

## Research Paper

## Exploring the interplay between depressive symptoms and seizure outcomes: A single-centre study of drug-resistant epilepsy patients treated with vagus nerve stimulation

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## ABSTRACT

**Background:** Vagus nerve stimulation (VNS) is a safe and effective treatment option for patients with drug-resistant epilepsy (DRE) and for those with treatment-resistant depression. VNS can lead to the amelioration of depressive symptoms in patients with DRE, independent of its impact on seizure control. However, the relationship between depressive symptoms and seizure outcomes in patients receiving VNS therapy remains uncertain.

**Objective:** This study aimed to assess whether the presence or absence of depressive symptoms influences seizure outcomes in patients with DRE treated with VNS.

**Methods:** This follow-up study included 51 consecutive adult DRE patients treated with VNS at the Neurology Outpatient Clinic at Tampere University Hospital. All patients underwent a psychiatric evaluation before VNS at baseline (pre-implantation). The severity of depressive symptoms was assessed using the Beck Depression Inventory-1A (BDI) at baseline and repeatedly throughout the follow-up period. We categorized patients into two groups based on the presence or absence of depressive symptoms, as determined by their BDI scores at baseline and during the follow-up after VNS implantation: i) patients with depressive symptoms (PWE + DS), with a BDI score > 12 at least once either at baseline or during the follow-up, and ii) patients without depressive symptoms (PWE - DS), with all BDI scores ≤ 12. The primary seizure outcome measure was the number of patients with > 50 % seizure reduction (responders) for their predominant seizure type.

**Results:** At baseline, psychiatric comorbidities were diagnosed in 29.4 % of patients, and the average baseline BDI score was 7.0 (median 5.0, range 0–41). PWE + DS comprised 41.2 % and PWE - DS 58.8 % of the study population. The median duration of follow-up was 39 months (range 6–102 months). The overall responder rate was 52.1 % for the predominant seizure type, with significantly more responders in the PWE + DS group than in the PWE - DS group (73.7 % vs. 37.9 %,  $p = 0.027$ ). Among the 11 patients whose predominant seizure type was focal to bilateral tonic-clonic seizures (FBTCS), 81.8 % were responders, and 72.8 % achieved seizure freedom for this seizure type.

**Conclusion:** Our study indicates that DRE patients with depressive symptoms respond better to VNS therapy for their predominant seizure type than those without depressive symptoms. This unexpected finding may be explained by the shared neurobiological background of seizures and depressive symptoms, potentially influenced by VNS treatment. Patients with FBTCS as their predominant seizure type achieved the most favourable

**Abbreviations:** ASM, antiseizure medication; DRE, drug-resistant epilepsy; PWE + DS, patients with depressive symptoms; PWE - DS, patients without depressive symptoms; VNS, vagus nerve stimulation; BDI, Beck Depression Inventory; FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; LOCF, last observation carried forward; PWE, people with epilepsy; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder.

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outcomes. Further investigations in a larger cohort of DRE patients with depressive symptoms are warranted to validate our results.

## 1. Introduction

Vagus nerve stimulation (VNS) is an established and safe adjunctive therapy option for patients with drug-resistant epilepsy (DRE), for whom the sustained seizure freedom has not been achieved despite adequate trials of at least two well-tolerated and appropriately chosen and applied anti-seizure medications (ASMs) [1]. Randomized controlled trials and prospective longitudinal studies have shown the effectiveness of VNS in seizure reduction, with responder rates (reduction of over 50 % in seizure count) of 28–60 %, seizure freedom rates of approximately 10 %, and increasing efficacy over time [2–7]. Clinical trials of VNS treatment have revealed additional positive effects on mood, ultimately paving the way for US Food and Drug Administration approval of VNS for treatment-resistant depression [8]. The positive effect of adjunctive VNS to quality of life has been shown as well among patients with DRE [9] and patients with treatment-resistant major depression [10], regardless of the effect on seizure frequency or depression.

Depression, a common comorbidity of epilepsy, is associated with several adverse outcomes among people with epilepsy (PWE), including reduced quality of life, drug resistance, and poor outcome after epilepsy surgery [11–15]. Disturbances in neurotransmitters, neuroinflammatory processes, and a hyperactive hypothalamic–pituitary–adrenal axis are among the known pathogenic mechanisms of depression which may play an additional pathogenic role in epilepsy, providing a possible explanation for this interconnection [13,16]. An increased understanding of the common underlying pathophysiological mechanisms of epilepsy and depression could influence the development of novel disease-modifying therapies targeting appropriate mechanisms [17].

A recent systematic review provided compelling evidence for the amelioration of depressive symptoms in DRE patients treated with VNS, and that the VNS effect on depression does not correlate with seizure response [18]. Conversely, a German study investigating the effect of VNS on seizure outcomes in patients with DRE with a comorbidity of different subtypes of depressive disorders revealed that there was a strong correlation between improvement in seizure frequency and amelioration of depressive symptoms [19]. However, there is little evidence of the effect of depressive symptoms on the seizure response in patients receiving VNS therapy.

In this study, we aimed to assess whether the presence or absence of depressive symptoms influences seizure outcomes in patients with DRE who were treated with VNS.

## 2. Patients and Methods

This was a registry-based retrospective study, in which the data was collected from a VNS quality register with a prespecified follow-up protocol at Tampere University Hospital. Since the study was non-interventional, ethics committee approval was not needed according to the Finnish Law on Research. Tampere University Hospital Research, Development and Innovation Centre granted access to the VNS quality register.

### 2.1. Patients

The study cohort included 51 patients with DRE who underwent VNS at Tampere University Hospital between 2013 and 2021. One patient was implanted with VNS Model 102, 28 patients with Model 106 [Aspire®] and 22 patients with Model 1000 [SenTiva®] from LivaNova PLC, London, UK. For three patients initially implanted with Model 102, the stimulator was replaced with Model 106 (for one patient) or Model

1000 (for two patients) by the time the battery was changed.

All the patients had undergone a presurgical evaluation and were either considered unsuitable candidates for resective epilepsy surgery or had undergone epilepsy surgery but did not achieve adequate seizure control. All patients fulfilled the ILAE criteria for DRE. Other inclusion criteria were age 18 years or older, an available self-reported Beck Depression Inventory-1A (BDI) before the implantation and one or more BDIs available at least 6 months after the implantation of VNS. Mild intellectual disability (ID) was not an exclusion criterion, but due to the use of a self-reported tool for depressive symptom screening, patients with moderate or severe ID were excluded. All patients underwent neuropsychological assessments as part of their presurgical evaluation at pre-implantation, which identified four patients with mild ID. Despite these cognitive limitations, all four patients demonstrated the ability to complete self-reported screening tools, which supported their inclusion in the study population.

Information on the etiology and type of epilepsy, age at epilepsy onset, duration of epilepsy, ASM use, duration of VNS, previous resective epilepsy surgery or other brain surgery, and psychiatric comorbidities (either present or past) were extracted retrospectively from the medical records. The frequency of seizures (for the predominant seizure type as well as for all seizure types) during the preceding 12 months prior to VNS implantation and the preceding three months before the last observation carried forward (LOCF), defined by the time of the last available BDI measurement, were extracted from the VNS quality register.

Seizure classification was based on video-electroencephalogram (vEEG) findings and seizure semiology. The individual patient's predominant seizure type was defined as the most disabling seizure type noted in the medical records as determined by the clinicians but not necessarily the most frequent seizure type [20]. Epilepsy types were categorized as temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), or other. The etiology of epilepsy was assessed based on MRI findings and clinical history. All patients were treated with ASMs along with VNS therapy.

### 2.2. Psychiatric evaluation

All the patients underwent a comprehensive psychiatric evaluation before the implantation of VNS. Psychiatric comorbidities and psychiatric medication use at baseline and at LOCF were assessed from medical records. To measure the severity of depressive symptoms, we used the BDI, a validated self-administered 21-item questionnaire, which previous studies have shown to be a functional and reliable tool for evaluating depressive symptoms in PWE [21–23]. The BDI was assessed before implantation and at follow-up visits based on Tampere University Hospital standard VNS protocol. According to BDI scores, the severity of depressive symptoms was divided into four categories: BDI scores between 0 and 12 indicated no depressive symptoms, scores between 13 and 18 indicated mild depressive symptoms, scores between 19 and 29 indicated moderate depressive symptoms, and scores  $\geq 30$  indicated severe depressive symptoms [24]. The cutoff points were chosen according to the Finnish Depression guidelines [25]. Due to irregularity in clinical follow-up, which was partly disrupted by the COVID-19 pandemic, the follow-up BDI measurements were conducted at different time points, leading to one follow-up measurement for 18 patients, two measurements for 17 patients, three measurements for 11 patients, four measurements for four patients and five measurements for one patient. In addition, the severity of depressive symptoms was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), but only at baseline [26].

A flowchart summarizing the BDI measurements at different time points after VNS implantation is presented in Fig. 1.

### 2.3. Procedure

Although the data were collected longitudinally with follow-up assessments, we did not analyze changes in BDI scores over time. Instead, we categorized patients into two groups based on the presence or absence of depressive symptoms, as determined by their BDI scores at baseline and during the follow-up after VNS implantation. These categorizations formed the basis of our study groups, allowing us to focus on the presence or absence of depressive symptoms rather than their trajectory.

All the patients with at least one BDI score revealing mild, moderate or severe depressive symptoms, i.e., BDI > 12, either at baseline (pre-implantation) or during the follow-up, were defined as patients with depressive symptoms (PWE + DS). Conversely, all the patients with solely normal BDI scores, i.e., all BDI scores  $\leq$  12 (at baseline and at follow-up), were defined as patients without depressive symptoms (PWE - DS).

Next, we classified patients as responders or non-responders to VNS



**Fig. 1.** Flowchart summarizing the BDI evaluations at different time points after VNS implantation. Each time point represents a specific duration in months as follows: 6 months (ranging from 6–8 months), 12 months (ranging from 8–18 months), 24 months (ranging from 18–30 months), 36 months (ranging from 30–42 months), 48 months (ranging from 42–54 months), 60 months (54–66 months), 72 months (66–78 months),\* 3 evaluations at 72 months and 8 evaluations between 75–102 months.

for comparison between the PWE + DS and PWE - DS groups. A responder's status was defined as a > 50 % reduction in the frequency of either predominant seizure type (primary outcome measure) or total seizure count at LOCF. Additionally, the proportion of patients achieving seizure freedom for the predominant seizure type as well as for all seizures was assessed separately.

### 2.4. Statistical analysis

Due to the skewed distribution of continuous variables, the nonparametric Kruskal-Wallis test or Mann-Whitney *U* test was used. To examine the association between groups and categorized variables, Pearson's chi-squared test, if assumptions were valid, or Fisher's exact test was used. For all the statistical tests, a *p* value < 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics for Windows software, version 28.0 (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Study cohort characteristics

All patients had focal epilepsy. Most of them had either frontal lobe (39.2 %) or temporal lobe (33.3 %) epilepsy, while 27.5 % of the patients had other epilepsy type (multilobar (13.7 %), multifocal (11.7 %) or parietal (2.0 %)). The most common etiology was unknown (52.9 %) followed by structural (33.3 %), immune (7.8 %), infectious (3.9 %) and genetic (2.0 %). The most common predominant seizure types at baseline were focal impaired awareness seizures (FIAS; 60.8 %) and focal to bilateral tonic-clonic seizures (FBTCS; 21.6 %), whereas only 13.7 % had focal aware seizures (FAS). At baseline, 62.7 % of the patients used 3–4 ASMs, whereas 37.3 % of the patients used only 1–2 ASMs. The demographics and clinical characteristics of the study population are presented in Table 1.

At baseline, the average BDI score was 7.0 (median 5.0, range 0–41), and the median MADRS score was 6 (range 0–29). At pre-implantation psychiatric evaluation, 29.4 % of patients were diagnosed with psychiatric comorbidities, including 19.6 % of patients with a past or present major depressive disorder (MDD), among whom 13.7 % had active MDD and 5.9 % were in remission during the study. Furthermore, 9.8 % of all patients had other psychiatric disorders.

There was no difference with regard to age at baseline or at epilepsy onset, sex, epilepsy duration, proportion of predominant seizure types or epilepsy types between patients with past/present MDD and patients without psychiatric disorders or between patients with other psychiatric disorders and patients without psychiatric disorders. The baseline BDI scores and MADRS scores were significantly higher in patients with past/present MDD than in patients without MDD ( $p < 0.001$  for both scores). Patients without psychiatric disorders did not use any psychiatric medications, whereas 60 % of patients with past/present MDD and 80 % of patients with other psychiatric disorders used psychiatric medications. The median duration of VNS was 39 months (range 6–102 months) for all the patients. The median duration of VNS was significantly longer for patients with past/present MDD than for patients without psychiatric disorders (44.5 months (range 35–102 months) vs. 36 months (range 6–97 months),  $p = 0.033$ ).

### 3.2. Assessment of clinical characteristics among the groups based on depressive symptoms

Among all patients, 41.2 % (21/51 patients) reported depressive symptoms either at baseline or during follow-up, comprising the PWE + DS group. 15.7 % (8/51) presented with depressive symptoms at baseline, and an additional 25.5 % (13/51) presented with depressive symptoms during follow-up but not at baseline. Conversely, 58.8 % of patients did not have depressive symptoms at baseline or during follow-

**Table 1**  
Comparison of demographics and clinical characteristics among the groups based on depressive symptoms.

Characteristics	All patients (n = 51)	PWE + DS (n = 21)	PWE - DS (n = 30)	P value
Age at baseline	32 (17–70)	31 (20–46)	32.5 (17–70)	0.287
Age at epilepsy onset	16 (1–63)	15 (4–39)	17 (1–63)	0.969
Sex (F/M)	27/24	14/7	13/17	0.100
Years of education	12 (9–17)	12 (9–16)	12 (9–17)	0.991
Epilepsy duration at baseline (years)	15 (2–44)	13 (2–41)	15 (5–44)	0.203
Epilepsy type, n (%)				0.418
FLE	20 (39.2)	7 (33.3)	13 (43.3)	
TLE	17 (33.3)	9 (42.9)	8 (26.7)	
Other (6 multifocal, 7 multilobar, 1 parietal)	14 (27.5)	5 (23.8)	9 (30.0)	
ILAE Etiology, n (%)				0.429
Structural	17 (33.3)	6 (28.6)	11 (36.7)	
Immune	4 (7.8)	3 (14.3)	1 (3.3)	
Genetic	1 (2.0)	1 (4.8)	0	
Infectious	2 (3.9)	1 (4.8)	1 (3.3)	
Unknown	27 (52.9)	10 (47.6)	17 (56.7)	
Predominant seizure type at baseline*, n (%)				0.242
FAS	7 (13.7)	4 (19.0)	3 (10.0)	
FIAS	31 (60.8)	11 (52.4)	20 (66.7)	
FBTCS	11 (21.6)	4 (19.0)	7 (23.3)	
Seizure free	1 (2.0)	1 (4.8)	0	
Previous brain surgery (resective or other), n (%)	11 (21.6)	5 (23.8)	6 (20.0)	0.774
VNS duration at LOCF (months)	39 (6–102)	37 (6–102)	39.5 (6–97)	0.553
Number of ASMs at baseline, n (%)				0.143
1–2 ASMs	19 (37.3)	5 (23.8)	14 (46.7)	
3–4 ASMs	32 (62.7)	16 (76.2)	16 (53.3)	
Psychiatric diagnosis at baseline, n (%)				0.003
Present MDD	7 (13.7)	6 (28.6)	1 (3.3)	
Past MDD	3 (5.9)	3 (14.3)	0	
Other**	5 (9.8)	1 (4.8)	4 (13.3)	
No	36 (70.6)	11 (52.4)	25 (83.3)	
Psychiatric medication use at baseline, n (%)	10 (19.6)	7 (33.3)	3 (10.0)	0.039
Type of psychiatric medication at baseline, n (%)				0.167
Antidepressants	5 (9.8)	5 (23.8)	0	
Other***	5 (9.8)	2 (9.5)	3 (10.0)	
BDI score at baseline	5 (0–41)	11 (2–41)	3 (0–10)	<0.001
MADRS score at baseline	6 (0–29)	10 (4–29)	4 (0–25)	<0.001

Age at baseline, age at epilepsy onset, epilepsy duration at baseline, BDI score and MADRS score at baseline, years of education and VNS duration at LOCF are presented as medians and ranges. \*One patient had missing information on predominant seizure type at baseline; \*\*organic mixed mood disorder, psychotic disorder, bipolar disorder and organic anxiety disorder. \*\*\*low-dose mirtazapine (<15 mg), risperidone, quetiapine, paliperidone, perphenazine, aripiprazole, olanzapine. VNS, vagal nerve stimulation; BDI, Beck's Depression Inventory; FLE, Frontal lobe epilepsy; TLE, Temporal lobe epilepsy; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; ASM, anti-seizure medication; PWE + DS, patients with depressive symptoms; PWE - DS, patients without depressive symptoms; FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; LOCF, last observation carried forward.

up, thus comprising the PWE - DS group. Based on BDI scores, at baseline and during the follow-up, most of the patients in our study had mild depressive symptoms (23.5 % (12/51)), whereas 9.8 % (5/51) had moderate depressive symptoms, and 7.8 % (4/51) had severe depressive symptoms. When analysed at the individual level, 7 out of the 8 patients with self-reported depressive symptoms at baseline had lower BDI scores at LOCF. The classification and evolution of BDI scores at baseline and during the follow-up for each individual patient are presented in Supplementary Tables 1 and 2.

There were no significant differences in demographic or clinical characteristics between the PWE + DS and PWE - DS groups (Table 1). The baseline BDI and MADRS scores were significantly higher in the PWE + DS group than in the PWE-DS group ( $p < 0.001$  for both scores). The use of psychiatric medications at baseline was more common in the PWE + DS group than in the PWE - DS group (33.3 % vs. 10.0 %,  $p = 0.039$ ). Moreover, a diagnosis of a present or past MDD at the baseline psychiatric evaluation was more common in the PWE + DS group, but a diagnosis of other psychiatric disorders was more common in the PWE-DS group ( $p = 0.003$ ).

Demographics and most of the clinical characteristics did not differ between the patients who experienced depressive symptoms at baseline ( $n = 8$ ) and those who experienced depressive symptoms during the follow-up ( $n = 13$ ). The use of psychiatric medications at baseline was more common for patients with depressive symptoms at baseline than for those who developed depressive symptoms during follow-up (62.5 % vs. 15.4 %,  $p = 0.026$ ). Seventy-five percent of patients with depressive symptoms at baseline had a psychiatric diagnosis at the pre-implantation psychiatric evaluation (62.5 % with present MDD and 12.5 % with past MDD) compared to 30.8 % of patients with depressive symptoms at follow-up (7.7 % with present MDD, 15.4 % with past MDD, and 7.7 % with other psychiatric disorders ( $p = 0.053$ )). The duration of VNS was significantly longer for patients with depressive symptoms at baseline (median 46.5 months, range 35–102) than for

**Table 2**  
Assessment of responders and non-responders within groups on the basis of depressive symptoms.

Change in predominant seizure status	All patients (N = 48) *	PWE + DS (n = 19)	PWE - DS (n = 29)	P value
Responders, n (%)	25 (52.1)	14 (73.7)	11 (37.9)	0.027 <sup>a</sup>
50–75 % seizure reduction	4 (8.3)	1 (5.3)	3 (10.3)	
75–99 % seizure reduction	6 (12.5)	5 (26.3)	1 (3.4)	
Seizure free	15 (31.3)	8 (42.1)	7 (24.1)	
Non-responders, n (%)	23 (47.9)	5 (26.3)	18 (62.1)	
Change in total seizure status	All patients (N = 45) #	PWE + DS (n = 17)	PWE - DS (n = 28)	P value
Responders, n (%)	19 (42.2)	9 (52.9)	10 (35.7)	0.337 <sup>a</sup>
50–75 % seizure reduction	5 (11.1)	2 (11.8)	3 (10.7)	
75–99 % seizure reduction	4 (8.9)	3 (17.6)	1 (3.6)	
Seizure free	10 (22.2)	4 (23.5)	6 (21.4)	
Non-responders, n (%)	26 (57.8)	8 (47.1)	18 (64.3)	

<sup>a</sup>Pearson's chi-square test, \*For changes in predominant seizure status analysis, three patients were excluded: one with seizure-free data and two without available seizure data; #For changes in total seizure status analysis, six patients were excluded: one with seizure-free data and five without available seizure data.

PWE + DS, patients with depressive symptoms; PWE - DS, patients without depressive symptoms.

those who developed depressive symptoms during the follow-up (median 36 months, range 6–70) ( $p = 0.025$ ).

### 3.3. Response to VNS based on the presence of depressive symptoms

The overall responder rate in our study was 52.1 % (25/48) for the predominant seizure type. Three of the 51 patients were excluded from the analysis (two patients without available seizure data and one was seizure free at baseline). A total of 31.3 % (15/48) of the patients achieved seizure freedom for the predominant seizure type.

The responder rate for the predominant seizure type (primary outcome measure) was significantly higher in the PWE + DS group than in the PWE - DS group (73.7 % vs. 37.9 %,  $p = 0.027$ ; Table 2). Moreover, among the PWE + DS group, 26.3 % achieved 75–99 % seizure reduction, and 42.1 % became seizure free, whereas among the PWE - DS group, 3.4 % achieved 75–99 % seizure reduction, and 24.1 % were seizure free.

The overall responder rate for the total seizure count was 42.2 % (19/45). Six out of the 51 patients were excluded from the analysis (five patients without available seizure data and one was seizure free at baseline). The seizure freedom rate for the total seizure count was 22.2 % (10/45). The percentage of responders for total seizures was 52.9 % in the PWE + DS group compared with 35.7 % in the PWE - DS group ( $p = 0.337$ , Table 2).

Assessment of responders and non-responders within groups PWE + DS and PWE - DS is presented in Table 2.

In further analyses, there were no other clinical or demographic factors explaining the significantly greater proportion of responders for the predominant seizure type in the PWE + DS group than in the PWE - DS group (Supplementary Tables 4 & 5). Comparison of clinical characteristics between responders and non-responders for total seizure count is presented in supplementary tables 6 and 7.

Furthermore, the seizure outcome did not differ either for the predominant seizure type or for the total seizure count, when we compared those PWE + DS patients who experienced depressive symptoms at baseline to the PWE + DS patients who developed depressive symptoms during the follow-up. The responder rate for predominant seizures was 83.3 % in PWE + DS at baseline and 69.2 % in PWE + DS at follow-up ( $p = 1.000$ ). For total seizure count, the responder rates were 80.0 % in PWE + DS at baseline and 41.7 % in PWE + DS at follow-up ( $p = 0.620$ ). For the PWE + DS group at baseline, the seizure freedom rates were 50.0 % and 20.0 % for the predominant seizure type and total seizure count, respectively. For the PWE + DS at follow-up, the seizure freedom rates were 38.5 % and 25.0 % for the predominant seizure type and total seizure count, respectively.

Moreover, among the groups classified by the severity of depressive symptoms, the responder rates did not differ between the patients with mild, moderate, or severe depressive symptoms for both predominant seizure types and total seizures (data not shown).

In addition, when seizure outcome was analysed in groups of patients with present/past MDD, other psychiatric disorders and no psychiatric disorders, there were no significant differences in the proportions of responders among these groups, either for the predominant seizure type or for the total number of seizures (Supplementary Table 3).

### 3.4. Response to VNS on the basis of predominant seizure type

Among the 11 patients with FBTCS as their predominant seizure type, 81.8 % became responders, with 72.7 % becoming seizure free. Among the patients with FIAS ( $n = 30$ ) and FAS ( $n = 7$ ) as their predominant seizure type, the responder rates were 46.7 % and 28.6 %, respectively. The seizure freedom rates were 20 % for patients with FIAS and 14.3 % for patients with FAS.

The difference in seizure outcome between PWE + DS and PWE - DS was observed in patients in whom FIAS and FAS were the predominant seizure types (Table 3). Among patients with FIAS, 81.8 % of PWE + DS

**Table 3**

Assessment of seizure outcomes within groups based on depressive symptoms and predominant seizure type.

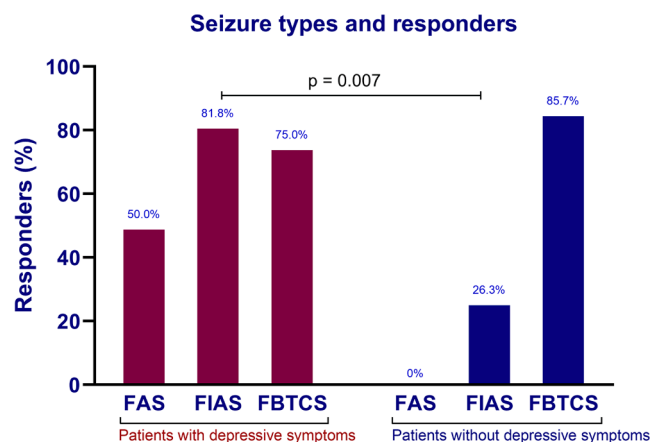
Seizure outcome categories (all patients, N = 48*)	FAS (n = 7)	FIAS (n = 30)	FBTCS (n = 11)
<b>50–75 % Seizure reduction (n = 4)</b>	0/7	4/30 (13.3 %)	0/11
PWE + DS	0/4	1/11 (9.1 %)	0/4
PWE - DS	0/3	3/19 (15.8 %)	0/7
<b>75–99 % Seizure reduction (n = 6)</b>	1/7 (14.3 %)	4/30 (13.3 %)	1/11 (9.1 %)
PWE + DS	1/4 (25 %)	4/11 (36.4 %)	0/4
PWE - DS	0/3	0/19	1/7 (14.3 %)
<b>Seizure free (n = 15)</b>	1/7 (14.3 %)	6/30 (20 %)	8/11 (72.7 %)
PWE + DS	1/4 (25 %)	4/11 (36.4 %)	3/4 (75 %)
PWE - DS	0/3	2/19 (10.5 %)	5/7 (71.4 %)
<b>Responders (n = 25)</b>	2/7 (28.6 %)	14/30 (46.7 %)	9/11 (81.8 %)
PWE + DS	2/4 (50 %)	9/11 (81.8 %)	3/4 (75 %)
PWE - DS	0/3 (0 %)	5/19 (26.3 %)	6/7 (85.7 %)
<b>Non-responders (n = 23)</b>	5/7 (71.4 %)	16/30 (53.3 %)	2/11 (18.2 %)
PWE + DS	2/4 (50 %)	2/11 (18.2 %)	1/4 (25 %)
PWE - DS	3/3 (100 %)	14/19 (73.7 %)	1/7 (14.3 %)

FAS, focal aware seizure; FIAS, focal impaired awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; PWE + DS, patients with depressive symptoms; PWE - DS, patients without depressive symptoms. \*Three patients were excluded from the analysis: one with seizure-free data and two without available seizure data.

were responders, whereas only 26.3 % of PWE - DS were responders ( $p = 0.007$ ). Among patients with FAS, 50 % of PWE + DS were responders, whereas 0 % of PWE - DS were responders ( $p = 0.429$ ). Among patients with FBTCS, seizure outcomes did not differ between PWE + DS and PWE - DS, as 75 % of PWE + DS and 85.7 % of PWE - DS achieved the status of a responder ( $p = 1.000$ ). Seizure outcomes within groups based on depressive symptoms and predominant seizure type are presented in Table 3. Proportion of patients with the status of a responder for different seizure types is presented in Fig. 2.

## 4. Discussion

Our study revealed a positive association between a reduction in seizure frequency and the presence of depressive symptoms in DRE patients treated with VNS. The responder rate for the predominant seizure type was significantly higher in the group of patients that reported depressive symptoms than in the group of patients without



**Fig. 2.** Proportion of responders (> 50 % seizure reduction) for different predominant seizure types.

depressive symptoms. In addition, most of the responders in the PWE + DS group became either seizure free or achieved more than 75 % seizure reduction for the predominant seizure type, representing highly favourable seizure outcomes. Second, more than 70 % of all patients with FBTCs became seizure free for this predominant seizure type.

Epilepsy and depression share a bidirectional and complex relationship. Depression is common in patients with epilepsy, and there is an elevated risk of epilepsy onset following incident depression, potentially due to common underlying pathophysiological mechanisms [13,17,27–29]. Prior findings concerning the association between depression and epilepsy indicate that depression imperils the successful management of epilepsy. The presence of past or current depression in PWE increases both the probability of developing DRE [12,15,30] and the risk of failing to achieve 1-year seizure freedom [28]. Furthermore, a diagnosis of depression subsequent to an epilepsy diagnosis is associated with an increased risk of acute hospital admission due to seizures [27]. Similarly, presurgical MDD is a risk factor for a poor outcome after epilepsy surgery [11].

To the best of our knowledge, the clinical seizure outcomes of VNS-treated patients with DRE have not been assessed in previous studies based on the presence or absence of depressive symptoms. One study including only DRE patients with comorbid depression reported a correlation between amelioration of depressive symptoms and seizure response among VNS-treated patients with mostly moderate or severe depressive symptoms [19]. In contrast, only 41.2 % of patients in the present study had depressive symptoms, and most of them were classified as mild (23.5 %) or moderate (9.8 %), with only 7.8 % of all patients presenting with severe depressive symptoms at baseline or throughout the follow-up. When analysed at the individual level, 7 out of the 8 patients in our study with self-reported depressive symptoms at pre-implantation had lower BDI scores at LOCF, implicating that those patients with baseline depressive symptoms benefited from VNS in terms of decreasing severity in their symptoms. A similar observation was reported in a review article strongly suggesting improvement in depressive symptoms in DRE patients treated with VNS therapy [18]. On the other hand, the same review concluded that the effect of VNS on depression was independent of seizure reduction rates [18]. While previous studies have mostly reported worse seizure outcomes in epilepsy patients with depression, we observed significantly better seizure outcomes in patients with depressive symptoms than in patients without depressive symptoms.

Our findings may be attributed to the specific influence of VNS on a partly shared neurobiological basis for both seizure generation and depressive symptoms [13,16]. Moreover, VNS is known to have both antidepressant and anticonvulsant effects, which are mediated through the enhancement of noradrenergic and serotonergic activity [18,31,32]. The mechanisms mentioned above may also apply to the subgroup of our patients who had depressive symptoms only during the follow-up but not at baseline. The other possible explanation for this subgroup could be forced normalization, in which psychiatric symptoms increase as a result of a decrease in seizure frequency or severity in patients with previously uncontrolled epilepsy. The most common psychiatric manifestation of forced normalization is psychosis, but subsequent studies have also shown the possible occurrence of mood disorders, including depression [33]. Furthermore, it is also possible that improved mood may lead to better lifestyle choices with regard to epilepsy, thus indirectly reducing seizure-triggering factors. This could be applied to those patients who had depressive symptoms prior to the implantation of VNS and had a decrease in BDI scores during the study follow-up.

Our sample is distinct from past trials in terms of patient selection, as most participants in our study exhibited normal cognition and were predominantly young adults. Moreover, most of our patients exhibited mild to moderate depressive symptoms, which could increase the uncertainty of the generalizability of our results concerning positive seizure outcomes to patients with severe depressive symptoms. In our study, the baseline prevalence of active MDD diagnosed by a psychiatrist

was 13.7 % compared to 23–34 % reported in some previous studies [34–36]. There were seven patients with present MDD diagnosed by a clinician at a baseline psychiatric evaluation, but two of these seven patients reported no depressive symptoms in their self-reported BDI at baseline. One patient reported depressive symptoms during the follow-up and was thus allocated to the PWE + DS group, whereas the other patient reported no depressive symptoms during the follow-up and was thus allocated to the PWE - DS group. Even though the BDI can be used as a relevant rating scale for evaluating depressive symptoms in PWE [22,23], it was originally designed as an instrument for assessing the severity of depression among patients with MDD [21].

The DRE patients in our study achieved a major reduction in seizure frequency as a result of VNS therapy. The overall responder rate in our study was 52.1 % for the predominant seizure type. Among those who became responders, the vast majority achieved either > 75 % seizure reduction or seizure freedom for the predominant seizure type. Moreover, the seizure freedom rates in our study were as high as 31.3 % for the predominant seizure type and 22.2 % for all seizures. The reason for this good seizure outcome could be the long duration of VNS (median 39 months), as it has been shown that the efficacy of VNS increases over time [6,7]. The other reason could be the exclusion of patients with moderate or severe ID, since ID has been considered a negative prognostic factor for seizure outcomes [7,37]. Furthermore, our good seizure outcome may be related to the increased use of VNS models enabling automatic stimulation in our study [32]. One study showed that the initiation of the autostimulation mode of VNS can lead to better seizure control; yet, the study was limited by the small patient population [38]. However, our responder rate is in accordance with findings from a Japanese national registry study of 385 DRE patients for the outcome of VNS therapy, with responder rates of 55.8 %, 57.7 %, and 58.8 % at 12, 24, and 36 months of VNS therapy, respectively [6].

The best clinical outcomes were achieved in patients with FBTCs irrespective of depressive symptoms, with almost three-quarters of patients gaining seizure freedom for this seizure type. This is in line with a recent Japanese study reporting that patients with tonic-clonic seizures were most likely to experience prolonged periods of seizure freedom with adjunctive VNS treatment [39]. Furthermore, compared with the reduction in the number of total seizures, the decrease in seizure frequency in the more severe seizure type was better, with several patients with two or more seizure types becoming either seizure free or gaining > 90 % reduction in predominant seizure type with a minor change in the less severe seizure type (FIAS vs. FAS, or FBTCs vs. FIAS/FAS). This suggests the prevention of seizure spread to brain networks either in terms of the conservation of awareness or the inhibition of seizure propagation with focal onset, leading to FBTCs [32,40]. This favourable outcome may also be related to increased usage of VNS models enabling autostimulation in our study [32].

The main limitation of our study was the retrospective, uncontrolled study design. Additionally, follow-up BDI measurements were conducted at different time points, partly due to irregularity in clinical follow-up during the COVID-19 pandemic. Furthermore, we exclusively used the BDI for the depressive symptom score, and the MADRS scale was available at baseline only. The use of other depression rating scales in conjunction with the BDI would have enhanced the reliability of our results. Moreover, numerous ASMs carry potential depressogenic side effects [41], which we were unable to address in the present study.

## 5. Conclusion

Our study suggests that among patients with DRE, patients with depressive symptoms, as defined by BDI scores, are more likely to respond to VNS treatment for their predominant seizure type than are patients without depressive symptoms. This unexpected observation may be attributed to the shared neurobiological basis for both seizures and depressive symptoms, which could be subject to modifications during VNS therapy. Additional research in a larger cohort of DRE

patients with depressive symptoms is needed to substantiate our preliminary findings.

### Data availability statement

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Ethics statement

This was a non-interventional study in which data were collected prospectively but analysed retrospectively from a VNS quality register at Tampere University Hospital; therefore, ethics committee approval according to Finnish Law on Research was not required.

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### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2025.110499>.

### Data availability

Data will be made available on request.

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