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VNS parameters for clinical response in Epilepsy

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ABSTRACT

Background: While vagus nerve stimulation (VNS) has been in use for over two decades, little professional guidance exists to describe dosing and titration of therapy which is the consequence of a limited amount of evidence developed during the pre-market phase of therapy development. Post-market surveillance of dosing practice has revealed significant deviations from dosing and titration guidance offered by professional societies as well as the manufacturer.
Objective: This analysis aims to identify a target dose for VNS Therapy in Epilepsy.
Methods: Herein, VNS clinical outcomes are linked to the patient-specific dosing parameters for each study visit ($n = 1178$ patients). A generalized linear mixed model was built to ascertain the relationship between key stimulation parameters (i.e., Output Current, Pulse Width, Signal Frequency, and Duty Cycle) and clinical response, defined as a 50% or greater reduction in seizure frequency from baseline. Other demographic parameters of interest, such as duration of epilepsy and age at implant, were also explored.
Results: A population level target output current and duty cycle for VNS therapy for epilepsy was identified as 1.61 mA and 17.1% duty cycle. Patients with shorter duration of epilepsy were identified to have a higher likelihood to respond to VNS therapy ($p < 0.001$). While patients who were on the therapy longer were more likely to respond to the therapy, the effect did not interact with the dosing settings - suggesting that patients who have been chronically underdosed may still benefit from achieving the target dose.
Conclusion: An opportunity exists to improve upon VNS outcomes by aligning clinical practice around this evidence-based target dose.

1. Introduction

Based on the 3-month findings from the premarket pivotal studies E−03 and E−05, presumably therapeutic doses of vagus nerve stimulation (VNS) led to mean seizure frequency reductions of 30.9% and 27.9%, respectively, and were shown to be more effective than presumably subtherapeutic doses of VNS which led to mean seizure frequency reductions of 11.3% and 15.2%, respectively [1–3]. These findings supported the regulatory approvals in Europe (in 1994) and subsequently in the United States (in 1997) of adjunctive VNS Therapy for the treatment of drug-resistant epilepsy (DRE), and the practical implementation of VNS in the clinic has evolved ever since. With the launch of the VNS Therapy System in the mid-1990s, there was a limited understanding of the dose-response profile of this device-based intervention. Unlike most pharmacotherapies where bioavailability and pharmacokinetic properties can often be measured easily, clinicians lack a biomarker of vagus nerve engagement that is reliably and easily measured in all patients, responds acutely to stimulation, and is readily deployable in most clinical settings. Instead, a more pragmatic approach of dose trialing is employed, which leads to high inter-practice variability and frequent misalignment with available

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practice guidance and manufacturer recommendations for use. Navigating this pragmatic dosing process is further obfuscated by the delayed nature of clinical neurostimulation effects.

Dosing a VNS system can be simplified functionally to a two-step process: 1) activate the nerve with an appropriate current and pulse width (the 'volume'), 2) modulate central nuclei via temporal code (the 'message') [4]. Canonical biophysical laws such as the strength-duration relationship [5] can partially mitigate the complexity of dosing by defining the relationship between output current and pulse width on neural activation [6]. It follows that for a given electrode-tissue interface (e.g. a lead with specific geometric properties), the output current and pulse width work in concert to activate neural tissues [7]. Assuming an appropriate combination of amplitude and pulse width ('volume') is delivered, the therapeutic 'message' of neural modulation depends on the signal frequency and duty cycle, which influence the temporal responses to peripheral modulation and may be specific to the disease being treated or its severity.

Practice guidelines were generated shortly after regulatory approval to define the objectives and process of VNS titration and dosing more clearly [8]. While the broader guidelines for VNS use have seen more significant changes since the early 2000s (e.g. use in populations beyond those studied in the pivotal studies), the dosing and titration recommendations have not been revised since 2002 [9]. The manufacturer has adopted some of these guidelines along with other evidence-based supplemental recommendations into their own labeling and now advocates for the programming of VNS to 1.5–2.25 mA when using a pulse width of 250 μsec, despite the original 2002 AAN guidelines suggesting lower output currents (including <1 mA) may sometimes be suitable. Guidelines developed for the titration and dosing of VNS were established based on VNS clinical evidence available at the time, namely the pre-2000s pivotal studies E–03 and E–05, and thus more recent evidence may provide valuable new insights. In fact, the American Academy of Neurology's (AAN) most recent 2013 guideline revision suggested further research to clarify the target settings for clinical benefit was needed [10]. Due to the multidimensional nature of VNS parameter selection and lack of an acute biomarker of response, an impractically large cohort study with long follow up is required to provide the highest level of evidence for robust dosing and titration guidance. Considering these limitations, a retrospective analysis of the substantial VNS population may be the most practical approach to determine the target VNS dose.

Here, we present results of retrospective analysis conceptualized around better understanding the dose response profile of VNS for people with DRE, with the objective of reducing the significant variability in VNS titration and dosing practice and improving patient outcomes. The initial scope of the analysis was directed towards the identification of target VNS parameters, as defined by clinical efficacy outcomes.

2. Methods and analysis

2.1. Database development

This analysis compiles patient data from 12 clinical studies sponsored by the manufacturer of VNS Therapy to explore the effects of VNS dose. Patient-level data were compiled directly from the manufacturer's historical clinical files rather than extracting from published manuscripts. For the pooling it was decided to adopt the standards of the Clinical Data Interchange Standards Consortium (CDISC) using as source electronic data capture (eDC) datasets, from which an integrated Study Data Tabulation Model (iSDTM) database was created (CDISC SDTM Version 1.7, www.cdisc.org), then iSDTM was the source for an integrated Analysis Data Model (ADaM) database (CDISC ADaM Version 2.1, www.cdisc.org). This strategy conferred the following advantages: aggregation at SDTM level (iSDTM) allowed alignment and standardization of controlled terminology and dictionary versions, harmonization of coding strategy, creating a single source for ADaM; the creation of integrated ADaM starting from iSDTM allows to focus on derivations, alignment of algorithms, and clear traceability to predecessor databases.

Studies included in this analysis consist of randomized controlled trials as well as open-label observational studies. Control arms were excluded in the database as those patients did not receive VNS, to limit the investigation to findings related to VNS outcomes. In most cases the studies were designed as open-label, and in cases where blinding did occur it should be noted that patients can generally detect when they are receiving active VNS. Not all studies included in the database collected seizure outcomes at all follow-up visits, nor did all studies include identical follow-up durations or time points. The full analysis set population was defined as all subjects with an initial VNS device for epilepsy. The full analysis set includes 1178 patients (Table 1). General information regarding the distribution of different programming settings are included in Supplemental 1.

All subjects included in the database initially affirmed their consent to participate in a VNS study; however, internal databases for each study were de-identified upon inclusion into this database to eliminate the possibility of violating patient privacy concerns. These data were initially explored within the context of a prospectively defined statistical analysis plan, but review of the initial results encouraged a more naïve approach for the follow up analysis described herein. Further *ad-hoc* investigation was proposed and undertaken by a multidisciplinary team of clinicians, statisticians, and neuromodulation experts.

2.2. Logistic GLMM for target dose

We used a generalized linear mixed model (GLMM) with responder status being the dependent variable of interest. Clinical response was defined as ≥50% reduction in total seizure frequency from baseline. The continuous measure of seizure frequency reduction from baseline was also explored but resulted in a poor model fit and was not suitable for interpretation (Supplemental 2). GLMM are known to be flexible and appropriate in cases where non-independence of observations is present, which is the case here, as the subjects can have multiple office visits with their seizure data collected. Since the outcome is binary (responder yes/no), we use a binomial model with logit link function. The model is of the form

$$logit\left(y_{ij}=1\middle|u_i\right)=x_{ij}\beta+z_{ij}u_i,\quad i=1,\ldots,n,\quad j=1,\ldots,d,$$

where i denotes the subject, j the visit, the parameters $\beta$are the fixed effects and the $u_i$are the random effects [11]. We assume the random effects to be independent and normally distributed.

The fixed effects quantify the overall effects across all subjects. The random effects quantify the variation across subjects but are not observable. For example, these could be important but unknown characteristics which influence the propensity to respond to therapy. Consequently, to account for subject heterogeneity, subject ID was treated as a random effect. The full model contained all candidate covariates, as well as interactions from device parameter settings. The available variables in the dataset were:

- age at implant in years,
- duration of epilepsy in years,

Table 1
Description of the database. Sample sizes of included patients from each study may differ from the original manuscript reports as patients programmed to presumed sub-therapeutic VNS settings (originally designed as sham arms) were excluded from the analysis.

Study ID	Manuscript(s)	Sample Size	≥18 years of age, n (%)	<4 years of age, n (%)	≥4–18 years of age, n (%)	Generalized epilepsy, n (%)	Focal epilepsy, n (%)	Unknown (%)	Median Age at Implant (S.D)	Median Epilepsy Duration (S.D)
E–03	Ben-Menachem et al. *Epilepsia* 1994; Ramsay et al. *Epilepsia* 1994	57	57 (100.0%)	0	0	0	57 (100.0%)	0	32 (8.27)	21.5 (9.30)
E–04	Labar et al. *Neurology* 1999	124	80 (64.5%)	1 (0.8%)	4 (34.7%)	27 (21.8%)	96 (77.4%)	1 (0.8%)	22 (11.79)	15.7 (9.86)
E–05	Handforth et al. *Neurology* 1998; DiGiorgio et al. *Epilepsia* 2000	94	81 (86.2%)	0	13 (13.8%)	0	94 (100.0%)	0	32 (10.68)	19 (10.59)
E–06		62	0	1 (1.6%)	61 (98.4%)	0	38 (61.3%)	24 (38.7%)	10 (3.46)	7.65 (3.53)
E–36	Boon et al. *Seizure* 2015	31	31 (100.0%)	0	0	1 (3.2%)	29 (93.5%)	1 (3.2%)	38 (13.40)	22 (13.88)
E–37	Fisher et al. *Neuromodulation* 2015	20	20 (100.0%)	0	0	0	20 (100.0%)	0	30.5 (14.11)	13 (10.56)
E–40		63	62 (98.4%)	0	1 (1.6%)	0	63 (100.0%)	0	36 (11.99)	19 (12.19)
E–100 E–101	Ryvlin et al. *Epilepsia* 2014	54	54 (100.0%)	0	0	0	51 (94.4%)	3 (5.6%)	36 (12.04)	25.45 (12.14)
E–103		118	95 (80.5%)	0	23 (19.5%)	0	93 (78.8%)	25 (21.2%)	34.5 (16.04)	22 (14.81)
E–104		171	89 (52.0%)	0	82 (48.0%)	0	100 (58.5%)	71 (41.5%)	19 (14.11)	12.9 (11.95)
E-JPN	Kawai et al. *Epi Disord* 2017	384	234 (60.9%)	25 (6.5%)	125 (32.6%)	144 (37.5%)	237 (61.7%)	3 (0.8%)	22 (14.70)	12.5 (11.05)
TOTAL		1178	803 (68.2%)	27 (2.3%)	348 (29.5%)	172 (14.6%)	878 (74.5%)	128 (10.9%)	26 (14.77)	15 (12.00)

- gender,
- time since implant in days,
- output current in mA,
- pulse width, with levels 130, 250, ≥500 μs,
- signal frequency with levels ≤25 (20 and 25) and 30 Hz,
- duty cycle = (ON time + 2 × 2sec triangular ramps)/(ON Time + OFF time × 60) * 100%,
- subject ID,
- study ID.

A quadratic term for output current and duty cycle, in addition to their main effects, were included to allow for a maximum or minimum effect on the interior of the feature space [0.25–3.5 mA; 2%–89% duty]. This quadratic term does not represent a physical construct of dosing, but rather exists as a statistical construct to allow for better model fit in the event of a non-linear relationship between these parameters and clinical response. The maximum follow-up time included in the model was 3.5 years (1278 days).

The random effect structure was chosen using the likelihood ratio test. Both random intercept and random slope models were considered, as well as the full model without random effects; the random slope provided the best fit and was used. Fixed effects were selected using the Akaike Information Criterion (AIC) [12], and thus some variables described above are eventually excluded from the final model. First, interaction terms among output current, pulse width, frequency, and duty cycle were removed as none was significant. Next, additional parameters were removed one at a time to determine the best fit model based on the AIC. The model with the lowest AIC was achieved by removing pulse width and frequency and accounted for 86% of the variance per the conditional R^2 value. There was no imputation of missing values as all missing data were considered as missing completely at random. All analyses were performed using R (R Core Team 2021), version 4.1. The logistic GLMM was run using LME4 package [13], graphs were created using ggplot2 [14], and the tables were created using SjPlot [15].

3. Results

The outputs of the final GLMM model are listed in Table 2. It includes a random intercept for subject identifier and a random slope for time on therapy. Its fixed effects are time on therapy, duration of epilepsy, age at implant, output current, duty cycle, the quadratic terms for output current and duty cycle, the study effects, and an intercept. Our final model was preferable to models which included terms for pulse width and/or frequency per our selection criterion, which will be discussed later.

Duration of epilepsy has a negative impact on the probability of response, while age at implant has a positive effect. Thus, older subjects responded better to VNS, as well as those implanted shortly after their initial epilepsy diagnosis, all other covariates being equal.

The output current and duty cycle variables have a positive effect, while the quadratic terms have a negative effect, meaning that the functions have peaks which are the target output current and duty cycle for our model. The peak of this output current effect identified by the GLMM is 1.61 mA and the peak duty cycle occurs at 17.1%, and these effects are independent from time on therapy. Fig. 1A shows the GLMM predicted probability of response at 12 months for a patient who is 26 years old with epilepsy duration of 15 years and duty cycle set at 10.3, which are population median values for the full analysis set. Model-predicted patient-specific

Table 2
Output of the generalized linear mixed model (GLMM) to assess the contribution of multiple sources of variance to responder status. Estimates for study effect and the intercept are not shown for conciseness.

Predictors	***Log-Odds***	***CI***	***p***
Age at Implant (Years)	0.04	0.02; 0.05	<0.001
Duration of Epilepsy (Years)	−0.04	−0.06; −0.02	<0.001
Time since IMplant (Days)	0.002	0.001; 0.002	<0.001
Output Current (MA)	1.50	0.83; 2.17	<0.001
(Output current^2)	−0.47	−0.71; −0.22	<0.001
Duty Cycle	0.08	0.01; 0.15	0.032
(Duty Cycle^2)	−0.002	−0.004; −0.001	0.003

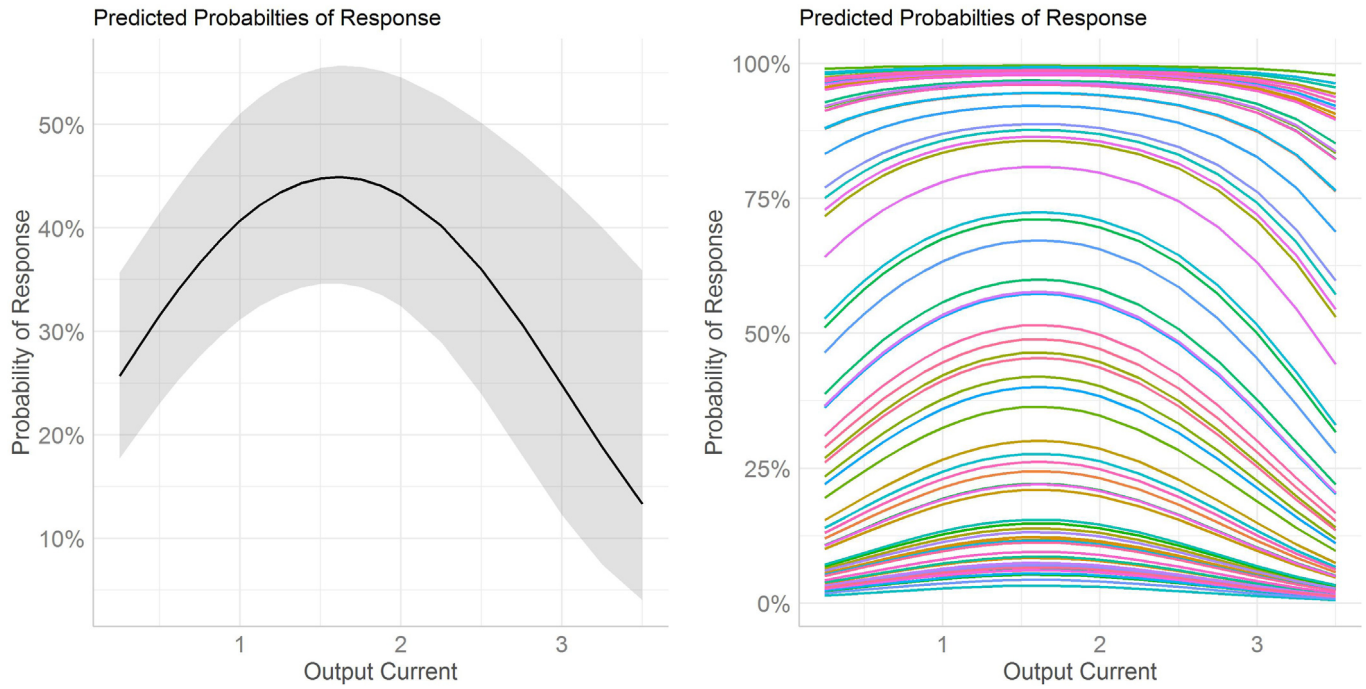

Fig. 1. GLMM predicted probability of 12-month response to VNS.
a) Average predicted probability of 12-month response for all patients included in the database. This representation does not define the actual response of patients programmed to a certain output current, but rather the prediction of the GLMM when supplied with patient-specific information from the database, in this case the median value of Age (26 years), Epilepsy duration (15 years) and Duty Cycle (10.3%) have been used. b) Predicted probability of 12-month response for a random sample of 50 patients. Each colored curve represents the output of the GLMM when the patient-specific random effects are used. This predicted response assumes the duty cycle is held at ~10%, while other characteristics (age, duration of epilepsy, etc.) were set to the population median. The large variability of predicted probability is due to large estimated random patient effects.

responses can also be derived by setting model values for certain variables to match those of individual patients, such as a random selection of 50 subjects from the Japan Post-Market Registry (Fig. 1B). In this case, because the curves are created using random effects of specific subjects, the large variability of predicted probability is due to large estimated random patient effects; however, for each curve the probability is maximized at 1.61 mA of output current.

The model's predicted probabilities of clinical outcomes are reproducible in the database. Seizure outcomes at 12 months for patients titrated near the target dose of 1.61 mA trend toward greater rates of clinical response (≥50% reduction in seizure frequency) than patients receiving VNS at doses under 1 mA (Table 3). The range of 1.5–1.75 mA was selected near the target intensity of 1.61 mA because older models of VNS did not include output current steps sizes that permitted programming of 1.625 mA, which would otherwise be the nearest setting to the target output current. For patients with output current programmed to 1.5–1.75 mA at 12 months, the percentage of responders is 47%, whereas 35% of patients respond to VNS at output currents less than 1 mA at 12 months. Patients titrated to the target output current tended to report lower rates of stimulation-associated adverse events than patients who did not achieve the target dose or patients who were titrated to higher output currents (Table 3).

As a post-hoc investigation of clinical outcomes of VNS responders at 12 months who achieved the target output current, patients with follow-up data at subsequent visits were assessed for increases or decreases to their therapeutic settings (Table 4). This analysis suggests that patients with initial response to VNS are highly likely to retain their clinical response over time and maintain clinically significant reductions in seizure frequency. This analysis also demonstrates a plateau effect, whereby patients titrated to output currents higher than the proposed target output current did not achieve greater likelihood of response or greater reductions in seizure frequency. An identical post-hoc analysis for target duty cycle obtained similar results where further increases in duty cycle did not confer additional higher response rates or reductions in seizure frequency (Supplemental 3).

4. Discussion

Analyzing this large cohort of patients from 12 clinical studies of VNS using a logistic GLMM, we found that an output current near the available setting of 1.625 mA is associated with the greatest likelihood of being a VNS responder following 1 year of therapy.

Table 3
Clinical outcomes of people with VNS titrated to settings near the proposed target dose of 1.625 mA. Patients in each group were selected to have the listed output current at any pulse width at 12-months of follow up. The response rate was calculated at 12 months after implant.

	N	RESPONDER RATE	MEDIAN SEIZURE REDUCTION	TOTAL ADVERSE EVENTS	ADVERSE EVENT RATE PER SUBJECT
OUTPUT CURRENT < 1 MA	44	36%	34.46%	37	0.84
OUTPUT CURRENT 1.5–1.75 MA	392	47%	43.27%	84	0.21
OUTPUT CURRENT ≥ 2.5 MA	32	41%	32.76%	17	0.53

Table 4
Long-term clinical outcomes of patients titrated to the target intensity of VNS (1.5 mA–1.75 mA) who were responders at 12 months after implant (n = 186 subjects). Patients initially titrated to this dose may have increased or decreased their VNS dose at follow up visits after 12 months. The table represents changes to therapeutic settings after the 12-month visit, and the associated clinical outcomes at each unique visit.

	N (unique Visits after 12 months)	Responder Rate	Median Seizure Frequency Reduction
Output Current <1.5 mA	7	71%	100.00%
Output Current 1.5–1.75 mA	209	87%	86.13%
OUTPUT CURRENT >1.75 MA	98	80%	75.72%

Additionally, patients programmed to duty cycles near 17% (e.g., 30 s ON and 3 min OFF) achieved the highest likelihood of response. The model for population-level target output current did not converge upon inclusion of a time interaction over the 3 years of follow-up in our dataset, so we conclude it is still worthwhile to increase a patient's VNS dose to this output current even if they have been previously underdosed. The presence of a peak probability of response implies that patients programmed to higher VNS intensities may not experience further improvements in efficacy, and some patients may not respond to VNS at any intensity. This finding is further supported, but not tested statistically, by the post-hoc analysis in Table 4. The following sections aim to describe the implications of these findings.

4.1. Vagus nerve activation and VNS dose: output current and pulse width

Output current and pulse width, combined with the physical size and shape of the VNS electrode, interact to define the intensity of electrical stimulation in the vicinity of the vagus nerve. It is possible to mathematically define a minimum level of current per pulse that is required to activate vagal fibers [7,16]. This relationship of output current and pulse width is commonly represented by a strength-duration curve (Fig. 2). Lines on the strength-duration plot describe an inverse relationship between stimulus intensity and duration that would equivalently activate neural fibers. The chronaxie of this relationship defines the pulse width at which the minimal energy requirement for neural tissue activation can be achieved. For two otherwise similar axons in a fiber bundle in a similar location, fiber diameter is the chief contributor to changes in the chronaxie. Thus, for the strength-duration curve of relevant small-to-medium diameter fibers in the vagus nerve (2–6 μm diameter), we can identify that there is little functional reason to utilize pulse widths over 250 μsec for clinical purposes due to battery considerations. Use of lower pulse widths requires careful consideration of the appropriate output current, while use of higher pulse widths with equivalent output currents results in faster battery depletion and can result in more frequent reports of stimulation-associated adverse events [17]. For this reason, and the fact that much of the data in our model was derived from patients set to 250 or 500 μsec, we advocate for the use of 250 μsec pulse widths for VNS despite results from the GLMM in this database that did not find statistically different clinical outcomes between pulse widths. Consideration of our findings for target output current should be viewed through this lens, as the combination of output current and pulse width are critically important to neural stimulation. If it is clinically necessary to use other pulse widths than 250 μsec, one should consider increasing or decreasing output current consistent with the vagal strength-duration relationship or look to the product manual for guidance on this topic.

The GLMM finding for target output current is consistent with current practice recommendations and current product labeling [20]. The manufacturer's recommended settings for VNS in epilepsy are 1.5–2.25 mA for pulse widths of 250 μs at 20 Hz. However, the manufacturer only provides recommendations for titration and dosing of the therapy and not firm guidance (e.g. prescribing information), so it is useful to put our findings within the context of clinical practice guidance developed by professional societies. Original recommendations on VNS dosing and titration from the American Academy of Neurology (AAN) were highly conservative, and prioritize tolerability of the therapy over clinical effectiveness (e.g. "… some patients do not tolerate output currents above 1.0 mA. Always adjust to patient tolerance.") [8]. The maximum dose target in the AAN guidance appears to be 1.5 mA at 250–500 μs, and further increases to output current are advocated against in favor of battery savings and tolerability. This conservative

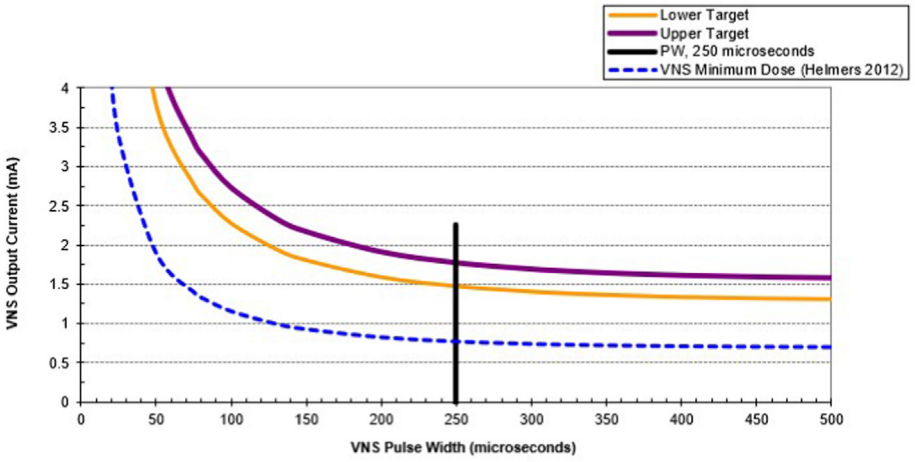

Fig. 2. Strength-duration relationship of the vagus nerve modeled by the Lapicque equation using experimentally collected nerve fiber recordings in canine [18,19]. This model represents upper and lower bounds around 1.625 mA, as these are the programming parameters available on older VNS device models. The minimum dose of VNS needed to activate afferent vagal fibers in the absence of glial scarring is derived from computational modeling [7].

approach was likely based on limited pre-market evidence and experience of the dose response profile of VNS at the time. There is little reason to continue to be conservative in titration, especially in the light of evidence presented here supporting stronger probability of VNS response, without an increase in rates of adverse events, at stimulation parameters that fall outside of the dosing recommendations of the AAN (Table 3, [8]). Further support for more aggressive titration comes from computational models developed in the past decade, which suggest a minimum target dose of 0.75 mA at 250μsec to achieve afferent fiber activation (not necessarily clinical effect) based on mathematical representation of ideal biological conditions [7]. In most practical settings, doses above this "best-case" minimum dose would be warranted, meaning that some patients who do not surpass 1 mA due to tolerability complaints may not experience therapeutic benefit.

In modern clinical practice, it is common to increase output current to approximately 2 mA if patients are experiencing inadequate response to therapy, then focus on increasing duty cycle. Our model describes a population mean probability of response that diminishes after 1.61 mA. We hypothesize this model output was partially driven by non-responder bias in the population set to higher output current, on account of clinical practice habits that advocate for increasing output current in patients that are unresponsive to therapy, as well as a flattening of the dose response curve in patients that were already responding to therapy. This hypothesis assumes that patients who respond to VNS at a lower output current do not receive additional benefit from being programmed to a higher output current, which is supported by the significance of the quadratic term for output current and prevalence of responders in our database, as well as the "all-or-none" nature of axonal transmission. While confirming this hypothesis was not plausible with our database, a post-hoc analysis was conducted to examine trends that could better inform this hypothesis. Patients that responded to VNS at or near the target output current at 12 months were followed for all of their remaining visits in the database (Table 4). In these subjects, there were cases where VNS parameters were changed. There was no indication in this long-term follow up that increasing output current resulted in higher likelihood of response or further improvements in seizure frequency Therefore, we conclude that use of output currents well beyond the target population level settings of 1.625 mA at 250μsec is unlikely to convert a non-responder into a responder, and unlikely to offer superior levels of response in patients that have already demonstrated response to VNS. As this represents the population-level target, it is possible that inter-patient variability will require use of slightly higher or lower currents.

4.2. Vagus nerve activation and VNS dose: signal frequency

Assuming a patient achieves a therapeutic combination of output current and pulse width, such as we advocate for through our results, the final dose parameter is Signal Frequency. Ascending nuclei in the central nervous system are responsible for decoding this message and may change their activity according to temporal and rate components of the stimulation pattern (for an early example in auditory neuromodulation, see Ref. [21]). Animal studies of the locus coeruleus (a key central anti-convulsive target of VNS, [22]) have identified highly synchronous clusters of neurons with target-specific projections for different forebrain targets, suggesting that temporal coding may be able to activate specific elements of the vagal afferent network [23,24]. In this work, we don't find strong evidence to advocate for a particular signal frequency, possibly because a very narrow range of possible frequencies were used, and more creative patterns of stimulation were not available in our database (e.g. bursting patterns). Preclinical animal studies initially indicated low frequencies (20 Hz–30 Hz) have a stronger anticonvulsive effect [25,26]. Frequencies near 20 Hz were found to evoke stronger vagal evoked potentials than higher frequencies (near 200 Hz) in cats [27]. In clinical practice, migration toward 20 Hz from the original manufacturer setting of 30 Hz occurred in response to anecdotal reports of improved mood effects at 20 Hz, without impact to anti-convulsive effect. These findings were used to support the manufacturer's decision to change the factory setting for signal frequency from 30 Hz to 20 Hz with the introduction of the most recent pulse generator.

4.3. Duty cycle and the dose frequency of VNS

Pulse width, output current, and signal frequency provide the therapeutic input as a bolus of VNS, so one could consider the duty cycle as the VNS dose frequency. In some ways duty cycle is independent of other stimulation parameters, but there is a key safety relationship that must be considered. High frequencies and duty cycles used in combination have been previously reported to damage neural tissue in animals [28]. The manufacturer cautions against programming duty cycles above 50%, even at lower frequencies, in favor of safety.

Some clinicians have developed interest in a technique called "rapid cycling" VNS, which is to program the device with higher duty cycle (definition varies from OFF-Time $\leq$1.8 min to a combination of ON-Time = 7 s and OFF-Time = 0.2–0.3 min) in case standard cycling is found to be not effective in a patient. This technique was shown to be safe and potentially more effective than the standard cycling in pediatric patients [29–31].

Our model predicts a target duty cycle of 17.1% associated with the highest probability of response. This outcome is not fully aligned with previous findings regarding duty cycle that suggested higher duty cycles result in improved clinical outcomes over time [32]. While DeGiorgio et al., 2001 has its own limitations regarding patient matching between subgroups, the contradictory result from our analysis may result from selection bias as most of the data (62%) comes from the ~10% duty cycle group, has a multimodal distribution, and is mostly skewed toward duty cycles under 20% (Supplemental 1). This bias risk in our retrospective analysis is further exacerbated by VNS clinical practice habits, as patients who are not yet responding to VNS are often programmed to higher duty cycles – resulting in those who may never respond to VNS receiving higher duty cycles. Can the use of higher duty cycles, either by techniques like rapid cycling or the implementation of low-threshold responsive VNS [33], provide better outcomes? While our model concludes that this is not the case, results of various prospective and retrospective studies are not concordant, and this issue should be explored in prospective studies such as the CORE-VNS registry (NCT03529045).

Guidance from professional societies and the manufacturer's label both agree that patients who have achieved a tolerable output current of VNS that still don't respond to VNS should consider using higher duty cycles. The present model suggests that this behavior could be beneficial but may have diminishing returns after 17% duty.

4.4. Age and duration of epilepsy

The GLMM identified two variables that impacted VNS response that were not associated with the dose of VNS – age at implantation and duration of epilepsy (Table 2). The results indicate that older people with epilepsy who receive VNS are more likely to achieve response, as are people that experience less delay between epilepsy diagnosis and eventual intervention with VNS. The GLMM

does not define age or duration limits of interest for further examination – only correlative trends.

While VNS is very commonly used in children, the finding that adult patients respond better to VNS is unsurprising. Indeed, pediatric patients treated with VNS are often very refractory, with frequent severe seizures driven by epileptic encephalopathies.

Pediatric patients tend to be biased toward shorter epilepsy durations due to having lived fewer years in total and having engaged parents that prioritize their care [34]. Thus, it is interesting that shorter duration of epilepsy is associated with improved response probability, despite younger patients being less likely responders. This independent effect of duration of epilepsy is also supported by other recent evidence [35,36], but our model is unique in that it looks at the problem as a linear effect rather than through *post-hoc* subgroup analysis. This growing body of evidence supports earlier intervention with VNS to achieve the best outcomes with the therapy.

4.5. Conclusions

The evidence supports the wider adoption of current manufacturer dosing recommendations, and more specifically of a population-level target output current of VNS for epilepsy near the available setting of 1.625 mA. Other biophysical data and modeling support the use of pulse widths at or below 250μsec pulses, with lower pulse widths requiring an increase in the selected output current. There are no robust data available at present to advocate for the use of frequencies other than 20, 25, or 30 Hz in epilepsy for the purpose of maximizing clinical response. Due to high risk of selection bias and a limited range of tested duty cycles, the model outcome for duty cycle (suggesting a target duty cycle of 17.1%) should be interpreted with caution. Patients titrated to available output currents near the target level of 1.61 mA tend to report fewer stimulation-associated adverse events than those titrated to higher or lower levels. Output current should be the principal consideration when titrating patients to their individualized optimal dose, and individual patients may have optimal VNS output currents above or below this population-level target depending on their unique circumstances.

While we have identified a target output current and duty cycle, this investigation offers no understanding of the impact of the time taken to reach that dose. People treated with VNS have demonstrated a delayed onset of clinical benefit. Better understanding the relationship between time-to-dose and time-to-response through survival analysis would be supportive of the data presented here. Also, we do not know much about the impact of increasing the dose in patients who are non-responsive at lower doses or decreasing the dose in patients who are responding at an output current level above the population-level target dose.

Our model evaluates efficacy in terms of responder rates. Considerations of limiting and occasionally enduring side effects may in practice call for use of different parameters. It is understood that, in practice, reduction of output current, pulse width, and signal frequency have all been independently associated with more tolerable stimulation. However, one must consider that these parameter changes may impact the efficacy of VNS Therapy according to our model.

4.6. Limitations

The method selected for this analysis was limited by its assumption of the normal and independent distribution of the random effects; however, there is evidence that misspecification does not have much of an impact on model outcomes [37]. Further challenges are the computational difficulty of these types of models, and subtleties in model selection and interpretation which are not present in simpler generalized linear models.

The primary study limitation is associated with the data used to inform the model. The studies were not controlled to test different dose settings and thus these results reflect observed associations without definitive causation. These data are compiled from a variety of studies with different designs, populations, follow-up durations, VNS generators, and most importantly calendar years. Standards of care in DRE and understanding of VNS have changed substantially over the past 25 years. One must not overstate the implication of this model output in present-day epilepsy patients. Our study population was comprised solely of drug-resistant epilepsy patients, and most of these DRE patients had failed 4 or more medications. Over 90% of the database describes outcomes from traditional VNS devices that did not have modern features like closed-loop stimulation functionality, which has demonstrated a clinical benefit beyond what is offered by older VNS models in multiple concordant case series [33,38–43]. Recently concluded studies of VNS therapy have tested novel stimulation parameters that include high frequency burst stimulation, which we could not assess here as the data were not available at the time of analysis. Thus, the risk exists that this analysis has identified a local maximum for response probability and that a true maximum exists for parameters that we were unable to test.

Our definition of target output current and duty cycle was based on seizure response, a binary variable. An alternative approach leveraging seizure frequency reduction as the clinical outcome was not selected for analysis because the initial model did not converge (Supplemental 2). In DRE, patients often derive benefits from a therapy beyond seizure control. We were forced to limit ourselves in this way due to the limitations of the data included in our database. Regardless, by focusing on a rigorous seizure-associated outcome, we may have overlooked how VNS parameters impact other seizure and non-seizure outcomes. Consider that there may be a different target VNS dose for mood or cognitive improvements that we could not identify.

Authors' contributions

FF and MB wrote the manuscript. LK was the principal biostatistician for the study, and SF built the study database. LK's and SF's work was overseen and reviewed by CG. MT and RE provided data interpretation, discussion content, and critical review.

Declaration of competing interest

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.

MB, LK, and CG are employees of LivaNova PLC (or a subsidiary), the manufacturer of the VNS Therapy System. SF was an employee of LivaNova PLC at the time of contribution to the work. In addition to being employees, MB, LK, and CG hold LivaNova stock or stock options.

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Appendix A. Supplementary data

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