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Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02)

S. Bauer [a,b,*], H. Baier [c], C. Baumgartner [d], K. Bohlmann [e], S. Fauser [f], W. Graf [g], B. Hillenbrand [h], M. Hirsch [i], C. Last [j], H. Lerche [k], T. Mayer [l], A. Schulze-Bonhage [i], B.J. Steinhoff [h], Y. Weber [k], A. Hartlep [m], F. Rosenow [a,b,1], H.M. Hamer [g,1]

[a] *Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, Neurocenter, Goethe University Frankfurt, Germany*
[b] *Epilepsy Center Hessen, Department of Neurology, Philipps University Marburg, Marburg, Germany*
[c] *Epilepsy Center Bodensee, Ravensburg, Germany*
[d] *Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Vienna, Austria*
[e] *Epilepsy Clinic Tabor, Epilepsy Centre Berlin/Brandenburg, Bernau, Germany*
[f] *Epilepsy Centre Bethel, Krankenhaus Mara, Bielefeld, Germany*
[g] *Epilepsy Center Erlangen, Department of Neurology, University of Erlangen-Nuremberg, Germany*
[h] *Epilepsiezentrum Kork, Kehl-Kork, Germany*
[i] *Epilepsy Center Freiburg, Department of Neurosurgery, University Hospital Freiburg, Freiburg, Germany*
[j] *Department of Neurology, University of Ulm, Germany*
[k] *Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany*
[l] *Saxonian Epilepsy Center Radeberg, Radeberg, Germany*
[m] *cerbomed GmbH, Erlangen, Germany*

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ABSTRACT

Background: Various brain stimulation techniques are in use to treat epilepsy. These methods usually require surgical implantation procedures. Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive technique to stimulate the left auricular branch of the vagus nerve at the ear conch.
Objective: We performed a randomized, double-blind controlled trial (cMPsE02) to assess efficacy and safety of tVNS vs. control stimulation in patients with drug-resistant epilepsy.
Methods: Primary objective was to demonstrate superiority of add-on therapy with tVNS (stimulation frequency 25 Hz, n = 39) versus active control (1 Hz, n = 37) in reducing seizure frequency over 20 weeks. Secondary objectives comprised reduction in seizure frequency from baseline to end of treatment, subgroup analyses and safety evaluation.
Results: Treatment adherence was 84% in the 1 Hz group and 88% in the 25 Hz group, respectively. Stimulation intensity significantly differed between the 1 Hz group (1.02 ± 0.83 mA) and the 25 Hz group (0.50 ± 0.47 mA; p = 0.006). Mean seizure reduction per 28 days at end of treatment was –2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p = 0.146). In contrast to controls, we found a significant reduction in seizure frequency in patients of the 25 Hz group who completed the full treatment period (20 weeks; n = 26, 34.2%, p = 0.034). Responder rates (25%, 50%) were similar in both groups. Subgroup analyses for seizure type and baseline seizure frequency revealed no significant differences. Adverse events were usually mild or moderate and comprised headache, ear pain, application site erythema, vertigo, fatigue, and nausea. Four serious adverse events were reported including one sudden unexplained death in epilepsy patients (SUDEP) in the 1 Hz group which was assessed as not treatment-related.

* Corresponding author. Tel.: +49 6421 2821922; fax: +49 6421 2821923.
E-mail address: bauerseb@staff.uni-marburg.de (S. Bauer).
[1] Both authors contributed equally.

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Conclusions: tVNS had a high treatment adherence and was well tolerated. Superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this relatively small study, which might be attributed to the higher stimulation intensity in the control group. Efficacy data revealed results that justify further trials with larger patient numbers and longer observation periods.

Introduction

Epilepsy is a chronic neurological disorder characterized by recurring, unprovoked seizures, and affects about 50 million people worldwide [1]. About 1/3 of the patients do not become seizure free despite anticonvulsant drug treatment [2]. A minority of these patients can be cured by resective epilepsy surgery. For the remaining patients, various brain stimulation therapies are available, among which invasive vagus nerve stimulation (iVNS) is most frequently used. It requires implantation of a stimulator and an electrode which connects to the left vagal nerve. Long-term iVNS decreased seizure frequency during initial treatment by 24.5% to 28% [3,4]. Seizure reduction increased over time up to 45% in several studies [5].

Transcutaneous vagus nerve stimulation (tVNS) is a newly developed method which intends to overcome the disadvantage of surgical implantation of the stimulation device [6]. The auricular branch of the vagus nerve (ABVN) supplies the cymba conchae [7]. The ABVN can be stimulated using an external device with a bipolar electrode attached to the skin of the left ear conch (Fig. 1). Pilot studies showed responder rates and mean seizure reduction of up to 55% [8,9].

We performed a randomized, double-blind controlled trial (cMPsE02) to assess efficacy and safety of 20 weeks of tVNS in patients with drug-resistant epilepsy. The primary objective of this study was to demonstrate superiority of add-on therapy with "high-level" tVNS (stimulation frequency 25 Hz) versus active control ("low-level" tVNS, 1 Hz) in reducing seizure frequency.

Methods

Patients

Patients between 18 and 65 years of age were eligible for this study if they suffered from epilepsy with focal and/or generalized seizures, had ≥3 seizures per month and not more than 21 consecutive seizure-free days. Seizure frequency was assessed retrospectively prior to screening and prospectively during the baseline period. Patients had to be on a stable regimen of ≤3 antiepileptic drugs (AEDs) for at least 5 weeks prior to study enrollment. This AED regimen had to be maintained throughout the study.

Patients with more than one episode of status epilepticus within 6 months prior to study enrollment, current or prior treatment with invasive VNS or deep brain stimulation, prior ablative epilepsy surgery, history of non-epileptic seizures, major psychiatric disorders, deteriorating neurological or medical conditions and/or relevant cardiac diseases were excluded.

Approval by all responsible ethic committees was obtained before patient enrollment. All participants provided written informed consent before entering the study. This clinical study was designed, implemented and reported in accordance with ISO 14155, with applicable local laws and regulations, and with the ethical principles laid down in the Declaration of Helsinki and described in the ICH-GCP guidelines. The study had been registered in the German Clinical Trials Register (ID: DRKS00003689).

Figure 1. tVNS device NEMOS®. Left side: programmable stimulation device and ear electrode. Right side: placement of ear electrode in the ear conch.

Study design and treatment

This was a randomized, two-arm, parallel group, prospective, double-blind, actively controlled study conducted at 9 sites in Germany and 1 site in Austria between 2012 and 2014. The study period per patient was 28 weeks.

Following an 8-week baseline period during which seizure rate was documented in a patient diary, patients were randomized in a 1:1 ratio to treatment with either high level t-VNS (active treatment, 25 Hz stimulation frequency, 250 μs pulse width, 30 s on/30 s off) or low level (active control, 1 Hz stimulation frequency, 250 μs pulse width, 30 s on/30 s off) t-VNS device for 4 hours daily for a period of 20 weeks. Two baseline visits (weeks 0 and 4) and 7 treatment visits (weeks 8, 9, 12, 16, 20, 24, 28) were performed.

Since tVNS causes a tingling sensation in the skin area touched by the electrode contacts, an active control was necessary to ensure blinding. Patients in the 25 Hz group received 180,000 stimuli per day, whereas patients in the 1 Hz group received 7200 stimuli per day. Compared to frequently used settings of iVNS (30 s "on" time, 5 min "off" time, stimulation frequency 30 Hz, resulting in about 235,000 stimuli per day), the 7200 stimuli per day in the 1 Hz group were considered subtherapeutic and therefore used as active control. Stimulation was performed using the CE certified t-VNS device NEMOS® (cerbomed GmbH, Erlangen, Germany).

Initially, the range between the patient's individual perception threshold and pain threshold was determined. The device was to be used with intensity above the patient's perception threshold, but below the pain threshold. The intensity level was appropriate if stimulation was felt as a tingling sensation. When the patient's perception changed during the study, intensity could be adjusted as necessary to maintain the correct sensation.

During the 8 weeks baseline period, medical data including seizure frequency and quality of life were recorded. The patients' current anticonvulsive drug treatment was not changed during the study. At the beginning of the 20 weeks treatment period, patients were randomized to low level or high level stimulation and started tVNS over a period of four hours per day divided into periods of at least one hour. The stimulation device recorded intensity and

daily percentage of target duration achieved. Seizure frequency was prospectively recorded in patient diaries. Adverse events were reported by patients. Vital signs, physical examination, and ECG were recorded at several time points.

Several additional measures were obtained during treatment visits:

Seizure severity was assessed by the Liverpool Seizure Severity Scale (LSSS), a validated questionnaire consisting of 20 questions, a maximum total score of 80, and with higher scores indicating more severe seizure symptoms [10].

Quality of Life in Epilepsy–31-P (QoLIE-31-P) is a standardized questionnaire to assess the patient's health-dependent quality of life [11]. The total score describes the location of raw values to the maximum possible value (i.e. the best value) in percent and ranges from 0 to 100, with higher scores representing better quality of life.

The Montgomery–Åsberg Depression Rating Scale (MADRS) [12] assesses the severity of the patient's depressive symptoms using a series of 10 questions. The maximum total score is 60; higher scores indicate a more severe depression.

The Clinical Global Impression rating scales for severity (CGI-S) and improvement (CGI-I) are subjective measures of symptom severity of mental illnesses and of treatment response based on the investigator's opinion.

Study outcomes

Primary efficacy variable was the relative change in mean seizure frequency from baseline to the end of treatment compared between treatment groups. Secondary efficacy variables comprised reduction in seizure-frequency from baseline to the end of treatment (within-group analysis), responder analyses, and changes in LSSS, QoLIE-31-P, MADRS, CSSRS and CGI.

Compliance was defined as [total duration of stimulation] × 100%/[supposed duration of stimulation].

Safety was primarily assessed by analysis of serious and non-serious treatment-emergent adverse events (TEAEs). A TEAE is an adverse (AE) event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state. Relation of AEs to treatment was judged by the respective investigator. Further safety measurements included vital signs, physical examination, and 12-lead electrocardiogram (ECG) variables.

Statistical analysis

All summary statistics are presented by treatment group (1 Hz vs. 25 Hz). For comparisons, unless otherwise specified, all statistical tests were carried out using 2-tailed tests at a 5% level of significance.

Efficacy was assessed in all randomized patients (intention to treat, ITT). For patients with missing seizure-frequency per 28 days at end of the treatment period the last available seizure frequency per 28 days was used (last-observation-carried-forward method).

Primary analysis was performed comparing treatments with respect to the primary efficacy variable (relative change of seizure-frequency per 28 days over the treatment period) in an analysis of covariance (ANCOVA) model with treatment as factor and baseline seizure frequency per 28 days as covariate. Treatment differences in least square (LS-) means and the corresponding 95% confidence intervals (CIs) were calculated from ANCOVA. In addition, LS-means for the change within each treatment group and the corresponding 95% CIs were computed. To compare seizure frequencies in both treatment groups, sensitivity analyses using different assumptions on the distribution of the primary endpoint were carried out. Subgroup analyses investigated the relevance of several baseline factors for the primary statistical model.

Secondary variables were analyzed as follows: Mean reduction in seizure-frequency per 28 days from baseline (absolute and relative changes from baseline) to the treatment phase within each treatment group was assessed using ANCOVA as for the primary efficacy variable and t-test for paired measure. For responder analysis (relative change in seizure-frequency per 28 days from baseline >25%, >50%, or 100%), the two treatment groups were compared using a logistic regression model that included treatment as factor and the log-transformed baseline seizure-frequency per 28 days as covariate. Estimates of the treatment odds ratio together with its 95% confidence interval (Wald method) were derived from these models. Other secondary variables (mean change from baseline in LSSS, QoLIE-31-P, MADRS, and CGI scores) were analyzed using ANCOVA with treatment as factor and baseline value as covariate.

Safety was assessed in all patients who had at least one stimulation session. Treatment emergent adverse events, vital signs, physical examination, and ECG results were analyzed using descriptive statistics.

Differences in average stimulation intensity and duration were assessed with the two-tailed Student's t-test.

Results

Seventy-six patients were randomized to the high-level (n = 37) or low-level (n = 39) stimulation group. The study was completed by 58 patients (76 %); 8 patients of the 1 Hz group and 10 patients of the 25 Hz group prematurely discontinued the study. Patient disposition and reasons for study discontinuation are shown in Fig. 2. Demographic and baseline data were comparable between both groups (Table 1).

Baseline seizure frequency was 50.4 ± 101.7 seizures in the 1 Hz group and 62.1 ± 147.6 in the 25 Hz group.

Treatment compliance was on a similar high level in both groups (Table 2).

The average duration of tVNS was 219 ± 34 minutes per day in the 1 Hz group and 227 ± 30 min in the 25 Hz group. The difference in stimulation duration was not statistically significant (p = 0.35). However, we found a significant difference in the average stimulation intensity between the 1 Hz group (1.02 ± 0.83 mA) and the 25 Hz group (0.50 ± 0.47 mA; p = 0.006).

Efficacy

Unadjusted mean seizure reduction per 28 days at end of treatment as compared to baseline was –2.9% (SD: 94.4) in the 1 Hz group and 23.4% (SD: 47.2) in the 25 Hz group. The LS-mean for relative change from baseline to end of treatment was –2.4% (95% CI: [–26.4%; 21.5%], p = 0.842) in the 1 Hz treatment group and 22.9% (95% CI: [–1.7%; 47.5%], p = 0.067) in the 25 Hz group. In the 25 Hz group, we found a significant reduction in seizure frequency in those patients who completed the full treatment period of 20 weeks (n = 26, 34.2%, p = 0.034). Mean seizure reduction for each visit is shown in Fig. 3.

The LS-mean for the difference between the two groups (25 Hz - 1 Hz) in seizure frequency at end of treatment was 25.3% (95% CI: [–9.0%; 59.7%], p = 0.146).

Individual treatment responses are shown in Fig. 4.

Average absolute changes in seizure frequency per 28 days were nearly 1 seizure per 28 days in the 1 Hz group (p = 0.386) and 2 seizures per 28 days in the 25 Hz group (p = 0.068). In those patients who completed the entire 20 weeks of stimulation, improvement was on average 1.2 seizure per 28 days in the 1 Hz group (p = 0.342) and 3 seizures per 28 days in the 25 Hz group (p = 0.031).

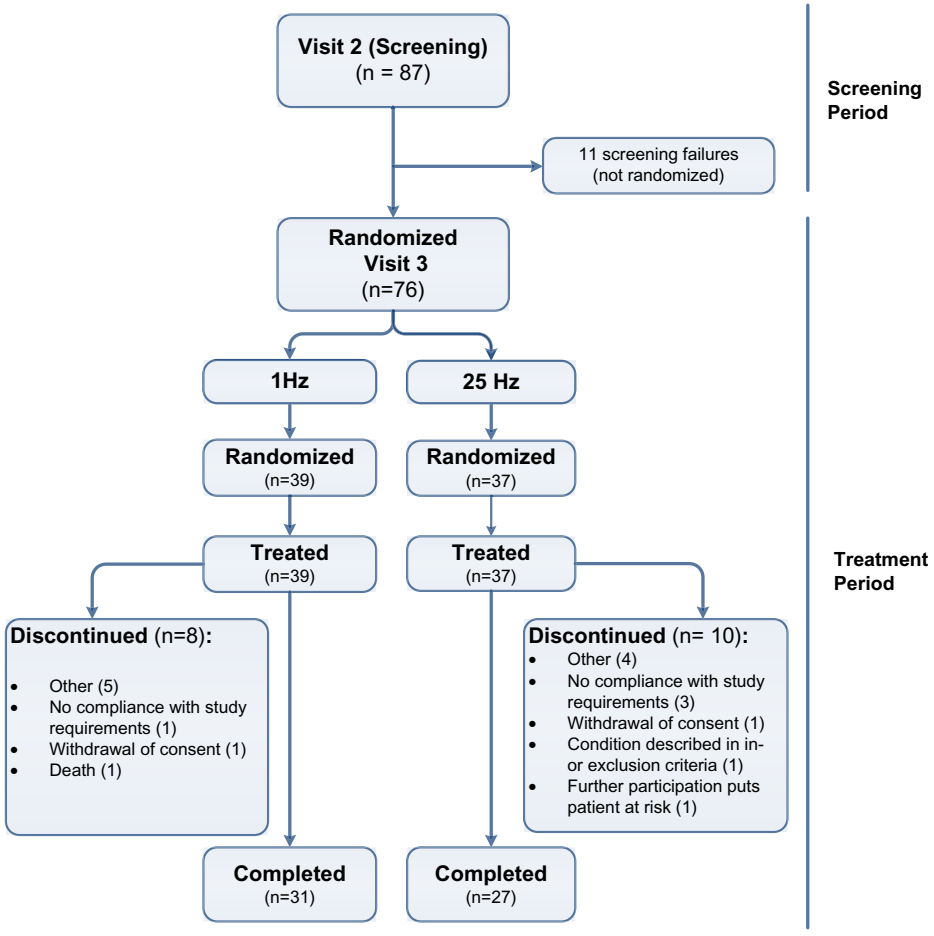

Figure 2. Patient disposition and reasons for study discontinuation.

Table 1
Patient characteristics at baseline (full analysis set).

		1 Hz	25 Hz	Total
n		39	37	76
Age [years]	Mean	37.5	40.1	38.8
	SD	12.2	12.7	12.5
Gender	Female	25	20	45
	Male	14	17	31
Seizure type	Partial	26	28	54
	Primarily generalized	13	9	22
Epilepsy duration [years]	Mean	24.2	23	23.6
	SD	13.8	15.4	14.5
Current AED	Patients on any AED	26	25	51
	LEV	9	17	26
	LTG	11	10	21
	OXC	8	6	14
	LCM	6	5	11
	PER	5	3	8
	CLB	4	3	7
	LZP	3	3	6
	ZNS	3	3	6
	PHT	2	2	4
	TPM	2	2	4
	Other	11	6	17

SD = standard deviation, AED = antiepileptic drug, LEV = levetiracetam, LTG = lamotrigine, OXC = oxcarbazepine, LCM = lacosamide, PER = perampanel, CLB = clobazam, LZP = lorazepam, ZNS = zonisamide, PHT = phenytoin, TPM = topiramate.

Responder rates (25%, 50%) were on a similar level in both groups. Complete seizure freedom during at lest the last 28 days of the study appeared in 3 out of 39 patients in the 1 Hz group and in 1 out of 37 patients in the 25 Hz group (Fig. 5).

Baseline LSSS values (mean ± SD) were 37.1 ± 5.0 points in the 1 Hz group and 36.9 ± 4.7 points in the 25 Hz group, respectively. The scores increased by 0.83 (1 Hz, $p = 0.194$) and 1.56 (25 Hz, $p = 0.017$) during treatment. The difference between both groups was not significant.

Baseline QoLIE-31-P scores (mean ± SD) were 57.5 ± 13.0 in the 1 Hz group and 56.2 ± 14.3 in the 25 Hz group, respectively. The scores increased by 4.65 (1 Hz, $p = 0.01$) and 2.68 (25 Hz, $p = 0.077$) during treatment. The difference between both groups was not significant.

Baseline MADRS scores (mean ± SD) were 7.3 ± 5.6 in the 1 Hz group and 7.8 ± 6.2 in the 25 Hz group, respectively. The scores declined by 0.93 points (1 Hz, $p = 0.112$) and 1.14 (25 Hz, $p = 0.059$)

Table 2
Treatment compliance.

Compliance [%]	1 Hz	25 Hz
Mean	84	88.2
SD	22.1	19.3
Median	93.3	96.7

Treatment compliance was defined as [total duration of stimulation] × 100/ [supposed duration of stimulation].

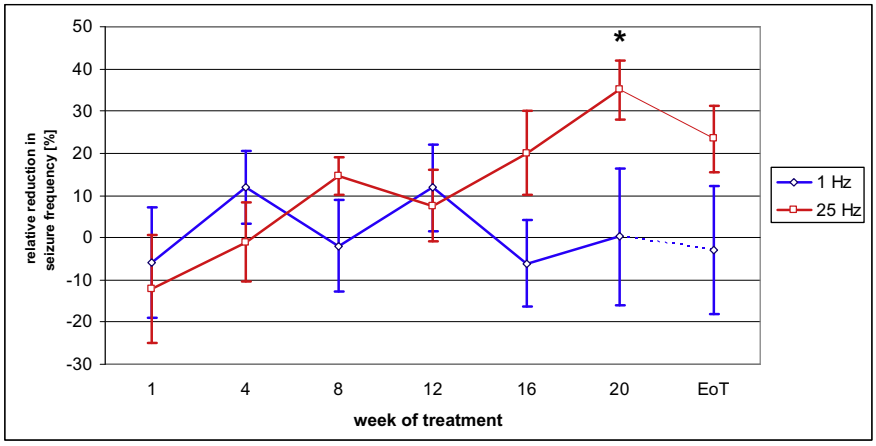

Figure 3. Mean relative reduction in seizure frequency at each study visit as compared to baseline seizure frequency. LS-means, *$p < 0.05$. Error bars: SEM.

during treatment. The difference between both groups was not significant.

The CGI-I showed improvement in about half of the patients in both groups while about 10% experienced a worsening in this parameter (Fig. 6).

Subgroup analyses were performed for gender, seizure type (focal vs. generalized), baseline seizure frequency (<30 vs. ≥30 per 28 days) and concurrent treatment with drugs other than AEDs (yes vs. no). No significant differences in treatment efficacy between these subgroups were found.

Safety

During the treatment period, 33/39 (84.6%) patients from the 1 Hz group experienced 183 treatment emergent adverse events (TEAEs) and 32/37 (86.5%) patients from the 25 Hz group experienced 191 TEAEs. The most frequent TEAEs are summarized in Table 3.

In the 1 Hz group, 29 AEs in 15 (38.5%) patients were classified as treatment related. In the 25 Hz group, 74 AEs in 22 (59.5%) patients were classified as treatment related. The most frequent related TEAEs were headache (1 Hz: 5.1%; 25 Hz: 18.9%), ear pain (1 Hz: 5.1%; 25 Hz: 16.2%), application site erythema (1 Hz: 2.6%; 25 Hz: 8.3%), vertigo (1 Hz: 2.6%; 25 Hz: 8.1%), fatigue (1 Hz: 5.1%; 25 Hz: 2.7%), and nausea (1 Hz: 2.6%; 25 Hz: 5.4%).

In the 1 Hz group, 38.5% of TEAEs were rated as “mild” by the patient, 38.5% were rated as “moderate”, 7.7% were rated as “severe”. In the 25 Hz group, 40.5% of TEAEs were “mild”, 29.7% were “moderate”, and 16.2% were “severe”.

Four TEAEs (palpitations, seizure worsening, syncope and erythema of the left ear) in 4 patients in the 1 Hz group and 5 TEAEs (vestibular neuronitis, suspected basal cell carcinoma, and combined occurrence of headache, exhaustion and nausea) in 3 patients in the 25 Hz group led to treatment discontinuation.

In each group, 2 serious adverse events (SAEs) were reported. Three of the 4 SAEs (1 in the 1 Hz group and the 2 in the 25 Hz group) were classified as possibly or probably treatment related: palpitations (n = 1, 1 Hz group), vestibular neuronitis (n = 1, 25 Hz group), and suspected basal cell carcinoma (n = 1, 25 Hz group; the suspected diagnosis was not confirmed by histology). One female patient (age 51) experienced a sudden unexplained death in epilepsy (SUDEP) 86 days after the first stimulation with the t-VNS device at 1 Hz stimulation frequency. The event was rated as having no relation to the t-VNS device by the investigator and by the sponsor.

The number of patients reporting at least one AE and the number of AE regardless of relationship were comparable in both treatment groups. More patients in the 25 Hz group reported at least one related AE and the number of related AEs was considerably higher compared to the 1 Hz group.

No relevant changes in vital signs or ECG parameters were noted at any visit during the study. No abnormal findings with respect to vital signs were reported as adverse events either.

Discussion

The null hypothesis (no difference between seizure frequencies in both treatment groups) could not be rejected. Hence, superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this study. The considerable seizure reduction rate of 23.4% within the 25 Hz group (as compared to an increase in seizure frequency of 2.9% in the control group) did not reach significance due to the very high variability in seizure frequencies in both groups.

However, seizure frequency decreased significantly by 34% in those patients who completed the intended 20 weeks of 25 Hz tVNS treatment. Higher patient numbers are required to confirm or refute efficacy with higher power in an intention to treat group.

In an animal model of pentylenetetrazole-induced seizures, tVNS appeared to be equally effective against EEG seizure activity as iVNS [13]. In initial randomized double-blinded studies, VNS was associated with 24.5%–28% reduction in total seizure frequency while the actively controlled group (low stimulation) experienced a 6.1%–15% reduction [3,4]. These efficacy data are comparable with the results of the current tVNS study. It is well known that seizure control increases over longer VNS periods. Therefore, further studies should focus on a comparison between iVNS and tVNS and should include long-term follow-up.

The 25 Hz tVNS was associated with a slight significant increase in seizure severity as measured by LSSS (+4%). This increase was too small to be considered clinically relevant. Interestingly, quality of life increased in both groups between baseline and end of study, but this increase was statistically significant only in the control group. The lower increase in the 25 Hz group might be associated with a higher rate of side effects and the higher portion of patients in this group that were rated with a worsened CGI.

Treatment compliance was high. In the 25 Hz group, 88% of the intended stimulation time was met. Drop-out rates (21% in the 1 Hz group, 27% in the 25 Hz group) were higher than in invasive VNS studies (2% [3];). For patients, it might be easier to discontinue treatment with a non-invasive device than with an implanted device that cannot easily be removed.

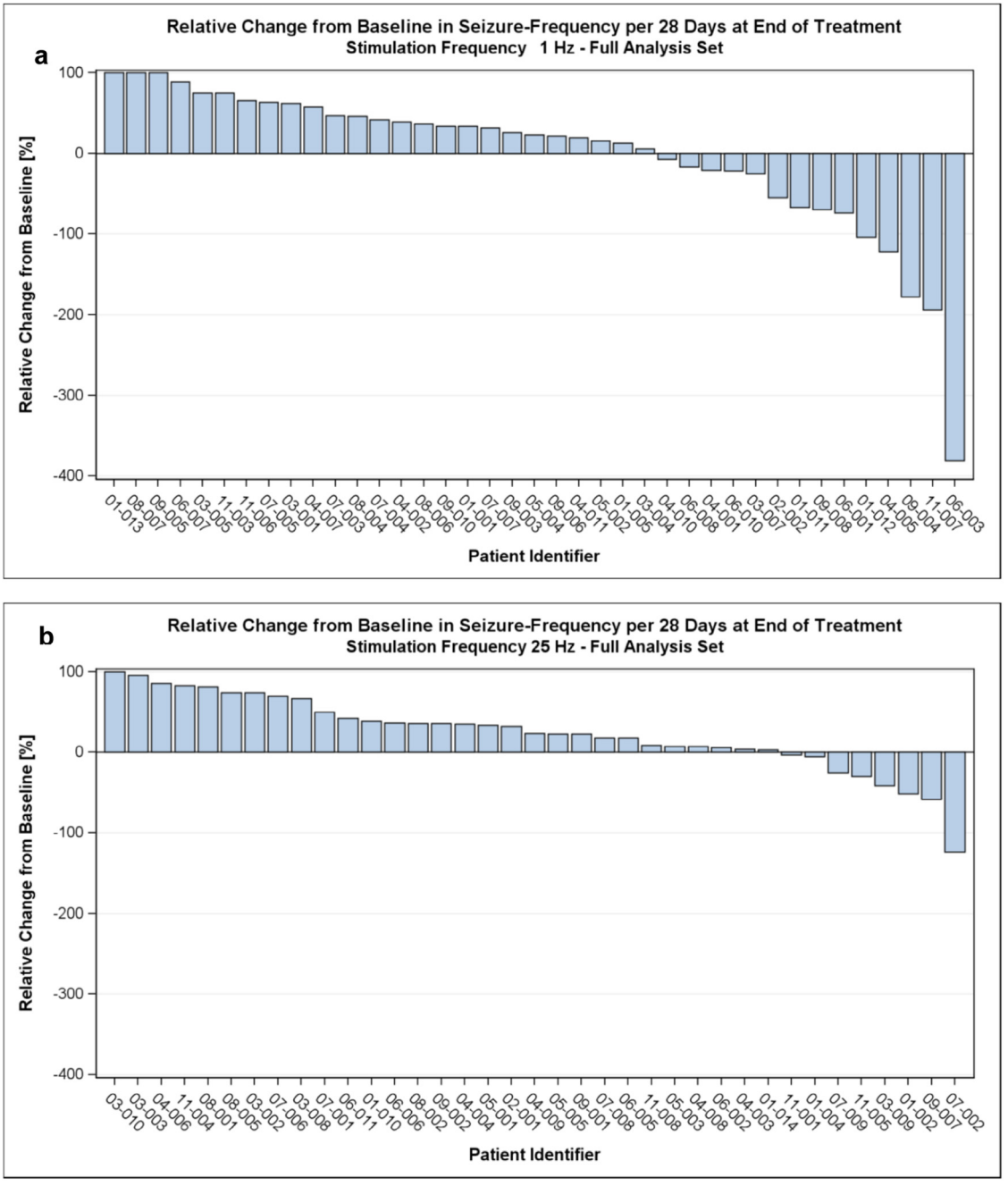

Figure 4. Individual treatment response for patients in 1 Hz (a) and 25 Hz (b) group.
Seizure reduction in % is represented by positive numbers on the y axis (upward bars), seizure increase by negative numbers (downward bars).

Overall, tVNS treatment was well tolerated in both groups. The most frequent treatment emergent adverse events were common medical conditions without obvious relation to tVNS treatment (headache, nasopharyngitis, dizziness, vertigo, nausea, fatigue, diarrhea) or mild side effects probably caused by the device (ear pain, application site erythema). Quality and quantity of TEAEs are comparable to those found in other tVNS studies [14,15]. Compared to earlier iVNS studies [3,4], tVNS less frequently caused "common" AEs such as pharyngitis (20–27% vs. 25–35%) or nausea (8% vs. 15–20%). In iVNS, voice alteration and coughing occur in up to 66%, while we did not observe these side effects. Headache, on the other hand, was reported more frequently in our study (up to 36%) than in iVNS trials (up to 24%).

Three out of the four SAEs that occurred in this study were rated as possibly or probably treatment related. Palpitations (n = 1, 1 Hz group) have been reported in an earlier tVNS study but appeared unlikely to be caused by the device [15]. Cardiac arrhythmias during VNS might appear due to the parasympathetic innervation of the heart by the vagus nerve. Although no relevant ECG alterations were observed in either treatment group, further studies should continue to turn attention on arrhythmias.

Vestibular neuronitis appeared in one patient of the 25 Hz group 17 days after therapy onset and led to treatment discontinuation. This AE hast not been reported earlier; relationship with treatment is unclear.

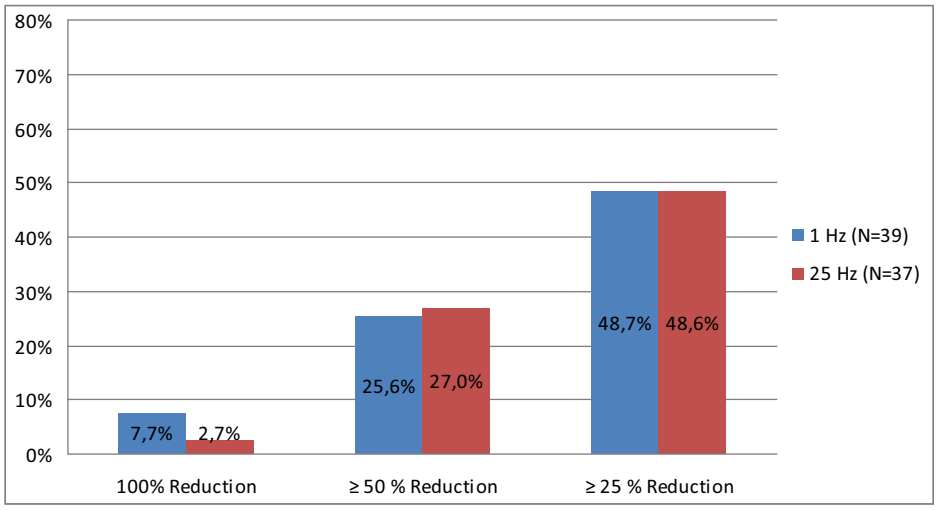

Figure 5. Responder rates.

A suspected basal cell carcinoma (n = 1, 25 Hz group) was not confirmed by histology.

One patient in the 1 Hz group died from SUDEP during the study. For our study population, a SUDEP rate of 5 per 1000 person years can be taken into account (1.1 to 9.3 per 1000 person years in patients with chronic refractory epilepsy and epilepsy surgery candidates [16]). Considering the 40 cumulative patient years in our study, probability for occurrence of 1 or more SUDEP was about 18%. Besides the fact that the SUDEP occurred in the control group, no relation to tVNS treatment was assumed by the attending physician.

The most relevant limitation of this study is the fact that stimulation intensity was significantly higher in the 1 Hz group as compared to the 25 Hz group which may have reduced the difference in treatment efficacy between both groups. Applying constant stimulation intensity in both groups would have interfered with blinding. However, aligning stimulation intensities to some extent

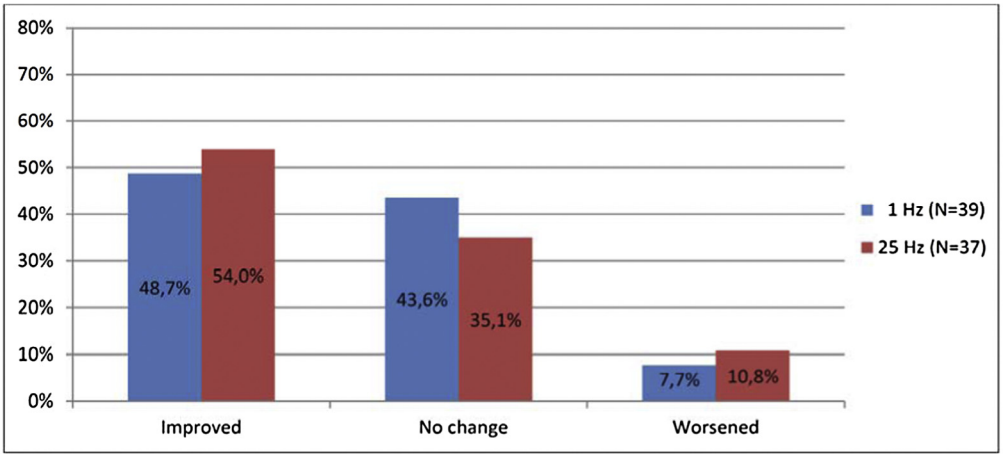

Figure 6. Clinical global impression (CGI) at end of treatment.

Table 3
Most frequent adverse events (AEs).

AE name	1 Hz (n = 39)			25 Hz (n = 37)		
	Events n	Patients n	Patients %	Events n	Patients n	Patients %
Headache	24	14	35.9	30	12	32.4
Nasopharyngitis	12	8	20.5	13	10	27.0
Ear pain	5	3	7.7	8	6	16.2
Dizziness	2	2	5.1	11	5	13.5
Vertigo	6	3	7.7	7	4	10.8
Nausea	7	3	7.7	8	3	8.1
Fatigue	5	5	12.8	2	1	2.7
Diarrhoea	5	3	7.7	2	2	5.4
Application site erythema	1	1	2.6	3	3	8.1

will be necessary in further studies to avoid too powerful stimulation in the control group.

Adverse events have been reported "subjectively" by patients. A structured questionnaire may help avoiding bias in further trials.

About 1/3 of the patients were not on any anticonvulsant medication when included in our study. Although pharmacoresistance had been proven in all patients earlier during their medical history, this is an unusual high rate and may limit generalizability of the results.

Another limitation (like of most trials for epilepsy treatment) is the restricted accuracy of seizure quantification by the use of seizure diaries [17]. Such inaccuracies might not change intraindividually between baseline and treatment period and, therefore, might have no influence on differences in seizure frequencies. Nevertheless, further studies should quantify seizure frequencies by video EEG monitoring as described in a tVNS pilot study [9].

Conclusions

Transcutaneous vagus nerve stimulation is a well tolerated procedure with high treatment compliance rates in patients with drug-resistant epilepsy. Although superiority of 25 Hz tVNS over 1 Hz tVNS could not be proven in this study, efficacy data revealed results that justify further trials with larger patient numbers. Since treatment effect appeared to set in after 20 weeks of treatment, longer observation periods are desirable in upcoming studies. Future trials should focus on comparison of tVNS and iVNS and should preferably include some period of video EEG monitoring for objective quantification of treatment results.

References

[1] Brodie MJ, Shorvon SD, Canger R, Halász P, Johannessen S, Thompson P, et al. Commission on European Affairs: appropriate standards of epilepsy care across Europe. ILEA. Epilepsia 1997;38:1245–50.
[2] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–19.
[3] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51:48–55.
[4] A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 1995;45:224–30.
[5] Boon P, Raedt R, de Herdt V, Wyckhuys T, Vonck K. Electrical stimulation for the treatment of epilepsy. Neurother 2009;6:218–27.
[6] Ellrich J. Transcutaneous vagus nerve stimulation. Eur Neurol Rev 2011;6:254–6.
[7] Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat 2002;15:35–7.
[8] He W, Jing X, Wang X, Rong P, Li L, Shi H, et al. Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. Epilepsy Behav 2013;28:343–6.
[9] Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia 2012;53:e115–18.
[10] Baker GA, Smith DF, Dewey M, Morrow J, Crawford PM, Chadwick DW. The development of a seizure severity scale as an outcome measure in epilepsy. Epilepsy Res 1991;8:245–51.
[11] Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 1998;39:81–8.
[12] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–9.
[13] He W, Zhu B, Rong P. A new concept of transcutaneous vagus nerve stimulation for epileptic seizure. Abstr - Soc Neurosci 2009;4.
[14] Kreuzer PM, Landgrebe M, Resch M, Husser O, Schecklmann M, Geisreiter F, et al. Feasibility, safety and efficacy of transcutaneous vagus nerve stimulation in chronic tinnitus: an open pilot study. Brain Stimul 2014;7:740–7.
[15] Kreuzer PM, Landgrebe M, Husser O, Resch M, Schecklmann M, Geisreiter F, et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Front Psychiatry 2012;3:70.
[16] Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011;378:2028–38.
[17] Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol 2007;64:1595–9.