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Programming in Vagus nerve stimulation therapy: Consensus from a Nordic Delphi Panel

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ABSTRACT

Purpose: Despite VNS therapy being established broadly as a second line treatment for drug resistant epilepsy, there are currently no guidelines or recommendations giving sufficient and detailed guidance and suggestions to fully utilize the increasing array of parameter options.

Methods: A panel of 22 experts from the Nordic countries (6 were pediatric neurologists, 14 neurologists and 2 treating both pediatric and adult patients) was assembled to share their experience with VNS therapy using a 5-step Delphi approach. Agreement level ≥80% was considered strong consensus and 60 to79% was considered medium consensus.

Results: After the third round of the Delphi process there were 70 statements in different sections as: How to start the VNS after implantation (9 statements), How to do further adjustment after the initial phase (13 statements), How to use Autostimulation mode (14 statements), How to use scheduled programming (8 statements), Are there special settings for special seizure types/diagnosis (6 statements), How to use day-night programming (3

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statements), What to know about Magnet mode (6 statements), How to manage side effects (3 statements), Considerations about gender/age and patient preferences (4 statements), and Practical programming (4 statements). In 46 statements (65.7%) the panel reached a strong consensus, in 11 (17.7%) a medium consensus, and in 13 (18.6%) no consensus was achieved.

Conclusion: The recommendations of the Delphi panel emphasize proactive deployment of available stimulation options including build up in duty cycle and the use of rapid cycling as well as increasing the output current if response with primary target current is insufficient. Additionally, the usage of Magnet mode and Autostimulation mode were encouraged. Guidance on how to use the newest stimulation options such as day-and-night and scheduled programming for improved feasibility and tolerability is provided.

Introduction

Drug-resistant epilepsy (DRE) was in 2010 defined by the International League Against Epilepsy (ILAE) as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [1]. About one third of patients with epilepsy develop DRE, and therefore there is a need for alternative non-medical treatment options such as resective epilepsy surgery, dietary treatments or neurostimulation therapies [2]. Vagus nerve stimulation (VNS) has been used in treatment of DRE for more than a quarter of century with evolving device technology.

The mode of function of a VNS system can be described functionally as a twostep process: 1) activate the nerve with an appropriate current and pulse width (the 'volume'), 2) modulate central nuclei via temporal code (the 'message') [3]. 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, both of which influence temporal responses to peripheral modulation and may be specific to the disease being treated [4]. On the other hand, VNS is proposed to have three different effects: immediate termination of a seizure [5], short-term anticonvulsive effect of stimulation [6], and long-term effects on neural circuitries [7]. Other mechanisms such as neuroimmunomodulation have been also implicated but not confirmed in a recent meta-analysis [8].

Modern VNS systems provide three different modes of stimulation. Early generations of VNS devices offered only two modes of stimulation; normal mode cyclic stimulation and patient triggered Magnet mode stimulation. Since 2015 a novel treatment mode based on heart rate variability, i.e., Autostimulation mode, which is also known as closed-loop responsive rVNS, has been available in VNS therapy system generators (first 106 AspireSR® and 2017 Sentiva® M1000) [9]. Autostimulation mode VNS algorithm was initially designed to detect rapid changes in heart rate associated with the onset of a seizure but has also recently been suggested to reflect known circadian changes in autonomic function [10]. The Sentiva® M1000 offers several novel features, including faster communication speed, day/night programming, and scheduled programming. In contrast, the AspireSR® Model 106 provides superior battery longevity, with a rated capacity of 1.7 amp-hours compared to 1.0 amp-hours in the Sentiva® M1000[9].

Guidelines were developed soon after regulatory approval to address the objectives and process of VNS titration and dosing more clearly, however, these have not been revised since 2002[11].The manufacturer has embraced some of these guidelines along with other evidence-based supplemental recommendations into their own labelling and has advocated for distinct settings for output current, pulse width, selection for mode of stimulation, and for Autostim usage [12]. Guidelines developed for the titration and dosing of VNS were based on best available clinical evidence, namely the pre-2000s pivotal studies E03 and E05. Thus, taking into consideration more current evidence may provide valuable new insights [4]. In fact, the American Academy of Neurology's (AAN) most recent 2013 guideline revision - reaffirmed in 2022 - also suggested that further research was needed to clarify the target settings to improve clinical outcomes [13].

Currently, there are no guidelines or recommendations giving sufficient and detailed guidance and suggestions to fully utilize the increasing array of parameter options. When otherwise costly and large cohort studies with long time follow-up would be needed a Delphi process can provide an alternative option to develop reliable and simple guidelines to be used in daily clinical practise for improvement of quality of VNS therapy utilization. The primary goal of this Nordic Delphi consensus was therefore to provide guidance to encourage proactive programming and use of the full arsenal of available programming options of VNS in a situation when scientific data is limited, and existing recommendations do not cover all possible options available at present

2. Materials and methods

2.1. Scientific committee

The project was initiated and led by a scientific committee consisting of two members of the expert panel (O. Henning, J. Peltola) and a facilitator (M. Bostrøm), who were responsible for the development of the first version of the questionnaire, which was then adjusted following input from the panel. Key responsibilities for the two members of the expert panel were to collate and summarize statements from the expert panel, and finally adjust statements based on comments from the expert panel. No outside consulting regarding the method took place.

2.2. Expert panel

In August 2020, an email invitation followed by three reminders was sent out to 262 neurologists and paediatric neurologists in the Nordics (Denmark, Finland, Norway and Sweden) which were registered as physicians either using VNS or interested in using VNS, inviting them to participate in an expert panel to quantify the level of consensus for mutual clinical guidelines in the Nordics for VNS treatment. 36 physicians responded. The selection of the expert panel was based solely on clinical experience within VNS therapy with two inclusion criteria to be eligible for the expert panel: minimum 5 years' VNS experience, and minimum of 20 VNS patients.

Based on these inclusion criteria's, the expert panel was finalized in October 2020 and consisted of 22 experts (on average each treating 144 patients with VNS and having 16.5 years of experience) from the Nordic countries: 5 from Denmark, 4 from Finland, 7 from Norway and 5 from Sweden. Of these, 6 were paediatric neurologists, 14 neurologists and 2 treating both paediatric and adult patients.

2.3. Delphi approach

The Delphi method was chosen to quantify the Nordic clinical experience within VNS therapy. A 5-step Delphi approach was implemented in the current study, using a web-based Delphi panel process to quantify the level of consensus for treatment of VNS Therapy in the Nordics. In accordance with the original Delphi study [14], all responses were anonymous in the current Delphi study. Exact levels of consensus are arbitrary and vary significantly between different Delphi studies. For the present study the following thresholds were defined during the start-up meeting: strong consensus (≥80%), medium consensus (60-<80%), or no consensus (<60%). In the analysis, the mean values for percent agreement were weighted for each expert group in terms of the number of group members. The process was started in January 2021 and concluded in November 2022. The Delphi process was extensive and covered various aspects of VNS treatment categorized as: Patient selection, Adjunctive treatments, Safety considerations, Patient communication, Stimulation parameters, Documentation, Results with VNS Therapy, Measuring outcome, and Battery replacement and therapy termination. For this article we choose to focus on stimulation parameters.

The summarized information about the 5-step Delphi process is outlined in Fig. 1. In step 1 the questionnaire was developed. When answering the questions in step 2, the expert panellists were asked to generate statements as one would explain to a less experienced colleague in using VNS therapy. It was emphasized that gathering their expert opinion was the target of the study, and that they therefore should not review the published level of evidence before answering. The expert panel were allowed to make several statements on each question. However, if one did not have enough experience within a specific topic, there was an option to withhold opinion. The statements submitted during the second step were final, and it was not possible to add new statements after this round.

During voting rounds (step 3, 4 and 5) participants were asked to choose one the following alternatives for each statement: "Agree", "Disagree", or "Withhold my opinion". The feedback was aggregated across all experts. Statements with strong consensus were removed from the coming rounds. In round 4 the expert panel was asked to rephrase the statements where they disagreed in a way that would enable them to agree. The goal was to rephrase the statements to get strong agreement on as many statements as possible. These rephrased statements were then sent out in the third voting round (step 5).

After the three voting rounds, each expert panellist had the opportunity to review their answers (step 6).

3. Results

3.1. Delphi process on stimulation parameters

After the third round of the Delphi process there were 70 statements in different sections: How to start the VNS after implantation (9 statements), How to do further adjustment after the initial phase (13 statements), How to use Autostimulation mode (14 statements), How to use scheduled programming (8 statements), Are there special settings for special seizure types/diagnosis (6 statements), How to use day-night programming (3 statements), What to know about Magnet mode (6 statements), How to manage side effects (3 statements), Considerations about gender/age and patient preferences (4 statements), and Practical programming (4 statements).

In 46 of 70 statements (65.7%) the panel reached a strong consensus, in 11 (17.7%) a medium consensus, and in 13 (18.6%) no consensus was achieved (Fig. 1). Data showing the results from the different rounds of the Delphi process, including the number of respondents consenting to each statement, is provided as supplementary information. An overview of the final results is also included, indicating in which round consensus was achieved (see Supplementary Information).

3.2. Statements on stimulation parameters

Levels of consensus are presented in Tables 1 and 2

4. Discussion

This is the first nordic consensus providing guidance to encourage proactive programming and use of the full arsenal of available programming options of VNS. We propose detailed suggestions for selection of initial target parameters for VNS including auto stimulation and day-night mode. In addition to previous VNS stimulation protocols, we have also included guidance both for the type and order of alternatives for VNS message modes and for signal volume changes if initial target settings do not give satisfactory response. Moreover, we have bestowed ideas for division of labour for medical professionals involved in VNS treatment. The degree of consensus among the Delphi panel for these suggestions was remarkable achieving either a strong or a median consensus in 81% of the statements in a situation where there is lack of scientific data exploring different options.

Initial stimulation parameters

When programming for initial target parameters, we provide suggestions separately both for the 'volume' and the 'message' aspects of stimulation. Firstly, for the stimulation 'volume' parameters, the goal was proposed to achieve a minimum output current of at least 1.5-1.75 mA and a primary target output current of 1.75-2 mA if tolerable. Conversely, the original 2002 AAN guidelines suggested that lower output currents including currents less than 1 mA may sometimes be suitable [11]. The most recent 2013 AAN guidelines stated that the output current should generally be increased to 2–3 mA as tolerated [13]. According to manufacturer's recommendation, the target output current range varies from 1.5 to 2.25 mA. A population level optimal output current for VNS therapy in epilepsy in a recent study was identified as 1.61 mA first time providing data for current targeting [4].

Furthermore, it was not considered necessary to take the age of the patient into consideration when choosing stimulation parameters since each patient was thought to have individual requirements and tolerability issues anyways. On the other hand, there was medium consensus proposing that one should aim for a higher target output current in children than in adults.

Secondly, there was 100% consensus defining that VNS should be started on 250 μsec pulse width. Both 2013 AAN guidelines [13] and the manufacturer's recommendation stated that both 500 μsec and 250 μsec options are possible, but the manufacturer's Scheduled Programming Default Settings suggest 250 μsec as the primary option. Other biophysical data and modelling support the use of pulse widths at or below 250 μsec pulses, with lower pulse widths requiring an increase in the selected output current [4]. According to manufacturer's database, the usage of 250 μsec pulse width has increased in popularity with 81% patients programmed on this pulse width in 2018, which was the most recent year available [15].

For stimulation 'message' aspect concerning Duty cycle initial default settings the concensus in the Delphi panel was 30s ON/5 min OFF (10% duty cycle) in accordance both with manufacturer's recommendation and 2013 AAN guidelines [13]. A population level optimal duty cycle for VNS therapy in a recent study based on clinical outcome data found a 17.1% duty cycle to provide best seizure outcomes [4].

Additionally, a strong Delphi panel consensus asserted that VNS should be started on 20 Hz frequency contrary to 2013 AAN guidelines which advocated the use of 30 Hz stimulation frequency [13]. According to the manufacturer's Scheduled Programming Default Settings both 30 Hz and 20 Hz options were deemed possible, but 20 Hz was considered the primary option Overall, 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 [4]. Again, according to manufacturer's database 71% of patients were programmed on 20 Hz in 2018[15].

Although the stimulation parameters are discussed above as distinct entities, it is important to consider their interactions—specifically output current, frequency, and pulse width—and their combined effects on both efficacy and tolerability [15]. VNS is an electroceutical therapy, and the degree of vagus nerve activation depends on the interplay of these three parameters, which follow a conventional strength-duration

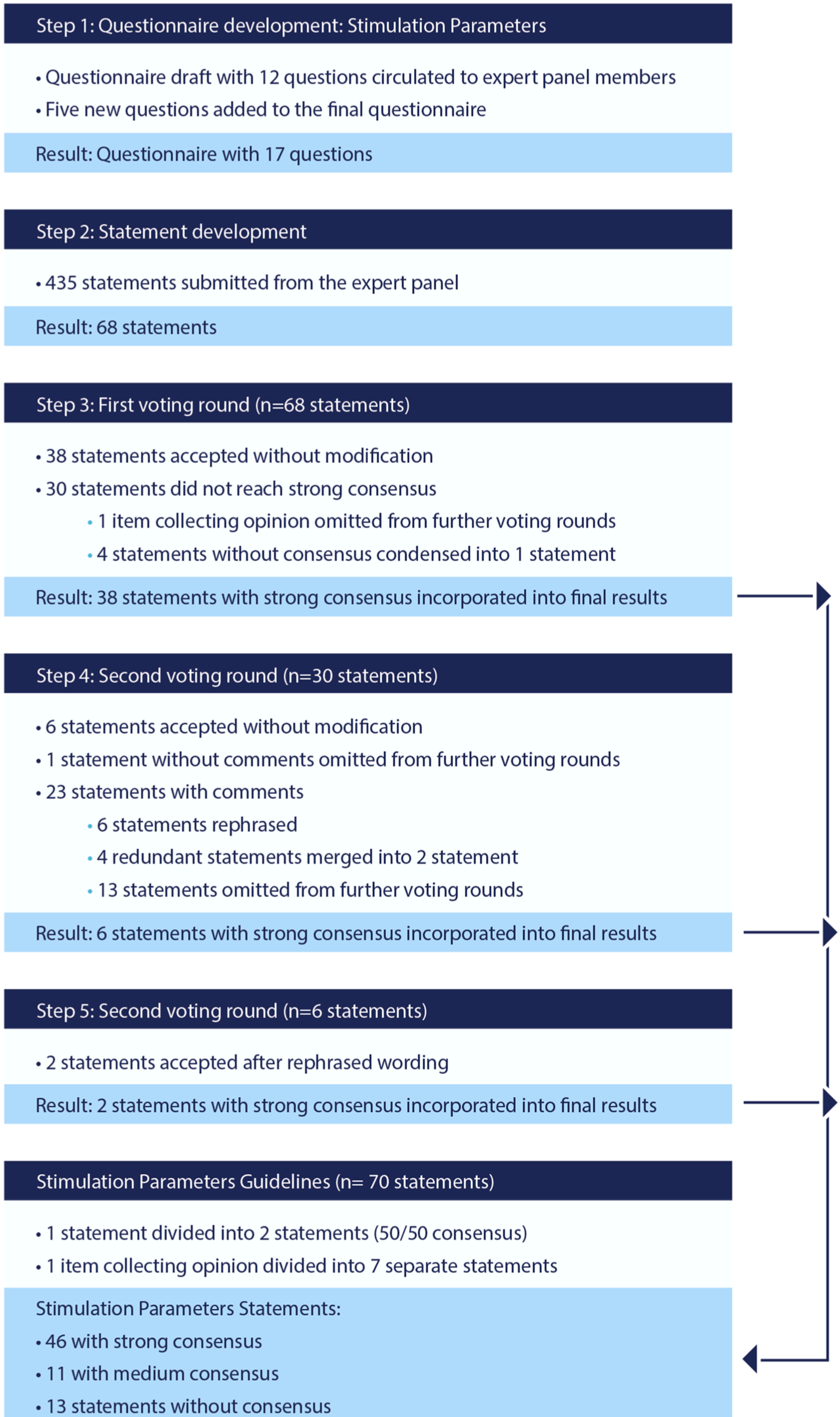

Fig. 1. Shows the 5 step Delphi approach used in the study.

relationship [15]. Recent studies and clinical recommendations support the findings of our Delphi panel. Lower pulse width (250 µs) and frequency (20 Hz) settings have demonstrated comparable therapeutic efficacy to higher settings (500 µs and 30 Hz), while also improving battery longevity. This increased efficiency may reduce the frequency of generator replacements, enhancing overall device sustainability [11,15,16].

Autostimulation mode

Previous guidelines have not included recommendations for the usage of the Autostimulation mode, which has been available since 2015 with 106 AspireSR® VNS device [9]. The expert panel showed more variation in recommendations compared to other initial stimulation parameters most likely due to lack of published data on this subject. The Delphi panel proposed that Autostimulation mode should be started on 30-40% threshold, but on the other hand median consensus was obtained for the recommendation that threshold for Autostimulation mode should be based on ictal-EEG-tachycardia-level, if available. Furthermore, the threshold for Autostimulation mode was recommended to be reviewed in each session until the most optimal setting is found based both on information comparing Autostimulation mode activations with Magnet mode stimulation and seizure outcomes. Finally, Autostimulation mode (preferably at threshold 20-30 %) should always be used in patients with tonic-clonic seizures.

AutoStim was initially investigated using the Model 106 AspireSR® generator in two multicenter studies: the E-36 study in Europe [17] and the E-37 study in the United States [18]. A trade-off exists between different AutoStimulation threshold settings. Data from both studies demonstrated that lower AutoStimulation thresholds were associated with shorter latencies between seizure onset and stimulation delivery. These shorter latencies, in turn, correlated with reduced seizure durations. Thus, lower thresholds may enable earlier detection of seizure-related heart rate elevations, potentially improving therapeutic response. However, they also increase the likelihood of non–seizure-related stimulations, thereby raising the overall duty cycle.

Ictal tachycardia is more frequently observed in temporal lobe epilepsy (TLE) compared to other focal epilepsy types [19], suggesting that patients with TLE may derive greater benefit from AutoStimulation. Supporting this, a recent study found that significantly more AutoStimulations were triggered in patients with TLE and multifocal epilepsies than in those with extratemporal lobe epilepsy [10]. Furthermore, a recent meta-analysis of patients with drug-resistant epilepsy (DRE) indicated that switching from traditional VNS to a device with activated AutoStimulation mode was associated with greater seizure reduction (≥50% and ≥80% thresholds), highlighting the potential added benefit of AutoStimulation for seizure control [20].

The Manufacturer's recommendation for Autostimulation mode differed from Delphi panels with a proposal to set the Autostimulation mode threshold at or below the patient's typical heart rate increase during a seizure, but if this information was not available, starting with 20% and adjustments based on clinical benefit or tolerability was advocated. Moreover, according to Scheduled Programming Default Settings Autostimulation mode was advised to be set at 60 sec ON and Autostimulation mode current 0,125 mA more than normal mode stimulation. Our Delphi panel did not achieve consensus regarding the optimal Autostimulation mode current or duration.

Magnet usage

The recommendations for Magnet mode use by the expert panel stated that Magnet mode should be set to 0.25 mA above normal the mode stimulation, to the same pulse width as normal the mode stimulation, and to a duration of 60 sec. These stimulation parameters differ from Manufacturer's recommendation where according to Scheduled Programming Default Settings magnet triggered stimulation settings are 0,5 mA higher than normal mode with 500 µsec pulse width and with 60 sec ON.

Moreover, the Delphi panel recommended that every patient should be instructed to try magnet triggered stimulation as fast as possible when a seizure starts to abort that seizure, which is similar to AAN guidelines recommending that patients may be counselled that VNS magnet activation may be associated with seizure abortion when used at the time of seizure auras [13]. Based on data from two Class III studies, seizure abortion with magnet-activated stimulation is possibly associated with overall response to VNS therapy, and based on three Class III studies, magnet-activated stimulation may be expected to abort seizures one fourth to two-thirds of the time when used during seizure auras [13]. Specifically, a retrospective analysis of magnet use during the E03 and E04 clinical trials of VNS therapy revealed notable findings. In the E03 trial, patients who actively used magnets to initiate stimulation were significantly more likely to report seizure improvement compared to those with inactive magnets ($P = 0.0479$). In the E04 trial, 22% of patients using the magnet reported seizure termination, while 31% reported a reduction in seizure severity [21].

On the other hand, according to the Delphi panel, patients and caregivers should be instructed of the possibility to switch off stimulation with the magnet in situations associated with stimulation related side-effects such as shorter speaking engagements and physical activity.

Timing of programming changes

According to Delphi panel, VNS should be started at 0.25 mA and for further titration, VNS should usually be increased by 0.25 mA steps either by an epilepsy nurse or a neurologist with an internal protocol for quality control. This starting point is like previous guidelines [11,13]. However, it was emphasized by the Delphi panel that the initial output current and the titration time frame should be made individually depending on how difficult the situation with epilepsy together with the patients and their family.

A recent study demonstrated a significant relationship between titration speed and onset of clinical response indicating that faster titration (<3 months) yields faster onset of clinical benefit and is especially practical in the paediatric population, though attempts to accelerate adult titration may still be warranted [22]. Manufacturer's recommendation also emphasizes that titration to target output current within 3 months per protocol can lead to a faster onset of clinical response.

The use of scheduled programming and day-night programming

Previous guidelines have not included recommendations for the use of scheduled programming or day-night programming, which has been available only since 2017 with the introduction of Sentiva® M1000 VNS device [9]. According to Delphi panel when scheduled programming is used, the programmed increase should be 0.125 mA/step with an

Table 1
Showing results for consensus regarding statements about how to start the VNS after implantation, how to do further adjustment after the initial phase, how to use Autostimulation mode, how to use scheduled programming. The degree of consensus is emphasized by colour coding. Green strong consensus (≥80%), yellow medium consensus (79-60%) and red no consensus (<60%).

(continued on next page)

Table 1 (*continued*)

How to start the VNS after implantation.	
100 %	VNS should be started on 250 µs pulse width.
90.9 %	VNS should be started on 20 Hz frequency.
77.3 %	VNS should be started at 0.25 mA.
72.7 %	For further titration, VNS should usually be increased by 0.25 mA steps.
90.5 %	The VNS startup output current and the titration time frame should be made individually depending on how difficult the situation with epilepsy is. If the epilepsy situation is difficult, the risk of possible side effects due to higher startup output current and fast titration should be taken into consideration.
81.8 %	The startup output current and titration time frame should be discussed with the patient and the decision about those made together with the patient.
59.1 %	If tolerable, increase should occur at least once a week.
50 %	VNS should be started the day after the operation.
50 %	VNS should be started 2 weeks after operation.
How to do further adjustment after the initial phase?	
95.5 %	After the titration period, one should wait for approximately 3 months before further adjusting stimulation parameters, depending on the seizure situation and tolerability.
80 %	Since each person is unique there is no single highest output current but ramp up should be slow to evaluate changes in seizure frequency and tolerability.
71.4 %	The goal is to achieve a minimum output current of at least 1.5-1.75 mA.
81.8 %	The goal is to achieve a target output current (if tolerable) of 1.75-2 mA.
70%	The maximum output current to be used is 2.5-3 mA.
95.5 %	Duty cycle should be increased stepwise, using a systematic approach to evaluate the most optimal response for VNS therapy.
95.2 %	When evaluating duty cycles, adjust every 3-6 months, depending on the seizure situation and tolerability.
95.5 %	After low or lack of response with initial default settings (30s ON/5 min OFF, 10%), gradual increase to rapid cycling (7s ON/0.3 min OFF, 44%) should be tried.
94.1 %	After low or lack of response with rapid cycling (7s ON (active stimulation)/0.3 min OFF (pause of stimulation), 44%), saturation cycling with an ON time of 60 s and gradually decreasing OFF time until 1.1 min should be tried.

(continued on next page)

Table 1 (*continued*)

83.3 %	With lack of response, pulse width of 500 µsec should be tried.
81.3 %	Changing pulse width can increase efficacy.
84.2 %	With lack of response, signal frequency of 30 Hz should be tried.
88.2 %	Changing signal frequency can increase efficacy.
How to use Autostimulation mode?	
80 %	AutoStimulation mode should be started on 30-40% threshold.
75%	Threshold for AutoStimulation mode should be based on ictal-EEG-tachycardia-level, if available.
90.5%	The threshold for AutoStimulation mode (%) should be reviewed in each session until the most optimal setting is found.
86.7 %	AutoStimulation mode threshold should be optimized by reviewing and comparing magnet stimulation and AutoStimulation mode stimulation during seizures. If AutoStimulation occurs at the same time or after magnet stimulation, the threshold should be reduced to activate AutoStimulation mode earlier in the start of a seizure.
88.9 %	Threshold for AutoStimulation mode should be reduced if seizure frequency and/or severity hasn't changed.
83.3 %	Threshold for AutoStimulation mode should be reduced (in steps of 10%) if low counts of AutoStimulations per day. Likewise, the threshold for AutoStimulation mode should be increased (in steps of 10%) if there is a very high number of AutoStimulation s per day and/or if side effects due to “false positive” AutoStimulations occur.
85.7 %	The effect of AutoStimulation mode should be reviewed frequently and deactivated if not obviously effective.
40.9 %	AutoStimulation mode should be started immediately.
31.8 %	AutoStimulation mode should be started in all patients.
27.3 %	AutoStimulation mode should be started when the response to normal mode stimulation has been established.
22.7 %	AutoStimulation mode should be started only in patients with suspected/documented ictal tachycardia.

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Table 1 (*continued*)

9.1 %	AutoStimulation mode should be started in patients who respond well to magnet stimulations.
13.6 %	AutoStimulation mode should be started when an output current of 1 mA has been reached.
4.6 %	AutoStimulation mode should be started when an output current of 1.25 mA has been reached.
How to use scheduled programming?	
68.4 %	When scheduled programming is used, the programmed increase should be 0.125 mA/step.
85 %	When scheduled programming is used, the programmed increase should occur with an interval of 7-14 days.
100 %	Scheduled programming should be used for patients with long travelling distance to the hospital.
100%	Scheduled programming should be used in patients who, for any reason, prefer not to visit the hospital.
85 %	Scheduled programming should be used in patients that are challenging to cooperate with (e.g. severe autistic patients).
81.3%	Scheduled programming should in general not be used in patients who need rapid titration.
76.5 %	Patients should be instructed to regularly use the magnet the days before a scheduled increase to get used to a higher output current.
100 %	Scheduled programming requires good communication with the patient or caregivers, and possibility of an appointment with short notice to change stimulation parameters if necessary.

interval of 7-14 days but should in general not be used in patients who need more rapid titration.

Feasibility issues were also deemed by the Delphi panel to be important for scheduled programming, which should be used for patients with long travelling distance to the hospital, or in patients that are challenging to cooperate with (e.g. severe autistic patients). Moreover, it was emphasized that scheduled programming requires good communication with the patient or caregivers, and possibility of an appointment with short notice to change stimulation parameters if necessary.

There was strong consensus within the expert panel regarding all statements about Day-night programming suggesting that Day-night programming should be used and adjusted according to individual variability in seizure frequency at certain diurnal periods. Furthermore Day-night programming can be used to reduce side effects (e.g. patients with sleep apnoea) by decreasing stimulation intensity at certain diurnal periods. Similarly, Day-night programming can be used to improve tolerability for daily activities (e.g. speaking, exercise).

Programming if initial target parameters fail to provide satisfactory response

There was either strong or medium consensus within the expert panel regarding all statements in this section with a recommendation that after the titration period reaching primary target parameters, one should wait for approximately 3 months before further adjusting stimulation parameters, depending on the seizure situation and tolerability. Adjustments to stimulation parameters should be explained and decided in collaboration with patients and caregivers to gain acceptance to the changes to ensure best possible compliance to the therapy.

The stimulation parameter changes can involve either the 'volume' or the 'message'. Regarding the 'volume' the maximum output current recommended to be used were within 2.5-3 mA, which is in line with AAN recommendations [11]' [13]. On the other hand, 'message' duty cycle according to the Delphi panel should be increased stepwise using a systematic approach to evaluate the most optimal response to VNS therapy with adjustments every 3 to 6 months, depending on the seizure

Table 2

Table 2. Showing results for consensus regarding statements about special settings for special seizure types/diagnosis, how to use day-night programming, what to know about Magnet mode, how to manage side effects, considerations about age and patient preferences, practical programming. The degree of consensus is emphasized by colour coding. Green strong consensus (≥80%), yellow medium consensus (79-60%) and red no consensus (<60%).

Are there special settings for special seizure types/diagnosis?	
84.2 %	Rapid cycling should be tried for patients with frequent daily seizures.
84.6 %	Rapid cycling should be tried early in the treatment pathway for patients with absence seizures.
80 %	AutoStim (preferably at threshold 20-30 %) should always be used in patients with tonic-clonic seizures (TCS).
88.9 %	Rapid cycling should be used for patients with frequent myoclonic seizures.
71.4 %	Rapid cycling should be used for patients with encephalopathic epilepsies.
55 %	There are no seizure types requiring any specific settings.
How to use day-night programming?	
100%	Day-night programming should be used and adjusted according to individual variability in seizure frequency at certain diurnal periods (e.g. patients with predominantly nocturnal seizures or seizures on awakening).
100%	Day-night programming can be used to reduce side effects (e.g. patients with sleep apnea) by decreasing stimulation intensity (output current, higher threshold for AS, longer off time) at certain diurnal periods.
100%	Day-night programming can be used to improve tolerability for daily activities (e.g. speaking, exercise).
What to know about Magnet mode?	
81.8 %	Magnet mode should be set to 0.25 mA above normal mode stimulation.
85.7 %	Magnet mode should be set to the same pulse width as normal mode stimulation.
100%	Every patient should be instructed to try magnet activated stimulation as fast as possible when a seizure starts to abort that seizure.
70.6 %	In case they do not have any sensations during stimulation, patients should be instructed to regularly check whether the VNS is functioning by using with the magnet.
100%	Patients/caregivers should be instructed of the possibility to switch off stimulation with the magnet (e.g. in situations with intolerable side effects, shorter speaking engagements, physical activity etc).
95.3%	Magnet triggered stimulation should be set to a duration of 60 sec.

(continued on next page)

Table 2 (*continued*)

How to manage side effects?	
95.5 %	Side effects can be alleviated by reducing output current, reducing duty cycle, reducing pulse width, and/or reducing frequency.
63.6 %	First step to reduce side effects: Reduce output current.
95 %	The threshold of AutoStim can be increased to alleviate side effects.
Considerations about age and patient preferences?	
85.7%	There is no need to take the age of the patient into consideration when choosing/changing stimulation parameters since each patient has individual requirements and tolerability.
62.5 %	You should aim for a higher target output current in children than in adults.
100%	Patient preferences should generally be taken into consideration when choosing/changing stimulation parameters, which should be explained and decided in collaboration with patients and parents/caregivers. It is necessary that the patient/parents/caregiver accept the changes to ensure best possible compliance to the therapy.
57.1 %	You should be more careful with older patients when choosing/changing stimulation parameters.
Practical programming?	
95.5%	Practical programming can be done by an epilepsy nurse.
100%	Practical programming can be done by a neurologist.
90.5%	Practical programming should follow an internal protocol for quality control.
50%	Practical programming can be done by a neurosurgeon at implantation.

situation and tolerability with gradual increase in percentage of active stimulation (duty cycle) from 10% to 44% by changing ON time(active stimulation) standard 30 s and OFF time (pause) 5 min to rapid cycling (7s ON/0.3 min OFF, duty cycle 44%). Conversely, 2013 AAN guidelines emphasized that the evidence was insufficient to support a recommendation for the use of standard stimulation vs. rapid stimulation to reduce seizure occurrence. This evaluation was based on three available Class III studies which were underpowered to detect a difference in efficacy between rapid stimulation used either after when standard stimulation was unsuccessful or as an initial treatment setting [13]. Moreover, according to the Delphi panel, rapid cycling should be tried for patients with frequent daily seizures, for patients with frequent myoclonic seizures, and moreover should be tried early in the treatment pathway for patients with absence seizures. There was also medium consensus that rapid cycling should be used for patients with encephalopathic epilepsies.

Manufacturer’s recommendations are more general with a suggestion to increase duty cycle over time (first 30s ON/3min OFF 16%, secondly 30s ON/1.8min OFF 25% mentioning that additional duty cycle options are available) and assess clinical outcome with adjustments to duty cycle with similar frequency as in the present Delphi recommendation. Finally, regarding the duty cycles, the panel suggested that after insufficient response with rapid cycling, saturation cycling with an ON time of 60 s and gradually decreasing OFF time until 1.1 min should be tried. As a final step if all previous attempts have failed, the panel suggested to try to increase pulse width to 500 μsec or signal frequency to 30 Hz.

Managing side effects

Strength-duration relationship in VNS electroceutical dosing is also important in managing side effects [15]. There was either strong or medium consensus within the expert panel regarding all statements in this section counselling that side effects can be alleviated by reducing output current, reducing duty cycle, reducing pulse width, and/or reducing frequency with reducing output current as the first step, moreover, that the threshold of AutoStim can be increased.

Manufacturer’s recommendation to deal with side effects are like the Delphi panel regarding the output current or Autostim, but they also include suggestions to decrease pulse width from 500 > 250 μsec or

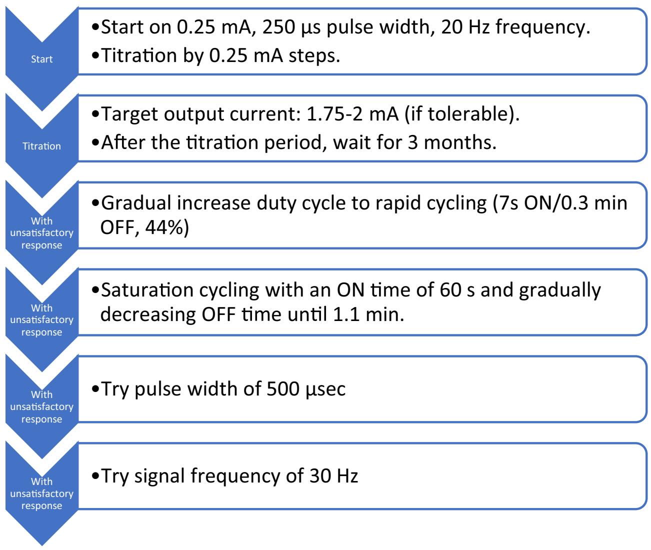

Fig. 2. showing the main conclusion for clinical practise, stop the whenever the result is satisfactory.

signal frequency from 30 >25 or 20 Hz, which are not relevant if the primary stimulation parameters recommendations by the Delphi panel are followed.

Strenghts and limitations

The limitations of this Delphi recommendation include issues inherent for the Delphi process itself. We followed a strict protocol in which all statements were generated by the expert panel members themselves. This process resulted in a large number of distinct statements, some of which were partially overlapping. In such cases, different aspects of the same topic were addressed. This, combined with some inconsistency among panel members, occasionally led to consensus on statements that were, to some extent, mutually exclusive.

This was not a systematic review of all available data and therefore may reflect practices that are idiosyncratic for the panellist. On the other hand, the Delphi panel was selected based on objective criteria intended to provide sufficient experience with VNS therapy including a wide selection of neurologists and paediatric neurologists for the first round to exclude bias. All the panellists were given a possibility to influence how the statements were formulated during the Delphi process to emphasize transparency of the activity. There is a large discrepancy between the number of invited physicians (262) and how many participated in the panel [22]. To be sure that we did not miss any physician who could fulfil the criteria to be part of the panel we sent invitation to all physicians who had been provided with the hardware necessary to adjust VNS and all physicians who had contacted the company providing VNS devices in the Nordic countries with questions about the use of VNS.

5. Conclusions

The recommendations of the Delphi panel emphasize proactive deployment of available stimulation options including build up in duty cycle and the use of rapid cycling as well as increasing the output current if insufficient response with primary target current (Fig. 2). Additionally, the usage of Magnet mode and Autostimulation mode were encouraged. We provide also guidance on how to use the newest stimulation options such as day-and-night and scheduled programming for improved feasibility and tolerability.

Author contributions

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Data availability statement

The data supporting the findings of this study are available upon request from the corresponding author.

Declaration of competing interest

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None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2025.08.014.

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