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Epilepsy patients with and without perceived benefit from vagus nerve stimulation: A long-term observational single center study

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ABSTRACT

Purpose: Vagus nerve stimulaton (VNS) has been used for adjunctive treatment of drug-resistant epilepsy for more than 25 years. The true efficacy has been debated, as blinded randomized controlled trials are unavailable. The aim of this study was to evaluate the patient-reported perceived benefit of VNS and to compare clinical characteristics of patients with and without benefit.

Methods: Observational study of all 43 adult patients receiving VNS for > 2 years at one single center. Mean duration of treatment was 9 years. At inclusion, a semi-structured interview on VNS effectiveness was performed. In patients without benefit, the VNS was turned off. The outcome was evaluated after an observation period of one year.

Results: 21 patients (49%) reported no clear benefit and stopped VNS. Only one of them resumed treatment within one year. Patients without benefit had received more new antiepileptic drugs (AEDs) during VNS treatment than those reporting benefit ($p = 0.05$). Other differences between the two groups were not found. Ten patients (23%) had been seizure free > 1 year at inclusion (5 in the benefit and 5 in the non-benefit group). Seizure control was attributed to the response of another new treatment in the majority of these patients.

Conclusion: Half of the patients had not perceived clear benefit from VNS, and all but one terminated VNS without worsening of seizures within one year. The true outcome of long-term VNS is difficult to assess in real-world practice. The effect may be overestimated due to confounding factors, particularly the common introduction of novel AEDs and the natural course of the disorder. Patients without perceived benefit from long-term VNS should not routinely remain on treatment and be subject to undue generator re-implantations.

1. Introduction

Vagus nerve stimulation (VNS) for the treatment of epilepsy has been designed to prevent or interrupt seizures by cycling or triggered electrical stimulation of the left vagus nerve. It is an empirically based method with limited knowledge on mechanisms of action. The vagus nerve has rich afferent connections to the brain stem and mesencephalon. The effect of VNS was suggested in animal studies and subsequently supported by randomized clinical trials in uncontrolled focal onset epilepsy. These findings led to European Community and US approval in 1994 and 1997, respectively [1]. The pivotal trials were designed with two arms, one with active therapeutic stimulation and the other with active control low amplitude stimulation [2,3]. At three months there was a seizure reduction of 24 and 28% in the arms with active treatment. Several limitations to these studies have been pointed out [4,5]. The net seizure reduction after subtraction of the control (sham) responses was modest, approximately 15% [5]. Longer term open follow-up surveys suggested an increasing effect with time [6,7], and an antiepileptogenic disease modifying effect has even been suggested [4,8]. Most patients experience local stimulation-related side effects, such as throat sensations, hoarseness, coughing and sometimes strained breathing [9], which usually are discreet and well tolerated, but still leave true randomized, blinded controlled data unavailable.

With a considerable enthusiasm of the option to effectively treat epilepsy by targeting the brain directly with a method lacking negative central nervous side effects and without exposing the entire body to further potential toxic drug effects, the first device was implanted at our center December 1994. Since then, VNS therapy has been offered to patients with drug resistance failing to meet surgical criteria. However, the effectiveness of long-term VNS has been difficult to sort out, both by

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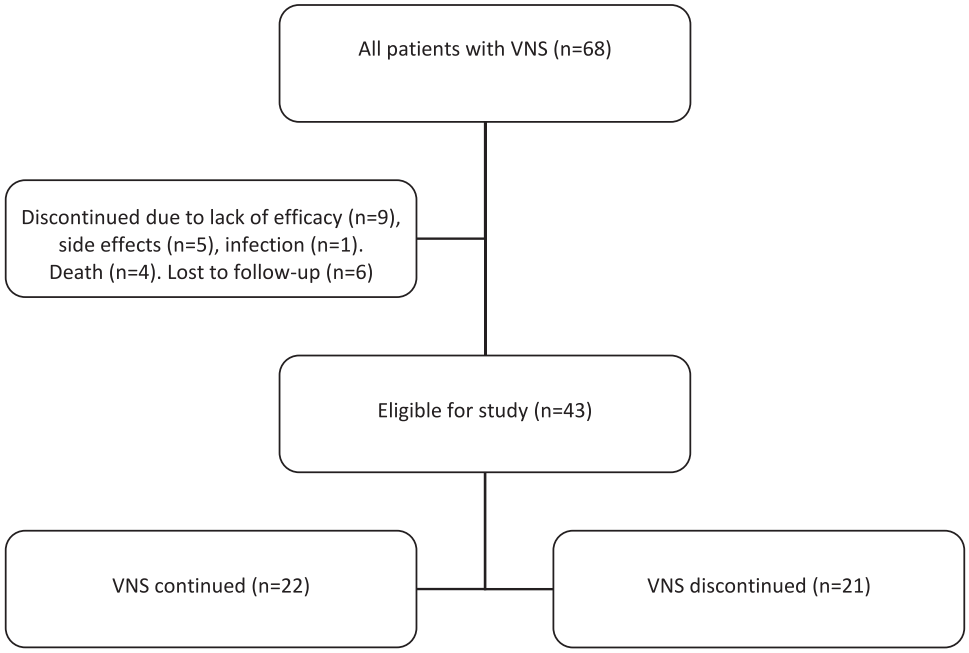

Fig. 1. Summary of patient inclusion.

the patients themselves and by the treatment providers. The bulk of literature on single arm surveys and anecdotal data suggesting positive effects have been immensely growing [9], but clear class I evidence-based data are missing [5]. Some open controlled studies have shown limited or no effect [10,11]. The true effectiveness of VNS remains controversial [12].

The purpose of this study was three-fold: a) to assess the portion of patients perceiving benefit from long-term VNS compared to patients reporting no benefit wishing to discontinue, b) to compare the clinical characteristics of these two groups, and c) to evaluate the outcome after one year in patients stopping VNS.

2. Methods

2.1. Patients

From 1994 to 2017 a total of 68 adult patients had been followed up for VNS treatment at the epilepsy outpatient clinic at St. Olav Hospital University Hospital, Trondheim, Norway (Fig. 1). A total of 15 patients had discontinued VNS; nine due to lack of efficacy and five because of adverse effects or complications (three due to painful throat/neck sensations, two with vocal cord palsy and one due to infection at the implant site). Four patients had died during ongoing VNS, one from cancer, two from probable sudden unexpected death in epilepsy (SUDEP) and one from unknown cause. Six had been lost to follow-up (moved/transferred to other hospitals).

VNS parameters were limited to conventional normal mode cycling stimulation combined with on-demand magnet stimulation, except in one patient who had an Aspire SR generator activated for heartrate-triggered autostimulation four months prior to the interview. Sporadic seizures continued as previously.

In 2017, 43 patients had ongoing treatment for more than two years and were eligible for the study.

2.2. Procedures

At consecutive outpatient visits during 2017, the perceived benefit of the treatment was systematically evaluated in all patients with long-term VNS using a semi-structured interview (Table 1). In case of cognitive deficits or intellectual disability, proxies with detailed knowledge of the patients' seizure disorder provided or supported the information.

Table 1
Elements of the inclusion interview.

Queries	Reply options
Benefit	
Do you think VNS is effective?	No; uncertain; yes: some/much
Effect on seizure frequency?	No; uncertain; yes
Effect on seizure severity?	No; uncertain; yes
Other effects?	Describe
Is magnet activation routinely used?	No; yes
Do you think the magnet works?	No; yes
Side effects	
Do you perceive uncomfortable side effects?	No; yes
Hoarseness during stimulation	No; yes
Breathing discomfort at exertion?	No; yes
Other discomfort?	No; yes: describe
Do side effects influence your quality of life?	No; yes
Discontinuation	
Do you wish to stop VNS?	No; yes

VNS, vagus nerve stimulation.

Perceived benefit was defined as the wish to continue VNS treatment. When lack of benefit from VNS was reported, patients or/and proxies were asked if they would consider stopping the treatment. In those who wished to discontinue, the generator was turned off while the device was left in place. Patients or care-givers were invited to contact the treatment providers in case of any worsening of their epilepsy. The situation was evaluated at outpatient visits after three to six months and at one year. Issues addressed were: seizure control, seizure severity, postictal symptoms as well as interictal mood, cognition and vigilance.

Clinical and treatment characteristics of patients with and without benefit from VNS were compared by aptly selected statistical methods (t-test, Fisher's Exact, Pearson Chi-Square). Statistical significance was set to $p < 0.05$ (two-sided).

2.3. Ethics

The study was approved by the Regional Committee for Ethics in Research (2017/2383).

Table 2
Comparison of clinical characteristics in 43 patients with and without perceived benefit from VNS.

Clinical characteristics	All (n = 43)	Perceived benefit (n = 22)	No benefit (n = 21)	p
Demographics				
Mean age at interview, years (SD)	34.7 (12.90)	33.7 (14.68)	35.7 (1090)	0.61
Mean age at epilepsy onset, years (SD)	7.3 (7.7)	8.0 (8.98)	6.7 (6.16)	0.59
Male gender [n (%)]	26 (61)	13 (59)	13 (62)	0.85
Intellectual disability [n (%)]	24 (56)	12 (55)	12 (57)	0.86
Epilepsy type [n (%)]				
Focal	33 (77)	18 (82)	15 (71)	0.24
Generalized	3 (7)	2 (9)	1 (5)	
Combined focal/generalized	6 (14)	1 (5)	5 (24)	
Unclassified	1(2)	1 (5)	0 (0)	
Mean seizure frequency last year prior to interview [n (%)]				
≥ weekly	26 (60)	13 (59)	13 (62)	0.81
< weekly ≥ monthly	4 (9)	3 (14)	1 (5)	
< monthly ≥ yearly	3 (7)	1 (5)	2 (10)	
No seizures last year	10 (23)	5 (23)	5 (24)	
AED treatment (SD)				
Mean number of AEDs prior to VNS	10.4 (3.3)	9.5 (3.34)	11.4 (3.13)	0.07
Mean number of introduced AEDs after VNS	4.3 (4.00)	3.2 (3.72)	5.5 (3.80)	0.05
Mean number of AEDs at interview	2.8 (0.79)	2.6 (0.79)	2.9 (0.77)	0.27
Mean number of new AEDs first 12 months after interview	0.2 (0.42)	0.2 (0.43)	0.2 (0.44)	0.94

VNS, vagus nerve stimulation; AED, antiepileptic drug; SD, standard deviation.

3. Results

At the inclusion interview, 21 of 43 patients with ongoing VNS treatment for more than two years (49%) reported that they had not perceived obvious effect from VNS and decided to stop the stimulation. Table 2 shows the clinical characteristics of all 43 patients. The 22 patients who perceived benefit from VNS were compared to patients without benefit who stopped treatment. Demographic data was similar. More than half of the patients had intellectual disability; they were equally distributed in the two groups. The mean duration of treatment was almost nine years (range 2–24 years) (Table 3).

The majority had focal epilepsy. Three had been diagnosed with generalized epilepsy (one with juvenile myoclonic epilepsy reported benefit and continued treatment, whereas two atypical cases with more than one seizure type did not). Six patients had combined focal and generalized epilepsy (four Lennox-Gastaut-like, two Dravet syndrome).

Ten patients had been seizure free for > 1 year prior to the inclusion interview, but only five believed that this was related to VNS. The other five decided to stop VNS, as seizure control had been clearly linked to the introduction of a new treatment, two with perampanel, two with stiripentol (Dravet syndrome) and one with transdermal nicotine (sleep-related hypermotor epilepsy with CHRNA4 mutation). The five seizure free patients who considered some benefit, also had had antiepileptic drug (AED) adjustments; in two seizure control was clearly time-linked with new AEDs (lamotrigine added to valproate and zonisamide, respectively).

There were no significant differences between patients with and without benefit from VNS, apart from the number of new drugs introduced during VNS treatment, which was higher in those without benefit with borderline significance (Table 2).

Only 15 (35%) of the patients reported an overall positive effect on the seizures (mild effect in 9, much effect in 6). As many as 19 patients (44%) considered the effect as uncertain. The majority of these patients (n = 12) decided to stop stimulation (non-benefit group), whereas seven wished to continue (Table 4).

In spite of efforts to adjust output currents to tolerable levels, nearly half of the patients reported stimulation-related adverse effects in the form of hoarseness, shortness of breath during exertion or sensory symptoms (Table 4). Other discomfort included coughing and wheezing, dysphagia and head tilting. The distribution of adverse effects was also not different in the two groups, although six in the non-benefit group felt discomfort that influenced their quality of life compared to two in the benefit group.

Twenty of the 21 patients who discontinued treatment reported no clear deterioration regarding seizure frequency or severity within one year of discontinuation. After two months, one single patient with intellectual disability returned to VNS treatment due to the public occurrence of habitual seizures leading to hospitalization. His allocation to the non-benefit group was maintained, as parents and caregivers still considered no favorable effect from VNS. He remained with an average of weekly seizures.

4. Discussion

4.1. Perceived benefit

To our knowledge, this is the first study that systematically evaluates the patient-reported overall benefit from long-term VNS in epilepsy. Half of the patients did not perceive benefit from VNS and terminated treatment; the other half wished to continue. Nevertheless, there was a considerable fraction within each group who ambiguously reported an uncertain effect, underscoring the difficulties in evaluating the long-term global effectiveness of this treatment modality in routine clinical practice (Table 4).

At interview, 60% of patients treated with long-term VNS had a mean frequency of at least weekly seizures. Surprisingly, this was similar in patients with and without perceived benefit. The reported composite effects of VNS on seizure frequency, severity and postictal symptoms are difficult to disentangle and may hamper quantitative assessments and meaningful statistical comparisons. Hence, we simply chose to use the perceived benefit as a broad outcome measure in these highly treatment resistant patients. Other complex factors with impact on wellbeing, including tolerability and various confounding

Table 3
Comparison of VNS treatment characteristics in 43 patients with and without perceived benefit from VNS.

VNS characteristics	All (n = 43)	Perceived benefit (n = 22)	No benefit (n = 21)	p
Mean implantation age [years (SD)]	25.4 (13.00)	25.2 (14.50)	25.7 (11.60)	0.91
Mean VNS treatment duration [years (SD)]	8.8 (4.3)	8.2 (5.55)	9.3 (2.39)	0.40
Mean duty cycle (SD)	17.0 (11.6)	15.7 (9.95)	18.3 (13.31)	0.46
Mean output current, normal mode [mA (SD)]	1.99 (0.40)	2.00 (0.32)	1.98 (0.48)	0.89
Standard stimulation (interval 3/5 minutes) [n (%)]	37 (86)	20 (91)	17 (81)	0.41
Rapid cycling (interval < 1.8 minute) [n (%)]	6 (14)	2 (9)	4 (19)	
Magnet activation used in long-term treatment [n (%)]	22(51)	13 (59)	9 (43)	0.29

VNS, vagus nerve stimulation; SD, standard deviation; n, number of patients; mA, milliampere.

Table 4
Effects and side-effects from VNS in 43 patients.

Effect and side-effect parameters [n (%)]	All (n = 43)	Perceived benefit (n = 22)	No benefit (n = 21)	p
Effect on seizures				
Uncertain overall effect	19(44)	7(32)	12(57)	0.78
Any positive effect	15 (35)	15 (68)	0	
Effect on seizure frequency	14 (33)	14 (64)	0	
Effect on seizure severity	12 (28)	12 (55)	0	
Effect from magnet stimulation	13 (30)	11 (50)	2 (10)	0.14
Side-effects				
Any side-effects	20 (47)	11 (50)	9(43)	0.76
Stimulation-related voice changes	23 (53)	13 (59)	10 (48)	0.35
Stimulation-related breath changes on exertion	15 (35)	8 (22)	7 (33)	0.75
Stimulation-related pain	7 (16)	3 (13)	4 (19)	0.68
Other discomfort	9 (21)	4 (18)	5 (24)	0.71
Influence on quality of life from side effects	8 (19)	2 (8)	6 (29)	0.12

VNS, vagus nerve stimulation; AED, antiepileptic drugs; n, number of patients.

circumstances, as well as subtle and obscure effects beyond the lessening of the seizure burden, may have influenced the decision to continue or stop VNS treatment.

Prior to the study, all patients had been encouraged to continue VNS therapy regardless of obvious effect, due to the notion that only a very modest and hardly perceptible improvement might influence the quality of life and be worth-wile in the long run. Nevertheless, nine of the 68 patients treated at our center had requested discontinuation due to missing efficacy prior to the study (Fig. 1). Only one of the patients who terminated VNS at study inclusion, resumed VNS treatment within an observation period of one year. During this year, the need for AED treatment change was low and equal in patients stopping and continuing treatment (Table 2).

4.2. Concomitant AED treatment

The era of VNS has coincided with a rapid and substantial growth in the number of available AEDs. The majority of patients in this study continued to be burdened by uncontrolled seizures. All of them were offered the opportunity to try out novel effective AEDs with new mechanisms of action along with VNS, sometimes with improvement. The mean number of introduced AEDs was 5.5 during the period of VNS prior to the inclusion interview. The number of drugs tried was higher in those without benefit (borderline significant), but the mean duration of VNS treatment was also slightly longer, and they had a somewhat earlier seizure onset, as well as a marginally higher number of previously tried AEDs and a slightly higher duty cycle (Table 3). Conceivably, these minor differences might reflect a somewhat more severe epilepsy from the outset in some of these patients.

A considerable fraction of patients receiving VNS obtained complete seizure control. However, of the ten patients that had been seizure free for at least one year at inclusion (23%), five chose to discontinue VNS, as seizure control was clearly related to the introduction of a novel medication. Of the five seizure free patients who wished to continue VNS, two also appeared to be responders to newly introduced drugs.

Some retrospective studies have tried to sort out the effect of AED change during long-term VNS treatment [7,13]. In the recent study by Revesz et al., a subgroup of patients remained on the same AEDs during the 5-years follow-up [7]. Noteworthy, even in this group the seizure frequency seemed to decline. In the present study, complete seizure control was clearly associated with novel pharmacological treatment. One open prospective randomized controlled trial endeavored to settle the AED effect by comparing best drug treatment with *versus* without VNS [14]. Superiority regarding both quality of life assessments and seizure frequency was suggested for VNS compared to best drug treatment alone. However, patient enrollment rate was low due to reluctance of being randomized, which led to early termination of the study by the sponsor. Data for analyses could only be collected for up to one year, and the study was limited by its open and flexible design, emphasizing the obstacles of the scientific approach to VNS treatment.

4.3. Other confounders

As already pointed out, improvement of epilepsy in patients receiving long-term VNS are not solely attributed to the stimulation treatment. Besides new treatments, the natural course of drug resistant epilepsy itself may also modify seizure control [15–18], particularly in those with very long follow-up. A “regression towards the mean” might influence the outcome in those with shorter treatment periods. All these effects are difficult to keep apart and might bias the outcome of VNS treatment in real-world practice. One recent surveillance even reported a decrease in the rate of SUDEP during the 10 years follow-up after VNS implantation [19], an effect, which by itself, would be a good reason to continue stimulation in these vulnerable patients. However, a later population-based study from Sweden showed that the incidence of SUDEP generally declines with follow-up in the same fashion, underscoring the requirement for appropriate control groups whenever assessing the effect of an intervention [20].

The same objections pertain to cost analyses demonstrating post-implantation reductions in healthcare consumption, including hospitalizations, duration of hospital stays and outpatient visits [21–25]. The majority of our patients received VNS as a last resort treatment option after rejection for epilepsy surgery or after a long period of time-consuming and futile therapeutic attempts. The evaluation for surgical treatment invariably requires numerous hospitalizations and various costly and sophisticated investigations. The implantation often coincides with the beginning of a new stage of life characterized by resignation and reorientation after the completion of a very challenging period of medical assessments. Conceivably, similar confounders are present in studies which has compared pre-and post-implantation health care expenses. Likewise, the onset of VNS treatment may be associated with a new and stabilized psychosocial situation, which by itself may have a positive impact on seizure control.

4.4. Study limitations and strengths

The small number of patients is an obvious weakness of this study, but in other respects a strength, as all these patients received close comprehensive follow-up of all aspects of their epilepsy by the author group throughout the years of VNS treatment as well as during the prospective study year. Particularly in patients with long-standing VNS, a recall bias may have influenced their beliefs about the effect of the treatment, conceivably affected by the potential confounding factors discussed above. Furthermore, a preselection towards perceived benefit probably was present as a total of 14 implant patients had already discontinued stimulation prior to the study due to lack of efficacy or

side effects (Fig. 1). Also, the follow-up time of one year after stopping therapy may be considered short, given the hypothesis that VNS may have long-term disease-modifying and antiepileptogenic properties [4,7,8], which in turn might take time to wane.

Most patients received standard treatment with stimulation for 30–60 s every five to three minutes with recommended duty cycles [9]. Only few patients received rapid cycling stimulation with shorter intervals and stimulation times, as the clinical evidence of an enhanced efficacy from these parameters is limited [26,27]. Subtle effects on mood, cognition and wakefulness could not be appropriately assessed in this real-world study, but changes were not obvious after cessation of treatment.

Moreover, it should be acknowledged that small single-centered studies may be prone to author biases. Nonetheless, the overall attitude of the treatment providers was fundamentally positive to non-pharmacological stimulation treatment with automatic adherence for patients with drug-resistant epilepsy who often is burdened by overmedication and cognitive deficits.

5. Conclusion

The overall effectiveness of long-term VNS in real world-practice is difficult to evaluate in drug treatment-resistant epilepsy. The introduction of novel AEDs as well as the natural course of chronic epilepsy may bias the outcome assessment. Half of the patients in this study did not experience benefit from long-term VNS, and all but one could discontinue treatment without apparent deterioration within one year.

Patients without benefit from VNS should not routinely be subject to undue re-implantations when generator expiration is pending, as this is expensive and exposes the patients to needless surgery. Unnecessary repeated visits to the clinic with focus on the stimulation treatment rather than on other aspects of epilepsy management should be avoided. Moreover, a large proportion of patients reports adverse effects, sometimes experienced as troublesome. In addition, an implanted VNS device may limit required MRI examinations.

VNS has been around for nearly three decades, but the true effect of this mode of treatment is still unsettled and is easily overestimated during long-term treatment due to confounding factors. Hopefully, ongoing and future technological developments will optimize neuromodulation therapy and allow for sound scientific evidence of its effectiveness in epilepsy.

Declaration of Competing Interest

None.

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