



Long-term effects of invasive and transcutaneous vagus nerve stimulation in patients with epilepsy: a retrospective cohort study

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Abstract

Objective: To compare the long-term effects of transcutaneous vagus nerve stimulation (tVNS) and invasive vagus nerve stimulation (iVNS) on seizure frequency and tolerability in patients with drug-resistant epilepsies.

Methods: A retrospective cohort study was conducted to compare the efficacy of iVNS vs. tVNS in patients with drug-resistant epilepsy. Treatment response was defined as a > 50% reduction in seizure frequency. Antiseizure medications (ASM) were continued and changed if deemed clinically necessary. Data were collected during outpatient visits or by telephone interview using a standardized questionnaire. The questionnaire covered various aspects, including seizure frequency, tolerability, adverse effects, mood, and quality of life.

Results: In total, 75 patients treated with VNS and ASM were included. In the VNS cohort, 18 patients (mean age 40.7 ± 15.49 years) were treated with tVNS and 57 patients (mean age 31.6 ± 11.15 years) used iVNS. The final analysis included 47 patients (53% male, 47% female) who had a follow-up period of 5 years for tVNS and 15 years for iVNS. In the tVNS treatment group the response rate was 30%, while in iVNS users the response rate was 32%. Kaplan–Meier analysis for iVNS and tVNS users revealed comparable effects over a 5-year period, with no statistically significant differences observed in response rates. Under both tVNS and iVNS devices, few and mild adverse effects were reported, and significant improvements in the quality of life were detected. No difference was observed in terms of their impact on mood or concentration.

Conclusion: Both tVNS and iVNS were found to be a viable and well-tolerated add-on treatment for patients with drug-resistant epilepsy. Both stimulation methods were well tolerated and seemed to be comparably effective in the treatment of epilepsies.

Keywords

VNS · tVNS · Ear · Epilepsy · Neuromodulation

The authors Kristina Krause and Susanne Knake contributed equally to the manuscript.



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Table 1 General demographics				
	Implanted (N = 57) (%)	Transcutaneous (N = 18) (%)	χ^2 (df)	p
<i>Sex</i>				
Female	31 (54.4)	8 (44.4)	2.08 (2)	0.354
Male	26 (45.6)	10 (55.6)	–	–
<i>Age at epilepsy onset^a</i>				
< 18 years	48 (85.7)	9 (50)	20.99 (2)	0.000**
≥ 18 years	8 (14.3)	9 (50)	–	–
<i>Epilepsy type^b</i>				
Generalized	8 (14.3) ²	2 (11.1)	0.359 (2)	0.836
Focal	48 (85.7) ²	16 (88.9)	–	–

^aThree persons with unknown age of epilepsy onset
^bOne person with unknown epilepsy
 * $p < 0.05$, ** $p < 0.01$

Introduction

For patients with drug-resistant epilepsy who are not eligible for epilepsy surgery, neuromodulation is a viable treatment option. Besides invasive treatments such as invasive vagus nerve stimulation (iVNS), deep brain stimulation, and responsive neurostimulation (available in the United States), transcutaneous vagus nerve stimulation (tVNS) was approved for the treatment of drug-resistant epilepsy in the early 1990s [1–7]. Moreover, tVNS has been approved and implemented as a treatment option in Europe since 2010 [8, 9]. Several studies have demonstrated the effectiveness and tolerability of iVNS therapy for both focal and generalized epilepsies [10–13]. Other studies on iVNS have reported a progressive improvement in seizure control over time [7]. Long-term observations have indicated a mean decrease in seizure frequency of approximately 40–50%, while short-term reductions have been noted at around 20–30% [14].

The rates of patients with at least a 50% reduction in seizure frequency (termed “responders”) ranged from 24.5% to 46.6% [7, 15]. Additionally, after 2 years of treatment, responder rates of approximately 50–60% were observed, with a tendency for responder rates to increase over time. However, complete seizure control was rare [16–18]. In a multicenter study, a response rate of 59% was reported, with 9% of patients experiencing seizure freedom [19].

Similar therapeutic effects have been reported for tVNS therapy. Previous stud-

ies have described a reduction in seizures over time with the use of tVNS [20–22]. A double-blind randomized controlled trial demonstrated a significant reduction in seizure frequency in patients in the stimulation group who completed the full 20-week treatment period [23]. Another study found a 54% response rate at 24 weeks [24].

Both tVNS and iVNS are recommended as adjunctive therapies in conjunction with antiseizure medications (ASMs; [25, 27–30]). Patient satisfaction with VNS therapy tends to be high, and adherence to the treatment regimen is generally favorable [17, 31].

Recent investigations have demonstrated notable improvements in quality of life associated with VNS treatment [23, 32–34], which did not seem to be solely dependent on reductions in seizure frequency [22, 34, 35]. Furthermore, several studies have reported that VNS therapy can enhance mood, cognitive function, and affective states [22, 26, 32, 35–38]. Some of these beneficial effects have even been observed independently of seizure control [33, 39].

Regarding safety and tolerability, VNS is generally regarded as a safe and well-tolerated treatment option [17]. There have been rare reports of complications arising from surgical procedures for VNS implantation in early studies [40]. However, tVNS, being a noninvasive method, offers the potential to broaden the spectrum of users and to enhance the safety and tolerability profile of VNS therapy [7, 14]. Adverse effects associated with iVNS stimulation, such as cough, hoarseness, voice changes,

and paresthesia, typically diminish over time [40] but they do not occur during tVNS. Notably, unlike treatment with ASMs, VNS therapy is not linked to systemic or negative cognitive side effects [15, 40]. Furthermore, there is no evidence of teratogenicity associated with VNS therapy [15]. So far, there are no studies comparing the efficacy and tolerability of iVNS and tVNS in clinical practice. We therefore investigated the long-term effects of tVNS and iVNS.

Patients and methods

Data were retrospectively collected from patients admitted to the Epilepsy Center of Hessen, Germany, who underwent any form of VNS treatment from January 1, 2002 to March 1, 2017. Ethics committee approval was obtained, and since it was a retrospective study, informed consent was waived. The study adhered closely to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Detailed information on various aspects of the study participants' medical history was extracted from electronic patient records. This included data on epilepsy syndrome, seizure frequency, the type of stimulation received (invasive or transcutaneous), initiation and discontinuation of treatment, concurrent ASM usage, device settings (standard or rapid cycling), and any reported adverse effects. Data were collected on various time points, including baseline (before starting VNS treatment), 1–3 months post-treatment initiation, and then around 3 years, 5 years, and 10 years after treatment initiation.

Since the introduction of tVNS occurred at a later stage than iVNS, the maximum observation period for tVNS in our study was limited to 5 years. Patients receiving tVNS were equipped with a Nemos® stimulator (tVNS-Technologies, Erlangen, Germany). During tVNS stimulation, an ear electrode was placed on the left tragus where the auricular branch of the vagus nerve is situated. The stimulation frequency was set to 25 Hz with an on-time of 30 s and an off-time of 30 s for 4 h/day.

The initial stimulation intensity was determined by the threshold method as the mean mA value between the correspond-

Table 2 Treatment-related demographics				
Stimulation type	iVNS (N = 57)	tVNS (N = 18)	T (df)	p
Age at VNS implementation (years)	31.6 (± 11.2)	40.7 (± 15.5)	−2.32 (22.8)	0.03*
Epilepsy duration to VNS treatment implementation (years)	10.1 (± 8.0)	17.9 (± 12.5)	−2.49 (21.71)	0.021*
Epilepsy duration total (years)	18.9 (± 11.8)	22.5 (± 13.1)	−0.811 (72)	0.42
Treatment duration (months)	110.7 (± 56.3)	47.3 (± 52.9)	4.22 (73)	0.000**
iVNS invasive vagus nerve stimulation, tVNS transcutaneous vagus nerve stimulation				
* $p < 0.05$, ** $p < 0.01$				

Table 3 Average seizure frequency per month			
	Total M; SD (n)	iVNS M; SD; (n)	tVNS M; SD; (n)
Pre-implementation	14.3 ± 11.1 (44)	15.0 ± 10.9 (34)	11.7 ± 12.1 (10)
3 months post	12.8 ± 11.3 (40)	14.6 ± 11.4 (30)	7.5 ± 9.5 (10)
2 years post	14.5 ± 11.7 (27)	15.6 ± 12.0 (24)	6.0 ± 2.0 (3)
5 years post	15.7 ± 12.0 (27)	16.4 ± 12.2 (25)	6.8 ± 3.2 (2)
10 years post	16.0 ± 12.6 (13)	16.0 ± 12.6 (13)	n.a.
M mean, SD standard deviation, iVNS invasive vagus nerve stimulation, tVNS transcutaneous vagus nerve stimulation, n.a. not available			

ing perception and pain thresholds. Patients could individually adjust the stimulation intensity, but were instructed to use an intensity that resulted in a perceptible stimulation, i.e., a slight tingling sensation when turned on. Records of individual readjustments were not available. Patients on iVNS used a VNS Therapy Deimplus 103 Device (Lianova, Houston, TX, USA).

A subset of patients were classified as adherent. Adherent patients were defined as those who either received iVNS or tVNS therapy continuously for up to 10 or 5 consecutive years, respectively, or were still undergoing VNS treatment at the time of analysis.

Seizure frequency, response rates, concomitant ASM usage, and adverse events were considered as outcome variables and were evaluated at each respective time point.

Repeated-measure ANOVAs were performed for each variable and treatment. The epilepsy was classified either as focal, generalized, or unknown.

Responders were defined as patients with at least a 50% reduction in seizure frequency.

Quality of life was rated on a ten-point rating scale from 0 ("none") to 10 ("full"). Patients were asked to rate the items mood, attention, and impairments in daily life as either better, worse, or unchanged since introduction of the VNS. Items were analyzed by means of chi-square tests. Analy-

ses were conducted using SPSS 24.0 (IBM, Chicago, IL, USA).

Results

Demographic characteristics

A total of 75 patients who received VNS treatment during the observation period were identified, of whom 47 patients (62.7%; 37 iVNS and 10 tVNS) were adherent. Reasons for exclusion from the sample of adherent patients were the discontinuation of VNS therapy due to discharged batteries of implanted devices, lack of seizure control, and loss to follow-up due to missed follow-up appointments, death, or moving.

The distribution of male and female patients was balanced: all patients = 39 male (52%) and 36 female (48%) patients; adherent patients = 53% male, 47% female; iVNS users = 56% male, 54% female; tVNS users: 40% male, 60% female. There was no significant correlation between sex and stimulation method ($\chi^2 = 0.89$, $df = 1$, $p = 0.346$). However, there was a significant difference in the number of prescriptions and application between the iVNS (76%) and tVNS (24%) groups as well as a significant difference in treatment duration for both devices, due to the fact that the iVNS device had been approved for the treatment of drug-resistant epilepsies more than 10 years before tVNS.

The majority of patients presented with focal (77.3%) rather than with generalized epilepsies (21.3%). Patients with iVNS were both younger and had shorter disease duration.

In patients with iVNS, 83% were set to standard cycling and 17% to rapid cycling. Rapid cycling was not performed in the tVNS group. For the analysis of seizure frequencies, responder rates, and medication, only data from adherent users were analyzed. The entire VNS sample was considered for the analysis of mood, attention, quality of life, and adverse events. Detailed demographic characteristics are presented in [Tables 1 and 2](#).

Seizure frequencies and responder rates

In the subgroup of adherent iVNS patients ($n = 34$), 23 (67.7%) reported a decrease in seizure frequency at least at one point of measurement. A total of 11 (32.4%) of these patients showed a permanent decrease in seizure frequency with more than 50% reduction of seizures and could therefore be considered to be responders; two patients were seizure free after 5 and 10 years, respectively. Nine patients (26.5%) had unchanged seizure frequencies. Median seizure frequencies did not change over time.

In the subgroup of adherent tVNS users, five (50%) showed a sustained reduction in seizure frequency. The responder rate was 30%. Three (30%) patients had no change in seizure frequency and two (20%) became seizure free, one at 2 years and one at 5 years. There was a trend toward a decrease in median seizure frequency over time compared to baseline (48.7% at 2 years, 61.5% at 5 years, not significant; [Table 3](#); [Fig. 1](#)).

Comparison of iVNS and tVNS users by Kaplan–Meier analysis revealed no

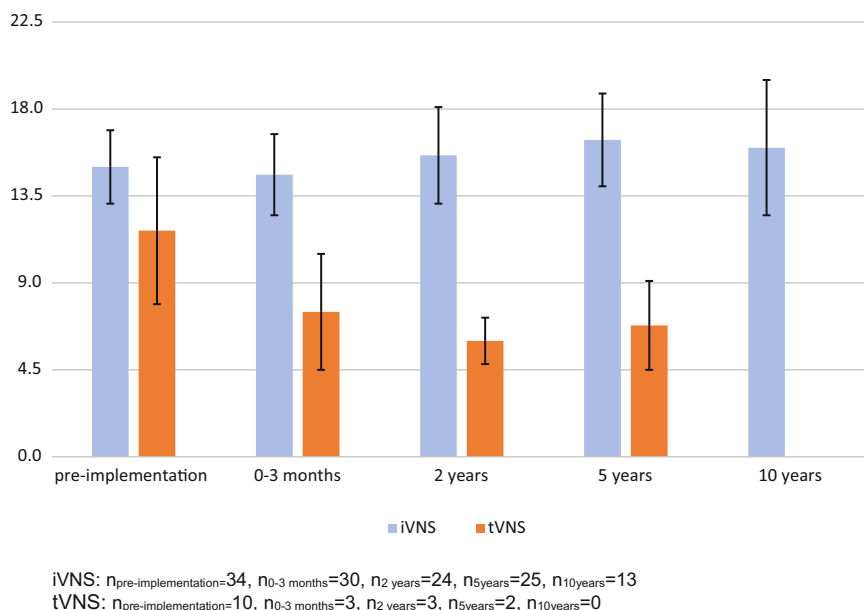


Fig. 1 ▲ Average seizure frequency per month. *iVNS* invasive vagus nerve stimulation, *tVNS* transcutaneous vagus nerve stimulation

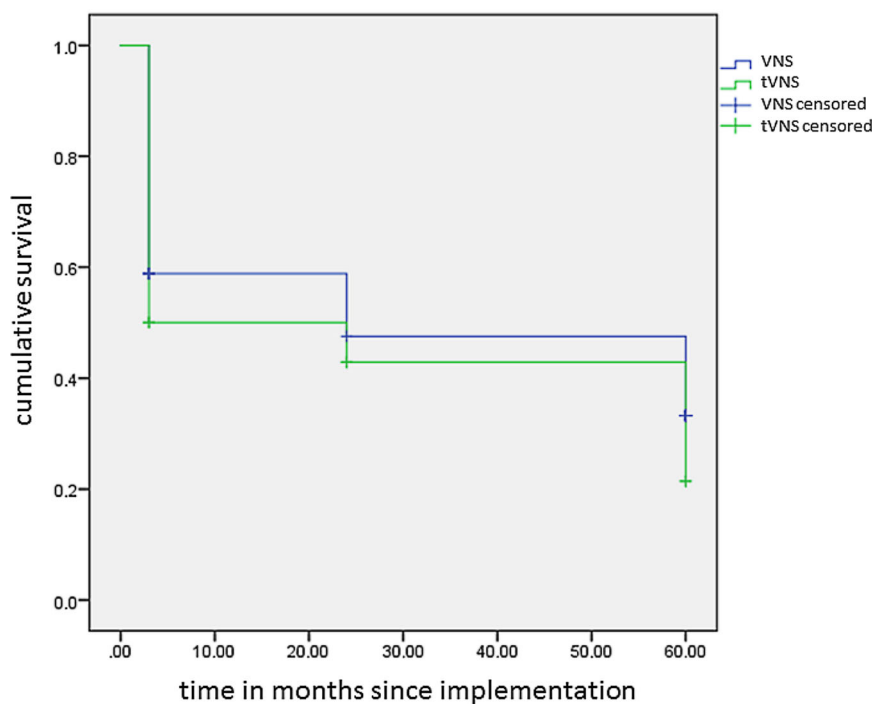


Fig. 2 ▲ Kaplan–Meier plot for patients remaining in treatment on *iVNS* and *tVNS* with a seizure frequency reduction of $\geq 50\%$. *iVNS* invasive vagus nerve stimulation, *tVNS* transcutaneous vagus nerve stimulation

significant interaction for responder rates (Tarone–Ware: $\chi^2=0.415$; $p=0.52$; **Fig. 2**).

The same approach was applied when investigating responder rates in *iVNS* ($n=23$), *tVNS* ($n=10$), and ASM ($n=19$) combined by Kaplan–Meier analysis.

There was a significant difference between the groups (Tarone–Ware: $\chi^2=8.69$; $p=0.013$), with mean estimates of $M=38.10$ ($SE=9.96$) in *tVNS*, $M=55.23$ ($SE=3.38$) in *iVNS*, and $M=58.00$ ($SE=2.31$) in ASM groups. However, this analysis should be

only regarded as explorative due to small and unequal sample sizes.

With regard to the seizure profile, there was no difference in the change in seizure frequency over time between focal and generalized epilepsies (**Fig. 3**).

In the subset of adherent *iVNS* patients, stimulation settings were available for 31 of 34 patients. Of these, 90.3% received standard cycling and 9.7% received rapid cycling. A higher median seizure frequency was observed in the rapid cycling group (**Table 4**).

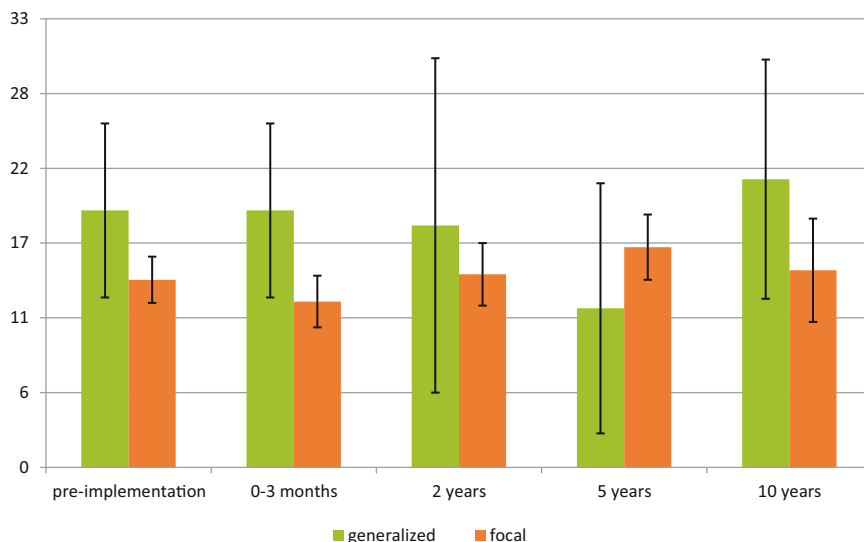
This may be because the switch to rapid cycling was usually made in patients who had failed treatment with standard parameters. There was no significant difference in seizure control between rapid cycling and standard cycling.

Antiseizure medication

Medication information was available for 10 adherent *tVNS* users and 29 adherent *iVNS* users. On average the *iVNS* patients were treated with 2.83 ASMs preoperatively, and the *tVNS* users had an average of 2.80 ASMs before starting VNS treatment. Initially there was a slight trend toward a reduction in ASMs in both samples but no significant change was seen over time. However, some individual patients were able to reduce their medication (**Table 5** and **Fig. 4**).

Adverse events

Adverse event information was available for 33 patients treated with *iVNS* and 12 patients treated with *tVNS*. Adverse events were observed in 85% of invasively stimulated and 42% of transcutaneously stimulated patients. There was no statistically significant difference in the number of adverse events between *iVNS* and *tVNS* ($M_{iVNS}=0.74$, $M_{tVNS}=0.67$, $p=0.80$). On average, both types of stimulation were associated with one adverse event per person and were well tolerable. The most common adverse event with invasive stimulation was hoarseness (55%), followed by cough (18%) and dysphagia (18%), but none of those was rated as severe. Noninvasive stimulation was commonly associated with local problems at the stimulation site such as paresthesia (25%) and local



generalized: $n_{\text{pre-implementation}} = 4$, $n_{0-3 \text{ months}} = 4$, $n_{2 \text{ years}} = 2$, $n_{5 \text{ years}} = 3$, $n_{10 \text{ years}} = 3$
 focal: $n_{\text{pre-implementation}} = 40$, $n_{0-3 \text{ months}} = 36$, $n_{2 \text{ years}} = 25$, $n_{5 \text{ years}} = 24$, $n_{10 \text{ years}} = 10$

Fig. 3 ▲ Seizure frequency per month in focal and generalized epilepsies. Generalized: $n_{\text{pre-implementation}} = 4$, $n_{0-3 \text{ months}} = 4$, $n_{2 \text{ years}} = 2$, $n_{5 \text{ years}} = 3$, $n_{10 \text{ years}} = 3$. focal: $n_{\text{pre-implementation}} = 40$, $n_{0-3 \text{ months}} = 36$, $n_{2 \text{ years}} = 25$, $n_{5 \text{ years}} = 24$, $n_{10 \text{ years}} = 10$

discomfort or pain (25%); for details please refer to [Table 6](#).

Mood and attention

Data on mood were available for 35 iVNS patients and 12 tVNS patients. Overall, 20% of the invasively stimulated patients and 25% of the transcutaneously stimulated patients reported an improvement in mood and activity ($\chi^2 = 0.86$, $df = 1$, $p = 0.35$).

Information on the ability to concentrate was available for 29 iVNS patients and 12 tVNS patients, with improvement noted in 17.2% (iVNS) and 16.7% (tVNS) of the patients ($\chi^2 = 0.002$, $df = 1$, $p = 0.97$). The remaining patients had no change.

Quality of life and treatment satisfaction

Patients reported a significant increase in quality of life after iVNS treatment when asked to rate their quality of life before and after treatment on a 10-point scale ($N = 25$, $M_{\text{pre}} = 4.81 \pm 1.945$; $M_{\text{post}} = 6.67 \pm 1.913$; $T = -3.341$, $p = 0.001$), indicating a moderate treatment effect ($r = -0.85$, Cohen's $d_{\text{repeated}} = 0.649$, $CI = 0.092-1.207$).

Regarding tVNS, patients also reported a significant improvement in quality of life

after initiation of tVNS treatment ($N = 11$, $M_{\text{pre}} = 5.1$, ± 1.044 ; $M_{\text{post}} = 6.9 \pm 1.758$; $T = -2.679$, $p = 0.036$), resulting in a large treatment effect ($r = -0.54$, Cohen's $d_{\text{repeated}} = 0.982$, $CI = 0.098-1.867$).

A one-way repeated ANOVA to compare the effect of the two types of vagus nerve stimulation on patients' quality of life before and after implantation showed no difference. In terms of treatment satisfaction, 59.5% of the 37 patients on iVNS reported they would choose iVNS again, and only 11.4% reported treatment limitations in their daily activities. Of nine patients on tVNS, 44.4% would have chosen tVNS again, 16.7% reported limitations in daily life. There was no significant interaction for the propensity to choose vagus nerve stimulation according to the type of stimulator ($\chi^2 = 0.664$, $df = 1$, $p = 0.415$) or for limitation in activities of daily living ($\chi^2 = 0.22$, $df = 1$, $p = 0.639$).

Discussion

This study evaluated the long-term efficacy, tolerability, and quality of life of VNS therapy in clinical practice using both types of stimulator. Over the 10-year observation period, 32% of patients treated with iVNS had a sustained reduction in seizures and were identified as responders. For tVNS

users, 50% reported a permanent seizure reduction at 5 years, with a responder rate of 30%.

Responder rates

Our results with tVNS are consistent with those of a recent randomized double-blind study showing a 27% responder rate [20, 23]. A pilot study found a gradual increase in responder rates over time from 28.57% to 53.85% [24].

A few studies described similar responder rates of 24.5–46.6% for iVNS treatment [17, 41, 42], but other studies found significantly higher responder rates of around 44.4–64.4% [16, 18, 19, 43].

Almost all of these previous studies of iVNS and tVNS described a reduction in seizure frequency over time, which could only be verified in our tVNS cohort.

This slight difference may be due to the limitations of systematic seizure frequency recording in our retrospective study design, as well as our severely affected patient population. In addition, due to our small sample size, patients with increasing seizure frequency had a greater impact on our results. This could also explain the findings of the survival analysis including tVNS, iVNS, and ASM patients combined, emphasizing the need for further large-scale investigations.

Seizure freedom was achieved in only a minority of patients treated with iVNS (5.9%), which is consistent with previous findings of approximately 6–9% [18, 19, 43].

By contrast, the seizure freedom rate in the tVNS cohort was relatively high (20%), but this may be due to the small sample size or concomitantly introduced ASM. Other studies have reported seizure freedom rates as low as 2.7% [23].

In line with previous studies, our results confirm the efficacy of VNS therapy in the treatment of refractory epilepsy.

Predictors of VNS efficacy

No significant predictors of seizure frequency reduction were identified in the present study. In line with previous studies [8, 36, 43], we found no difference in treatment response with regard to the epilepsy type or seizure semiology, whereas a re-

Table 4 Seizure frequency per month in standard and rapid cycling mode		
	Standard cycling, M (SD)	Rapid cycling, M (SD)
Pre-implementation	14.6 (10.9)	13.5 (6.1)
0–3 months post	13.7 (11.2)	21.8 (8.8)
2 years post	15.2 (12.2)	17.7 (11.2)
5 years post	14.2 (12.2)	23.8 (11.3)
10 years post	14.5 (12.2)	21.2 (15.3)
<i>M</i> mean, <i>SD</i> standard deviation		

Table 5 Average number of concomitant ASMs in total sample			
	iVNS M; SD; (n)	tVNS M; SD; (n)	TAU M; SD; (n)
Pre-implementation	2.89 ± 0.78 (45)	2.56 ± 0.98 (18)	1.80 ± 0.80 (56)
3 months post	2.60 ± 0.81 (40)	2.44 ± 0.51 (16)	1.89 ± 0.79 (55)
2 years post	2.71 ± 0.94 (34)	2.83 ± 0.41 (6)	2.06 ± 0.77 (50)
5 years post	2.72 ± 0.85 (36)	2.50 ± 0.71 (2)	2.27 ± 0.92 (51)
10 years post	2.65 ± 1.19 (23)	.	2.24 ± 0.75 (38)
<i>M</i> mean, <i>SD</i> standard deviation, <i>iVNS</i> invasive vagus nerve stimulation, <i>tVNS</i> transcutaneous vagus nerve stimulation			

Table 6 Reported adverse events of iVNS and tVNS treatment		
	iVNS (n = 33)	tVNS (n = 12)
Hoarseness	18 (54.5%)	0
Paresthesia	2 (6.1%)	3 (25%)
Pain	1 (3.0%)	3 (25%)
Erythema	0	2 (16.7%)
Feeling of pressure	0	2 (16.7%)
Skin lesions	0	2 (16.7%)
Nausea	1 (3.0%)	0
Changes in hearing	1 (3.0%)	0
Toothache	1 (3.0%)	0
Weight change	1 (3.0%)	0
Cardiac problems	1 (3.0%)	0
Dyspnea	3 (9.1%)	0
Dysphagia	6 (18.2%)	0
Cough	6 (18.2%)	0
Frequent infections	1 (3.0%)	0
<i>iVNS</i> invasive vagus nerve stimulation, <i>tVNS</i> transcutaneous vagus nerve stimulation,		

cent systematic review and examination of patients from the VNS Therapy Patient Outcome Registry on predictors of seizure freedom suggested that treatment response is more frequent in patients with generalized seizures [15].

It should be noted that the number of patients with generalized epilepsy in the present study was low, which may influence the results, but in conjunction with the controversial findings of previous studies, the type of epilepsy does not seem to have a major influence on seizure control.

Regarding stimulation settings, there was no improvement in seizure control

with rapid cycling compared to standard cycling, which is consistent with other studies [24, 25, 36, 44, 45]. The disadvantage of higher battery consumption in rapid cycling suggests that the decision to switch to rapid cycling should be made on a case-by-case basis.

In our study, concomitant ASMs were changed and adjusted. Consistent with other studies [26, 44], the number of ASMs remained almost stable with a tendency to increase after 5 and 10 years of treatment. Although some previous studies have reported a similar treatment response without a change in medication [6, 43, 46],

a synergistic effect of VNS and medical treatment can be assumed.

Tolerability and quality of life

Adverse effects reported by our patients were consistent with previous studies [20, 36, 47]. On average, patients reported only a single side effect, indicating that all VNS therapies are well tolerated.

Patients reported a significant improvement in quality of life after VNS treatment. Positive effects on mood and concentration were also reported. These results are in line with recent studies [20, 28, 30, 36]. Some authors suggest that the improvement in well-being is independent of seizure control [17, 29, 37]. Our results support this assumption, as significantly more patients (59.5%) would choose VNS therapy again than benefited from it in terms of seizure frequency reduction (32%).

Invasive versus transcutaneous VNS

Our second aim was to compare invasive and transcutaneous stimulation.

No differences were found between iVNS and tVNS users in terms of response rates, quality of life, and effects on mood and concentration. The profile of adverse effects was different, but few events occurred with either type of stimulator. A high percentage of patients in both cohorts would choose VNS therapy again. It can be concluded that invasive and transcutaneous VNS seem equally effective, safe, and well tolerated. Our results should, however, be interpreted with caution as the sample of the tVNS group was small.

The marked differences, with iVNS patients being both younger and having a shorter duration of epilepsy, potentially limit the comparability between iVNS and tVNS; however, they may reflect a clinical reality in which VNS is more often prescribed to drug-resistant epilepsy patients who lack the cognitive resources or maturity to implement and adhere to tVNS treatment.

Limitations

The limitations are mainly due to our retrospective study design, which made com-

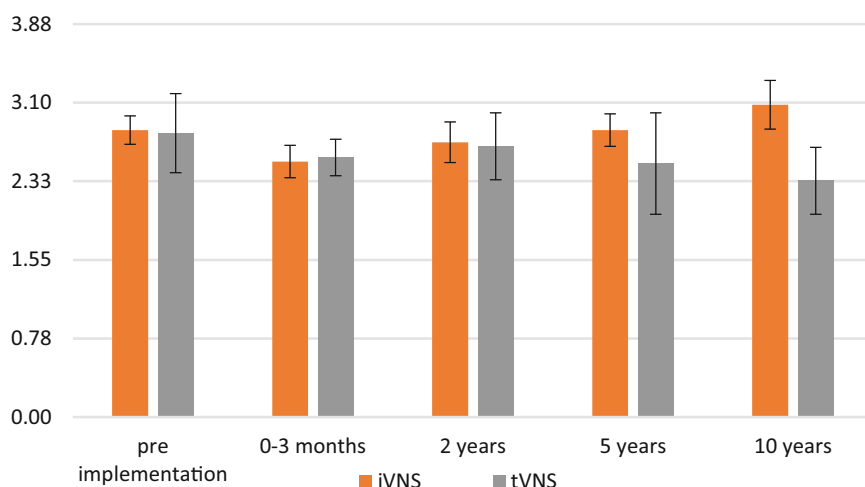


Fig. 4 ▲ Average number of concomitant antiseizure medications. iVNS invasive vagus nerve stimulation, tVNS transcutaneous vagus nerve stimulation

plete data collection difficult and resulted in a high heterogeneity of the patient population. However, it is worth noting that the present study is highly reflective of clinical reality, in which there was no artificial adjustment of ASMs, stimulation settings, or other influencing components.

Another limiting factor was our relatively small sample size, especially the tVNS group and at later follow-up time points, which may have led to a potential selection bias. In addition, in many cases we had to rely on retrospective information from patients, family members, or caregivers. Therefore, inaccuracies in reporting must be taken into account.

We did not use standardized scales of quality of life, well-being, and mood, as these would have been too complex to assess retrospectively by telephone interview; however, our results are in line with current literature.

Conclusion

In drug-resistant epilepsy, vagus nerve stimulation (VNS) is a reasonable and safe adjunctive therapy for both focal onset and generalized seizures. Approximately one third of patients achieve a 50% or greater reduction in seizure frequency, but seizure freedom is rare. In comparison, transcutaneous VNS (tVNS) and invasive VNS (iVNS) seemed almost equally effective. The choice between tVNS and iVNS depends mainly on patient comorbidities and compliance, while improved quality

of life is to be expected with both tVNS and iVNS. Predictors of outcome are still uncertain, and therefore further trials with more statistical power are needed to address this question.

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Data Availability Statement. The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request and local IRB approval.

Declarations

Conflict of interest. S. Knake received speaker's honoraria from Bial, Destin Arzneimittel, Eisai, Jazz Pharma, Merck Serono and UCB. C. Nimsky is scientific consultant for Brainlab, BK medical, and Zeiss. F. Rosenow has received personal fees from Angelini Pharma, Desitin Arzneimittel, Eisai GmbH, Jazz Pharma, Roche Pharma, Stoke therapeutics and UCB Pharma and grants from the Detlev-Wrobel-Fonds for Epilepsy Research, the Deutsche Forschungsgemeinschaft (DFG), the Federal Ministry of Education and Research (BMBF), the LOEWE Programme of the State of Hesse, and the European Union. A. Strzelczyk has received personal fees and grants from Angelini Pharma, Biocodex, Desitin Arzneimittel, Eisai, Jazz Pharmaceuticals, Takeda, UCB Pharma, and UNEEG Medical. F. Rosenow and A. Strzelczyk are members of the editorial board of *Clinical Epileptology*. A.M. Weyand, N. Cordes, L. Linka,

S. Strehlau, P.-E. Tsalouchidou, B. Carl, M. Gjorgjevsky, A. Grote, L. Möller, L. Habermehl, F. Zahnert, C. Münchberger, L. Hakel, K. Menzler, I. Immisch, and K. Krause declare that they have no competing interests.

Ethics committee approval was obtained, and since it was a retrospective study, informed consent was waived. The study adhered closely to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Langzeitwirkungen der invasiven und transkutanen Vagusnervstimulation bei Patienten mit Epilepsie: eine retrospektive Kohortenstudie

Ziel: Vergleich der Wirksamkeit und Verträglichkeit der transkutanen Vagusnervstimulation (tVNS) und der invasiven Vagusnervstimulation (iVNS) bei Patienten mit therapierefraktären Epilepsien.

Methoden: Retrospektive Kohortenstudie zum Vergleich der Wirksamkeit der zusätzlichen Therapie mit iVNS und tVNS bei Patienten mit therapierefraktären Epilepsien. Als Therapieansprechen wurde eine Verminderung der Anfallshäufigkeit um > 50% definiert. Die Gabe von Antiepileptika (ASM) wurde fortgesetzt und, falls es klinisch erforderlich erschien, verändert. Die Daten wurden im Rahmen der Ambulanzbesuche oder per Telefoninterview anhand eines standardisierten Fragebogens erhoben. Es wurden neben Anfallsfrequenz auch Daten zu verschiedenen Aspekten wie Verträglichkeit, unerwünschten Wirkungen, Stimmung und Lebensqualität erfragt.

Ergebnisse: Insgesamt wurden Daten von 75 Patienten, die mit VNS und ASM behandelt wurden, ausgewertet. Innerhalb der VNS-Kohorte wurden 18 Patienten mit tVNS und 57 Patienten mit iVNS behandelt. Die endgültige Analyse umfasste 47 Patienten (53 % männlich) mit einer Nachbeobachtungszeit von 5 Jahren für die tVNS und 15 Jahren für die iVNS. In der tVNS-Behandlungsgruppe lag die Ansprechrates bei 30 %, in der iVNS-Gruppe bei 32 %. Eine Kaplan-Meier-Analyse über einen Zeitraum von 5 Jahren ergab vergleichbare Effekte für iVNS- und für tVNS-Anwender, es wurde keine signifikanten Unterschiede bei den Ansprechraten zwischen den beiden Behandlungsmodalitäten tVNS und iVNS festgestellt. In beiden Gruppen traten nur wenige, leichtgradige unerwünschte Wirkungen auf, in beiden Gruppen wurde eine erhebliche Verbesserung der Lebensqualität festgestellt. Es fand sich kein Unterschied in Bezug auf die Effekte auf Stimmung oder Konzentration.

Schlussfolgerungen: Sowohl die tVNS als auch die iVNS zeigten sich als wirksame und gut verträgliche Therapie von therapierefraktären Epilepsien. Beide Stimulationsmethoden erwiesen sich als vergleichbar wirksam, wurden gut vertragen und waren sicher, beide scheinen eine gute zusätzliche Behandlungsoption für Patienten mit therapierefraktären Epilepsien darzustellen.

Schlüsselwörter

VNS · tVNS · Ohr · Epilepsie · Neuromodulation

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