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Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data

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ABSTRACT

Objective: Drug-resistant epilepsy is a devastating disorder associated with diminished quality of life (QOL). Surgical resection leads to seizure freedom and improved QOL in many epilepsy patients, but not all individuals are candidates for resection. In these cases, neuromodulation-based therapies such as vagus nerve stimulation (VNS) are often used, but most VNS studies focus exclusively on reduction of seizure frequency. QOL changes and predictors with VNS remain poorly understood.

Method: Using the VNS Therapy Patient Outcome Registry, we examined 7 metrics related to QOL after VNS for epilepsy in over 5000 patients (including over 3000 with ≥12 months follow-up), as subjectively assessed by treating physicians. Trends and predictors of QOL changes were examined and related to post-operative seizure outcome and likelihood of VNS generator replacement.

Results: After VNS therapy, physicians reported patient improvement in alertness (58–63%, range over follow-up period), post-ictal state (55–62%), cluster seizures (48–56%), mood change (43–49%), verbal communication (38–45%), school/professional achievements (29–39%), and memory (29–38%). Predictors of net QOL improvement included shorter time to implant (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.1–1.6), generalized seizure type (OR, 1.2; 95% CI, 1.0–1.4), female gender (OR, 1.2; 95% CI, 1.0–1.4), and Caucasian ethnicity (OR, 1.3; 95% CI, 1.0–1.5). No significant trends were observed over time. Patients with net QOL improvement were more likely to have favorable seizure outcomes (chi square [χ^2] = 148.1, $p < 0.001$) and more likely to undergo VNS generator replacement ($\chi^2 = 68.9$, $p < 0.001$) than those with worsened/unchanged QOL.

Significance: VNS for drug-resistant epilepsy is associated with improvement on various QOL metrics subjectively rated by physicians. QOL improvement is associated with favorable seizure outcome and a higher likelihood of generator replacement, suggesting satisfaction with therapy. It is important to consider QOL metrics in neuromodulation for epilepsy, given the deleterious effects of seizures on patient QOL.

1. Introduction

Epilepsy is a devastating neurological disorder affecting approximately 1% of the population, and seizures are resistant to antiepileptic drugs (AEDs) in about one-third of patients [1,2]. Drug-resistant epilepsy leads to significantly diminished quality of life (QOL), increased morbidity, and a 2–3 fold elevated risk of mortality [3,4]. In many patients with focal seizures and a localizable epileptogenic zone (EZ), surgical resection or ablation may lead to a cessation of seizure activity and improved QOL. After resection, seizure freedom is achieved by approximately 60–80% of patients with mesial temporal lobe epilepsy and 40–60% of individuals with focal neocortical epilepsy [5–7]. Numerous studies have demonstrated improvement in various aspects of QOL after resective epilepsy surgery, as well as reduced morbidity and mortality [8–11]. However, not all individuals with drug-resistant seizures are candidates for surgical resection.

Candidacy for resective epilepsy surgery may be prevented by a primary generalized epilepsy syndrome, non-localizable or multifocal seizure onset, or an epileptogenic zone in an eloquent location [12]. In these individuals, neuromodulation-based surgical therapies are often considered, of which vagus nerve stimulation (VNS) is the most common [13], though not approved by the FDA for primary generalized

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epilepsy. These palliative neurostimulation therapies often result in reduced seizure frequency, although seizure freedom is significantly less common than with resection [14]. Unlike with resective therapy, very few studies of VNS or other forms of neuromodulation have specifically examined QOL outcomes with therapy, and the vast majority of investigations focus on percent decrease in seizure frequency and/or overall rate of response to stimulation [15–17]. Thus, even though improved QOL is a critical outcome goal with any therapy for epilepsy, changes in QOL with VNS are poorly understood.

Here we present the first large-scale study of QOL metrics with VNS therapy. Using registry-based data, we analyzed physician survey responses for over 5000 patients before and after implantation to gauge improvement or worsening in several QOL metrics and identify potential predictors of improvement. We also estimated net QOL change with VNS therapy, and related QOL outcomes to both seizure outcomes and to the likelihood of generator (i.e., battery) replacement – an indirect estimate of patient satisfaction with therapy.

2. Methods

2.1. Patient outcome registry data collection

Data were obtained from the VNS Therapy Patient Outcome Registry maintained by the manufacturer of the device, Livanova (previously Cyberonics, Inc.), Houston, TX, USA. This database was established in 1999, after USA FDA approval of VNS therapy for epilepsy in 1997, in order to monitor patient outcomes systematically. Neurologists treating patients with VNS were provided standard case report forms from the registry, and participation was fully voluntary. Although refusal to participate was not explicitly tracked, during active data collection, the registry included approximately 18% of all VNS devices implanted. Overall, data were prospectively collected by 1285 prescribing physicians from 978 centers (911 within the USA and Canada and 67 international) at patients' baseline before implantation and at various intervals during therapy. Previous studies have authenticated the integrity of the systems for collecting and processing data in the VNS registry using an independent auditing agency [18], and registry outcomes have been compared to and corroborated by outcomes reported across the independent literature [19]. The registry was IRB approved and individual patients provided consent.

At baseline, a patient history and implant form was submitted including information on patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, and current AED use. At each follow-up visit, medications, VNS therapy settings, seizure frequency and type, generator replacements, device malfunctions, and QOL metrics were tracked. With respect to 7 metrics which may influence patient QOL, each individual was subjectively rated by the treating physician on a scale including worsened, no change, or improved compared to pre-implantation state. These metrics included: alertness, verbal communication, memory, social/professional achievements, mood changes, post-ictal state, and cluster seizures. In addition, as part of a "physician global assessment," providers were asked to rate the patient's overall condition as worsened, no change, or improved compared to pre-implantation state.

Data points collected in the registry at each follow-up visit included seizure frequency (overall and by seizure type), current AEDs, and QOL metrics. Seizure types classified as "generalized" included primary and secondarily generalized tonic-clonic, atonic (drop attacks), and absence seizures, while those classified as "partial" (focal) seizures included complex partial (focal with impairment of consciousness) and simple partial (focal without impairment of consciousness), including auras. Epilepsy etiologies classified as "lesional" included tumor, cyst, vascular malformation, mesial temporal sclerosis, tuber, and malformation of cortical development, while those classified as "non-lesional" included post-infectious, inflammatory, post-ischemic, Lennox-Gastaut or similar infantile syndrome, post-traumatic, cerebral palsy/perinatal event, or unknown/idiopathic. Between points of data submission by providers, it was assumed that therapy remained constant since the previous data point. For example, if data for a particular patient was submitted during a 4-month follow-up period and then again at a 12-month follow-up period, constant therapy was assumed between those data points.

2.2. Registry data analysis

The database was queried in February 2015, and all seizure and QOL outcomes reported with the 0–4, 4–12, 12–24, and 24–48 month time ranges after VNS device implantation were extracted and compared to patient pre-operative baseline. Duplicate visits for the same individual within the same time period were excluded from analysis. The patient was rated as worsened, no change, or improved on each individual QOL metric at each visit. In addition, to estimate net change across all seven QOL metrics ("net QOL change"), the total number of metrics rated as worsened (-1), no change (0), or improved $(+1)$ was summed for each patient at each follow-up period. A positive total was estimated as improvement, a negative total was estimated as worsening, and a zero total was estimated as no change. Additionally, using the physician global assessment, providers recorded patient's overall status at each visit as worsened, no change, or improved compare to pre-implantation state. Overall percent decrease (or increase) in seizure frequency compared to baseline was also calculated at each follow-up visit. Patients with ≥50% decrease in seizure frequency after VNS therapy compared to pre-operative baseline were designated seizure "responders" while those with <50% reduction in seizure frequency were labeled seizure "non-responders," and this overall responder rate was tracked over time.

2.3. Statistical analyses

Outcomes over time were evaluated for significant trends with linear regression analysis, including individual QOL metrics, estimated net QOL change, reported physician global assessment, change in seizure frequency, and seizure responder status. Univariate analysis with Pearson Chi square (χ^2) with Yates correction was used to evaluate potential relationships between QOL metrics (improved vs. worsened/no change), seizure outcome (responder vs. non-responder), and VNS generator replacement status (replaced vs. not replaced). To examine potential predictors of net QOL improvement across all visits, multivariate analysis was performed using binary logistic regression with backward elimination of factors. Predictors were reported using odds ratio (OR) with a 95% confidence interval (CI). Bonferroni correction was applied for multiple comparisons for all analyses where appropriate, and the level of significance was set at 0.05 after correction. Statistical analysis was performed using JMP 10.0 and SAS version 9.2 (SAS Institute, Inc., Cary, NC).

3. Results

Query of the VNS Patient Outcome Registry revealed data from 12,319 unique physician visits by 5554 patients with drug-resistant epilepsy. Of these, analysis included 4666 unique visits during the 0–4 month follow-up period after VNS implantation, 3277 visits at 4–12 months, 3182 visits at 12–24 months, and unique 1194 visits during the 24–48 month period. Altogether, 47% of patients in the registry were female, and the average age at implantation was 27 years (median 26, range 0–87 years). These and other patient characteristics are summarized in Table 1.

3.1. Change in QOL metrics with VNS therapy

The percentage of epilepsy patients rated as improved, worsened, or no change with regard to 7 metrics related to QOL was determined during each follow-up period after VNS implantation (Fig. 1A).