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The efficacy and tolerability of auto-stimulation-VNS in children with Lennox-Gastaut syndrome

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ABSTRACT

Objective: Lennox-Gastaut syndrome (LGS) is a severe drug-resistant epilepsy (DRE) of childhood. The Vagus Nerve Stimulator (VNS) is established as a safe and effective treatment for DRE. This study assesses efficacy and tolerability of the auto-stimulation VNS models in pediatric patients with LGS.

Methods: This is a retrospective chart review of a cohort of pediatric patients (Age 1–18 years old) with LGS implanted with an auto-stimulation VNS model at a single level four pediatric epilepsy center. Patient responder's rate was measured as seizure reduction over baseline and improvements in five quality-of-life measures as reported by the patients and families. Efficacy and tolerability were assessed at 1, 3, 6, 12, 18 and 24 months compared to baseline.

Results: This cohort includes 71 consecutive children with Lennox-Gastaut syndrome who underwent implantation with one of two models of the auto-stimulation VNS. The average age of the children at implantation was 20.82 months. Of those patients, 55 % of patients achieved greater than 50 % seizure reduction at six months, 67.7 % at 12 months, and 65 % at 24 months. At 12 months 11 % of the patients were completely seizure free and at 24 months 17 % were seizure free. By 24 months post implantation most of the patient families reported at least a 50 % improvement rate in one or more of the quality-of-life measures. The most commonly reported adverse events were dysphonia, paresthesia, and shortness of breath, all of which were tolerated and subsided by 24 months.

Significance: This study provides evidence that VNS models with the auto-stimulation paradigm based on detection of tachycardia are well tolerated and effective in a pediatric population with LGS. Furthermore, this study shows that for this population, the auto-stimulation models of the VNS may provide additional benefits over the earlier VNS versions.

1. Introduction

The first vagus nerve stimulator (VNS) was approved in the United States in 1997 for patients with drug resistant epilepsy (DRE). DRE is defined by the International League Against Epilepsy (ILAE) as persistent seizures within a 12-month period during which time an individual with epilepsy is treated with at least two properly chosen, properly dosed and well-tolerated anti-seizure medications (ASM) [1]. VNS therapy was reviewed by the American Academy of Neurology in 1997 [2], 1999 [3], and 2013 [4] and found to be both safe and effective in the treatment of epilepsy. The observation that up to 82 % of epileptic

seizures are associated with an increase in heart rate [5] led to the development of the auto-stimulation models of the VNS. The auto-stimulation VNS models include a detect-and-respond mode that detects ictal tachycardia and responds by delivering an extra stimulation to the Vagus nerve. Like the older VNS models, in addition to the auto-stimulation paradigm, these devices include a standard mode that allows care takers to stimulate with a magnet over the device, triggering a pulse of slightly higher current intensity over the baseline pulses. This additional pulse is designed to disrupt the epileptic discharge, thereby ending the clinical seizure [6]. Two auto-stimulation VNS models are currently available; in 2015, the Aspire SR VNS model was approved by

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the FDA followed, in 2017, by the SenTiva™ model. The FDA has approved the use of VNS as an adjunctive therapy in adults and children older than 4 years old with “partial onset seizures that are refractory to medications” (https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s207b.pdf) currently known as focal seizures according to the latest ILAE classification. Hamilton et al. showed that in an adult population with epilepsy the Aspire SR™ model provided a significant improvement in seizure control over the previous models (59 % of new insertion had a >50 % seizure improvement and 71 % of patients with a previously inserted VNS reported a >50 % seizure improvement on the Aspire SR™ model) [7]. Tzadok et al. presented very similar results in a population of 46 patients, both pediatric and adult. In this paper that included 13 children (< 12 years old) and 30 adolescents (13–18 years old), the authors showed that approximately 60 % of patients had a 50 % seizure reduction or better in patients newly implanted as well as those who underwent replacement for a previous device. The patient’s epilepsy etiology was varied and included genetic, structural, infectious, immune and unknown causes [8].

Lennox-Gastaut syndrome (LGS) is a severe childhood epilepsy with onset typically before eight years of age that is almost always pharmacologically resistant [9]. Different clinical characteristics are usually required for a diagnosis of LGS to be made, including the presence of multiple seizure types [10,11]. This epilepsy is now classified as a mixed epilepsy syndrome in recognition of the fact that patients with LGS can have both generalized and focal seizures [12]. The two most common seizure types are tonic and atypical absence seizures. Electrographically, seizures present as slow spike-wave complexes or generalized paroxysmal fast activity [13]. Cognitive impairment and intellectual disability are prominent features of the disorder and are clinically present in 20–60 % of patients at the time of diagnosis [10]. About 75 % of patients with LGS have an identifiable etiology such as a genetic, structural, or metabolic cause, with the most common cause being structural brain abnormalities. In rare cases, progressive metabolic disorders have been reported as a cause for LGS [9,14,15]. Due to the refractory nature of LGS, patient treatment goals are shifted to reduce the number of seizures, especially atonic and tonic-clonic seizures, as those are often the most incapacitating.

The efficacy of VNS therapy in LGS has been reported in several studies. In a retrospective multicenter study of 50 LGS patients treated with VNS, the median seizure reduction was 42 % after one month and 58.2 % after three months. When the data was further categorized by seizure type, atonic seizures were found to decrease by a median of 47 % after one month, 55 % after three months and 88 % after six months [16]. Several other studies of patients with LGS implanted with the VNS have reported 24 %–42 % reduction in seizures [17–23]. However, to date no study has reported the efficacy of the auto-stimulation VNS models when used in patients in LGS. In this study, we examine the outcome of patients with LGS who were either newly implanted with the auto-stimulation models of the VNS or switched from an older model to the auto-stimulation model.

2. Methods

This is a retrospective chart review of 71 consecutive children between the age of 1–18 years old with LGS at a single level four pediatric epilepsy center who were implanted with an auto-stimulation VNS between January 1, 2015 and December 31, 2019. For the purpose of data gathering, all patient notes and communications in the form of clinic visits or messages with the neurology clinic were included. All patients were from a single quaternary epilepsy referral center in the Midwest (Children’s Mercy Kansas City). All patients had a diagnosis of Lennox-Gastaut syndrome as determined by an epileptologist and were implanted with an auto-stimulation model of the VNS (Aspire SR™ or SenTiva™). Prior to implantation with the auto-stimulation model, some patients had an older model of the VNS without the auto-stimulation feature while others were new implants. All patients

followed our standard VNS programming protocol (Supplementary Table 1). Note that patients varied in terms of the frequency and timing of follow-up visits. As a result, the number of patients reported at each time point varies.

The last four clinic visits before the Aspire SR™ or SenTiva™ VNS models were implanted were analyzed to calculate an average number of seizures per month. Following implantation, patient communications at 3, 6, 12, 18, and 24 months, or the communication time that was the closest to each timeline benchmark, were analyzed for seizure type, epilepsy type, seizure frequency, quality of life, and side effects. If the patient had recorded communications with the epilepsy clinic one month or less after the surgery, it was reported as an initial chart review. Family and caretaker accounts were used to determine the average number of seizures the patients had per month using the Epilepsy Foundation seizure diary (<https://diary.epilepsy.com/home>) and McHugh’s et al. classification of outcome after VNS insertion [24]. This number was then compared to the average seizure frequency before implantation with the auto-stimulation model. For the data analysis patients were divided into the following groups: increase, no change, or decrease in seizure activity. The patients with decrease in seizure activity were further subdivided into less than 50 % change, 50%–75% change, 75%–90% change, greater than 90 % change, and seizure freedom. All of the comparisons were made to the average seizure burden prior to implantation with the auto-stimulation model of the VNS. Quality-of-life measures assessed were alertness, sleep, development, academic performance, and attention. Outcomes were divided into improvement, no improvement, or data not available.

3. Results

A systematic chart review resulted in 71 consecutive patients with LGS who were implanted with one of the auto-stimulation models of the VNS. The reason for reimplantation with the auto-stimulation model from the previous model was battery depletion in 100 % of the patients. The average age at implantation was 20.82 months and the average age of epilepsy onset was 18 months with the range being 0–14 years old and the median being 10 months of age. 47 patients (66.2 %) were males. Of the 71 patients, 35 (49.3 %) had a mixed epilepsy (patients with a combination of both focal and generalized seizures), 10 (14.1 %) had a focal epilepsy, and 26 (36.6 %) had a generalized epilepsy. The seizure types were distributed as follows: 47 patients (66.2 %) had tonic-clonic seizures, 21 (29.6 %) had clonic seizures, 41 (57.7 %) had atonic seizures, 56 (78.9 %) had myoclonic seizures, 25 (35.2 %) had absence seizures, 27 (38 %) had epileptic spasms, 24 (33.8 %) had focal seizures with impaired awareness and 59 (83.1 %) had tonic seizures. 47 patients had genetic testing, with 26 patients having a confirmed genetic abnormality. 11 patients had metabolic testing, of those 2 patients had confirmed abnormalities and 65 patients had MRI studies, of those 46 patients had MRI structural abnormalities. Of the 71 patients, clinical information was available for 26 patients at 1 month, 32 at 3 months, 44 at 6 months, 37 at 12 months, 24 at 18 months and 23 at 24 months.

At the start of the study the average number of anti-epileptic medications (AED) per patient was 3.4 (median 3, range 0–7). There were 7 patients on ketogenic diet. At the last visit for each of the patients, the average number of AEDs was 3.7 (median 4, range 0–8). There were 10 patients on ketogenic diet. There was no significant change in the number of AEDs per patients ($p = 0.7$).

Of the 71 patients enrolled in the study, 26 had communication within one month of implantation (reported as “initial chart review”). Of those, 4 (15 %) had an increase in seizure frequency, 7 (27 %) had no change, 15 (58 %) had a decrease and 3 (12 %) became completely seizure free (Table 1 and Fig. 1). Nine (35 %) of these patients were switched from the older VNS models to the auto-stimulation model. As compared to the older VNS models, 7 had a decrease and 2 experienced no change in seizure frequency. Of the patients that had a decrease, 3 had a <50 % decrease, 2 had a >50 % decrease, 1 had a >75 % decrease,

Table 1
Change in seizure frequency for all patients implanted with the auto-stimulation VNS.

| Seizure Frequency | Seizure Frequency | | | | | |
|-----------------------|----------------------|-------------------|-------------------|--------------------|--------------------|--------------------|
| | Initial chart review | 3-month follow up | 6-month follow up | 12-month follow up | 18-month follow up | 24-month follow up |
| No change | 7 (27 %) | 10 (31 %) | 9 (21 %) | 2 (5%) | 1 (4%) | 1 (4%) |
| Decrease | 15 (58 %) | 18 (56 %) | 32 (73 %) | 29 (78 %) | 18 (75 %) | 19 (83 %) |
| <50 % | 5 (19 %) | 4 (13 %) | 8 (18 %) | 4 (11 %) | 2 (8%) | 4 (17 %) |
| >50 % | 4 (15 %) | 8 (25 %) | 8 (18 %) | 12 (32 %) | 1 (4%) | 4 (17 %) |
| >75 % | 2 (8%) | 3 (9%) | 6 (14 %) | 7 (19 %) | 6 (25 %) | 4 (17 %) |
| >90 % | 1 (4%) | 0 | 5 (11 %) | 2 (11 %) | 4 (17 %) | 3 (13 %) |
| Seizure free | 3 (12 %) | 3 (9%) | 5 (11 %) | 4 (11 %) | 5 (21 %) | 4 (17 %) |
| Increase | 4 (15 %) | 4 (13 %) | 3 (7%) | 6 (16 %) | 5 (21 %) | 3 (13 %) |
| Total patients | 26 | 32 | 44 | 37 | 24 | 23 |

and 1 became seizure free (Table 2 and Fig. 2). In terms of quality-of-life, the majority of patients with a contact at one month or less post-implantation reported improvements in at least one of the variables assessed. The most common improvements reported were alertness and attention, with 7 (27 %) reporting improvement in each of those

categories (Fig. 3a).

At the 3-month follow up, 32 of the 71 patients had communications with the epilepsy clinic. Of those, 4 (13 %) had an increase in seizure frequency, 10 (31 %) had no change, 18 (56 %) had a decrease and 3 (9%) became seizure free (Table 1 and Fig. 1). Six (19 %) of these patients had a VNS without auto-stimulation previously implanted. As compared to the older VNS models, 3 of these patients had a decrease in seizures and 3 experienced no change in seizure frequency. Of the patients that had a decrease, 1 had <50 % decrease, 1 had >50 % decrease, and 1 became seizure free (table 3 and Fig. 2). The majority of 32 patients with a contact at the 3-month visit reported an improvement in quality-of-life in at least one the variables assessed. The most common improvement seen was sleep quality with 9 patients (27 %) reporting improvements in this variable (Fig. 3b).

At the 6-month follow up visit, 44 of the 71 patients had communication with the epilepsy clinic. Of those, 3 (7%) had an increase in seizure frequency, 9 (21 %) had no change, 32 (73 %) had a decrease and 5 (11 %) became seizure free (Table 1 and Fig. 1). Thirteen (30 %) of these patients were switched from an older version of the VNS to the auto-stimulation model. As compared to the older VNS models, 1 patient had an increase, 6 patients had a decrease and 6 experienced no change in seizure frequency. Of the patients that had a decrease, 3 had <50 % decrease, 1 had >50 % decrease, and 2 had >90 % decrease (Table 2 and Fig. 2). The majority of the patients reported an improvement in quality-of-life in at least one of the measured variables. The most common improvements seen in were in alertness and attention with 22 (51 %) reporting improvements in each of those categories (Fig. 3c).

At the 12-month follow up visit, 37 of the 71 patients had communication with the epilepsy clinic. Of those 6 (16 %) had an increase in seizure frequency, 2 had no change (5%), 29 (78 %) had a decrease and 4

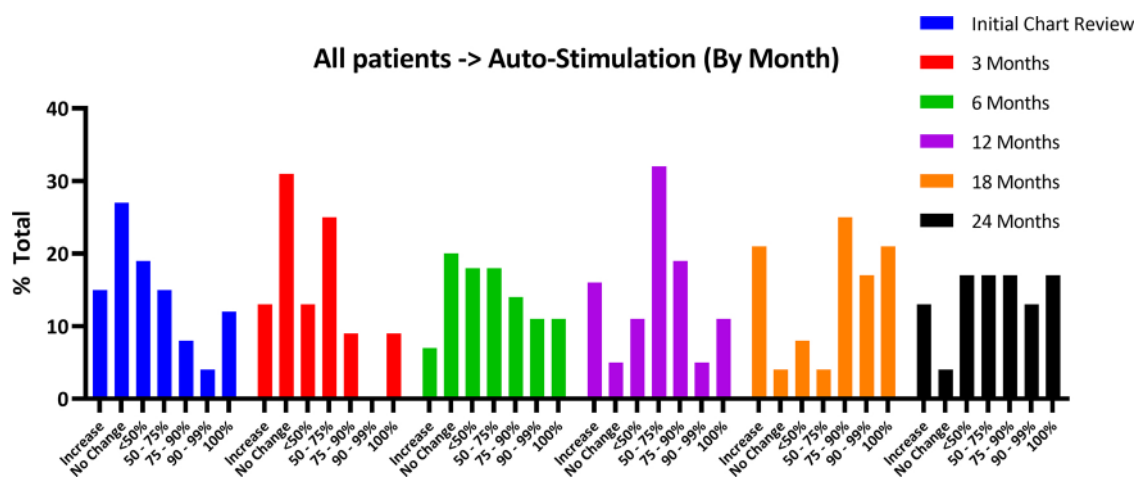


Fig. 1. Grouped data for all patients with implantation of the auto-stimulation VNS model. The x axis shows the percent decrease in seizure frequency at each clinical contact. The y axis shows the percent of patient reporting the respective percent changes in seizure frequency.

Table 2
Change in seizure frequency for the patients who were switched from the traditional VNS to the auto-stimulation model.

| | Seizure Frequency | | | | | |
|-----------------------|----------------------|-------------------|-------------------|--------------------|--------------------|--------------------|
| | Initial chart review | 3-month follow up | 6-month follow up | 12-month follow up | 18-month follow up | 24-month follow up |
| No change | 2 (22 %) | 3 (50 %) | 6 (46 %) | 1 (8%) | 0 | 1 (13 %) |
| Decrease | 7 (78 %) | 3 (50 %) | 6 (46 %) | 8 (67 %) | 5 (71 %) | 5 (63 %) |
| <50 % | 3 (33 %) | 1 (17 %) | 3 (23 %) | 0 | 1 (14 %) | 1 (13 %) |
| >50 % | 2 (22 %) | 1 (17 %) | 1 (8%) | 6 (50 %) | 1 (14 %) | 2 (25 %) |
| >75 % | 1 (11 %) | 0 | 0 | 0 | 1 (14 %) | 2 (25 %) |
| >90 % | 0 | 0 | 2 (15 %) | 2 (17 %) | 1 (14 %) | 0 |
| Seizure free | 1 (11 %) | 1 (17 %) | 0 | 0 | 1 (14 %) | 0 |
| Increase | 0 | 0 | 1 (8%) | 3 (25 %) | 2 (29 %) | 2 (25 %) |
| Total patients | 9 | 6 | 13 | 12 | 7 | 8 |

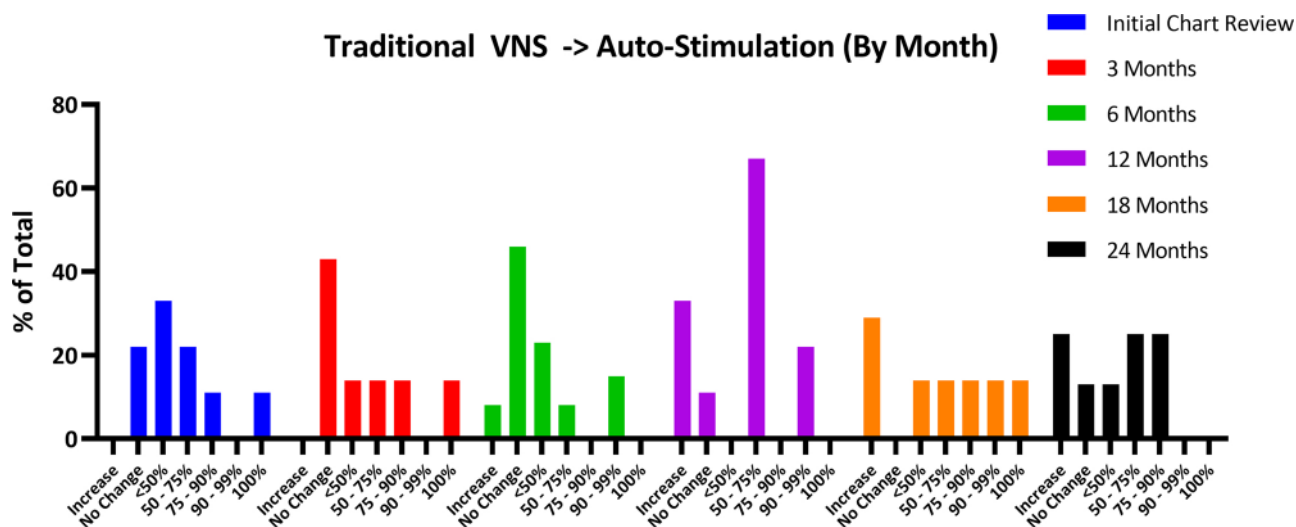


Fig. 2. Patients switched from a traditional VNS model to the auto-stimulation model. The x axis shows the percent decrease in seizure frequency at each clinical contact. The y axis shows the percent of patient reporting the respective percent changes in seizure frequency.

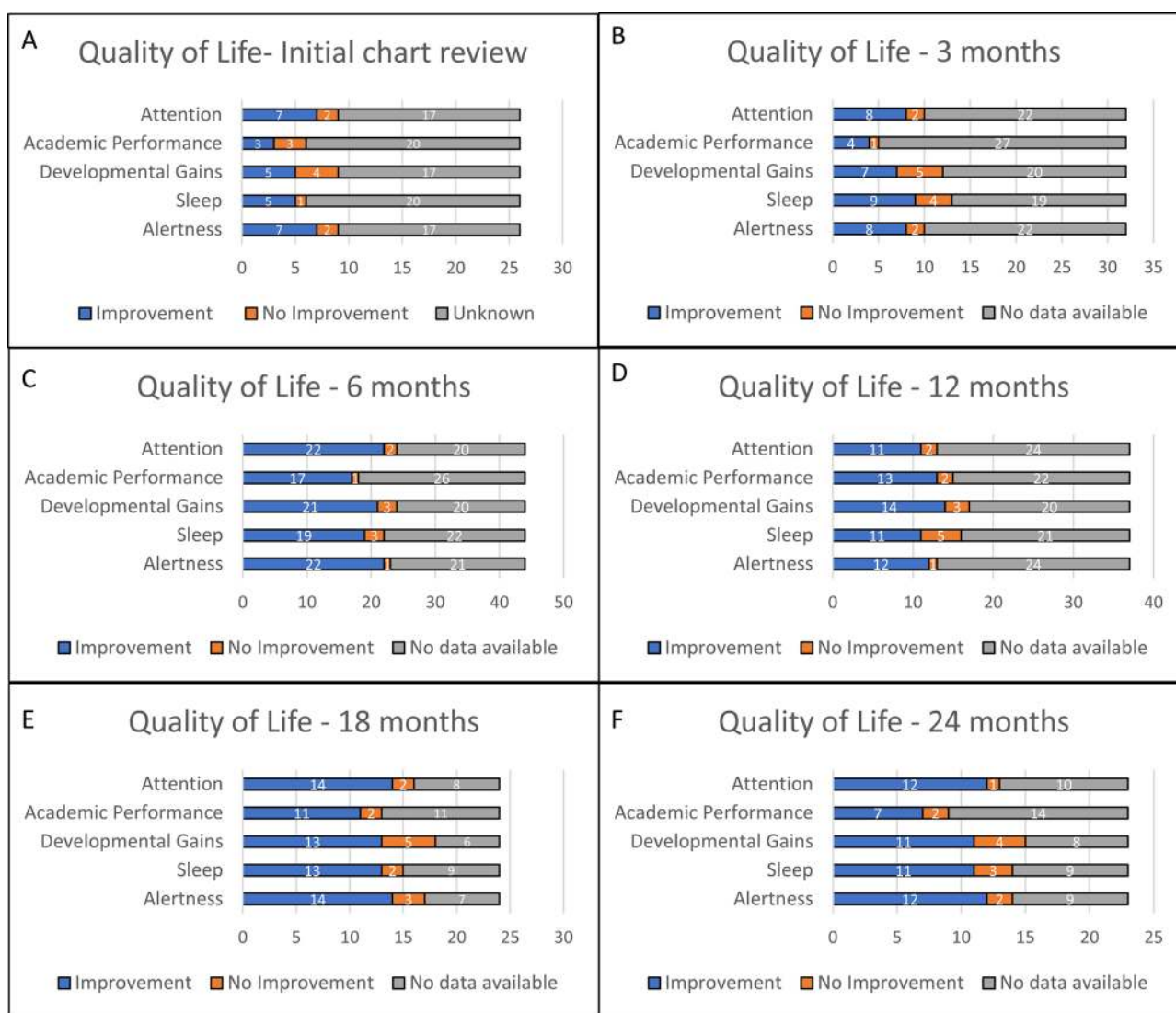


Fig. 3. Changes in quality-of-life. Changes in quality-of-life plotted at initial chart review 3a, 3-month 3b, 6-month 3c, 12-month 3d, 18-month 3e, and 24-month 3f. The numbers within the bins represent the number of patients in each group.

(11 %) became seizure free (Table 1 and Fig. 1). Twelve (32 %) of these patients had a VNS without auto-stimulation previously implanted. As compared to the older model of the VNS, 3 patients had an increase, 8 had a decrease, and 1 patient experienced no change in seizure frequency. Of the patients that had a decrease, 6 had a >50 % decrease, and 2 had a >90 % decrease (Table 2 and Fig. 2). The majority of patients reported an improvement in quality-of-life in at least one of the measured benchmarks. The most common improvement reported was in developmental gains with 14 (39 %) reporting improvements in that category (Fig. 3d).

At the 18-month follow up visit, 24 of the 71 patients had communication with the epilepsy clinic. Of those, 5 (21 %) had an increase in seizure frequency, 1 had no change (4%), 18 (75 %) had a decrease and 5 (21 %) became seizure free (Table 1 and Fig. 1). Seven (29 %) of these patients had a VNS without auto-stimulation previously implanted. As compared to the older VNS models, 2 had an increase and 5 had a decrease in seizure activity. Of the patients that had a decrease, 1 had a <50 % decrease, 1 had a >50 % decrease, 1 had a >75 % decrease, 1 had a >90 % decrease, and 1 became seizure free (Table 2 and Fig. 2). Most of the patients reported an improvement in quality-of-life in at least one of the measured variables. The most common improvements observed were in sleep quality and developmental gains with 13 (57 %) reporting improvements in these two clinical areas (Fig. 3e).

Finally, 23 of the 71 patients had communications with the epilepsy clinic at the 24-month visit. Of those, 3 (13 %) had an increase in seizure frequency, 19 (83 %) had a decrease and 4 (17 %) became seizure free (Table 1 and Fig. 1). Eight (35 %) of these patients had a VNS without auto-stimulation previously implanted. As compared to the older VNS models, 2 had an increase, 5 had a decrease, and 1 had experienced no change in seizure frequency. Of the patients that had a decrease, 1 had a <50 % decrease, 2 had a >50 % decrease, and 2 had a >75 % decrease (Table 2 and Fig. 2). The majority of patients reported an improvement in quality-of-life in at least one of the measured variables. The most common improvements reported were in attention and alertness with 12 (55 %) reporting improvements in each of those categories. It is worth noting that a significant number of patients reported improvements in sleep and developmental abilities, with 10 (43 %) patients reporting an improvement in at least one of those variables (Fig. 3f).

Both models of the auto-stimulation VNS (Aspire SR™ and Sentiva™) were well tolerated. The most common side effects were voice change, pain (discomfort with stimulation), and breathing issues (Fig. 4). The side effects were most prevalent at the initial contact following the surgery when 10 out of 26 patients reported some type of side effects. With time, the side effects subsided, with only one patient still reporting mild side effects at the 24-month visit. Four patients

required programming adjustments due to discomfort with stimulation. No patients reported any side effects from the auto-stimulation.

4. Discussion

There is an overwhelming amount of data to suggest that LGS is associated with a decreased quality-of-life. In 80–90 % of patients seizures will persist into adulthood [25–27]. Certain risk factors have been shown to worsen the prognosis for LGS patients including a symptomatic etiology, a history of infantile spasms, onset before 3 years of age and cognitive dysfunction [28]. It is also known that LGS patients have a 5–17 % increase in mortality rate [28,]29. These deaths are directly related to seizure frequency.

There has not previously been a study that has assessed the efficacy of the auto-stimulation model of the VNS in children diagnosed with LGS. One study of 347 children implanted with older models of the VNS reported that the subset of patients with LGS responded well with 32.5 %, 37.6 %, and 43.8 % achieving greater than 50 % reduction in seizures at 6, 12, and 24 months respectively [29]. Two studies to date have examined the benefit of the new VNS devices in both children and adults. Hamilton et al. showed that in an adult population with epilepsy the Aspire SR™ model provided a significant improvement in seizure control over the previous models [7]. Similarly, Tzadok et al. showed that in a group of children and adults with epilepsy of various etiologies the same Aspire SR™ model provided benefits for both the newly implanted patients and those undergoing replacement of an older model. They also showed that the benefits continued to accrue up to 24 months post implantation [8]. Closed loop VNS provides more accurate, and timely delivery of electrical stimulation in response to ictal tachycardia allowing for a more precise duty cycle. The auto-stimulation models are engineered to enforce a refractory period preventing over-stimulation as a result of either the normal cycle resuming or a second ictal tachycardia [30,31].

In our study, the patient responder's rate was higher with 55 %, 67.7 %, and 65 % of children achieving greater than 50 % reduction in seizures frequency at 6, 12, and 24 months respectively. In addition, 11 % of the patients were completely seizure free at 12 months and 17 % were seizure free at 24 months. Furthermore, when we separated the subgroup of patients that went from the older VNS models to an auto-stimulation model, we noted that an additional 60–70% of the patients had a further reduction in seizure frequency over their baseline with the older VNS models (Table 2). These data suggest that the newer versions of the VNS with the auto-stimulation paradigm provide additional seizure reduction over the pre-auto-stimulation models. In addition, the majority of patients had an improvement in at least one

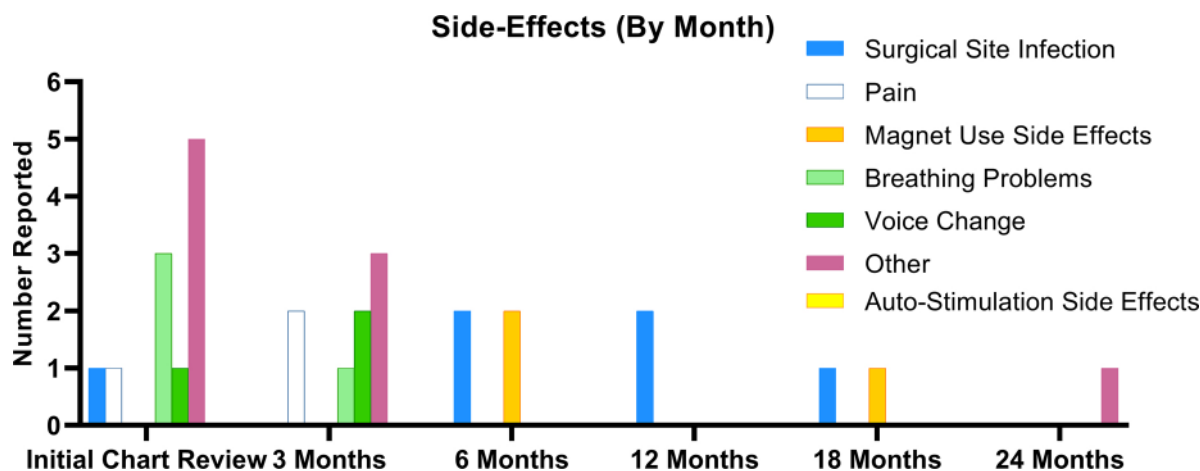


Fig. 4. Side-effects. Side effects were reviewed in all 71 patients. The visit time points are plotted on the x-axis and the number of patients reporting each side-effect on the y-axis. Pain refers to discomfort associated with stimulation. Note that no patient reported any side effects from the auto-stimulation paradigm.

measure related to quality-of-life with a positive trend over time. By 24 months post-implantation, most of the patient families reported at least a 50 % improvement rate in one or more of the quality-of-life measures. Consistent with previous observations of the pre-auto-stimulation VNS models, very few patients experienced side effects and those that did had a rapid resolution. The most common side effects reported were dysphonia, paresthesia, and shortness of breath. None of the patients died over the course of this study.

Overall the devices were well tolerated. While a little less than half of the patients reported side effects at the initial contact following implantation, the side effects were well tolerated and steadily decreased over time. None of the patients required removal or turning off the device and only four patients required programing adjustments due to side effects. The rate of side effects reported in our cohort is lower than previously reported [32,33]. Our site follows a standardized protocol for VNS programing (Supplement Table 1). This protocol has been effective in minimizing side effects of the VNS and we believe that likely accounts for the generally modest severity of the side effects reported in this cohort. In summary, the data presented herein is consistent with the auto-stimulation VNS model providing addition seizure reduction over the older VNS models. Furthermore, in our cohort, the side effect profile of the auto-stimulation model was better than previously reported for the older models. However, as mentioned above, we cannot be sure that the improved side effect profile can be ascribed to the auto-stimulation model.

This study has limitations. Given the retrospective nature of the study, it is subject to parental and physician bias. Furthermore, variability in charting can be challenging in extracting information from the medical records. For example, some of the epileptologists do not systematically report the quality-of-life categories that the study was designed to collect; this resulted in some patients missing data for these variables. Also, quality-of-life is a highly subjective measure that is subject to reporter bias. The study also relied on parental recall for seizure frequency. Although this was mitigated by the fact that the data was obtained at regular intervals, this type of recall is not as reliable as actual seizure counts and journals. Finally, due to the retrospective nature of this study, we could not control for AED changes that could have confounded the data analysis and not all patients were seen at each time point.

5. Conclusion

This study provides evidence that the auto-stimulation VNS models based on detection of tachycardia are effective, well tolerated and may provide an additional benefit over the earlier VNS models across generalized and focal epilepsy types, different seizures types and etiologies, with structural, metabolic, genetic and unknown etiology epilepsy types represented in the study. In this study, 83 % of the patients at the 24-month visit reported both a decrease in seizures and improvements in quality-of-life, with at least 50 % of patients reporting an improvement in one or more of the quality-of-life measures. Furthermore, patients who went from the earlier versions of the VNS to an auto-stimulation model showed additional improvements in seizure frequency. Given the retrospective nature of this work, further studies will be important. We believe that the results reported herein are promising for auto-stimulation VNS models considering the significant improvement in the overall seizure frequency and quality-of-life.

Disclosures

Ahmed Abdelmoity received honoraria for consulting or serving on the speaker bureau for Livanova, UCB and Greenwich. No external funding received for the work presented. All co-authors have been substantially involved in the study and the preparation of the manuscript; no undisclosed groups or persons have had a primary role in the study and/or preparation of the manuscript; all co-authors have seen

and approved the submitted version of the paper and accept responsibility for its content.

Declaration of Competing Interest

The remaining authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2021.02.015>.

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