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Single-center long-term results of vagus nerve stimulation for epilepsy: A 10–17 year follow-up study

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ABSTRACT

Purpose: The paper presents a long-term follow-up study of VNS patients, analyzing seizure outcome, medication changes, and surgical problems.
Method: 74 adults with VNS for 10 to 17 years were evaluated yearly as: non-responder – NR (seizure frequency reduction <50%), responder – R (reduction ≥ 50% and <90%), and 90% responder – 90R (reduction ≥ 90%). Delayed R or 90R (≥ 4 years after surgery), patients with antiepileptic medication changes and battery or complete system replacement were identified. Statistical analysis of potential outcome predictors (age, seizure duration, MRI, seizure type) was performed.
Results: The rates of R and 90R related to the patients with outcome data available for the study years 1, 2, 10, and 17 were for R 38.4%, 51.4%, 63.6%, and 77.8%, and for 90R 1.4%, 5.6%, 15.1%, and 11.1%. The absolute numbers of R and 90R increased until years 2 and 6. Antiepileptic therapy was changed in 62 patients (87.9%). There were 11 delayed R and four delayed 90R, with medication changes in the majority. At least one battery replacement was performed in 51 patients (68.9%), 49 of whom R or 90R. VNS system was completely replaced in 7 patients (9.5%) and explanted in 7 NR (9.5%). No significant predictor of VNS outcome was found.
Conclusions: After an initial increase, the rate of R and 90R remains stable in long-term follow-up. The changes of antiepileptic treatment in most patients potentially influence the outcome. Battery replacements or malfunctioning system exchange reflect the patient's satisfaction and correlate with good outcomes.

1. Introduction

Since the first implantation in humans in 1988 and Food and Drug Administration (FDA) approval in 1997, vagus nerve stimulation (VNS) has become an accepted palliative treatment modality for patients with drug-resistant epilepsy not suitable for resective surgery. The effect of VNS on seizure frequency and severity was confirmed by randomized controlled trials [1,2,3,4]. However the follow-up period in the first three studies did not exceed 26 weeks [1,2,3]. The last paper, a metanalysis of 74 studies with 3321 enrolled patients, proved a significant reduction of seizures at 3–12 months after surgery (36%) and an increasing effect of VNS on seizure reduction at >1year after surgery [4]. Other studies confirm a cumulative effect of VNS in medium-duration follow-up. For example, the median seizure reduction in 454 patients enrolled in five double-blind US studies improved from 35% to 44% at two years [5]. Similarly, a European study confirmed that treatment duration was significantly correlated with the percentage of seizure frequency reduction [6]. With increased experience, studies reporting post-VNS outcomes for up to 5 years [7,8] and studies covering follow-up periods exceeding 10–11 years have been published [9,10,11,12]. The effect of VNS on seizure reduction has been discussed in combination with other aspects of VNS: post-VNS quality of life [12] and surgical problems [9].

Abbreviations: FDA, food and drug administration; VNS, vagus nerve stimulation; ILAE, international league against epilepsy; MRI, magnetic resonance imaging; NR, non-responder; R, responder; 90R, 90% responder; DBS, deep brain stimulation.

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The first aim of the study is to present the results of VNS systems implanted for ≥ 10 years in patients with drug-resistant epilepsy followed in a specialized epilepsy center in a longitudinal time axis. The effect of VNS on seizure reduction is quantified yearly in terms of responder rates for the entire study period from stimulation onset to study completion. There were marked developments in the field of antiepileptic drugs during the study period. In terms of new medications during the study period (January 2000–November 2017), the date of levetiracetam registration was 29 Sept 2000, for zonisamide 10 Mar 2005 and for pregabalin 6 July 2004. The impact of medication changes during the follow-up period on seizure outcome is also studied, particularly in patients with late or delayed VNS response.

The satisfaction with VNS treatment can be quantified by sophisticated scales evaluating the different aspects of the quality of life [13], but a simple criterion – the frequency of battery replacement after depletion (indicating the patient's or the physician's will to continue VNS therapy in mutual agreement) – can provide a simplified answer. Moreover, surgical problems with the implanted system require revision and replacement and the rate of patients willing to undergo the surgery to continue the VNS therapy during the prolonged follow-up period also provide data about patient satisfaction with the results. Therefore the second aim of the study is the analysis of surgical problems of long-term VNS, with attention to reoperations and system complications in the long-term follow-up period, for which there are only a few comparable papers [10,12]. Finally statistical analysis of potential long- term VNS outcome predictors was performed; unfortunately there are currently no universally accepted outcome predictors for VNS. However, based on previously published papers aiming to find VNS outcome predictors, age, seizure duration, age at seizure onset, MRI findings (diffuse, focal, mesiotemporal sclerosis and negative) and the prevailing seizure type (complex partial seizure – focal aware – ILAE 2017, simple partial seizure – focal impaired awareness – ILAE 2017, and other), were selected as potential predictors for statistical analysis [4,14–16].

2. Material and methods

Adult patients (age ≥ 18 years) with VNS systems (Cyberonics, Inc., Houston, Texas, USA) implanted at the author's department for ≥ 10 years ago were retrospectively identified from a prospectively constructed database of the patients who had surgery for drug-resistant epilepsy at the comprehensive Brno Epilepsy Center. Prior to VNS implantation, all patients underwent a detailed preoperative investigation at the center and were ruled out as suitable candidates for resective epilepsy surgery. After standard implantation of the left vagus nerve stimulation system (ZN, JC), all the patients were followed at the First Department of Neurology at regular intervals (2, 4, 6, 12 and 18 months; then yearly). VNS parameter adjustments and modifications of antiepileptic medication were made strictly according to the clinical decision of the epileptologist.

Based on post-VNS seizure reduction, the patients were graded at the follow-up visits as non-responders – NR (seizure frequency reduction <50%), responders – R (reduction ≥ 50% and <90%), or 90% responders – 90R (reduction ≥ 90%). When the VNS system was switched off due to a response that was not clinically relevant, the patient was moved to the "stimulation off" category and remained there until the end of the follow-up period; other patients were categorized as having had system explantation ("explantation"), as lost to follow-up care ("patient lost"), or as having died for any reason ("dead"). Missing data for a single follow-up visit moved the patient to the "data missing" category for that particular follow-up point. Patients with late response to VNS (shifting from the NR category to the R category, or from the R to the 90R category at ≥ 4 years after surgery), as well as patients with fluctuating or worsening response to VNS during the follow-up period, were identified. The percentages of R, 90R, and Good outcomes (R + 90R) for each study year were related to all the patients with follow-up results available for the defined study year (excluding patients categorized as "dead", "data missing", or "lost").

The medical reports of late responders were checked for medication changes during the year prior to the improved response. The percentage of patients with medication changes (including permanent dosage changes) during the follow-up period was also calculated.

Patients with battery replacement during the follow-up period were identified from the database and confirmed from surgical reports. Similarly, patients requiring complete VNS system replacement (including the helical electrode) were identified, and the cause of system failure was determined from the surgical report. The rates of 90R and Good outcomes were selected as the endpoints of the statistical analysis. The time points for analysis were defined at year 10 and final follow up. Absolute and relative frequencies were accepted for the description of endpoints occurrence. Logistic regression was used for the analysis of relation between predictors and endpoints; odds ratios, their 95% confidence intervals and statistical significance were used for the description of this relationship.

3. Results

The study included 74 adult patients (33 males, 41 females) who had VNS implanted between January 2000 and November 2007. The mean patient age at implantation was 31.1 years (range 18–59 years; standard deviation 10.65 years). There was a history of previous neurosurgical operations in 20 patients (simple lesionectomies in six patients, failed extratemporal or temporal resections in four patients, stereotactic lesional surgeries in seven patients, stereoelectroencephalography not providing adequate data for resective surgery in three patients). Two patients had brain hypothermia. The first case was a 35-year-old male with seizure onset at the age of 2 years (frontal absences with secondary generalization). Hypothermic treatment was administered at the age of 17 years, but without effect on seizure frequency or severity. MRI showed gliotic changes after ventricular punctures. Because the investigations failed to localize the epileptogenic focus, the patient had VNS system implanted, and was categorized as a Responder. The second patient (a 37-year-old male) was treated at another department for multifocal epileptic seizures by stereotactic surgeries (coagulation of the right Forel field, rostral cingulum, and right thalamic nuclei) and with brain hypothermia. After VNS, he was graded as 90R.

Six patients were lost to follow-up before study year 10 (one 90R and five R at the last follow-up). Two patients died before study year 10 (one NR suffered a severe brain injury after epileptic seizure and one NR due to malignant retroperitoneal tumor). The outcome data at the year 10 follow-up visits were available for 66 patients.

Follow-up data of patients with VNS implanted for 17 years were available for nine patients (two patients were lost to follow up; one patient died from neurodegenerative disease).

During the whole study period, there were 8 patients lost to follow-up care (one 90R and 7 R at the last follow-up). Five patients died during the follow-up period. In three patients, the cause of death was unrelated to epilepsy (retroperitoneal malignancy, urinary bladder cancer, and neurodegenerative disease). In one patient, the death was related to epilepsy: a fatal brain injury caused by a fall during an epileptic seizure. The possibility of SUDEP could not be excluded in one patient who reportedly died from heart failure.

Table 1
VNS outcomes – years 1–9.

Study Year	1	2	3	4	5	6	7	8	9
NR	44	30	28	21	16	11	10	9	6
R	28	37	37	36	36	37	38	38	41
90R	1	4	7	10	12	13	11	12	10
Stimulation Off	0	0	1	2	3	3	4	4	6
Explantation	0	1	1	1	3	4	4	4	4
Patient Lost	0	0	0	2	3	5	5	6	6
Dead	0	0	0	0	0	1	1	1	1
Data Missing	1	2	0	2	1	0	1	0	0
Together	74	74	74	74	74	74	74	74	74
Good results (R + 90R)	29	41	44	46	48	50	49	50	51
Bad results (NR+ Stimulation Off + Explantation)	44	31	30	24	22	18	18	17	16
R rate (%)	38.4	51.4	50.0	51.4	51.4	54.4	56.7	56.7	61.2
90R rate (%)	1.4	5.6	9.5	14.3	17.1	19.1	16.4	17.8	14.7
R + 90R rate (%)	39.8	57.0	59.5	65.7	68.5	73.5	73.1	74.5	75.9

General overviews of the results are presented in Table 1 (follow-up years 1–9) and Table 2 (follow-up years 10–17) and Graphs 1 and 2.

The rates of R, 90R and Good outcomes can be related to the complete group of patients (including patients with no available data because they were lost to follow-up, dead, or had data missing). This calculation underestimates the percentage of good results, because it in fact presumes that all patients with unavailable results had bad outcomes. The second possibility is that the rates of R, 90R, and Good outcomes are related to the patients with available follow-up data. This calculation overestimates the percentage of good results when the data unavailability is caused by the dropout of patients who are not doing well. Seven of the patients who were lost to follow-up were categorized as R and one as 90R before their loss. Of the five patients who died during the study period, two patients were graded before their death as 90R, one as R, and two as NR. Three of the patients categorized as "data missing" at a certain follow-up point were graded as NR at the next follow-up; two of them finally reached R grading. The other two patients categorized as "data missing" at a certain visit were evaluated as R and 90R at the next follow-up. Because good results were documented in the vast majority of the patients who were lost to follow-up care, dead, or had data missing, the rates of R and 90R were related to the group of patients with follow-up data available (excluding "lost", "dead", or "data missing"); in author's opinion, this minimizes the distortion of results. The probable reason that patients with good outcomes dropped out was their choice to continue follow-up care in their native country or closer to their home (our center was the first in the country to start systematic VNS implantation).

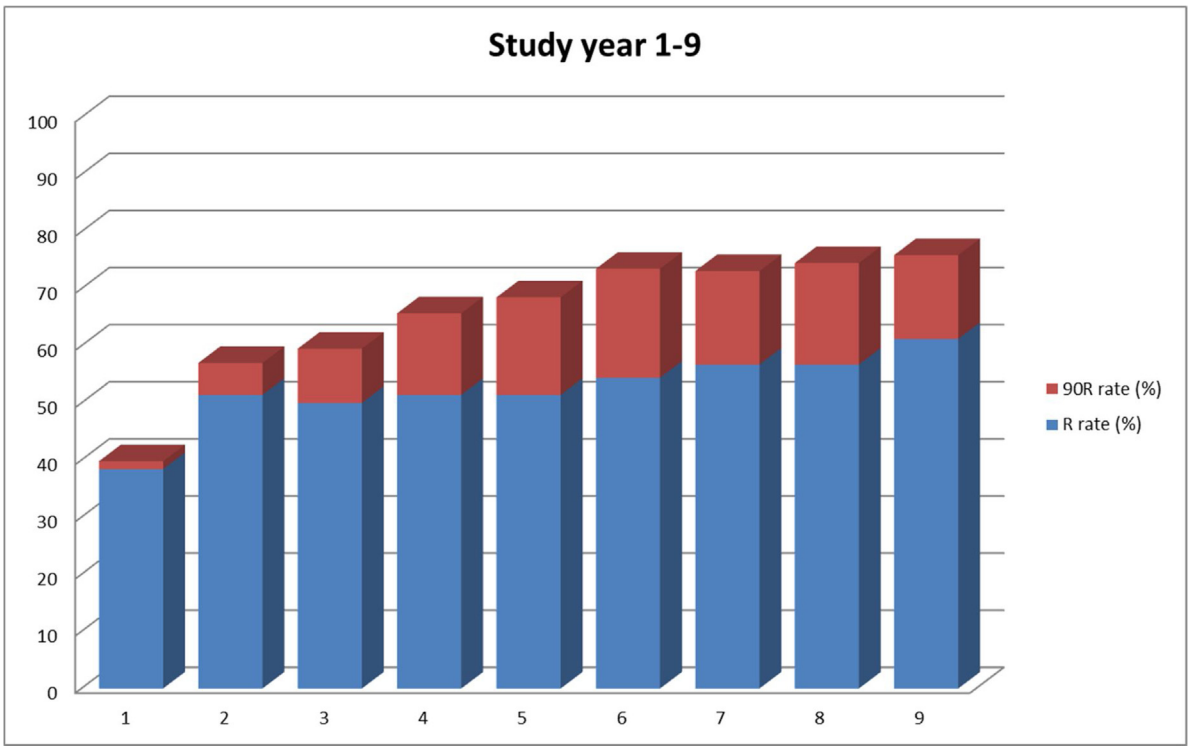
From the 28 patients evaluated as VNS responders at the one-year follow-up visit, the number of responders increased to 37 at the two-year follow-up visit and remained stable with minimal fluctuations (36–42) until study year 10. The number of 90R increased until study year 6. This trend is also reflected in the dynamics of Good outcomes (R + 90R): the peak number was reached at study year 6 and then remained stable with minimal fluctuations (49–52). The nearly steady number of R from study year 2 can be explained by the dynamic equilibrium of patient inflow from the NR to R category together with the outflow from R to 90R and by the dropout of Responders. The 90R rate increases from 1.4% at year 1 to 19.1% at study year 6, then slightly decreases due to the dropout of two 90R patients reaching 15.4% at study year 10. The R and Good outcome rates increase from 38.4% and 39.8% at study year 1, to 51.4% and 57.0% for study year 2, and to 63.1% and 78.7% at study year 10.

Because the number of study patients decreased during years 10 to 17, only the rates of R, 90R and Good outcomes were analyzed. The 90R rates fluctuate between 11.1% (study year 17; only 9 patients available for analysis) and 20% (study year 15). The R rate remains relatively stable between years 10 and 16 (56.1% to 63.1%) with an R rate of 77.8% at study year 17. The Good outcomes rate varies between 70.8% and 81.8% for study years 10–16 and reaches 88.9% for study year 17.

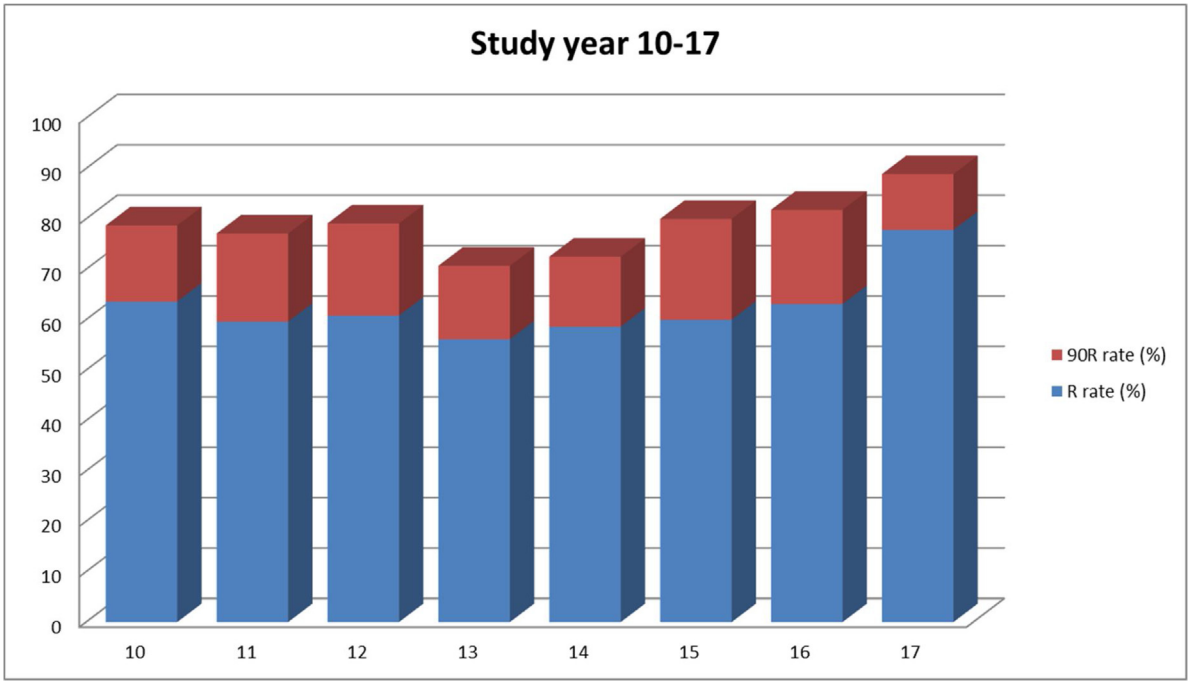
Twelve patients were graded as 90R at their final follow-up visit (including one patient lost to subsequent follow-up care and one patient who died of neurodegenerative disease). A seizure-free period lasting at least one year prior to the final follow-up was achieved in two patients (one patient had a 13 year-seizure-free period after three years evaluated as NR; one patient was 9 years seizure free after a one-year follow-up evaluation as NR).

Table 2
VNS outcomes – years 10–17.

Study year	10	11	12	13	14	15	16	17
NR	3	3	1	1	0	0	0	0
R	42	34	28	23	17	15	10	7
90R	10	10	9	6	4	5	3	1
Stimulation Off	6	5	4	4	3	1	1	0
Explantation	5	5	7	7	5	4	2	1
Patient Lost	6	3	3	3	3	2	2	2
Dead	2	2	2	4	4	4	2	1
Data Missing	0	0	0	0	0	0	0	0
Together	74	62	54	48	36	31	20	12
Good results (R + 90R)	52	44	37	29	21	20	13	8
Bad results (NR+ Stimulation Off + Explantation)	14	13	12	12	8	5	3	1
R rate (%)	63.6	59.6	60.8	56.1	58.6	60.0	63.1	77.8
90R rate (%)	15.1	17.5	18.3	14.6	13.9	20.0	18.7	11.1
R + 90R rate (%)	78.7	77.1	75.5	70.7	72.5	80.0	81.8	88.9



Graph 1. The dynamics of R and 90R rate in time – study years 1–9.



Graph 2. The dynamics of R and 90R rate in time – study years 10–17.

During the study period, previously switched off VNS systems were explanted in seven NR patients because of further evaluation for resective surgery, deep brain stimulation (DBS), or at the patient's request. The system was completely removed in six patients. In one patient the battery was removed for cosmetic reasons and the helical electrodes around the nerve were intentionally left at the patient's request.

Antiepileptic therapy remained unchanged during the study period in nine patients (12.1%).

11 patients (14.8%) achieved an R grade not earlier than at the year 4 follow-up visit. During the last year before their favorable response, there were medication changes in nine of them (Table 3); six had increased their medication dose. Four patients improved from R to 90R not earlier than at the year 4 follow-up visit. Three of

Table 3
VNS patients with delayed R rate.

Patient number	Year of significant response	Medication change	Type of change
1	4	no change	no change
2	8	yes	increased lacosamide dose
3	4	yes	increased topiramate dose
4	6	yes	increased zonisamide dose
5	4	no change	no change
6	7	yes	increased levetiracetam dose
7	4	yes	stopped levetiracetam, started lamotrigine
8	6	yes	increased pregabalin dose
9	10	yes	clonazepam added
10	4	yes	stopped primidone, started topiramate
11	4	yes	increased levetiracetam dose

Table 4
VNS patients with delayed 90R rate.

Patient number	Year of 90R	Grading before 90R	Medication change	Type of medication change
1	4	R	no change	no change
2	4	R	yes	carbamazepine dose reduction, increase of VNS stimulation
3	4	R	yes	stopped pregabalin, started clonazepam
4	5	R	yes	added clonazepam and lamotrigine

them had changes in antiepileptic treatment in the previous year (Table 4).

Three patients with fluctuating response to VNS were identified. One patient was initially graded as R; at the years 3 and 4 visits, she deteriorated to the NR category, but during all the following visits she was graded as R. Another patient was graded as R during the entire follow-up period except for at the years 5 and 6 follow-up visits, where she was graded as NR. One patient with a fluctuating response deteriorated to NR after the year 5 follow-up visit (R year 1, NR years 2 and 3, R years 4 and 5, NR after year 5).

During the study period, one or more battery replacements were performed due to the depleted battery in 51 patients (68.9%). At the time of battery replacement, 49 patients (66.2%) were graded as R or 90R. Battery replacement was also indicated in two NR patients; the seizure reduction rate was 30–40% in both with positive effects from extrastimulation. In 11 patients, the battery was replaced twice; in one patient, it was replaced three times. A complete system replacement was necessary for seven patients (categorized as R before system problems) (9.5%); in one of them, the entire system had to be replaced twice. In all patients, the indication for system replacement was excessive system impedance with decreasing stimulation efficacy. During surgical revision, only fibrosis around the helical electrodes and nerve was found in all patients. There was no case of electrode violation or helical electrode dislocation.

Further surgeries in NR patients were performed after VNS system explantation; these included DBS (bilateral anterior thalamic nucleus) in two patients and resective surgeries in two patients (anteromedial temporal resection initially refused by the patient and frontal topectomy after stereoelectroencephalography). In all the patients operated on after VNS explantation, the results of postexplantation MRI did not differ from the preVNS findings. Among the remaining nonresponders who underwent VNS explantation, there was no case with a resectable lesion detected even using high field MRI.

The rate of VNS system infection and wound breakdown was 0%. There was one case of seroma and another case of hematoma around the battery, both conservatively treated without further consequences.

Among the parameters potentially predicting long term VNS outcome no significant predictor of VNS outcomes as measured by the frequencies of endpoints (90R and Good outcomes) was found using the selected statistical methodology.

4. Discussion

The presented study has a long follow-up period, lasting from 10 to 17 years. The results confirm that the benefit to patients with VNS from systematic treatment in a specialized epilepsy center increases over time. When comparing our results with a long-term study by Wasade et al. [12] with 207 patients, the overall results regarding seizure control are comparable (>50% seizure reduction in 68% of patients) with the exception of higher seizure freedom rates in the Wasade study (20%). In the Wasade study, 22 patients were surveyed from a group of 36 patients with VNS durations of 10 to 14 years (13 with favorable outcomes), and 11 patients were surveyed from a group of 24 patients with follow-up care lasting over 15 years (seven favorable outcomes). Our study had a higher rate of patients available for analysis.

The steady rise of good outcome rates (R + 90R) after study year 2 together with the percentage of patients with late response to VNS (>4 years postimplantation) support prolonging the waiting period before evaluating VNS as ineffective. The adequate duration of this period is unclear [8]. Salinsky et al. [17] suggested that patient response during the first three months could foretell subsequent treatment effectiveness. However, Schachter et al. [18] encouraged continuing VNS for up to two years before discontinuation due to inefficacy. A long-term increase in VNS responder rates was supported by the extensive multicenter study published by Kuba et al. [19] with responder rates of 44.4% at one year after stimulation was initiated increasing to 58.7% after two years and 64.4% at five years. In a paper by Uthman et al. [20], the decrease of seizure frequency was 26% after one year, 30% after five years, and 52% after 12 years of VNS. Ryzí et al. [21] assessed long-term seizure outcomes in a group of 15 children with the mean seizure reduction of 42.5% at one year, 54.9% at two years, and 58.3% at five years. The responder rates remained stable at study year 2, at 60%, and at study year 5, at 60%. Serdaroglu et al. [11] confirmed that, once achieved, positive VNS results are stable or improve over time. In our study, only one patient deteriorated to NR after five years of follow-up observation with a fluctuating response. Despite

the difficult calculations of the R rate and 90R rate considering the drop of patients, the results are comparable with the literature data both for study period years 1–10 and years 11–17.

During the study period, antiepileptic treatment was changed in 87.9% and remained unchanged in 12.1% of patients. The high percentage of patients with antiepileptic medication changes was undoubtedly related to the boom in this field. In a paper by Arcand et al. [22], the percentages of VNS patients with medication changes in type or dose during follow-up care were 57% at 6 months, 33% at 12 months, 59% at 24 months, and 81% at 36 months (mainly dose increases). The percentage of responders did not match the increased number of patients with medication changes – 43% at 6 months, 48% at 12 months, 41% at 24 months, and 50% at 36 months. A detailed analysis proved that maximum improvements correlated with the time of changed medication. These results correlate with our findings about medication changes in patients with late VNS response: in the year prior to the delayed VNS response improvement, there was an antiepileptic drug dose increase in 54.5% and a medication change in 27.2% of delayed responders. Medication was changed in 50% of the delayed 90R patients. Not all papers confirm the positive role of medication adjustments in VNS outcome. In a paper by García-Pallero et al. [23], the percentage of responders in the group with no medication changes allowed was 63%; in the comparable group of patients with medication changes permitted, 45.2% were responders. According to the authors, the absence of changes in antiepileptic drugs helps to optimize the stimulation parameters.

The most frequent reason for revision surgery of the VNS system in our group was battery replacement due to battery depletion. In a study of 1234 patients, Lam et al. [24] reported the average incidence of revision surgeries within six years of follow-up care as <1% for electrode revision, <3% for battery revision or removal, 4–10% for battery replacement, and <1% for infection washout, confirming the highest frequency for battery replacements during a shorter follow-up period. In a study by Couch et al. [25] describing 1144 VNS procedures, 46% of patients required at least one battery replacement or revision surgery, mostly for battery depletion (27%), poor seizure control efficacy (9%), lead malfunction (8%), and infection (2%). In our patients, the indications for battery replacement were decreasing or depleted battery capacity. Attention should be paid to the timing of system revision or battery replacement. According to Vonck et al. [26], pre-replacement seizure control could not be regained in 2 of 14 patients with replacement postponed for several months. Similarly, Tatum et al. [27] support battery replacement before the end of battery life because of the symptoms preceding the end of battery life, such as seizure and behavioral worsening. In our study, no case was observed of the loss of the pre-replacement seizure control after battery depletion and replacement.

The indication for system replacement in our study was increased system impedance with the clinical correlation of seizure worsening; there were no cases of infection or system violation. During surgery, fibrosis around the nerve portion with helical electrodes was found in all patients. No case of electrode displacement was observed. The 9.5% incidence of complete system replacement correlates with literature data reporting the incidence of device malfunction at 4–16.8% of implanted systems [28].

Apart from standard surgical problems of battery or complete system replacement, other aspects of VNS revision surgeries should be discussed. The effect of VNS therapy may be measured by seizure reduction, but also by patient satisfaction and the impact of VNS on the patient's quality of life. For example, Ryvlin et al. [13] proved that VNS therapy as a treatment adjunct to best medical practices in patients with pharmacoresistant focal seizures was associated with a significant improvement in health-related quality of life compared with best medical practices alone. In addition to sophisticated scales, the willingness of the patient (or the physician) to continue therapy by means of undergoing a relatively simple surgery (battery replacement) or a more difficult intervention, such as complete VNS system replacement, may be considered an indicator of treatment success. Based on this simple criterion, the VNS success rate is 78.5% (battery replacement rate 68.9% and complete system replacement 9.5%). This figure correlates with a study reporting that 80% of the surveyed patients considered the VNS worthwhile [12].

Although the incidence of infection was 0%, the increasing risk of implant complications during the prolonged follow-up treatment cannot be excluded despite the smaller battery and cable size as compared to currently available DBS hardware. This assumption is supported by a study of 247 VNS patients with a mean follow-up period of 12 years, in which the incidence of complications was 8.6%, including postoperative hematoma (1.9%) and infection (2.6%) [10].

5. Conclusions

The paper provides an exceptionally long-term follow-up view of VNS patients, involving seizure outcome and other factors. Long-term follow-up results indicate that vagus nerve stimulation is a safe and effective palliative treatment option for drug-resistant epilepsy and its efficacy does not decrease with time. After an initial steady increase until year 6 the number of patients with good VNS outcomes (R + 90R) remained stable. Changes in antiepileptic treatment took place during the entire follow-up period in 87.9% of patients, with potential impacts on seizure reduction. In most patients with delayed response to VNS the improved seizure control was preceded by a change in antiepileptic treatment during the previous year. Patient's age, seizure duration, age at seizure onset, MRI findings and the prevailing seizure type are not significant predictor of long term VNS outcomes.The patient's or treating physician's satisfaction and willingness to continue VNS treatment is indicated by the rate of depleted battery replacement and complete system replacement and corresponds with the rate of good VNS outcomes. In terms of surgical complications in this long-term follow-up study, VNS proved to be a safe technique with a very low rate of transient treatable problems.

Conflict of interest

The authors have no conflict of interest to declare.

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