

# The Use of Vagus Nerve Stimulation (VNS) in the Management of Patients with Difficult-to-Treat Major Depressive Disorder (MDD): An Expert Consensus Statement

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**Purpose:** Substantial evidence supports the effectiveness of implanted Vagus Nerve Stimulation (VNS) in the management of unipolar difficult-to-treat depression (DTD). While the treatment is included in several national and international guidelines, there is limited information to guide clinicians regarding patient selection and use of VNS in clinical practice.

**Patients and Methods:** A group of 32 experts in the use of VNS were identified from the main countries currently providing the treatment globally. A modified Delphi technique was used to document views on 55 statements regarding the goals, patient selection, and use of VNS treatment in routine clinical practice. Statements were rated on a 9-point Likert scale from “strongly disagree” to “strongly agree”. Over the course of three rounds of voting, with statements modified based on anonymous comments from panelists, consensus agreement or disagreement was deemed if at least 75% of panel members scored a statement between 7 and 9, or 1 and 3, respectively.

**Results:** Consensus was reached by the panel on 75% of the statements covering a wide range of issues. There was agreement that the main goals for VNS are long-term management of symptoms and improvement in quality of life, that the treatment is appropriate for all ages of patients and that there are few contraindications.

**Conclusion:** A set of expert recommendations for the use of VNS for DTD was generated. These should be of value to clinicians to ensure current best practices are followed when considering this treatment.

**Keywords:** vagus nerve stimulation, difficult-to-treat depression, major depressive disorder, consensus, Delphi panel

## Introduction

Treatment-resistant depression (TRD) is common, disabling, and often deadly. TRD is usually defined as failure to achieve meaningful benefit from at least two well-delivered trials of antidepressant interventions with established efficacy. However, TRD is heterogeneous, and some patients may experience inadequate benefit despite treatment with a much larger number of antidepressant treatments, including evidence-based psychotherapies, pharmacological augmentation strategies, and neuromodulation interventions with established efficacy in TRD, such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). The extent of treatment resistance predicts both the likelihood of benefit from subsequent interventions and the likelihood of relapse or recurrence if short-term benefit is achieved. Patients with markedly TRD are often excluded from antidepressant clinical trials because they are expected to show limited therapeutic effects. The term difficult-to-treat depression (DTD) refers to this group of patients with markedly TRD in whom depression continues to cause significant burden despite multiple treatment efforts.<sup>1,2</sup> As such it reflects a moment in the care of a patient with depression when there is mutual recognition between the clinician and patient that alternative strategies need to be considered.<sup>1</sup> The concept of DTD also includes patients who display chronic or highly recurrent illness and do not receive adequate treatment trials due to intolerance or psychosocial factors that limit access to potential therapeutic interventions. DTD is common and associated with increased risk of hospitalization and suicidality, health care costs, and mortality compared with treatment-responsive major depressive disorder (MDD) or even TRD.<sup>3–6</sup> The management of DTD is complex and requires a broad bio-psycho-social perspective.<sup>1</sup>

In a non-randomized naturalistic registry study, 5-year follow-up of a cohort of nearly 500 patients with DTD who received cervical Vagus Nerve Stimulation (VNS) adjunctive to treatment as usual (TAU) reported significantly higher cumulative rates of response and remission compared to 300 similar patients who received TAU alone (67.6% vs 40.9%,  $p < 0.001$  and 43.3% vs 25.7%,  $p = 0.001$ , respectively).<sup>7</sup> Other post-hoc analyses demonstrated that VNS led to a greater improvement in patients' quality-of-life (QoL), not fully attributable to improvement in depressive symptoms.<sup>8</sup> The beneficial effects of VNS in DTD leading to clinically meaningful improvements in the domains of depressive symptoms, function, and QoL were recently supported by a large randomized, blinded, sham-controlled, year-long trial, the RECOVER study. Despite not achieving statistical separation on the novel primary outcome metric, the active and sham VNS groups differed on multiple measures within each domain, and especially at assessments late in the 1-year observation period.<sup>9–12</sup>

Implanted VNS is an invasive procedure associated with significant upfront costs. Surgery involves placing a pacemaker-like device under the skin of the upper chest connected to the left vagus in the neck via a wire. The procedure is usually performed under general anesthesia and involves two incisions, one in the chest and one in the neck. Surgery typically takes around 1.5 hours. Its routine use in managing DTD is currently restricted to specialized centers where it is reimbursed or otherwise funded. To date, there is little evidence to inform patient selection for VNS. Patients receiving VNS have had very marked levels of treatment resistance.<sup>13,14</sup> VNS is discussed as a treatment option in a number of national and international guidelines for the management of depression, and while there are some published

guidelines regarding patient selection, there is a relative lack of published information to inform clinicians regarding which patients might respond best, when VNS might be considered and how it should be implemented in clinical practice.<sup>14–20</sup> To address this gap and enhance awareness of current best practices, we undertook a Delphi procedure with a panel of clinical experts drawn from specialist centers with significant experience of providing implanted VNS as a treatment for DTD.

## Materials and Methods

### Composition of Steering Committee and Delphi Panel

The plan to conduct a Delphi process to generate a set of consensus views and recommendations regarding the use of VNS to treat DTD was agreed at a meeting of 10 European and Israeli psychiatrists who met in 2023 to discuss recent evidence and clinical uncertainties around the use of VNS (meeting supported by LivaNova, the company manufacturing the VNS therapy device). It was agreed that the composition of the Delphi panel should include panelists from the countries around the world where VNS is used to treat DTD. The intention was to include individuals who had significant personal experience in using (indexed by having 10–20 plus patients treated with VNS) and/or investigating VNS for DTD. Individuals were identified by the initial group of psychiatrists, with consultation with LivaNova to ensure that all those with significant experience were approached. Four VNS experts from Europe and USA (RHMW, STA, BTB, HAS) agreed to form the VNS expert steering committee (SC). The SC then sent invitations to all identified VNS experts. This invitation to be a Delphi panel member made clear that (a) this invitation was not conditional; (b) the aim was to generate a set of consensus statements using the Delphi approach; (c) all responses would be anonymous; and (d) all panel members would be included as authors of this paper if they wished and provided input into the manuscript and approved the final draft. Consent was implicit based on the experts agreeing to join the panel and by completion of the Delphi questionnaires. Twenty-eight experts agreed to join the Delphi panel (in addition to the 4 SC members). Ethical approval was deemed not to be required due to the survey not involving any patient data or panel member personal information.

LivaNova agreed to provide financial support for the Delphi process but had no input regarding the content of the Delphi process or this manuscript. To further ensure that this effort was industry independent, a third party (VI Research, Dubai, United Arab Emirates) was contracted to provide logistical support for the Delphi process (IT infrastructure to present statements to panelists and record responses; analysis of data). The SC led the project, drafting the initial set of statements, editing the statements prior to rounds two and three, and drafting this manuscript.

### Development of Statements

The statements considered during the Delphi process all pertained to MDD rather than bipolar depression. An initial set of statements regarding the use of VNS were generated during a day-long meeting in June 2023 of 10 European and Israeli psychiatrists (described above). These were further refined at a follow-up meeting in September 2023. The statements and questions were then developed further by the SC based on the existing evidence base. Statements were designed with the expectation by the SC that some would tend towards agreement by the panel, while others would tend towards disagreement. The statements were not intended to be framed as clinical recommendations, but rather as statements about issues in the use of VNS requiring clinical decision-making. Panelists were left to interpret terms in the statements as they saw fit, but their feedback regarding wording was considered when revisions were made before the second and third rounds of voting. Note that the statements were generated, and all rounds of the Delphi process completed, prior to the publication of the first outcome data from the RECOVER trial on 14 December 2024. Fifty-two statements (numbered 1a–e and 2–48) were initially included in the modified Delphi process. Prior to round 3, three statements (numbers 2, 13, and 41) were split into two parts, “a” and “b”, giving a final total of 55 statements. As indicated, all statements were generated and modified independent of industry involvement.

### Delphi Process

Statements were sent to panel members by VI Research, using a dedicated survey platform for the three rounds of voting. Panelists indicated their level of agreement with each statement on a 9-point Likert-type scale (1 = Strongly disagree to 9

= Strongly agree) and provided free text qualitative comments for each statement anonymously during each round. No guidance was given as to how panelists should judge the level of their agreement with the statement. The assumption was that this would be based on an amalgamation of their knowledge of the evidence base and clinical experience.

Consensus on each statement was defined as achieved if  $\geq 75\%$  of the panelists indicated agreement (7–9), neutrality (4–6), or disagreement (1–3). All statements where there was lack of consensus were considered for revision by the SC based on comments of the panelists.

Only panelists who responded to the previous round were able to respond in subsequent rounds. In rounds two and three, panelists were able to see average scores given to statements in the previous round, together with any qualitative comments made (presented anonymously).

Due to the non-interventional nature of the study, and the fact that patient data was not accessed, ethics approval is not applicable to this study.

The study methodology is illustrated in [Figure 1](#).

## Results

The first round of voting commenced on 30 August 2024 and the third round was completed on 9 December 2024.

### Round 1

Twenty-nine out of the 32 (91%) invited panelists completed round 1 with consensus reached on 21 out of 52 (40%) statements. Based on the panelists' comments, the SC members amended the wording on six statements ([Supplementary Table 1](#)).

### Round 2

Twenty-eight out of 29 panelists responded, with consensus achieved on six more statements, bringing the total to 27 (52%). Based on comments provided, the SC amended the wording of most remaining statements, as well as splitting some into two parts to improve clarity. A few statements were removed as they had absolute answers from the literature. The amendments are documented in [Supplementary Table 2](#).

### Round 3

After the 3rd round of voting, in which 27 out of 28 panelists responded, consensus was achieved on 14 more statements, with a total of 41 out of the final 55 statements (75%) achieving consensus. The final results for all statements are shown in [Table 1](#).

## Summary of Delphi Responses

### Goal of VNS Treatment

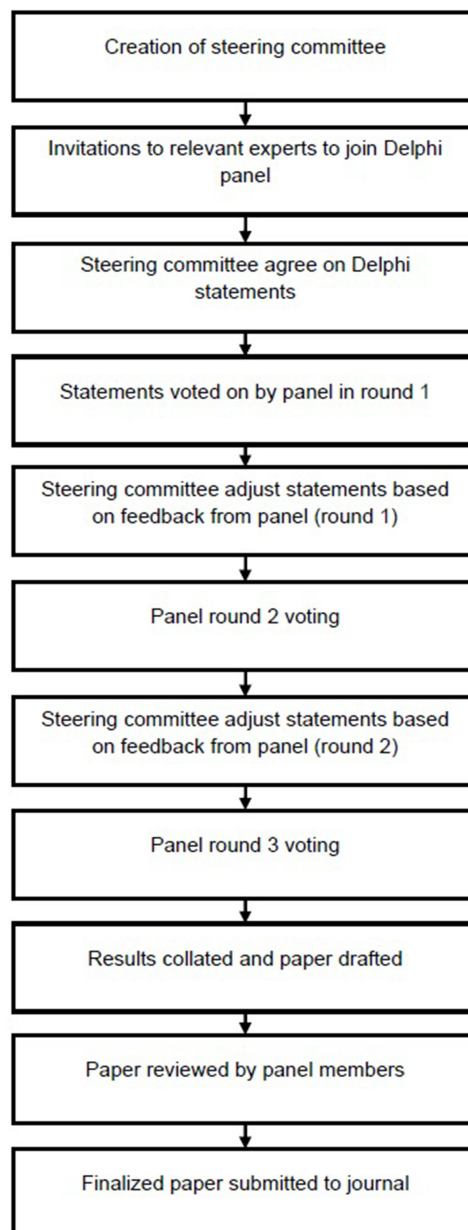
There was agreement that the primary treatment goals relating to VNS treatment for DTD include producing sustained symptom improvement (statement 1b); long-term prophylaxis against relapse (statement 1c); and improving QoL (statement 1d). There was also consensus that acute treatment of current depressive symptoms is not a goal of VNS (disagreement with statement 1a), due to the antidepressant effects of VNS taking several months longer to become evident. Panelists mentioned that in general it should be used in conjunction with more rapidly acting treatments.

There was a lack of consensus as to whether a goal of treatment with VNS is a reduction in excess mortality associated with DTD (statement 1e). While the all-cause mortality rate in those patients treated with VNS plus TAU was less than half that seen in the TAU cohort in the 5-year registry study, the number of actual deaths was small and the difference between treatment groups was not significant.<sup>7</sup> The view of panelists was that there was insufficient evidence to agree to this statement.

### Factors Influencing Patient Selection

#### Demographics

Panelists disagreed that VNS was contraindicated in patients under the age of 22 years (statement 4), though there were views expressed that it is unusual for individuals as young as 22 to have sufficient history of treatment resistance that their MDD be



**Figure 1** Flow diagram of study methodology.

viewed as DTD. There were also comments noting that VNS is used for epilepsy in adolescents and even young children, suggesting no safety concerns. There was a consensus that VNS can proceed without heightened safety concerns in individuals over age 65 (statement 5), with reports of successful treatment of patients aged >85 years. There was disagreement with the statement that VNS is contraindicated in women planning on getting pregnant in the next 5 years (statement 6). Some panelists reported having had patients with a VNS device becoming pregnant for whom no issues arose. However, there were notes of caution due to the lack of evidence regarding effects of VNS on the pregnant mother and unborn child (with the literature restricted to single-case reports mostly relating to women with epilepsy) and suggestions that there should be close perinatal monitoring.<sup>21</sup>

**Table 1** Full List of Statements Showing Scores and Consensus After Up to Three Rounds of Voting

No	Statement	Round consensus Achieved	Consensus Type	Percent Agreed, Disagreed, or Neutral	Average Score	Consensus value
1a	Based on the evidence, one of the goals of VNS treatment for MDD includes the acute treatment of current depressive symptoms	3	Disagree	81.48%	2.81	1
1b	Based on current evidence, a goal of VNS treatment for MDD includes to produce a sustained symptom improvement	1	Agree	93.10%	8.14	9
1c	Based on current evidence, a goal of VNS treatment for MDD includes to provide long term prophylaxis against a depressive relapse	1	Agree	82.76%	7.69	9
1d	Based on current evidence, a goal of VNS treatment for MDD includes to improve quality of life for patients	1	Agree	86.21%	7.83	9
1e	There is some evidence that suggests that one of the goals of VNS treatment for MDD may include a reduction in the excess mortality associated with difficult-to-treat depression (DTD)	N/A	Not achieved	59.26% agree	6.15	7
2a	VNS should not be used if the patient has current suicidal ideation	3	Disagree	92.59%	1.85	1
2b	VNS should not be used if the patient is also acutely suicidal	N/A	Not achieved	42.44% disagree	4.48	1
3	VNS should not be used for patients with chronic suicidality	1	Disagree	89.66%	1.90	1
4	VNS for TRD/DTD is contraindicated in individuals under the age of 22 years	3	Disagree	77.78%	2.48	1
5	VNS should be used with caution in patients over the age of 65 years	1	Disagree	79.31%	2.79	1
6	VNS is contraindicated in any woman planning on getting pregnant in the next five years	3	Disagree	77.78%	2.48	1
7	VNS is contraindicated for patients who may require frequent MRI scans	N/A <sup>a</sup>	Not achieved	42.86% disagree	3.70	5
8	VNS should not be considered for patients with MDD who experience mixed affective episodes	1	Disagree	86.21%	2.76	3
9	VNS should not be used for patients with MDD and comorbid OCD	1	Disagree	75.86%	2.62	1
10	VNS should be used with caution in patients with MDD and significant comorbid GAD	1	Disagree	75.86%	2.62	1
11	VNS should not be used in patients with MDD who have a significant tendency to exhibit anxiety focused on somatic symptoms	3	Disagree	77.78%	2.74	2

(Continued)

Table 1 (Continued).

No	Statement	Round consensus Achieved	Consensus Type	Percent Agreed, Disagreed, or Neutral	Average Score	Consensus value
12	Given the current evidence base, VNS should be used with caution for patients with MDD who have current psychotic symptoms	3	Agree	77.78%	6.78	7
13a	VNS should be used with caution for patients with MDD and a past history of mood congruent psychotic symptoms	N/A	Not achieved	55.56% disagree	4.07	2
13b	VNS should be used with caution for patients with MDD and a past history of mood incongruent psychotic symptoms or a diagnosis of schizophrenia or schizoaffective disorder	N/A	Not achieved	66.67% agree	6.33	7
14	VNS should be used with caution in patients with evidence of that, compared to the MDD that is present, a personality disturbance is the primary driver of a significant proportion of the person's psychosocial functional impairment	3	Agree	85.19%	7.04	7
15	VNS should be used with caution in patients with untreated significant current substance misuse	3	Agree	81.48%	6.96	7
16	VNS should be avoided in patients with a significant history of psychological trauma	1	Disagree	82.76%	2.59	2
17	VNS should be used with caution in patients with untreated sleep apnoea	N/A	Not achieved	44.44% disagree	4.41	3
18	VNS is contraindicated in patients with a left vagotomy	N/A <sup>a</sup>	Not achieved	71.43% agree	7.33	9
19	VNS should be avoided in patients who have not responded to ECT	1	Disagree	100.00%	1.41	1
20	VNS is a good option to consider if a patient has previously shown a response to ECT	1	Agree	79.31%	7.21	9
21	VNS is a good option in patients currently being treated with maintenance ECT	1	Agree	89.66%	7.72	9
22	VNS is a good option to consider in patients being treated with maintenance esketamine or ketamine	2	Agree	92.86%	7.82	8
23	In patients treated with VNS, a history of fewer past antidepressant treatment failures is associated with better response	3	Agree	77.78%	6.89	7
24	In patients treated with VNS, the shorter the duration of the current episode of depression, the better the chance of response	3	Agree	77.78%	6.89	7
25	VNS is a better option for patients with a more recurrent (eg 2–3 plus previous episodes generally shorter than 2 years), rather than chronic (eg single episode lasting longer than 2 years), pattern	N/A	Not achieved	40.74% neutral	5.67	5

(Continued)

**Table 1** (Continued).

No	Statement	Round consensus Achieved	Consensus Type	Percent Agreed, Disagreed, or Neutral	Average Score	Consensus value
26	VNS is a good option for comorbid DTD and epilepsy	1	Agree	79.31%	7.14	8
27	VNS should be considered for any patient with MDD that has not responded to four or more adequate trials of different medications in the current episode	1	Agree	75.86%	6.66	7
28	VNS should be considered for any patient with MDD that has not responded to four or more adequate trials of different antidepressant medications in their lifetime	N/A	Not achieved	70.37% agree	6.11	7
29	VNS should be considered for any patient with MDD that has not responded to four or more adequate trials of different anti-depressants treatments (ie medication/ neurostimulation and/or psychotherapy) in the current episode	3	Agree	81.48%	7.00	7
30	The possible use of esketamine or ketamine should always be considered prior to considering VNS	N/A	Not achieved	44.44% Agree	4.93	7
31	The possible use of TMS should always be considered prior to considering VNS	3	Agree	81.48%	6.81	7
32	The possible use of ECT should always be considered prior to considering VNS	N/A	Not achieved	55.56% agree	5.93	8
33	VNS should be considered for any patient who has had more than 3 episodes of mood disorder in the last 5 years, and/or their current episode has lasted for at least 2 years despite appropriate treatment with at least 4 treatments	3	Agree	81.48%	7.37	9
34	VNS is an option to consider in patients experiencing significant difficulties with long term prophylactic medications (eg experiencing renal impairment on lithium)	2	Agree	78.57%	7.43	8
35	VNS is an option for patients for whom long term prophylactic medication (eg lithium) is contraindicated due to physical health issues (eg renal impairment)	2	Agree	82.14%	7.39	7
36	Detailed discussions of VNS with a patient with MDD should only be done by an individual with expertise of using VNS	N/A	Not achieved	51.85% disagree	4.70	2
37	VNS should be raised and discussed with the patient by their treating psychiatrist prior to referral for a specialist consultation regarding the treatment	2	Agree	75.00%	6.82	8
38	It is best to start discussion about the use of VNS once a patient has recovered from their current episode of illness	1	Disagree	93.10%	1.93	1
39	Patients should be hospitalised for assessment prior to implantation with VNS	1	Disagree	96.55%	1.45	1

(Continued)

Table 1 (Continued).

No	Statement	Round consensus Achieved	Consensus Type	Percent Agreed, Disagreed, or Neutral	Average Score	Consensus value
40	Avoid reducing ongoing medication post VNS implantation for at least a year and then do so cautiously and gradually	2	Agree	75.00%	6.86	9
41a	Once VNS has been implanted ideally leave all current medications unchanged	N/A	Not achieved	55.56% agree	5.67	7
41b	Once VNS has been implanted continue to optimise the patient's pharmacotherapy	3	Agree	85.19%	7.52	9
42	No medications are contraindicated because a patient has VNS	1	Agree	79.31%	7.14	8
43	Patients with VNS should not receive ECT	1	Disagree	93.10%	1.59	1
44	Patients with VNS should not be treated with TMS	1	Disagree	86.21%	1.93	1
45	MRI scans can be safely conducted in patients with VNS	2	Agree	75.00%	6.96	7
46	Surgical diathermy should not be used in patients with VNS	N/A <sup>a</sup>	Not achieved	42.86% neutral	5.74	5
47	If there has been a lack of response to VNS after 1 year, it should be turned off and explanted	1	Disagree	89.66%	2.00	1
48	The time frame to observe maximal benefit can be as long as 18 months	1	Agree	82.76%	7.21	8

**Notes:** Consensus was deemed to have occurred if there was  $\geq 75\%$  of panel members responding who scored the statement 1–3 (disagreeing), 4–6 (neutral), or 7–9 (agreeing). The degree of consensus is indicated by the “stability” score. The direction of the consensus is indicated by the average score (ie if  $\leq 3$  then the consensus was “disagree”, or if  $\geq 7$  then “agree”) and the consensus value (which indicates the choice that received the majority of votes within the consensus range). There was no consensus neutral position for any statement. For statements where consensus was not reached, the stability figure is followed by the most common position of panel members: disagree/neutral/agree.

**Abbreviations:** N/A, not applicable (because consensus was not reached); N/A<sup>a</sup>, not applicable (statements that were withdrawn after round 2. All other statements not reaching consensus were voted on over all three rounds).

## Symptomatology

### Suicidality

The panel of VNS experts agreed that VNS could be used in a patient with DTD and current suicidal ideation (disagreement with statement 2a) or chronic suicidality (disagreement with statement 3). However, there was a lack of consensus on whether VNS should be avoided if the patient is currently acutely suicidal (statement 2b). It was argued by some that acute suicidal risks should be managed before proceeding with VNS, in part because of concerns that an acutely suicidal patient may well not be able to take the long-term perspective required when considering whether to consent to VNS.

### Anxiety

Data from the 5-year registry study of VNS suggests that baseline anxiety does not affect response to VNS.<sup>7</sup> In line with this, panelists felt that there was not any need for caution in using VNS in patients with MDD and significant comorbid GAD (statement 10), OCD (statement 9) or anxiety focused on somatic symptoms (statement 11). However, there were concerns that VNS may not help anxiety, and those with anxiety may experience problematic somatization related to VNS adverse effects. There were comments that experts would use VNS for DTD with secondary OCD, but not primary OCD, due to insufficient data in primary OCD beyond a small open-label study.<sup>22</sup>

### Psychosis

While the RECOVER randomized trial excluded patients with current or lifetime histories of psychotic symptoms, panelists felt that VNS could be used with caution for patients with MDD who have current psychotic symptoms (statement 12).<sup>14</sup> Some experts felt that psychosis is simply a marker of depression severity and so is not a reason to restrict VNS use, while others felt that if the psychosis was not prominent and/or the symptoms were mood-congruent, then there was less concern about using it. Others advised that the psychotic symptoms should first be treated with medications or ECT.

While there was no consensus on whether VNS should be used with caution for patients with MDD and a past history of mood congruent psychotic symptoms (statement 13a), or MDD and a past history of mood incongruent psychotic symptoms or a diagnosis of schizophrenia or schizoaffective disorder (statement 13b), the trend was for the panel to disagree with the former and agree with the latter, consistent with comments made regarding statement 12. There was a view expressed that there may be less concern about a past history of schizoaffective disorder than schizophrenia.

### Comorbidities

The Delphi panel considered a range of physical and mental health comorbidities. There was consensus that there is no reason to avoid using VNS in patients who have either a history of psychological trauma (statement 16) or mixed affective episodes (statement 8). These responses were based on the panelists' view that past trauma does not negatively impact on VNS outcomes and evidence regarding the efficacy of VNS in bipolar disorder.<sup>23</sup> There was also consensus reached in the third round that VNS should be used with caution in patients with untreated current substance use disorder (statement 15) after the wording of the statement had been changed to include the word "untreated". Several panelists reflected that substance use itself was not a contraindication but that there should have at least been some progress in managing this prior to starting VNS.

Many comments were generated by the question of whether a "personality disturbance" (ie, a presentation negatively impacted by personality traits or personality disorder) should lead to caution in using VNS. It was pointed out that it is hard to diagnose a personality disorder in patients with an axis 1 disorder, and that after years of DTD a patient may present with a personality disorder whether or not this was present pre-morbidly. Several panelists suggested that the presence of a personality disorder should be a caution but not contraindication to VNS, and that, if present, it may complicate overall management of the patient's DTD. Consensus was reached in round 3 that there should be caution in using VNS once the wording of the statement had been adjusted to include that the "...personality disturbance is the primary driver of a significant proportion of the person's psychosocial functional impairment".

There was consensus that VNS is a good option for a patient with both DTD and epilepsy (statement 26). However, consensus could not be reached as to whether VNS should be avoided in patients with untreated sleep apnea (statement 17). While there is evidence that VNS can exacerbate sleep apnea, some of the concerns regarding the statement was because of the absolute nature of the word "avoided".<sup>24</sup> Some panelists felt that caution was required rather than VNS being contraindicated, depending on the severity of the sleep apnea and/or whether it has been treated.

### Illness History

There was agreement that VNS should be considered for any patient who has had more than 3 episodes of depression in the last 5 years, and/or their current episode has lasted for at least 2 years (statement 33). Panelists also agreed that in patients treated with VNS, the shorter the duration of the current episode of depression, the better the likelihood of response (statement 24), and that a history of fewer past antidepressant treatment failures is associated with better response (statement 23). However, there was no consensus as to whether VNS is a better option for more recurrent, rather than chronic, MDD (statement 25), reflecting a relative lack of data regarding this distinction.

### General Treatment History

There was agreement that VNS should be considered for any patient with MDD that has not responded to four or more adequate trials of different **medications** in the **current episode** (statement 27) – consistent with the FDA label for VNS Therapy and eligibility criteria for the 5-year cohort study and the RECOVER trial.<sup>7,14</sup> However, there was lack of

agreement on whether this threshold also related to **lifetime treatment** (with 70.4% agreeing, short of the 75% for consensus). Some panelists indicated that four failed antidepressants over a lifetime might not be sufficient to indicate severe DTD and that these patients might still have a good response with less invasive treatments. Panelists similarly disagreed with a threshold for considering VNS as failure to respond to four or more adequate trials of different **anti-depressive treatments** (ie medication/neurostimulation and/or psychotherapy) when this was across the patient's lifetime (statement 29 in rounds 1 and 2) but also when this was in the current episode (adjusted statement 29 in round 3).

There was consistency with the panel agreeing that VNS should be considered an option if a patient is having difficulties with long-term prophylactic medication, for example lithium leading to renal impairment (statement 34), or if such treatments were contraindicated due to pre-existing physical health issues (statement 35).

### Specific Treatment Histories

There was consensus that VNS is a good option to consider for patients being treated with maintenance ECT (statement 21), esketamine, or ketamine (statement 22), in line with published case series.<sup>25,26</sup> While there was consensus that VNS is a good option to consider in ECT responders (statement 20), there was also a consensus that VNS can be used in ECT non-responders (statement 19).

While consensus was reached that TMS should be considered prior to considering VNS (statement 31), this was not the case for ECT (statement 32) or esketamine or ketamine (statement 30). While TMS is perceived as a well-tolerated treatment with little to be lost in offering this to patients with DTD, concerns were raised regarding the tolerability and possible adverse effects of ECT. Some panelists noted that the word "offered" was used in these three statements and hence indicated agreement with them. Others suggested that all three treatments are acute treatments that might be used in parallel, rather than instead of, VNS.

### Cautions

Four statements regarding cautions when using VNS related to information provided in the device's label (see [Supplementary Table 3](#)). While the panel agreed that some types of MRI scans can be conducted safely in patients with VNS (statement 45), no consensus was reached after two rounds for the other three statements and, as these were partly related to issues of "fact", the statements did not proceed to round 3. Statement 7 related to whether VNS is contraindicated in patients who may require frequent MRI scans. The reasons for the lack of consensus regarding this statement as opposed to statement 45 seemed to relate to some uncertainty regarding the frequency that was referred to and comments that it depends on the location and type of MRI.

Statement 18 was that VNS is contraindicated in patients with a left vagotomy, consistent with the VNS Therapy device label (see [Supplementary Table 3](#)). However, consensus on the statement was not achieved. While several panelists said that they assumed a left vagotomy was a contraindication, a few indicated that they had some experience of right-sided VNS. The use of left-sided VNS is generally recommended due to reduced impact on cardiac function relative to right-sided VNS, though in a study where patients with heart failure were randomized to either left- or right-sided VNS, no difference in adverse effects was seen.<sup>27</sup> Statement 46 was that surgical diathermy should not be used in patients with VNS. Again, there was no consensus reached despite the statement in the device's label (see [Supplementary Table 3](#)). Panelists indicated that it may be safe depending on the placement of electrodes, and that bipolar is safer than monopolar diathermy. There are similar concerns regarding the safety of diathermy in patients with any implanted device, such as a cardiac pacemaker or implantable cardioverter defibrillator (ICD) due to a theoretical risk of heating from the diathermy triggering activation of the devices. There is published guidance regarding the use of diathermy for patients with ICDs and this may be appropriate to follow for patients with an implanted VNS device.<sup>28</sup>

### Using VNS

Panelists disagreed that discussion about the use of VNS should start once a patient has recovered from their current episode of illness (statement 38), centered around the view of benefits of VNS being long term and that a long-term plan can reduce anxiety and increase engagement and adherence in patients who are acutely depressed.

While there was no consensus on whether detailed discussions regarding VNS should only be done by an individual with expertise in using it (statement 36), there was agreement that VNS should be raised and discussed with the patient

by their treating psychiatrist prior to referral for a specialist consultation regarding the treatment (statement 37). Comments in relation to statement 36 suggested that more detailed information about VNS, and informed consent for the VNS surgical procedure and follow-up, should be provided by a specialist. Panelists disagreed that patients should be hospitalized for assessment prior to implantation with VNS (statement 39).

Panelists agreed that the time frame to observe maximal benefit can be as long as 18 months (statement 48), with some indicating that even 4–5-year timeframes may be necessary. There was disagreement that VNS should be turned off and explanted if there has been a lack of response after 1 year (statement 47), in part due to the timescales over which increasing benefit of VNS may be seen, that the device can be turned off rather than explanted and that the risks of explantation may out-weigh the benefits of leaving it in situ, including the opportunity of turning the device back on again at some point in the future.

### Using Other Treatments in Patients with VNS

Panelists agreed that reducing ongoing medication should be avoided for at least a year following VNS implantation and then done gradually (statement 40); that once VNS has been implanted, the patient's pharmacotherapy should continue to be optimized (statement 41b); and that no medications are contraindicated because of adjunctive VNS (statement 42).

In terms of neurostimulator treatments, there was consensus that both ECT and TMS can be used for patients after VNS implantation (disagreement with statement 43 and 44 respectively). This points toward using TMS and ECT for acute episodes while using VNS for long-term management. While not included in the Delphi statements, it is believed that in practice the VNS device is turned off (or magnet applied to interrupt treatment) during ECT or TMS treatments.

## Discussion

The study helped to identify current best practices regarding implanted VNS for DTD as determined by an international group of clinical experts. After three rounds of voting, consensus was reached on 41 out of 55 (75%) of statements. For those statements where consensus was not reached, panelists' reasons were generally consistent. The findings of this Delphi process provide guidance on the use of VNS in difficult-to-treat MDD that complements advice for clinicians on setting up a clinic to provide VNS.<sup>29</sup>

## Recommendations Based on the Results of the Delphi Process

The recommendations based on the results from the Delphi process are summarized in [Box 1](#).

## Strengths, Limitations, and Future Directions

The strength of these consensus statements is that they are based on the views of clinicians with significant experience in the use of VNS for patients with DTD from the main countries currently providing the treatment globally. Nevertheless, the Delphi panel was small, including just 32 members, with 27 completing all three rounds of voting. In addition, although all responses were provided anonymously, most members of the panel knew most others well and so the opinions expressed may not be fully independent.

Limitations of the study included a lack of explicit guidance to panelists to rate statements based on a combination of their knowledge of the existing evidence base at the time plus their clinical experience. In addition, some statements included terms without definition (eg “acute” or “several”). The intention was for panelists to respond in a more generic basis rather than focusing on to exactly where cut offs or thresholds should be placed. It is not known how panelists interpreted the phrase “with caution”. The presumption was that it was similar to how the phrase is interpreted when included in the Summary of Product Characteristics (EU) or Package Insert (USA) of a medication.

The consensus statements were all voted on prior to the publication of the main outcomes of the MDD arm of the RECOVER trial.<sup>9,10</sup> Papers on key findings, including on durability of the effect of VNS, remain to be published. However, RECOVER had significant patient exclusions including current or lifetime history of psychotic features in any depressive episode or psychotic disorder, a history of substance use disorder in the year prior to implantation and borderline or other severe personality disorder.<sup>14</sup> In clinical practice, VNS may be used more widely (as reflected in some of the statements included in the Delphi process). A more naturalistic study is the RESTORE-LIFE prospective,

**Box I Recommendations for the Use of VNS in the Management of MDD Based on the Results of the Delphi Process**

<p><b>Goals of VNS therapy</b></p> <ul style="list-style-type: none"> <li>● VNS should not be seen as an acute treatment for MDD due the timescale required to see significant reductions in symptoms.</li> <li>● Patients and clinicians should expect VNS to be associated with sustained symptomatic improvement, long-term prophylaxis from depressive relapse and improvements in quality of life.</li> </ul>
<p><b>Patient selection</b></p> <ul style="list-style-type: none"> <li>● Patient selection should not be restricted with regard to an upper age limit.</li> <li>● VNS should be used with caution in patients with current or a lifetime history of psychotic symptoms due to lack of data. If symptoms are mood-congruent and an expression of the severity of the episode of depression, this is less of a concern than if they are mood incongruent and/or part of a schizophrenic illness.</li> <li>● The presence of mixed affective features is not a contraindication.</li> <li>● Neither current suicidal ideation or past suicidality (the risk of suicide, usually indicated by suicidal ideation or intent) should be considered a contraindication to VNS, though acute suicide risk may need to be managed first.</li> <li>● Comorbid or secondary GAD or OCD should not be considered a contraindication.</li> <li>● Anxiety focused on somatic symptoms should not be a contraindication to VNS, but such patients may present management complexity. For example, adverse effects of the VNS such as tingling around the site of stimulation, voice alteration, or breathlessness on exertion may trigger increased anxiety or even panic attacks.</li> <li>● Past psychological trauma is not a contraindication.</li> <li>● Untreated substance use disorder should usually be treated first.</li> <li>● VNS should be used with caution in patients with a significant personality disorder, especially if this is the primary driver of the patient's impairment.</li> <li>● VNS should be considered a good option for a patient with DTD and comorbid epilepsy.</li> <li>● VNS should be used with caution in patients with sleep apnea, especially if severe and currently untreated.</li> <li>● The possibility of a future pregnancy should not be considered a contraindication to VNS being used in a woman who may become pregnant. However, it is noted that there is limited data regarding outcomes and safety of VNS for mothers and infants exposed during pregnancy. Clinicians should seek further information from the manufacturer.</li> <li>● For patients without a left vagus nerve, it may be possible to undertake VNS of the right-sided nerve, but this is contrary to the label and there are limited data regarding the safety and efficacy of this variation.</li> <li>● In terms of treatment history: <ul style="list-style-type: none"> <li>a. VNS should be considered if the patient has had more than three episodes in 5 years and/or the current episode lasting more than 2 years, with failure to respond to at least four adequate trials of antidepressants in the current episode.</li> <li>b. Patients with shorter durations of current episode and fewer past treatment failures may do better than those with longer durations and more treatment failures.</li> <li>c. VNS should be considered in patients who are experiencing adverse effects or have physical comorbidities limiting use of prophylactic medication.</li> <li>d. VNS should be considered for patients currently receiving maintenance ECT, esketamine, or ketamine.</li> <li>e. Past ECT response may indicate a greater chance of a good outcome with VNS, but ECT non-response is not a contraindication to VNS.</li> <li>f. TMS should be considered prior to VNS. It may also be prudent to consider ECT, esketamine, and ketamine. However, these treatments should also be considered for use acutely in parallel to implantation of a VNS device.</li> </ul> </li> </ul>
<p><b>Managing patients before and after VNS implantation</b></p> <ul style="list-style-type: none"> <li>● The possible use of VNS should be raised and discussed with the patient by their treating psychiatrist, with more detailed information provided, and consent obtained, by a specialist in VNS.</li> <li>● There is no need to wait until the current acute episode of depression has resolved before discussing VNS.</li> <li>● Hospitalization should not be considered essential for assessment for VNS.</li> <li>● Patients should be advised that maximal benefit of VNS treatment may take 18 months or longer and that lack of response at 1 year is not justification for explantation.</li> <li>● Explantation should not be considered essential if the device is deemed not to have led to benefit.</li> <li>● Post implantation, treatment for the acute depressive episode should be optimized as needed. No medication is contraindicated with VNS, and both TMS and ECT can be administered in patients with implanted VNS. The VNS device should be turned off during ECT or TMS treatment sessions.</li> <li>● If a patient shows a good response to VNS, avoid reducing dosage or withdrawing psychiatric medications for at least a year and then only do so gradually.</li> <li>● MRI scans can be safely conducted for most parts of the body in a patient with VNS: the specific guidance provided by the manufacturer should be followed.</li> <li>● The risk of excessive heating of implanted device components should be considered when surgical diathermy is used in a VNS patient; this risk is less with bipolar than monopolar diathermy, and the risk depends on where in the body the diathermy is being applied.</li> </ul>

observational, European multi-site, post-market study of VNS therapy added to ongoing usual treatment in patients with DTD.<sup>30</sup> Both RECOVER and RESTORE-LIFE studies are following patients treated with VNS for up to 5 years. As a result, it will take time for clinicians to digest the RECOVER and RESTORE-LIFE data and integrate them into their knowledge and experience base when using VNS clinically. It remains to be seen what impact these studies might have in modifying the views of the panelists. The consensus statements specifically related to patients with MDD, rather than bipolar disorder. While there is evidence that VNS has similar efficacy in bipolar depression and MDD, pending the completion of recruitment to the bipolar arm of the RECOVER study, there are less data on this subtype of affective disorders.<sup>1,14</sup> An additional important area of future research into VNS therapy for DTD are mechanistic studies

exploring neurobiological correlates of response to help identify predictive biomarkers – of particular relevance for an invasive long-term treatment.

## Conclusion

A Delphi process, involving a panel of global experts, successfully generated a set of consensus statements about the clinical use of VNS for the management of DTD in the context of MDD. The consensus views were based on integration of the Delphi panel's knowledge of the evidence base and their clinical experience in using VNS in this population. The outcome is a set of recommendations regarding patient identification and clinical use of VNS in this patient population that is, to our knowledge, more detailed than any other current guideline worldwide.

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In the past 24 months, Dr. Murrugh has provided paid consultation services for Autobahn Therapeutics, Inc., Biohaven Pharmaceuticals, Inc., Cliniclabs, Inc., Clexio Biosciences, Ltd., Compass Pathfinder, Plc., Dr Jay, Frontier Pharma, LLC, Janssen Pharmaceuticals, LivaNova, Plc., Merck & Co., Inc., Otsuka Pharmaceutical, Ltd, WCG Clinical, Inc., and Xenon Pharmaceuticals, Inc. ZN is a consultant to LivaNova, Turing Medical, Magnus Medical, and Motif and has also received research support from LivaNova. CBN is supported by the National Institute of Mental Health, and the National Institute of Alcohol Abuse and Alcoholism. 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