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ORIGINAL ARTICLE

Norwegian population-based study of effectiveness of vagus nerve stimulation in patients with developmental and epileptic encephalopathies

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Abstract

Objective: Evaluate the long-term efficacy of vagus nerve stimulation (VNS) in patients with developmental and epileptic encephalopathies (DEE) compared with epilepsy patients without intellectual disability (ID).

Methods: Long-term outcomes from a Norwegian VNS quality registry are reported in 105 patients with DEEs (Lennox–Gastaut syndrome [LGS] $n=62$; Dravet $n=16$; Rett $n=9$; other syndromes $n=18$) were compared with 212 epilepsy patients without ID, with median follow-up of 88 and 72 months, respectively. Total seizure reduction was evaluated at 6, 12, 24, 36, and 60 months. Effect on different seizure types was evaluated at baseline and last observation carried forward (LOCF).

Results: Median monthly seizure frequency at LOCF was reduced by 42.2% ($p<0.001$) in patients with DEE and by 55.8% ($p<0.001$) in patients without ID. In DEE patients, ≥50% seizure reduction at 6 and 24 months were 17.1% and 37.1%, respectively, and 33.5% and 48.6% for patients without ID. Seizure reduction ≥75% at 60 months occurred in 14.3% of DEE patients and 23.1% of patients without ID. Highest median reduction was for atonic seizures, most notably 64.6% for LGS patients. A better effect was seen at 2 years among DEE patients with unchanged medication compared with those with changed medication (54.5% vs. 35.6% responders, $p=0.078$). More DEE patients were reported to have greater improvement in ictal or postictal severity (43.8% vs. 28.3%, $p=0.006$) and alertness (62.9% vs. 31.6%, $p<0.001$) than patients without ID. For both groups, use of the magnet reduced seizure severity. Hoarseness was the most common adverse effect in both groups. In addition, DEE patients were frequently reported to have sleep disturbance, general discomfort, or abdominal problems.

Significance: Our data indicate that VNS is very effective for atonic seizures. Patients without ID had best overall seizure reduction, however, patients with DEE had higher retention rates probably due to other positive effects.

Plain Language Summary: DEE refers to a group of patients with severe epilepsy and intellectual disability. Many of these patients have restricted lifestyles with frequent seizures. VNS is a treatment option for patients who do not respond well to medicines, either because of insufficient effect or serious adverse effects. Our study shows that VNS is well tolerated in this patient group and leads to a reduction in all seizure types, most notably for seizures leading to fall. Many patients experience other positive effects like shorter and milder seizures, as well as improvement in alertness.

KEYWORDS

atonic seizures, Dravet syndrome, Lennox–Gastaut syndrome, long-term effects, vagus nerve stimulation

1 | INTRODUCTION

The concept of developmental and epileptic encephalopathies (DEE) refers to a group of epilepsies with developmental impairment that may be due to the underlying etiology and/or due to superimposed epileptic activity causing cognitive and behavioral impairment.[1,2] DEEs caused by single gene defects, like Dravet and Rett syndromes, have their onset in infancy or early childhood.[3–5] Lennox–Gastaut syndrome (LGS), which has heterogenous etiologies,[5–7] usually occurs before 8 years of age,[8,9] but about 10%–20% of patients can have late-onset disease.[7,9] The hallmarks of the DEEs are recurrent and severe seizures, along with pathological electroencephalography (EEG) with prominent background slowing and frequent epileptic activity.[10] The burden of DEEs extends far beyond recurring seizures, as many of these patients have severely restricted lifestyles resulting from gait and movement disorders, recurrent infections, and feeding problems, in addition to cognitive and behavioral impairments due to intellectual disability (ID) and autism spectrum disorders. Seizure-related injuries, status epilepticus, and mortality rates[11–14] are increased, with a SUDEP rate of 9.3/1000-person years for Dravet syndrome, the only documented syndrome-specific SUDEP rate.[15]

LGS is associated with a poor prognosis regarding both seizure control and cognitive outcome,[16] while patients with Dravet and Rett syndromes usually enter a stabilization stage after 10–12 years of age.[3,17,18] Despite the emergence of new antiseizure medications (ASM),[19,20] complete seizure freedom is highly unlikely for patients with DEEs.[21] Non-pharmacological treatment methods, like ketogenic diets, corpus callosotomy (CC), and vagus nerve stimulation (VNS), are important in managing this treatment-resistant population.[6,22,23] VNS has been shown to have effect among 40%–65% of patients with LGS.[24,25] Among patients with Dravet syndrome, VNS has been shown to result in ≥50% seizure reduction in 55% and 63% of patients at 24 and 36 months, respectively.[26] The limited knowledge we have regarding the effect of VNS on patients with Rett syndrome is largely based on case series, with 9/11 of cases reported in the literature having ≥50% seizure reduction.[27] We have previously published data on the long-term effects, safety, and predictors of response of VNS treatment in drug-resistant epilepsy, where patients

Key points

- Vagus nerve stimulation effects are investigated in epilepsy patients with developmental and epileptic encephalopathies (DEE) or without intellectual disability (ID).
- Seizure reduction increased over time for all patients, even with unchanged antiseizure medications.
- Atonic seizures had the highest median reduction in seizure frequency.
- Most adverse effects were mild and improved over time; profiles and frequencies of reported adverse events differed between patient groups.
- Seizure reduction was best in patients without ID, but retention rate was higher in patients with DEE.

experienced an increasing effect over time, but ID was a negative predictor of effect.[28]

The aim of the present study was to evaluate the efficacy of VNS treatment in patients with DEEs compared with the effect of VNS treatments on epilepsy patients without ID. As previous studies have mostly reported overall effects without differentiating between seizure types, we also wanted to evaluate the effect of VNS on different seizure types.

2 | METHODS

2.1 | Patient selection and characteristics

We retrieved patient data from the prospective Norwegian National Center for Epilepsy (NCE)'s VNS-quality registry. All patients who had been implanted between July 1, 1993, and December 31, 2012, with a minimum follow-up of 6 months until the end of 2017, were included in this study.

An interdisciplinary team examined all patients for epilepsy surgery as part of the national epilepsy surgery program. Long-term video EEG recordings of habitual seizures had been used to validate the diagnosis and classify the epilepsy. Etiological workup included diagnostic imaging, and, when indicated, immunological, metabolic, and genetic testing. Results from these procedures, together with EEG findings and clinical information, had been used to give specific electroclinical syndrome diagnosis when possible.[2,29] Patients who were considered ineligible for, or had previously failed, epilepsy surgery had been offered treatment with VNS.

From the VNS quality registry, we identified 105 patients with DEE out of a total population of 436 patients with efficacy data (NCE cohort).[28] The group consisted of patients with LGS ($n = 62$), Dravet syndrome ($n = 16$), Rett syndrome ($n = 9$), and 18 with other syndromes. These patients with DEE were compared with patients without ID ($n = 212$). The diagnosis of ID had been based on clinical and neuropsychological evaluation in standard clinical care. No additional neuropsychological evaluations were done as part of the present study.

2.2 | Study design

During the 3 months prior to VNS implantation, a baseline evaluation had been conducted. The number of seizures had been calculated using seizure diaries from patients or caregivers and hospital records. Patients with absences or myoclonic jerks often experienced numerous seizures daily, many of which were not detected by the patients or caregivers. Therefore, changes in the frequency of absences and myoclonic jerks were excluded from the overall analysis of seizure frequency and only reported descriptively. Analysis was conducted for the total amount of seizures and each seizure type, including tonic–clonic seizures (TCS), focal seizures with impaired awareness (FIAS), and tonic and atonic seizures.[30] The effect of VNS treatment on different seizure types was evaluated at baseline and last observation.

Follow-up visits were scheduled every third month. Seizure frequency at each visit was determined by averaging the monthly totals from the previous 3 months. Each patient's total number of seizures, excluding absences and myoclonus, at 6, 12, 24, 36, and 60 months follow-up, and also the last observation carried forward (LOCF) were compared with those at baseline. Effect was analyzed and reported as intention to treat.

The classification of outcomes by McHugh et al.[31] was modified, and patients were categorized into five classes according to the treatment effect observed[28]:

1. Class I—Seizure-free.
2. Class II—≥75% seizure reduction.
3. Class III—≥50% to <75% seizure reduction.
4. Class IV—Some effect but not responders (25% to <50% seizure reduction).
5. Class V—No effect or worsening.

Classes II–IV were further subdivided: Class A, improved ictal or postictal severity; Class B, no improvement[31] Assessment of changes in mood, alertness, improvement in ictal or postictal severity, and the effect of the magnet used were based on the registration of the patients' or caregivers' subjective reports that had been recorded at each visit. Standardized questionnaires were not used in this study.

Previously tried ASMs and those that were in use at baseline and LOCF had been recorded, and information regarding changes in medication was obtained at each visit, with medication changes recorded in the database in one of three categories: "no change," "decrease in dosage or number of ASMs," or "increase in dosage or number of ASMs." Data on the exact changes and when they occurred had not been recorded.

2.3 | VNS surgery and stimulation adjustment strategy

VNS implantation had been performed as outpatient surgery at the Department of Neurosurgery, Oslo University Hospital. Models 100–106 had been used for the first

implantation, most commonly 103 (45%) but 12% of the patients had received model 106 Aspire. Newest available models were used for reimplantations. Patients had then been transferred to NCE for hospitalization for, on average, 10–14 days; this is also the current practice. The standard initial stimulation parameters were as follows: 30 s on/5 min off, output current (OC) 0.25 mA, frequency 20 Hz, and pulse width 250 μs. Prior to 2002, a frequency of 30 Hz and pulse width of 500 μs had been used. The OC goal of 0.75–1.25 mA was achieved in ≥95% of patients during hospitalization. The recommendation was that patients should utilize the magnet routinely for all seizures detected.

Adjustments of stimulation parameters were attempted for all patients according to effect/tolerance and followed a uniform protocol. For detailed information on stimulation strategy, please refer to our previous publication.[28]

2.4 | Statistics

Non-parametric values are provided where data are not normally distributed. Significance testing was performed with Pearson chi-squared test (χ^2), McNemar, Student *t*-test, and Wilcoxon signed-rank test. The two-sided significance threshold was defined as $p \leq 0.05$. As a measure of the spread of the results, we used standard deviation (SD), range, and interquartile range (IQR). Sensitivity analysis was performed in relation to age at implantation and changes in ASM.

The statistical analyses were performed in IBM SPSS v.28.

3 | RESULTS

3.1 | Patient demographics and follow-up

Patient demographics and clinical data for patients with DEE ($n = 105$) and patients without ID ($n = 212$) are summarized in Table 1. Median follow-up was 88 months (IQR: 40–130) for patients with DEE and 72 months (IQR: 39–114) for patients without ID. Median retention rate at 5 years was 75.9% for patients with DEE and 65.1% for patients without ID.

3.2 | Effect following VNS implantation

We found a significant reduction in the median number of monthly seizures, excluding absences and myoclonic jerks, from 70.0 (IQR: 33.0–180.0) at baseline to 39.0 (IQR: 15.0–91.0) seizures at LOCF for patients with DEE, corresponding to a median reduction of 42.2% ($p < 0.001$). The monthly reduction for patients without ID was from 10.0 (IQR: 4.0–30.0) at baseline to 4.0 (IQR: 1.0–11.8) seizures at LOCF, corresponding to a median reduction of 55.8% ($p < 0.001$).

There was a significant increase in responder rate (≥50% seizure reduction, Class III) between 6 and 24 months for all patients with DEE ($p < 0.001$) and patients without ID ($p < 0.001$), as well as in the subgroup of patients with LGS ($p = 0.006$, Figure 1). A trend toward an increase in median responder rate was also observed in patients with Dravet ($p = 0.171$), Rett syndrome ($p = 0.063$), and other epileptic encephalopathies ($p = 0.219$). There were no significant differences in responder rates between 24 and 60 months for any groups. There was significant increase in Class II effect (≥75% seizure reduction) between 6 and 60 months for patients with DEE (from 2.9% to 14.3%, $p = 0.004$) and for patients without ID (from 7.5% to 23.1%, $p < 0.0001$, Figure 2). Seven patients with LGS (11%), three patients with Rett syndrome (25%), and one patient with other DEE syndromes reported Class II at 5 years. None of the patients with DEE became seizure-free (Class I) at any time point. Among patients without ID, 9.0% became seizure-free at 2 years and 12.3% at 5 years. No significant difference in effect according to implantation before or after 12 years of age was found for patients with LGS, or Dravet and Rett syndromes (data not shown).

3.3 | Effect on different seizure types

Seizure reduction for all syndromes and patients is shown in Table 2 and Figure 3. At the group level, there was significant reduction for all seizure types in patients with DEE and patients without ID, but patients without ID had a better overall response. Atonic and tonic seizures responded best to VNS treatment in all patient groups. Patients with LGS had a significant median reduction for TCS (33.3%, $p = 0.001$), atonic seizures (64.6%, $p < 0.001$), tonic seizures (50.0%, $p < 0.001$), and FIAS (33.6%, $p < 0.001$). Seven patients with LGS had previously undergone CC surgery, and of these three were responders and one became free of atonic seizures.

Only patients with LGS had epileptic spasms, and these were reduced by a median of 21.7% ($n = 7$; IQR: 0%–42.7%; range 0%–85%; $p = 0.068$). Seven of 12 LGS patients reported clinically significant reductions in myoclonic jerks and 1 reported becoming free of this seizure type. Five of nine LGS patients with atypical absences reported clinically significant reductions in atypical absences but none were seizure-free. Only patients without ID had reported focal aware seizures, and these were reduced by a median

TABLE 1 Demographics and clinical data.

Demographics	LGS	Dravet	Rett	Other DEE	All DEE	Without ID
N	62	16	9	18	105	212
Sex—*n* (%)						
Female	26 (41.9)	8 (50.0)	8 (88.9)	7 (38.9)	49 (46.7)	100 (47.2)
Male	36 (58.1)	8 (50.0)	1 (11.1)	11 (61.1)	56 (53.3)	112 (52.8)
Age distribution—*n* (%)						
Children (<12 years)	28 (45.2)	13 (81.3)	7 (77.8)	9 (50.0)	57 (54.3)	17 (8.0)
Children (12≤18 years)	15 (24.2)	2 (12.5)	1 (11.1)	4 (22.2)	22 (21.0)	29 (13.7)
Adults (≥18 years)	19 (30.6)	1 (6.2)	1 (11.1)	5 (27.8)	26 (24.8)	166 (78.3)
Epilepsy duration—median (IQR; range)						
Age of debut (years)	1.0 (0.25–3.3; 0–19)	0.6 (0.4–1.0; 0.3–3)	0.8 (0.1–2.3; 0–2)	0.8 (0.1–2.3; 0–8)	0.83 (0.25–3.0; 0–19)	8.0 (3.0–14.0; 0–52)
Duration prior to VNS implantation (years)	10.8 (5.3–18.2; 2–48)	5.5 (3.7–8.0; 3–37)	8.8 (6.5–9.5; 6–21)	10.0 (3.0–18.6; 1–35)	9.0 (5.0–15.0; 2–48)	20.0 (9.6–30.0; 2–65)
Age at VNS implantation (years)	13.0 (7.8–20.0; 2–52)	7 (4.3–8.75; 3–37)	9.0 (8.0–11.5; 6–24)	0.8 (0.1–2.3; 2–42)	11.0 (7.0–17.5; 2–52)	30 (20.0–42.0; 4–67)
Epilepsy classification—*n* (%)						
Focal/multifocal	9 (14.5)	0	4 (44.4)	2 (11.1)	15 (14.3)	162 (76.4)
Generalized	53 (85.5)	16 (100)	5 (55.6)	16 (88.9)	90 (85.7)	50 (23.6)
Etiology—*n* (%)						
Genetic	8 (12.9)	16 (100)	9 (100)	3 (16.7)	36 (34.3)	39 (18.4)
MCD	12 (19.4)	–	–	1 (5.6)	13 (12.4)	19 (9.0)
Perinatal asphyxia	7 (11.3)	–	–	1 (5.6)	8 (7.6)	12 (5.7)
Infection	2 (3.2)	–	–	2 (11.1)	4 (3.8)	14 (6.6)
Trauma	–	–	–	–	–	13 (6.1)
Tumor	–	–	–	–	–	5 (2.4)
Vascular	–	–	–	–	–	7 (3.3)
MTS	–	–	–	–	–	7 (3.3)
Other	–	–	–	2 (11.1)	–	3 (1.4)
Unknown	33 (53.2)	0	0	9 (50.0)	44 (41.9)	93 (43.9)
Mental retardation—*n* (%)						
None	3 (4.8)	–	–	–	3 (2.9)	212 (100)
Unspecified	12 (19.4)	4 (25.0)	2 (22.2)	1 (5.6)	19 (18.1)	–
Mild	12 (19.4)	1 (6.3)	–	–	13 (12.4)	–

(Continues)

TABLE 1 (Continued)

Demographics	LGS	Dravet	Rett	Other DEE	All DEE	Without ID
Moderate	12 (19.4)	5 (31.3)	1 (11.1)	3 (16.7)	21 (20.0)	–
Severe	23 (37.1)	6 (37.5)	6 (66.7)	14 (77.8)	49 (46.7)	–
ASM—mean ± SD (range)						
Number of ASM failed	9.7 ± 2.8 (3–15)	9.3 ± 2.0 (6–13)	11.2 ± 2.5 (7–15)	9.6 ± 2.4 (5–14)	9.8 ± 2.6 (3–15)	8.5 ± 2.3 (2–15)
Number of ASM at implantation	2.6 ± 0.8 (1–5)	2.5 ± 0.6 (1–3)	2.9 ± 0.6 (2–4)	2.3 ± 1.0 (1–4)	2.6 ± 0.8 (1–5)	2.3 ± 0.8 (1–5)
Surgery before VNS—*n* (%)						
Corpus callosotomy	7 (11.3)	0	0	0	7 (6.7)	1 (0.5)
Resection	0	0	0	0	0	15 (7.1)
Reoperation	0	0	0	0	0	17 (8.0)
Gamma knife	0	0	0	0	0	1 (0.5)
Total	7 (11.3)	0	0	0	7 (6.7)	34 (16.0)
Ketogenic diet—*n* (%)						
Prior to VNS implantation	6 (9.7)	3 (18.8)	0	4 (22.2)	13 (12.4)	2 (0.9)

Abbreviations: ASM, anti-seizure medication; DEE, developmental and epileptic encephalopathies; ID, intellectual disability; LGS, Lennox–Gastaut syndrome; MCD, malformation of cortical development; MTS, mesial temporal sclerosis; SD, standard deviation; VNS, vagus nerve stimulation.

of 50% during VNS treatment ($n = 47$; IQR: 20%–86.7%; range −650% to 100%; $p < 0.001$).

3.4 | Antiseizure medications

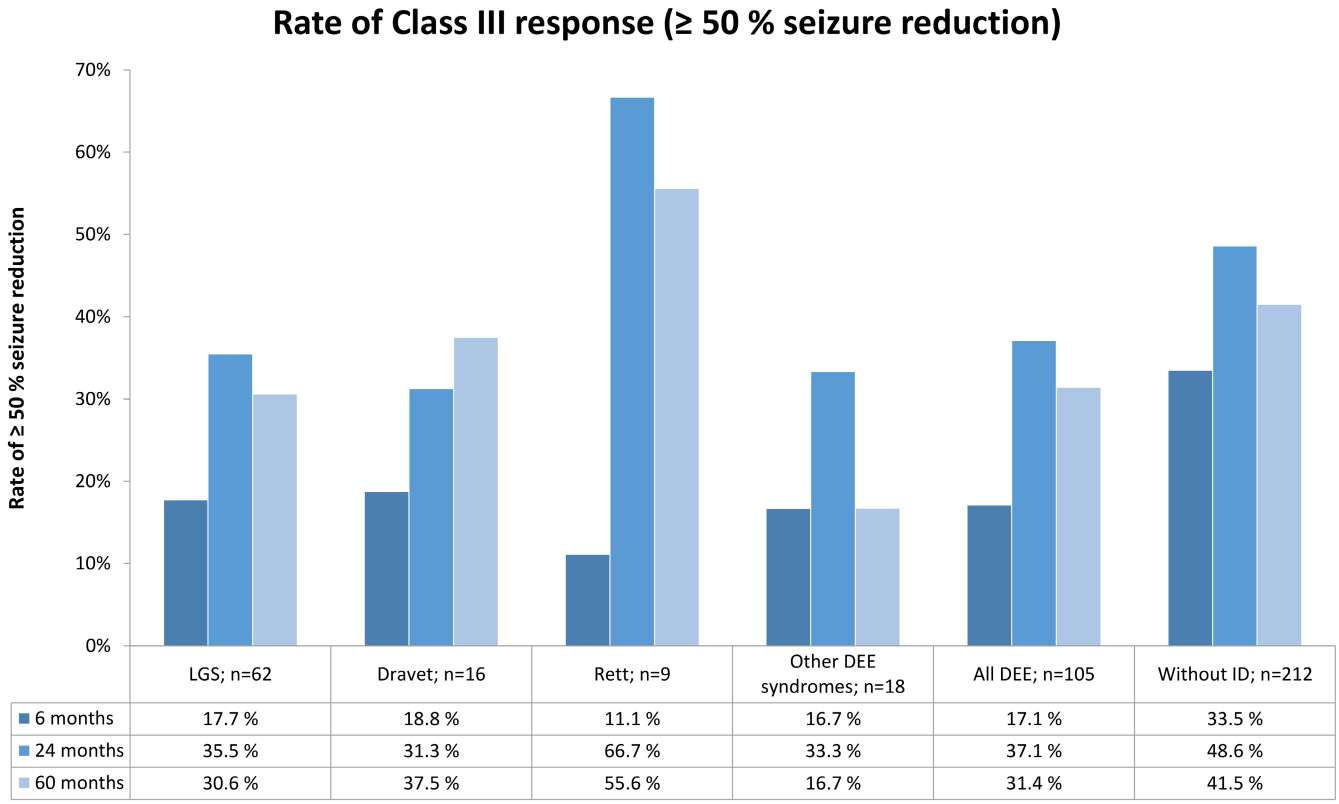
Patients with DEE had previously tried a mean number of 9.76 (±2.61 SD) different ASMs and were using a mean of 2.55 (±0.81 SD) ASMs at implantation; this was not significantly changed at LOCF (2.65 ± 0.85 SD, $p = 0.158$). Patients without ID had previously tried a mean of 8.45 (±2.34 SD) ASMs and used 2.32 (±0.81 SD) at implantation; this was significantly reduced to 2.22 (±0.97 SD, $p = 0.032$) at LOCF. Among DEE patients, there was no change in medication in 25/105 (23.8%), 16/105 (15.3%) decreased the number or dosage of ASMs, and 61/105 (58.1%) increased the dosage or changed ASM. There was no information about changes in ASM in 3/105 patients (2.9%). ASMs were changed after a median of 12 months (IQR = 9.75–27.0). There was a trend for a better effect at 2 years among patients with DEE who had not changed their medication compared with those who had changed ASM (54.5% vs. 35.6% responders, $p = 0.078$).

3.5 | Other positive effects

Improvement in ictal or postictal severity (Class A)[31] was reported in 43.8% of DEE patients, compared with 28.3% among patients without ID ($p = 0.006$). Improved alertness was reported in 62.9% of patients with DEE, compared with 31.6% in patients without ID ($p < 0.001$). No significant differences between the two patient groups were seen regarding the effect of the magnet for reducing seizure duration or severity, which was, respectively, reported in 61.0% of DEE patients and 52.4% of patients without ID ($p = 0.148$). Further analysis of data from DEE patients showed that there were significant differences in positive effects between responder and non-responder patients. Whereas 56.9% of responders with ≥50% seizure reduction reported an improvement in seizure severity, only 31.5% reported this among the non-responders ($p = 0.009$). Similarly, an increase in alertness was reported in 74.5% of responders, and 51.9% of non-responders ($p = 0.016$). Magnet effect was reported by 74.5% among responders but only by 48.5% of non-responders ($p = 0.006$).

3.6 | Adverse effects / postoperative complications

VNS was generally well tolerated. Most adverse effects (AE) were mild and improved over time and following



	LGS; n=62	Dravet; n=16	Rett; n=9	Other DEE syndromes; n=18	All DEE; n=105	Without ID; n=212
6 months	17.7 %	18.8 %	11.1 %	16.7 %	17.1 %	33.5 %
24 months	35.5 %	31.3 %	66.7 %	33.3 %	37.1 %	48.6 %
60 months	30.6 %	37.5 %	55.6 %	16.7 %	31.4 %	41.5 %

FIGURE 1 Intention-to-treat rates of ≥50% seizure reduction at 6, 24, and 60 months. DEE, developmental and epileptic encephalopathies; ID, intellectual disability; LGS, Lennox–Gastaut syndrome.

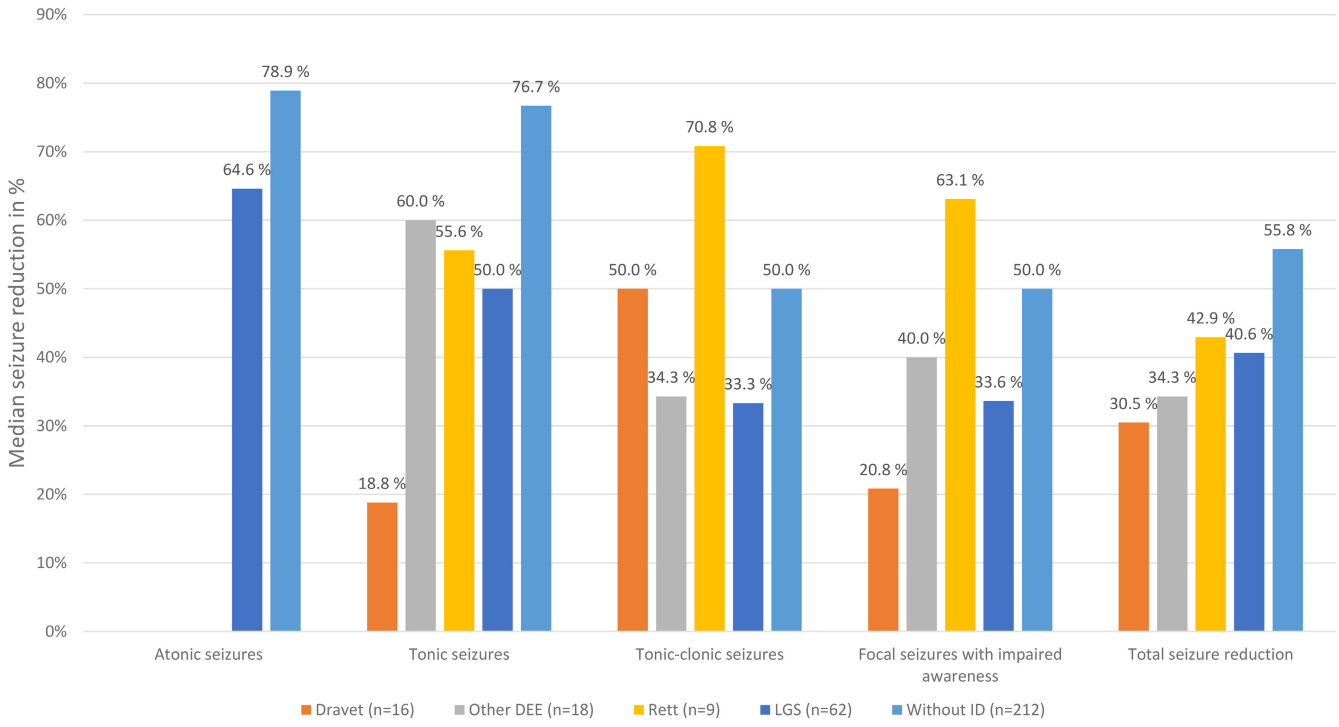


FIGURE 2 Median reduction for different seizure types in percentage. ID, Intellectual disability; LGS, Lennox–Gastaut syndrome.

adjustment of stimulation parameters. Different frequencies of AE were reported among patients with DEE and patients without ID (Figure 3). Hoarseness (40.1%), local irritation (29.2%), and dyspnea (22.6%) were the most commonly reported AEs among patients without ID. Hoarseness (14.3%) was also the most common AE among

TABLE 2 Seizure reduction for different seizure types and epilepsy syndromes.

Epilepsy syndrome	LGS ($n=62$)	Dravet ($n=16$)	Rett ($n=9$)	Other DEE syndromes ($n=18$)	All DEE ($n=105$)	Without ID ($n=212$)
% Seizure reduction (all seizure types[a]; n)	62	16	9	18	105	212
Median reduction (%) (IQR)	44.1 (17.1–67.9)	30.5 (−16.8–66.8)	42.9 (10–90)	34.3 (18.8–59.8)	42.2 (15.5–61.3)	55.8 (14.3–91.3)
Reduction range (%)	−16.7 to 90	−100 to 95	31.7 to 67.5	−15 to 88	−100 to 95	−220 to 100
p-Value[b]	<0.001[c]	0.02[c]	0.08	0.002[c]	<0.001[c]	<0.001
% Seizure reduction (tonic–clonic seizures; n)	41	15	4[d]	10	70	132
Median reduction (%) (IQR)	33.3 (0–68.3)	50.0 (−38.9 to 70)	70.8	34.3 (15.0–65.6)	38.8 (0–70.0)	50.0 (0–100)
Reduction range (%)	−300 to 100	−100 to 100	50 to 100	−15 to 100	−300 to 100	−900 to 100
p-Value[b]	0.001[c]	0.038[c]	0.068	0.015[c]	<0.001[c]	<0.001[c]
% Seizure reduction (tonic seizures; n)	40	6	3[d]	10	54	8
Median reduction (%) (IQR)	50.0 (12.5–78.8)	18.8 (−6.3–59.0)	55.6	60 (21.3–73)	50.0 (15.6–75.3)	76.7 (50–95.8)
Reduction range (%)	−300 to 100	−25 to 100	50 to 90	−20 to 100	−300 to 100	−100 to 100
p-Value[b]	<0.001[c]	0.357	0.109	0.03[c]	<0.001[c]	0.05[c]
% Seizure reduction (atonic seizures; n)	18	1[d]	0	1[d]	20	5
Median reduction (%) (IQR)	64.6 (26.7–100)	88.2	–	10.0	64.6 (15.8–97.5)	78.9 (47.1–100)
Reduction range (%)	−100 to 100	–	–	–	0 to 100	0 to 100
p-Value[b]	<0.001[c]	–	–	–	<0.001[c]	0.144
% Seizure reduction (FIAS; n)	10	6	2[d]	6	24	118
Median reduction (%) (IQR)	33.6 (10.5–52.5)	20.8 (0–50)	63.1	40.0 (6.7–52.1)	40 (11.7–50.0)	50.0 (16.1–88.9)
Reduction range (%)	0 to 70	0 to 50	40 to 83	−33 to 58	0–93	−400 to 100
p-Value[b]	0.008[c]	0.066	0.18	0.172	<0.001[c]	<0.001[c]

Abbreviations: DEE, developmental and epileptic encephalopathies; FIAS, focal seizures with impaired awareness; ID, intellectual disability; LGS, Lennox–Gastaut syndrome.

[a]Reduction for all seizure types except for absences and myoclonic jerks.

[b]Wilcoxon signed-rank test.

[c]Significant value—threshold of 0.05.

[d]Interquartile range (IQR) was calculated for groups larger than five.

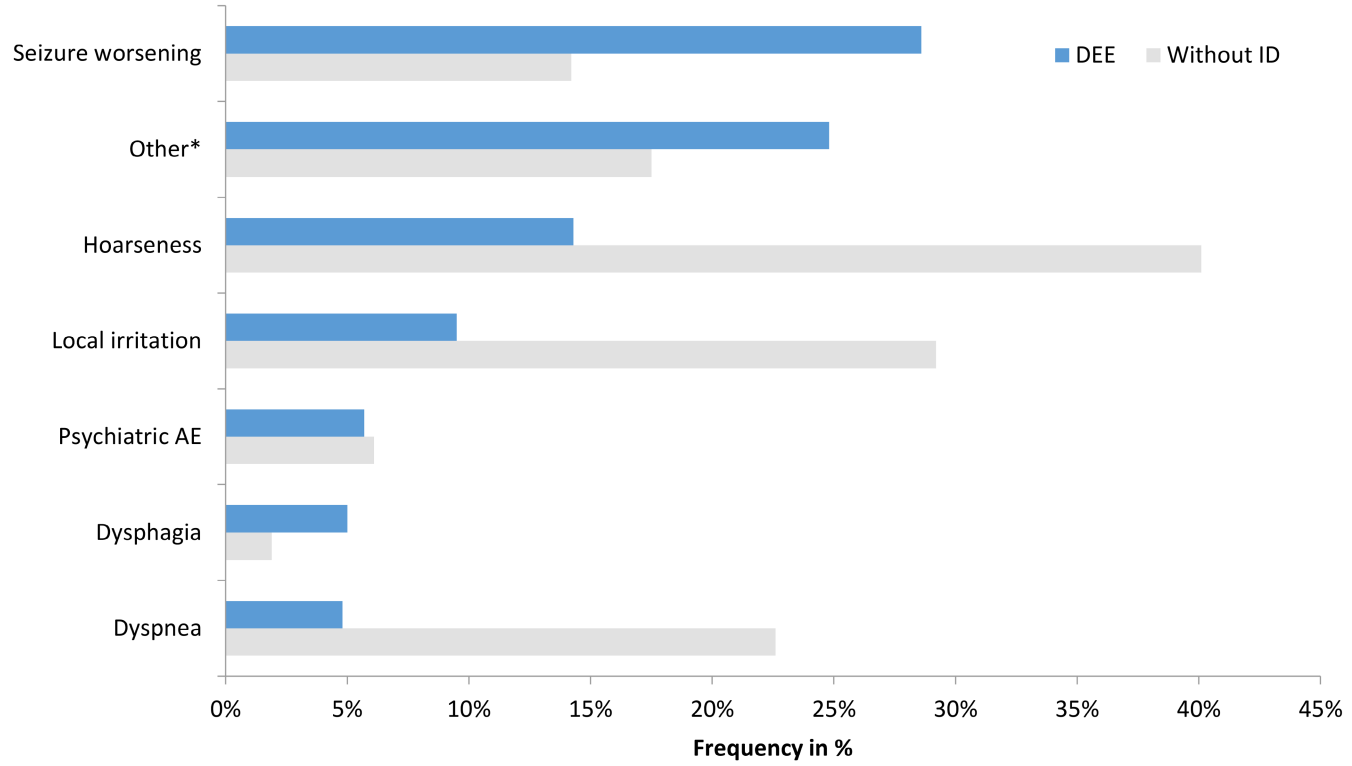


FIGURE 3 Frequency of reported adverse effects (AEs) at some time point among patients with developmental and epileptic encephalopathies (DEE) and patients without intellectual disability (ID). * Other AEs included sleep disturbance, general discomfort, and abdominal problems.

patients with DEE; however, 24.8% of patients with DEE reported other AEs including sleep disturbance, general discomfort, or abdominal problems. Seizure worsening was reported at some time point in 28.6% of patients with DEE, and in 14.2% of patients without ID, while 2.9% and 0%, respectively, reported seizure worsening at LOCF.

Complications were seen in 21.9% of patients with DEE and 17.0% of patients without ID. For both groups, the most common complications were lead breakage/fibrosis and infection, respectively, 13.3% and 3.8% of patients with DEE, and 9.4% and 3.3% of patients without ID. Twelve of 105 patients with DEE (11.4%) and 44/212 (20.8%) of patients without ID were explanted. In patients with DEE, explantation was due to: infection (1%), lead breakage (1%), AEs (1%), and perceived lack of efficiency (8.6%). In patients without ID, explantation was due to: lead breakage (0.9%), AEs (3.8%), and perceived lack of efficacy (16.0%).

4 | DISCUSSION

We provide new, clinically relevant information on the evolution of the effect of VNS over time in patients with DEE and its effect on different seizure types. Atonic seizures had the highest median seizure reduction (64.6%) in LGS patients. There was an increase in responder rate between 6 and 24 months and increase in Class II effect (≥75% seizure reduction) between 6 and 60 months for patients with DEE. There was higher retention rate at 5 years among patients with DEE than patients without ID probably due to the considerable reduction in both atonic and tonic seizures, leading to fewer injuries but also due to other positive effects such as increased alertness, milder seizures, and shorter postictal phase, as well as effect of the magnet for reducing seizure severity. A prospective study analyzing the effect of VNS in patients with ID demonstrated significant improvements in attention span, word usage, clarity of speech, and ability to perform household chores at both 1 and 2 years.[32]

Different stages of the disease are distinguishable for patients with Dravet and Rett syndromes,[3,17,18] with frequent seizures during the early years followed by a stabilization phase where seizure burden decreases, and some seizure types may even disappear; behavior tends to improve but cognitive impairment often persists. In contrast, the stabilization stage may be less apparent or never emerge, for patients with LGS.

Changes in medication were performed according to best medical practice due to the open-label nature

of the study. There were more increases in dosage of medication in DEE patients than in patients without ID, which might be explained by the difference in age as 75.1% of DEE patients were children, in whom dosages need to be increased as the child grows to keep the concentration of the medication stable. However, there was a large group of patients who continued with the same ASMs throughout, who showed a near-significant trend for better overall effect than patients who changed their medication. Thus, the observed seizure reduction is likely a reflection of the "true" effect of VNS and not due to the natural evolution of epilepsy or to changes in medication.

To the best of our knowledge, this is the largest single-center study on the effect of VNS in patients with LGS. Another single-center study, with a mean follow-up of 30 months, reported a responder rate of 65% (30/46), similar to a registry study with 18 months of follow-up that reported a responder rate of 64% (107/167).[24,33] A European multicenter study with follow-up of 24 months reported a responder rate of 39% (34/87), which is comparable to the responder rate of 35.5% (22/62) obtained in our study.[25] The overall median seizure reduction for LGS patients in our study was 40.6%, which is lower than data provided for VNS in a recent meta-analysis on the role of surgical treatments of LGS of 54.6% (95% CI: 42.9%–66.3%).[34] In that meta-analysis, VNS treatment had a significantly lower effect than that obtained by CC (74.1%; 95% CI: 64.5–83.7%).[34]

Evidence on the effect of VNS in patients with Dravet syndrome is more limited as most studies are insufficiently powered. Studies with more than 10 patients with Dravet syndrome have reported responder rates of 50% in 38%–65%,[25,26,35] compared to 31.3% of patients at 24 months, and no seizure-free patients found in our study. A meta-analysis identified 107 patients with Dravet syndrome from 15 studies, where 56% were responders and 7.5% became seizure-free.[36]

Atonic seizures, often leading to injuries and a restricted lifestyle, have a poor prognosis and most patients are pharmacoresistant.[37] Many patients are therefore treated surgically by CC or VNS. However, there is no consensus on which treatment to offer first.[38] In our study, we observed a considerable reduction in atonic seizures in all patient groups, most notably in patients with LGS who had a median seizure reduction of 64.6%. Patients with previous CC also benefitted from VNS, as 3/7 patients were responders. A recent meta-analysis on management of atonic seizures in the pediatric population showed an overall effect size of 0.40 (95% CI: 0.28–0.51) for VNS and 0.73 (95% CI: 0.69–0.77, $p = 0.003$) for CC.[39] In this meta-analysis, CC was associated with a higher prevalence of complications requiring reoperation (6.6% vs. 3.8% in VNS) and 14% developed symptomatic disconnection syndrome.[39] A decision analytic model showed CC to have 15% greater likelihood of a positive outcome for all seizures, but per-patient costs for CC were over $68 000 more than those of VNS. For atonic seizures, CC had 27% greater likelihood of positive outcome and the same incremental cost.[40] Considering the significant reduction in seizure rate, the lower occurrence of complications, and the cheaper cost per positive outcome, we propose that patients with atonic seizures should be treated first with VNS rather than CC.

In our study, there was a moderate seizure reduction (30%–50%) for TCS and FIAS. A recent study in patients with LGS and genetic generalized epilepsy reported that the best effect of VNS was for TCS.[41] A prospective study in LGS patients reported a mean reduction in TCS frequency from 8.3 seizures/day to 2.0 seizures/day.[42] Many patients with Dravet syndrome experience a significant reduction in convulsive seizures when they enter the stabilization stage,[3] and this may partly explain the relatively large median reduction of 50% for TCS among Dravet patients in our study. Similarly to previous reports, we observed a considerable, but non-significant, reduction in all seizure types in patients with Rett syndrome.[43] One possible explanation for this reduction is that many patients with Rett syndrome experience a decline in epilepsy severity after adolescence, with decreased seizure frequency both for TCS and overall.[44]

In our study, VNS treatment was generally well tolerated in all patient groups and most AE were mild and improved over time and with adjustment of stimulation parameters. The ability to perceive AE may explain the difference in AE profiles between groups. Caregivers of patients with DEE report more objective symptoms, while patients without ID may report more subjective symptoms. Furthermore, some AEs, such as sleep disturbance, general discomfort, and abdominal problems, could be related to the underlying conditions and comorbidities of patients with DEE, including gait and movement disorders, frequent infections, more sedentary lifestyle, and other medical issues such as feeding problems. In contrast, epilepsy patients without ID often have a more active lifestyle, and this could explain why dyspnea was frequently reported in that group. In our study, more than two of three the DEE patients had moderate or severe intellectual disability, many with speech impairment; this is a likely reason that hoarseness was more rarely reported in that group, rather than because of a difference in frequency. Almost 30% of DEE patients experienced a transient increase in seizure frequency, probably due to natural fluctuations in

epilepsy and a transient paradoxical effect of VNS, as seizure frequency mostly normalized following adjustment of stimulation parameters.

The prospective patient follow-up and standardized protocol for VNS titration all contribute to the strengths of our long-term, single-center study. To the best of our knowledge, it is also the first nationwide population-based study. All patients were screened through the epilepsy surgery program, and patient selection was based exclusively on medical factors. We thus believe that our research cohort is representative of these patient populations and that our results should be generalizable. Nevertheless, the study has its limitations. The statistical analysis was conducted using data from the VNS registry, with the inherent limitations of an open-label design, with no placebo control group, lack of data verification, and incomplete data for some patients. Due to long follow-ups, many patients had been implanted with older VNS models. The newest models (Aspire and Sentiva) offer possibilities for more personalized treatment, where some patients can have additional effects; however, the clinical benefits on a group level are still uncertain. Reporting of seizure frequencies and AE for patients with DEE depends to a large extent on the caregivers and healthcare personnel, and improvements in QoL parameters were based on subjective reports. We have addressed some of these weaknesses by accounting for changes in ASMs as well as analyzing the effect according to age at implantation.

5 | CONCLUSION

Our study provides new data indicating that the effect of VNS increases over time for different patient groups, even when medications are unchanged. The best effect was seen for atonic seizures and our results indicate that VNS should be used preferentially for patients with this seizure type. In patients with DEE, the retention rate at 5 years was high, despite seizure reduction being lower than in epilepsy patients without ID. This probably reflects other positive effects of VNS treatment such as increased alertness and milder, shorter seizures.

AUTHOR CONTRIBUTIONS

All co-authors have been 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 co-authors have seen and approved the submitted version of the paper and accept responsibility for its content.

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CONFLICT OF INTEREST STATEMENT

O. Henning reports personal fees from Eisai, UCB, and Livanova, outside the submitted work. J. Peltola reports grants, personal fees, or others from Eisai, UCB, and Livanova; personal fees and others from Medtronic and Orion Pharma; others from Bial, Angelini Pharma, Jazz Pharma, Novartis, and Pfizer, outside the submitted work. M. I. Lossius reports personal fees from Eisai, UCB, and Arvelle, outside the submitted work. The remaining authors have no conflicts of interest. 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 Centre 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.

DATA AVAILABILITY STATEMENT

Individual participant data that underlie the results reported in this article after de-identification (text, tables, figures, and appendices) can be presented by request from qualified investigators.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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