. In DS patients with positive results, all types of seizures decreased. In the LGS group, we did not find differences between the symptomatic and cryptogenic patients either in terms of the severity of mental retardation or seizure reduction, or differences between those patients who had previously had West syndrome (WS) and those who had not. In patients with focal epilepsies, focal seizures decreased. Effectiveness of VNS according to epileptic syndrome is summarised in *table 1* and according to seizure type is summarised in *table 2*.

Therapy

Over a follow-up of between 12 and 108 months, the number of AEDs was reduced in 13/64 children, while the dose was reduced in ten without compromising seizure control. Ten patients received psychotropic medications for concomitant behavioural disturbances and these pharmacotherapies were subsequently discontinued in four children. Two patients responded well to the combination of VNS and zonisamide; for one of these patients with LGS and a seizure reduction of 80%, zonisamide was added leading to complete seizure control.

Neuropsychological outcome

Comparing the changes in QOL questionnaire responses at baseline and after six months of VNS therapy, all patients except three showed a significant improvement in behavioural disturbances and cognitive abilities related to seizure and AED reduction and the severity of mental retardation pre-VNS. The patients also showed improvement with regards to energy levels, social aspects, and fear of seizures. The cognitive test showed that all patients who responded well to VNS had improved mental age.

Side effects

The surgical implantation of the device was well tolerated in all patients without significant complications. In three patients, transient pain was reported at the neurostimulator implantation site. Sixteen patients complained of hoarseness and coughing during the setting phase when the stimulation parameters were increased. Both these side effects disappeared within one to two days after stimulation adjustments. A change in vocal timbre was reported in all patients except one during the stimulation period, however, this was not considered a significant problem. Two patients presented with an infectious complication; in one the device was changed to the right side. No other significant side effects were observed in this series of patients. One patient of our series died due to pneumonia.

Discussion

In this study of VNS, in addition to the positive results for epileptic encephalopathies, we observed good seizure control in patients with focal epilepsies. In patients implanted with VNS, there may be a change in the severity of seizures. Therefore, even when seizure frequency is only slightly reduced, QOL may improve considerably due to fewer episodes of status epilepticus resulting in less visits to the hospital and more seizure-free days (Shahwan *et al.*, 2009). Thus, VNS therapy may have a direct positive effect on mood, behaviour, and attention, often independently of seizure reduction.

According to the modified Engel score (McHugh *et al.*, 2007), our study shows that 48.5% of the patients had a reduction in seizure frequency of 80% or more. The results of VNS treatment in the children in our series support those of earlier reports (Lundgren *et al.*, 1998; Murphy *et al.*, 2000; Schmidt and Bourgeois, 2000; Schermann *et al.*, 2001; Rychlicki *et al.*, 2006). It is interesting to note that, similar to other series

Table 1. Effectiveness of VNS in a series of 64 patients with refractory epilepsy.

Epileptic syndrome	Total	Class 1A	Class 1B	Class 2A	Class 2B	Class 3A	Class 3B	Class 4	Class 5
LGS	46	28	0	12	0	6	0	0	0
Focal epilepsy	10	3		4	0	3	0	0	0
DS	3	0	0	1	0	1	0	0	1
EMAS	3	0	0	2	0	1	0	0	0
WS	2	0	0	1	0	1	0	0	0

The number of patients are summarised as a function of epileptic syndrome and class.

LGS: Lennox-Gastaut syndrome; DS: Dravet syndrome; EMAS: myoclonic-astatic seizures; WS: West syndrome.

Table 2. Effectiveness of VNS according to seizure type in a series of 64 patients.

Epileptic syndrome	Focal seizures	Tonic seizures	AA	Drop attacks	SGTCS	Myoclonic seizures	ES	GTCS
LGS	+	+++	++	+++	No SGTCS	No Myoclonic seizures	+	No GTCS
Focal epilepsy	+++	No tonic seizures	No AA	No drop attacks	+++	+	No ES	No GTCS
DS	+	No tonic seizures	+	No drop attacks	+	++	No ES	No GTCS
EMAS	No focal seizures	No tonic seizures	++	++	No SGTCS	++	No ES	+
WS	No focal seizures	No tonic seizures	No AA	No drop attacks	No SGTCS	+	++	No GTCS

AA: atypical absences; SGTCS: secondary generalised tonic-clonic seizures; ES: epileptic spasms; GTCS: generalised tonic-clonic seizures; +++: very good seizure control; ++: good seizure control; +: regular seizure control. LGS: Lennox-Gastaut syndrome; DS: Dravet syndrome; EMAS: myoclonic-astatic seizures; WS: West syndrome.

published, patients who experienced a > 80% seizure reduction account for the largest group (Rychlicki *et al* 2006; Alexopoulos *et al.*, 2006). None of our patients became completely seizure-free. Results in the literature show that only 2-3% of all treated patients become seizure-free while around 20% have a seizure reduction of >75% (Ben-Menachem *et al.*, 1999; Ben-Menachem, 2002; Boon *et al.*, 2001) and 41.4% of patients experience a seizure reduction of at least 75% (Elliott *et al.*, 2011a; Elliott *et al.*, 2011b).

This study supports our previous observation that VNS is also effective and safe in children with epileptic encephalopathies. The present series includes patients with LGS, DS, EMAS, and WS. Paediatric VNS series are often heterogeneous including different types of epileptic syndromes, however, studies of patients with epileptic encephalopathies, mainly LGS, have previously been published (Parker *et al.*, 1999; Murphy *et al.*, 2000; Hosain *et al.*, 2000; Majoie *et al.*, 2001; Frost *et al.*, 2001). Several studies have shown that VNS produces satisfactory seizure control in patients with LGS, while others have failed to do so (Parker *et al.*, 1999; Labar, 2000; Rychlicki *et al.*, 2006; Abd-El-Barr *et al.*, 2010). VNS was found to be more effective in patients with symptomatic LGS in one study (Rychlicki *et al.*, 2006). Effectiveness also depends on the severity of mental retardation (Majoie *et al.*, 2001; Rychlicki *et al.*, 2006). Currently, VNS is considered the treatment of choice for LGS patients as it is less invasive than callosotomy, is reversible and has few serious side effects (Frost *et al.*, 2001; You *et al.*, 2008). In our series, seizure control was no better in LGS patients treated with VNS who had had a previous callosotomy than in those who did not have a previous callosotomy.

It is worth mentioning that one patient in our series with LGS associated with hypothalamic hamartoma, as well as two patients with double-cortex dysplasia, had an excellent response to VNS. Another patient with hypothalamic hamartoma treated with VNS was published by Murphy *et al.* (2000). In patients with refractory LGS, VNS associated with the ketogenic diet may be a rational polytherapy (Kossoff *et al.*, 2007). We did not find a good synergic effect between VNS and levetiracetam (Werz and Smith, 2001). These findings should be confirmed by studies with larger numbers of patients. Since patients with LGS had WS in the first years of life and one of the patients with WS responded well to VNS, we consider that an earlier VNS implant may be beneficial for patients with refractory epileptic spasms.

In our series, a good response was achieved early after the device was implanted and improved gradually confirming the cumulative effect of VNS (De Giorgio *et al.*, 2000; Aldenkamp *et al.*, 2002; Schachter, 2002; Wilder *et al.*, 2004). This early good response to VNS may have been obtained with a non-therapeutic amplitude of stimulation. This observation has recently been suggested (Rychlicki *et al.*, 2006) and supports the idea that, at least for paediatric patients, intensities of stimulation lower than those commonly used in clinical practice in adults may be therapeutic. However, the role of the stimulation parameters has not been clearly defined so far.

The majority of our patients improved in terms of behavioural disturbances, cognitive abilities, and quality of life. Similar results have been described in the literature (Majoie *et al.*, 2001; Hallbrook *et al.*, 2005; Sherman *et al.*, 2008; Mikati *et al.*, 2009).

As in other series, the side effects of short and long-term VNS were mild (De Giorgio *et al.*, 2000; Aldenkamp *et al.*, 2002; Schachter, 2002). The most common side effects, such as coughing, hoarseness, and voice alteration, are related to the stimulation of the device and usually improve and disappear progressively. In only two cases were infectious reactions to the device observed.

Based on the outcome in these patients with particular focus on the epileptic syndromes, we believe that VNS is an important alternative option for patients with refractory epileptic encephalopathies and focal epilepsy (Parker *et al.*, 1999; Hosain *et al.*, 2000; Majoie *et al.*, 2001; Frost *et al.*, 2001; Buoni *et al.*, 2004; De Giorgio *et al.*, 2000; Aldenkamp *et al.*, 2002; Schachter, 2002; Rossignol *et al.*, 2009; Kabir *et al.*, 2009; Colicchio *et al.*, 2010; Coykendall *et al.*, 2010; Abd-El-Barr *et al.*, 2010; Elliott *et al.*, 2011a; Elliott *et al.*, 2011b).

Conclusions

VNS is an effective treatment for patients with refractory epileptic encephalopathies and focal epilepsies and effectiveness is also shown for different types of epileptic seizures.

In our series of patients with LGS, an important number of cases showed a significant improvement in seizure control, with a reduction in seizure frequency.

We also found a significant improvement in seizure control, with a reduction in seizure frequency of at least 50% in patients with DS, EMAS, and WS.

Additionally, VNS should be considered in patients with hypothalamic hamartoma, double-cortex dysplasia and refractory epilepsy.

A good clinical response was evident at an early stage and effectiveness progressively improved with the duration of treatment up to 40 months.

QOL and neuropsychological performance improved in patients who not only had a reduction in seizure frequency, but also in the severity of the seizures.

The classification by McHugh is useful to measure the outcome after VNS therapy beyond seizure frequency reduction alone. Use of the classification will allow for better comparisons between future studies of VNS therapy. □

Disclosure.

None of the authors has any conflict of interest to disclose.

References

Abd-El-Barr MM, Joseph JR, Schultz R, Edmonds JL, Wilfong AA, Yoshor D. Vagus Nerve Stimulation for drop attacks in a pediatric population. *Epilepsy Behav* 2010; 19: 394-9.

Aldenkamp AP, Majoie HJM, Berfelo MW, *et al.* Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. *Epilepsy Behav* 2002; 3: 475-9.

Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bindaman WE. Long-term results with vagus nerve stimulation in children with pharmaco-resistant epilepsy. *Seizure* 2006; 15: 491-503.

Ben-Menachem E, Hellstrom K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology* 1999; 52: 1265-7.

Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol* 2002; 1: 477-82.

Benifla M, Rutka JT, Logan W, Donner EJ. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at the Hospital for Sick Children. *Childs Nerv Syst* 2006; 22: 1018-26.

Boon P, Vonck K, De Reuck J, Camaert J. Vagus nerve stimulation for refractory epilepsy. *Seizure* 2001; 10: 448-55.

Buoni S, Zannolli R, Macucci F, *et al.* Delayed response of seizures with vagus nerve stimulation in Lennox-Gastaut syndrome. *Neurology* 2004; 63: 1539-40.

Cersósimo R, Bartuluchi M, De Los Santos C, Bonvehi I, Pomata H, Caraballo R. Vagus Nerve Stimulation: effectiveness and tolerability in patients with epileptic encephalopathies. *Childs Nerv Syst* 2011; 27: 787-92.

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: 811-9.

Commission on classification and terminology of the International League Against Epilepsy. "Proposal for revised clinical and electroencephalographic classification of epileptic seizures". *Epilepsia* 1981; 22: 489-501.

Coykendall DS, Gauderer MW, Blouin RR, Morales A. Vagus Nerve Stimulation for the management of seizures in children: an 8-year experience. *J Pediatr Surg* 2010; 45: 1479-83.

Cramer J, Ben Menachen E, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res* 2001; 47: 17-25.

De Giorgio CM, Schachter SC, Salinsky M, Thompson J. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia* 2000; 41: 1195-2000.

Elliott RE, Rodgers SD, Bassani L, *et al.* Vagus Nerve Stimulation for children with treatment-resistant epilepsy. Consecutive series of 141 cases. *J Neurosurg Pediatr* 2011a; 7: 491-500.

Elliott RE, Morsi A, Kalthorn SP, *et al.* Vagus nerve Stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav* 2011b; 20: 57-63.

Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; 42: 796-803.

- Engel J Jr. Report of the ILAE classification core group. *Epilepsia* 2006; 47: 1558-68.
- Frost M, Gates J, Helters S, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut Syndrome. *Epilepsia* 2001; 42: 1148-52.
- Hallbook T, Lundgren J, Stjenqvist K, Blennow G, Stromblad LG, Rosen I. Vagus nerve stimulation in 15 children with therapy resistant epilepsy: its impact on cognition, quality of life, behaviour and mood. *Seizure* 2005; 14: 504-13.
- Helters SL, Wheless JW, Frost M, et al. Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. *J Child Neurol* 2001; 16: 843-8.
- Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol* 2000; 15: 509-12.
- Kabir SM, Rajaraman C, Rittey C, Zaki HS, Kemeny AA, McMullan J. Vagus Nerve Stimulation in children with intractable epilepsy: indications, complications and outcome. *Childs Nerv Syst* 2009; 25: 1097-100.
- Kossoff E, Pyzik P, Rubenstein J, et al. Combined ketogenic diet and vagus nerve stimulation: rational polytherapy? *Epilepsia* 2007; 48: 77-81.
- Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS study Group. *Neurology* 1999; 52: 1510-2.
- Labar D. Vagus nerve stimulation for intractable epilepsy in children. *Dev Med Child Neurol* 2000; 42: 496-9.
- Lundgren J, Amark P, Blennow G, Strombald LG. Vagus nerve stimulation in 16 patients with refractory epilepsy. *Epilepsia* 1998; 9: 809-13.
- Majoie HJM, Berfelo MW, Aldenkamp AP, Evers SMAA, Kessels AGH, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome. *J Clin Neurophysiol* 2001; 18: 419-28.
- McHugh J, Singh H, Philips J, Murphy K, Doherty C, Delenty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. *Epilepsia* 2007; 48: 375-8.
- McLachlan RS, Sadler M, Pillay N, Guberman A, Wiebe S, Schneiderman. Quality of life after vagus nerve stimulation for intractable epilepsy: Is seizure control the only contributing factor? *Eur Neurol* 2003; 50: 16-9.
- Mikati MA, Ataya NF, El-Ferezli JC, et al. Quality of life after vagal nerve stimulation insertion. *Epileptic Disord* 2009; 11: 67-74.
- Murphy JV, Wheless JW, Schmoll CM. Left nerve vagal stimulation in six patients with hypothalamic hamartomas. *Pediatr Neurol* 2000; 23: 167-8.
- Parker APJ, Polkey CE, Binnie CD, Madigan NP, Ferrie CD, Robinson LA. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics* 1999; 103: 778-821.
- Rossignol E, Lortie A, Thomas T, et al. Vagus Nerve stimulation in pediatric epileptic syndromes. *Seizure* 2009; 18: 34-7.
- Rychlicki F, Zamponi N, Trignani R, Ricciuti R, Iacoangeli M, Scerrati M. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients. *Seizure* 2006; 15: 483-90.
- Sabaz M, Cairns DR, Lawson JA, et al. Validation of a new quality of life measure for children with epilepsy. *Epilepsia* 2000; 41: 765-74.
- Schachter S. Vagus nerve stimulation therapy summary: five years after FDA approval. *Neurology* 2002; 59: 15-20.
- Schermann J, Hope C, Kral T, Scramm J, Elger CE. Vagus nerve stimulation. Clinical experience in a large patient series. *J Clin Neurophysiol* 2001; 18: 408-14.
- Schmidt D, Bourgeois B. A risk-benefit assessment of therapies for Lennox-Gastaut syndrome. *Drug Saf* 2000; 22: 467-77.
- Shahwan A, Bailey C, Maxiner W, Harvey S. Vagus Nerve Stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *Epilepsia* 2009; 50: 1220-8.
- Sherman EM, Connolly MB, Slick DJ, Eylr KL, SteinbokP KL, Farrell K. Quality of life and seizure outcome after vagus nerve stimulation in children with intractable epilepsy. *J Child Neurol* 2008; 23: 991-8.
- Tatum WO, Johnson KD, Goff S, Ferreira JA, Vale FL. Vagus nerve stimulation and drug reduction. *Neurology* 2001; 56: 561-3.
- Uthman BM, Reichl AM, Dean JC, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: A 12-year observation. *Neurology* 2004; 63: 1124-6.
- Werz MA, Smith J. Response to vagus nerve stimulation predicts response to levetiracetam. *Epilepsia* 2001; 42(Suppl.7):188.
- Wilder BJ. Effectiveness of vagus nerve stimulation in epilepsy patients. a 12-year observation. *Neurology* 2004; 63: 1124-6.
- You S, Kang H, Ko T, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *Brain Dev* 2008; 30: 195-9.
- Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus Nerve Stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. *Neurosurg Rev* 2008; 31: 291-7.