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Research paper

Baseline characteristics of a European patient population with difficult-to-treat depression (RESTORE-LIFE) treated with adjunctive vagus nerve stimulation

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ABSTRACT

Background: Major depressive disorder is a complex heterogeneous disorder. Treatment is especially challenging for patients with "difficult-to-treat depression" (DTD): a less stigmatizing and more clinically relevant framework defining depression that continues to cause significant burden despite usual treatment efforts.
Methods: RESTORE-LIFE is a prospective, observational, multicenter, post-market study being conducted in Europe and is designed to reflect real-world clinical application of adjunctive Vagus Nerve Stimulation Therapy (VNS) for DTD. Baseline characteristics of RESTORE-LIFE patients were analyzed and compared to published treatment-resistant depression (TRD) trials.
Results: This analysis includes the initial 98 RESTORE-LIFE patients who commenced treatment with VNS. Patients had a mean of 11.4 failed anti-depressant treatments, 1.1 suicide attempts, 87 % had prior electroconvulsive therapy, and 36 % had an endocrine/metabolic comorbidity. On average, disease severity was comparable to that in TRD trials (n = 15,463). However, RESTORE-LIFE patients appear to have been experiencing DTD for a longer duration and their DTD was characterized by a lack of positive mental health and meaningfulness of life, to a greater degree than by excess of negative mood. Despite high comorbidity rates in RESTORE-LIFE, VNS implantation was performed safely with no discontinuations due to surgical adverse events.
Limitations: RESTORE-LIFE enrolls any patient receiving adjunctive VNS for DTD. Prescription of VNS may be biased by differences in practices amongst sites and countries.
Conclusions: The present analysis offers insight into contemporary real-world use of VNS Therapy for DTD in Europe representing a comprehensive characterization of DTD and how this population may differ from those in the TRD literature.

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1. Introduction

Major depressive disorder (MDD) is a common, burdensome, and complex disorder. This complexity is at least partially due to the heterogeneity of the patient population.

Firstly, qualitative differences within a patient population can be remarkably great based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD. For example, a patient with MDD may have decreased appetite and another patient with MDD may have increased appetite; or one could suffer from depressed mood and four additional symptoms, while the other could suffer from anhedonia and four other symptoms (Fried, 2015).

Secondly, quantitative (clinical) differences within different patient populations can be remarkably great, such as duration of previous treatments, baseline severity, and accepted comorbid conditions that vary from study to study. Notably, the duration of each treatment step can vary from country to country and even from region to region. For example, the duration of the first step of treatment for MDD in the United Kingdom (UK) was >16 weeks in 27 % of patients in a Newcastle sample, 49 % of an Oxford sample, and 59 % of a London sample (Day et al., 2021).

Thirdly, sociodemographic characteristics can differ substantially between studies and are well known to influence the clinical outcome (Demyttenaere et al., 2009; Sinyor et al., 2010). For example, the mean age in different samples of patients with treatment-resistant depression (TRD) from different centers including Oxford, London, Newcastle, Israel, and a European TRD cohort study, varied between 39 and 51 years (Day et al., 2021; Heerlein et al., 2022; Sharman Moser et al., 2022).

Fourthly, patients in randomized clinical trials (RCTs) with specific study entry criteria are poorly representative of patients in clinical practice, and therefore, it is challenging to translate findings from the 'gold standard' placebo controlled RCTs to clinical practice. For example, it has been reported that <20 % of clinic patients meet the entry criteria for RCTs, thereby, underscoring the need for real-world, observational, and naturalistic studies (Demyttenaere et al., 2009; Wisniewski et al., 2009; Zimmerman et al., 2002).

Fifthly, important concerns exist about assessment questionnaires utilized for MDD. From the content of 'gold standard' depression rating scales Hamilton Depression Rating Scale (HAMD) or the Montgomery Åsberg Depression Rating Scale (MADRS), and what patients expect from treatment to differences in observer-rated and self-rated assessments of severity and of changes in severity. Moreover, the specificity of some standard questionnaires has recently been questioned. Comparable scores on depression rating scales are often not sensitive to important differences in symptom profile. For instance, the Patient Health Questionnaire-9 (PHQ-9), that closely mirrors DSM criteria for MDD, seems to assess general distress rather than specific depressive symptoms. Improvement on PHQ-9 scores were indeed comparable in patients treated for depression, depression with comorbidities, post-traumatic stress disorders, schizophrenia, personality disorders, alcohol use disorder, or illicit drug use disorders (Katz et al., 2021). Moreover, there is growing awareness that when assessing outcomes, measures should go beyond symptoms and that lack of interest and pleasure, as well as lack of positive affect, are not sufficiently represented in standard depression scales, despite being a core DSM criterion for MDD. In this context, levels of social functioning, quality of life (QoL), and meaningfulness of life have gained interest as clinically relevant outcome metrics (Carpiniello et al., 1997; Demyttenaere et al., 2009; Zimmerman et al., 2002), being arguably more relevant proxy measures of overall health.

All of the above are particularly relevant for the significant proportion of patients suffering with MDD who do not achieve sustained response to treatment (Rush et al., 2006). These patients are often classified as suffering with TRD, a widely reported concept, despite the lack of consensus on definition. TRD is often categorically defined as inadequate response to two different appropriate antidepressant treatment trials (Brown et al., 2019). Although in many trials, variations on this definition are used: thresholds for inclusion vary from one failed trial to up to four failed treatments (Gaynes et al., 2020). This supports the idea that we should move from a more categorical approach (YES or NO for TRD) to a more dimensional approach as seen in the TRD staging models (Sackeim et al., 2019). Importantly, few definitions seldom mention treatment modalities other than pharmacotherapy, such as psychotherapy and neuromodulation (Brown et al., 2019). The lack of a clear and universally accepted definition of TRD is an important source of heterogeneity in the literature.

Different psychotherapeutic, pharmacological, and neuromodulation treatments have been proposed for this heterogeneous patient population, despite the little empirical evidence regarding at which stage to prescribe certain treatment modality (Sackeim, 2021). This has important implications for clinical management, as TRD is often used to delineate patient populations and to stratify and regulate access to more specialist or invasive treatments.

Regulatory approval for a threshold giving access to certain treatment options is also variable and apparently rather arbitrary. Quetiapine was approved as an add-on treatment for patients with MDD who have shown "suboptimal response" to antidepressant monotherapy (Tran and Argaez, 2020). Esketamine is indicated, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI), for patients with TRD who have not responded to at least two different treatments with antidepressants in the current moderate to severe depressive episode (Vasiliu, 2023). Repetitive transcranial magnetic stimulation (rTMS) is indicated for patients with MDD who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode (EUnetHTA, 2017). Vagus Nerve Stimulation (VNS Therapy) was approved in the European Union in 2001 for the adjunctive long-term treatment of chronic or recurrent depression in patients who are in a 'treatment-resistant or treatment-intolerant' major depressive episode. Therefore, there are four different target population definitions available for treatments that arguably target similar or overlapping groups of patients in real-world practice, even if at different stages of a hypothetical treatment pathway.

The concept of difficult to treat depression (DTD) has been developed to offer a less stigmatizing and a more clinically relevant framework (McAllister-Williams et al., 2020; Rush et al., 2019). The definition of DTD is that of "depression that continues to cause significant burden despite usual treatment efforts." This embraces the heterogeneity of clinical scenarios as well as health care settings. Perhaps the most relevant advantage of DTD over TRD is the conceptual change from the management of acute episodes to a chronic disease model (such as used in the management of diabetes or hypertension), where it is understood that the optimal management of symptoms—even to the point of symptomatic remission—does not eliminate the risks of relapse. Furthermore, it acknowledges the importance of multidisciplinary approaches, giving equal weight to biological approaches as well as social and psychological interventions, and focusing on overall QoL outcomes for patients.

VNS Therapy is an implantable neurostimulation treatment approved for the treatment of DTD—either MDD or bipolar disorder—in patients who did not find benefit or were unable to tolerate several treatment modalities including psychotherapy, pharmacotherapy, and/or electroconvulsive therapy (ECT). The American Psychiatric Association as well as the Canadian Guidelines for the management of MDD recommend VNS as a long-term adjunctive treatment option or as a maintenance strategy for long-term disease management in these patients with DTD (Gelenberg et al., 2010; Milev et al., 2016). The National Institute for Health and Care Excellence (NICE) in the UK has stated that VNS Therapy may be used for TRD when there are "special arrangements for clinical governance, consent, and audit or research" (NICE, 2020). A recently published article proposed that selection of patients for VNS Therapy should consider global treatment history, service

utilization, and ECT treatment history, arguably making the population of patients implanted with VNS Therapy to have a high disease burden (McAllister-Williams et al., 2021).

RESTORE-LIFE is a prospective, observational, multicenter, post-market study evaluating the effectiveness and efficiency of adjunctive VNS Therapy in patients with DTD. The study is being conducted at multiple centers in Europe. Inclusion in RESTORE-LIFE is compatible with the requirements for inclusion of patients in a clinical study of VNS Therapy in the UK. Therefore, the RESTORE-LIFE study population represents a multicenter naturalistic sample of patients with DTD in Europe.

The present study aims to describe the baseline clinical characteristics of the initial patients enrolled in RESTORE-LIFE. The relations between these clinical characteristics are investigated and compared with published TRD treatment trials and the TRD Registry which is a registry of TRD patients who received adjunctive VNS Therapy or only treatment-as-usual (TAU) in Studies D23 and D21 in the USA (Aaronson et al., 2017; Li et al., 2021; Nunez et al., 2022). Additionally, our study aims to offer insight into the safety of the surgical implantation of VNS Therapy in patients with DTD in a real-world clinical setting by assessing adverse events in implanted patients who received the first dose of stimulation.

2. Methods

RESTORE-LIFE is a prospective, observational, multicenter, post-market study in patients with DTD where there has been a clinical decision to use adjunctive VNS Therapy. The primary objective is to assess short-, mid- and long-term clinical outcomes following VNS Therapy. The present analysis includes patients who were experiencing a major depressive episode at the time of enrolment based on a baseline MADRS total score $\geq$ 20 which is considered equivalent to moderate to severe depression. The study protocol design and rationale have been described previously (Young et al., 2020). Enrollment was initiated in December 2017. The study is registered at ClinicalTrials.gov (Identifier NCT03320304).

2.1. Study participants

Participants with a primary diagnosis of MDD or bipolar affective disorder were identified clinically as appropriate to receive VNS Therapy based upon a lack of satisfactory response to an adequate number of antidepressant treatments, as per local clinical guidelines and practices. In addition, participants also met the following criteria: aged 18 years or older, with a documented diagnosis of chronic (>2 years) or recurrent (two or more prior episodes) major depressive episode. All patients with unipolar depression were receiving at least one antidepressant treatment, such as antidepressant medication, maintenance ECT, or psychotherapy. All patients with bipolar affective disorder were receiving at least one mood stabilizer, such as lithium, anticonvulsant, or second-generation antipsychotic.

2.2. Study design

During the baseline visit, each study participant's diagnosis of depression (primary diagnosis of MDD or bipolar affective disorder) and comorbid diagnosis was confirmed using the Mini-International Neuropsychiatric Interview (MINI). The MADRS was used to assess the severity of depressive symptoms over the previous week. The modified Antidepressant Treatment History Form (ATHF) was used to assess the adequacy and response to previous antidepressant treatments, for current and past episodes.

All patients completed self-reported questionnaires, including the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR), Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), the five-level EuroQoL instrument (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire for Depression (WPAI-D), and Leuven Affect and Pleasure Scale (LAPS) using an electronic patient reported outcome (ePRO) system (Demyttenaere et al., 2019; Herdman et al., 2011; Reilly et al., 1993; Rush et al., 2003; Stevanovic, 2011). Optional assessments, including the Altman Self-Rating Mania Scale (ASRM), THINC-Integrated Tool (THINC-it), and Generalized Anxiety Disorder Assessment 7 item version (GAD-7), were completed by a subset of the study participants based upon the clinician's clinical judgement and site interest (Altman et al., 1997; McIntyre et al., 2017; Spitzer et al., 2006).

Information collected at baseline included demographics, psychiatric history, prescribed treatments, diagnoses of special interest including cardiovascular disease, chronic pain, diabetes, asthma, chronic obstructive pulmonary disease, epilepsy, inflammatory bowel disease, and ulcerative colitis, as well as information on healthcare utilization related to DTD and comorbidities.

Information on all adverse events (AEs), VNS Therapy related AEs, and device deficiencies were collected using the study's electronic Case Report Form (eCRF). Relationship to the implant procedure, device and/or stimulation, unexpectedness, as well as the seriousness of all serious adverse events (SAEs) were assessed by both the study clinician and the study sponsor. Quality control and data validation procedures were applied to ensure the validity and accuracy of the clinical database.

2.3. Search strategy and data extraction from published trials

Published TRD trials were identified from two recent systematic reviews and meta-analyses of pharmacological augmentation and neuromodulatory treatments (Li et al., 2021; Nunez et al., 2022). All articles were written in the English language. Publications were excluded if they met any of the following criteria: full text article was not available; bipolar patients were included in the sample but without a clear description of the cohort proportion; or the study was concerning VNS Therapy.

2.4. TRD registry

The TRD Registry was a registry of TRD patients who received adjunctive VNS Therapy or only treatment-as-usual (TAU) in Studies D23 and D21 in the USA (Aaronson et al., 2017). The studies were registered: ClinicalTrials.gov NCT00320372 and NCT00305565.

2.5. Statistical analyses

Descriptive statistics were used to describe the demographics, clinical characteristics, and safety measures. For continuous variables, number of non-missing observations, mean, standard deviation (SD), minimum and maximum values, median, and quartiles were calculated. For categorical variables, count and proportions were calculated.

Correlation analysis was performed to evaluate the relationship between the rating scale scores, using Pearson correlation coefficients, along with a heat map based on the correlation coefficients.

A generalized linear regression analysis was conducted to investigate the relationship between the LAPS item "I feel my life is meaningful" with other rating scale scores, including scores for MADRS, GAD-7, WPAI total activity, and the other domains from LAPS.

AEs were summarized based on the number and proportion of participants with at least one AE in the respective reporting category.

3. Results

3.1. Enrollment in RESTORE-LIFE

At the time of this analysis, 108 patients with DTD had provided informed consent to participate in RESTORE-LIFE at 15 clinical study sites in four countries (Austria, Belgium, Germany, and UK). Of these, 5

patients terminated their study participation before the implant visit, 2 patients had yet to undergo implantation at the time of analysis, and 1 patient did not meet the adjunctive therapy criterion (not receiving any antidepressant or mood stabilizing treatments).

Of the remaining 100 patients who had completed the baseline visit and undergone implantation of VNS Therapy, 2 patients had not yet received the first dose of stimulation at the time of this analysis. The remaining 98 patients include 74 patients (69 %) enrolled in Germany, 9 patients (8 %) in Austria, 8 patients (8 %) in the UK, and 7 patients (7 %) in Belgium.

3.2. Review of TRD treatment trials

For comparison with the results from RESTORE-LIFE and the TRD Registry, a review was conducted of the baseline characteristics of patients included in published TRD treatment trials (Aaronson et al., 2017).

We identified 122 unique trials described as analyzing samples of patients with TRD (Li et al., 2021; Nunez et al., 2022). Seven trials were excluded from the analyses for the following reasons: full text articles were not available (3 trials); there was no information on the proportion of bipolar patients in the study sample (3 trials); or because the trial was evaluating VNS Therapy (1 trial). Therefore, we reviewed the results from 115 TRD trials with a total sample of 15,463 patients. Detailed information from the 115 included studies is provided in Supplementary Table S1.

Only 8 of the included trials involved patients with bipolar depression and therefore, an underlying diagnosis of bipolar affective disorder.

Many of the variables of interest were either not reported or only provided as thresholds (eg, the number of previous episodes of depression being reported as $\geq$2) and hence not available for analysis. There was also heterogeneity amongst some variables, specifically 'failed lifetime treatments' which was reported in several different ways across studies, including: number of past anti-depressants, number of prior trials, number of treatments, and listing of individual antidepressants participants had previously received. Where possible, baseline severity scores were converted to MADRS scores.

Pooled demographic and baseline characteristic data from the TRD review are provided in Supplementary Table S2. The mean total duration of illness (15.5 $\pm$ 7.0 years) and the mean total duration of the current episode (21.6 $\pm$ 35.4 months). If duration of illness was not reported but could be inferred from the mean age of study participants, the mean age of onset of current episode, and the episode duration, then it was included. It should be noted that for both variables, especially the duration of the current episode there is a very large variation between studies; the duration of illness ranged from 0.9 to 30.2 years and the duration of the current episode ranged from 2.5 to 166 months.

3.3. Patient profiles from RESTORE-LIFE, TRD trials review, and TRD registry

Patient demographics and baseline clinical characteristics are summarized in Table 1 for the initial 98 patients in RESTORE-LIFE, the patients from the 115 TRD trials that were reviewed, and the patients who were included in the TRD Registry (Aaronson et al., 2017).

A comparison of the baseline characteristics in the RESTORE-LIFE patients versus the total patients in the TRD Registry and the patients in the reviewed TRD trials, showed that the RESTORE-LIFE patients had a higher mean age at baseline (50.5 years, vs 49.9 and 44.0 years), a lower proportion of female patients (60 %, vs 71 % and 65 %), and a higher proportion of white patients (99 %, vs 95 % and 87 %). In the RESTORE-LIFE sample, the body mass index (BMI) was 28.4 kg/m^2, compared with 31.5 kg/m^2 in the TRD Registry sample (data was not available from all reviewed TRD trials).

The mean age at onset of depression in the RESTORE-LIFE sample (27.6 years) was similar to the reviewed TRD trials (28.3 years) and higher than the TRD Registry (21.0 years). On the other hand, the proportion of patients with bipolar disorder in the RESTORE-LIFE sample (26 %) was similar to the TRD Registry (26 %) and higher than the reviewed TRD trials (7 %).

The 3 patient cohorts were similar in terms of baseline severity of depressive symptoms (mean MADRS score ranging from 27.9 to 31.3). In addition, the diagnoses in the RESTORE-LIFE sample were comparable to those in the TRD Registry: 63 % with recurrent unipolar major depressive disorder, 11 % with single episode major depressive disorder, 17 % with bipolar affective disorder type I (with a current depressive episode) and 8 % with bipolar affective disorder type II (with a current depressive episode). In the TRD Registry, the same proportions were 58 %, 15 %, 18 % and 10 % respectively.

Notably, comorbidities that are frequently an exclusion criterion in RCTs of patients with TRD, was common in the RESTORE-LIFE sample. About 35.7 % of patients had a diagnosis of endocrine metabolic comorbidity of which more than half (51.4 %) were diagnosed with hypothyroidism. The second most frequent endocrine/metabolic diagnosis (14.3 %) was hypercholesterolemia. Cardiovascular diagnoses were the second most common category of comorbidities, occurring in 33.5 % of patients in the RESTORE-LIFE sample. Of these cardiovascular diagnoses, hypertension was most common (45.5 %). The third most common category of comorbidities was diagnoses of neurological or psychiatric diseases (beyond major depressive or bipolar disorder),

Table 1
Baseline characteristics of the RESTORE-LIFE sample in comparison to the samples of the TRD Registry and the review of TRD trials.

Baseline characteristic	RESTORE-LIFE (N = 98)	TRD Registry [1]			Review of 115 TRD trials [2] (N = 15,463)
		VNS + TAU (N = 494)	TAU (N = 301)	Total (N = 795)	
Mean age (SD), years	50.5 (12.2)	48.9 (10.1)	49.9 (11.1)	49.3 (NA)	44.0 (6.4)
Female, %	60 %	71 %	70 %	71 %	65 %
White, %	99 %	97 %	91 %	95 %	87 %
Mean age (SD) at onset of depression, years	27.6 (13.9)	20.9 (11.8)	21.1 (11.4)	21.0 (11.6)	28.3 (6.4)
Mean age (SD) at diagnosis of depression, years	33 (12.8)	28.9 (10.8)	29.5 (11.9)	29.1 (11.2)	NA
Number of patients with bipolar disorder, %	26 %	27 %	24 %	26 %	7 %
Mean number of major depressive episode (SD)	NA	14.9 (24.1)	12.0 (23.9)	13.5 (24)	4.5 (1.9)
Mean number of failed treatment trials (SD)	11.4 (6.6)	8.2 (3.3)	7.3 (2.9)	7.9 (3.2)	5.5 (4.1)
Number of patients with prior electroconvulsive therapy (ECT), %	87 %	57 %	40 %	49 %	22 %
Mean number (SD) of psychiatric hospitalizations within 5 years prior to enrolment	NA	3.0 (4.6)	1.9 (4.7)	2.5 (4.7)	1.7 (1.9)
Mean number (SD) of suicide attempts	1.1 (2)	1.8 (4.0)	1.2 (2.4)	1.6 (3.5)	1.5 (2.4)
Mean MADRS score (SD)	30.4 (9.0)	33.1 (7.0)	29.4 (6.9)	31.3 (7)	27.9 (5.1)

Abbreviations: MADRS, Montgomery Åsberg Depression Rating Scale; NA, not available; SD, standard deviation; TAU, treatment as usual; TRD, treatment resistant depression; VNS, vagus nerve stimulation.
[1] TRD Registry: D23 (NCT00320372) and D21 (NCT00305565) combined (Aaronson et al., 2017).
[2] The review includes data from 115 individual trials of treatments for TRD (none of these trials included VNS Therapy).

which occurred in 25.5 % of patients. Within this group of comorbidities, the most common diagnoses were epilepsy and migraine, both occurring in 12 % of patients.

A striking difference was evident in the number of previous failed antidepressant treatment trials and the proportion of patients who had previously received ECT. In RESTORE-LIFE, patients had a mean of 11.4 failed antidepressant treatment trials which was higher than the TRD Registry (mean of 7.9 trials) and almost double that of the sample from the review of TRD trials (mean of 5.5 trials) (Table 1). Furthermore, in RESTORE-LIFE, most patients (87 %) had a history of prior ECT which was almost double the proportion in the TRD Registry (49 %) and almost four times the proportion in the reviewed TRD trials (22 %).

3.4. Psychiatric diagnoses determined by MINI

Primary diagnoses based on MINI are presented in Fig. 1. It is noteworthy that the MINI revealed that 8.2 % of patients in this RESTORE-LIFE sample had a mood disorder with psychotic features and 5.1 % had a psychotic disorder; both of which were exclusion criteria in the TRD Registry.

3.5. Suicide attempts and suicidal ideation

The mean number of prior suicide attempts were slightly lower in the RESTORE-LIFE patients (mean of 1.1 attempts) compared with the TRD Registry (mean of 1.6 attempts) and TRD trials (mean of 1.5 attempts) (Table 1).

With regards to current suicidal ideation in the RESTORE-LIFE sample, there were differences between clinician-rated and self-rated measures: study clinicians scored 25 % of the patients as suicidal based on the MADRS Item 10, while 41 % of patients reported suicidal thoughts on the QIDS-SR Item 12.

3.6. Assessment tools utilized in RESTORE-LIFE

A heat map of the Pearson correlation coefficients between the LAPS component scores and other rating scales' scores is provided in Fig. 2. The total QIDS-SR score had stronger correlations with all LAPS component scores than the MADRS or GAD-7. The MADRS, QIDS-SR, GAD-7, Q-LES-Q and WPAI scores had the strongest correlation with LAPS negative affect, while the EQ-5D-5L-VAS score had the strongest correlation with the LAPS 'I feel happy' component. Suicidality assessment (MADRS Item 10) had the strongest correlation with LAPS 'I feel my life is meaningful' component. The MADRS, QIDS-SR, GAD-7, WPAI, and LAPS negative affect and Q-LES-Q scores were strongly correlated. The LAPS 'I feel my life is meaningful' score was strongly correlated with LAPS positive affect, LAPS hedonic tone and LAPS 'I feel happy' scores.

In a regression analysis with LAPS 'I feel my life is meaningful' score

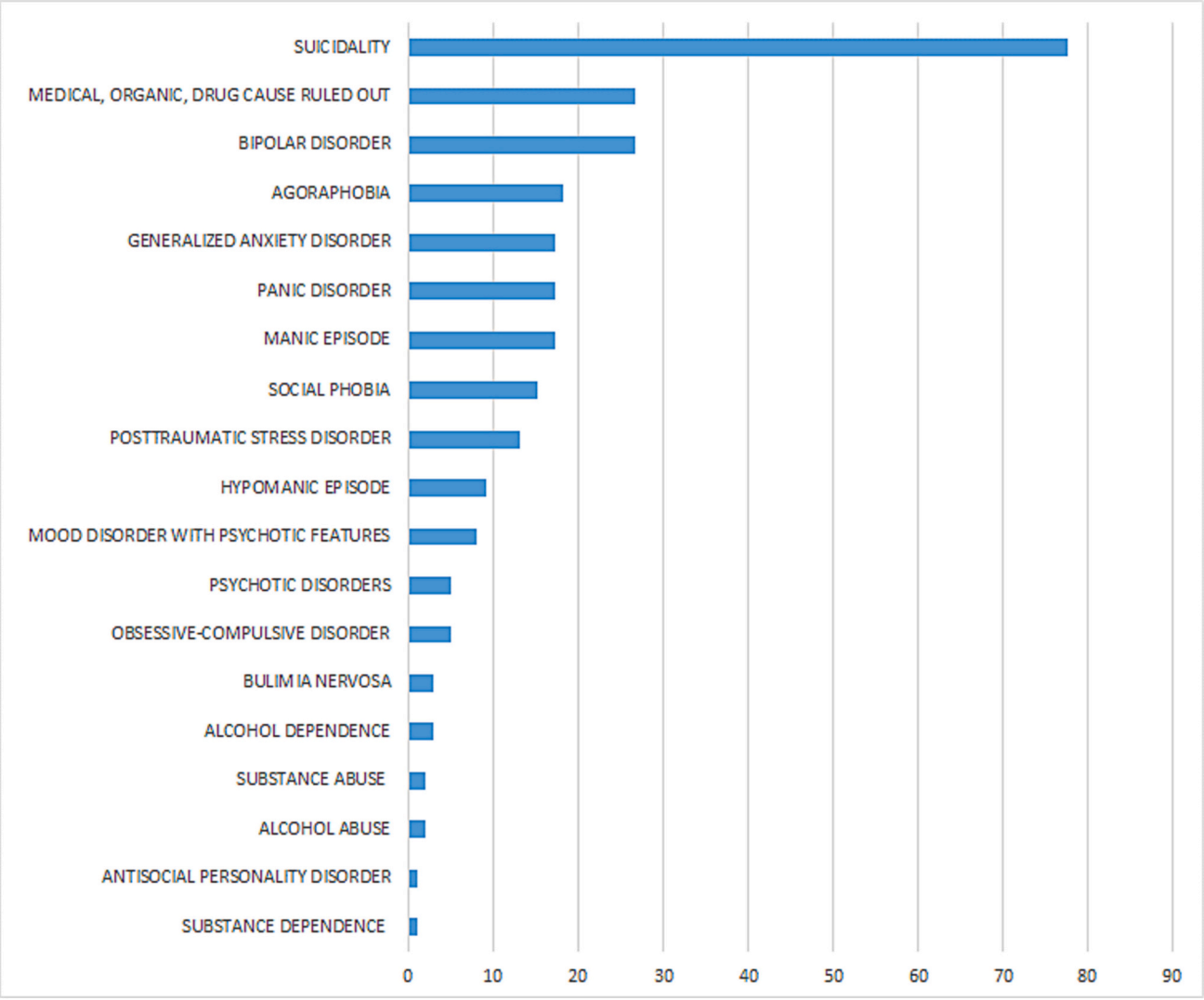

Fig. 1. Proportion of patients in RESTORE-LIFE with comorbid psychiatric diagnoses determined by the Mini-International Neuropsychiatric Interview (MINI).

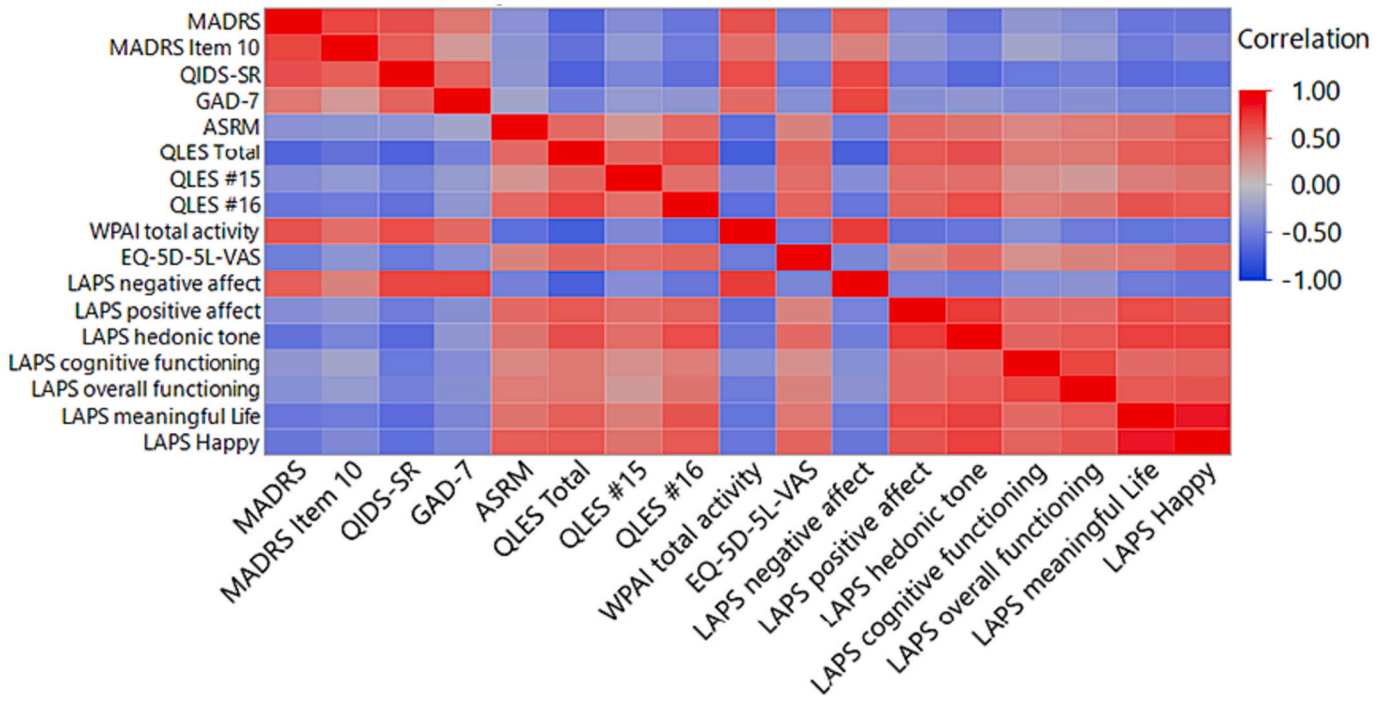

Fig. 2. Heat map of Pearson correlations between different instrument scores.

as a dependent variable and the MADRS, GAD-7, LAPS negative affect, LAPS positive affect, LAPS hedonic tone, LAPS cognitive functioning, LAPS overall functioning, and WPAI total activity scores as independent variables; the LAPS positive affect score was the only significant predictor of the LAPS 'meaningfulness of life' score (estimate 0.51, 95 % confidence interval 0.18–0.85, $P = 0.003$, R2 = 0.24).

3.7. Safety related to implantation surgery

Surgical safety was assessed by examining AEs related to the surgical procedure in the 98 patients who underwent VNS implantation and received a first dose of stimulation.

A total of 19 patients (19.8 %) reported 29 AEs that were either classified as related to the surgical procedure ($n = 25$) or the relationship to the surgical procedure was unknown ($n = 4$).

The AEs related to the surgical procedure were dysphonia ($n = 6$), dyspnea (n = 4), pain at the electrode site during stimulation (n = 4), stiff neck ($n = 1$), anxiety related to surgery (n = 1), left sided vocal cord paralysis (n = 1), seroma (n = 1), cough (n = 1), sleep apnea (n = 1), akathisia (n = 1), post-operative wound infection (n = 1), facial spasm (n = 1), abdominal pain with C-reactive protein elevation (n = 1), and mild dysphagia with vocal cord paresis (n = 1). In most patients who experienced AEs related to the surgical procedure (15 out of the 19 patients), AEs occurred within 30 days of implantation.

Of the four AEs where the relationship to the surgical procedure was unknown, one AE (intermittent feeling of pressure on the larynx and speech problems once a week) was classified as being related to the VNS Therapy stimulation. The remaining 3 AEs (headache, myelitis, and recurring orthostatic dysfunction) were classified to be unknown with regards to their relation to the stimulation.

Serious AEs related to the surgical procedure were reported in 3 patients: 1 event of implantation site infection and 2 events of pain/neck pain during stimulation. There were no unexpected AEs and none of the AEs related to the surgery led to the discontinuation of VNS Therapy.

4. Discussion

We have described here the demographics and baseline clinical characteristics of the initial group of 98 patients who enrolled in RESTORE-LIFE and received the first dose of stimulation at the time of analysis. These characteristics were compared to samples from a review of TRD treatment trials and the TRD Registry. Additionally, this study aimed to describe the safety of the surgical implantation of the VNS Therapy in DTD patients in a real-world clinical setting.

Our results suggest that patients enrolled in RESTORE-LIFE are affected by severe DTD, as indexed by the average age of onset of depression, number of failed treatment trials, and prior history of ECT. The degree of severity of the DTD in patients in RESTORE-LIFE may be slightly worse than the average for TRD studies identified in the literature and a possible explanation may be that RESTORE-LIFE patients experienced DTD for a longer duration. DTD in the RESTORE-LIFE sample was characterized by a lack of positive mental health and meaningfulness of life, to a greater degree than the excess of negative mood. Despite the high rates of psychiatric, metabolic, and cardiovascular comorbidities in the RESTORE-LIFE sample, VNS implantation was performed safely, resulting in zero discontinuations of therapy due to surgical AEs.

Based on their average MADRS and QIDS-SR scores, the RESTORE-LIFE patients suffer from severe depression and the scores on the observer- and self-rating questionnaire scores are convergent (Bernstein et al., 2010; Carmody et al., 2006). The depression severity of this patient cohort appears to be comparable to the patient populations in the TRD Registry. The mean GAD-7 anxiety scores suggest that at least 25 % suffer from comorbid generalized anxiety disorder. Interestingly, the LAPS 'negative affect' score was only one standard deviation higher than healthy controls, but the LAPS positive affect, hedonic tone, cognitive functioning, overall functioning, 'my life is meaningful', and 'I feel happy' scores were all more than two standard deviations lower than healthy controls (Demyttenaere et al., 2019). These findings suggest that in this cohort of chronically depressed patients, the lack of 'positive' mental health (ie, positive affect, hedonic tone, and happiness) and the lack of 'meaningfulness of life' are more pronounced than the 'excess' of negative mood. The average severity of the depressive episodes was further documented by the low score on the EQ-5D-5L-VAS of 38.3. Bipolar depression was diagnosed in about 25 % of the RESTORE-LIFE sample, which considering its overall lower prevalence in the general

population, suggests that bipolar depression is indeed more difficult to treat.

ECT had been previously administered to 87 % of patients in the RESTORE-LIFE sample. It is well known that large geographic differences exist in the use of ECT, and the high proportion of ECT use in RESTORE-LIFE may be partially due to the fact that the patients were enrolled in Austria, Belgium, Germany, and UK, where ECT is more commonly used compared to other countries (Leiknes et al., 2012). For example, a recently published study on the epidemiology of TRD in Israel reports only 2.9 % of patients having received ECT (Sharman Moser et al., 2022). Additionally, the high rates of ECT usage in our sample may also be explained by the fact that ECT responders are known to be more likely to respond to VNS Therapy; and therefore, may have been preferentially referred for implantation (Aaronson et al., 2021).

A clinically important finding was the discrepancy between the proportion of clinician-rated (25 %) and self-rated (41 %) suicidal ideation. This is worrisome with regards to instrument validity, warning against relying solely on clinician rating in the assessment of suicidality. However, it is notable that the wording in both questionnaires is not completely identical: a score of 4 on MADRS Item 10 ("probably better off dead or suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention") versus a score of 2 on Item 12 of the QIDS-SR ("I thought of suicide or death several times a week for several minutes" over the past 7 days). Still, it cannot be ruled out that clinician assessments are underestimating suicidality, especially within the context of a "clinical trial," where the physician-patient relationship is different than in routine clinical practice.

The BMI in the RESTORE-LIFE sample was 28.4 kg/m^2 compared to 31.5 kg/m^2 in the TRD Registry, which means that most of the enrolled patients were overweight and at least a third were obese. Therefore, it is not surprising that endocrine, metabolic, and cardiovascular comorbidities were present in a third of the patient sample. Also, the likely use of anti-psychotics as augmentation agents is likely to aggravate metabolic comorbidity, although our analysis does not allow us to make any inferences on this.

The scores on the different scales and their correlations suggest that standard symptom scales (MADRS, QIDS-SR, and GAD-7) perform better in capturing negative affect and work productivity, than in capturing positive affect (positive affect, hedonic tone, and overall QoL as measured with the EQ-5D-5L-VAS or with the Q-LES-Q). Since 'meaningfulness of life' and positive mental health (and hence not only negative mood) are very highly rated by patients in their expectations of antidepressant treatment and since only positive affect seems to predict meaningfulness of life (and not MADRS, QIDS-SR or GAD-7), positive affect should become an additional standard outcome measure for psychopharmacological, psychotherapeutic or neuromodulation treatments of depression (Demyttenaere et al., 2015; Zimmerman et al., 2006).

The demographics of the RESTORE-LIFE sample are roughly comparable to the results of our review of TRD trials, with regards to baseline MADRS score, gender distribution, and age at depression onset. However, taken together, the lower number of failed treatments (5.5 trials vs 11.4 trials), lower number of patients receiving ECT (22 % vs 87 %) and younger age (44.0 years vs 50.4 years) in the review of TRD trials suggests that patients included in RESTORE-LIFE (and potentially also in the TRD Registry) have been affected by DTD for a longer period prior to enrolment. This comparison is relevant given the heterogeneity in the definitions of TRD in the literature.

4.1. Limitations

Limitations of the present study mainly stem from the fact that RESTORE-LIFE is an observational registry that allows for inclusion of any patient receiving adjunctive VNS Therapy for DTD. Bias may be associated with variations of referral practices for VNS Therapy amongst the different sites and different countries, as well as variations in treatments for DTD administered in combination with VNS but also prior to VNS Therapy.

5. Conclusions

This baseline analysis of the first 98 implanted patients who received the first stimulation dose in RESTORE-LIFE suggests that the patients enrolled in this European registry are affected by severe DTD and potentially have been affected longer than the patients included in the majority of TRD studies identified in the literature. DTD in the RESTORE-LIFE population was characterized by the lack of positive mental health and meaningfulness of life being even more pronounced than the excess of negative mood. Despite the patients in RESTORE-LIFE displaying high rates of psychiatric, metabolic, and cardiovascular comorbidities, VNS Therapy implantation could be performed safely and there were no discontinuations of therapy due to surgical adverse events.

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Author statement

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Declaration of competing interest

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Appendix A. Supplementary data

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