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Comprehensive long-term outcome of best drug treatment with or without add-on vagus nerve stimulation for epilepsy: A retrospective matched pairs case–control study

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ABSTRACT

Purpose: In the treatment of epilepsy, the recommendation to add vagus nerve stimulation (VNS) to the best available drug therapy (BDT) mostly relies on uncontrolled studies which provide limited information about VNS-specific benefits. We report findings from a retrospective matched pairs case–control study comparing the long-term (>2 years) outcomes of BDT with or without VNS.
Methods: Included were adult patients with therapy-refractory epilepsy who had undergone the presurgical work-up (baseline) and subsequently received BDT with VNS (BDT + VNS) or BDT alone (BDT group). Patients were matched in pairs for age, gender and follow-up. Health outcomes were assessed at least 24 months after the baseline by comprehensive postal surveys and included established psychometric scales.
Results: We obtained data from 20 matched pairs of case and control patients. In both groups, seizures, health-related quality of life and mood improved over time. More BDT patients experienced a complete cessation of "major" seizures (12/20 *vs.* 4/20) whereas, in non-seizure free patients, BDT + VNS patients showed better seizure frequency reduction (>50% reduction: 12/19 *vs.* 7/16). BDT + VNS patients experienced equal drug related and additional VNS related side effects. No clinically relevant effect of VNS treatment was found on any psychological/psychosocial outcome measure.
Conclusion: This retrospective study provided no positive evidence for therapeutic benefits of adding VNS to BDT. The follow-up health status of BDT + VNS patients was slightly worse than in patients receiving BDT alone. Despite minor group differences at baseline the two patient groups who had failed presurgical evaluation were comparable. Therapeutic improvements during long-term BDT alone are often underestimated resulting in a misattribution of positive changes to VNS in uncontrolled studies and reviews. Currently, there is no incontrovertible evidence for the clinical effectiveness of adding VNS to BDT.

1. Introduction

Since its approval as an add-on treatment for drug therapy-refractory epileptic seizures (Europe: 1994, USA: 1997), vagus nerve stimulation (VNS) has been widely accepted as the third approach to the treatment of epilepsy.[1–3] As of November 2011, over 60,000 epilepsy patients had been implanted with a VNS device and VNS was available in more than 70 countries (personal communication, Cyberonics Europe Inc.). VNS spearheaded the concept of (peripheral) neurostimulation for neurological and neuropsychiatric symptoms.[4] However, VNS is associated with considerable additional costs, risks and adverse effects. Furthermore, there are specific restrictions for the diagnostic application of high-field magnetic resonance imaging (3.0 T+) in patients with implanted or incompletely removed medical devices. Most critically, about half of the patients receiving VNS are not expected to experience therapeutic benefits in terms of seizure frequency reduction, and no model for identifying the most suitable patients has been established thus far.[1–3]

Given this background, the addition of VNS to best available drug treatment (BDT) requires unequivocal evidence of the therapeutic superiority of combined treatment (*i.e.* BDT + VNS). Sustained clinical effectiveness of add-on VNS can only be shown by active-control trials in realistic clinical settings which directly compare the long-term outcomes of BDT + VNS *vs.* BDT alone. Leaving clinical effects at the individual patient level aside, one must ask for clinically relevant group effects indicating VNS-specific therapeutic benefits which more than compensate for the VNS-specific costs, risks and adverse effects.

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The present study was motivated by the evident discrepancy between the widely accepted notion of the therapeutic benefits of add-on VNS and the lack of compelling supportive evidence from active-control studies and, more generally, the lack of adequate studies of VNS for refractory epilepsy.[5] Of note, the pre-marketing double-blind, randomized controlled trials of VNS[6–8] and similar studies[9–11] did not address clinical effectiveness, *i.e.* the therapeutic utility of adding VNS to BDT, but therapeutic efficacy, *i.e.* the effects of different stimulation conditions in implanted patients. In a recent meta-analysis, 69 of 74 identified studies of VNS for epilepsy treatment were uncontrolled.[1] However, to assign therapeutic changes in uncontrolled studies to the 'effects' of the treatment given – or even to VNS as a particular part of this treatment – means making a logical misattribution error. In these studies, positive changes occurring by chance or through BDT alone are often underestimated or ignored.[12]

We are aware of only two studies which evaluated the longer term (12 months) clinical effects of BDT + VNS as compared to BDT alone.[5,13] Both studies used a prospective active-control study design and neither study involved randomization or matching of cases and controls. Sherman et al.[5] assessed the seizure and HRQOL outcome in pediatric patients under BDT with and without add-on VNS but no VNS-specific anti-seizure effect was obtained. McGlone et al.[13] assessed HRQOL and memory functions in small samples of adult epilepsy patients under VNS (*i.e.* BDT + VNS), "medical management" (*i.e.* BDT) or resective surgery, but also found no beneficial effect of adjunctive VNS as compared to BDT at the one-year follow-up.

In the present study, we evaluated the therapeutic long-term (>2 years) effects of adding VNS to BDT in adult epilepsy patients by employing a retrospective matched pairs case–control study. We followed therapy-refractory patients after failure of the presurgical evaluation and hypothesized that patients receiving VNS in addition to BDT should be better off with regard to seizures, drug tolerability or health-related quality of life 2 years later. In addition, we expected the therapeutic benefits obtained through additional VNS to more than compensate for the costs, risks and side effects of this treatment.

2. Methods

2.1. Patients

Data recording started in 2006. As the follow-up interval was intended to be longer than 2 years, the VNS device had to have been implanted no later than in 2004. From 1998 (when regular implantations began in our unit) until 2004, 180 adult epilepsy patients were implanted with the VNS system. In our unit, add-on VNS is only offered to patients if resective epilepsy surgery has been excluded as a treatment option or has failed. Therefore, most of the patients underwent the pre-surgical work-up and were implanted shortly thereafter. As we were interested in long-term outcomes, failure of VNS leading to explantation or switching off of the device was an exclusion criterion for this study. We also excluded patients who had previously undergone epilepsy surgery.

BDT was defined as the state-of-the-art use and adaptation of drugs and dosages with no study-related constraints. BDT control patients were selected from the more than 500 patients who underwent the comprehensive presurgical work-up between 1997 and 2004, but who did not qualify for epilepsy surgery (and, of course, were not implanted with VNS). Control patients were matched for gender, chronological age at the baseline, and the follow-up interval to VNS patients in a case-wise fashion. Of note, these matching criteria strongly reduced the number of eligible patients. No specific VNS outcome predictors were known at the time of the study set-up[14,15] but the impact of predictive factors which were proposed later[16,17] was considered during data analysis.

Patient selection and matching was performed based on the data from the presurgical evaluation before any recording of outcome data was initiated. All procedures were consistent with the Declaration of Helsinki (1991) and the study design was approved by the local ethical review board (no. 137/06). All patients included provided written informed consent. No reimbursement was paid to the patients for study participation.

2.2. Measures

Clinical data were copied from patient charts to allow further evaluation of the clinical status at the onset of the treatment interval under examination. Psychological data and the current health outcome were assessed via two comprehensive postal surveys. In the first survey, patients completed several newly defined forms on their current seizure status and antiepileptic drug (AED) treatment as well as a series of standardized psychometric questionnaires on HRQOL, mood, personality and health-related attitudes including the *Adverse Events Profile*,[18] the *Quality of Life Inventory in Epilepsy* (10-item form),[19] the *Subjective Handicap of Epilepsy* questionnaire,[20] the *Beck Depression Inventory*,[21] the *Self-Rating Anxiety Scale*,[22] and the *Befindlichkeits-Skalen*.[23] For reasons of consistency, patients were asked to answer all items enquiring about the "current status" in relation to the last four weeks. For the individual diagnostic evaluation, patients were categorized as "impaired/salient" *vs.* "non-impaired/non-salient" based on the published cut-off scores of the respective mood and HRQOL outcome measures. In addition, attitudes toward seizures and social support during seizures were recorded (*Bonn Psychosocial Scales on Epilepsy*[24]), and health-related personality measures (*Questionnaire on Locus of Control*,[25] *Tellegen Absorption Scale*[26]) were applied to evaluate possible mediating effects of psychological and psychosocial factors (see the supplementary material for details of all applied psychometric scales).

In a second survey that was conducted not before two weeks after receipt of the completed material, patients were asked to retrospectively complete a subset of similar questionnaires on mood and HRQOL as experienced during their presurgical evaluation several years ago (*i.e.* retrospective baseline). Although explorative in nature, these retrospective data have at least some potential to indicate psychological group differences which might already have existed at the baseline (*e.g.* higher levels of depression in one group). Evidently, missing group effects on these measures does not exclude the possibility of preexisting group differences.

2.3. Data analysis

Baseline data derived from medical charts or retrospective patient-reports were analyzed separately. As most of the applied psychometric measures do not provide age-related or other specific normative data, the raw scores were used for data analysis. Mean differences between the matched groups were tested with non-parametric matched tests (Wilcoxon test, χ^2-test) or with student's *T*-test for paired samples where appropriate. Mann–Whitney *U*-test was used for non-parametric evaluation of the mean differences between independent groups (*e.g.* seizure responder/non-responders). Group differences on the scores obtained from the psychometric questionnaires were tested by multivariate unifactorial analyses of variance (MANOVA) with patient group (BDT + VNS *vs.* BDT) as the main factor (paired). Mood and HRQOL changes from baseline to follow-up were tested with repeated measures MANOVA including "time of reference" (baseline *vs.* follow-up) as the repeated measures factor. To allow linear modeling of the effects of group, time and their interaction

on seizures, seizure counts from medical charts and surveys were normalized by using their natural logarithm; this implies the exclusion of seizure-free patients from all analyses referring to follow-up data. According to the explorative nature of this retrospective study, *post hoc* univariate tests (*T*-tests for paired samples) were performed in the absence of significant multivariate effects and without correcting the significance level for multiple testing. Correlations were calculated as Spearman's rank correlation. The level of significance was generally set to $\alpha = 0.05$ (two-sided), but near-significant trends ($p < 0.10$) are reported as well. All data entries and statistical analyses were performed with IBM SPSS Statistics 19 (SPSS Inc.; German release 19.0.0).

3. Results

We were able to recruit 20 matched pairs of BDT and BDT + VNS patients. The sociodemographic and clinical characteristics of the included patients are shown in Table 1. The mean follow-up interval for both patient groups was 6.8 years (SD 2.1, range: 2–13 years).

3.1. Case–control matching

Due to pair-wise matching, the patient groups showed no differences with regard to gender, age at presurgical work-up and the follow-up interval. Recently, bilateral *vs.* unilateral interictal epileptic discharges, cortical malformations *vs.* other brain pathologies, and lower *vs.* higher age at epilepsy onset were proposed as predictive factors for seizure freedom under VNS treatment.[16,17] The patient groups showed no difference with regard to these clinical factors.

However, further analysis revealed that the BDT + VNS patients were more severely affected by epilepsy at the baseline. BDT + VNS patients showed an increased frequency of multifocal epilepsies (χ^2-test, $p = 0.02$) and complex partial seizures (CPS; Wilcoxon-test, $p = 0.046$) and a non-significant trend toward increased total seizures ($p = 0.07$) as documented in the medical records. In addition, both groups strongly differed with regard to the mean baseline number of monthly simple partial seizures (SPS). Of note, this difference relied on single outliers and therefore did not become significant in a non-parametrical statistical test. Finally, BDT + VNS patients used more AEDs at the baseline (*T*-test, $p = 0.005$; >2 drugs: BDT + VNS 10/20 *vs.* BDT 2/20).

Table 1
Patient characteristics at baseline.

	BDT + VNS ($N = 20$)	BDT ($N = 20$)	*p*-value
Matching variables			
Age at presurgical work-up	39.8 (10.2)	39.0 (8.5)	0.60[b]
Sex: male/female	12/8	12/8	1.00[a]
Follow-up interval[d] (years)	6.7 (2.4)	7.0 (1.7)	0.38[b]
Clinical characteristics[e]			
Age at epilepsy onset	14.1 (8.8)	18.1 (12.2)	0.27[b]
Duration of epilepsy at presurgical work-up	25.7 (13.4)	21.0 (9.2)	0.22[b]
Etiology: cryptogenic/symptomatic/unclear	7/12/1	5/15/0	0.44[a]
MRI lesion: yes/no	12/8	16/4	0.17[a]
MRI lesion side: left/right/bilateral	7/3/2	8/4/4	0.86[a]
MRI lesion site: TL/FL/other[f]	9/3/1	12/3/1	0.99[a]
Pathologies: cortical malformation/hippocampal sclerosis/tumor/trauma/others	2/5/1/2/2	3/7/1/2/3	1.00[a]
Epilepsy syndrome: focal/multifocal/unclear	8/11/1	12/3/5	0.02[a]
Number of antiepileptic drugs: 1/2/3/4	1/9/9/1	6/12/2/0	0.02[a]
Mean number of antiepileptic drugs (SD)	2.50 (0.69)	1.80 (0.62)	0.005[b]
Seizures and EEG[g]			
Semiology: TLE/FLE/others/unclear	11/3/2/4	10/1/1/8	0.37[a]
SPS (yes/no)	8/12	7/13	0.74[a]
CPS (yes/no)	18/2	17/3	0.63[a]
SGS (yes/no)	10/10	12/8	0.53[a]
Mean number of SPS per month	59.5 (201.6)	2.8 (7.5)	0.22[c]
Mean number of CPS per month	7.9 (8.8)	5.0 (8.6)	0.046[c]
Mean number of SGS per month	1.0 (2.4)	0.5 (1.2)	0.20[c]
Mean number of total seizures per month	68.4 (206.3)	8.2 (10.4)	0.07[c]
EEG, interictal epileptic discharges: left/right/bilateral/none[h,i]	4/8/4/2	5/6/3/5	0.62[a]
EEG, interictal epileptic discharges: FL/TL/FL + TL/central/other/none[i]	1/11/1/1/2/2	1/6/5/2/0/5	0.17[a]
EEG, ictal epileptic discharges: left/right/bilateral/no event/no correlate[j]	3/3/3/2/6	4/3/5/1/6	0.93[a]
EEG, ictal epileptic discharges: TL/FL + TL/central region/no event/no correlate[j]	7/2/0/2/6	4/2/6/1/6	0.13[a]
Retrospective patient-reported seizure baseline data			
"Small seizures" (per month)	8.2 (8.2)	8.4 (10.1)	0.76[c]
"Big seizures" (per month)	3.5 (4.6)	4.5 (11.2)	0.41[c]
Total seizures (per month)	11.7 (10.0)	12.9 (13.6)	0.83[c]

CPS, complex-partial seizures; FL, frontal lobe; SGS, secondarily generalized seizures; SPS, simple partial seizures; TL, temporal lobe.
[a] χ^2-test.
[b] *T*-test for matched samples.
[c] Wilcoxon-test.
[d] Time interval between presurgical work-up to survey.
[e] Data was copied from patient chart.
[f] Multiple MRI lesion sites possible.
[g] Baseline seizure data rely on the medical charts from the presurgical work-up.
[h] The single seizure-free VNS patient (PSN12) interictally showed infrequent sharp-wave complexes in the right temporal lobe with phase reversal over T4–T2 or T6 and bitemporal theta–delta dysrhythmias (pronounced on the right side).
[i] Interictal EEG: only epilepsy-specific elements were considered (*e.g.* sharp-wave complexes). Sample sizes: BDT + VNS, $n = 18$; BDT, $n = 19$.
[j] Ictal EEG: refers to the beginning of a (clinical) seizure. Sample sizes: BDT + VNS, $n = 17$; BDT, $n = 19$.

Table 2
Seizure outcome.

	BDT + VNS ($N = 20$)	BDT ($N = 20$)	p-value
Self-reported seizure status at follow-up			
Seizure free/only auras/seizures	1/0/19	4/0/16	0.15[a]
"Big seizures": seizure free/seizures	4/20	12/20	0.01[a]
Seizure types: SPS/CPS/GM/drop attack	10/8/8/5	7/10/4/5	>0.16[c]
Maximum interval of seizure-free days (if not seizure-free)	18.1 (14.0)	19.8 (16.0)	0.71[b]
Mean number of "small seizures" per month (SD)	4.4 (5.8)	3.6 (3.4)	0.96[b]
Mean number of "big seizures" per month (SD)	2.8 (4.4)	1.5 (2.6)	0.11[b]
Total monthly seizure frequency	7.2 (8.4)	5.0 (4.8)	0.59[b]
Objective change (baseline: medical charts)			
Mean %-reduction of "big seizures" (CPS/SGS) [median]	65.0% [80.9%]	59.8% [100.0%]	0.72[b]
Mean %-reduction of total seizures [median]	39.8% [64.9%]	−97.6% [−6.8%]	0.052[b]
Seizure response categorized: worsened (<−100%)/unchanged/response (>50%)/good response (>75%)/seizure free (100%) [%]	2/6/4/7/1 [10/30/20/35/5]	8/5/1/2/4 [40/25/5/10/20]	0.04[a]
Subjective change (baseline: retrospective patient-report)			
Mean %-reduction of "small seizures" [median]	40.7% [50.0%]	54.7% [50.0%]	0.25[b]
Mean %-reduction of "big seizures" [median]	29.4% [50.0%]	38.3% [80.0%]	0.11[b]
Mean %-reduction of total seizures [median]	43.8% [47.7%]	53.5% [50.0%]	0.64[b]
Seizure response categorized: worsened (<−100%)/unchanged/response (>50%)/good response (>75%)/seizure free (100%) [%]	0/10/8/1/1 [0/50/40/5/5]	0/9/6/1/4 [0/45/30/5/20]	0.54[a]
%-change of maximum interval of seizure-free days (if not seizure-free) [median]	105.6% [50.0%]	160.0% [42.9%]	0.47[b]
Seizure frequency change rating[d]	1.2 (2.4)	1.8 (2.3)	0.31[b]
Seizure severity change rating[d]	1.4 (2.3)	1.0 (2.1)	0.59[b]
Impact of seizures on...[e]			
Bodily well-being	2.1 (1.4)	1.9 (1.4)	0.55[b]
Bodily performance	2.4 (1.7)	1.8 (1.5)	0.14[b]
Cognitive performance	2.1 (1.8)	1.8 (1.5)	0.70[b]
Emotional well-being	2.4 (1.7)	2.9 (1.8)	0.48[b]

[a] χ^2-test.
[b] Wilcoxon-test.
[c] Multiple χ^2-tests on each single seizure type (yes/no).
[d] Change rating scale from −5 = strongly worsened, to +5 = strongly improved.
[e] Scale from 0 = no impact, to 5 = strong impact.

3.2. Medical outcome

The seizure outcome is presented in Table 2. Regarding the current seizure status, no significant group differences were obtained in any of the applied measures. Of note, 4/20 BDT patients as compared to 1/20 BDT + VNS patients reported a complete release from seizures (duration of seizure freedom: 15–72 months). No differences were shown with regard to the distribution of self-reported seizure types.

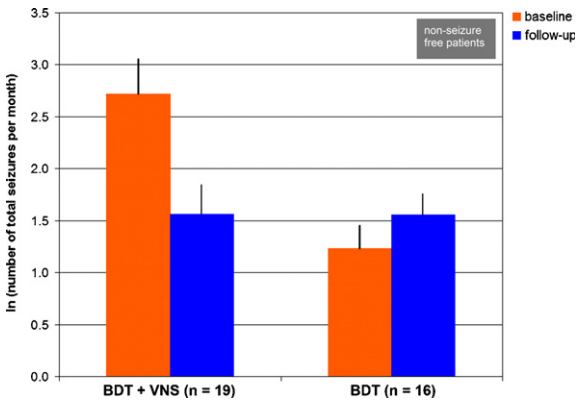

Fig. 1. Seizure frequency reduction in non-seizure free patients. To allow repeated measures ANOVA, the total seizure counts from baseline (medical charts) and follow-up were normalized by expressing them as natural logarithms (ln); this excludes seizure-free patients from analysis. Shown are the group mean and the standard error of the mean of the ln (seizure total count). Effects: group (paired): $F[1,14] = 8.52$, $p = 0.01$; time: $F[1,14] = 3.96$, $p = 0.07$; "group × time" interaction: $F[1,14] = 8.21$, $p = 0.01$.

The following analyses of seizure change refer to the medical chart baseline data (for comparison with retrospective subjective data, see supplementary material). As more BDT patients worsened or became seizure free and more BDT + VNS showed moderate seizure improvements over time (>50% and >75% reduction), the categorized seizure response distribution showed a significant group effect (χ^2-test, $p < 0.04$; see Supplementary Fig. 1). Also with regard to present "big seizures" (current subjective classification) and baseline CPS and SGS (medical charts), patients from both groups experienced significant improvements (equal responder rates of >80%), but more BDT patients reported being free from these types of seizures (12/20 *vs.* 4/20 BDT + VNS; χ^2-test, $p = 0.01$). For pairs of non-seizure free patients ($n = 15$), repeated measures ANOVA on the total seizure counts (normalized) revealed a main effect of the group ($F[1,14] = 8.52$, $p = 0.01$) indicating a higher seizure frequency in BDT + VNS patients irrespective of time; a near-significant trend toward a main effect of time ($F[1,14] = 3.96$, $p = 0.07$) indicating seizure reduction across time in both groups; and a significant "group × time" interaction effect ($F[1,14] = 8.21$, $p = 0.01$) indicating better seizure reduction in non-seizure free BDT + VNS patients as compared to non-seizure free BDT patients from baseline to follow-up (Fig. 1).

The current AED and VNS treatment as well as the patient-rated treatment efficacy and tolerability are shown in Table 3. Repeated measures ANOVA on the number of AEDs showed a main effect of the paired group factor ($F[1,15] = 10.95$, $p = 0.005$), indicating that BDT + VNS patients used more AEDs than BDT patients irrespective of time. However, there was no effect on time ($p = 0.22$) and no "group × time" interaction effect ($p = 0.19$), indicating no significant change in the number of AEDs in the total sample or any of the two groups over time. However, *post hoc* group-wise testing revealed a significant increase in the number of AEDs in BDT

Table 3
Treatment evaluation: AED and VNS.

	BDT + VNS ($N = 20$)	BDT ($N = 20$)	p-value
Antiepileptic drug treatment			
Number of AEDs: (missing data)/1/2/3/4	(1)/2/7/9/1	(3)/0/13/4/0	0.09[a]
Mean number of AEDs (SD)	2.47 (0.77)	2.24 (0.44)	0.03[b]
AED side effects: AEP total score	35.8 (8.6)	32.5 (10.6)	0.12[b]
AED side effects: AEP salient/non-salient[c]	4/16	4/16	1.00[a]
AED efficacy rating (1 very good … 6 very bad)	3.3 (1.1)	3.0 (1.4)	0.39[b]
AED tolerability rating (1 very good … 6 very bad)	2.5 (1.1)	2.7 (1.5)	0.92[b]
AED impact on bodily well-being (0 none … 5 strong impact)	1.8 (1.6)	2.2 (1.4)	0.23[b]
AED impact on bodily performance (0 none … 5 strong impact)	2.0 (1.5)	2.2 (1.2)	0.68[b]
AED impact on cognitive performance (0 none … 5 strong impact)	2.0 (1.7)	2.3 (1.4)	0.55[b]
AED impact on emotional well-being (0 none … 5 strong impact)	1.9 (1.6)	2.5 (1.4)	0.18[b]
AED efficacy change since baseline[d]	1.1 (1.9)	1.4 (2.3)	0.38[b]
AED tolerability change since baseline[d]	0.5 (2.0)	0.3 (1.6)	0.58[b]
Vagus nerve stimulation			
VNS cycle[e]: standard/rapid	10/10	–	–
VNS output current (mA): <0.75/0.75–1.25/>1.25	4/15/1	–	–
VNS efficacy rating (1 very good … 6 very bad)	3.6 (1.5)	–	–
VNS tolerability rating (1 very good … 6 very bad)	2.1 (1.4)	–	–
VNS efficacy change since baseline[d]	1.7 (1.6)		
VNS tolerability change since baseline[d]	0.5 (1.7)		

AED, antiepileptic drugs.
[a] χ^2-test.
[b] Wilcoxon-test.
[c] AEP cut-off score: >44.
[d] Change rating scale from −5, strongly worsened, to $S+5$, strongly improved.
[e] VNS cycles: standard (on 30 s, off 300 s, pulse width 500 ms, pulse frequency 50 Hz), rapid (on 7 s, off 30 s, pulse width 250 ms, pulse frequency 25 Hz).

patients (T-test, $T[16] = -2.43$, $p < .05$), indicating that the drug load in non-implanted patients gradually approached the higher baseline number of AEDs in BDT + VNS patients. In fact, all 6 BDT patients who were under monotherapy at the baseline currently used at least two AEDs. Regarding the stability of the AED regimen, 20/40 patients (50%) did not continue taking any of their baseline AEDs until the follow-up, 18 patients continued 1 drug, and 2 patients continued 2 drugs, with similar variability in both groups (χ^2-test, $p = 0.81$). No significant group effects were obtained for patient-reported treatment side effects (AEP) and ratings of AED efficacy and tolerability. Patients rated the efficacy of both treatments, AEDs and VNS, slightly below "satisfactory" (>3.0) on average. Seizure responders evaluated AED efficacy similar to non-responders (Mann–Whitney test, $p = 0.35$), but experienced better tolerability ($p = 0.013$). The number of AEDs at the follow-up was neither correlated with the patients' efficacy nor tolerability ratings. The efficacy and tolerability ratings for VNS from the BDT + VNS patients were similar to those for AEDs from the total sample. VNS seizure responders evaluated the efficacy (Mann–Whitney test, $p = 0.23$) and tolerability ($p = 0.43$) of VNS similar to seizure non-responders, but only 5/12 seizure responders rated VNS efficacy as "good" or "very good". Most VNS patients (18/19) evaluated VNS tolerability as "satisfactory" or better. Of note, in BDT + VNS patients VNS-associated side-effects added to the unchanged drug-related side effects. Patient change ratings indicated "little" improvement with regard to seizures, AED treatment and VNS. Again, no effect of the treatment group factor was obtained.

3.3. Psychological and psychosocial outcome

Outcomes regarding HRQOL and mood, psychosocial status and personality are reported in the supplementary material (Supplementary Tables 2–4) as, with two exceptions, no VNS-specific group effects were obtained. The categorized SAS score indicated that more BDT + VNS patients showed an elevated score for anxiety at the follow-up, in contrast to an equal distribution of the retrospectively reported anxiety scores at the baseline. Furthermore, BDT + VNS patients showed significantly higher satisfaction with their living conditions at the follow-up.

4. Discussion

We report the findings from a retrospective matched pairs case–control study on the long-term effects (>2 years) of BDT with or without add-on VNS in adult patients with therapy-refractory epilepsies. In the following, we will discuss the clinically relevant findings.

4.1. Seizure outcome

As mentioned above, the only study which adequately checked for the effects of BDT found no evidence for a VNS-specific anti-seizure effect, because the non-VNS patients showed quite comparable clinical improvements.[5] Evaluation of the obtained seizure outcomes in the present study requires careful consideration of the possible selection bias, the obtained seizure freedom rates, and the seizure response rates in non-seizure free patients.

Due to its retrospective design, this study is biased toward the treatment. For example, by only including those patients with at least 24 months of activated VNS, patients experiencing treatment failure during this period (which approaches 30% in our unit) were excluded. Thus, the reported seizure outcome of our study probably overestimates the anticonvulsant effect of VNS. In addition, we applied an explorative statistical strategy to minimize the risk of missing existent effects.

Importantly, the seizure outcomes of both groups were in good accordance to outcomes reported by other groups. Numerous single-arm studies on add-on VNS found a comparable rate of seizure-free patients (3–5%) and a comparable rate of seizure responders (30–50%).[1–3,27,28] However, the titles and conclusions of many of these reports are suggestive for a VNS-specific anticonvulsant effect although, for evident logical reasons, changes occurring over time may never be attributed to the treatment or a single part of it if no control condition was applied. The misconception relies on the tacit assumption that the mere continuation of BDT is unlikely to obtain therapeutic improvements over time. But actually, the outcome of BDT is surprisingly good and comparable to our own findings in the BDT sample. For example, Callaghan et al.[12] found an annual rate of seizure

remission of 5% in adult therapy-refractory epilepsy patients under BDT which cumulated in a seizure remission rate of 33% after 7 years; seizure remission was defined as being seizure-free for at least 12 months.[12] In our study, 12/20 patients (60%) under BDT reported complete release from "big" seizures at the follow-up as compared to only 4/20 patients (20%) under BDT + VNS (completely seizure free: 4/20 *vs.* 1/20). The seizure remission rate in BDT + VNS patients, therefore, appears even lower than in BDT alone which might either indicate that these patients suffer from more severe epilepsies or that BDT is performed in a less efficient way for VNS patients (see below).

In contrast, within the subgroup of non-seizure free patients, BDT + VNS patients reported better improvements of the seizure frequency. Actually, the obtained 'group × time' interaction effect provides the first evidence for VNS-specific long-term effects on seizures, namely alignment of BDT + VNS patients to BDT patients over time. However, this finding must be interpreted with caution as the mean %-reduction in the frequencies of "big" seizures was equal in both groups while the group differences in the baseline total seizure count and the seizure response seem to partly rely on the extremely variant frequencies of SPS in both groups. To give an extreme example, one BDT control patient (#18b) with 1.6 CPS per month and no SPS at the baseline experienced a complete release from "big" seizures at the follow-up but as she now reported 12 "small" seizures per month her seizure frequency increased by 650%.

4.2. Treatment and adverse effects

The seizure remission rate under BDT + VNS might have been lower for BDT only patients because medication changes or dosage adjustments were handled in a more restrictive and finally less efficient way in implanted patients. In fact, while BDT + VNS patients remained on a constantly high number of AEDs a marginal increase in the number of AEDs was found in BDT patients; however, the drug load at the follow-up was still higher in BDT + VNS patients. Some authors suggested that the reduction of AEDs under VNS is safe but the empirical evidence for this possibility is inconclusive so far[29–31] and this option was not systematically evaluated in the present study. With regard to the continuity of the AED regimens over time no group effect was obtained.

We found an equal burden of AED-related side effects in patients from both groups at the follow-up. In consequence, BDT + VNS patients suffer from the typical AED-related and additional VNS-specific adverse effects even after more than 2 years of VNS treatment. Our finding is in line with data from other groups indicating that patients under BDT + VNS have the highest subjective complaint scores regarding adverse treatment effects.[32]

4.3. Psychological and psychosocial outcome

We found a tendency toward general psychological improvements over time for both patient groups, but no compelling evidence for clinically relevant VNS-specific effects on HRQOL, mood or the psychosocial outcome. Although the retrospective patient reports provided no evidence for group differences at the baseline, it cannot be totally excluded that the similarity of both groups at the follow-up actually resulted from a therapeutic alignment of BDT + VNS patients to BDT patients over time.

Minor treatment effects in favor of BDT + VNS were revealed in two measures with, however, little or no clinical relevance. Firstly, more patients under BDT + VNS showed elevated anxiety scores, but this effect likely represents an artifact resulting from the fact that the SAS cut-off score equals the mean SAS score of the BDT + VNS patients. Accordingly, the treatment factor exhibited no effect on the non-classified SAS scores. To the best of our knowledge, increased anxiety has never been reported as a systematic (and paradoxical) effect of VNS. Secondly, the BDT + VNS patients showed higher satisfaction with their current living conditions. Satisfaction with the living conditions (and also with the professional status) generally increased over time in both groups (in relation to the retrospective reports), but BDT + VNS patients reported marginally more improvements. As this concept is quite broad and likely to depend on many unspecific external factors, we are not aware of any specific mechanism by which VNS might have caused this improvement.

If no control condition had been implemented the obtained psychotropic improvements of our BDT + VNS patients could have easily been misinterpreted as VNS effects. Several single-arm studies on VNS assessed the short-term outcome (6 months or less) and reported diverse psychological improvements which, however, must not be causally attributed to the treatment for logical reasons.[7–9,32–39] Of note, several other open-label studies failed to find compelling evidence for VNS-specific improvements in cognitive functioning or emotional well-being.[5,6,13,36,40–42] This "negative" evidence and, more generally, the lack of adequately controlled studies on VNS-specific psychotropic effects, were not always taken into account appropriately in more recent reviews.[14,15,43–46]

Regarding personality, we found no significant effect of the treatment indicating that VNS did not exhibit specific effects on personality. Absorption ability (as an estimate of suggestibility) was positively correlated with the subjective evaluation of the seizure response, but beyond this effect no important bias of personality measures on the outcome evaluation could be confirmed.

5. Conclusion

At the long-term follow-up, patients under BDT + VNS showed a slightly worse health status than patients under BDT only as more BDT patients were free from "big" seizures and BDT + VNS patients suffered from additional VNS-related side effects. Thus, our study did not obtain positive evidence for specific therapeutic benefits of adding VNS to BDT. The baseline group differences (*e.g.*, seizures, AEDs) were not large enough to question the relatively high comparability of patients who all failed the presurgical evaluation. Future prospective active-control studies should assess VNS effects in patients matched for seizure and AED status. In particular, there is no good reason to not ascribe those improvements seen in non-implanted patients under BDT to the BDT + VNS patients. This, however, leaves almost nothing over for VNS-specific improvements. Therapeutic improvements during long-term BDT are often underestimated resulting in a causal misattribution of positive changes to VNS in numerous uncontrolled studies and review papers. VNS is related with high costs, risks, diagnostic constraints, and adverse effects and the rate of expected treatment failures is high (about 50%). Currently, no incontrovertible evidence for the clinical effectiveness of adding VNS to BDT is available.

Conflict of interest

J.M.H. and C.E.E. have received grants from and served as paid consultants for Cyberonics Inc. Europe. C.H. has been employed as a research assistant in a project sponsored by Cyberonics Inc. Europe (1998–2000) and was the scientific administrator of the "PuLsE" study (2005–2009; CONSORT/ISRCTN51185809; ClinicalTrials.gov/NCT00522418). The remaining co-authors (L.W., M.v.L.) declared no conflict of interests.

All co-authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.11.003.

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