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FULL-LENGTH ORIGINAL RESEARCH

Norwegian population-based study of long-term effects, safety, and predictors of response of vagus nerve stimulation treatment in drug-resistant epilepsy: The NORPulse study

Konstantin H. Kostov[1] | **Hrisimir Kostov**[1] | **Pål Gunnar Larsson**[2] | **Oliver Henning**[1] | **Christian Alexander Cornelius Eckmann**[1] | **Morten Ingvar Lossius**[1,3] | **Jukka Peltola**[4]

[1]National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

[2]Neurosurgical Department, Oslo University Hospital, Oslo, Norway

[3]Institute for Clinical Medicine, University of Oslo, Oslo, Norway

[4]Department of Neurology, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

Correspondence
Konstantin H. Kostov, National Center for Epilepsy, Oslo University Hospital, G. F. Henriksensvei 29, Sandvika, Oslo, Norway.
Email: konstantin.kostovbg@gmail.com

Funding information
National Center for Epilepsy in Sandvika, Norway

Abstract

Objective: This study was undertaken to evaluate the efficacy of vagus nerve stimulation (VNS) over time, and to determine which patient groups derive the most benefit.

Methods: Long-term outcomes are reported in 436 epilepsy patients from a VNS quality registry (52.8% adults, 47.2% children), with a median follow-up of 75 months. Patients were stratified according to evolution of response into constant responders, fluctuating responders, and nonresponders. The effect was evaluated at 6, 12, 24, 36, and 60 months. Multivariate regression analysis was used to identify predictors of response.

Results: The cumulative probability of ≥50% seizure reduction was 60%; however, 15% of patients showed a fluctuating course. Of those becoming responders, 89.5% (230/257) did so within 2 years. A steady increase in effect was observed among constant responders, with 48.7% (19/39) of those becoming seizure-free and 29.3% (39/133) with ≥75% seizure reduction achieving these effects within 2–5 years. Some effect (25%–<50%) at 6 months was a positive predictor of becoming a responder (odds ratio [OR] = 10.18, $p < .0001$) and having ≥75% reduction at 2 years (OR = 3.34, $p = .03$). Patients without intellectual disability had ORs of 3.34 and 3.11 of having ≥75% reduction at 2 and 5 years, respectively, and an OR of 6.22 of being seizure-free at last observation. Patients with unchanged antiseizure medication over the observation period showed better responder rates at 2 (63.0% vs. 43.1%, $p = .002$) and 5 years (63.4% vs. 46.3%, $p = .031$) than patients whose antiseizure medication was modified. Responder rates were higher for posttraumatic (70.6%, $p = .048$) and poststroke epilepsies (75.0%, $p = .05$) than other etiologies (46.5%).

Significance: Our data indicate that the effect of VNS increases over time and that there are important clinical decision points at 6 and 24 months for evaluating and adjusting the treatment. There should be better selection of candidates, as certain patient groups and epilepsy etiologies respond more favorably.

KEYWORDS
drug-resistant epilepsy, long-term effect, population study, predictors of response, VNS

1 | INTRODUCTION

Drug-resistant epilepsy (DRE) is reported in 20%–30% of patients with epilepsy.[1–3] Vagus nerve stimulation (VNS) became an approved treatment for patients with DRE not amenable to epilepsy surgery following randomized controlled trials (RCTs) showing the efficacy of VNS.[4–6] As the mechanisms of action of VNS and appropriate dosing were unknown, the design of the regulatory RCT for VNS was modeled on antiseizure medication (ASM) trials.[7] However, this design may be suboptimal for understanding the true efficacy of VNS treatment, as retrospective studies have since reported progressive effects over time.[8–11]

Although VNS therapy was initiated 30 years ago, several issues regarding evolution of response over time and patient selection remain poorly defined.[12] Comprehensive, long-term follow-up studies in a well-characterized patient population are needed to assess the real-world effectiveness of VNS. Thus, we wanted to evaluate the efficacy of VNS therapy over time for an extended follow-up period in a large, consecutive, well-characterized patient cohort in which patients were followed up and data recorded in a quality register. Furthermore, we wanted to identify predictive factors that accounted for the fluctuating course of epilepsy, as well as control for other confounding factors such as changes in ASMs.

Key Points

- In this population-based cohort, the effect of VNS on seizure reduction increases over time with unchanged ASMs
- Important clinical decision points for evaluating and adjusting the treatment effects were identified at 6 and 24 months
- Patients without intellectual disability had a higher chance of achieving ≥75% seizure reduction or seizure freedom
- Patients with poststroke and posttraumatic etiology achieved significantly better effect
- The treatment was generally well tolerated, and most of the adverse effects reported initially improved over time and with adjustment of stimulation parameters

2 | MATERIALS AND METHODS

2.1 | Patient selection and demographics

We obtained patient data from the VNS quality registry at the National Center for Epilepsy (NCE). For this study, all patients implanted from July 1, 1993 to December 31, 2012, with a minimum follow-up of 6 months until the end of 2017, were included. This cohort accounts for approximately 90% of all VNS-operated patients during that period in Norway.

All patients had DRE and were evaluated for epilepsy surgery by a multidisciplinary team through the national epilepsy surgery program. The diagnosis was confirmed by long-term video-electroencephalographic recordings of habitual seizures, which were used for classification into focal or generalized epilepsy. Patients were offered VNS treatment if they were considered ineligible for epilepsy surgery.

The study population initially consisted of 462 patients (flowchart in Figure 1; 53.8% male, 46.1% female, 47.2% <18 years and 31.6% <12 years of age); 52.8% ($n = 244$) had intellectual disability (ID), which was moderate or severe in 26.8% ($n = 124$). The diagnosis of ID was obtained from the medical record, which was based on clinical and neuropsychological evaluation. Median age at implantation was 19.5 years (interquartile range [IQR] = 1–34). Median age at epilepsy onset was 3.5 years (IQR = .8–9.0), and median duration of epilepsy before implantation was 13.0 years (IQR = 7.0–25.0). Median observation period was 75.0 months (IQR = 43–120). A total of 414 patients were implanted after the year 2000.

Efficacy data for 26 patients were missing (Figure 1), and therefore efficacy analysis was performed on 436 patients (NCE cohort). However, data from all 462 patients were included in demographics, etiology, and device-safety analysis.

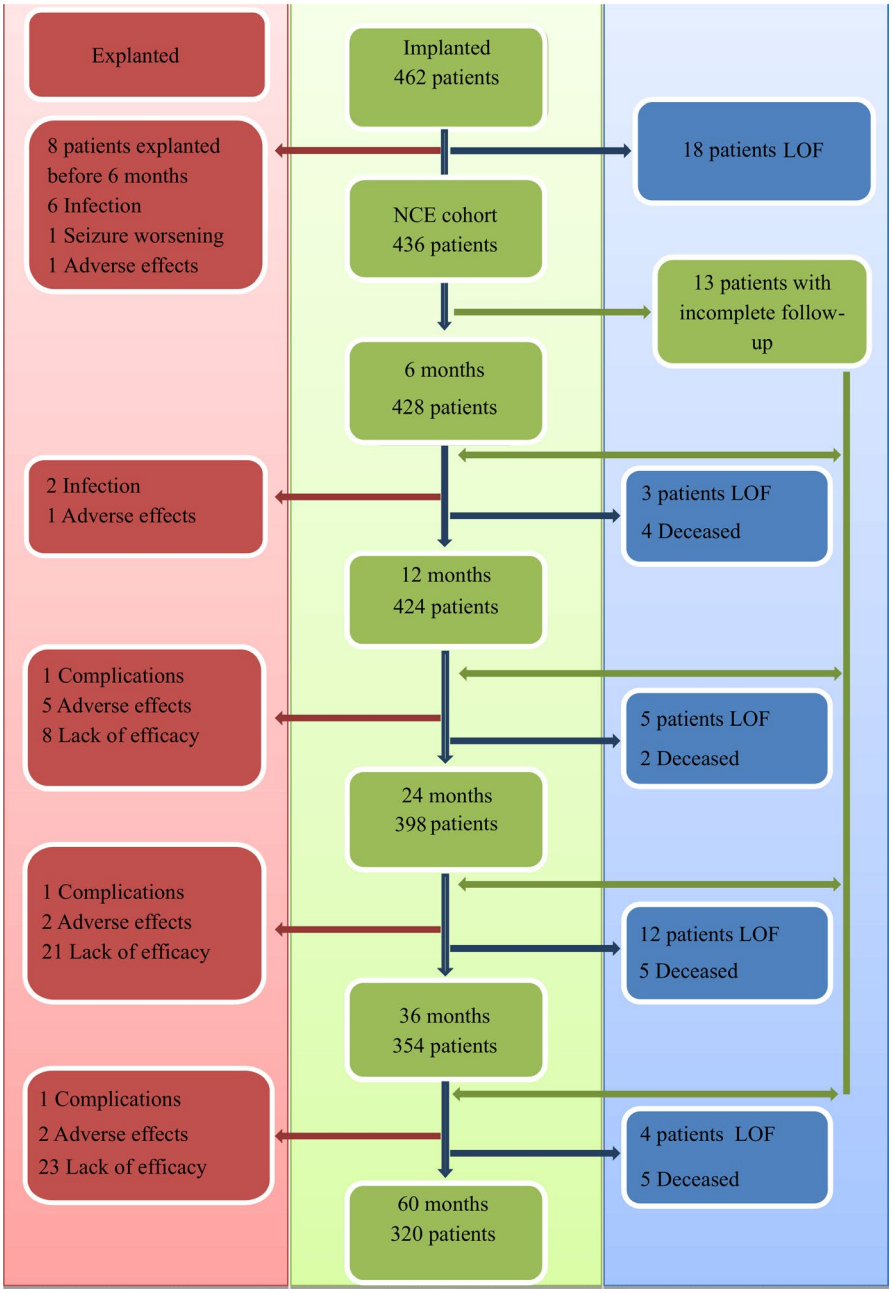


FIGURE 1 Flowchart of patient inclusion. Patients with incomplete follow-up ($n = 13$) are depicted with double-sided arrows to indicate that these patients did not complete all appointed controls. LOF, lost to follow-up; NCE, National Center for Epilepsy

2.2 | Study design

A baseline assessment occurred over the 3 months prior to implantation. Seizure count was based on seizure diaries and recording seizures during hospitalization. Most patients with absences and myoclonic jerks had multiple seizures daily, some of which were not perceived by the patients themselves. Thus, for these seizure types, the mean number of seizures per month was either estimated by the patient by counting all seizures for several days or classified as "many hourly," "many daily," "daily," or "less frequently than daily." Changes in seizure frequency for these seizure types could thereby be roughly estimated and were not included in the analysis on total seizure frequency.

Total seizure burden was evaluated and compared for each patient with baseline at the following time points: 6, 12, 24, 36, and 60 months, and last observation carried forward. Seizure frequency at each time point was the mean number of seizures per month for the previous 3 months.

Efficacy analysis was performed for the following groups: intention-to-treat (effect analysis according to all patients included in the study, $n = 436$), per-protocol (all patients followed for at least 5 years with effect data for all time points, $n = 314$), and cross-sectional (patients who are still in the study at each time point; 6 months, $n = 428$;

12 months, $n = 424$; 24 months, $n = 398$; 36 months, $n = 354$; 60 months, $n = 320$).

According to different patterns of seizure response, patients were stratified into constant responders (CRs), fluctuating responders (FRs), and nonresponders (NRs). CRs were defined as reporting a stable or progressive reduction in seizures of ≥50% for at least two consecutive periods and until the end of observation. FRs had an unstable pattern of response, whereby they were responders at some point in time, but later had at least two periods with <50% response. NRs did not achieve ≥50% seizure reduction at any time during the observation period.

The classification of outcomes by McHugh et al.[13] was modified, and patients were categorized into five classes according to effect:

Class I: seizure-free.
Class II: ≥75% seizure reduction (subdivided into ≥75%–90% and >90%–99% for some analyses).
Class III: 50%–<75% seizure reduction.
Class IV: some effect, but not responders (25%–<50% seizure reduction).
Class V: no effect or worsening.
Classes II–IV were further subdivided: Class A, improved ictal or postictal severity; Class B, no improvement.[13] Assessment of changes in mood and alertness, improvement in ictal or postictal severity, and the effect of the magnet were based on the patients' or caregivers' subjective accounts.

2.3 | VNS surgery and stimulation adjustment strategy

Patients were implanted with Models 100–106, most frequently Model 103, at the Department of Neurosurgery, Oslo University Hospital. Patients were subsequently transferred to NCE for an average hospitalization of 10–14 days, which is also the current practice. The standard initial stimulation parameters were 30 s on/5 min off, output current (OC) = .25 mA, frequency = 20 Hz, and pulse width = 250 μs; prior to 2002, frequency = 30 Hz and pulse width = 500 μs were used. The OC goal of .75–1.25 mA was achieved in ≥95% of patients during hospitalization. Patients were instructed to use the magnet routinely for all detected seizures.

Follow-up visits for interrogation and adjustment of the device were scheduled every third month. Adjustments of stimulation parameters were attempted in all patients according to effect/tolerance following a uniform protocol. Following implantation, the first step was to increase the OC gradually up to 1.5–2.00 mA depending on tolerance. If effect was insufficient, duty cycle was gradually increased to more frequent and shorter stimulation toward rapid cycling: 30 s on/3 min off (16%), 30 s on/1.8 min off (25%), 21 s on/.8 min off (36%), and 7 s on/.3 min off (44%). Subsequently, saturation stimulation with 60 s on-time and increase in duty cycling was attempted: 60 s on/5 min off (18%); 60 s on/3 min off (27%); 60 s on/1.8 min off (38%); 60 s on/1.1 min off (51%). If changes in duty cycling were ineffective or not tolerated, the duty cycle was changed to the standard 30 s on/5 min off and increase in pulse width to 500 μs and/or frequency to 30 Hz were attempted. The last step was to increase duty cycling to 7 s on/.3 min off or 60 s on/1.1 min off with changed pulse width and frequency. If there was no perceived decrease in seizure frequency or other positive effects, the stimulator was turned off for a minimum of 3 months, during which time ASMs were kept unchanged, to evaluate whether the VNS had any possible positive effect before eventual explantation.

Data after each visit were recorded in the VNS quality register by one of the authors (H.K.). An anonymized research database was established in January 2018 based on the quality register.

2.4 | Statistics

Nonparametric values are provided where data were not normally distributed. Significance testing was performed with Pearson chi-squared tests (χ^2), Student *t*-tests, and Wilcoxon signed-rank test. The two-sided significance threshold was defined as $p \leq .05$, whereas near significant trends were defined as $p \leq .10$. Multivariate logistic regression analysis with odds ratios (ORs) and 95% confidence intervals (CIs) were performed to identify predictors of effect. Independent variables included in the analysis were sex, age at epilepsy onset, duration of epilepsy before VNS, epilepsy type, etiology, changes in medication, and ID. The dependent variables were seizure frequency, responder rate (percentage of patients with ≥50% seizure reduction), Class I effect (seizure freedom), and Class II effect (≥75% seizure reduction).

The statistical analysis was performed with IBM SPSS v26. The table and figures were made in Microsoft Excel 2019, Tableau v10, and R.

3 | RESULTS

3.1 | Effect following VNS implantation

We found a significant reduction in the median number of monthly seizures, excluding myoclonic and absence seizures, from 35.0 (IQR = 10.0–100.0) at baseline to 15.0

(IQR = 3.0–48.0) at the last observation ($p < .005$). Among the 436 patients, 44.0% ($n = 192$) were CRs, 14.9% ($n = 65$) were FRs, and 41.5% ($n = 181$) were NRs.

The longitudinal follow-up represented in Figure 2 shows the cumulative probability of achieving an effect. Of those who reported being a responder at some point (CR+FR), 89.5% ($n = 230$) did so within 2 years. The cumulative probability of seizure freedom at 5 years was 10.5% ($n = 46$), of which 39 patients (8.9%) were among the CRs. Four patients among the FRs became seizure-free after changes of ASMs. In total, 69.3% ($n = 133$) reported Class I and II effect (i.e., seizure-free and ≥75% effect) among CRs compared with 36.9% ($n = 24$) among FRs. An earlier effect was seen in FRs, with 37.5% in this group reporting a Class II effect at 6 months compared with 18.0% among CRs. A steady progression in effect was observed among CRs, with 29.3% ($n = 39/133$) of those reporting ≥75% reduction doing so within 2–5 years. Nineteen of 39 patients (48.7%) became seizure–free within 2–5 years. Twenty-four patients (5.2%) were lost to follow-up between 6 and 60 months; 14 of those had ≥50% seizure reduction, and three were seizure-free at their last observation at NCE.

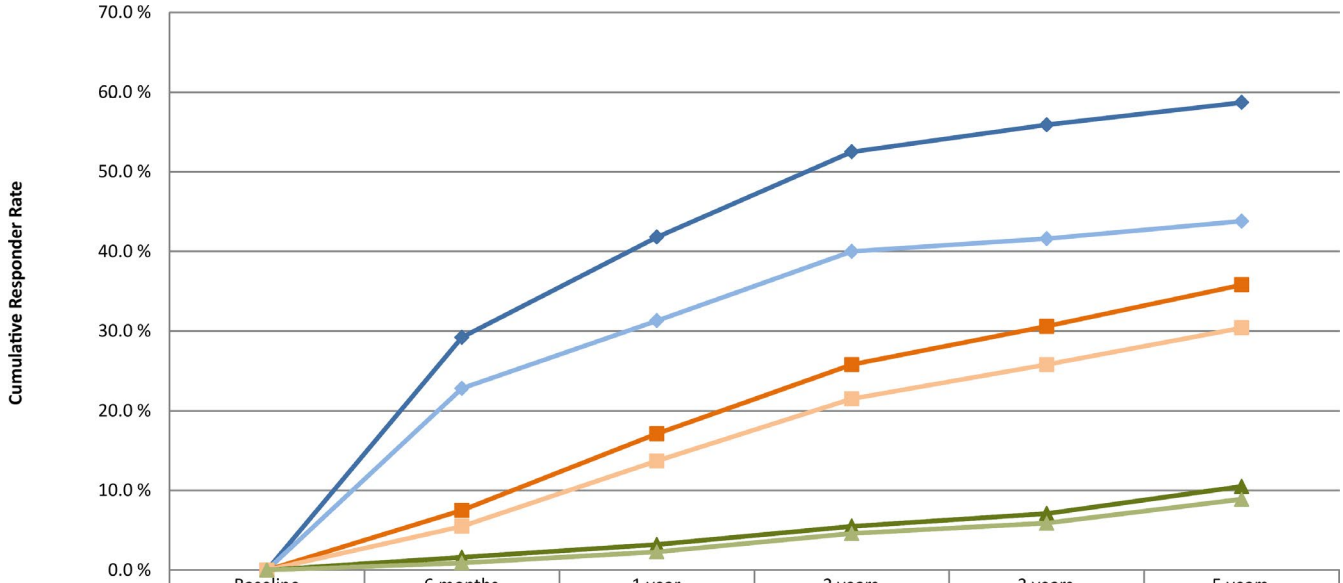
Effect over time is represented in Figure S1 for three different groups: intention-to-treat, per-protocol, and cross-sectional. Progressive effect over time was observed for all three groups.

3.2 | Predictors of effect

Of the 462 patients enrolled initially, epilepsy was classified as focal in 53.6%, generalized in 43.1%, and unclassified in 3.1%. Etiology was identified in 60.0% (Figure 3).

The best effect was observed in posttraumatic epilepsy (PTE; 70.6% responders; $p = .048$, χ^2) and poststroke epilepsy (75.0% responders; $p = .05$, χ^2), compared 46.5% for other etiologies. Furthermore, PTE and poststroke epilepsy had a higher chance of achieving Class I and II effect, respectively 47.0% and 50.0% compared to 30.8% for other etiologies. Regression analysis showed the same trend, with p-value of .066 and .075 for PTE and poststroke epilepsy, respectively (Figure 3). A tendency to respond less favorably to VNS was observed for tumor (32.3% responders, 0% seizure freedom) and infectious etiologies (27.3% responders, 3.2% seizure freedom).

The short-term result "some effect but not a responder (25%–<50%; Class IV)" at 6 months was a strong predictor of both becoming a responder, and later Class I and Class II



	Baseline	6 months	1 year	2 years	3 years	5 years
Class III - All	0.0.%	29.2 %	41.8 %	52.5 %	55.9 %	58.7 %
Class III - CR*	0.0 %	22.8 %	31.3 %	40.0 %	41.6 %	43.8 %
Class II - All	0.0.%	7.5 %	17.1 %	25.8 %	30.6 %	35.8 %
Class II - CR*	0.0 %	5.5 %	13.7 %	21.5 %	25.8 %	30.4 %
Class I - All	0.0 %	1.6 %	3.2 %	5.5 %	7.1 %	10.5 %
Class I - CR*	0.0 %	0.9 %	2.3 %	4.6 %	5.9 %	8.9 %

FIGURE 2 Cumulative probability for all patients of becoming a responder. The constant responder (CR*) group is compared with all responders, the difference between the groups being the fluctuating responders. Class I, seizure-free; Class II, 75%–99% seizure reduction; Class III, 50%–74% seizure reduction. Patients with better response rates are included in Classes II and III, as depicted in this figure. Three patients in the constant effect group had breakthrough seizures and were no longer seizure-free at the last observation, but nevertheless had ≥75% effect

	No (%)	Median Seizure reduction	Class I (Seizure-free)	Class II (75 % - 99 %)			Class III (50 % - 74 %)			Class I - III (>50 %)	*p*-Value [a]	*p*-Value[b]	Odds ratio (95 % CI)
				Total	A	B	Total	A	B				
Genetic	97 (21.0 %)	35.2 %	12.8 %	26.1 %	23.9 %	2.2 %	7.6 %	6.5 %	1.1 %	46.5 %	.87	.68	1.11 (0.68 – 1.80)
MCD	53 (11.5 %)	41.7 %	8.5 %	23.4 %	23.4 %	0.0 %	12.8 %	10.6 %	2.1 %	44.7 %	.85	.76	0.95 (0.70 – 1.30)
Perinatal asphyxia	36 (7.8 %)	50.0 %	15.6 %	12.5 %	12.5 %	0.0 %	25.0 %	15.6 %	9.4 %	53.1 %	.35	.49	1.09 (0.86 – 1.39)
Infection	32 (6.9 %)	44.0 %	3.2 %	19.4 %	16.1 %	3.2 %	9.7 %	9.7 %	0.0 %	32.3 %	.09	.09	0.85 (0.70 – 1.03)
Trauma	17 (3.7 %)	68.0 %	17.6 %	29.4 %	17.6 %	11.8 %	23.5 %	17.6 %	5.9 %	70.6 %	.05	.07	1.22 (0.99 – 1.52)
Post-stroke	13 (2.9 %)	75.0 %	8.3 %	41.7 %	25.0 %	16.7 %	25.0 %	25.0 %	0.0 %	75.0 %	.05	.08	1.19 (0.98 – 1.44)
Tumor	12 (2.6 %)	26.2 %	0.0 %	0.0 %	0.0 %	0.0 %	27.3 %	27.3 %	0.0 %	27.3 %	.18	.23	0.87 (0.70 – 1.09)
Unknown	185 (40.0 %)	40.0 %	7.8 %	19.8 %	17.4 %	2.4 %	18.0 %	14.4 %	3.6 %	45.5 %	.69	.67	1.00 (0.98 – 1.02)
Total		42.9 %	9.2 %	21.6 %	18.5 %	3.1 %	15.7 %	12.4 %	3.3 %	46.5 %			

FIGURE 3 Classification of outcome according to etiology. Etiologies with fewer than 10 patients are not included in the figure. Patients with mesial temporal sclerosis ($n = 7$) had a median seizure reduction of 30.0%, and 42.9% were responders; none of the three patients with global hypoxia were responders and had a median seizure reduction of 29.4%; all three patients with degenerative etiology were responders, with a median seizure reduction of 60.0%. The two patients with metabolic etiology were not responders. Green indicates better response than the mean, whereas red indicates poorer response than the mean. Darker shades indicate larger deviation from the mean. Significant *p*-values (<.05) and *p*-values <.10 are also color-coded; green indicates significant difference and red close to significant difference. *Two-sided Pearson chi-squared with significance threshold of .05. **Multivariate regression analysis adjusted for the following independent variables: sex distribution, epilepsy duration, and intellectual disability. A, improved ictal or postical severity; B, no improvement in ictal or postictal severity; CI, confidence interval; MCD, malformations of cortical development

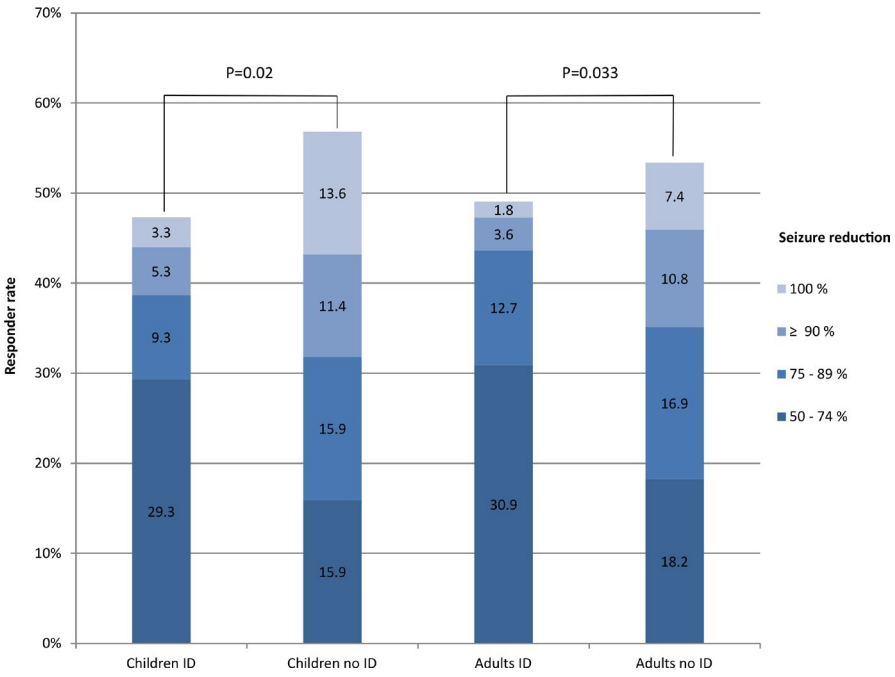


FIGURE 4 Responder rates in adults and children with or without intellectual disability (ID) at 2-year follow-up. Significance was tested by χ^2

effects when compared to "no effect" at 6 months. Patients who reported ≥75% reduction at 2 years had a significantly higher likelihood of having ≥50% effect at 5 years than patients with 50% seizure reduction at 2 years (OR = 4.92, 95% CI = 1.87–12.96). Patients without ID had ORs of 3.34 (95% CI = 1.50–7.45) and 3.11 (95% CI = 1.47–6.58) of having ≥75% reduction at 2 and 5 years, respectively, and of being seizure-free at the last observation (OR = 6.22, 95% CI = 1.61–24.00). We saw no significant difference in effect between adults and children, including children aged <12 years (Figure 4). Although type of epilepsy was not a predictor of being a responder, patients with generalized epilepsy were more likely to be seizure-free at the last observation (OR = 4.25, 95% CI = 1.13–15.95). Although epilepsy duration was not a predictor of being a responder or having ≥75% reduction later, patients with duration < 10 years were more likely to be responders at 1 year (Table 1 and Figure 3).

Prior to VNS implantation, 50 patients (10.8%) had previously had epilepsy surgery, 40 patients had resective surgery of whom 19 were reoperated, eight patients had corpus callosotomy, and two patients had been treated with gamma knife. We saw no significant difference in effect of VNS between patients with prior surgery and those without (data not shown).

TABLE 1 Predictors of effect

		≥50% effect at 1 year		≥50% effect at 2 years		≥75% effect at 2 years		≥75% effect at 5 years		Seizure-free at last observation	
	n	Odds ratio (95% CI)	*p*[a]	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Sex											
Male [ref]	249	1		1		1		1		1	
Female	213	.74 (.38–1.43)	.37	1.15 (.64–2.07)	.64	1.80 (.84–3.86)	.13	.91 (.46–1.81)	.79	.42 (.12–1.49)	.18
Duration											
>10 years [ref]	258	1		1		1		1		1	
<10 years	194	2.04 (1.01–4.11)	.046[b]	1.44 (.78–2.66)	.25	1.06 (.47–2.40)	.88	1.25 (.62–2.54)	.54	1.84 (.56–6.10)	.32
ID											
No ID [ref]	215	1		1		1		1		1	
ID	230	1.39 (.68–2.84)	.36	1.03 (.55–1.94)	.93	.44 (.19–1.00)	.05[b]	.32 (.15–.68)	.003[b]	.16 (.04–.62)	.008[b]
Effect at 6 months											
No effect [ref]	170	1		1		1		1		1	
Some effect [25%–<50%]	130	28.5 (11.48–7.84)	<.0001[b]	10.18 (5.50–18.87)	<.0001[b]	3.34 (1.50–7.45)	.03[b]	2.16 (1.08–4.32)	.029[b]	1.77 (.56–5.61)	.33
Type of epilepsy											
Focal [ref]	249	1		1		1		1		1	
Generalized	199	.71 (.35–1.47)	.36	1.16 (.62–2.20)	.64	1.08 (.47–2.49)	.85	1.84 (.87–3.89)	.11	4.25 (1.13–15.95)	.032[b]

Abbreviations: CI, confidence interval; ID, intellectual disability.

[a]Multivariate regression analysis adjusting for gender, age, duration, ID, and type of epilepsy.

[b]Statistically significant.

3.3 | Antiseizure medications

The mean number of ASMs at implantation was 2.4, with a mean of 9.1 different ASMs having been tried previously. We saw no difference in number of ASMs used before and after implantation. Medication remained unchanged in 27.3% (126/462), and for 17.3% (80/462) the number and/or dosage of ASMs decreased. Among CRs, 53.1% (102/192) had the same or reduced ASMs. In the whole cohort, 48.7% (225/462) changed ASMs, with incomplete data about ASMs for 6.7%.

Patients with unchanged ASMs had better responder rates at both 2 years (63.0% vs. 43.1%, $p = .002$; Figure 5) and 5 years (63.4% vs. 46.3%, $p = .031$). No significant differences were found between those who changed ASMs and those who did not, regarding the following variables: sex, debut, duration, epilepsy type, etiology, ID, and number of ASMs tried before VNS implantation.

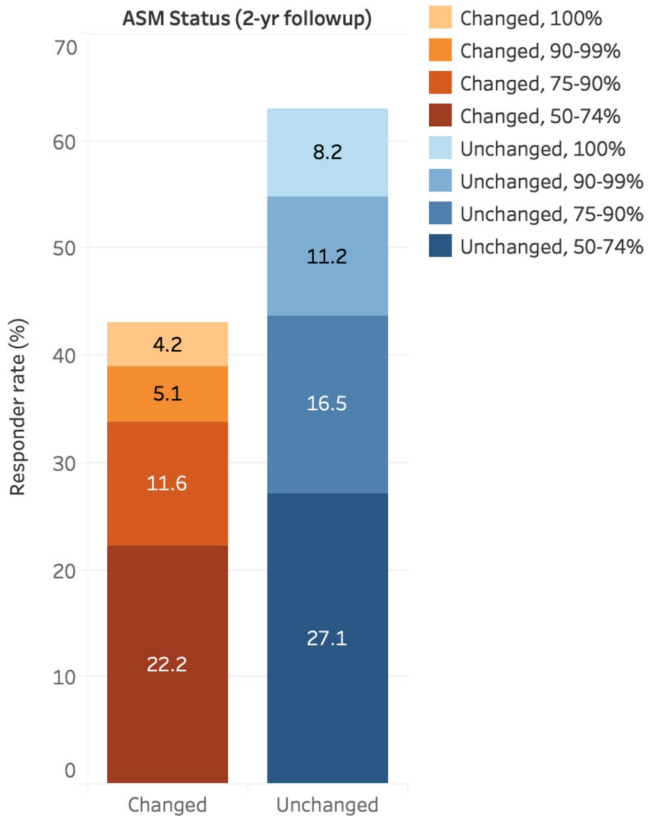


FIGURE 5 Total responder rate (%) according to change in antiseizure medications (ASMs). "Changed" includes changes in ASMs or increased dosage ($n = 225$). "Unchanged" ($n = 206$) includes no changes ($n = 126$) or reduction of dosage/number of ASMs ($n = 80$). Data were incomplete for 31 patients who are not included in this analysis. Significance was tested by χ^2

3.4 | Other positive effects

Improvement in ictal or postictal severity was reported in 67% (Class A).[13] A positive effect of the magnet was reported in 49% of all patients, 57% among responders and 44% among NRs. Increased alertness was reported in 46.8% of all patients, 59% among responders and 30% among NRs, and 3% of all patients reported reduced alertness. Seventeen patients had one or several status epilepticus episodes in the 5 years prior to implantation compared with five patients in the 5 years after implantation ($p < .0005$, χ^2).

3.5 | Adverse effects/postoperative complications

VNS was generally well tolerated; 72.4% reported adverse effects (AEs) during the first year of observation, with 38.4% reporting more than one AE. Most AEs were mild and improved over time and with adjustment of stimulation parameters (Figure S2); 19.2% experienced seizure worsening; 8.9% experienced increase in frequency, of which some had more severe seizures; and 10.3% experienced only longer seizures. These mostly resolved following adjustment of stimulation parameters. A total of 27.4% experienced no AEs, and 80.5% reported no AEs at the last observation.

Postoperative complications were seen in 18.1%. The most common were lead breakage/fibrosis (10.1%) and infection (4.1%). A total of 16.0% were explanted: 1.7% due to infection, .6% due to lead breakage, 2.2% due to AEs, 1.7% due to seizure worsening, and 9.7% due to lack of efficacy (Figure 1).

Our cohort included 3090 person-years of follow-up and 31 deaths, including 10 probable SUDEP or seizure-related deaths, in which cases seven reported ≥50% effect at the last observation and one was seizure-free. SUDEP rate was 3.27/1000 for the whole observation period. Median age of death was 26 years (IQR = 15–47 years). Median follow-up of the deceased patients was 61 months after VNS implantation (IQR = 39–100 months).

4 | DISCUSSION

In this large epilepsy cohort ($n = 436$), we provide new, clinically relevant information on prognostic factors related to the patient outcomes and evolution of response by defining important decision points over the course of VNS treatment. Furthermore, we provide a more granular definition of being a responder to VNS therapy. We found that the cumulative probability of being a responder following

VNS implantation was almost 60%. However, for 15% of patients, the course was fluctuating. Despite the very refractory population, 44% were CRs, with increasing effect over time; 69% of CRs had ≥75% seizure reduction, and 10% were seizure-free at last observation. In both adults and children, patients without ID had the best seizure outcomes. Moreover, certain etiologies, such as PTE and poststroke epilepsy, were associated with better responses. Some effect after 6 months of VNS therapy was predictive of being a responder later. Most patients who became responders did so within 2 years of follow-up. Our results indicate that there are important clinical decision points at 6 months and 2 years, which can be used for evaluating the likely success of VNS therapy as well as whether VNS should be continued.

Patients in our study were stratified into three groups to account for fluctuating responses over time: CRs (44.0%), FRs (14.9%), and NRs (41.5%). An increasing effect over time was observed, with the most pronounced increase among CRs, which accounted for most of the patients with Class I (seizure-free) and Class II effect (≥75%). Moreover, 53.1% of CRs had unchanged or reduced ASMs during the observation period, indicating this reflects the "true" efficacy of VNS. Other positive effects included increased alertness, reduced duration and strength of the seizures, shorter postictal phase, and fewer episodes of status epilepticus. The treatment was generally well tolerated, with decreasing side effects over time, and at the last observation, 80.5% reported no AEs. We saw different patterns of response in the two responder groups, with 37.5% among FRs reporting Class I and Class II effects at 6 months compared with 18% among CRs. This earlier effect among FRs may be partly due to placebo effect, associated with higher expectations related to surgical interventions, or may represent the regression to mean effect.[14] Experiencing some effect although not being a responder (25%–<50%, Class IV) at 6 months compared to no effect was also a strong predictor of both becoming a responder later (OR = 28.5 at 1 year, 10.18 at 2 years) and having ≥75% reduction at 2 years (OR = 3.34).

Reduction in the number of responders was observed between 24 and 60 months in the intention-to-treat and per-protocol groups; 58.3% of patients transferred to other centers were responders at the last observation, and a possible explanation for the reduction in responders could be that patients with good effect are more likely to be transferred for follow-up elsewhere, whereas patients with more refractory epilepsy are followed up at NCE.

VNS studies have been criticized for drawing conclusions about the efficacy of the treatment without considering changes in medication and the fluctuating nature of refractory epilepsy.[15] Several studies have shown that 15%–20% of both newly diagnosed and refractory patients have a fluctuating course of epilepsy.[16–18] One study reported that the cumulative probability of 12-month seizure remission was 33.4% by 7 years, but 71.2% relapsed within 5 years.[19] In most cases, the reasons for fluctuations are unknown, and this topic requires further investigation. A recent article proposed that controlled prospective studies over longer periods are best suited to evaluate the real-world effect of VNS.[7] However, other authors note that difficulties may arise from attempting to assess a surgical intervention in an open-label randomized trial, as patients are reluctant to be randomized over longer periods and surgical interventions create larger expectations of effect, which increases the placebo effect in the surgical group.[14] Thus, long-term follow-up studies like ours may be more appropriate and feasible for assessing the outcome of surgical interventions over time.

Previous studies have shown that VNS reduces seizure frequency by ≥50% in 30%[14] to >50%.[20] A register study described progressive response over time, with 49% being responders and 5.1% achieving seizure freedom 4 months after implantation, compared with 63% being responders and 8.2% seizure freedom at 24–48 months.[21] A meta-analysis of efficacy and predictors of response reported an average reduction in seizure frequency of 45%, with 36% reduction at 3–12 months and 51% reduction after >1 year of therapy.[22]

Having ≥50% seizure reduction is a frequently used endpoint in evaluating VNS, but many patients consider this reduction level as arbitrary; previous studies show that seizure freedom provides the greatest improvement in quality of life.[23–25] Seizure freedom, a quality measure for resective surgery, is rarely achieved in patients with DRE with new ASMs. After the fourth ASM, there is 1% or lower probability of seizure freedom for each new ASM.[26] We found that having ≥75% seizure reduction at 2 years after VNS implantation was a strong predictor of still being a responder at 5 years (OR = 4.92). We therefore propose that "true" VNS responders should be defined as having Class I (seizure freedom) and Class II (≥75%) effect. To achieve this level of response, selection of patients should be improved, as ≥40% were NRs in our study.

Despite their exclusion from initial approval of VNS, we found that both adults and children with generalized epilepsy benefited significantly from VNS and had a higher chance of seizure freedom at the last observation than patients with focal epilepsy (OR = 4.25). The findings are in concordance with a meta-analysis.[22]

Adults and children with ID in our study were less likely to have Class II effect (ORs = .44 and .32 at 2 and 5 years, respectively) and to be seizure-free at the last observation (OR = .16). These findings are in accordance with a meta-analysis that reported VNS to be less effective in pediatric epilepsy patients with ID.[27] To the best of our

knowledge, this negative effect has not been previously reported in adult patients with ID. Some recent studies have shown that there is altered connectivity in patients with ID.[28] One study indicated that patients with Lennox–Gastaut syndrome have abnormal network connectivity in subcortical structures as well as changes in association cortex.[29] These data may partly explain why patients with ID might derive less benefit from VNS implantation.

We found high median seizure reduction (68%) and responder rate (70.6%) at the last observation for PTE, which concurs with results from a previous study.[30] Similarly, we found high median seizure reduction (75%) and responder rates (75%) in patients with poststroke epilepsy, which has to the best of our knowledge not been previously reported. Recent studies have suggested that there is a strong inflammatory component to epileptogenesis in certain epileptic pathologies such as PTE, poststroke epilepsy, temporal lobe epilepsy due to hippocampal sclerosis, and cortical dysplasia.[31–34] It has been recently discussed that vagus nerve has a key role in mediating inflammatory signals between the central nervous system and the periphery. The hypothesis is that the vagus nerve has anti-inflammatory properties through both afferent (activation of the hypothalamic–pituitary–adrenal axis through cytokine receptors of vagal afferents) and efferent fibers (the anti-tumor necrosis factor [TNF] α effect of the cholinergic anti-inflammatory pathway), placing it at the intersection of the brain–gut axis.[35] Based on this hypothesis, Bonaz et al. piloted VNS in patients with Crohn disease; five of seven patients were in clinical, biological, and endoscopic remission 6 months after VNS.[36] Moreover, VNS in patients with rheumatoid arthritis significantly reduced disease severity and inhibited peripheral blood production of TNF, interleukin (IL)-1β, and IL-6.[37]

The SUDEP rate of 3.27/1000 patient-years is in accordance with a previous study, which had an average SUDEP rate of 2.28/1000 patient-years.[38] Furthermore, despite a very refractory population in our study, the SUDEP rate is considerably lower than the SUDEP rate for epilepsy surgery patients (9/1000 patient-years).[39]

Our study's strengths include that it was long term and single center, with patients followed up prospectively using a uniform protocol for adjustment of VNS. To the best of our knowledge, it is also the first population-based nationwide study. All patients were evaluated through the epilepsy surgery program, and patient selection was based solely on medical criteria. We therefore think our study population is representative of patients with DRE and that our findings should be generalizable to other countries. There are several limitations in the study. The statistical analysis was performed on data from the VNS registry, with the inherent limitations of an open-label design, with no control group to account for placebo, lack of data verification, and incomplete data for some patients. These limitations have been addressed by accounting for the natural fluctuation of epilepsy and changes in ASMs, as well as providing efficacy results for three groups: intention-to-treat, per-protocol, and cross-sectional cohorts. Furthermore, ≥70% of patients completed the study protocol by following each scheduled visit for 5 years. A substantial number of patients without ASM changes provides the possibility of assessing the "true efficacy" of VNS.

5 | CONCLUSIONS

Our study provides new data indicating that the effect of VNS increases over time, even if ASMs were unchanged. We identified important clinical decision points at 6 and 24 months for evaluating and adjusting the treatment effects. In selecting suitable candidates, it should be noted that patients without ID had excellent outcomes, with a good chance of achieving >90% response or total seizure freedom. However, many patients with ID chose to continue VNS treatment because of other positive effects on mood and alertness, as well as less-severe seizures and fewer status epilepticus events. We also found that patients with poststroke and posttraumatic etiology achieved significantly better effect.

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CONFLICT OF INTEREST

O.H. reports personal fees from Eisai, UCB, and LivaNova, outside the submitted work. J.P. reports grants, personal fees, or other from Eisai, UCB, and LivaNova, personal fees and other from Medtronic and Orion Pharma, and other from Bial, Arvelle, Novartis, and Pfizer, outside the submitted work. M.I.L. reports personal fees from Eisai, UCB, and Arvelle, outside the submitted work. None of the other authors has any conflict of interest to disclose. The study was approved as a quality improvement project by the Regional Committee for Medical and Health Research Ethics, which determined that informed consent was not required (REK; Ref. Number 2018/2183). The project was also approved by the Norwegian Center for Research Data (Personvernombud; Ref. Number 18/19827). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

All coauthors were substantially involved in the study and/or the preparation of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that there are no undisclosed groups or persons who have had a primary role in the study and/or in manuscript preparation. All coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

ORCID

Konstantin H. Kostov https://orcid.org/0000-0002-7750-4480
Hrisimir Kostov https://orcid.org/0000-0001-6033-9039
Pål Gunnar Larsson https://orcid.org/0000-0002-2248-8970
Oliver Henning https://orcid.org/0000-0001-5562-0854
Morten Ingvar Lossius https://orcid.org/0000-0002-5982-7737
Jukka Peltola https://orcid.org/0000-0002-4119-8063

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SUPPORTING INFORMATION

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