Epilepsy & Behavior Reports 29 (2025) 100734

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Practical Considerations for the rapid titration of VNS

Riëm El Tahry [a,b,*], Maxine Dibué [c], Arnaud Szmalec [b,d,e], Roshani Patel [c], Ryan Verner [c], Massimiliano Boffini [c], Firas Fahoum [f,g], Michal Tzadok [g,h]

[a] Institute of Neuroscience, Université Catholique de Louvain (UCLouvain), Brussels, Belgium
[b] Center for Refractory Epilepsy, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[c] Medical Affairs Neuromodulation, LivaNova PLC, London, United Kingdom
[d] Psychological Sciences Research Institute, Université Catholique de Louvain (UCLouvain), Louvain-la-Neuve, Belgium
[e] Department of Experimental Psychology, Universiteit Gent (UGent), Gent, Belgium
[f] Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[g] Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[h] Pediatric Neurology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel

ARTICLE INFO

Keywords:
Vagus Nerve Stimulation
VNS
Practice Survey
Dosing
Titration

ABSTRACT

For patients with drug-resistant epilepsy who are not candidates for epilepsy surgery, Vagus nerve stimulation (VNS) is the most widely available neuromodulation option and has been available in several countries for 30 years. Given its broad availability and extended history on the market, many healthcare providers (HCPs) have developed individualized practice habits regarding the titration and dosing of VNS. This study provides novel evidence to describe the extent to which VNS management differs among providers and discusses recent literature that indicates how unique programming approaches may impact patient outcomes. In this work, practice habits regarding the titration and dosing of VNS were explored through a survey of HCPs and an examination of ongoing study data collected as part of the CORE-VNS Study. The global survey revealed significant variability in dosing and titration habits. Providers reported a wide range of initial/maximum target doses and time-to-dose, even if the population averages approximated guidance from professional societies and the manufacturer's labeling. Variable dosing and titration were reflected in varied perception of how long it takes to realize the clinical benefits of VNS. In the CORE-VNS Study, this reported experience was represented in how different generator models were used, with users of SenTiva (and the Scheduled Programming feature) depicting faster time-to-dose than those using earlier models of VNS. Our results suggest VNS providers would benefit from continued training on the use of VNS and the use of the scheduled programming feature to enhance consistency of VNS management among providers.

1. Introduction

People with drug-resistant epilepsy (DRE) assess many therapies without success. People with DRE are uncertain about the possibility of achieving a satisfactory level of seizure control, especially in terms of seizure frequency and intensity [1]. Epidemiological studies indicate that in the absence of candidacy for resective surgery, the likelihood of seizure freedom in people who have tried over four anti-seizure medications (ASMs) is very low with further drug trials offer diminishing returns [2,3]. People with DRE most desire seizure freedom but can find satisfaction with some measure of control of their epilepsy. However, their ideal therapy must offer predictable clinical outcomes (both in terms of onset timing and durability of effect) with minimal side effects.

One important aspect of treatment in DRE is the idea that the administered therapy should be appropriately selected, administered in sufficient doses, and well tolerated. This concerns not only ASMs, but also applies to neuromodulation. An adjunctive treatment for people with DRE, VNS therapy offers seizure response (>50 % reduction) in a median 60 % of those who receive it; with mainly transient side effects that are acceptable to most users and well-managed over time [4–10]. Nevertheless, high variability in the approach to titration and dosing is present within the epilepsy community [11,12]. Differences in practice habits may drive different perceptions of the effectiveness of VNS at the provider level, especially if VNS outcomes derived from certain unique

* Corresponding author at: Centre for Refractory Epilepsy, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium.
E-mail address: riem.eltahry@saintluc.uclouvain.be (R.E. Tahry).

https://doi.org/10.1016/j.ebr.2024.100734
Received 14 October 2024; Received in revised form 11 December 2024; Accepted 12 December 2024
Available online 13 December 2024

practice habits are not aligned with published real-world experience data collected from multiple institutions or clinical data collected under a defined protocol.

VNS management differs among providers and recent literature indicates how unique programming approaches may impact patient outcomes [12,13]. In this article, we examine the practice habits driving these different perceptions of VNS dosing and outcomes and provide evidence to support what practices could be incorporated into clinics to improve VNS outcomes. We looked at multiple sources of evidence to achieve this aim, combining data from post-market surveillance of VNS titration and dosing with a global survey of healthcare professionals to address the heterogeneity of titration and dosing in the epilepsy community worldwide.

2. Methods and analysis

The data presented herein were compiled from multiple sources to present a comprehensive picture of global VNS management. Recent VNS management was characterized through a globally distributed electronic survey and the global observational study: CORE-VNS [14].

2.1. CORE-VNS Database

CORE-VNS (NCT03529045) is a multinational observational study sponsored by the manufacturer of the VNS Therapy™ System. The study follows patients who receive their initial VNS implant and those seeking battery replacements for up to 3 years. It collects a multitude of clinical effectiveness and safety outcomes.

As the study is observational, the sponsor does not provide any direct guidance on management of the VNS device within the study protocol. For this reason, CORE-VNS is the most relevant source of data addressing the relationship between contemporary clinical practice with VNS and the outcomes associated with those practice habits.

2.2. CORE-VNS Database analysis

The CORE-VNS study was used to answer two questions:

1) Does the "Scheduled Programming" (automated titration) feature impact the speed of titration?
2) Does the use of the Scheduled Programming (SP) feature impact the number of office visits associated with titration to the initial target output current?

To answer these questions, all available data from enrolled patients in the CORE-VNS study implanted with VNS for the first time (no battery replacement patients) were collected for up to 3 years after implant. Patients were separated into subgroups based on generator type, combining all previous models (Pulse, Demipulse, AspireSR) and comparing to the most recently released model, SenTiva, the only generator with a SP feature. The extent to which patients with SenTiva were titrated with the SP feature was assessed by splitting patients with SenTiva VNS units into two groups: SP used < 3 times vs SP used ≥ 3 times. SP events were defined as the number of programming steps that were programmed with the feature. The time taken in days for patients in each group to achieve an output current and pulse width aligned to the VNS Therapy System labeling was calculated. The number of manual programming events was used as a measure of the number of office visits associated with titrating patients to the target dose.

2.3. Clinician survey

Between July and December of 2022 (a period that CORE-VNS was active), an online survey was distributed to healthcare professionals (HCPs) attending the European Epilepsy Congress (Geneva, Switzerland), Canadian League Against Epilepsy (Kelowna, Canada), and American Epilepsy Society (Nashville, USA). The objective was to collect responses from a regionally diverse set of HCPs. The survey contained twenty-eight questions intended to better understand the practice habits of HCPs that manage VNS. Survey questions were developed as a collaboration of the authorship team, which included industry and medical/academic experts familiar with VNS Therapy, and an experimental psychologist to minimize the risk of bias in the survey questions and responses. The survey's content, and the methods for data collection including consent procedures, were reviewed and approved by the ethical committee of Saint-Luc Hospital, Brussels, Belgium (2022/07AVR/157).

3. Results

3.1. Clinical survey

The survey was active for 6 months during which 135 consenting responses were collected to use their responses in a research study. Of these responses, 42 were excluded from the analysis for the following reasons: 15 responses were from providers that did not manage patients with any neuromodulation therapies in their practice, and 27 respondents reported no direct responsibility for managing the device programming. For these HCPs, the survey ended and further responses on VNS management were not collected. Therefore, complete survey data were collected from 93 respondents who used neuromodulation to treat DRE in their practice and were directly responsible for programming the device.

Supplemental Fig. 1 describes the demographic profile of survey respondents. Most survey responses were collected from physicians in North America and Western Europe, which geographically represents the greatest use of VNS. Respondents largely worked with adult patients (72 %), although approximately one in eight respondents served both adult and pediatric patients. All respondents used VNS, and over half of the respondents managed only VNS in their practice (likely related to the global nature of the survey and limited access to Deep Brain Stimulation and Responsive Neurostimulation in regions outside the US or Western Europe). The number of providers with distinct levels of VNS experience was evenly distributed, as defined by the number of patients managed with the therapy within their practice history. For purposes of analysis, we analyzed differences in reported practice habits of the respondents with <20 patients treated ($n = 23$) against the respondents with >100 patients treated ($n = 21$). The remaining 49 respondents with a history of treating 20–100 patients with VNS were not compared.

3.2. Current practices in dose selection

Our practice survey data reveals significant variability in current dosing practice. HCPs reported titrating patients to a wide range of initial target output currents (0.25–2.5 mA), but most respondents selected initial target output currents between 1 mA and 2 mA (Fig. 1A). When asked about the maximum output current that respondents felt comfortable titrating to, there was a similar wide range of response (0.5–6 mA). Most respondents selected values above 2.5 mA (Fig. 1B). Three respondents reported maximum output currents that were outside of the functional range of commercial VNS units, which goes up to 3.5 mA. Approximately half (44 %) of respondents reported targeting an initial dose of VNS less than 1.5 mA.

3.3. Modern VNS output current Trends during titration

Recent VNS programming data from CORE-VNS describes a titration paradigm which slowly increases VNS output current over several months after implant. The proportion of patients reaching the target dose range achieved an asymptotic maximum around 18 months after implantation (Fig. 2A), with 60 % of patients still below the target dose of 1.5 mA (at 500μsec) or 1.75 mA (at 250 μsec) at 6 months.

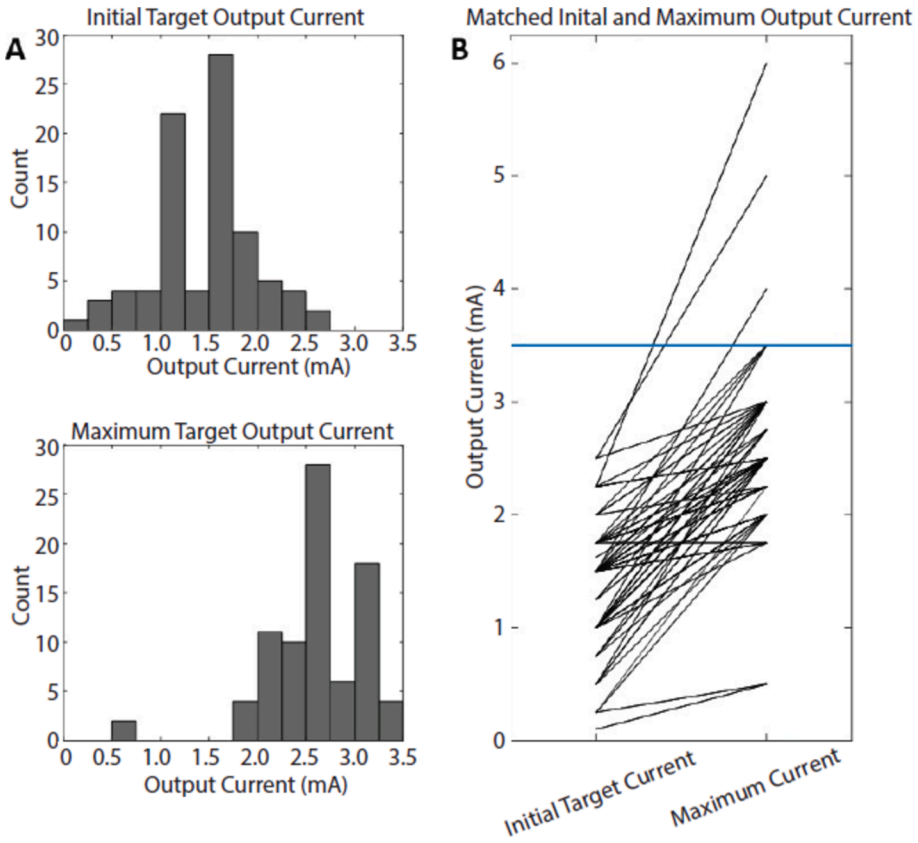

Fig. 1. Survey responses regarding the initial target output current for VNS and the maximum target output current. **A:** Respondents were most likely to use output currents between 1 mA and 2 mA as an initial target dose for VNS and maximum output currents above 2 mA. **B:** Paired initial and maximum output current (OC) responses for each respondent. Several providers reported narrow ranges of acceptable VNS output currents while others are wider. Black lines represent the paired initial target and upper limit of output current responses for each provider. Certain providers reported use of maximum output currents above the device's limit of 3.5 mA.

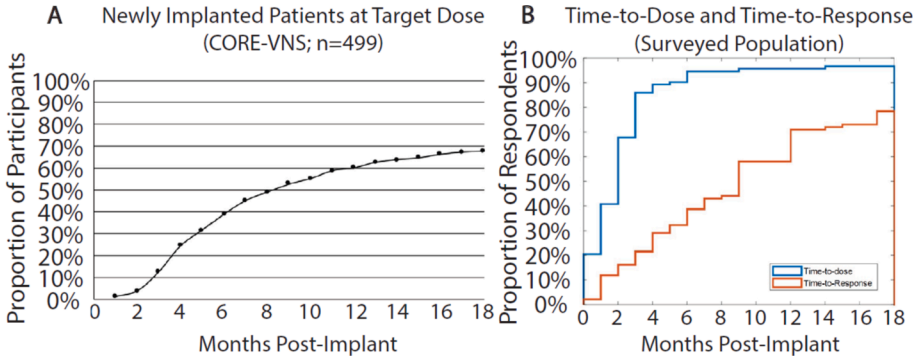

Fig. 2. Titration speed, both real and perceived, and the provider-reported delay between titration and response. **A:** CORE-VNS describes a prolonged titration period, with the median time-to-dose of approximately 8 months and less than 70 % of participants achieving the target dose range (per VNS Therapy labeling) by 18 months of therapy. **B:** Conversely, approximately 90 % of survey respondents described a titration period lasting < 5 months. They also reported waiting many months to assess the clinical benefit of VNS after titration, with half waiting longer than 10 months.

When asked to report about their titration practices, ~ 90 % of surveyed respondents (providers) stated reaching their target dose in 5 months or less (Fig. 2B). This self-reported titration speed is consistent with surveillance data, given that many respondents also reported targeting doses under 1.625 mA. Once a patient achieved the target dose, respondents reported waiting for the onset of VNS response over a wide range of time (Fig. 3B). Approximately half of respondents felt they could assess the impact of VNS earlier than 10 months after the target dose was achieved.

3.4. Use of Scheduled programming (SP) to reduce Time-To-Dose

SP is a feature included on the most recent model of VNS (SenTiva) that allows a clinician to pre-program automated, out-of-office titration steps. Up to seven programming steps are available, wherein the size and timing of these steps is dependent on clinician discretion.

In the CORE-VNS Study, all available VNS devices (Pulse, Demipulse, AspireSR and SenTiva) were examined to better understand device- and feature-specific differences in titration rate (Fig. 3A). In the specific model 1000 (i.e., SenTiva) devices, the population was further

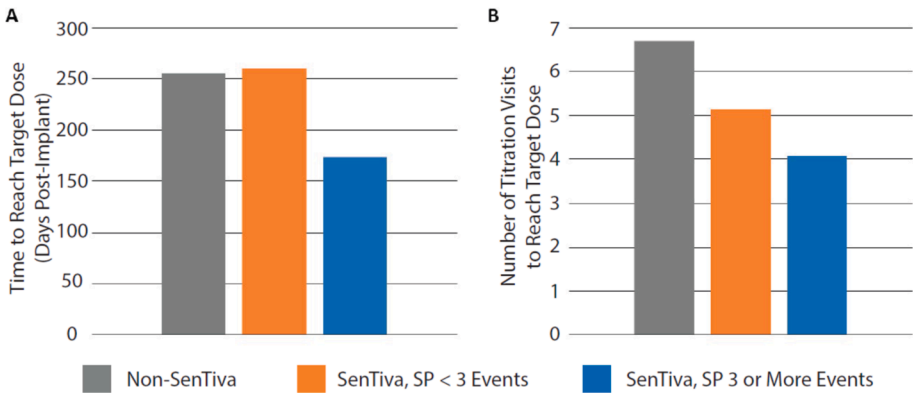

Fig. 3. The impact of SP and/or following the manufacturer's recommended protocol. **A:** Patients implanted with their first VNS device in the CORE-VNS study experienced shorter average time-to-dose when implanted with a Model 1000 ("Sentiva") pulse generator only when using ≥ 3 SP programming events. **B:** Average number of office visits required to reach the target dose range per the manufacturer's labeling reduced for patients that underwent more titration steps using the SP feature.

subdivided into patients that were predominantly manually titrated, versus automated titration with three or more steps. These subgroup selections were based on our common clinical practice observations in the study; many providers only used the SP feature to skip a single visit, such as, if the patient or provider were unable to schedule an appropriately timed in-person visit. Titration with SP decreased the time to achieve the labeling-defined target dose range compared to any type of manual titration, and using additional SP steps further reduced time-to-dose (Fig. 3A). In patients that used three or more SP steps, 35 of 46 (76.1 %) patients achieved the target dose range in less than 12 months, compared to 268 of 453 (59.2 %) patients in the other groups. Time-to-dose in days was markedly lower for the group that titrated VNS predominantly with the SP feature. SP was associated with two features, titration efficiency in reaching the target dose and reduced number of office visits required to get patients to the target dose (Fig. 3B).

Next, survey respondents addressed the techniques they use to accomplish their goals for titration. Approximately 6 of 10 respondents with access to the feature reported not using SP during the titration process (Fig. 4).

3.5. *Impact of experience with VNS on practice habits*

To examine the impact of experience on titration habits, we segregated respondents based on the number of VNS patients the respondent reported managing during their career. Less experienced VNS users described more risk-averse behavior while titrating. Specifically, nearly half of less experienced respondents report stopping titration when patients express discomfort or experienced side effects of the therapy. Whereas only a quarter of the more experienced responders expressed similar approaches (Fig. 5). The VNS labeling does not indicate that titration should be discontinued when a patient experiences side effects, but rather that the output current or pulse width should temporarily be reduced to allow the patient to acclimate to the new settings. Despite concerns for side effects being greater in the less experienced population, results indicate that both groups of providers had a similar proportion of respondents that only stop titration once they achieved (what they believe) a therapeutic dose of VNS. Both low and high levels of experience of VNS users prefer to increase the output current or duty cycle (either directly, or indirectly by reducing the AutoStim threshold setting) in patients that have not responded to VNS at presumed therapeutic settings. Less experienced users reported a greater likelihood to alter the signal frequency of VNS or use higher pulse widths to improve the patient outcome. Ninety-five percent of experienced providers use increased output current and duty cycle (or reduced AutoStim threshold, which increases duty cycle) to improve the likelihood of response to VNS.

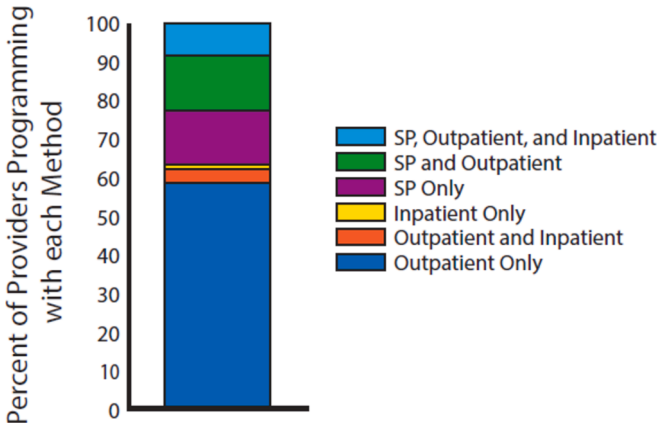

Fig. 4. Respondents to the survey describe how and where they conduct titration of VNS.

4. Discussion

The results of our survey show a high variability in VNS dosing habits and highlights differences in behaviors of clinicians linked to overall experience and familiarity with VNS therapy. This appears to point towards gaps in training and clinical skills. These discrepancies may reduce the likelihood of VNS response for patients treated with VNS. We observed differences among individual respondents regarding target output current and maximum output current that deviate dramatically from evidence-based practice (Fig. 1). Although most HCPs estimated the target output current to remain between 1 and 2 mA, only a minority (11 %) target an initial dose between 1.5 mA and 1.75 mA, which has been described in the manufacturer's labeling and product training for decades and for which the highest likelihood of response was observed earlier [11]. Often, time to titrate patients to target dose exceeds three months – potentially depriving patients of the outcomes they sought when they undertook the risk of surgery. Recent retrospective analysis reveals this long period of titration may negatively impact outcomes of VNS patients and delays the final clinical evaluation of the efficacy of VNS, potentially exposing patients unnecessarily to continued seizures and their well-known risks [12].Also, despite the benefits of reduced time-to-dose (Fig. 3A), the impact that titration speed has on time-to-response [12], and reduced office visits required to achieve the target dose (Fig. 3B), SP remains underutilized. Continued use of practices that may delay favorable clinical outcomes could be driven by a training gap, which is apparent by the number of respondents who reported (1) using

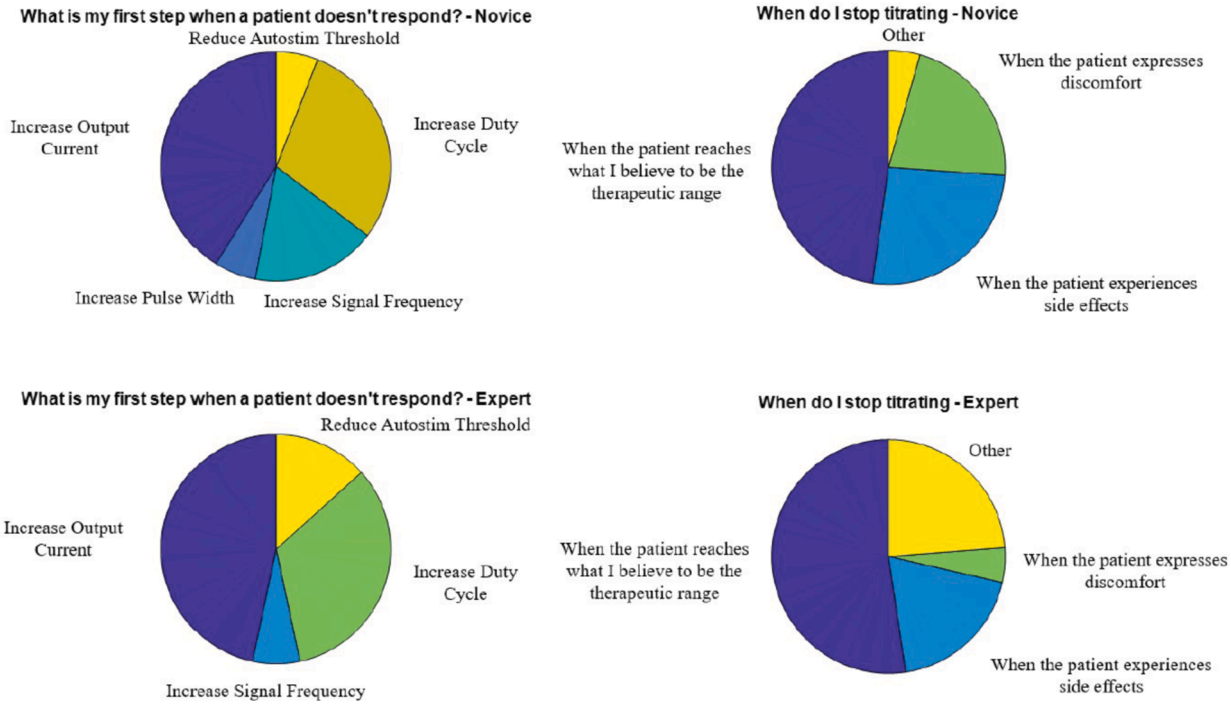

Fig. 5. "Expert" (>100 patients treated) versus "Novice" (<20 patients treated with VNS) respondents described differences in how they react to specific outcomes during titration. **Left:** When patients do not respond to VNS within the target range that the respondent initially programmed, Novice users were more likely to change the signal frequency than Expert users, despite there being little existing evidence to support this practice. Most users employed a strategy that increased the effective dose of VNS by increasing output current or pulse width or increasing the duty cycle (either directly or through the AutoStim feature). **Right:** Novice providers reported greater risk aversion, or concern about side effects, than Expert users. This risk aversion may influence a premature end to the titration process and underdosing.

output currents beyond the available range of parameters on the device and (2) use of settings inconsistent with the manufacturer's recommended titration protocol despite stating they follow said protocol.

Our survey revealed widespread selection of initial target doses for VNS that are well below the manufacturer's recommended dose, along with prolonged "watchful waiting" periods after achieving that initial target. The combination of these factors may be associated with an increased risk of seizure-associated injury and comorbidity [15] by delaying response to the therapy. A minimal dose of VNS is necessary to achieve clinical effects, which can be directly calculated as the current density sufficient to activate A-beta and B fibers believed to predicate the anti-seizure effect of VNS [16–19]. Because vagotopy is highly variable amongst individuals, as it is in other mammals [20,21], variability in dosing of patients should be expected. Nevertheless, sufficient current is needed to activate these fibers and achieve therapeutic effects [11,18]. The data of Tzadok et al clearly shows that faster titration yields a rapid onset of response accompanied by a minimal increase of side effect burden, specifically if the target dose of 1.625 mA at 250μsec is achieved in less than three months [12]. Given the transient nature of VNS side effects and lack of interaction with other drug-based therapies, the "start slow, go slow" mantra, commonly practiced with the use of ASMs to reduce the occurrence of side effects (especially with drug-drug interactions and polytherapy) is likely an unsuitable guidance for most patients treated with VNS.

There is little data to support the reluctance of HCPs to titrate VNS rapidly (in three months or less, if tolerated). However, evidence of rapid VNS titration exists in literature, with no significant increase in clinical side effects. Indeed, when used as an adjunctive treatment for difficult-to-treat depression, one study reported a rapid VNS dosing regime in six patients, in which titration was performed within 1 to 4 days after surgery. All patients received 1.0 mA output current after 8 to 14 days post-surgery [22]. No side effects were reported, and the antidepressive effect could be reached earlier than using slow titration [23]. Also, in the case of life-threatening refractory status epilepticus, sedation allows for the rapid increase up to 1.5 mA or 1.75 mA over periods varying between 36 and 48 h, or immediately starting at 1 mA after surgery [24]. Our investigation of post-market surveillance data reveals that rapid titration is possible but not implemented in most patients (Fig. 3). There are two obvious impediments to rapid titration, with VNS: side effects associated with increased stimulation after each titration step and patient access to office visits for titration.

From our survey, we observed a tendency of less experienced users to limit target output current whenever a patient experiences side effects, while the data suggests prioritizing the path to 1.625 mA and adapting pulse width or frequency whenever side effects occur. While most of the less experienced VNS users increase the total dose of the VNS (target output current, duty cycle or threshold of AutoStim) to improve the likelihood of response to VNS, these users were also more likely to change the signal frequency or pulse width as compared to the more experienced users. Despite the difference in therapeutic approaches among the less and more experienced users, a similar proportion of respondents stop titration when they achieve what they believe to be a therapeutic dose of VNS. Prioritization of titration to achieve efficacious doses of VNS ought to be preferred, as the reported side effects from stimulation tend to decrease over time. Efficient titration to the target dose can also be supported by proactive patient counselling and sufficient experience of the physician. In fact, advising patients of the side effects they can expect during routine increases to output current may help to increase patients' tolerance to or acceptance of the stimulation. Education of novice VNS users on how to manage patient expectations regarding transient side effects during the titration process is highly encouraged.

More recent models of VNS include an automatic titration feature that aims to address the second impediment of patient accessibility during the titration phase. The Model 1000 "Sentiva" model includes an optional SP feature that applies a standard or custom-made protocol to

automatically increase output currents. The use of SP is an important strategy to simplify and standardize dosing according to FDA approved labeling for VNS and published VNS guidelines [25]. The use of SP may be of special interest in cases such as institutionalized patients with decreased mobility or in the case of a new pandemic. In practice, SP is typically programmed during the first out-patient office visit, which should ideally be 2 weeks after surgery. The interval of increase can be chosen between 0.125 mA every week or 0.25 mA every 2 weeks. HCPs have the option of choosing either the full automated titration or using only a few of the available seven steps and regularly monitoring the patient in-between to assess clinical tolerability. Indeed, our survey revealed that clinicians were nearly evenly split on the use of 0.125 mA steps versus 0.25 mA steps with SP, and the median number of steps programmed with the feature was four. Our results show that regular SP use decreases the average time-to-dose by almost 50 %, making this an essential programming feature (Fig. 3). These automated, out-of-office titration steps also reduce the number of office visits required to achieve the target dose, which is an attractive ancillary benefit for patients who may have poor access to the hospital (disability, inability to drive, etc.) or live in rural settings. However, our survey did not elucidate reasons for not using the SP feature, even when HCPs had access to it (Fig. 4). Potential reasons may include the necessity to evaluate side effects at office visits or patient and HCP concerns. Furthermore, it is likely that some HCPs are uninformed of how to utilize the SP features, due to training gaps we have previously discussed.

In addition to increasing titration speed, the SP could potentially prevent situations where patients are not titrated to target output current at all. After 12 months of follow-up, patients who used the SP feature were more likely to have achieved the target dose than those who did not. It is important to recognize there are reports of patients achieving robust clinical effect at doses below the labeling-defined target dose range, indicating there could be reasons to halt titration prior to achieving the target we defined for our analysis.

5. Conclusion

Management of VNS is highly unique, which likely contributes to the diversity of opinions held about the effectiveness of the therapy and time course thereof. Evidence suggests that enhanced standardized approaches to the management of VNS will likely improve patient outcomes. Efficient titration to an initial target dose of 1.625 mA at 250μsec in three months or less, which is consistent with the manufacturer's labeling would likely improve patient outcomes in practices that do not currently follow these recommendations. The SP feature may be a useful tool for providers to help patients achieve the target dose if access to the clinic is an issue. Critically, coaching patients through transient stimulation-associated side effects during titration may help them achieve the target dose sooner, improving their health outcome in the long-term.

6. Authors' contribution statement

RET and RV wrote the initial draft of the manuscript, while AS, MD, RP, MB, FF, and MT provided critical feedback. Survey design was led by RET, AS, and MD. Survey distribution was shared by all authors and supported by LivaNova staff led by MB. Survey analysis was conducted by RV, while all other authors provided critical input.

CRediT authorship contribution statement

Riëm El Tahry: Writing – original draft, Conceptualization. **Maxine Dibué:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Arnaud Szmalec:** Writing – review & editing, Validation, Methodology, Conceptualization. **Roshani Patel:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Data curation. **Ryan Verner:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Massimiliano Boffini:** Writing – review & editing. **Firas Fahoum:** Writing – review & editing. **Michal Tzadok:** Writing – review & editing, Validation, Conceptualization.

Declaration of competing interest

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

Acknowledgement

Funding statement: No funding or financial support was awarded for this work. David A. Mays, PharmD, MBA provided general manuscript administrative and scientific oversight for its submission. The authors thank Shivani K Maffi for providing editorial support for submission of the manuscript, which was funded by LivaNova in accordance with GPP3 guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100734.

References

[1] Watson GDR, et al. *A journey into the unknown: An ethnographic examination of drug-resistant epilepsy treatment and management in the United States*. Epilepsy Behav 2021;124:108319.
[2] Kwan P, Brodie MJ. *Early identification of refractory epilepsy*. N Engl J Med 2000;342(5):314–9.
[3] Chen Z, et al. *Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study*. JAMA Neurol 2018;75(3):279–86.
[4] Frost M, et al. *Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome*. Epilepsia 2001;42(9):1148–52.
[5] Uthman BM, et al. *Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation*. Neurology 2004;63(6):1124–6.
[6] Alexopoulos AV, et al. *Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy*. Seizure 2006;15(7):491–503.
[7] Amar AP, Apuzzo ML, Liu CY. *Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry*. Neurosurgery 2004;55(5):1086–93.
[8] Elliott RE, et al. *Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response*. Epilepsy Behav 2011;20(1):57–63.
[9] Elliott RE, et al. *Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years*. Epilepsy Behav 2011;20(3):478–83.
[10] Kostov KH, et al. *Norwegian population-based study of long-term effects, safety, and predictors of response of vagus nerve stimulation treatment in drug-resistant epilepsy: The NORPulse study*. Epilepsia 2022;63(2):414–25.
[11] Fahoum F, et al. *VNS parameters for clinical response in Epilepsy*. Brain Stimul 2022;15(3):814–21.
[12] Tzadok M, et al. *Rapid titration of VNS therapy reduces time-to-response in epilepsy*. Epilepsy Behav 2022;134:108861.
[13] Fahoum F, et al. *VNS Parameters for Clinical Response in Epilepsy*. Brain Stimul 2022.
[14] Sen A, et al. *Vagus nerve stimulation therapy in people with drug-resistant epilepsy (CORE-VNS): rationale and design of a real-world post-market comprehensive outcomes registry*. BMJ Neurol Open 2021;3(2):e000218.
[15] Laxer KD, et al. *The consequences of refractory epilepsy and its treatment*. Epilepsy Behav 2014;37:59–70.
[16] Krahl SE, et al. *Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation*. Epilepsia 1998;39(7):709–14.
[17] Krahl SE, Senanayake SS, Handforth A. *Seizure suppression by systemic epinephrine is mediated by the vagus nerve*. Epilepsy Res 2000;38(2–3):171–5.
[18] Helmers SL, et al. *Application of a computational model of vagus nerve stimulation*. Acta Neurol Scand 2012;126(5):336–43.
[19] Blanz SL, et al. *Spatially selective stimulation of the pig vagus nerve to modulate target effect versus side effect*. J Neural Eng 2023;20(1).
[20] Settell ML, et al. *Functional vagotopy in the cervical vagus nerve of the domestic pig: implications for the study of vagus nerve stimulation*. J Neural Eng 2020;17(2):026022.
[21] Upadhye AR, et al. *Fascicles split or merge every ~560 microns within the human cervical vagus nerve*. J Neural Eng 2022;19(5).

[22] Moeller S, et al. *Rapid titration protocol - Experiences with a dynamic novel titration regime for vagus nerve stimulation in a group of depressive patients*. J Clin Neurosci 2020;74:262–4.
[23] Eidelberg D, et al. *Early differential diagnosis of Parkinson's disease with 18F-fluoro-deoxyglucose and positron emission tomography*. Neurology 1995;45(11):1995–2004.
[24] Zeiler FA, et al. *VNS for refractory status epilepticus*. Epilepsy Res 2015;112:100–13.
[25] Morris GL, et al. *Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology*. Neurology 2013;81(16):1453–9.