

Rapid titration of VNS therapy reduces time-to-response in epilepsy

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ABSTRACT

Background: Common titration strategies for vagus nerve stimulation (VNS) prioritize monitoring of tolerability during small increases in stimulation intensity over several months. Prioritization of tolerability is partially based on how quickly side effects can be perceived and reported by patients, and the delayed onset of clinical benefits from VNS. However, many practices assess the clinical benefit of VNS at one year after implantation, and excessive caution during the titration phase can significantly delay target dosing or prevent a patient from reaching a therapeutic dose entirely.

Objective: This study aimed to characterize the relationship between titration speed and the onset of clinical response to VNS.

Methods: To assess differences between more aggressive titration strategies and more conservative ones, we analyzed the relationship between time-to-dose and time-to-response using a weighted Cox regression. The target dose was empirically defined as 1.625 mA output current delivered at 250 microsecond pulse widths at 20 Hz. Patient-level outcomes and dosing data were segregated into fast (<3 months), medium (3–6 months), and slow (>6 months) cohorts based on their titration speed.

Results: The statistical model revealed a significant relationship between titration speed and onset of clinical response, defined as a 50% reduction from baseline in seizure frequency. Frequency of adverse events reported between each cohort trended toward higher rates of adverse events in adults who were titrated quickly; however, the pediatric population appeared to be more tolerant of titration at any speed.

Conclusions: This analysis indicates that faster titration yields faster onset of clinical benefit and is especially practical in the pediatric population, though attempts to accelerate adult titration may still be warranted.

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1. Introduction

Vagus Nerve Stimulation (VNS) is a well-established therapeutic intervention for people with drug-resistant epilepsy (DRE). The therapy delivers electrical pulses to the vagus nerve in a “dose” combination of output current, pulse width, and frequency to modulate neural circuits for anticonvulsant effect, and doses are delivered at a cadence defined by the duty cycle [1–3]. Patients are titrated to a therapeutic dose over the course of several weeks to months after VNS system implantation. Titration speed is

largely dependent on factors that include ease of patient access for titration visits and the potential occurrence of stimulation-associated side effects like voice alteration and cough as VNS intensity is increased. While some patients respond to the therapy as early as weeks after initiating [4,5], the onset of clinical benefits from VNS tends to be delayed (e.g. 1–3 months after reaching target dose) and typically improves with time [6–8].

Recommendations by the manufacturer and professional societies for the use of VNS have provided some albeit limited guidance concerning programming of the multiple parameters that comprise VNS “dosing” [9,10]. Recently, Fahoum et al 2022 [11] explored existing clinical outcomes data associated with programmed VNS parameters to build population-level hypotheses around the target dose of VNS. Analysis of an aggregated database of sponsored trials

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revealed that over 50 % of patients have taken more than 6 months to reach the target population-level dose of 1.625 mA (Table 1). While this analysis serves to underscore the general importance of titrating patients to an appropriate VNS dose, it does not help us understand the specific relationship between the dose of VNS that is administered and the clinical response that occurs in the time domain. A better understanding of this relationship would help patients and providers to set expectations for outcomes as VNS is implemented and to potentially achieve better outcomes sooner with VNS.

In this analysis, we utilized clinical outcomes data from sponsored, prospective clinical trials to evaluate the occurrence of a 50 % reduction in seizures by time-to-event relative to the total duration of VNS titration. Patients were sub-divided by time-to-final VNS dose into a fast, medium and slow titration-speed group (<3 months, 3–6 months, or >6 months). Adverse events were also analyzed by time-to-event relative to the total duration of VNS titration for each titration group to develop an exploratory understanding of patient safety relative to the speed of VNS titration.

2. Materials and methods

This analysis compiled patient data from completed clinical trials for epilepsy sponsored by the manufacturer of VNS Therapy to explore the relationship of titration speed and the onset of initial clinical response, defined as a greater than or equal to 50 % reduction in total seizure frequency from baseline. All subjects included in the database initially affirmed their consent to participation in a VNS study; however, data included in these analyses were further de-identified to eliminate the possibility of violating patient privacy concerns. These data were explored within the context of a prospectively defined statistical analysis plan, and further *ad hoc* investigation was proposed and undertaken by a multidisciplinary team of clinicians, statisticians, and neuromodulation experts.

2.1. Database

A total of 12 clinical studies sponsored by LivaNova from 1990 to 2017 were included in the database for analysis. Only manufacturer-sponsored studies were included due to ease of access to patient-level data. The sole requirement for study inclusion was electronically available clinical outcomes data with prospective or retrospective baseline and/or safety data at all time points that could be mapped to programming settings at each study visit. These studies consist of randomized control trials as well as open observational studies. Control arms were excluded in the database to limit the investigation to findings related to

VNS outcomes. Further demographic information on the population can be found in Fahoum et al 2022, in their Table 1 [11].

2.2. Cox models for time-to-first-response

The statistical analysis plan called for initial investigation using a Cox proportional hazard (PH) model with time-dependent covariates with first response being the event of interest. A responder was defined as a patient having at least 50 % reduction in seizure frequency compared to baseline over the relevant time interval. The maximum follow-up time for this analysis was 1 year, as patients are typically titrated in less than 1 year and initial response to VNS is often assessed at 1 year after implant. The covariates included in our analysis were:

- Output current in mA
- Duty Cycle = (On time + 4) / (On Time + Off time * 60) * 100 %
- Quadratic terms for output current and duty cycle
- Duration of Epilepsy in years
- Age at Implant in years
- Study ID
- Dose Pace: categorical variable with 3 groups

The 3 groups for dose pace are:

- Fast Pace: reaching 1.625 mA or higher within 3 months post-implant;
- Medium Pace: reaching 1.625 mA or higher between 3–6 months post-implant;
- Slow Pace: reaching 1.625 mA or higher in more than 6 months or not reaching it at all during follow-up.

Patients who had less than 6 months of follow-up data following implantation and did not reach an output current of ≥ 1.625 mA within that time frame were excluded from this analysis ($n = 183$, or approximately 15.5 % of subjects), as they could not be classified to a dose pace group.

No variable selection was performed for this model; the covariates were chosen using the final model of Fahoum et al 2022 except for the dose pace groups, which were selected based on post-market surveillance of VNS titration data and published titration protocols [11,12]. All effects were significant in this Cox PH model; however, the model failed the proportional hazards assumption on certain covariates as well as globally. Therefore, a weighted Cox-regression model was fitted using the approach from Schemper and Heinze [13] to correct for non-proportionality. Weighted estimation is a parsimonious approach in the presence of non-proportional hazards and appropriate to

Table 1
Demographics of titration speed in the database.

ID	Total Count	Percentage of Total Samples	Total Samples (Fast/Med/Slow)	Epilepsy Type			Patient Age Group	
				Focal	Generalized	Unknown	Adults	Children (<18)
E03	48	5 %	21 / 9 / 18	48 (100 %)	0	0	48 (100 %)	0
E04	96	10 %	24 / 12 / 60	73 (76 %)	22 (23 %)	1 (1 %)	62 (65 %)	34 (35 %)
E05	91	9 %	33 / 16 / 42	91 (100 %)	0	0	78 (86 %)	13 (14 %)
E06	60	6 %	6 / 15 / 39	37 (62 %)	0	23 (38 %)	0	60 (100 %)
E100	30	3 %	3 / 4 / 23	30 (100 %)	0	0	30 (100 %)	0
E103	112	11 %	6 / 10 / 96	88 (79 %)	0	24 (21 %)	89 (79 %)	23 (21 %)
E104	159	16 %	3 / 22 / 134	98 (62 %)	0	61 (38 %)	84 (53 %)	75 (47 %)
E36	30	3 %	0 / 3 / 27	28 (94 %)	1 (3 %)	1 (3 %)	30 (100 %)	0
E37	7	1 %	0 / 0 / 7	7 (100 %)	0	0	7 (100 %)	0
Japan	362	36 %	9 / 6 / 347	227 (63 %)	135 (37 %)	0	223 (62 %)	139 (38 %)
all	995	100 %	105 / 97 / 793	727 (73 %)	158 (16 %)	110 (11 %)	651 (65 %)	344 (35 %)
All Adults	651	65 %	77 / 55 / 519					
All Children	344	35 %	28 / 42 / 274					

verify the robustness of the Cox PH model, and provides an unbiased estimate of the average hazard effect [13]. No imputation on missing values was performed as all missing data were considered as missing at random. All analyses were done using R (R Core Team, 2021, version 4.1). The survival package [14] was used for the initial Cox PH model with time-dependent covariates; the coxphw package [15] was used for the weighted Cox regression. Graphs were created using ggplot2 [16], and the tables were created using SjPlot [17].

2.3. Mean adverse events curves

To visualize the effect of rapid titration on adverse event occurrence, we adapted a mean cumulative function approach [18] to obtain a “mean adverse event curve”. At any point in time when an adverse event occurred in one of the three dosing groups, the number of patients at risk at that time point in the respective group was determined; and the mean adverse event curve of the group increased by 1 divided by the number of patients at risk. The time of being at risk for each patient was determined by their last available follow-up visit. This approach is non-parametric and accounts for the different follow-up times of subjects.

3. Results

Titrating patients with VNS to the target dose of 1.625 mA in less than 3 months resulted in the fastest onset of response when compared to the Slow and Medium titration speeds. The Medium Pace group was indistinguishable from Slow Pace titration. When non-responders were excluded from the analysis, the impact of Fast Pace titration on time-to-response grew substantially, and Medium Pace titration significantly separated from Slow Pace. Fast Pace titration appears to be tolerable in children and adults managed in post-market VNS studies.

As a post-hoc analysis, an “Age Group” term (categorical: adults vs children) and an interaction of Age_Group*Dose_Pace was added to the model and it was re-assessed. These terms were not found to be significant, suggesting there is no evidence that these findings would differ between adults and children.

3.1. Cox regression – time to first response

Weighted Cox regression indicates that titration efficiency influences the time required to reach the onset of VNS response. The Fast Pace group had a significantly shorter time-to-first response compared with the Slow Pace group (Avg. HR 1.84; CI 1.12–3.04; Table 2) and the Medium Pace group (Avg. HR 2.23; CI 1.25–3.97). The Medium Pace group was not significantly different from the Slow Pace group. Patient age at the time of VNS system implantation and duration of epilepsy before implantation were not found to contribute significantly to the onset of response.

To assess the impact of responder bias which may be driven by different responder rates in each dose pace group (Table XX), a subgroup analysis was conducted that included only patients who responded to VNS Therapy (Supplementary Table 1). In this analysis, both the Fast Pace (Avg. HR 4.54; CI 2.77–7.43) and Medium Pace (Avg. HR 2.32; CI 1.51–3.56) groups were associated with faster onset of clinical response. The hazard ratio of this ‘responders only’ analysis was nearly three times greater than the hazard ratio in the ‘all-comers’ analysis, suggesting that the impact of titration efficiency is even stronger in patients that will eventually respond to the therapy. The Fast Pace group was also associated with a faster onset of response than the Medium Pace group (Avg. HR 1.96; CI 1.16–3.30). The duration of epilepsy before VNS implantation also became significant in this ‘responder only’ anal-

Table 2

Weighted Cox Regression – Time to First Response. The Slow Pace group is not listed in this table as the Dose Pace hazard ratios are relative to the performance of the Slow Pace group. Study effects have been removed to improve readability of the table.

Parameter	Estimate	Exp. Estimate	Confidence Interval
Fast Dose Pace	0.612	1.845	1.121; 3.035
Medium Dose Pace	−0.187	0.829	0.518; 1.327
Output Current	−2.008	0.134	0.079; 0.229
(Output Current) ²	0.455	1.576	1.284; 1.934
Duty Cycle	0.028	1.029	0.943; 1.123
Duty Cycle ²	−0.002	0.998	0.996; 1.001
Age At Implant	0.005	1.005	0.994; 1.017
Duration of Epilepsy	−0.009	0.991	0.978; 1.003

ysis (Avg. HR 0.98; CI 0.972–0.995), indicating that early implant of VNS after epilepsy diagnosis results in faster onset of response in patients that will respond to VNS.

Other effects, such as output current and the square of output current, are displayed and had significant effects (Table 2, Supplementary Table 1). Output current was identified as the primary contributor to the failure of the Cox proportional hazards assumption but was still included in the weighted Cox regression and corrected. The significance of both the linear and quadratic terms for output current indicates the relationship between output current and time-to-response is nonlinear. Essentially, the nature of this quadratic relationship suggests that some patients with VNS will respond to VNS at output currents below the population level target dose and thus will have the fastest time to response, while others that require higher output currents to respond will see stronger benefit when titrated to higher doses very quickly.

3.2. Cumulative adverse events associated with rapid titration

Stimulation-related adverse events, such as cough or voice alteration, reported after implantation were tabulated for each dose group and for adults versus children (<18 years old) independently.

In adults, adverse event reports appear to increase proportionally with titration speed. Furthermore, even after the target dose of 1.625 mA is achieved (e.g. >90 days in the Fast Pace group), adverse events are still reported at a higher rate in the Fast and Medium Pace groups compared to the Slow Pace group. In children, there does not appear to be an association between dose pace and adverse event reports – suggesting no obvious penalty for rapid titration in children.

In the adult patients, a high proportion of adverse events were attributed to a single study: E05. This randomized controlled trial was conducted prior to commercial launch, so clinical experience in the management of VNS titration was limited. Due to the outlying nature of the findings from this study, we have prepared a supplemental analysis of the cumulative adverse event curves excluding the E05 study (Supplementary Fig. 1). Here, the adult population no longer exhibits a monotonic trend of increasing adverse event reports with faster titration.

3.3. Slow titration rate profile for VNS titration

The definition for the Slow Pace group in this database did not have an upper bound. Thus, some patients in this group require over 12 months to achieve the target dose. Approximately 50 % of patients in the Slow Pace group did not achieve the population level target dose of VNS (1.625 mA) at 12 months after implantation (Fig. 2).

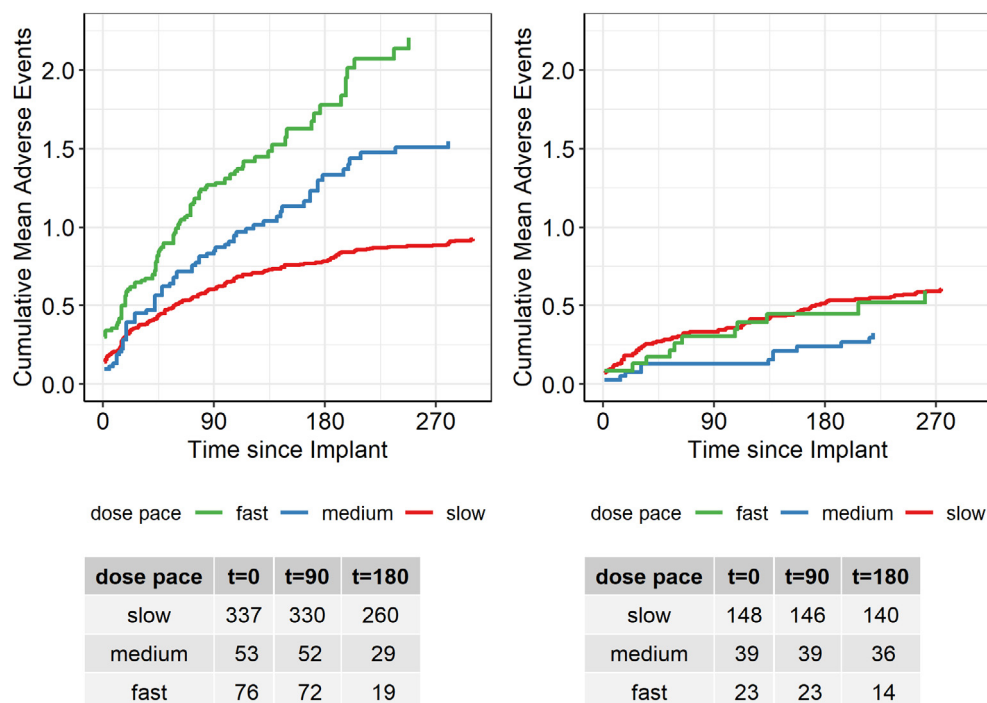


Fig. 1. Cumulative stimulation-related adverse events over time are impacted by titration speed in adults, but not in children with VNS. Adverse events from the Japan Registry could not be included because they were not originally adjudicated as procedure- or stimulation-related. An extremely high influence of a single study (E05) was noted in the adult (top left) outcomes; an examination of the influence of these outcomes can be found in Supplementary Fig. 1. Children appear to tolerate all titration speeds well (top right). Total count of adults (bottom left) and children (bottom right) for each titration speed with available duration of follow-up (in days) are included.

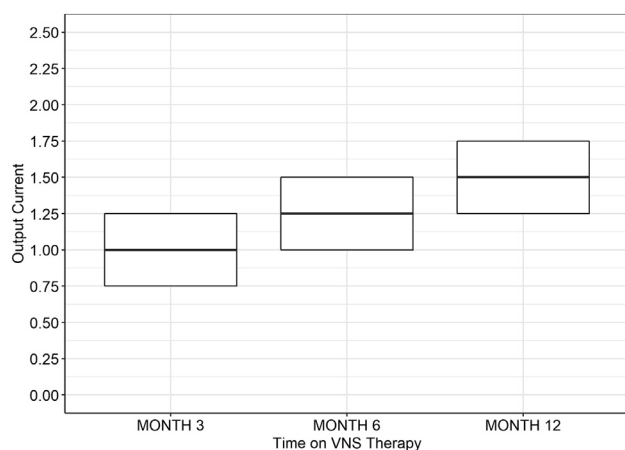


Fig. 2. Inner-quartile range of titrated output current over time from patients in the Slow Pace group only. Slowly titrated patients may not achieve target dose by 12 months after implant.

4. Discussion

In this retrospective analysis of aggregated data, survival analysis indicates that patients titrated in less than 3 months achieve a faster onset of first response (Table 2). Despite fast titration being aligned with the manufacturer's labeling, it was rare in our database (Table 1). The tolerability profile of rapid titration, compared to the more typical practice of titrating slowly, could improve patient outcomes by providing a faster onset of clinical benefit without significant increases in side effects (Fig. 1, Supplementary Fig. 1). Post hoc investigation revealed that these clinical impacts are not associated with age of the patient, so adults and children could both benefit from more efficient titration strategies.

4.1. Model selection

This retrospective analysis of aggregated data from prospective sponsored clinical trials used a weighted Cox regression to assess the impact of rapid titration on seizure outcomes, specifically time to first response. A regression analysis was used as it allows to account for other covariates, unlike other forms of survival analysis like Kaplan–Meier. The Cox PH model is the most popular model in these circumstances. As we are dealing with non-proportional hazards, we used a weighted Cox regression. All effects of the weighted Cox regression were in the same direction as in the PH model.

4.2. Rapid titration of VNS therapy results in earlier onset of response

For patients with DRE, the target dose combination should be considered as an output current of 1.625 mA at a pulse width of 250 μ sec, with a signal frequency of 20 Hz [11]. This dose combination is considered as the target dose for this analysis because it is derived from modeling intended to maximize clinical response (in terms of ≥ 50 % responder rate), tolerability, and battery life. The current weighted Cox regression indicates that rapid titration to this target is associated with an earlier onset of clinical response (Table 2).

A typical titration strategy is to achieve the target dose by increasing total charge delivery, typically by increasing output current in small, 0.25 mA steps, every 2 weeks during on-site clinic visits [9]. Two principal weaknesses of this strategy are that it is highly dependent on subject compliance with office visit scheduling as well as acceptance of transient minor adverse events like a mild cough at the onset of a new stimulation bout. Thus, this approach may lead to high variability in the onset of notable seizure frequency reduction if not carefully managed by the physician. An achievable goal, provided inefficiencies and barriers to

the titration process are mitigated, is to rapidly titrate to the target dose in less than 3 months. To reach the target dose quickly, it is possible to increase the output current in multiple steps during a given office visit (taking consideration of patient tolerance), or to take multiple steps on the first office visit before proceeding according to a more typical titration strategy with 0.25 mA steps. If intolerable side effects of cough or voice alteration occur while titrating multiple steps during an office visit, it is possible to step back to the last previously tolerated output current [19]. Employing any combination of these tactics may support the strategy of rapid titration, leading to a rapid onset of response and, based on available evidence, sustained clinical outcomes [6–8,20].

Patients and providers commonly assess the impact of VNS at 12 months after implantation to consider further changes to epilepsy management. Our analysis indicates that a substantial number of patients that are titrated too slowly may not have experienced therapeutic doses of VNS by 12 months after implant (Fig. 2). If more patients were able to reach the target dose in the first 3 months after implant, we hypothesize that more patients would be responsive to VNS at 12 months after implant. Furthermore, an initial, directional assessment with the goal of seizure reduction and/or improved quality of life could be done at 6 months. Patients with early onset of effect have been demonstrated to have durable response past 12 months [11,21].

There are many reasons for which a patient may choose to continue with VNS beyond seizure reduction. VNS has documented impact on non-seizure outcomes, healthcare costs, and certain cardiac comorbidities [22–27]. The current analysis does not assess the onset of those benefits, and that should be considered as an opportunity for future work.

4.3. The safety profile of rapid titration

The well-characterized side-effect profile associated with VNS includes more tolerable side effects like pharyngeal dysesthesias, change in voice, and dyspnea, as well as less tolerable but infrequent side effects like brady-arrhythmias, and asystole [28]. Most frequent side effects tend to be tolerated, are often limited to moments of active stimulation, and diminish over time [9,29]. However, previous studies of VNS have not published the rate of adverse events during titration and linked those events to various stimulation parameters. While this work attempts to remediate that gap, an opportunity to examine such events exists for the global CORE-VNS Registry, which has completed enrollment as of 2021.

The reduced burden of VNS side effects in children is well-documented in clinical literature [25,30,31]. Based on the findings from this analysis, the side effects during faster and slower titration schedules are comparable in children. In adults, the side-effect profile appears to favor slower titration; however, this finding is largely related to adverse events reported in the premarket E05 study (solely responsible for 47 % of all AEs reported in this database) and exclusion of this study dampens the risk associated with rapid titration in all groups (Supplementary Fig. 1). Across all subjects in this database, the three most common stimulation-related adverse events were infrequent and mild: dysphonia 21.2 %, cough 10.5 %, dyspnea 6.1 %. These results help to characterize the risk–benefit tradeoff of rapid titration and may help some patients navigate adverse events if they desire a more rapid onset of clinical benefit.

4.4. Real-world examples of rapid titration

There are a few examples of rapid titration reported in literature. In Tzadok et al 2019, 46 patients (mean age 15.7, range 5–31 years) with refractory epilepsy with different etiologies

(32.6 % unknown, 30.4 % genetic, 21.8 % structural, 13 % immune, 2.2 % infectious) were titrated to a mean output current of 1.4 mA (with a majority at 500µsec pulse width) and 20 Hz in <3 months. Improvement was observed at a median follow-up time of 5 months and a responder rate of 60.9 % was achieved after a maximal follow-up of 29 months [32]. Response was achieved faster among the replacement cohort than the new-insertion cohort, suggesting a potential cumulative effect of being previously dosed with VNS, or perhaps a biological effect of having the device implanted over time (e.g. plasticity). Our database does not include patients reimplanted with VNS, so we cannot comment on this phenomenon.

As a rather extreme example, cases of super refractory status epilepticus (SRSE) allow for nearly immediate titration of VNS to the target dose. In these patients, titrating directly to the target dose is possible due to sedation. Specchio et al rapidly titrated VNS at steps of 0.25 mA per day in 2 patients with super refractory status epilepticus [33]. A teen patient was remitted from status in 7 days (32 days total in status) at a dose of 1.75 mA/500µsec, and an infant remitted in 10 days (68 days total in status) at a dose of 1 mA/500µsec. A more holistic review of stimulation parameters in SRSE can be found in Dibué et al 2019 [34].

4.5. Rapid titration in children

One finding of this study was that children were not only more tolerant of VNS in general, but also more tolerant of rapid titration (Fig. 1, right panels). The reasons for high tolerability of VNS in children remain unclear, and the retrospective nature of this analysis does not permit further mechanistic investigation of the phenomenon.

4.6. Why is VNS titrated so slowly?

The source data for this analysis do not permit an investigation of reasons for faster or slower titration; however, it is curious that such a substantial percentage of the patients in this database were titrated in greater than 6 months compared to less than 3 months given the strong relationship between faster titration and clinical effectiveness. Of all the studies included in this database, patients were never required to follow a specific titration protocol with the exception of within the E-40 “ASCEND” trial – which did not describe clinical outcomes and was thus only included in the safety analysis herein.

There could be many valid reasons for slow titration of patients with VNS. In our analysis, it appears as though tolerability issues may contribute to slower titration in adults (Fig. 1 left, upper and lower) even though the postmarket experience with VNS differs strongly from premarket findings (Supplemental 1 left, upper and lower). This would not, however, explain differences in titration speed in children who are typically more tolerant of the therapy. A potentially more likely contributor is the complexity of neuromodulation therapy management, given titration of neuromodulation therapies often requires interaction between the patient and provider. Compare neuromodulation device titration with pharmaceutical titration which can be managed by the patient with an at-home protocol according to specific prescribing information. Novel VNS devices provide an avenue to mitigate this complexity with the addition of scheduled programming, which allows for at-home titration without sequential office visits. From the author's personal practice experience, this feature can significantly reduce the patient and provider burden during the titration period and hasten the time to dose [32].

Notably, this analysis should be considered agnostic to the role of titration tactics on outcomes, provided the titration reaches the target dose. The Cox regression considers only the time between

implant and when the dose is achieved. Missed visits, size of titration steps, tolerability, or other inefficiencies do not impact the nature of these results. Thus, these results should be considered as an impetus to titrate to target more quickly while not providing any justification for particular tactics.

4.7. Early implantation of VNS

While the effect of epilepsy duration on time-to-response was not significant in the 'all-comers' analysis, it was significant in the 'responders only' analysis (Supplementary Fig. 1). It is interesting that this demographic predictor of VNS outcomes was apparent both in this analysis as well as our precursor study, Fahoum et al 2022 [11]. This finding is not novel, however, as a previous meta-analysis by Jain and Arya also indicated the importance of this demographic factor [35]. As of yet, this effect has only become apparent when meta-analyzing large volumes of data, and to our knowledge the effect has not been tested prospectively. Based on these concordant outcomes, further exploration into early intervention with VNS is warranted.

5. Conclusions

Our analysis revealed efficient titration to the target dose in less than 3 months can result in significantly faster onset of response, and that the side-effect profile for VNS in patients with DRE may be similar for faster and slower titration schedules. Unfortunately, approximately half of patients who undergo slower titration of VNS ultimately achieve a target dose in greater than 12 months after VNS implantation (Fig. 2). The reasons for the pervasiveness of slow titration are not completely understood. In everyday clinical practice, we can assume that reliability of office visit attendance, variability in VNS titration tactics, and tolerability of stimulation-related side effects are the principal drivers of titration speed. Focusing on improvements to VNS patient management and titration strategies will allow for faster clinical response to VNS.

6. Limitations

The primary limitation of our analysis focuses on the source of the data that comprise our database. First, it should be noted that the data used in this analysis were collected over a long period of time, and epilepsy care has changed significantly during the past 25 years. New therapies have been introduced, and existing therapies (VNS included) have seen their indications for use expand with time. One potentially significant factor on the outcome of this work is the role of anti-seizure medications and how they changed over the course of the first year of VNS. While it is typical to hold adjunctive medications relatively stable while trialing a new therapy, we cannot say with certainty that this was the case for all subjects in this database for the entire first year of VNS. Furthermore, VNS has changed significantly in the past 7 years with the emergence of the AutoStim feature, also known in the literature as responsive VNS. In our database, less than 10 % of subjects had this feature available to them, and as such we could not draw firm conclusions as to the impact of this feature on our results. Further examination of the role of responsive VNS on dosing and titration should be explored in the ongoing CORE-VNS Registry.

Further analysis limitations include the retrospective nature of our study and model assumptions. We attempted to limit the biases associated with retrospective analysis by predetermining a statistical analysis plan prior to database creation. We were able to abide by this prospective statistical plan for this analysis except for adjustment for non-proportional hazards in our Cox regression. The main limitation of the weighted Cox regression is that the

effect is averaged over time, i.e., the time dependency of the effect cannot be investigated. However, the main purpose of our analysis was the effects of the dosing groups, and these did not display non-proportionality of hazards.

Finally, this analysis was conducted over a limited amount of time (maximum follow up of 12 months). While this selection was made based on clinical rationale, it cannot be ignored that VNS outcomes (as well as other neuromodulation therapies) have been reported to improve with time. The effect of dose pace on outcomes beyond 1 year was not assessed.

Author contributions

MT and RV wrote the manuscript. LK was the principal biostatistician for the study, and DT executed analysis on the database. LK's and DT's work was overseen and reviewed by CG. FF and RE provided data interpretation, discussion content, and critical review.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FF, MT, and RET have received previous consultancy fees from LivaNova, but no fee was received related to the analysis of data or writing of this manuscript. RV, LK, DT, and CG are employees of LivaNova PLC (or a subsidiary), the manufacturer of the VNS Therapy System. In addition to being employees, RV, LK, DT, and CG hold LivaNova stock or stock options.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2022.108861>.

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