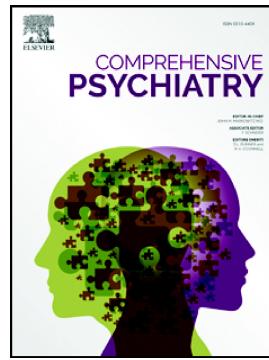


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## VAGUS NERVE STIMULATION (VNS) THERAPY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

### Background

Vagus nerve stimulation (VNS) therapy is approved for treatment-resistant depression (TRD). A recent 5-year comparative study prompted this review of its impact in this very severe population. Previous systematic literature reviews (SLR) cited concerns in terms of missing studies or patient duplication.

### Methods

This SLR addressed these criticisms, assessed all outcomes of longer-term adjunctive VNS in all studies, irrespective of TRD severity, comparing where feasible with treatment-as-usual (TAU). We searched for adult VNS+TAU studies (January 1, 2000 to June 24, 2019). Comparative and single-arm studies were eligible. All reported efficacy, safety and quality of life (QOL) outcomes were assessed. Where possible, meta-analysis was used to calculate overall pooled effect estimates across studies at several time points.

### Results

Of 22 identified studies, there were two randomized controlled (RCT), sixteen single-arm and four non-randomized comparative studies. Numerous depression-specific, safety and QOL measures were reported. Meta-analysis was possible for three efficacy [Montgomery-Asberg Depression Rating Scale, Clinician Global Impression-Improvement, Hamilton Rating Scale for Depression] and three safety [serious adverse events, study drop-outs and all-cause mortality] but no QOL measures. Data beyond 2 years was not poolable. Analyses demonstrated that antidepressant benefits improved to 24 months and safety issues were minimal. Heterogeneity was high and statistically significant.

### Conclusions

Despite limitations in the evidence base, our comprehensive summary of VNS+TAU outcomes suggests that this treatment provides improving benefit and hope for this very hard-to-treat chronic population. More comparative TRD studies should describe safety and QOL.

### KEY WORDS

Treatment resistant depression; vagus nerve stimulation (VNS) therapy; systematic review; meta-analysis; long-term outcomes

## Abbreviations and acronyms

- ASEX: Arizona Sexual Experience Scale  
BD: Bipolar disorder  
BDI: Beck Depression Inventory  
CGI-I: Clinical Global Impressions Scale - Improvement  
DBS: Deep brain stimulation  
ECT: Electro Convulsive Therapy  
GAF: Global Assessment of Functioning  
HAMA: Hamilton Anxiety Rating Scale  
HAMD: Hamilton Rating Scale for Depression  
IDS-C: Inventory of Depressive Symptomatology - Clinician  
IDS-SR: Inventory of Depressive Symptomatology - Self report  
MADRS: Montgomery Asberg Depression Rating Scale  
MDD: Major Depressive Disorder  
MDE: Major Depressive Episode  
NICE: National Institute for Health and Care Excellence  
NIHR: NHA National Institute for Health Research  
NIMH LCM-p: National Institute of Mental Health prospective life charting methodology  
PRO: Patient Reported Outcome  
QIDS-SR: Quick Inventory of Depressive Symptomatology - Self Report  
Q-LES-Q: Quality of life Enjoyment and Satisfaction Questionnaire  
QOL: Quality of life  
RAVLT: Rey Auditory Verbal Learning test  
RCBD: Rapid cycling bipolar disorder  
RCT: Randomized controlled trial  
ROCF: Rey-Osterrieth Complex Figure test;  
rTMS: Repetitive transcranial magnetic stimulation  
SAE: Serious adverse event  
SDMT: Symbol Digit Modalities Test  
SLICE: Streamlined Longitudinal Interval Continuation Evaluation  
SLR: Systematic literature review  
TAU: Treatment as usual  
tDCS: Transcranial direct current stimulation  
TRD: Treatment resistant depression  
VNS: Vagus nerve stimulation  
YMRS: Young Mania Rating Scale

## 1. Introduction

Depression is a leading cause of global burden of disease, estimated to affect over 350 million people worldwide (World Health Organization, 2017). Though there is no definitive definition of treatment resistant depression (TRD) at this juncture, evidence supports that TRD can be defined as the failure to respond to two or more antidepressants, used at an appropriate dose for an adequate time frame (Gaynes et al., 2018). Some 25 to 30% depressed patients suffer from TRD (Rush et al., 2006), (Nemeroff, 2007) and presentation of such hard-to-treat patients poses a serious challenge to primary care and psychiatric healthcare professionals.

Vagus nerve stimulation (VNS) therapy requires the use of an implantable device in patients with severe TRD, enabling intermittent electrical stimulation of the left cervical vagus nerve using the electrical stimulator to occur. In the USA and Europe, VNS therapy is approved for the adjunctive long-term treatment of TRD patients not responsive to 4 antidepressant treatments, namely a more severe degree of TRD. Since its introduction in 2000, numerous studies have been published and systematic literature reviews (SLRs) have reviewed and critiqued the evolving evidence base.

To date seven SLRs have reported that adjunctive VNS therapy (namely VNS therapy plus treatment as usual (TAU)) is associated with patient benefit in TRD, and that such benefit is sustained (Berry et al., 2013, Cimpianu et al., 2017, Daban et al., 2008, Martin and Martin-Sanchez, 2012, Milev et al., 2016, McGirr and Berlim, 2018, Lv et al., 2019). Despite similarities in their TRD findings, these SLRs and meta-analyses differed in their approach and focus. They included different VNS studies and different outcomes; some broad-ranging SLRs cited more than one intervention in TRD (McGirr and Berlim, 2018) while others reviewed VNS Therapy in more than one condition (Martin and Martin-Sanchez, 2012), (Cimpianu et al., 2017). Furthermore, concerns were voiced about the VNS in TRD literature in terms of limited availability of randomized controlled trials (RCTs), patient duplication or incomplete inclusion of all VNS studies, in particular single-arm studies not sponsored by device manufacturers.

VNS therapy is used in clinical practice as an adjunct to TAU (often also referred to as standard of care). TAU typically comprises a number of management strategies, including pharmacotherapy, psychotherapy, electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) or deep brain stimulation (DBS), in this hard-to-treat chronic population. These strategies are necessarily individualized based on the patients' needs and their previous treatment history.

This SLR aimed to evaluate all reported outcomes of longer-term adjunctive VNS, compared, where feasible, with TAU. Specifically, this study aimed to provide an up-to-date comprehensive SLR and meta-analysis of all studies of adjunctive VNS in TRD, including recent much longer-term experience of VNS. In contrast to previous SLRs and in order to address previous criticisms of the VNS evidence, this review aimed to investigate the overall impact of adjunctive VNS via analysis of all poolable

evidence across as many patient-relevant outcomes as possible. These included alleviation of symptoms of depression and impact on quality of life (QOL) using all reported Patient Reported Outcome (PRO) measures and safety of VNS in TRD.

## 2. Material and methods

This systematic review of the literature used methods published by the Centre for Reviews and Dissemination (CRD, 2008) and is consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Liberati et al., 2009). A broad approach was adopted in the search protocol to ensure all relevant publications describing the clinical effectiveness, safety, and QOL of adjunctive VNS Therapy in TRD were identified.

### 2.1. Search strategy

A comprehensive search for English-language publications from January 1, 2000 through 24 June 2019 (including two subsequent updates of the original September 2015 search) was conducted in a wide range of electronic resources including general health, biomedical and specialist databases and websites. To ensure no relevant studies were missed in both our 2017 and 2019 updates, overlaps in search dates were introduced.

We searched bibliographic databases including Embase and Medline, the Cochrane Library, National Library of Medicine, National Institute for Health and Care Excellence (NICE), NHS National Institute for Health Research (NIHR), and established clinical trial databases such as ClinicalTrials.gov and the EU Clinical Trial Registry. The New York Academy of Medicine Grey Literature Report was also examined.

Search terms including index and text terms for VNS, TRD and study design were used. Searches were not restricted by comparator to ensure retrieval of all studies that compare VNS therapy to any routine TRD treatment or management option. The search strategy, databases and other resources, search and indexing terms are detailed in the online Supplementary APPENDIX A.

### 2.2. Study selection

All the identified titles and abstracts were assessed for inclusion independently by two authors. Potentially relevant articles were obtained in full text and independently assessed for inclusion by two authors.

Studies were included based on the following criteria: i) they described clinical and safety outcomes with VNS+TAU or TAU alone in an adult population with TRD who all have failed at least two routinely available treatments including antidepressants; ii) the design was a RCT, prospective or retrospective comparative study, prospective case series or single-arm study; iii) the study used any comparator including none; iv) the publication described 5 or more patients; v) the study was published in English

in 2000 or afterwards. To address criticisms in previous SLRs of missing VNS+TAU evidence, our definition of TRD was broad and included the more severe and difficult-to-treat patients with rapid cycling bipolar disorder (RCBD). Publications 'in press' were included. Bibliographies of identified studies and any systematic reviews or meta-analyses were scrutinized to identify any additional studies. Duplicate citations were removed and multiple reports of the same study were collated ensuring that a study, rather than a publication, was the unit of analysis in the review.

### **2.3. Data extraction and quality assessment**

Data extraction and quality assessment were carried out by two independent reviewers. Authors of included studies were approached to obtain unreported details about their study patients where publications suggested relevant outcomes information was collected but not reported.

The quality of RCTs was assessed using the NICE Single Technology Appraisal quality assessment tool (National Institute for Health and Care Excellence, 2015). Other types of clinical studies were evaluated using criteria specified by the Centre for Reviews and Dissemination (CRD, 2001).

### **2.4. Analysis**

#### **2.4.1. Scope**

The analysis aimed to assess all reported efficacy, safety and QOL outcomes of adjunctive VNS+TAU in TRD and, where feasible, to compare VNS+TAU to TAU alone. Data were assessed for suitability for statistical pooling by considering the amount of data and the extent to which the studies and outcomes reported were similar. Given that the evidence from the direct comparative RCTs was limited, we also carried out meta-analyses of all the single-arm and non-randomized comparative studies, including more recent longer-term studies of VNS.

Use of different efficacy outcomes and variation in definitions of responders across the evidence base necessitated a pragmatic approach to pooling response and remission across the studies. For example, even when the same instrument was used, the criteria for defining response differed (e.g. in the case of HAMD, response could be defined in 3 ways across studies: i) number of patients achieving a  $\geq 50\%$  improvement, or ii) % change, or iii) absolute change in HAMD score from baseline).

Therefore in our analyses, efficacy analyses defined response to treatment as 'patients achieving  $\geq 50\%$  reduction from baseline in the depression rating scale'. Patients achieving a CGI-I rating "1" or "2" ("Very much improved" or "Much improved") post-baseline were also considered 'responders'. Remission was defined as maintenance of response and MADRS score of  $\leq 9$  or  $\leq 10$  (reflecting developments over time in the use of the MADRS scale). Opportunity for assessment of adjunctive VNS on as many efficacy, safety and QOL outcomes as possible based on available data was explored.

Time points considered in all the analyses were 6, 12 and 24 months.

#### **2.4.2. Statistical methodology**

All the outcomes considered were binary and results of the analyses were reported as the proportion of patients experiencing each outcome and its associated 95% binomial exact confidence interval. All analyses were implemented in Stata IC version 14.1.

Individual study results for each outcome were pooled using fixed- and random-effects models. The Freeman-Tukey Double Arcsine Transformation was applied to stabilize the variances (Freeman and Tukey, 1950). Heterogeneity was assessed by the Cochran's Q test and the  $I^2$  statistics (Higgins and Thompson, 2002). The random-effects model was chosen where the p-value associated with Cochran's Q test was significant at the 10% threshold ( $p \leq 0.10$ ) or the 95% confidence interval around the  $I^2$  measure did not include 0.

### **3. Results**

#### **3.1. Study selection**

Results of the initial search in 2015 and the update searches in 2017 and 2019 (adopting the same search strategy), together with most common reasons for exclusion, are shown in Figure 1.

[INSERT FIGURE 1 HERE]

The searches identified 39 eligible records, which were assessed for relevance in accordance with the methods outlined above. Twenty two clinical efficacy and safety studies were included in this SLR, comprising 2 RCTs (Aaronson et al., 2013, Rush et al., 2005), 4 non-randomized comparative studies (Aaronson et al., 2017, George et al., 2005, Muller et al., 2013, Sperling et al., 2009), 15 VNS+TAU single-arm studies (Albert et al., 2015, Bajbouj et al., 2010, Christmas et al., 2013, Cristancho et al., 2011, Dell'Osso et al., 2013, Franzini et al., 2008, Marangell et al., 2008, Muller et al., 2017, Nahas et al., 2005, O'Keane et al., 2005, Perini et al., 2017, Salloum et al., 2017, Tisi et al., 2014, Trottier-Duclos et al., 2018, Desbeaumes Jodoin et al., 2018) and 1 TAU single-arm study (Dunner et al., 2006). One other study identified in the 2017 update (Oldani et al., 2015) was found to report on the same study as reported by Dell'Osso and colleagues (Dell'Osso et al., 2013) identified in the original search. Conway and colleagues (Conway et al., 2018) and Kumar et al (Kumar et al., 2019) identified in the 2019 update both report new findings on some of the patients already reported in the TRD Registry (Study 3,(Aaronson et al., 2017)).

Online Supplementary APPENDIX B provides comprehensive details of all seven SLRs used as a check on the search strategy. Our checks confirmed that we did not miss any VNS Therapy studies and that our literature search was comprehensive

### 3.2. Study characteristics

#### 3.2.1. Clinical studies included in analysis

Key characteristics across the 22 clinical studies are outlined in Table 1. Studies are listed according to study design and quality (first listing the RCTs, then non-randomized comparative studies and lastly single arm trials). Of the 22 studies, 7 were company-sponsored.

[INSERT TABLE 1 HERE]

Patients displayed characteristics of severe TRD (e.g. in terms of number of prior major depressive episodes (MDE) or number of failed treatments in the current MDE). Some studies looked at patients failing two or more treatments while others some four or more. Table 1 shows the VNS study populations are a very severely ill group typically excluded from most other clinical trials; for example many of the studies also included patients with bipolar disorder (BD), not generally seen within TRD studies. Study 14, a 10-patient US single-arm pilot study described a more severe and difficult to treat series of RCBD patients. Samples sizes across the included studies ranged from 5 to 795 patients, with the smaller non-company sponsored studies describing between 5 and 27 patients.

Follow up periods ranged from 3 months to over 6 years and, if reported, the stimulation parameters of VNS therapy varied across the studies reflecting individualized dosing to patient tolerance. Only one non-randomized comparative study (Study 3) and five small single-arm studies (Studies 12, 16, 17, 19 and 21) reported outcomes for time-points beyond 2 years.

#### 3.2.2. Outcomes reported in clinical studies included in analysis

Efficacy outcomes reported and collated across the eligible evidence base included treatment response and remission using many different depression-specific measures (e.g. Hamilton Rating Scale for Depression (HAMD), Montgomery Asberg Depression Rating Scale (MADRS), Inventory of Depressive Symptomatology, Clinician or Self-Report (IDS-C or IDS-SR), Clinical Global Impressions Scale (CGI), Beck Depression Inventory (BDI), Streamlined Longitudinal Interval Continuation Evaluation (SLICE), Young Mania Rating Scale (YMRS), Global Assessment of Functioning (GAF) and Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)). Eight safety outcomes included adverse events (AE), hospitalizations, serious adverse events (SAEs), suicide, mortality (all cause, including suicide), mania, drop outs (all cause), discontinuation due to AEs. QOL impacts were reported using the following three PROs: Short Form 36 (SF-36), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Arizona Sexual Experience Scale (ASEX).

### 3.3. Quality and risk of bias across eligible studies

Scrutiny of selection, performance and reporting bias indicated the RCTs might reasonably be seen as low risk of bias. Review of the two company RCT study protocols demonstrated appropriate

methods of randomization. Most of the other studies were deemed to be at moderate or high risk of bias, this assessment largely was due to poor reporting of key study details. In the four non-randomized comparative studies, the outcomes assessors were not blinded to intervention. Full details relating to quality and risk of bias for RCTs, non-randomized comparative trials and single-arm studies can be found in Online Supplementary APPENDIX C.

### **3.4. Overview of clinical and quality of life evidence**

Table 2 summarizes all results and opportunities for potential data pooling across the twenty two identified studies in which 1,171 patients were treated with VNS+TAU and 409 patients were treated with TAU alone. There were two RCTs: Study 1 comparing VNS+TAU to sham VNS+TAU at 10 weeks and Study 2 comparing different levels of VNS stimulation in addition to TAU at week 22. No data was available that would allow a direct comparison between VNS+TAU and TAU beyond 10 weeks.

[INSERT TABLE 2 HERE]

There was a large variation in the depression outcomes and timelines reported across the studies. Eighteen studies reported HAMD and in ten studies it was the primary endpoint. The second most frequently reported outcome measure was MADRS (13 studies; primary endpoint in two) and third CGI-I (12 studies). The IDS-SR featured in seven studies (primary endpoint in one). Individual studies reported other depression outcome measures (e.g. Streamlined Longitudinal Interval Continuation Evaluation (SLICE) and Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) both in Study 3, and the Inventory of Depressive Symptomatology - Clinician (IDS-C) in one study (Study 3)). The Beck Depression Inventory (BDI) and the Global Assessment of Functioning (GAF) were reported in two studies each while the Young Mania Rating Scale (YMRS) was described in three studies. Seven studies reported QOL outcomes, including the Short-Form 36 (SF-36) in five studies or the Arizona Sexual Experience Scale (ASEX) or the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) in two studies.

#### **3.4.1. VNS therapy randomized controlled trials**

The incremental benefit of adjunctive VNS therapy compared with TAU was reported in one RCT, Study 1, (Rush et al., 2005). Rush and colleagues described a 10-week randomized comparison of adjunctive VNS versus sham treatment in 222 evaluable TRD outpatients (VNS 112 patients; sham treatment 110 patients). The study revealed modest benefit per the primary measure, the HAMD response rate; this difference was not statistically significantly different up to 10 weeks. Response rates with a secondary outcome, the IDS-SR, were noted to demonstrate a statistically significant benefit for VNS. The authors considered that the lack of definitive evidence of short term efficacy in this chronically ill population could be due to either the study being too short in its follow up or underpowered. Adjunctive VNS was in general well tolerated although 3 patients withdrew due to

adverse events. The active and the sham VNS patients did not differ in their QOL (as measured using the SF-36).

Study 2, the second RCT (Aaronson et al., 2013) compared three active adjunctive VNS treatment groups in which 331 patients were randomized to three different levels of VNS dose stimulation (low, medium and high) over a 22 week "acute phase". This was followed by a 28-week "long-term" phase (where the blinded investigators could modify VNS dosing as clinically indicated) to assess durability of response. The primary outcome was change in IDS-C score from baseline at 22 weeks. While all three groups showed statistically significant improvement in the primary endpoint, the study demonstrated no dose-response relationship over 22 weeks as there were no differences between the three dosing groups (although post hoc analyses suggested higher doses may result in better and more sustained responses). In the longer term, IDS-C scores (together with MADRS, QIDS-C and IDS-SR rating scales) continued to improve but there were no significant differences in response rates between the three VNS treatment groups. Overall, VNS was well tolerated and most adverse events were distributed evenly across the three treatment groups. The researchers did not study QOL in this RCT (Aaronson et al., 2013).

Both RCTs indicated ongoing improvement with treatment, suggesting addition of VNS to TAU can benefit patients with TRD.

### **3.4.2. Inclusion of observational studies**

The VNS therapy experience, apart from the two RCTs, was observational and contributed significantly to the complete TRD evidence base in study and patient numbers and also to the longer term outcomes. Observational studies typically reflect routine clinical practice. While observational studies are considered to be biased estimates of treatment effects, they are the only source of evidence available to address the aim of this review, namely the added impact of adjunctive VNS compared with TAU on efficacy, safety and QOL over time as the two higher quality RCTs did not address this question.

We therefore looked to assess whether the observational research reported at 3 months was biased by checking if the absolute effects of the adjunctive VNS arms in the RCTs at 3 months differed from that seen in the available observational studies. Results of this bias check are seen in Online Supplementary APPENDIX D. Broadly similar absolute effects across a number of outcomes at 3 months, irrespective of study design, were evident. This reassured the authors that inclusion of the longer-term observational data was a reasonable approach to assess all available evidence in this review.

It should be noted that the patient characteristics across the contributing studies confirmed patients were all severe TRD cases. In all but one study (Marangell et al., 2008), characteristics were largely similar in terms of severity of TRD, hence reducing the risk of confounding. For completeness, this review also included the even more severe RCBD cohort of 10 patients in Study 14 (Marangell et al.,

2008). The explanation for the larger responses compared to other studies seen for all reported outcomes in Study 8 (Bajbouj et al., 2010) remains unclear, although this could reflect a slightly higher VNS dosing employed in this small single-arm European study. However, since Aaronson and coworkers concluded in the above-mentioned RCT (Study 2) there was no evidence VNS dosing made a difference to outcomes (Aaronson et al., 2013), the differing levels of stimulation across the studies were pooled. Of note, Study 8 included 20 of 74 (27%) patients with bipolar disorder (BD) (Bajbouj et al., 2010) and Study 22 also exhibited large response rates and recruited 6 of 14 patients with BD (Desbeaumes Jodoin et al., 2018).

### **3.5. Meta-analyses results of longer-term data**

The most commonly reported (and poolable) efficacy outcomes were MADRS, HAMD and CGI. Many other depression-specific efficacy measures were used but only in a few of these studies. This meant that IDS-SR, IDS-C, QIDS-SR, YMRS, GAF, BDI and SLICE efficacy outcomes data could not be pooled and were excluded from further data synthesis. Despite a broad range of safety outcomes reported across the eligible studies, based on availability of evidence and poolability, the safety analyses could only meta-analyze the following outcomes: SAEs, drop outs (all cause) and all cause mortality (including suicide). Only seven studies reported QOL but as these described different PRO outcomes at different time-points these could not be pooled and were excluded from the formal meta-analyses.

#### **3.5.1. Efficacy**

##### **MADRS**

MADRS findings are shown on Figure 2 (response) and Figure 3 (remission).

For patients treated with VNS+TAU, the pooled MADRS response rates (95% confidence interval) across all studies were 23.9% (20.9, 27.0), 38.9% (30.2, 47.9) and 52.6% (34.2, 70.6) at 6, 12 and 24 months (Figure 2A, 2B and 2C, respectively). Significant heterogeneity was observed at 12 and 24 months with a  $I^2$  of 78.3% and 80.3%, respectively.

[INSERT FIGURE 2 HERE]

TAU MADRS responder rates (95% confidence interval) over 6, 12 and 24 months come from only one study, Study 3, (Aaronson et al., 2017) and were 13.8% (9.6, 19.1), 17.5% (12.5, 23.6), and 18.5% (12.6, 25.8), respectively.

The corresponding VNS+TAU MADRS remitter rates were 12.1% (9.9, 14.6), 25.1% (16.7, 34.4) and 37.7% (17.9, 59.7) at 6, 12 and 24 months, respectively (Figure 3A, B and C), with high levels of heterogeneity ( $I^2$  84.4% at 12 months) (Figure 3B) and 86.2% at 24 months (Figure 3C).

INSERT FIGURE 3 HERE

For patients receiving TAU in the one non-randomized comparative study (Aaronson et al., 2017) (Study 3), the proportion of MADRS remitters at 6, 12 and 24 months were reported as 6.3% (3.5, 10.3), 8.2% (4.8, 13.0), and 11.0% (6.4, 17.2), respectively.

### CGI-I

Figure 4 shows the impact of either VNS+TAU or TAU over time with CGI-I. The CGI-I response rates increase from 6 months to 12 months (Figure 4A and Figure 4B) and the VNS+TAU rates at 12 months were numerically higher than those seen for TAU at 12 months (Figure 4B versus Figure 4C).

[INSERT FIGURE 4 HERE]

The VNS+TAU pooled rates (95% confidence interval) across all studies for CGI-I responders were 29.9% (26.7, 33.1) and 43.6% (40.0, 47.2) at 6 and 12 months, respectively. No significant heterogeneity was observed.

TAU CGI response rates (95% confidence interval) at 6, 12 and 24 months come from only one long-term non-randomized comparator study (Aaronson et al., 2017) (Study 3) and one single arm observational study (Dunner et al., 2006) (Study 20) but data were only poolable at the 12 month time point (Figure 4C). These CGI-I response rates were 11.6% (8.0, 16.1), 14.9% (11.2, 19.1) (Figure 4C) and 23.8% (17.7, 30.9) respectively.

### HAMD

An overview of the HAMD outcomes are seen on Figure 5 (response) and Figure 6 (remission). Both the VNS+TAU HAMD response and HAMD remission rate increased over time, and while TAU rates were only available at 12 months, they were numerically less than those seen for VNS+TAU at 1 year.

[INSERT FIGURE 5 HERE]

The VNS+TAU pooled rates (95% confidence interval) across all studies for HAMD responders were 29.9% (14.5, 48.0), 43.4% (31.5, 55.7) and 36.7% (20.1, 43.4) at 6, 12 and 24 months, respectively (Figure 5A, 5B and 5C). Significant heterogeneity was observed at 6 and 12 months, with  $I^2$  levels of 89% and 69% respectively. The pooled TAU HAMD responder rates (95% confidence interval) was only available at 12 months and was 9.6% (4.2, 16.4) (Figure 5D).

The corresponding VNS+TAU HAMD remitter rates were 14.4% (5.4, 26.7), 27.3% (17.7, 37.8) and 21.7% (16.2, 27.6) at 6, 12 and 24 months, respectively (Figure 6A, 6B and 6C). Significant heterogeneity was observed again, with  $I^2$  levels of 83.4% and 60.8% at 6 and 12 months.

INSERT FIGURE 6 HERE

The TAU HAMD remitter rates (95% confidence interval) were only available at 12 months , and were 6.7% (2.7, 13.4).This TAU analysis was informed by one company-sponsored study single-arm trial so was not poolable (Dunner et al., 2006) (Study 20).

### 3.5.2. Safety

#### Serious Adverse Events (SAEs)

The pooled VNS+TAU rate of patients with SAEs (95% confidence intervals) at 12 months across all studies was 5.5% (0.5, 13.6) (Figure 7). Significant heterogeneity was observed with  $I^2$  value of 81.8% across the 7 contributing studies.

INSERT FIGURE 7 HERE

No SAE data were available at 6 months for VNS+TAU and for TAU at any of the time points.

#### Study drop-outs

Figure 8 shows the rate of patients dropping out of studies (all causes) at 12 and 24 months.

[INSERT FIGURE 8 HERE]

The pooled drop-out rates (95% confidence intervals) for patients treated with VNS+TAU were 7.6% (3.6, 12.6) and 19.0% (9.0, 31.4) at 12 and 24 months respectively (Figure 8A and 8B) while the  $I^2$  were significant at 49.4% and 85.7%, respectively. The pooled 24-month drop-out rates on TAU was 34.0% (29.5, 38.6) (Figure 8C).

#### Mortality

Figure 9 shows the mortality (all causes, including suicide) on VNS+TAU in all studies up to 24 months.

[INSERT FIGURE 9 HERE]

The rate of patient deaths (all cause) on VNS+TAU at 3, 12 and 24 months across all studies was 0.0% (95% CI: 0.0,0.4), 0.4% (95%CI: 0.0,2.0) and 1.4% (95% CI: 0.0,4.9), respectively (Figure 9A, 9B and 9C). There is a moderately high amount of heterogeneity at 12 and 24 months, which is significant. The 12-month mortality rate observed in the Study 14 (Marangell et al., 2008) is very high compared to the other studies (Figure 9B). As noted earlier, this cohort described 10 severely ill RCBD patients, a population not eligible for recruitment into any of the company-sponsored VNS studies. Nevertheless, they are included in this meta-analysis for completeness since this study was identified in the search and was identified in SLRs of others.

The rate of patient deaths (all cause) on TAU at 3, 6, 12 and 24 months across all studies was 0.3% (95%CI: 0.0,1.8), 0.3% (95%CI: 0.0,1.8), 0.3% (95%CI: 0.0,1.8) and 0.7% (95%CI: 0.1,2.4),

respectively. These TAU data are from one study at all time points (Study 3) and are not from any pooled analysis. They represent two deaths over a 2-year period in 301 patients (Aaronson et al., 2017).

### 3.5.3. Quality of life

It was not possible to pool QOL outcomes in the formal meta-analyses, as studies were mostly short-term, single-arm, included few patients and described different QOL measures at different time points. For completeness a brief summary of QOL findings across the six VNS+TAU and one TAU only study is presented next.

Study 1 used the SF-36 and reported no difference at 12 weeks between the active and sham VNS groups on either the physical or mental component of the SF36 (Rush et al., 2005). The non-randomized comparative study, Study 3 (Aaronson et al., 2017) collected Q-LES-Q and ASEX outcomes and the Q-LES-Q findings were more recently reported by Conway and coworkers (Conway et al., 2018). In this long-term naturalistic TRD Registry where patients received either VNS+TAU or TAU the authors (Conway et al., 2018) reported that long term VNS+TAU (in 328 patients) significantly improves QOL compared to TAU (271 patients) using the Q-LES-Q measure, with significant comparative benefit evident from 3 months and sustained through 5 years on VNS+TAU. Furthermore, patient self-perceived QOL improvement (deemed to be clinically important) matched physician-reported improvement in the CGI-I. The authors considered this to be a significant achievement in a population at a high risk of relapse (Dunner et al., 2014, Rush et al., 2006). Notably, this clinically meaningful QOL improvement was observed with VNS+TAU even when the total change in MADRS score from baseline was less than 50%, underlying the importance of capture of QOL as well as clinical outcomes in TRD studies.

Single arm Study 7 (Nahas et al., 2005) reported modest and increasing percentage of functional improvements on the SF-36 at 3, 12 and 24 months in General health perception and the components of the SF-36. Single arm Study 9 (Albert et al., 2015) reported non-significant changes in SF-36 physical and mental summary scores at 3, 6, 9 and 12 months. Single arm Study 11 (Cristancho et al., 2011) reported the Q-LES-Q did not change at 6 or 12 months post VNS implant. Single arm VNS+TAU Study 21 (Trottier-Duclos et al., 2018) followed up 10 TRD outpatients (7 with unipolar and 3 with BD) over 6 years post implant and evaluated the patients QOL using the SF-36 (and their clinical symptoms using HAMD and the Hamilton Anxiety Rating Scale (HAMA)). Clinically and statistically significant improvement in mental QOL ( $p=0.012$ ), physical QOL ( $p<0.002$ ), depressive symptoms ( $p<0.001$ ) and anxiety symptoms ( $p<0.001$ ) were reported.

Study 20 (Dunner et al., 2006)) reported that 124 TRD patients receiving TAU alone experienced "globally poor quality of life" as measured using the SF-36 and when compared with other depression cohorts or other chronic conditions such as congestive heart failure. Changes in the SF-36 scores were minimal over the 2 year study period.

The studies generally reported that the mean QOL was either maintained or modestly improved on treatment with VNS+TAU or that no difference could be seen between patients on adjunctive VNS compared with TAU.

### 3.6. Assessment of funding bias

The authors also investigated another potential bias, namely funding bias, where the impact of restricting analyses to sponsor studies only was examined. Where data allowed, we repeated specific analysis at all possible opportunities to look at pooled estimates for i) sponsor studies only and ii) all studies (across a variety of outcomes and largely at the 12 month time point). Without exception, responder analyses restricted to sponsor studies alone gave very similar findings to analyses for all studies per outcome at 12 months.

The 12 month pooled VNS+TAU MADRS responder analysis restricted to company-sponsored studies only (Figure 10A) gave similar findings (37.8% (30.0, 45.9)) to the 12 month analysis across all studies (38.9% (30.2, 47.9)) (Figure 10B). High levels of heterogeneity were seen with  $I^2$  of 78.9% (Figure 10A) and 78.3% (Figure 10B), respectively

[INSERT FIGURE 10 HERE]

The 12-month CGI-I responder analysis restricted to company-sponsored studies gave very similar findings 43.4% (37.3, 49.6) with  $I^2=66.1\%$  (Figure 11A) to all studies 43.6% (40.0, 47.2) (Figure 11B)

[INSERT FIGURE 11 HERE]

When restricting analyses to company-sponsored studies only at the 12 months time point, the VNS+TAU pooled rates (95% CI) HAMD responder analyses gave very similar findings of 42.2% (27.1, 58.1) (Figure 12A) to the analysis of all studies 43.4% (31.5, 55.7) (Figure 12B). High heterogeneity was evident, as seen with  $I^2$  levels of 84.1% and 69.7%, respectively.

[INSERT FIGURE 12 HERE]

The pooled VNS+TAU 12 month analysis of patients with SAEs (95% CI) restricted to the two company-sponsored studies showed a higher SAE rate of 20.7% (17.5, 24.2) (Figure 13A) than that for all studies at 5.5% (0.5, 13.6) (Figure 13B). High heterogeneity was evident with  $I^2$  value of 81.8% across the 7 contributing studies in Figure 13B.

[INSERT FIGURE 13 HERE]

These sensitivity analyses revealed no differences between the response efficacy results whether studies were company-sponsored or not. Safety outcomes for SAEs were modestly higher in analyses restricted to company studies only compared with all study analyses, which may be a reflection of the close monitoring associated with sponsor studies. Across all outcomes there was significant

heterogeneity in data. Additional funding bias sensitivity analyses for HAMD remitter, study drop-out and all cause mortality are seen in Online Supplementary APPENDIX E.

#### 4. Discussion

Our aim was to carry out a comprehensive up-to-date systematic review of all studies investigating adjunctive VNS therapy in TRD, including analyses of all possible reported outcomes, to include recent 5-year real-world treatment experience of VNS and to address previous criticism relating to incompleteness of evidence cited in the identified SLRs. Here, we describe more outcome measures, include more studies and describe longer-term impact than in previous SLRs.

The similarities and differences across the seven SLRs are described in detail in Online Supplementary APPENDIX B. In brief, their latest search dates in 2018 translated into the longest follow-up reported of only one year treatment with adjunctive VNS. Three of the SLRs focused solely on TRD (Berry et al., 2013, Daban et al., 2008, Lv et al., 2019), two SLRs included other conditions, (both TRD and drug-resistant epilepsy (Martin and Martin-Sanchez, 2012) and experiences in any psychiatric condition (Cimpianu et al., 2017)). The sixth (Milev et al., 2016) was a clinical guideline in adults with major depressive disorder based on a SLR while McGirr and Berlim critically appraised meta-analyses of therapeutic neuromodulation techniques (including VNS Therapy, rTMS, tDCS and DBS) in major depression in the last decade (McGirr and Berlim, 2018). Lv and colleagues searched for RCTs in TRD, and identified two RCTs, one was VNS Therapy (Study 1, (Rush et al., 2005)) but the second study described auricular transcutaneous VNS as opposed to VNS Therapy (Lv et al., 2019).

The outcomes reported in the SLRs differed. These included MADRS responders and remitters and CGI-I responders (Berry et al., 2013); HAMD responders and remitters (Daban et al., 2008) and also HAMD scores and response rates (Martin and Martin-Sanchez, 2012) while suicide rate was the primary focus in one (Lv et al., 2019). Across the SLRs, and as evidence matured in the more recent of the SLRs, there was a consensus the studies show benefit of VNS in TRD and that responses improved and were sustained over time. Authors also acknowledged the need for longer-term quality VNS Therapy studies.

The two identified RCTs suggest the use of adjunctive VNS is beneficial in TRD however the RCT data was limited in terms of the study design and short duration. Given the majority of the real-world clinical VNS evidence is from observational evidence, we attempted to explore any potential bias by comparing observational short-term results to those available from the RCTs. As the identified differences were not considered excessive, we hypothesized the long-term observational data may provide a credible estimate of longer-term outcomes in this chronic debilitating condition (see online Supplementary APPENDIX D). The results of the meta-analyses of observational studies suggest adjunctive VNS may provide long-term benefit in patients with TRD.

Our analyses significantly and comprehensively extend the VNS experience in both the length of study follow-up (pooling data where possible to 2 years) and also in describing many more efficacy and safety outcome measures than in previous SLRs, albeit in analyses largely populated by observational studies (in order to interrogate and assess the majority of the total VNS in TRD experience).

We could only pool and try to compare experience of VNS+TAU to TAU over 2 years since there was only one real-world registry (Study 3) of the long-term use of VNS+TAU versus TAU up to 5 years. Study 3 demonstrated that VNS combined with any treatment available to psychiatrists (including electroconvulsive therapy (ECT)) was superior to standard treatment without VNS, achieving greater cumulative response (50% reduction in depressive symptoms) and remission rates and lowering overall suicide rates (Aaronson et al., 2017).

In all of the analyses, irrespective of efficacy or safety measures reported, outcomes for VNS+TAU (and where data were reported for TAU) improved over 24 months. Furthermore, despite there being no standard TAU in this refractory patient population (this being governed by individual patient histories), and estimates coming from heterogeneous single-arm studies, in the analyses it was possible to undertake VNS+TAU outcomes were numerically superior to TAU. Notwithstanding the evident high heterogeneity across the evidence base in our pooled analyses, our observations are consistent with previous reviews and also extend and strengthen evidence of the benefit of VNS+TAU.

#### **4.1. Limitations**

Although we attempted to identify all studies of VNS+TAU in TRD, our conclusions are limited by the availability (and hence poolability) of clinical evidence. Reassuringly, across time points, important safety measures such as the rates of all-cause mortality (range 0.0-1.4%), fatal suicide (range 0.0-0.2%) and suicide attempts (range 0.0-3.7%) were very low in the VNS+TAU patients.

Our major limitation was the unavailability of RCTs and the fact that the available RCTs did not address the scope of our review. Although we attempted to identify all clinical evidence, the lack of availability of RCT data limits our conclusions.

In addressing criticisms that earlier SLRs did not include all VNS trials, this review made every effort to investigate all studies of adjunctive VNS in TRD. They all reflect a severely ill population typically excluded from other studies, including in some cases patients with BD, such patients often not being eligible in TRD trials. Some VNS populations were even more severe (e.g. the more severe RCBD cohort (Marangell et al., 2008)) and both single arm adjunctive VNS as well as comparator groups likely comprised varying TAU samples, reflecting patient histories and localities. Another challenge of our task was that some studies looked at patients with two or more failed treatments while others evaluated four or more. Many of our meta-analyses were therefore associated with high heterogeneity, reflective of different severity of illness, prior treatment failures, study designs, sizes,

durations of follow-up, locations, differing VNS dosing and differing TAU across the studies (albeit sponsor studies encouraged trial patients to keep any TAU unchanged where clinically possible). Study 8 (Bajbouj et al., 2010) and Study 22 (Desbeaumes Jodoin et al., 2018) described markedly better outcomes than other studies and accounted for heterogeneity in some of the analyses. Both studies included BD patients, however both were small single-arm studies, and consequently they were given proportionately little weight in the meta-analyses and did not influence the results greatly.

Aaronson and colleagues (Aaronson et al., 2017) suggested that patients with a history of positive ECT response did especially well over time with VNS + TAU and studies (e.g. 8 and 22) including BD patients reported somewhat higher response rates. Available data informing our meta-analysis did not allow any exploration of any such baseline predictors of outcome.

The majority of the adjunctive VNS in TRD experience (in terms of patient numbers and duration of treatment) was found in observational studies, reflecting real-world, but by default more biased. The authors made attempts to assess the similarities of short-term RCT versus observational study and remained satisfied that the similarities enabled a hypothesis that longer-term observational data may offer credible insights into longer term outcomes in TRD.

There was considerable disparity between the outcomes and time points at which data were collected across studies, making it difficult to combine all the evidence in a meta-analysis. The general lack of safety data reporting for both VNS+TAU and TAU (especially in non-sponsor studies where the focus of reporting was efficacy) also precluded the analysis of many safety endpoints and hence opportunities for a more detailed safety assessment.

Although other more sophisticated methods could also be considered to address the heterogeneity in patient populations (e.g. matching adjusted indirect comparisons), the type and amount of data available precluded such comparisons.

Management options for this extremely difficult to treat TRD population remain limited and challenging for the patient and the managing physician. The healthcare community has seen a resurgence in neurostimulation interventions (non-invasive methods such as rTMS and tDCS and invasive techniques including DBS and VNS therapy) for these patients in recent times (McGirr and Berlim, 2018). These authors noted that research on VNS therapy demonstrated preliminary effectiveness despite the severity of the target pathology (McGirr and Berlim, 2018).

## 5. Conclusion

Despite the caveats and limitations noted, our comprehensive assimilation of all VNS data offers a summary of the best available evidence suggesting that adjunctive VNS offers improving benefit, tolerance and hope for this very severe chronic TRD population over a 2 year period. Evidence gaps suggest areas for future research involve data collection of QOL outcomes together with more comprehensive safety and efficacy outcomes, especially for TAU alone, with a view to evidence

poolability. This review suggests the importance of assessing both clinical and QOL outcomes to more accurately capture the totality of the therapeutic and patient-relevant impact of VNS+TAU in this hard-to-treat population.

## **Conflict of interest**

J Bottomley, C LeReun, A Diamantopoulos and S Mitchell have received consultancy payments from LivaNova. B Gaynes has received consultation payments from LivaNova addressing models of treatment resistant depression.

## **Contributors**

J Bottomley and C LeReun designed the search protocol and statistical analysis plan. J Bottomley conducted the 2015 and 2019 search and data extraction. A Diamantopoulos oversaw the 2017 update. J Bottomley, A Diamantopoulos and S Mitchell assessed evidence eligibility and quality. C LeReun collated the data and performed all statistical analyses. J Bottomley wrote the manuscript. B Gaynes reviewed all versions of the manuscript and contributed to the discussion. All authors reviewed and revised the paper. All authors reviewed all drafts and have read and approved the final version of this article.

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# VAGUS NERVE STIMULATION (VNS) THERAPY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

## FIGURE LEGENDS

Figure 1. PRISMA Flowchart showing clinical studies identified in the original (2015) and two update searches in 2017 and 2019 combined (searches used the same search strategy)

Figure 2. Absolute effects of VNS + TAU: MADRS - Proportion of responders. A) 6 months; B) 12 months; C) 24 months

Figure 3. Absolute effects of VNS + TAU: MADRS - Proportion of remitters. A) 6 months; B) 12 months; C) 24 months

Figure 4. Absolute effects of VNS+ TAU: CGI I - Proportion of responders: : A) 6 months; B) 12 months; C) 12 months (TAU only)

Figure 5. Absolute effects of VNS+ TAU: HAMD - Proportion of responders: A) 6 months; B) 12 months; C) 24 months; D) 12 months (TAU only)

Figure 6. Absolute effects of VNS+ TAU: HAMD - Proportion of remitters: A) 6 months; B) 12 months; C) 24 months

Figure 7. Absolute effects of VNS+ TAU: Patients experiencing SAEs: at 12 months

Figure 8. Absolute effects of VNS+ TAU: Proportion of Study drop outs: A) 12 months; B) 24 months; C) 24 months (TAU only)

Figure 9. Absolute effects of VNS+ TAU: Study Mortality (all causes): A) 3 months; B) 12 months; C) 24 months

Figure 10. Absolute effects of VNS+ TAU: MADRS Response rate at 12 months: A) Sponsor studies only B) All studies

Figure 11. Absolute effects of VNS+ TAU: CGI Response rate at 12 months: A) Sponsor studies only B) All studies

Figure 12. Absolute effects of VNS+ TAU: HAMD Response rate at 12 months: A) Sponsor studies only B) All studies

Figure 13. Absolute effects of VNS+ TAU: SAEs at 12 months: A) Sponsor studies only B) All studies

**VAGUS NERVE STIMULATION (VNS) THERAPY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS****TABLE DESCRIPTIONS****Table 1. Summary characteristics of TRD studies and patients included in review**

This table describes the study designs, patient characteristics and primary and secondary outcomes. The table footnotes also contain additional records per study & citation

**Table 2. . Overview of outcomes reported across the VNS+TAU evidence base**

This table shows every outcome reported per study to enable an "at a glance" view of the opportunities to pool study outcomes across the eligible studies

**TABLE 1. Summary characteristics of TRD studies and patients included in review**

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
<b>Randomized control trials</b>							
<b>STUDY 1.</b>  Rush 2005 (USA & Canada)  Company sponsored (D-02)  ----- [6 Additional Records: 1. Rush et al 2005 <sup>a</sup> ; 2. George et al 2005 <sup>ii</sup> , 3. Burke and Husain 2006 <sup>iii</sup> , 4. Sackeim et al 2007 <sup>v</sup> , 5. Nierenberg et al 2008 <sup>v</sup> 6. Company data on file <sup>vi</sup> ]	12 weeks	Randomised , DB, PG, placebo- sham controlled trial	<b>N=119</b> randomised to active VNS+TAU (20 Hz, 500µs pulse width, and on/off cycle of 30 sec on and 5 min off) during 2-week stimulation adjustment and acute phase trial 10 week treatment period.) Output current, beginning at 0.25 mA, increased gradually (in 0.25 mA increments) to comfortable level reached vs.  <b>N=116</b> randomised to sham VNS+TAU, (device implanted but not activated).  [Those receiving sham VNS were offered active VNS after 12 week RCT]	Current DSM-IV primary diagnosis MDD, BD I or BDII. Current major depressive episodes (MDE) ≥2 years or at least 4 lifetime MDEs including current MDE.  Ages range from 24-72 years (age 18 to 80 eligible).  Baseline HAMD24 (average of 2) ≥20. BD patients had to be resistant to or intolerant of lithium.  For the current MDE, subjects must have had at least 2 adequate trials of different classes of antidepressant medication but not more than 6.  Patients had to have shown no substantial response to at least 6 weeks psychotherapy during any MDE	<b>MDEs:</b> ≥4 (incl current)  <b>Treatments:</b> ≥2 but ≤6	≥50% reduction in HAMD24 after 10 weeks	MADRS, IDS- SR30, YMRS, CGI-S, CGI-I, SF-36, safety outcomes
<b>STUDY 2.</b>	22 weeks	Multicentre, DB, PG study with patients	<b>N=113</b> , VNS+TAU, High level stimulation (1.25-1.5 mA, 250 µs PW)	Age ≥18 eligible (actual mean age 47.9 (SD 10.8);  Chronic (>2 years) or recurrent (≥	<b>MDEs:</b> ≥4 (incl current)	Mean change from baseline to week 22 of acute phase of	Response & remission in QIDS-C, MADRS, IDS-

Study No., Primary Author, (Country), Sponsor [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
Aaronson 2013 (USA)  Company sponsored (D-21)  ----- [0 Additional Records]		randomised to 3 VNS dose groups (Low, Medium, or High level stimulation)	vs.  <b>N=107</b> , VNS+TAU, Medium level stimulation (0.5-1.0 mA, 250 µs PW)  vs.  <b>N=111</b> , VNS+TAU Low level stimulation (0.25 mA, 130 µs PW)  For 22 weeks active treatment	2 prior episodes) MDD or BD; Current diagnosis of MDE; MDE for >2 years or >4 MDE's lifetime (including current episode);  ≥4 unsuccessful treatment trials in current MDE from 2 different medication classes; MADRS score ≥24 and ≤25% decrease in MADRS between pre-study and BL visit needed for randomisation.  Patients with BD had to be receiving a mood stabilizer and be able to complete all evaluations. Stable regimen of current antidepressant treatments for at least 4 weeks before BL.	<b>Treatments:</b> ≥4 from 2 medication classes	study in IDS-C (ITT)	SR, CGI-I, safety outcomes

**Non-randomized comparative studies**

STUDY 3. Aaronson 2017 (USA)  Company sponsored (D-23)  ----- [2 Additional Records 1. Olin et al 2012 <sup>vii</sup> 2. Company data on	5 Years	Long term prospective multicentre open-label longitudinal naturalistic observational study of the clinical course and outcomes of 2 large cohorts of TRD patients, i.e. VNS+TAU	<b>Cases<sub>a</sub>:</b> N=335 - VNS+TAU (D-23 'original')  <b>Cases<sub>b</sub>:</b> N=159 - VNS+TAU (D-21 'rollovers')  <b>Controls:</b> N=301 - TAU  This study was designed to be an observational registry, thus all treatments were to be observed and recorded and were not to be dictated by the sponsor	<b>Cases<sub>a</sub>:</b> Adults (age >18) experiencing an active major depressive episode ≥2 years in duration (unipolar or bipolar depression) or a history of ≥3 depressive episodes; and a history of ≥4 failed antidepressant treatments (including electroconvulsive therapy).  Treated with VNS+TAU  <b>Cases<sub>b</sub>:</b> VNS+TAU completers of study D-21 (D-21 rollovers)  <b>Controls:</b> As for 'Cases <sub>a</sub> ' but only treated with TAU.	<b>MDEs:</b> ≥3 (incl current)  <b>Treatments:</b> ≥4 (incl ECT)	Response rate - ≥50% decrease in MADRS score from baseline to any post-baseline visit during the 5 year study.  Response rates were cumulative.	Responses and remissions using CGI-I, QIDS-SR, SLICE, remission with MADRS, recurrence & relapse based on MADRS and QIDS-SR, QOL (Q-LES-Q and ASEX), safety outcomes
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Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
file <sup>viii]</sup>		or TAU. Registry patients elected to be treated with either VNS+TAU or TAU only					Response rates were cumulative.
<b>STUDY 4.</b> Sperling 2009 (Germany) ----- [0 Additional records]	12 months	Prospective study of VNS+TAU treated TRD patients vs. sex- and age- matched control TRD patients in a pre- and post implantation study design (typical VNS use as in clinical practice in 1 centre)	<b>Cases:</b> N=9 - VNS+TAU (VNS dose adjustments made every 4 weeks based on response and AE (range 0.25 - 2mA.5 and frequency 15 - 30 Hz, 30 seconds 'ON' and 5 minutes 'OFF')  <b>Controls:</b> N=9 - TAU (medication and psychotherapy)	<b>Cases:</b> Major depression (DSM- IV) and treatment refractory disease. Single case permission granted by Health Insurance Bodies for VNS+TAU patients  <b>Controls:</b> Major depression (DSM-IV) and treatment refractory disease  Inclusion criteria were not formally reported in the publication, but the demographics of the two groups very similar	<b>MDEs:</b> Number not specified but duration of TRD approx 7 years in both groups  <b>Treatments:</b> Mean = 4 per group	Changes in HAMD28 between BL and end of study	Economic: hospitalisation (and duration), consultations, medications, illness-related absence from work
<b>STUDY 5.</b> George 2005	12 months	Open, nonrandomi sed, comparative, longitudinal	<b>Cases:</b> N=205 - VNS+TAU (study D-02)  <b>Controls:</b> N=124 - TAU (study D- 04)	<b>Cases:</b> The evaluable 12 month sample of the D-02 long term open label study was the VNS+TAU group [See STUDY 1]	<b>STUDY 1</b> <b>MDEs:</b>	Difference in IDS-SR30 per month between the two groups,	A range of outcomes collected, including: MADRS,

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
(USA & Canada)  Company sponsored (D-02/04)  ----- [1 Additional Record 1. Company data on file <sup>ix</sup> ]		observational study conducted over similar time period and overlapping sites to offer a clinically relevant active treatment control to VNS+TAU		<b>Controls:</b> Patients entered into a prospective, 12-month, longitudinal, multicenter observational study (D-04) [See STUDY 20 for characteristics].	$\geq 4$ (incl current)  <b>Treatments:</b> $\geq 2$ but $\leq 6$  <b>STUDY 20</b>  <b>MDEs:</b> $\geq 4$ (incl current)  <b>Treatments:</b> $\geq 2$ but $\leq 6$	interpreted as the average amount of improvement in IDS-SR30 score in 1 month that VNS+TAU patients would experience beyond those experiences with TAU only	HAMD24, YMRS, CGI-S, CGI-I, safety (D-02), SF-36 (from D-04)
STUDY 6.  Müller 2013 (Germany)  ----- [0 Additional Records]	12 months	Retrospective, single centre, 2-arm, PG, case-control design to examine 2 VNS groups in terms of strength & frequency of VNS stimulation.  Patients treated with standard	<b>Cases:</b> N=10 - VNS+TAU (high strength/low frequency)) $>1.5\text{mA}$ , 15 Hz. ON & OFF periods constant*  <b>Controls:</b> N=10 - VNS+TAU (low strength/high frequency: $\leq 1.5\text{mA}$ , 20 Hz. ON & OFF periods constant*)  *500 $\mu\text{s}$ PW, duty cycle 30 seconds 'ON', 5 minutes 'OFF'	<b>Cases:</b> N=10 - VNS+TAU (high strength/low frequency)  <b>Controls:</b> N=10 - VNS+TAU (low strength/high frequency)  To be eligible, patients treated with the routine clinical procedures for VNS were retrospectively assigned to 1 of 2 groups. There were no differences between the 2 groups at baseline with regard to age, sex, time since implantation, or HAMD score.	<b>MDEs:</b> Not reported  <b>Treatments:</b> Not reported	Reduction in HAMD (version not specified) scores from BL to end of follow up (approx 12 months)	None reported

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
		VNS clinical procedures were retrospectively assigned to 1 of 2 groups					
<b>Single arm studies</b>							
<b>STUDY 7.</b> Nahas 2005 USA & Canada)  Company sponsored (D-01) ----- [6 Additional Records 1. Marangell et al 2002 <sup>x</sup> , 2. Rush et al 2000 <sup>xi</sup> , 3. Sackheim et al 2001 <sup>xii</sup> , 4. Sackheim et al 2007 <sup>xiii</sup> , 5. Schlaepfer et al 2008 <sup>xiv</sup> 6. Company data on file <sup>xv</sup> ]	24 months	OL pilot study - consisted of a screening and BL period, single-blind run in period then acute dosing	<b>60 patients</b> had VNS+TAU implant surgery, followed by a 2-week recovery period. Then stimulation parameters were turned on and adjusted to patient comfort over the next 2 weeks. Thereafter, parameters were kept constant for next 8 weeks [if possible]. Initial acute period (3 months) extended to 24 months where more flexibility in VNS+TAU and concomitant medications was allowed	Inclusion criteria comprised DSM-IV diagnosis of unipolar or BD I or II; MDE >2 years and >4 MDEs in lifetime (including current episode); 18 to 70 years old; not responded to ≥2 adequate antidepressant medication treatments from ≥2 different classes during current MDE. At BL, score ≥20 on HAMD28, ≤50 on GAF, IQ ≥70. BD patients resistant, intolerant, or had a medical contraindication to lithium. Patients excluded if met DSM-IV criteria for atypical or psychotic depression, had a history of schizoaffective disorder, schizophrenia, or other non-mood disorder psychosis, currently had RCBD or had a current secondary diagnosis or signs of dementia, delirium, amnesia, or other cognitive disorder. Patients also had to have received > 6 weeks of psychotherapy	<b>MDEs:</b> ≥4 (incl current)  <b>Treatments:</b> ≥2 (different classes)	% patients responding (defined as ≥50% improvement in HAMD28 score) and % patients remitting (defined as HAMD28 score ≤10)	CGI, MADRS, YMRS, GAF, SF-36, safety outcomes

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
<b>STUDY 8.</b> Bajbouj 2010 (Belgium, Sweden, Germany, Ireland, Switzerland, UK)  Company sponsored (D-03) ----- [2 Additional Records 1. Corcoran et al 2006 <sup>xvi</sup> 2. Schlaepfer et al 2008 (as in Study 7)]	24 months	OL single arm longitudinal study	As above (Study 7).  This EU study in <b>74 patients</b> was conducted to assess if US D-01 results could be replicated using a similar VNS+TAU protocol with a different population, severity, location, and healthcare environment.	Inclusion criteria comprised DSM-IV diagnosis of unipolar or BD I or II MDE for >2 years and >4 MDE's in lifetime (including current episode); 18 to 80 years old, not responded to ≥2 and not >6 adequate antidepressant medication treatments from ≥2 different classes during current MDE.  History of psychotherapy with no clinical improvement.  Exclude patients with > 6 ATHF failures in the current episode.  At BL, score ≥20 on the HAMD24 (as opposed to the HAMD28 in the D-01 study). BD patients had to be resistant, intolerant, or have medical contraindication to lithium.  20 of 74 patients had BD	<b>MDEs:</b> ≥4 (incl current)  <b>Treatments:</b> ≥2 but ≤6 (from 2 different classes)	Responders (≥50% reduction in HAMD28 from BL) and Remitters (HAMD28 score ≤10)	MADRS, IDS-SR30, CGI, safety outcomes
<b>STUDY 9.</b> Albert 2015 (Italy) ----- [0 Additional Records]	12 months	Naturalistic follow up single arm study	<b>5 Patients</b> all received VNS+TAU approx 1mA at 3 months; then in 4 of the 5 patients this was increased to 1.25mA over 12months	Inclusion criteria comprised: Current MDE, chronic (actual episode ≥2years or recurrent (h/o at ≥4 lifetime MDEs), age ≥18, failure to respond to ≥2 adequate trials of antidepressants in current MDE, minimum total HAMD17 score of 20, stable medications for 4 weeks	<b>MDEs:</b> Number not reported, but TRD duration mean 26.8 (SD 5.5) years  <b>Treatments:</b> Mean 8.4 (SD 2.7)	Response (≥50%) and remission (score ≤7) according to HAMD17	MADRS, CGI-S, SF-36

Study No., Primary Author, (Country), Sponsor [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
<b>STUDY 10.</b>  Christmas 2013 (Scotland) ----- [0 Additional Records]	12 months	Case series	Cohort of <b>13 patients</b> treated with VNS+TAU in the context of a specialist mood disorders service in Dundee.  Mean 1.5 mA current delivered for 30s every approx 2.5min, frequency 20Hz, and PW average 263µs (a higher total charge compared with "standard" settings)	Chronic, treatment-refractory unipolar major depression. Patients with a diagnosis of bipolar disorder were excluded.	<b>MDEs:</b> Not reported.  <b>Treatments:</b> ATHF mean 9.4 (SD 3.9)	Composite endpoint: Either ≥50% improvement in HAMD17 or MADRS, or a score of 1 or 2 on CGI-I	No
<b>STUDY 11.</b>  Cristancho 2011 (USA & Canada) ----- [0 Additional Records]	12 months	OL study VNS in TRD in clinical practice	VNS+TAU dosing ( <b>15 patients</b> ) varied per clinical practice & patient need.  At 6 months the median dose was higher (1.5mA) to that at 12 months (1.3mA)	This clinical practice study post FDA approval recruited patients according to indication, with "DSM-IV diagnosis of MDD or BD disorder and were currently in a MDE"	<b>MDEs:</b> Number not reported, but TRD duration mean 31.7 (SD 11.1) years  <b>Treatments:</b> Not reported	Change in BDI score at 6 months and 12 months vs. BL	HAMD17, HAMD24, BAI, BHS, Q-LES-Q, CGI-I, hospitalisations, suicide attempts in 12m
<b>STUDY 12.</b>  Dell'Osso 2013 (Italy) ----- [1 Additional Record 1. Oldani et al 2015 <sup>xvii</sup> ]	1 and 5 years treatment & follow up.	OL study	"Standard" recommended VNS+TAU stimulation parameters applied.  All <b>6 patients</b> reached the intensity of 1mA within 9 weeks of implant	Depression - DSM-IV. >18 and < 65 years old.  MDD at least 2years duration; resistance in current episode to at least 2 different classes antidepressants.  Non response to psychotherapy or lithium if BD.	<b>MDEs:</b> Number not reported, but TRD duration mean 19.5 (SD 14.8) years  <b>Treatments:</b> Mean 4.7 (SD 1.6)	Not clear: HAMD21, MADRS, CGI, recurrence collected	Not clear: HAMD21, MADRS, CGI, recurrence collected
<b>STUDY 13.</b>	Follow up reported	Case series	<b>9 patients</b> VNS+TAU Dosing was 'according	These patients in clinical practice had:	<b>MDEs:</b>	Response and remission	Not reported

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
Franzini 2008 (Italy) ----- [0 Additional Records]	ranged from 4months to 7years.  12 month outcomes assessed in this review		to sponsor indications': 0.25 mA, 30 Hz, 500μsec, 30 seconds 'ON', 5 minutes 'OFF'	Current episode at least two years; Failed at least four antidepressant trials [ATHF].  None benefitted from a minimum of six months of psychotherapy	Number not reported  <b>Treatments:</b> All patients had failed at least 4 antidepressant trials", exact mean across series not reported	(<10) according to HAMD21	
STUDY 14.  Marangell 2008 (USA) ----- [0 Additional Records]	12 months treatment & follow up.	OL, single arm, longitudinal pilot study	<b>10 patients</b> with RCBD treated with VNS+TAU.  The initial VNS dose was 0.25mA increasing in 0.25mA increments to a maximum of 0.75mA.	Inclusion criteria comprised: Age 18-70; RCBD defined per DSM-IV- TR. A h/o depressive, manic or hypomanic symptoms at least 50% time in previous year despite ongoing treatment according to NIMH LCM-r. Treatment resistance defined as intolerance or no response to both lithium & valproate plus at least 2 of the following, either in monotherapy or in combination: carbamazepine, lamotrigine, gabapentin, topiramate, olanzapine, risperidone, quetiapine or clozapine	<b>MDEs:</b> Duration RCBD approx 19y  <b>Treatments:</b> Not reported	Symptom severity assessed by NIMH LCM-p 44 weeks post implant	HAMD24, MADRS, IDS- SR30, YMRS, CGI, GAF
STUDY 15.  O'Keane 2005 (Ireland) -----	3 months treatment & follow up	Case series	<b>11 patients</b>  Limited detail of VNS+TAU other than maximum current did not exceed 1.5mA	Inclusion criteria comprised: Depression - DSM-IV. >18 and <65 years old. MDD at least 2years; resistance in current episode to ≥2 different classes antidepressants. Non response to psychotherapy or lithium if BD.	<b>MDEs:</b> Current MDE mean 56.3 (SD 8.7) months  <b>Treatments:</b>	Response on HAMD28	MADRS, IDS- SR, YMRS

Study No., Primary Author, (Country), Sponsor [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
[0 Additional Records]				All patients had failed at least 4 antidepressant trials", exact mean across series not reported			
<b>STUDY 16.</b>  Tisi 2014 (Italy) ----- [0 Additional Records]	Follow up to 5 years in some patients	Case series	<b>27 patients</b>  No details of VNS+TAU dosing reported.	Inclusion criteria comprised HAMD21 score ≥20.  Lack response to at least 4 full dosage antidepressant trials & at least 6months psychotherapy.  Current MDE at least 2 years without remission or response to treatment	<b>MDEs:</b>  Number not reported, but TRD duration mean 18.5 (SD 13.3) years  <b>Treatments:</b>  Not reported	Response and remission (<7) according to HAMD21	None reported
<b>STUDY 17.</b>  Müller 2017 (Germany) ----- [0 Additional Records]	Range 3 to 200 months	Retrospective single centre study	<b>18 patients</b>  VNS+TAU Mean output current intensity 1.46 mA (range 0.5-2.0 mA), mean pulse frequency 23.61 Hz (range 20-25 Hz); pulse width and duty cycle time not reported	Inclusion criteria not reported. Authors described "... retrospectively analyzing data from 18 long-term treated patients".  Mean age 54.0; 66.7% male; TRD and MDE duration not reported; baseline HAMD not reported; concomitant therapy not reported	<b>MDEs:</b>  Not reported,  <b>Treatments:</b>  Not reported	Not clear: HAMD collected	Not clear: HAMD collected
<b>STUDY 18.</b>  Perini 2017 (Italy)	12 months	Single arm trial	<b>6 patients</b>  VNS+TAU -  Output current intensity initially set to 0.25 mA and subsequently increased based on tolerance; 20-30 Hz pulse frequency; 250-500 µs pulse width; initial duty cycle	Inclusion criteria comprised age 18 to 65; chronic (≥2 years) current MDE and/or history of recurrent MDEs (at least 4 including current MDE). TRD was defined as no response to ≥2 different drug categories in current MDE.  Mean age 51.3; 66.7% male; the	<b>MDEs:</b>  5.17 (SD 1.60)  <b>Treatments:</b>  Lifetime (ATHF) 7.00	Not clear: HAMD21, BDI, hippocampal volumes collected	Not clear: HAMD21, BDI, hippocampal volumes collected

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
----- [0 Additional Records]			was set to 30 s on and 4.5 min. off (adjustments allowed)	mean duration of current MDE was 33.67 months; Unipolar TRD duration not reported; mean baseline HAMD 26.8 (SD 7.85); mean baseline BDI score 33.4 (SD 18.55).  Patients with other concurrent or previous mental (including bipolar disorder) or neurological disorders and patients with history of suicide attempts and acute suicidal behavior or ideation were excluded.  Concomitant medication: antidepressants, benzodiazepines, and/or second generation antipsychotics and/or mood stabilizers; therapy optimized at least 8 weeks before the VNS intervention; not changed in the first year after VNS implantation.	(SD 1.26)		
<b>STUDY 19.</b>  Salloum 2017 (USA)  ----- [0 Additional Records]	Follow up over 5 years	Chart review of patients in VNS+TAU trials at a single centre (Aaronson 2017, Rush 2005, Aaronson 2013)	<b>6 patients</b>  VNS+TAU Mean output current intensity 0.83 mA, mean pulse frequency 20 Hz; mean pulse width 293 µs; duty cycle time not reported	The authors reported "... a series of 6 TRD patients... following VNS implantation, experiencing an average of over 9 years of sustained antidepressant remission.. These patients had previously participated in prospective studies..."  Mean age 60.3; 66.7% male; mean duration of current MDE 35 months; TRD duration not reported; baseline MADRS not reported; concomitant therapy not reported	<b>MDEs:</b>  Mean duration of illness 20.5y  <b>Treatments:</b>  Mean 8.5 failed adequate dose- duration antidepressant trials	Not clear: MADRS collected	Not clear: MADRS collected

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
<b>STUDY 20.</b>  Dunner 2006 (USA)  Company sponsored (D-04)  -----  [2 Records  1. George et al 2005 <sup>xviii</sup> 2. Company data on file <sup>xix</sup> .]	24 months	Prospective observational study	<b>124 patients</b>  Patients followed up over 2 years receiving TAU only (standard of care defined as the plan doctor and patient chose to follow)	Aged 18 to 80 eligible. Current treatment-resistant MDE defined by DSM-IV. Current MDE chronic (lasting ≥2 years) or a h/o recurrent MDEs (≥4 in lifetime, including current MDE).  For the current MDE, subjects had at least 2 adequate trials of different classes of antidepressant medication but not more than 6 (as defined by modified ATHF)	<b>MDEs:</b>  Number not reported, but TRD duration mean 25.8 (SD 13.2) years  <b>Treatments:</b>  Mean 4.3 (SD 1.6)	Response (≥50% improvement) and remitter (score ≤14) in IDS-SR30	SF-36  [HAM24, CGI not reported in this paper, see George 2005]
<b>STUDY 21</b>  Trottier-Duclos 2018	6 years  Assessments over a 72m follow up - 10 evaluations	Long term naturalistic study single arm trial	10 patients with TRD  Initial stimulation at 0.25 mA output current and 30 Hz with 250 µs impulse duration, 30 seconds on and 5 minutes off was modified over follow up based on response and tolerability	Eligible TRD patients were defined as MDE including BD meeting DSM 4th edition criteria despite 3 antidepressant trials and at least 1 pharmacological potentiation. Exclusion criteria were active neurological disorder, acute medical disorder, severe Axis II disorder or another major Axis I disorder  Mean age 50 years (SD, 4.7), 7/10 patients had unipolar depression and 3/10 had BD	<b>MDEs:</b>  4 (SD, 1.3)	QOL (SF36)	Depression (HAMD)  Anxiety (HAMA)
<b>STUDY 22</b>	12 months	Naturalistic study single arm trial	14 patients with TRD (MDD or BD)	Patients with MDD or BD were eligible if they had achieved either partial or no response to ≥4	<b>MDEs:</b>  Mean 3.3 (1.1)	Mood (MADRS) and cognition	

Study No., Primary Author, (Country), Sponsor  [Additional records per study (n) & citation]	Study duration & follow-up	Study design	Number of patients, Interventions and dose,	Summary of inclusion criteria and main population characteristics	Number of prior MDEs / unsuccessful treatments	Primary outcome(s)	Secondary outcome(s)
Desbeaumes Jodoin 2018		Goal was to study long term cognitive effects of VNS and its relationship to changes in mood.	<p>Initial stimulation at 0.25 mA output current gradually increased in 0.25 mA increments, 30 seconds on and 5 minutes off was modified over follow up based on response and tolerability.</p> <p>At 12m, output currents ranged from 0.75 to 1.75 mA (mean 1.42 mA; median 1.5 mA). Most patients were stimulated with frequency 30 Hz with 250 µs pulse width</p>	<p>antidepressant medications at minimum adequate dose and duration.</p> <p>All patients had also received at least 6 weeks cognitive behavioural therapy</p> <p>9 female, 5 male patients mean age at implantation <math>50 \pm 6.2</math> years. 8/14 patients had MDD and 6/14 had BD</p> <p>Mean age of depression onset was 25 years (16-47 years)</p>	<p>Unipolar =3 BP=3.7</p> <p>No. mood disorder treatment trials mean 4.9 (1.0)</p>	(verbal (RAVLT) and visuospatial (ROCF) memory, attention/executive functions & psychomotor speed (incl SDMT)	

ASEX - Arizona Sexual Experience Scale; ATHF - Antidepressant Treatment History Form; BAI- Beck Anxiety Inventory; BD - bipolar disorder; BDI - Beck Depression Inventory; BHS - Beck Hopelessness Scale; BL - baseline; BD - bipolar disorder; CGI-I - Clinician Global Impression - Improvement; DB – double blind; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition; GAF - Global Assessment of Function; HAMA - Hamilton Anxiety Rating Scale; HAMD - Hamilton Rating Scale of Depression; IDS-C - Inventory of Depressive Symptomatology - Clinician; IDS-SR - Inventory of Depressive Symptomatology - self report; ITT – intention to treat; MADRS - Montgomery-Asberg Depression Rating Scale; MDD - major depressive disorder; MDE - major depressive episode; NIMH LCM-r - National Institute of Mental Health retrospective life charting methodology; OL - open label; PG – parallel group; PW=pulse width; QIDS-C - Quick Inventory of Depressive Symptomatology-Self Report; Q-LES-Q - Quality of life Enjoyment and Satisfaction Questionnaire; RAVLT - Rey Auditory Verbal Learning test; RCBD - Rapid Cycling Bipolar Disorder; ROCF - Rey-Osterrieth Complex Figure test; SDMT - Symbol Digit Modalities Test; SLICE - Streamlined Longitudinal Interval Continuation Evaluation; TRD - treatment resistant depression; YMRS - Young Mania Rating Scale

## ADDITIONAL REFERENCES ASSOCIATED WITH EACH STUDY IN TABLE 1

- 
- <sup>i</sup> Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: A naturalistic study. *Biol Psychiatry* 2005;58(5):355-363
- <sup>ii</sup> George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 2005;58(5):364-373
- <sup>iii</sup> Burke MJ and Husain MM. Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. *Journal of ECT* 2006;22(3):218-22
- <sup>iv</sup> Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS™). *Int J Neuropsychopharmacol* 2007;10(6):817-826
- <sup>v</sup> Nierenberg AA, Alpert JE, Gardner-Schuster E, Seay S, Mischoulon D. Vagus Nerve Stimulation: 2-Year Outcomes for Bipolar Versus Unipolar Treatment-Resistant Depression. *Biol Psychiatry* 2008 Sep 15;64(6):455-460
- <sup>vi</sup> Study 1. Sponsor SF-36 Data on File (D-02). (2002)
- <sup>vii</sup> Olin B, Jayewardene AK, Bunker M, Moreno F. Mortality and Suicide Risk in Treatment-Resistant Depression: An Observational Study of the Long-Term Impact of Intervention. *PLoS ONE* 2012 Oct 25;7(10).
- <sup>viii</sup> Study 3. D23 Final Study Report July 2015
- <sup>ix</sup> Study 5. Sponsor SF-36 Data on File 2 (D-02 / D-04) (2002)
- <sup>x</sup> Marangell LB, Rush J, George MS et al. Vagus nerve Stimulation (VNS) for major depressive episodes: One year outcomes. *Biol Psychiatry* 2002;51:280-7
- <sup>xi</sup> Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biol Psychiatry* 2000;47(4):276-286
- <sup>xii</sup> Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, et al. Vagus nerve stimulation (VNS™) for treatment-resistant depression: Efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001;25(5):713-728
- <sup>xiii</sup> Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS™). *Int J Neuropsychopharmacol* 2007;10(6):817-826
- <sup>xiv</sup> Schlaepfer TE, Frick C, Zobel A et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med* 2008;38(5):651-61
- <sup>xv</sup> Study 7. Sponsor SF-36 Data on File
- <sup>xvi</sup> Corcoran CD, Thomas P, Phillips J and O'Keane V. Vagus nerve stimulation in chronic treatment-resistant depression: Preliminary findings of an open-label study. *British Journal Psychiatry* 2006;189:282-3

<sup>xvii</sup> Oldani L, Dell'Osso B, Altamura AC. Long-term effects of vagus nerve stimulation in treatment-resistant depression: a 5-year follow up case series. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 2015; 8(6):1229-30

<sup>xviii</sup> George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005;58(5):364-373

<sup>xix</sup> Study 20. Company SF-36 Data on File (D-04) 2002

**TABLE 2. Overview of outcomes reported across the VNS+TAU evidence base**

Study (Author, year)	FU (months)	HAMD (version)	MADRS	IDS-SR	IDS-C	QIDS-SR	YMRS	GAF	CGI	BDI	SLICE	QOL*	SAFETY**	Comment***
<b>STUDY 1.</b> Rush 2005	24	X(24)	X	X				X				X SF-36	X	RCT
<b>STUDY 2.</b> Aaronson 2013	12		X	X	X				X				X	RCT
<b>STUDY 3.</b> Aaronson 2017	60		X			X			X		X	X Q-LES-Q, ASEX	X	159 STUDY 2 rollovers
<b>STUDY 4.</b> Sperling 2009	12	X(28)												
<b>STUDY 5.</b> George 2005	12	X(24)	X	X					X				X	Duplication STUDY 1 & 20
<b>STUDY 6.</b> Müller 2013	12	X(?)												Different stimulation regimens
<b>STUDY 7.</b> Nahas 2005	24	X(28)	X				X	X	X			X SF-36	X	
<b>STUDY 8.</b> Bajbouj 2010	24	X(28)	X	X					X				X	
<b>STUDY 9.</b> Albert 2015	12	X(17)	X						X			X SF-36		

<b>STUDY 10.</b> Christmas 2013	12	X(17)	X						X						Composite primary
<b>STUDY 11.</b> Cristancho 2011	12	X(17,24)							X	X		X Q-LES-Q			
<b>STUDY 12.</b> Dell'Osso 2013	12	X(21)	X						X						
<b>STUDY 13.</b> Franzini 2008	12****	X(21)													
<b>STUDY 14.</b> Marangell 2008	12	X(24)	X	X				X	X	X					RCBD patients only
<b>STUDY 15.</b> O'Keane 2005	3	X(28)	X	X			X								
<b>STUDY 16.</b> Tisi 2014	≤60	X(21)													
<b>STUDY 17.</b> Müller 2017	3-200	X(?)													Data format unusable
<b>STUDY 18.</b> Perini 2017	12	X (21)							X						
<b>STUDY 19.</b> Salloum 2017	>60		X												Updates of patients included in different VNS+TAU trials at a single US centre
<b>STUDY 20.</b> Dunner 2006	24	X(24)		X					X			X SF-36			
<b>STUDY 21</b> Trottier-Duclos 2018	72	X(28)										X SF-36			Anxiety symptoms (HAMA)

<b>STUDY 22</b> Desbeaumes Jodoïn 2018	12		X												Cognitive effects: cognition (verbal (RAVLT) and visuo- spacial (ROCF) memory, attention/ executive functions & psychomotor speed (incl SDMT)
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BDI: Beck Depression Inventory; CGI-I: Clinical Global Impressions Scale - Improvement; FU: Follow up; GAF: Global Assessment of Functioning; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Rating Scale for Depression; IDS-C: Inventory of Depressive Symptomatology - Clinician; IDS-SR: Inventory of Depressive Symptomatology - Self report; MADRS: Montgomery Asberg Depression Rating Scale; NIMH LCM-p: National Institute of Mental Health prospective life charting methodology; RAVLT - Rey Auditory Verbal Learning test; RCBD: Rapid cycling bipolar disorder; ROCF - Rey-Osterrieth Complex Figure test; SDMT - Symbol Digit Modalities Test; SLICE: Streamlined Longitudinal Interval Continuation Evaluation; YMRS: Young Mania Rating Scale.

Study primary endpoints based on this measure shown in **bold**. FU=maximum duration of follow up within the study

\*Three QOL measures (always secondary endpoints) used across the evidence base (Short Form 36 (SF-36), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Arizona Sexual Experience Scale (ASEX).

\*\*Safety outcomes included: % patients with adverse events (AE), hospitalizations, serious adverse events (SAEs), suicide, mortality, mania, drop outs (all cause), discontinuation due to AEs

\*\*\*Other variables could include NIMH LCM-p severity scale for RCBD patients; \*\*\*\*FU ranged from 4 months to 7 years.

## VAGUS NERVE STIMULATION (VNS) THERAPY IN PATIENTS WITH TREATMENT RESISTANT DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

### HIGHLIGHTS

- This VNS therapy review includes new, longer-term patient-relevant findings in TRD
- 2-year experience of more clinical and QOL outcomes than other reviews are analyzed
- All criticisms of VNS evidence cited in previous reviews are addressed
- Despite evidence limitation our review provides a summary of the best available data
- For all outcomes assessed, VNS+TAU offered consistent patient-relevant benefit
- VNS evidence suggests improving benefit and hope for this hard-to-treat population

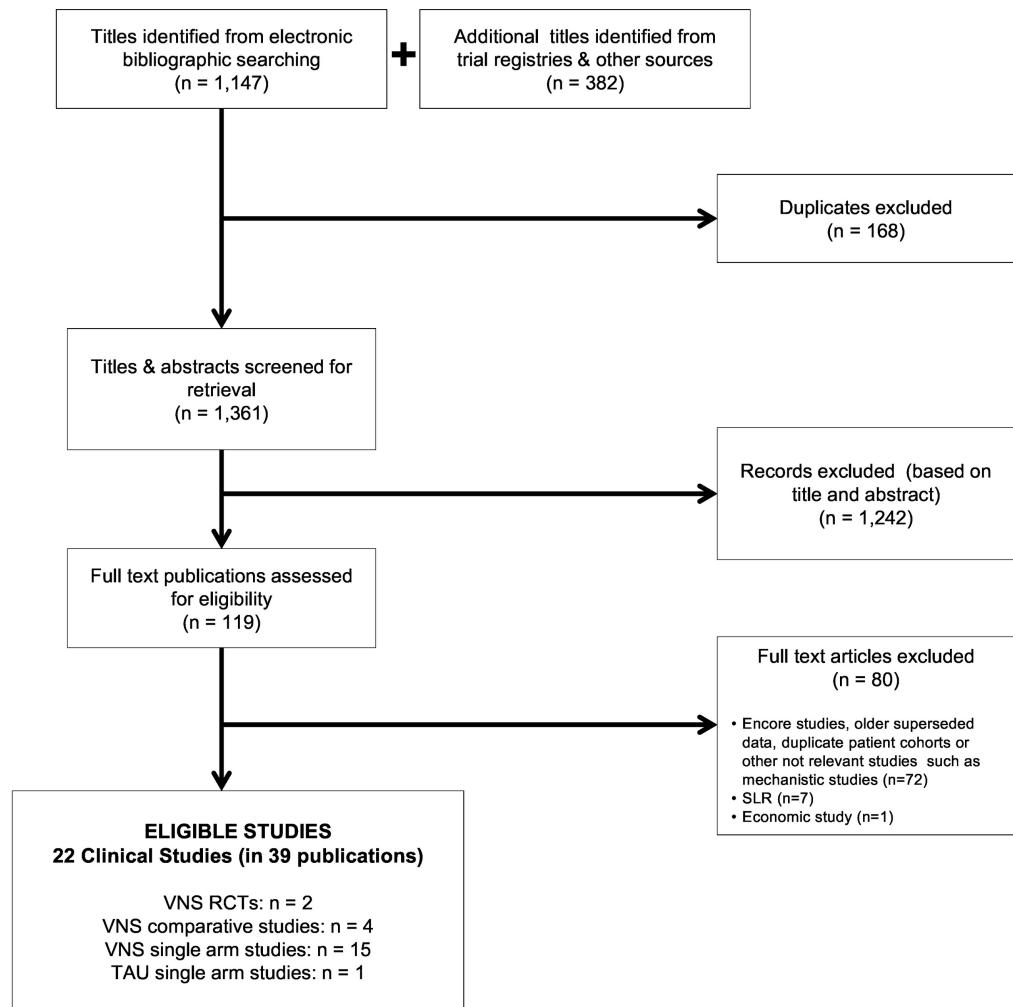
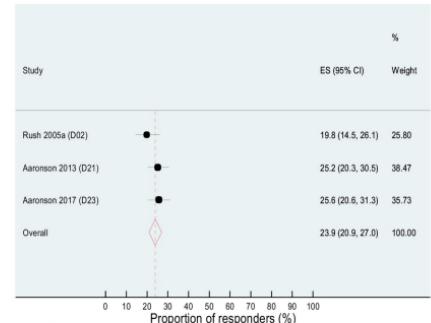


Figure 1

### MADRS response at 6 months (OC)

Patients treated with VNS+TAU

A



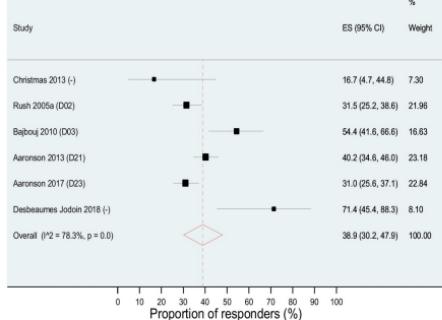
Fixed-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Astberg Depression Rating Scale.

### MADRS response at 12 months (OC)

Patients treated with VNS+TAU

B



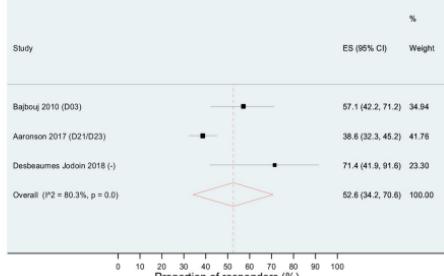
Random-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Astberg Depression Rating Scale.

### MADRS response at 24 months (OC)

Patients treated with VNS+TAU

C



Random-effects model

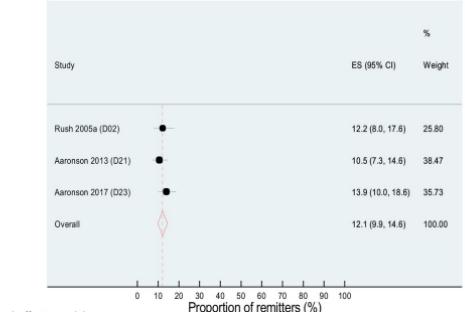
OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Astberg Depression Rating Scale.

Figure 2

### MADRS remission at 6 months (OC)

Patients treated with VNS+TAU

A



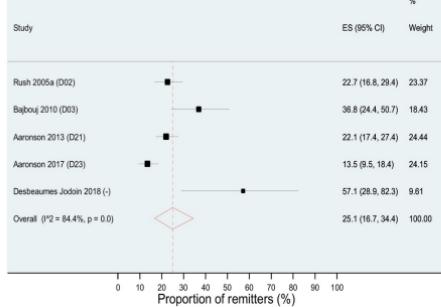
Fixed-effects model

OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Asberg Depression Rating Scale.

### MADRS remission at 12 months (OC)

Patients treated with VNS+TAU

B



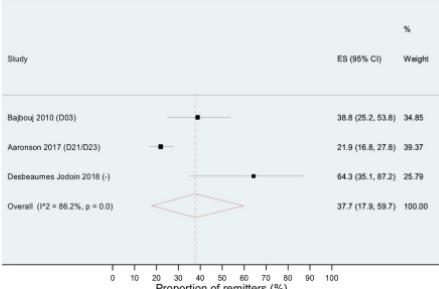
Random-effects model

OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Asberg Depression Rating Scale.

### MADRS remission at 24 months (OC)

Patients treated with VNS+TAU

C



Random-effects model

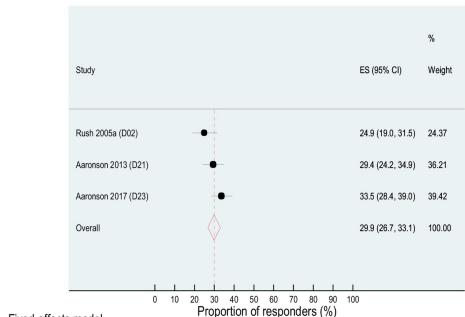
OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. MADRS: Montgomery-Asberg Depression Rating Scale.

Figure 3

### CGI-I response at 6 months (OC)

Patients treated with VNS+TAU

A



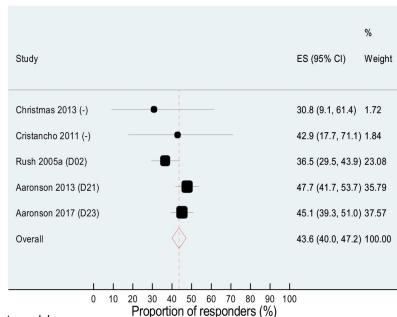
Fixed-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. CGI-I: Clinical Global Impression-Improvement.

### CGI-I response at 12 months (OC)

Patients treated with VNS+TAU

B



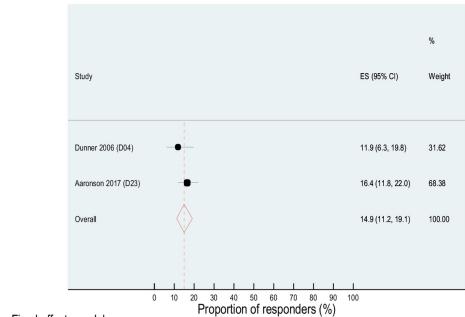
Fixed-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. CGI-I: Clinical Global Impression-Improvement.

### CGI-I response at 12 months (OC)

Patients treated with TAU

C



Fixed-effects model

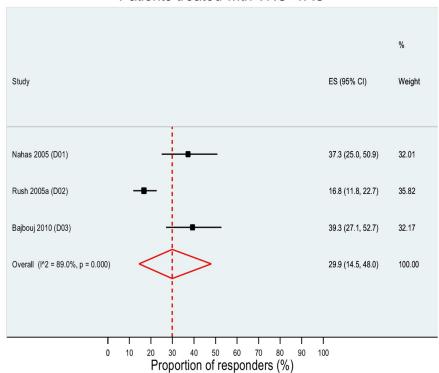
OC: observed cases. ES: effect size (% of responders). TAU: treatment as usual. CGI-I: Clinical Global Impression-Improvement.

Figure 4

## HAMD response at 6 months (OC)

Patients treated with VNS+TAU

A



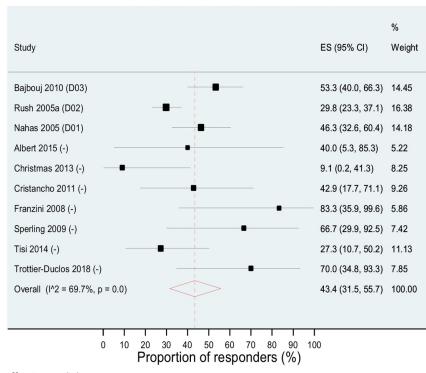
Random-effects model

OC: observed cases; ES: effect size (% of responders); VNS: vagal nerve stimulation; TAU: treatment as usual; HAMD: Hamilton Rating Scale for Depression.

## HAMD response at 12 months (OC)

Patients treated with VNS+TAU

B



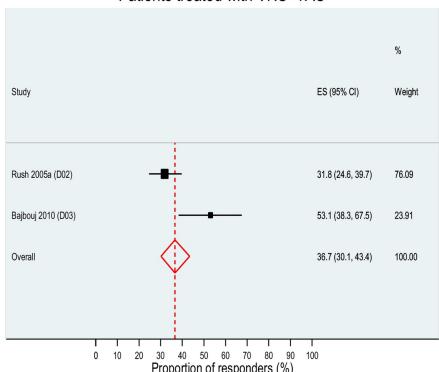
Random-effects model

OC: observed cases; ES: effect size (% of responders); VNS: vagal nerve stimulation; TAU: treatment as usual; HAMD: Hamilton Rating Scale for Depression.

## HAMD response at 24 months (OC)

Patients treated with VNS+TAU

C



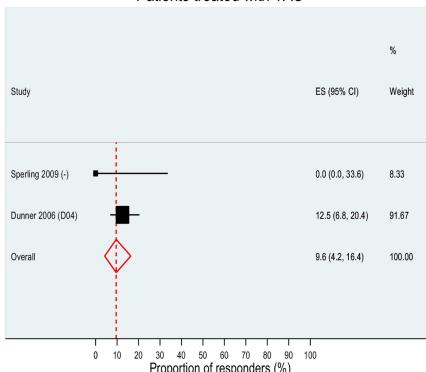
Fixed-effects model

OC: observed cases; ES: effect size (% of responders); VNS: vagal nerve stimulation; TAU: treatment as usual; HAMD: Hamilton Rating Scale for Depression.

## HAMD response at 12 months (OC)

Patients treated with TAU

D



Fixed-effects model

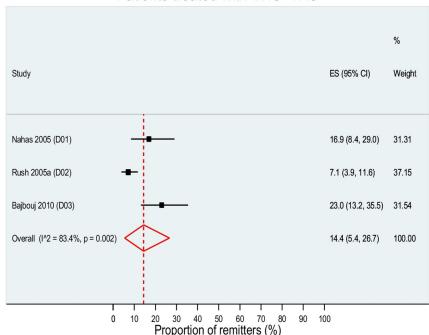
OC: observed cases; ES: effect size (% of responders); TAU: treatment as usual; HAMD: Hamilton Rating Scale for Depression.

Figure 5

### HAMD remission at 6 months (OC)

Patients treated with VNS+TAU

A



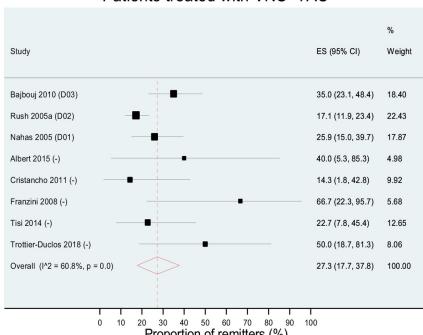
Random-effects model

OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. HAMD: Hamilton Rating Scale for Depression.

### HAMD remission at 12 months (OC)

Patients treated with VNS+TAU

B



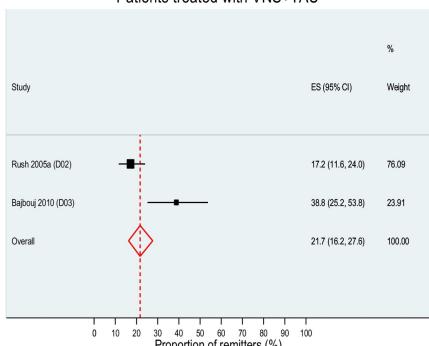
Random-effects model

OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. HAMD: Hamilton Rating Scale for Depression.

### HAMD remission at 24 months (OC)

Patients treated with VNS+TAU

C



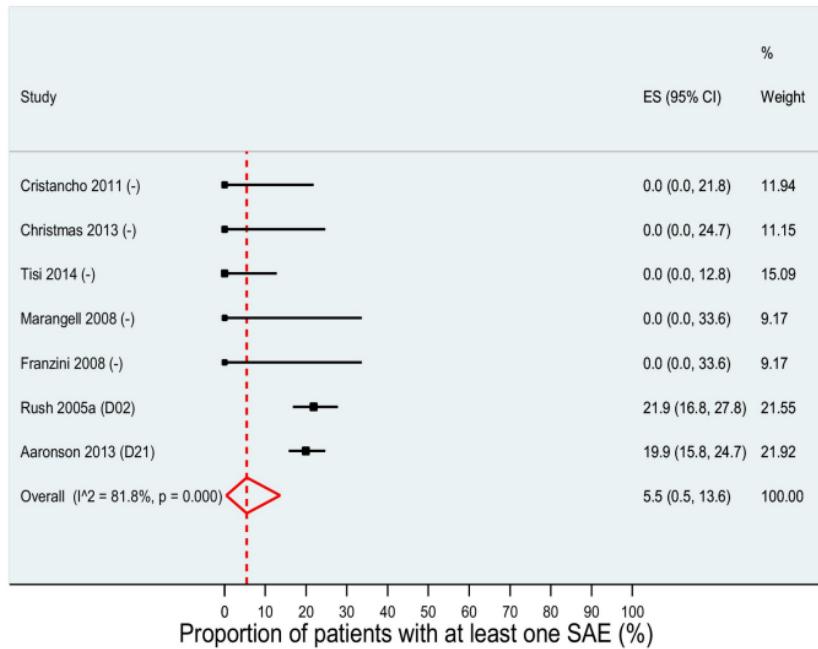
Fixed-effects model

OC: observed cases. ES: effect size (% of remitters). VNS: vagal nerve stimulation. TAU: treatment as usual. HAMD: Hamilton Rating Scale for Depression.

Figure 6

# Patients with at least one SAE at 12 months

## Patients treated with VNS+TAU



Random-effects model

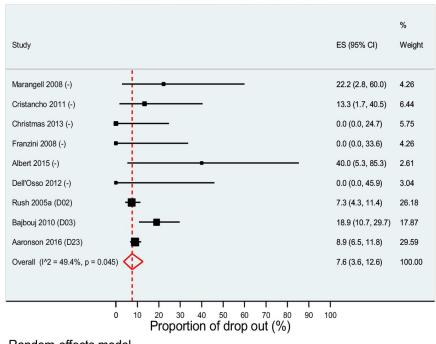
ES:effect size (% of patients with at least one SAE). VNS:vagal nerve stimulation. TAU: treatment as usual. SAE: serious adverse event.

Figure 7

## Patients dropping out at 12 months

### Patients treated with VNS+TAU

A



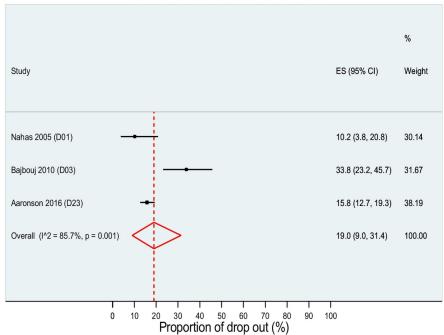
Random-effects model

ES: effect size (% of drop out); VNS: vagal nerve stimulation; TAU: treatment as usual.

## Patients dropping out at 24 months

### Patients treated with VNS+TAU

B



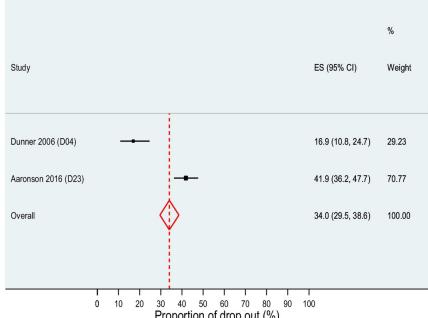
Random-effects model

ES: effect size (% of drop out); VNS: vagal nerve stimulation; TAU: treatment as usual.

## Patients dropping out at 24 months

### Patients treated with TAU

C



Fixed-effects model

ES: effect size (% of drop out); TAU: treatment as usual.

**Figure 8**

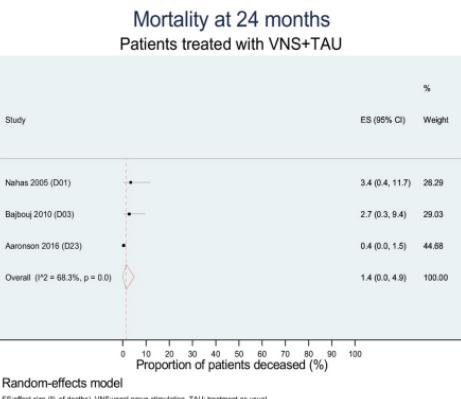
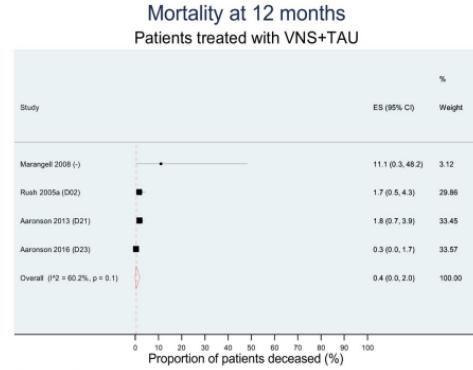
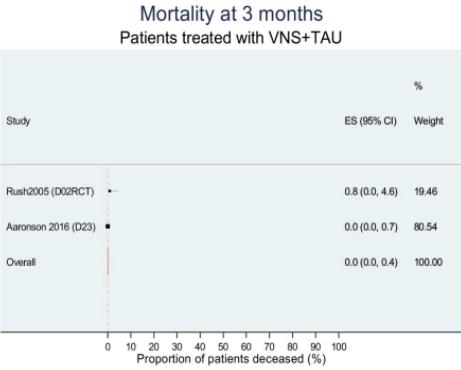
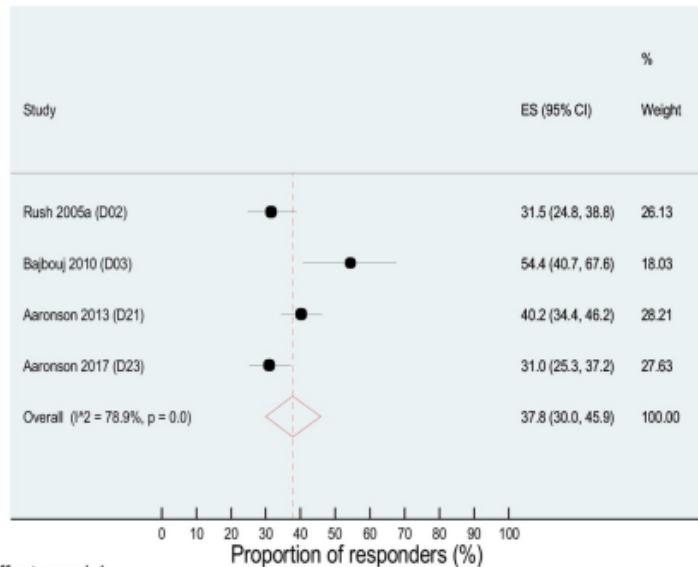


Figure 9

## MADRS response at 12 months (OC)

Patients treated with VNS+TAU - LivaNova studies only

A



## MADRS response at 12 months (OC)

Patients treated with VNS+TAU

B

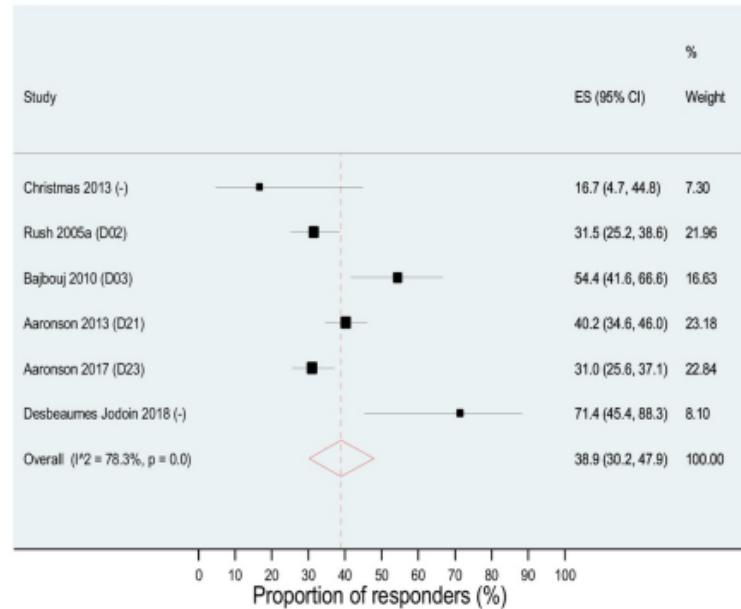
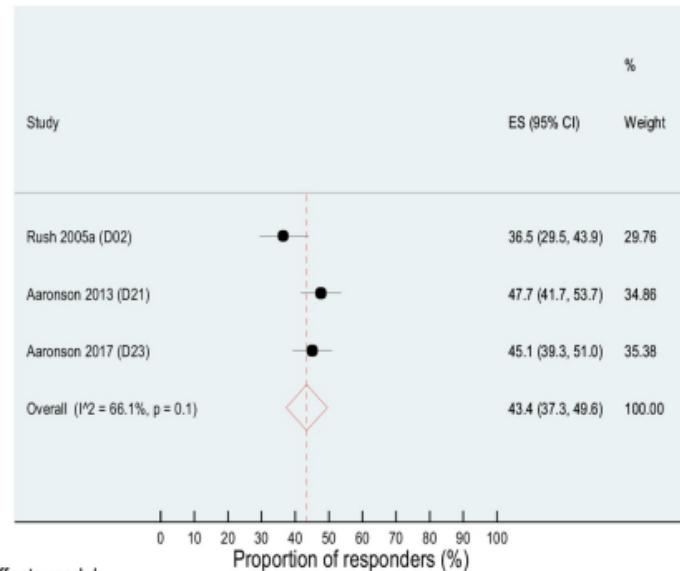


Figure 10

## CGI-I response at 12 months (OC)

Patients treated with VNS+TAU - LivaNova studies only

A



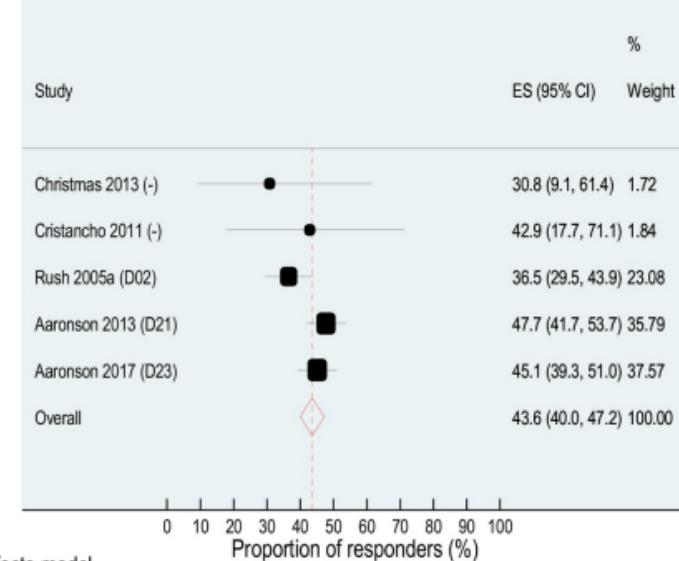
Random-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. CGI-I: Clinical Global Impression-Improvement.

## CGI-I response at 12 months (OC)

Patients treated with VNS+TAU

B



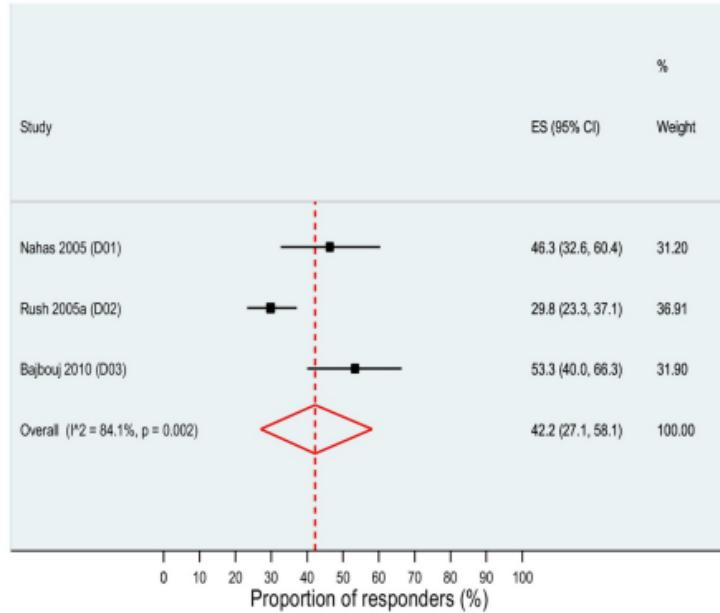
Fixed-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. CGI-I: Clinical Global Impression-Improvement.

Figure 11

## HAMD response at 12 months (OC)

Patients treated with VNS+TAU - LivaNova studies only

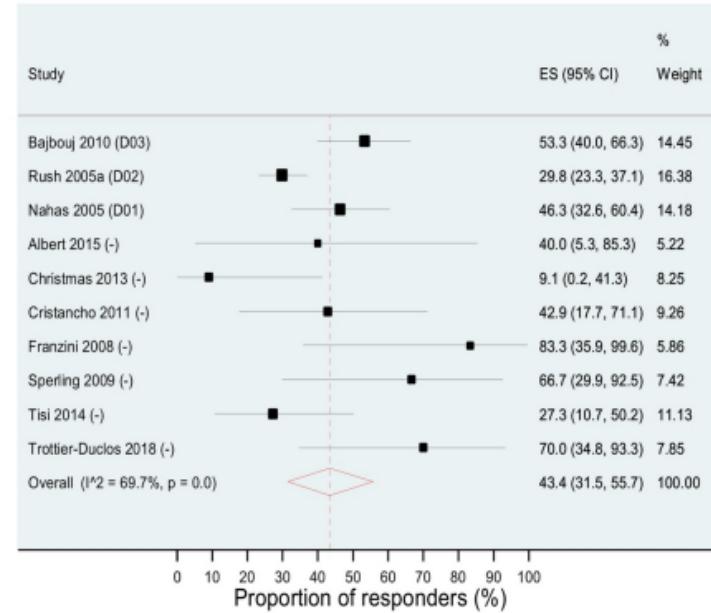


Random-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. HAMD: Hamilton Rating Scale for Depression.

## HAMD response at 12 months (OC)

Patients treated with VNS+TAU



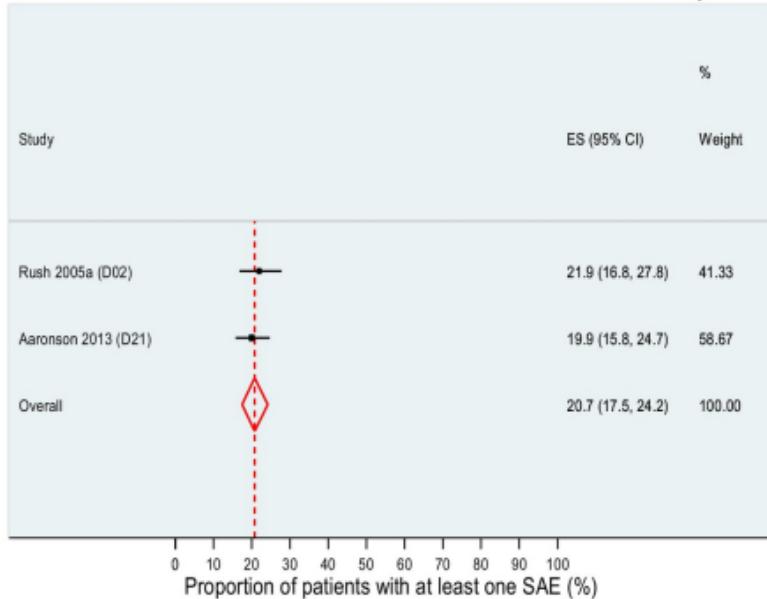
Random-effects model

OC: observed cases. ES: effect size (% of responders). VNS: vagal nerve stimulation. TAU: treatment as usual. HAMD: Hamilton Rating Scale for Depression.

Figure 12

**Patients with at least one SAE at 12 months**  
 Patients treated with VNS+TAU - LivaNova studies only

**A**

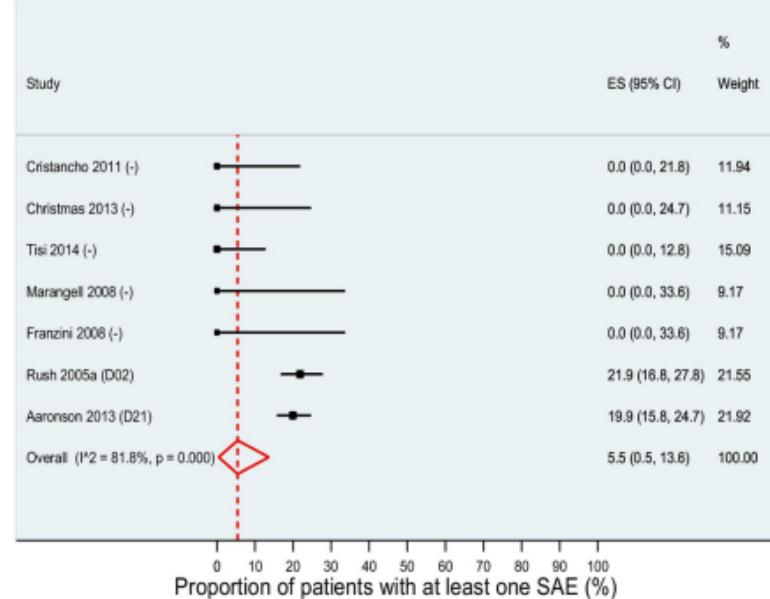


Fixed-effects model

ES:effect size (% of patients with at least one SAE). VNS:vagal nerve stimulation. TAU:treatment as usual. SAE: serious adverse event.

**Patients with at least one SAE at 12 months**  
 Patients treated with VNS+TAU

**B**



Random-effects model

ES:effect size (% of patients with at least one SAE). VNS:vagal nerve stimulation. TAU:treatment as usual. SAE: serious adverse event.

**Figure 13**