NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of implanted vagus nerve stimulation for treatment-resistant depression

Depression is treatment resistant when symptoms have not improved after at least 2 standard treatments. In this procedure, a small electrical stimulator is put under the skin of the chest (through a small cut) and its wires are passed under the skin to the left side of the neck. The wires are connected to the vagus nerve, which carries electrical signals to the brain. The aim is to improve mood by sending signals to the brain through the vagus nerve.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2019.

Procedure name

- Implanted vagus nerve stimulation for treatment-resistant depression.

Specialist societies

- Royal College of Psychiatrists

Description of the procedure

Indications and current treatment

Depression is characterised by low mood, loss of interest and enjoyment in life, and a range of associated emotional, cognitive, physical and behavioural symptoms. Depression is treatment-resistant when symptoms have not improved after at least 2 standard treatments.

The diagnosis and management of depression is described in the NICE clinical guideline for depression in adults and the NICE guideline for depression in children and young people. Standard treatment for depression includes antidepressants or psychological therapies (including cognitive behavioural therapies) or a combination of both. When 2 or more conventional treatments do not work, neurostimulation (for example, electroconvulsive therapy, transcranial magnetic stimulation, or transcranial direct current stimulation) may be considered.

What the procedure involves

The aim of implanted vagus nerve stimulation for treatment-resistant depression is to reduce symptoms and improve mood by periodic stimulation of the vagus nerve.

The procedure is done with the patient under general or local anaesthesia. An incision is made on the left side of the neck and the left vagus nerve is identified. A stimulator electrode is put around the nerve and the leads of the electrode are guided under the skin to the left chest wall. They are attached to a pulse generator unit, which is implanted into a subcutaneous pocket. The stimulator settings can be adjusted or turned off using an external (wireless) programming device.

Outcome measures

The Montgomery–Åsberg Depression Rating Scale (MADRS) is a 10-item diagnostic questionnaire to measure the severity of depressive episode. This self-reported questionnaire has 4 cut-off-points: i) 0 to 6 – normal or symptom absent; ii) 7 to 19 – mild depression; iii) 20 to 34 – moderate depression; and iv) above 34 – severe depression.

The 36-item Medical Outcome Study Short-Form Health Survey (MOS-SF-36) is a self-reported questionnaire to assess health-related quality of life in 8 domains: i) vitality; ii) physical functioning; iii) bodily pain; iv) general health perceptions; v) physical role functioning; vi) emotional role functioning; vii) social role functioning; viii) mental health. Scores range from 0 to 100, with a lower score indicating more disability and a higher score suggesting less disability.

The Inventory of Depressive Symptomatology (IDS) is an assessment tool to assess the severity of depression. The IDS is available in 2 versions: a clinician-administered (IDS-C) and a self-reported (IDS-SR), with a higher score indicating severe condition.

The Clinical Global Impression (CGI) rating scales are measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders.

- The Clinical Global Impression - Improvement scale (CGI-I) is a 7-point scale. The clinician assesses the changes in the condition compared with the baseline, with 1 being very much improved and 7 being very much worse.
- The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale. The clinician rates the severity of the patient's condition at the time of assessment, with 1 being normal, not at all ill and 7 being the most extremely ill.

The Hamilton Rating Scale for Depression (HRSD), also called the Hamilton Depression Rating Scale (HDRS), abbreviated HAM-D, is a multi-item (for example, 24 items [$HDRS_{24}$] and 28 items [$HDRS_{28}$]), clinician-administered depression assessment scale. A lower score indicates normal and a higher score shows severity of the condition.

The Hamilton Anxiety Rating Scale (HAM-A) is used to measure the severity of anxiety symptoms. This clinician-administered scale consists of 14 item and each item is score ranged from 0 (not present) to 4 (severe), with a total score range of 0 to 56. Lower than 17 indicates mild severity, 18 to 24 is mild to moderate severity and 25 to 30 is moderate to severe.

Efficacy summary

Improvement in depressive symptoms

Clinician-administered scales

Hamilton Depression Rating Scale (HDRS)

In a randomised controlled trial of 235 patients with treatment-resistant depression, the mean $HDRS_{24}$ improvement from baseline did not statistically significantly differ between the active and sham vagus nerve stimulation (VNS) groups (16.3±28.1 and 15.3±25.5 respectively, p=0.639) at 10 weeks[3]. During the open-label therapy of 12 months, there was statistically significant within-group improvements of 0.45 (standard error [SE]=0.05) points per month (repeated measures t=8.25, degrees of freedom [df]=654, p<0.001) in the mean $HDRS_{24}$ score for both groups as a whole over the 12 months[3].

In a systematic review and meta-analysis of 14 studies (821 patients), a HDRS response (50% or more reduction from the baseline score at follow up) rate of 34% (24% to 45%, p=0.005, I^2=69.82%) was seen in 5 case series of 380 patients with treatment-resistant depression during the 20-week period[2]. In the randomised controlled trial of 235 patients, there was no statistically significant difference in the $HDRS_{24}$ response rates between patients in the active VNS group (15%) and patients in the sham VNS group (10%, χ^2=1.32, df=1, p=0.251) at 10 weeks after the procedure[3]. During the open-label therapy of 12 months, the $HDRS_{24}$ response rate was 29% (52/177) and the sustained response (50% or more reduction from baseline at least once during months 9, 10, 11, or 12, or 40% or more reduction from baseline on at least 2 other assessments in the same period) rate was 27% (47/177)[3]. In a case series of 10 patients with treatment-resistant depression, there was a clinically and statistically significant improvement in the $HDRS_{28}$ score ($F_{9,81}$=14.745, p<0.001) over the 6-year follow up[7]. In the same study, there was an $HDRS_{28}$ response rate in 30% of patients at

1 month, 70% at 12 months, and 80% at 72 months. There was an $HDRS_{28}$ remission (7 or more in $HDRS_{28}$ score) rate in 30% of patients at 1 month, 50% at 12 months, and 50% at 72 months[7].

Clinical Global Impressions - Improvement scale (CGI-I)

In a meta-analysis of 6 studies (1,576 patients with chronic treatment-resistant depression), the CGI-I response (1 being very much improved or 2 being much improved at the follow up) rates for patients having VNS and treatment as usual (TAU) at 12, 24, 48, and 96 weeks were 14%, 23%, 40%, and 50% compared with 3%, 4%, 10%, and 14% for patients receiving TAU alone[1]. Patients who had VNS and TAU had a lower CGI-I score (mean difference [MD]=−0.49 points; 95% CI −0.59 to −0.39) and there was a greater chance of response (odds ratio [OR]=7, 95% CI 4.63 to 10.83) compared with patients who had TAU[1]. In the same meta-analysis, for patients whose symptoms had responded to VNS and TAU at 24 weeks (n=251), the OR for sustained CGI-I response was 3.09 (95% CI 2.09 to 4.70) at 48 weeks and 7.04 (95% CI 3.39 to 17.27) at 96 weeks[1].

In the randomised controlled trial of 235 patients, there was no statistically significant difference in the CGI-I response rates between the active VNS group (14%) and the sham VNS group (12%, χ^2=0.208, df=1, p=0.648) at 10 weeks of the stimulation therapy. During the open-label therapy phase, the CGI-I response rate for both groups was 34% (68/200) at 12 months[3].

In a non-randomised comparative study of 795 patients with treatment-resistant depression, there was a statistically significant difference in the cumulative response rates in CGI-I between the VNS+TAU group (76%, 95% CI 72.3 to 79.9) and the TAU group (49%, 95% CI 43.0 to 54.8, p<0.001) through the 5-year follow-up period[4]. In the same study, the VNS plus TAU group had a statistically significantly higher cumulative remission rate in CGI-I (50%, 95% CI 45.5 to 54.3) compared with the TAU group (21%, 95% CI 16.7 to 26.4, p<0.001) through the 5-year follow-up period[4].

Inventory of Depressive Symptomatology - clinician-administered (IDS-C)

In a randomised controlled trial of 331 patients with treatment-resistant depression, all groups with different stimulation levels (LOW: 0.25 mA, 130 microseconds; MEDIUM: 0.5 mA to 1.0 mA, 250 microseconds; HIGH: 1.25 mA to 1.5 mA, 250 microseconds) showed statistically significant improvement in mean IDS-C score from baseline over weeks 10 (−9.0±10.6), 14 (−10.3±11.7), 18 (−11.1±11.4) and 22 (−11.1±12.6, p=0.0023). There were no statistically significant differences for any of the comparisons between-stimulation groups over time: LOW compared with MEDIUM, p=0.8131; LOW compared with HIGH, p=8027; MEDIUM compared with HIGH, p=0.9921[6]. In the same study, a

higher level of electrical stimulation was associated with statistically significant decrease in IDS-C score ($r=-0.21$, $p<0.001$)[6].

Patient-reported scales

Montgomery–Åsberg Depression Rating Scale (MADRS)

Mean MADRS score

In the meta-analysis of 6 studies (1,576 patients), patients who had VNS and TAU had lower MADRS scores than those who had TAU (MD=−3.26; 95% CI −3.99 to −2.54) over 96 weeks of the stimulation therapy[1].

In the randomised controlled trial of 235 patients, the mean MADRS improvement from baseline did not statistically significantly differ between the active and sham VNS groups (17.1±31.2 compared with 12.4±27.1, p=0.208) at 10 weeks. During the 12-month open-label therapy, there was a statistically significant reduction in the mean MADRS score for both groups from the baseline (30.8±6.9) to month 12 (22.2±11.7, $p<0.001$)[3]. In the randomised controlled trial of 331 patients, during the 22 weeks, there was a statistically significant improvement in mean MADRS score for all 3 stimulation groups combined from baseline ($p<0.0001$, data not shown). This was not the case for any of the between-stimulation group comparisons over time[6]. In a case series of 14 patients, overall there was a statistically significant improvement in MADRS score over the 24 months ($F_{4,48}=30.4$, $p<0.001$, $\eta^2=0.72$)[8].

MADRS response rates

In the meta-analysis of 6 studies (1,576 patients), the MADRS response (50% or more reduction in baseline MADRS score at the follow-up) rates for patients in the VNS and TAU group at 12, 24, 48, and 96 weeks were 12%, 18%, 28%, and 32% compared with 4%, 7%, 12%, and 14% for patients in the TAU group. Also, when compared with patients having TAU only, patients who had VNS and TAU had greater chance of response in MADRS (OR=3.19, 95% CI: 2.12 to 4.66) over 96 weeks of the stimulation therapy[1]. In the same study, the OR for sustained response for patients whose symptoms had responded to VNS plus TAU at 24 weeks compared with TAU patients was 1.98 (95% CI 1.34 to 3.01) at 48 weeks and was 3.42 (95% CI 1.78 to 7.31) at 96 weeks[1].

In the randomised controlled trial of 235 patients, there was no statistically significant difference in the MADRS response rates between the active VNS group (15%) and the sham VNS group (11%, $\chi^2=0.778$, df=1, p=0.378) at 10 weeks of stimulation therapy[3]. During the open-label therapy phase, the MADRS response rate for both groups was 28% (57/202) at 12 months[3]. In a

case series of 14 patients with treatment-resistant depression, the MADRS response rate was 71% (10/14) at 3, 12 and 24 months[8].

In a non-randomised comparative study of 795 patients, a statistically significant difference was seen in the cumulative MADRS response rates between patients in the VNS plus TAU group (68%, 95% CI 63.4 to 71.7) and patients in the TAU group (41%, 95% CI 35.4 to 47.1, p<0.001) through the 5-year follow-up period[4].

MADRS remission rates

In the meta-analysis of 6 studies (1,576 patients), the MADRS remission (MADRS score below 10 points at follow up) rates for patients in the VNS plus TAU group at 12, 24, 48, and 96 weeks were approximately 3%, 5%, 10%, and 14%, compared with 1%, 1%, 2%, and 4% for patients in the TAU group[1]. Also, when compared with patients who had TAU only, patients who had VNS and TAU had a greater chance of remission in MADRS (OR=4.99, 95% CI 2.93 to 7.76) over 96 weeks of the stimulation therapy[1]. In the same study, for patients who had remission after the VNS and TAU treatment (n=111), the sustained MADRS remission was more likely to happen at 48 weeks (OR=2.73, 95% CI 1.49 to 5.54) and at 96 weeks (OR=2.64, 95% CI 1.16 to 7.19)[1]. In the case series of 14 patients, the remission rate in MADRS was 29% (4/14) at 1 month, 50% (7/14) at 3 months, 57% (8/14) at 12 months, and 64% (9/14) at 24 months[8].

In the non-randomised comparative study of 795 patients, the VNS plus TAU group had a statistically significantly higher cumulative MADRS remission rate (43.3%, 95% CI 38.9 to 47.7) compared with the TAU group (25.7%, 95% CI 20.7 to 31.1, p<0.001) through the 5-year follow-up period[4].

Inventory of Depressive Symptomatology – self-reported (IDS-SR)

In the randomised controlled trial of 235 patients, the mean IDS-SR_{30} score did not statistically significantly differ between the active and sham VNS groups (21.2±25.4 compared with 16.3±26.2, p=0.158) at 10 weeks of stimulation therapy[3]. In the same study, there was a statistically significant difference in the IDS-SR_{30} response rates between the active VNS group (17%) and the sham VNS group (7%, X^2=4.62, df=1, p=0.032) at 10-week follow-up[3]. During the open-label therapy phase, the IDS-SR_{30} score statistically significantly improved 0.52 (SE=0.08) points per month (repeated measures t=6.79, df=631, p<0.001) for both groups[3].

In the non-randomised comparative study of 795 patients, a statistically significant difference was noted in the cumulative QIDS-SR response rates between the VNS plus TAU arm (65%, 95% CI 60.7 to 69.2) and the TAU arm (42%, 95% CI 35.9 to 47.5, p<0.001) through the 5-year follow-up period[4]. In the same study, the VNS plus TAU group had a statistically significantly higher

cumulative QIDS-SR remission rate (40%, 95% CI 36.2 to 44.9) compared with the TAU group (25%, 95% CI 19.9 to 30.1, p<0.001) over 5 years[4].

Improvement in quality of life

In the randomised controlled trial of 235 patients, the active and sham VNS groups did not differ on either physical or mental component of the MOS-SF36 at 10 weeks of stimulation therapy. For the physical component score (PCS), mean change was −0.9 (SD=8.3) for the VNS group (n=107) and −1.6 (SD=8.4) for the sham group (n=107; F=0.50, df=1, 208, p=0.480). For the mental component score (MCS), mean change was 5.0 (SD=11.6) for the VNS group (n=107) and 4.0 (SD=10.2) for the sham group (n=107; F=−0.69, df=1, 208, p=0.406)[3].

In a non-randomised comparative study of 599 patients, on average, patients in the VNS and TAU group showed a significantly, comparative quality-of-life advantage over patients in the TAU group (non-overlapping 95% confidence bands). This started at 3 months and was sustained over 5 years (exact data were not reported)[5]. In the case series of 10 patients, through a follow up of 6 years, there was a statistically significant improvement in MCS ($F_{9,81}$=2.566, p=0.012) and in PCS ($F_{9,81}$=3.479, p<0.002), and a statistically significant positive linear trend was found for MCS ($F_{1,9}$=5.937, p=0.037) and for PCS ($F_{1,9}$=15.410, p=0.003)[7].

Cognitive improvement

In the case series of 14 patients, there was a statistically significant improvement between the sessions across the memory measures (Λ=0.218, $F_{16,125,895}$=5.081, p<0.001, $\eta^2_{partial}$=0.78), a statistically significant effect of evaluation time in information-processing speed (Λ=0.672, $F_{8,102}$=2.808, p=0.007, $\eta^2_{partial}$=0.33), a statistically significant effect of evaluation time across the attention and executive functions (Λ=0.572, $F_{8,104}$=4.108, p<0.001, $\eta^2_{partial}$=0.43) for patients having VNS stimulation therapy over 2 years[8].

Associations between quality of life and cognitive and clinical improvement

In the non-randomised comparative study of 599 patients with treatment-resistant depression, a clinically meaningful quality of life improvement was an 11.89% maximum increase from baseline using the quality-of-life enjoyment and satisfaction questionnaire short form of 14 items. To have this, patients in the VNS and TAU group could have, on average, at least 34% of the MADRS drop from baseline compared with patients in the TAU group, with at least 56% of the drop[5]. In the same study, on average, for a 50% of reaching CGI-I category 1 or 2, a MADRS drop of at least 48% was enough for a patient having VNS plus

TAU compared with at least 95% for a patient having TAU, with an estimated OR of 2.78 (95% CI 2.17 to 3.57) to have a response[5].

In the case series of 14 patients, the improvement in MADRS scores was not statistically correlated with changes in any of the cognitive scores (all r values were less than −0.443, all p values were less than 0.15) at 1 month. At 12 months, the change in MADRS score was significant correlated with several measures (stroop interference: r=−0.65, p=0.01; verbal fluency: r=−0.63, p=0.01; rey-osterrieth complex figure: r=−0.58, p=0.05)[8].

Suicide attempt and mortality

In the randomised controlled trial of 235 patients, there were suicide attempts in 7 patients. There were 2 patients who each made 1 suicide attempt (1 coded by COSTART as an overdose) during the first 3 months, and 5 patients who made 6 suicide attempts over the next 9 months (1 patient made 2 attempts) during the open-label therapy phase[3]. Of the 7 patients, 4 had a previous history of 1 or more suicide attempts[3]. In the non-randomised comparative study of 795 patients, patients in the VNS plus TAU group showed a greater reduction in the suicidality profile compared with patients in the TAU group, based on QIDS-SR item 12 (OR=2.11, 95% CI 1.28 to 3.48; p=0.035), the investigator-completed suicidality assessment (OR=2.04, 95% CI 1.08 to 3.86, p=0.029), and MADRS item 10 (OR=1.67, 95% CI 0.98 to 2.83, p=0.058)[4].

In the systematic review and meta-analysis of 14 studies (821 patients), suicide or attempted suicide was reported with a cumulative incidence of 5% (2.8% to 7.3%, p<0.0001, I^2=0.00%) during stimulation therapy (in 4 uncontrolled, before-after studies of 348 patients)[2].

In the non-randomised comparative study of 795 patients, all-cause mortality was markedly lower in patients having VNS and TAU (3.53 per 1,000 person-years [95% CI 1.41 to 7.27]) than patients having TAU alone (8.63 per 1,000 person-years [95% CI 3.72 to 17.01])[4]. The rate of completed suicides was also lower in the VNS group (1.01 per 1,000 person-years [95% CI 0.11 to 3.64]) than in the TAU group (2.20 per 1,000 person-years [95% CI 0.24 to 7.79])[4].

In the randomised controlled trial of 331 patients, when compared across the low, medium and high stimulation groups, suicide attempts were reported in 6%, 1% and 4% of patients respectively[6]. One patient from the low stimulation group died; the patient had a history of 2 suicide attempts during their life[6].

Hospitalisation

In the systematic review and meta-analysis of 14 studies (821 patients), hospitalisation caused by worsened depression was described with a cumulative

incidence of 12% (8.6% to 16.7%, I^2=17.13%) during the stimulation therapy (in 4 studies of 368 patients)[2]. In the randomised controlled trial of 235 patients, hospitalisation was reported in 35 patients, including 5 in the active VNS group during the acute phase, and 30 during the 12-month open-label therapy[3]. Of the 30 patients, 80% (24/30) had a history of hospitalisation for worsening depression before study enrolment[3]. In a single case report, hospitalisation for suicidal ideation was reported in 1 patient with treatment-resistant depression at month 2 of stimulation therapy[9].

Safety summary

New onset of depression or mania

New onset of depression was reported in 17% (121/700) and 13% (46/344) of the patients during the first and second years of the stimulation therapy (in 4 studies) in the meta-analysis of 6 studies[1]. New onset of depression was reported in 18% (60/331) of patients during the 50-week stimulation therapy in the randomised controlled trial of 331 patients[6]. This event was reported as a serious adverse event in the low (7%), medium (6%) and high (4%) stimulation groups[6]. In the same study, there was anxiety in 12% (38/331) of patients during the 50-week stimulation therapy[6].

Mania or hypomania was reported in 5 patients, including 2 in the active VNS group during the acute phase, 2 during the first 3 months of stimulation therapy, and 1 during the subsequent 6 months in the randomised controlled trial of 235 patients[3]. The mania symptoms in the first 4 patients resolved in 1 to 2 weeks. The last patient who had a manic reaction had this when stimulation was 2.25 mA, and this was stopped on the day that the participant was hospitalised. Stimulation remained off during the episode, which lasted about 2 months, and was restarted at 0.50 mA about a month after the episode ended. This increased to 1.00 mA about 2 weeks later, and to 1.50 mA about 2 weeks after that[3]. Mania or hypomania showed a cumulative incidence of 3% (1.4% to 5.1%, I^2=0.00%) during stimulation therapy (in 4 studies of 368 patients) in the systematic review and meta-analysis of 14 studies (821 patients)[2].

Cardiac complications

Asystole happened in 1 patient during the surgery in the active VNS group in the randomised controlled trial of 235 patients[3].

Bradycardia was reported in 1 patient during the surgery in the active VNS group in the randomised controlled trial of 235 patients[3].

Palpitations were seen in 5% of patients in the active VNS group (n=119) compared with 3% in the sham VNS group (n=116) during the acute phase of 10 weeks in the randomised controlled trial of 235 patients[3].

Second- and third-degree AV heart block with 5 to 6 seconds of ventricular standstill was reported in the single case report of a patient with treatment-resistant depression[9]. This event was caused by VNS stimulation at the maximum settings at month 7[9].

Pain, infection and localised reaction

Pain was reported in 28% (199/700) and 12% (41/344) of the patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Pain as an implantation-related complication was reported in 6% (20/331) of patients and as a post-implantation-related complication in 32% (105/331) of patients in the randomised controlled trial of 331 patients[6].

Device-site pain was reported in 14% (98/700) and 3% (11/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Device-site pain, which was considered related to the implantation, was reported in 1% (4/331) of patients in the randomised controlled trial of 331 patients[6].

Incision pain was reported in 26% (181/700) and 4% (15%) of the patients during first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Incision pain as an implantation-related complication happened in 19% (62/331) of patients, and as a post-implantation-related complication in 25% (84/331) of patients in the randomised controlled trial of 331 patients[6].

Device-site reaction was reported in 12% (82/700) and 8% (27/744) of the patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Device-site reaction was seen in 3% (11/331) of patients as an implantation-related complication and in 10% (33/331) of patients as a post-implantation-related complication in the randomised controlled trial of 331 patients[6].

Incision-site reaction was reported in 16% (113/700) and 4% (15/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Incision-site reaction as an implantation-related complication was seen in 9% (31/331) of patients and as a post-implantation-related complication in 13% (42/331) of patients in the randomised controlled trial of 331 patients[6].

Wound infection was seen in 8% of patients in the active VNS group (n=119) compared with 2% in the sham VNS group (n=116) during the 10-week acute phase in the randomised controlled trial of 235 patients[3].

Headache was reported in 22% (153/700) and 8% (29/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Headache was seen in 18% (61/331) of patients after implantation in the randomised controlled trial of 331 patients[6].

Neck pain was reported in 20% (139/700) and 16% (55/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Neck pain happened in 21% of patients in the active VNS group (n=119) compared with 10% in the sham VNS group (n=116) during the 10-week acute phase, and in 16% (38/232), 11% (25/225), 14% (31/218) and 13% (27/209) at 3, 6, 9 and 12 months during the open-label therapy phase[3]. Neck pain as an implantation-related complication was reported in 2% (5/331) of patients and as a post-implantation-related complication in 14% (46/331) of patients in the randomised controlled trial of 331 patients[6].

Laryngopharyngeal complications

Voice alteration was reported in 69% (485/700) and 52% (179/344) of the patients during the first and second years of the stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Voice alteration was seen in 68% of patients in the active VNS group (n=119) compared with 38% in the sham VNS group (n=116) during the 10-week acute phase, and happened in 58% (135/232), 60% (135/225), 57% (125/218) and 54% (113/209) at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Voice alteration as an implantation-related complication was reported in 8% (25/331) of patients and as a post-implantation-related complication in 72% (239/331) of patients in the randomised controlled trial of 331 patients[6].

Dyspnoea was reported in 30% (211/700) and 21% (71/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Dyspnoea occurred in 23% of the patients in the active VNS group (n=119) compared with 14% in the sham VNS group (n=116) during the acute phase, and in 14% (33/232), 16% (35/225), 15% (33/218) and 16% (34/209) of patients at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Dyspnoea as a post-implantation complication was reported in 32% (107/331) of patients in the randomised controlled trial of 331 patients[6].

Increased cough happened in 26% (185/700) and 14% (47/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Increased cough was reported in 29% of patients in the active VNS group (n=119) compared with 9% in the sham VNS group (n=116) during the acute phase, and in 24% (55/232), 9% (20/225), 7% (15/218) and 6% (13/209) at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Increased cough happened in 25% (83/331) of patients after the implantation in the randomised controlled trial of 331 patients[6].

Laryngismus was seen in 11% of patients in the active VNS group (n=119) compared with 2% in the sham VNS group (n=116) during the 10-week acute phase, and in 10% (23/232), 8% (18/225), 7% (16/218) and 5% (10/209) of patients at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients [3].

Pharyngitis was reported in 17% (122/700) and 7% (25/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Pharyngitis was reported in 6% (14/235), 4% (8/225), 4% (8/225) and 5% (11/209) of patients at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Pharyngitis was reported in 2% (6/331) of patients as an implantation-related complication, and in 17% (57/331) of patients as a post-implication related complication in the randomised controlled trial of 331 patients[6]. Nasopharyngitis was reported in 14% (45/331) of patients after implantation in the randomised controlled trial of 331 patients[6].

Dysphagia was reported in 16% (115/700) and 9% (32/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Dysphagia was reported in 21% of patients in the active VNS group (n=119) compared with 11% in the sham VNS group (n=116) during the acute phase, and in 13% (31/232), 8% (19/225), 7% (15/218) and 4% (9/209) at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Dysphagia was reported in 14% (45/331) of patients after implantation in the randomised controlled trial of 331 patients[6].

Gastrointestinal complications

Vomiting happened in 11% of patients in the active VNS group (n=119) compared with 5% in the sham VNS group (n=116) during the 10-week acute phase in the randomised controlled trial of 235 patients[3].

Nausea was reported in 15% (107/700) and 4% (12/344) of patients during the first and second years of the stimulation therapy (in 4 studies) in the meta-analysis of 6 studies[1]. Nausea was reported in 12% (39/331) of patients after implantation in the randomised controlled trial of 331 patients[6].

Dyspepsia was seen in 10% of patients in the active VNS group (n=119) compared with 5% in the sham VNS group (n=116) during the 10-week acute phase in the randomised controlled trial of 235 patients[3].

Nervous system complications

Paraesthesia was reported in 23% (159/700) and 11% (39/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Paraesthesia happened in 16% of patients in the active VNS group (n=119) compared with 10% in the sham VNS group (n=116) during the 10-week acute phase, and in 11% (26/232), 7% (15/225), 3% (7/218) and 4% (9/209) of patients at 3, 6, 9 and 12 months during the open-label therapy phase in the randomised controlled trial of 235 patients[3]. Paraesthesia was reported as an implantation-related complication in 2% (8/331) of patients, and as a post-implantation-related complication in 32% (105/331) of patients in the randomised controlled trial of 331 patients[6].

Hypertonia was reported in 13% (92/700) and 9% (31/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Hypertonia was reported in 17% (56/331) of patients after the implantation in the randomised controlled trial of 331 patients[6].

Insomnia was reported in 11% (75/700) and 6% (22/344) of patients during the first and second years of stimulation therapy (in 4 studies) in the meta-analysis of 6 studies (1,576 patients)[1]. Insomnia was reported in 11% (36/331) of patients after implantation in the randomised controlled trial of 331 patients[6].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: generally well tolerated. They did not list any theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to implanted vagus nerve stimulation for treatment-resistant depression. The following databases were searched, covering the period from their start to 31 July 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with treatment-resistant depression.
Intervention/test	Vagus nerve stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 4,382 patients from 2 systematic reviews and/or meta-analysis[1,2], 2 randomised controlled trial[3,6], 2 non-randomised comparative studies[4.5], 2 case series[7,8] and 1 single case report[9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on implanted vagus nerve stimulation for treatment-resistant depression

Study 1 Berry SM (2013)

Details

Study type	**Meta-analysis**
Country	5 studies: USA and Canada (multiple centres) 1 study: Europe (multiple centres)
Recruitment period	Search date: not reported Publication years for the included studies: 2000 to 2012
Study population and number	n=**1576 (6 studies; 1035 VNS+TAU versus 541 TAU)** Patients with chronic treatment-resistant depression
Age and sex	VNS+TAU: mean 47.8 years; 66.2% female TAU: mean 48.7 years; 69.7% female
Patient selection criteria	Inclusion criteria: Adult patients with a diagnosis of a major depressive episode (unipolar or bipolar disorder) according to DSM-IV Diagnosis Criteria; had a history of chronic (≥2 years) or recurrent (at least 2 or 4 episodes); had an inadequate response to antidepressant treatment from at least 2 different treatment categories; was able to comply with all testing and visit requirements per protocol. A score ≥20 on the 24-item or 28-item HDRS. Exclusion criteria: A history of schizophrenia, schizoaffective disorder, any other psychotic disorder, or a current major depressive episode that includes psychotic features; or is currently psychotic. Simultaneous enrolment in another investigational trial, previously received VNS therapy, presence of other cognitive disorders (such as delirium or dementia), other neurological problems (such as central nervous system disease or injury), current alcohol or substance abuse, clinically significant suicidal intent, and cardiac or pulmonary disorders (such as history of myocardial infarction or cardiac arrest).
Technique	The VNS procedure was performed using VNS Therapy (Cyberonics, Inc, Houston, TX, USA).
Follow-up	**96 weeks**
Conflict of interest/source of funding	Cyberonics, Inc (Houston, TX, USA) is the manufacturer of VNS Therapy and sponsored the studies included in the meta-analysis. Two authors are employees and stakeholders of Cyberonics. One author is employee of Cyberonics. Two authors are employees of Berry Consultants (Austin, TX, USA), which was commissioned by Cyberonics to perform independent statistical analysis. One author has received consulting fees from Otsuka Pharmaceutical Co, Ltd, University of Michigan, and Brain Resource Ltd; speaker fees from Singapore College of Family Physicians; royalties from Guilford Publications and the University of Texas Southwestern Medical Center; a travel grant from CINP; and research support from the National Institute of Mental Health and Duke-NUS Graduate Medical School, Singapore.

Analysis

Follow-up issues: The withdrawal rates during the acute (12 weeks) and long-term (24, 48 and 96 weeks) phases were comparable (23.6% for VNS + TAU and 22.2% for TAU). The most common reasons for withdrawal were: patient

withdrew consent (3.4% for VNS + TAU and 6.3% for TAU), protocol non-compliance by patient (2.1% for VNS + TAU and 4.9% for TAU), and lack of efficacy (2.3% for VNS + TAU and 0% for TAU).

Study design issues: This patient-level meta-analysis compared the response and remission rates in patients with chronic treatment-resistant depression treated with VNS therapy plus treatment as usual (VNS+TAU) or with TAU alone using Bayesian hierarchical models. There was no information relating to articles identification, screening, inclusion, eligibility, data extraction and quality assessment. Outcomes of interest were response, remission and sustained response based on the 10-item Montgomery - Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions scale's Improvement subscale (CGI-I).

- Response using the MADRS: a patient was considered to be a responder if their MADRS score at the follow-up visit was at least a 50% reduction from their baseline MADRS score.
- Response using the CGI-I: a patient was considered to be a responder if their CGI-I score at the follow-up was 1 ("very much improved") or 2 ("much improved").
- Remission using the MADRS: a patient was considered to be in remission if their MADRS score at the follow-up was, 10 points.

For safety assessment, each patient was counted only once per AE within each year even though some patients might have reported multiple occurrence of the same event. All studies were sponsored by Cyberonics, Inc.

Study population issues: Of the 6 included clinical studies, there were 2 single-arm studies of VNS+TAU (Studies D-01 and D-03), 1 randomized trial of VNS+TAU versus TAU (Study D-02), 1 single arm study of patients who received TAU (Study D-04), 1 randomized trial of VNS + TAU comparing different VNS stimulation intensities (Study D-21), and 1 nonrandomized registry of patients who received either VNS+TAU or TAU (Study D-23).

More Caucasian patients were found in the VNS+TAU group (96.5%) than in the TAU group (90.6%, p=1.000). The VNS+TAU population had statistically significantly greater chronicity and treatment resistance; including more patients who received VNS+TAU had ECT (56.1% versus 39.5% in the TAU group, p<0.001), more had unsuccessful prior drug treatment trials (6.9±2.2 versus 5.9±2.2 in the TAU group, p<0.001), and more had lifetime depression-related hospitalizations (3.4±6.0 versus 1.9±4.3 in the TAU group, p<0.001). In terms of the MADRS score and CGI severity score at baseline, there were statistically significantly higher scores for patients in the VNS+TAU group (33.0±6.4 and 5.2±0.8, respectively) than for patients in the TAU group (29.4±6.9 and 4.7±0.7, respectively, p<0.001).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1576 (6 studies; 1035 VNS+TAU versus 541 TAU)**

Repeated measures analysis of CGI-I and MADRS over 96 weeks

Model-estimated treatment effect	CGI-I		MADRS	
	Estimate	95% CI	Estimate	95% CI
Average difference in scores: VNS+TAU versus TAU	-0.49	-0.59 to -0.39	-3.26	-3.99 to -2.54
OR of response: VNS+TAU versus TAU	7.00	4.63 to 10.83	3.19	2.12 to 4.66
OR of remission: VNS+TAU versus TAU	N/A	N/A	4.99	2.93 to 7.76

Model-based response rates at weeks 12, 24, 48 and 96 weeks

	12 weeks	24 weeks	48 weeks	96 weeks

Safety

Adverse events reported during years 1 and 2 on VNS therapy (4 studies)

Adverse event, n(%)	Year 1 (n=700)	Year 2 (n=344)
Voice alteration	485 (69.29)	179 (52.03)
Dyspnoea	211 (30.14)	71 (20.64)
Pain	199 (28.43)	41 (11.92)
Increased cough	185 (26.43)	47 (13.66)
Incision pain	181 (25.86)	15 (4.36)
Paraesthesia	159 (22.71)	39 (11.34)
Headache	153 (21.86)	29 (8.43)

MADRS response rate				
VNS+TAU	12%	18%	28%	32%
TAU	4%	7%	12%	14%
CGI-I response rate				
VNS+TAU	14%	23%	40%	50%
TAU	3%	4%	10%	14%
MADRS remission rate				
VNS+TAU	3%	5%	10%	14%
TAU	1%	1%	2%	4%

Sustained response and remission rates at weeks 48 and 96 by response or remission status at week 24

	Status at 24 weeks for VAS+TAU		**Status at 24 weeks for TAU**	
	Non-response	**Response**	**Non-response**	**Response**
MADRS response 48 weeks				
Non-response	410 (75%)	64 (29%)	197 (83%)	26 (44%)
Response	137 (25%)	153 (71%)	39 (17%)	33 (56%)
MADRS response 96 weeks				
Non-response	146 (70%)	34 (33%)	95 (86%)	11 (52%)
Response	64 (30%)	70 (67%)	15 (14%)	10 (48%)
CGI-I response 48 weeks				
Non-response	378 (69%)	47 (19%)	223 (86%)	23 (43)
Response	173 (31%)	204 (81%)	36 (14%)	31 (57%)
CGI-I response 96 weeks				
Non-response	140 (64%)	30 (25%)	91 (72%)	14 (67%)
Response	78 (36%)	90 (75%)	34 (27%)	7 (33%)
	Non-remission	**Remission**	**Non-remission**	**Remission**
MADRS remission 48 weeks				
Non-remission	564 (86%)	37 (33%)	249 (92%)	14 (56%)
Remission	89 (14%)	74 (67%)	21 (8%)	11 (44%)
MADRS remission 96 weeks				
Non-remission	208 (81%)	21 (37%)	110 (92%)	5 (45%)
Remission	49 (19%)	36 (63%)	10 (8%)	6 (55%)

For patients who had responded to VNS+TAU at 24 weeks:

- Sustained MADRS response at 48 weeks: OR=1.98, 95% CI: 1.34 to 3.01
- Sustained MADRS response at 96 weeks: OR=3.42, 95% CI: 1.78 to 7.31

Neck pain	139 (19.86)	55 (15.99)
Pharyngitis	122 (17.43)	25 (7.27)
Depression	121 (17.29)	46 (13.37)
Dysphagia	115 (16.43)	32 (9.30)
Incision-site reaction	113 (16.14)	15 (4.36)
Nausea	107 (15.29)	12 (3.49)
Device-site pain	98 (14.00)	11 (3.20)
Hypertonia	92 (13.14)	31 (9.01)
Device-site reaction	82 (11.71)	27 (7.85)
Insomnia	75 (10.71)	22 (6.40)

Each patient was counted only once per AE within each year even though some patients might have reported multiple occurrence of the same event.

Adverse events were reported in ≥10% of total patients in the 1st year following implantation. There was a trend towards diminishing adverse events over the 2 years of treatment with VNS.

- Sustained MADRS remission at 48 weeks: OR=2.73, 95% CI: 1.49 to 5.54
- Sustained MADRS remission at 96 weeks: OR=2.64, 95% CI: 1.16 to 7.19
- Sustained CGI-I response at 48 weeks: OR=3.09, 95% CI: 2.09 to 4.70
- Sustained CGI-I response at 96 weeks: OR=7.04, 95% CI: 3.39 to 17.27

Numbers needed to treat for benefit for VNS+TAU (versus TAU)

	Number needed to treat (for benefit)	95% CI
Acute studies at 12 weeks	8	6 to 12
Long studies at 24 weeks	7	5 to 12
Long studies at 48 weeks	6	4 to 9
Long studies at 96 weeks	4	3 to 6

Abbreviations used: CGI-I, Clinical Global Impressions-Improvement; CI, confidence interval; MADRS, Montgomery - Åsberg Depression Rating Scale; OR, odds ratio; TAU, treatment as usual; VNS, vagus nerve stimulation; NA, not applicable

Study 2 Martin JLR (2012)

Details

Study type	**Systematic review and meta-analysis**
Country	Country/ies for each study: not reported
Recruitment period	Searches conducted: until 2010 Publication years for the included studies: 2000 to 2010
Study population and number	**n=821 (14 studies; 8 studies on depression and 6 studies on epilepsy)** 661 patients with depression and 160 patients with depressive phase, epilepsy
Age and sex	Mean 11.3 years to 48.42 years; 61% female
Patient selection criteria	Inclusion criteria: any RCT in which the intervention studied was VNS, applied to any value of intensity, frequency and pulse width among patients in whom depressive symptomatology had been measured. All analytical studies in which VNS had been applied to and depressive symptomatology measured in the study patients pre- and post-intervention (before-after designs) were located.
Technique	VNS was performed but there was variation in the techniques relating to current intensity, pulse frequency (20 , 30, or 50 Hz), pulse width (250 or 500 μs), and stimulation duration (30/300 or 60/600 s).
Follow-up	**Depression: 4 weeks to 48 weeks** **Epilepsy: 12 weeks to 96 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Ten studies had a follow-up of 12 weeks to 48 weeks. In terms of losses to follow-up, 3 withdrawals were reported in an RCT of 222 patients with depression, and all were in the VNS group and were because of severe adverse events (hoarseness, explantation due to infection, and suicide). Losses to follow-up were not described in other included studies.

Study design issues: This systematic review and meta-analysis determined the efficacy of VNS for treatment of depression, with the efficacy outcomes being the level of depression using depressive symptomatology scales; and percentage of responders, defined as subjects whose depressive symptomatology scores showed a ≥50% change over baseline. For safety analysis purposes, all adverse events reported by the respective studies were recorded and subsequently analysed by grouping them according to the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) classification. A comprehensive search strategy was used, and the searches were conducted across several databases. Two reviewers independently examined the papers, extracted and recorded the data, and assessed the quality of the included papers.

Study population issues: Of the 14 included studies, 5 could not be meta-analysed as 2 failed to present the data available for analysis; 1 reported data in medians; and 2 were clinical trials that were individually described in the result section. In terms of study designs, 1 of the 8 studies that included patients with depression was an RCT, with the remainder being before-after studies without a control group. Of the 6 studies on epilepsy, 1 was an RCT and the remaining 5 had different analytical designs. All studies focused on adult patients except for 1 which included children with a mean age of 11.3 years. In respect of previous use of ECT, 4 studies reported on this, ranged from 33% to 63%.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **821 (14 studies; 8 studies on depression [n=661] and 6 studies on epilepsy [n=160])**

1 RCT (222 patients with depression with 10-week follow up) **compared the VNS group with the placebo group**:

- HDRS response rate: OR=1.61, 95% CI, 0.72 to 3.62; p=0.25
- IDS-SR_{30} response rate: p=0.03
- **Level of depression** measured by depressive symptomatology scales:
  - HDRS: p=0.78
  - MADRS: p=0.23
  - IDS-SR_{30}: p=0.16

5 uncontrolled, before-after studies (380 patients with depression refractory):

- HDRS Response rate: 33.5% (23.9% to 44.8%), p=0.005, I^2=69.82%

7 uncontrolled, before-after studies (399 patients with depression refractory):

- Level of depression: SMD=1.94 (1.36 to 2.52), p<0.0001, I^2=83.86%

Explanation of heterogeneity (7 studies of patients with depression): the meta-regression analysis of mean baseline severity of depression and the effect size: slope=0.11, R^2_{Adj}=0.66, p<0.0001

Serious events in 4 studies (whether these studies relating to depression or epilepsy were not reported)

Serious events	Number of study (n)	Cumulative incidence, %	Incidence density[c]
Suicide or suicide attempt	4 (348)	4.6 (2.8 to 7.3)*	0.085 (0.052 to 0.14)
Worsening depression caused hospitalisation	4 (368)	12.1 (8.6 to 16.7)**	0.225 (0.168 to 0.303)

*p<0.0001, I^2=0.00%

**I^2=17.13%

Safety

Adverse events in 6 uncontrolled studies (whether these studies relating to depression or epilepsy were not reported)

Body system adverse events	Effect size		
	Short term: ≤12 weeks, %	Medium term: >12 weeks, <48 weeks, %	Long terms: ≥48 weeks
Body as a whole			
Incision site pain	19.3 (4.5 to 41.3)	No data	No data
Headache	11.9 (4.3 to 28.7)	3.9 (2.1 to 6.8)	3.7 (2.0 to 6.8)
Pain	15.8 (6.8 to 32.3)	6.9 (4.4 to 10.6)	6.2[a]
Chest pain	10.8 (4.2 to 24.9)	No data	No data
Neck pain	15.5 (12.2 to 19.5)	9.6 (6.3 to 14.5)	13.1 (9.5 to 17.7)
Infection	5.6 (2.4 to 12.8)	No data	No data
Respiratory system			
Voice alteration	67.3 (50.7 to 80.5)	19.4 (0.6 to 90.8)[b]	22.9 (6.7 to 55.2)[b]
Pharyngitis	11.6 (5.8 to 21.8)	3.9 (2.2 to 6.9)	5.2 (3.1 to 8.6)
Dyspnea	15.2 (11.9 to 19.1)	12.7 (7.0 to 22.1)	15.0 (11.1 to 20.0)
Coughing	23.4 (15.6 to 33.6)	10.6 (4.6 to 22.7)	6.0 (3.7 to 9.5)
Digestive system			
Dysphagia	13.2 (10.2 to 17.0)	8.4[a]	4.1 (2.3 to 7.3)
Dyspepsia	7.1 (2.8 to 16.8)	3.3[a]	3.3[a]
Nausea	5.9 (3.8 to 9.0)	2.5 (1.2 to 5.1)	2.3 (1.0 to 5.0)
Nervous system			
Dizziness	7.0 (3.2 to 14.8)	No data	No data
Paraesthesia	6.9 (2.9 to 15.7)	6.7[a]	4.3[a]
Hypertonia	10[a]	No data	3.3[a]
Twitching	4.4 (2.0 to 9.6)	No data	No data
Insomnia	4.5 (2.6 to 7.5)	2.2	0.95

	Skin and appendages
	Rash-Pruritis: 0.7 (3.9 to 12.2) | No data | No data

[a]Only 1 study reported available data.

[b]No statistical significance: number of studies (without parentheses) and sample size (number of patients) showed in parentheses.

Serious adverse events in 4 studies (whether these studies relating to depression or epilepsy were not reported)

Serious events	Number of study (n)	Cumulative incidence, %	Incidence density[c]
Mania or hypomania	4 (368)	2.7 (1.4 to 5.1)[c]	0.094 (0.049 to 0.180)

[c]I^2=0.00%

Abbreviations used: HDRS, Hamilton depression rating scale; MADRS, Montgomery-Asberg depression rating Scale; IDS-SR_{30}, 30-item Inventory of depressive symptomatology-self-report; SMD, standardised mean difference.

Study 3 Rush AJ (2005a, 2005b) (included in studies 1 and 2)

Details

Study type	**Randomised controlled trial**
Country	USA (multiple centres; 21 sites)
Recruitment period	Not reported
Study population and number	n=**235 (119 active VNS versus 116 sham VNS)** Patients with treatment-resistant depression (201 major depressive disorder and 25 depressed phase, bipolar disorder).
Age and sex	Acute phase: Mean 46.5 years: 63% female Long-term phase (open label therapy): 46.3 years; 64% female
Patient selection criteria	Inclusion criteria: For the acute phase, patients were aged 18 years to 80 years; had to have a current DSM-IV primary diagnosis of major depressive disorder or bipolar I or II disorder; were in the current major depressive episode for ≥2 years or had at least 4 lifetime major depressive episodes, including their current MDE; and the baseline score of the $HRDS_{24}$ (average of 2 measures) to be ≥20. Patients with bipolar disorder had to be resistant to intolerance of, or have a medical contraindication to lithium. Women could not be pregnant and had to use acceptable birth control methods (including abstinence). For the additional follow-up phase: Patients, who were in the sham VNS group, had to have 2 $HDRS_{24}$ assessments after 8 and 10 weeks of sham VNS with an average score of ≥18. Patients, who were in the active VNS group, had to have at least 1 $HDRS_{24}$ assessment after completing the acute phase study. The degree of treatment resistance was gauged by the number of unsuccessful treatments according to the antidepressant treatment history form qualified trails in the current MDE. Exclusion criteria: for the acute phase, patients had to have atypical or psychotic features in any MDE; lifetime history of any non-mood psychotic disorder (e.g. schizophrenia); current rapid cycling bipolar disorder; or a current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder (based on DSM-IV criteria). Patients with clinically significant current suicidal intent and those with certain risks related to the surgical implantation of the VNS device.
Technique	The VNS device was implanted. For the active VNS group, the protocol called for 20 Hz, 500 μs pulse width, and on/off cycle of 30 sec on and 5 min off during the 2-week stimulation adjustment and acute phase trial period. The output current, beginning at 0.25 mA as the lowest dose, was increased gradually (in 0.25 mA increments) until a comfortable level was reached. Once this level was attained, participants left the clinic with the VNS device programmed at those settings. Additional increases (in 0.25 mA steps) could be made up to 3.5 mA at any time during the stimulation adjustment period over the next 2 weeks. Patients could take up to 5 antidepressant, mood stabiliser, or other psychotropic medications with a stabilised dosage. After the acute phase, patients in the sham VNS group were offered active VNS therapy.
Follow-up	**Acute phase: 10 weeks** **Long-term phase (open label therapy): 9 months for active VNS and 12 months for sham VNS**
Conflict of interest/source of funding	This study was supported by Cyberonics, Inc., through contracts to investigating sites, and authors declared financial relationships with the manufacturer. Statistical analyses were conducted by Quintiles Inc. and reviewed by the senior authors.

Analysis

Follow-up issues: Of the 235 implanted patients, 13 were not evaluable for the short-term efficacy: 4 did not meet eligibility criteria for continuing in the acute trial after implantation (their $HDRS_{24}$ scores were <18), and 9 had protocol violations after randomisation (e.g. medication additions in violation of the requirement for a stable medication regimen). Patients were followed up at weeks 1 and 2 (recovery period), weeks 3 and 4 (stimulation adjustment period), and weeks 5, 6, 8, 10, and 12 (fixed-dose stimulation period). For the long-term phase, 205 patients were evaluated and 177 constituted the completer sample. This sample was followed up at months 3, 6, 9, and 12.

Study design issues: This double-masked, randomised, sham-controlled trial examined the efficacy and safety of VNS in treatment-resistant depression, with the primary outcome being the $HDRS_{24}$ response rate and the second outcomes being the response rates for MADRS, IDS-SR_{30}, and CGI-I. A response was defined as ≥50% reduction relative to the mean score obtained at the 2 baseline visits for the relevant measure. Remission was defined as a score ≤9 on the $HDRS_{24}$, ≤14 for the IDS-SR_{30}, or ≤10 on the MADRS. Sustained response referred to achieving a ≥50% reduction in baseline symptoms ($HDSR_{24}$) at least once during months 9, 10, 11, or 12, and achieving a ≥40 reduction from baseline on at least 2 others of the $HDRS_{24}$ assessments in the same period.

The trial used 1:1 randomisation to sham VNS or active VNS. Those who received sham VNS were offered active VNS after the acute phase. A third party, independent from the investigators and any staff at the study sites, served as the randomisation agent. Patient numbers were assigned in sequence for all study participants, regardless of the randomisation assignment. The device programmer obtained the randomisation assignment for each patient. Patients had to score ≥18 at 14 days post-implantation to enter the acute treatment phase. The device programmer, who was not involved in any patient care or clinical assessments, turned on or off the device and made all adjustments in stimulation parameters including the sham adjustments, as well as collecting all adverse events. The patients, outcome raters and all other staff involved in clinical care and management, were masked to whether or not VNS was active or sham. Patients were scheduled to avoid overlap in the waiting room to further ensure masking.

Clinical assessments of depressive symptoms included the $HRDS_{28}$ ($HRDS_{24}$ results were reported), and the 10-item MADRS. Self-reported depressive symptoms were measured using IDS-SR_{30}. Manic/hypomanic symptoms were rated by the Young Mania Rating Scale, with a threshold of ≥15. The DSM-IV criteria for mania were applied to declare the presence or absence of mania. Overall symptom severity and change were assessed using the clinical global severity (CGI-S) and improvement (CGI-I) ratings. Functional outcomes (or quality of life) were assessed using the medical outcomes study short form-36 (MOS SF-36). Adverse events and concomitant medications were coded using the COSTART.

Study population issues: There was no statistically significant differences in the clinical and demographic features between the active and the sham groups. On average, patients in both groups had received over 16 unique mood disorder treatments before they entered the study, and had tried more than 9 medications during the current MDE. The active and sham VNS groups did not differ in the mean and distributions of the number of adequate trials during the current MDE (p=0.5020, Cochran-Mantel-Haenszel). In terms of ECT, 53% of the patients had a history of ECT, and 36% had received ECT during the current MDE.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **235 (119 active VNS vs 116 sham VNS)**

Clinical outcomes for VNS versus sham (at 10 weeks LOCF)

Rating	Treatment (n=112)	Control (n=110)	χ^2 (df)	p
$HDRS_{24}$ response rate (%)	15.2	10.0	1.32 (1)	0.251[a]
MADRS response rate (%)[c]	15.2	11.0	0.778 (1)	0.378[c]
CGI-I response rate (%)[d]	13.9	11.8	0.208 (1)	0.648[d]

Safety

Adverse events occurring in ≥5% of patients receiving stimulation and 1.5% sham control group at the acute phase

Adverse event	Active VNS (n=119)	Sham VNS (n=116)
Voice alteration	68%	38%
Cough increased	29%	9%
Dyspnoea	23%	14%
Dysphagia	21%	11%
Neck pain	21%	10%
Paraesthesia	16%	10%
Vomiting	11%	5%

IDS-SR_{30} response rate (%)[b]	17.0	7.3	4.62 (1)	**0.032[b]**
$HDRS_{24}$ (mean, SD)	16.3±28.1	15.3±25.5	-	0.639
MADRS (mean, SD)	17.1±31.2	12.4±27.1	-	0.208
IDS-SR_{30} (mean, SD)	21.2±25.4	16.3±26.2	-	0.158

[a]Primary outcome, X^2=1.32, df=1.

[b]One patient in the control group did not have an IDS-SR_{30} assessment completed during the study, χ^2=4.62, df=1.

[c]One patient in the control group did not have a MADRS assessment completed during the study, χ^2 =0.778, df=1.

[d]One patient in the treatment group and 1 in the control group did not have a CGI assessment completed during the study, χ^2=0.208, df=1.

A repeated measures linear regression analysis showed, at 12 weeks, the estimated difference for the $HDRS_{24}$ was -0.769, SE 0.80, 95% CI (-2.34, 0.80), *p*=0.336 and the estimated difference for the IDS-SR was -2.374, SE 1.23, 95% CI (-4.78 to 0.03), *p*=0.053.

Clinical outcomes at baseline and 12 months (mean, SD)

	Baseline	**12 months (Observed)[e]**	**12 months (LOCF)**	**p**
$HDRS_{24}$	28.0±5.7 (n=205)[f]	19.6±9.7 (n=180)	20.6±9.9 (n=205)[g]	<0.001
IDS-SR_{30}	42.9±10.0 (n=204)	32.6±15.3 (n=180)	33.6±15.4 (n=204)	<0.001
MADRS	30.8±6.9 (n=205)	21.2±11.5 (n=181)	22.2±11.7 (n=205)	<0.001

[e]The observed sample included participants with data available for each measurement at each time point.

[f]Active VNS (28.7) versus sham VNS (24.6; t=4.55, df=227, p<0.001).

[g]Active VNS statistically significantly improved over time (active versus sham estimate of $HRDS_{24}$ averaged across all time points=-1.96, SE=0.63; repeated measures t=3.14, df=253, p=0.002).

Symptoms improvement over the 12-month period (n=205):

- $HDRS_{24}$: improved 0.45 points per month (SE=0.05; repeated measures t=8.25, df=654, p<0.001)
- IDS-SR_{30}: improved 0.52 points per month (SE=0.08; repeated measures t=6.79, df=631, p<0.001)
- MADRS: statistically significantly improvement over 12 months was observed.

Clinical outcomes at 12 months

	12 months (observed)		**12 months (LOCF)**	
	Response rate	**Remission**	**Response rate**	**Remission**

Laryngismus	11%	2%
Dyspepsia	10%	5%
Wound infection	8%	2%
Palpitations	5%	3%

Serious adverse events in active VNS during the acute phase:

- **Asystole**: 1 case happened during surgery.
- **Bradycardia**: 1 case occurred during surgery.
- **Mania or hypomania**: 2 patients who did not undergo VNS dose reduction or discontinued VNS. Both resolved spontaneously after 1 to 2 weeks.

Adverse events occurred in ≥5% of patients across the 2 groups by quarters

	3 months (n=232)	**6 months (n=225)**	**9 months (n=218)**	**12 months (n=209)**
Adverse event				
Headache	5% (12)	4% (9)	4% (9)	4% (8)
Neck pain	16% (38)	11% (25)	14% (31)	13% (27)
Pain	6% (13)	6% (14)	5% (11)	6% (13)
Dysphagia	13% (31)	8% (19)	7% (15)	4% (9)
Nausea	6% (13)	2% (5)	2% (5)	2% ($)
Insomnia	4% (10)	2% (5)	3% (6)	1% (2)
Paraesthesia	11% (26)	7% (15)	3% (7)	4% (9)
Cough increased	24% (55)	9% (20)	7% (15)	6% (13)
Dyspnoea	14% (33)	16% (35)	15% (33)	16% (34)
Laryngismus	10% (23)	8% (18)	7% (16)	5% (10)
Pharyngitis	6% (14)	4% (8)	4% (8)	5% (11)
Voice alteration	58% (135)	60% (135)	57% (125)	54% (113)
Serious adverse event				
Mania	1% (2)*	<1% (1)**	0	0

*Both participants had mild manic symptoms that resolved in 1 to 2 weeks.

**The participant with a manic reaction had a diagnosis of unipolar depression at baseline. Stimulation, which was 2.25 mA when the episode began, was stopped on the day that the participant was hospitalized. Stimulation remained off during the episode, which lasted about 2 months, and

$HDRS_{24}$	29.8% (54/181)	17.1% (31/181)	27.2% (55/202)	15.8% (32/202)
IDS-SR_{30}	21.7% (39/180)	15.0% (27/180)	19.9% (40/201)	13.4% (27/201)
MADRS	31.5% (57/181)	22.7% (41/181)	28.2% (57/202)	20.3% (41/202)

$HDRS_{24}$ response and sustained response at 12 months:

- Response rate: 29.4% (52/177), including a sustained response rate of 73.1% (38/52).
- Sustained response rate: 26.6% (47/177), including 66% (31/47) met the criteria for response at all 4 points (9, 10, 11, and 12 months)

MADRS response rate at 12 months: 28.2% (57/202)

CGI-I response rate at 12 months: 34.0% (68/200)

MOS-SF36 outcomes:

	Active VNS (n=107)	**Sham VSN (n=107)**	**F (df)**	**p**
Physical component improvement (mean, SD)	-0.9 (8.3)	-1.6 (8.4)	0.50 (1, 208)	0.480
Mental component improvement (mean, SD)	5.0 (11.6)	4.0 (10.2)	0.69 (1, 208)	0.406

Worsened depression requiring hospitalisation:

- **active VNS during the acute phase**: 5 patients including 1 who did not receive stimulation but was assigned to the active VNS group.
- **sham VNS during the acute phase:** 7 patients

Serious events over 12 months

	3 months (n=232)	**6 months (n=225)**	**9 months (n=218)**	**12 months (n=209)**
Suicide attempts	1% (2)	1% (3)	<1% (1)[h]	<1% (1)
Worsening depression	5.2% (12)	6.7% (15)	4.6% (10)	5.7% (12)
Hospitalisations	13	19	14	14

[h]Two attempts

During the 12-month study, 30 participants had worsening of depression enough to require hospitalisation. Of these 30 participants, 24 (80%) had a history of hospitalisation for worsening depression before study enrolment.

was restarted at .50 mA about a month after the episode ended, increased to 1.00 mA about 2 weeks later, and increased to 1.50 mA about 2 additional weeks later.

Abbreviations used: CGI-I, clinical global improvement ratings; df, degrees of freedom; IDS-SR30, 30 item Inventory of depressive symptomology-self-report; LOCF, last observation carried forward; $HDRS_{24}$, 24-item Hamilton depression rating scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MAOI, monoamine oxidase inhibitor, SSRIs, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VNS, vagus nerve stimulation.

Study 4 Aaronson ST (2017)

Details

Study type	**Non-randomised comparative study**
Country	USA (multiple centres; 61 sites)
Recruitment period	2006 to 2015
Study population and number	n=**795 (494 VNS+TAU** [including 159 D-21 rollover patients] **versus 301 TAU)** Patients with treatment-resistant depression
Age and sex	VNS arm: mean 48.9 years; 71% (350/494) female TAU arm: mean 49.9 years; 70% (211/301) female
Patient selection criteria	Inclusion criteria: patients had to be age 18 or older; have a current major depressive episode of ≥2 years in duration (unipolar or bipolar depression) or have a history of at least three depressive episodes including the current major depressive episode; and have a history of inadequate response to at least 4 depression treatments. Diagnoses of psychiatric conditions were made by trained psychiatrists at each recruiting site. Patients had a CGI-S score ≥4; no history of schizophrenia, schizoaffective disorder, any other psychotic disorder, or a current major depressive episode that included psychotic features; not currently psychotic; no history of rapid-cycling bipolar disorder; and no previous use of VNS (other than the D-21 rollover patients).
Technique	Patients in the VNS arm underwent the implantation surgery before visit 2 (baseline).
Follow-up	**5 years**
Conflict of interest/source of funding	The registry was sponsored by Cyberonics, Inc. (LivaNova), through contracts to investigative sites. Statistical analyses were performed by Cyberonics and reviewed by the senior author. Some authors declared financial relationships with Cyberonics, Inc.

Analysis

Follow-up issues: Patients were followed up at months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60. Of the 494 patients in the VNS+TAU arm, 461 (93%) completed year 1 of the registry, 289 (59%) year 2, 313 (63%) year 3, 334 (68%) year 4 and 300 (61%) year 5. Of the 301 patients in the TAU arm, 224 (74%) completed year 1 of the registry, 185 (62%) year 2, 168 (56%) year 3, 149 (50%) year 4 and 138 (46%) year 5. Of the 358 patients (45%) who withdrew early, 195 were from the VNS+TAU arm (40%) and 163 were from the TAU arm (54%). The reasons for early withdrawal were similar between the treatment arms, including withdrew consent, nonadherence, not meeting the eligibility criteria, physician's decision, death, and others.

Study design issues: This 5-year, prospective, open-label, non-randomised, observational registry study (the treatment-resistant depression registry) investigated whether adjunctive VNS with TAU in treatment-resistant depression has superior long-term outcomes compared with treatment as usual only. The primary efficacy measure was the MADRS response rate and safety outcomes focused on suicidality, which was assessed on the basis of 3 measures: a score of 2 or 3 on QIDS-SR item 12, a response of "yes" to the question "Has the patient made a suicidal gesture or attempt since the last visit?" on the investigator-completed suicidality assessment, and a score ≥4 on MADRS item 10. The ITT population included patients who completed their baseline visit, received their respective treatment, and completed at least 1 post-baseline assessment.

Study population issues: At baseline, statistically significant differences between the VNS+TAU and TAU arms were observed, relating to the past treatment with ECT (57% versus 40%, p<0.001), the mean number of failed treatments for depression (8.2±3.3 versus 7.3±2.9, p=0.010), the mean number of psychiatric hospitalisation within 5 years before enrolment (3.0±4.6 versus 1.9±4.7, p<0.001), the mean lifetime number of attempted suicides (1.8±4.0 versus 1.2±2.4, p=0.020), the mean baseline MADRS score (33.1± 7.0 versus 29.3± 6.9, p<0.001), and the mean baseline QIDS-SR score (18.2± 4.6 versus 15.7± 4.9, p<0.001).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed for efficacy: 765 (489 VNS+TAU and 276 TAU)

Cumulative response rates through the 5-year follow-up period:
<table>
<tr><th></th><th>VNS+TAU, 95% CI</th><th>TAU, 95% CI</th><th>p</th></tr>
<tr><td>MADRS</td><td>67.6% (63.4 to 71.7)</td><td>40.9% (35.4 to 47.1)</td><td><0.001</td></tr>
<tr><td>CGI-I</td><td>75.9% (72.3 to 79.9)</td><td>48.6% (43.0 to 54.8)</td><td><0.001</td></tr>
<tr><td>QIDS-SR</td><td>64.7% (60.7 to 69.2)</td><td>41.7% (35.9 to 47.5)</td><td><0.001</td></tr>
</table>
Cumulative remission rates through the 5-year follow-up period:
<table>
<tr><th></th><th>VNS+TAU, 95% CI</th><th>TAU, 95% CI</th><th>p</th></tr>
<tr><td>MADRS*</td><td>43.3% (38.9 to 47.7)</td><td>25.7% (20.7 to 31.1)</td><td><0.001</td></tr>
<tr><td>CGI-I</td><td>49.7% (45.5 to 54.3)</td><td>21.4% (16.7 to 26.4)</td><td><0.001</td></tr>
<tr><td>QIDS-SR</td><td>40.4% (36.2 to 44.9)</td><td>25.0% (19.9 to 30.1)</td><td><0.001</td></tr>
</table>
*Based on a MADRS total score ≤9 at any postbaseline visit.

Time to first response:
- MADRS: Median time to first response was significantly shorter for patients in the VNS+TAU arm than for those in the TAU arm (12 months compared with 48 months; p<0.001).
- QIDS-SR: Median time to first response was significantly shorter for patients in the VNS+TAU arm than for those in the TAU arm (22 months compared with 47 months; p<0.001).

Response duration:
- MADRS: Patients in the VNS+TAU arm had a significantly longer median time to recurrence than patients in the TAU arm (12 months compared with 7 months; p=0.001) (data not shown).
- QIDS-SR: Patients in the VNS+TAU arm had a longer median time to recurrence than did patients in the TAU arm (10 months compared with 7 months; p=0.14).

Time to first remission:
- MADRS: Patients in the VNS+TAU arm had a significantly shorter median time to remission than patients in the TAU arm (49 months compared with 65 months; p<0.001).

Duration of remission:
- MADRS: Patients in the VNS+TAU arm had a longer median duration of remission than those in the TAU arm (40 months compared with 19 months, p=0.10).
- QIDS-SR: Patients in the VNS+TAU arm had a longer median duration of remission than did patients in the TAU arm (30 months compared with 18 months; p=0.20).

Sub-analysis based on prior ECT exposure: The 5-year cumulative MADRS response rate for patients in the VNS+TAU arm who had previously responded to ECT was
</td><td>
The safety analysis population: 795 (494 VNS+TAU and 301 TAU)

The safety profile based on frequency, intensity and burden of side effects rating scale was similar between the 2 arms, showing that adjunctive VNS does not lead to an additional side effect burden compared with TAU only (exact data were not shown).
</td></tr>
</table>

statistically significantly higher (71.3%, 95% CI, 64.3 to 77.4) than the ECT responders in the TAU arm (56.9%, 95% CI, 44.8 to 68.2, p=0.006).

Suicidality reduction:

- MADRS: OR=1.67, 95% CI, 0.98 to 2.83; p=0.058
- QIDS-SR item 12: OR=2.11, 95% CI, 1.28 to 3.48, p=0.035
- Investigator-completed suicidality assessment: OR=2.04, 95% CI, 1.08 to 3.86; p=0.029

Suicidality and mortality

	VNS+TAU (n=494)	**TAU (n=301)**
Number of deaths during study participation	7	8
Exposure (patient-years)	1,985.08	926.49
All-cause mortality per 1,000 person-years, 95% CI	3.53 (1.41 to7.27)	8.63 (3.72 to 17.01)
Number of suicides during study participation	2	2
Suicides per 1,000 person-years, 95% CI	1.01 (0.11 to 3.64)	2.20 (0.24 to 7.79)

Death: 7 in the VNS+TAU arm and 8 in the TAU arm.

Abbreviations used: CI, confidence interval; CGI-I, clinical global impressions-improvement; ECT, electroconvulsive therapy; QIDS-SR, quick inventory of depressive symptomology-self-report; MADRS, Montgomery - Åsberg depression rating scale; OR, odds ratio; TAU, treatment as usual; VNS, vagus nerve stimulation.

Study 5 Conway CR (2018) (part of study 4)

Details

Study type	**Non-randomised comparative study**
Country	USA (multiple centres; 61 sites)
Recruitment period	2006 to 2015
Study population and number	**n=599 (328 VNS+TAU versus 271 TAU)** Patients with treatment-resistant depression
Age and sex	VNS+TAU: mean 48.8 years; 68.6% (255/328) female TAU: mean 50.0 years; 70.8% (192/271) female
Patient selection criteria	Inclusion and exclusion criteria: same as study 4 except for patients who rolled over from a previous VNS dose-finding study where patients did not have post-baseline Q-LES-Q-ST assessments until the 18-month visit to ensure both VNS+TAU and TAU patients had the same follow-up period; and patients who were not depressed at baseline (MADRS score of <10).
Technique	Same as study 4 - patients in the VNS arm underwent the implantation surgery before visit 2 (baseline).
Follow-up	**5 years**
Conflict of interest/source of funding	This research was supported by Cyberonics, Inc. (LivaNova, PLC), Houston, Texax, which sponsored the patient registry through contracts to investigative sites. Four authors declared potential conflicts of interest.

Analysis

Follow-up issues: Patients were followed up at months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60. Losses to follow up were 159 patients in the VNS+TAU group and 128 in the TAU group at month 60. The reasons why patients were not followed up were similar to study 4.

Study design issues: As part of a 5-year VNS clinical registry, this study compared quality of life change associated with VNS+TAU versus TAU (any antidepressant treatment) in a population of patients with unipolar and bipolar treatment-resistant depression. Quality of life was measured using the Q-LES-Q-SF, a 14-item scale that measures improvements across a wide range of life areas including physical health, mood, work, economic situation and social relationships. Q-LES-Q-SF percent max score was used to ensure that results could be compared with the MCID value. The change in QoL for patients receiving VNS+TAU versus TAU for similar drops in MADRS score was compared. The patient-reported QoL measured using Q-LES-Q-SF score was also compared with clinician-reported improvement in QoL measured using CGI-I score to determine if the results from the 2 measures concurred. An exploratory post hoc sub-analysis of the 14 functional domains of the Q-LES-Q-SF was performed to analyse which domains differentiated VNS+TAU from TAU. The authors stated that the depression symptoms (MADRS) were assessed single-blinded via offsite central raters; patients receiving either TAU or adjunctive VNS knew which treatment they were receiving when they completed the Q-LES-Q-SF. This study was open label, which could potentially influence the aggressiveness of adjunctive pharmacotherapy.

Study population issues: In terms of the baseline data for patients in the VNS+TAU group and for patients in the TAU group, the mean (±SD) numbers of failed treatments for depression were 8.0±3.04 and 7.4±2.93 respectively, the mean lifetime numbers of diagnosed depressive episodes were 15.1±24.34 and 11.7±24.56 respectively, the mean lifetime numbers of attempted suicides were 2.0±4.35 and 1.2±2.32 respectively, the mean MADRS scores were 33.2±7.67 and 29.5±6.40 respectively, the mean CGI-I scores were 5.2±0.78 and 4.7±0.72 respectively, the mean QIDS-SR scores were 18.3±4.67 and 15.8±4.92 respectively, and the mean Q-LES-Q-SF percentage of possible maximum scores were 38.4±14.97 and 40.8±15.77 respectively.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **599 (328 in the VNS+TAU arm versus 271 in the TAU arm)**

Longitudinal QoL changes

On average, there was a comparative QoL advantage observed for the VNS+TAU group over the TAU group (as demonstrated via non-overlapping 95% confidence bands) as early as 3 months, which was sustained throughout the entire 5-year duration of the study (exact data were not reported).

Change in QoL for VNS+TAU patients versus TAU patients for similar drop in MADRS score

There was a statistically significantly larger improvement in Q-LES-Q-SF percent max score from baseline in the VNS+TAU group compared to the TAU group from the same drop in MADRS score (p value and exact data were not reported).

On average, to achieve **a clinically meaningful increase in Q-LES-Q-SF percent max score of 11.89**:

- VNS+TAU patients: the MADRS drop from baseline was at least **34%**
- TAU patients: the MADRS drop from baseline was at least **56%**

A combined linear regression model showed that a VNS+TAU patient was expected to have an additional mean improvement in Q-LES-Q-SF percent max score of 3.96 (95% CI: 2.32 to 5.61) compared to a TAU patient for the same drop in MADRS score.

Association of QoL with CGI-I scores

On average, to achieve **a 50% chance of reaching CGI-I category 1 or 2 (having a response)**:

- VNS+TAU patients: the MADRS drop from baseline was at least **48%**
- TAU patients: the MADRS drop from baseline was at least **95%**

To achieve a response, VNS+TAU patients compared with TAU patients: the estimated OR was 2.78 (95% CI: 2.17 to 3.57).

Sub-analysis of QoL domains influenced by VNS+TAU versus TAU

Q-LES-Q-SF	MADRS percentage change	VNS+TAU, 95% CI	TAU, 95% CI
Physical health	-50	0.22 (0.14 to 0.31)	0.24 (0.13 to 0.34)
	-30	0.13 (0.06 to 0.21)	0.14 (0.04 to 0.23)
	-10	0.05 (-0.04 to 0.13)	0.03 (-0.06 to 0.13)
Mood*	-50	1.00 (0.92 to 1.07)	0.74 (0.65 to 0.83)
	-30	0.75 (0.68 to 0.83)	0.50 (0.42 to 0.58)
	-10	0.50 (0.42 to 0.59)	0.25 (0.18 to 0.33)
Work	-50	0.82 (0.71 to 0.93)	0.66 (0.53 to 0.8)
	-30	0.65 (0.54 to 0.76)	0.50 (0.37 to 0.62)
	-10	0.47 (0.36 to 0.59)	0.33 (0.21 to 0.46)
Household activities*	-50	0.80 (0.73 to 0.88)	0.54 (0.45 to 0.63)
	-30	0.65 (0.58 to 0.73)	0.40 (0.32 to 0.48)
	-10	0.50 (0.42 to 0.58)	0.25 (0.17 to 0.33)
Social relationship	-50	0.75 (0.67 to 0.83)	0.58 (0.48 to 0.68)
	-30	0.57 (0.49 to 0.65)	0.40 (0.32 to 0.49)
	-10	0.40 (0.31 to 0.48)	0.23 (0.15 to 0.31)
Family relationship	-50	0.54 (0.45 to 0.62)	0.35 (0.25 to 0.44)
	-30	0.42 (0.34 to 0.5)	0.23 (0.15 to 0.32)

	-10	0.30 (0.21 to 0.4)	0.12 (0.04 to 0.2)
Leisure activity*	-50	0.83 (0.75 to 0.91)	0.54 (0.44 to 0.64)
	-30	0.65 (0.57 to 0.73)	0.38 (0.28 to 0.47)
	-10	0.47 (0.38 to 0.55)	0.21 (0.12 to 0.3)
Ability to function*	-50	0.89 (0.82 to 0.96)	0.62 (0.54 to 0.71)
	-30	0.69 (0.63 to 0.76)	0.42 (0.34 to 0.5)
	-10	0.50 (0.43 to 0.57)	0.22 (0.14 to 0.3)
Sex drive	-50	0.49 (0.41 to 0.58)	0.35 (0.25 to 0.45)
	-30	0.40 (0.32 to 0.49)	0.26 (0.18 to 0.34)
	-10	0.32 (0.23 to 0.4)	0.17 (0.09 to 0.25)
Economic status	-50	0.18 (0.1 to 0.25)	0.32 (0.23 to 0.41)
	-30	0.12 (0.05 to 0.2)	0.24 (0.15 to 0.32)
	-10	0.07 (-0.01 to 0.15)	0.15 (0.07 to 0.24)
Living/housing situation	-50	0.24 (0.16 to 0.32)	0.15 (0.06 to 0.24)
	-30	0.17 (0.09 to 0.25)	0.07 (-0.01 to 0.15)
	-10	0.11 (0.02 to 0.19)	-0.01 (-0.09 to 0.07)
Ability to get around	-50	0.10 (0.01 to 0.19)	0.01 (-0.08 to 0.11)
	-30	0.05 (-0.04 to 0.13)	-0.06 (-0.14 to 0.03)
	-10	-0.01 (-0.1 to 0.09)	-0.12 (-0.21 to -0.04)
Ability to do work	-50	0.42 (0.32 to 0.53)	0.27 (0.15 to 0.38)
	-30	0.31 (0.21 to 0.41)	0.18 (0.08 to 0.28)
	-10	0.20 (0.1 to 0.31)	0.09 (-0.01 to 0.19)
Overall well-being*	-50	0.92 (0.84 to 0.99)	0.68 (0.59 to 0.78)
	-30	0.70 (0.63 to 0.77)	0.49 (0.41 to 0.57)
	-10	0.48 (0.4 to 0.56)	0.29 (0.21 to 0.38)

*Additional improvement in the domain score for the VNS+TAU group compared to the TAU group was statistically significant (without any multiplicity adjustment). Significance was determined by absence of overlap of CIs between groups when comparing the regression of a given Q-LES-Q-SF domain at each MADRS percent decrease (without multiple comparisons).

Abbreviations used: MADRS, Montgomery - Åsberg depression rating scale; OR, odds ratio; QoL, quality of life; Q-LES-Q-SF, quality of life enjoyment and satisfaction questionnaire short form; TAU, treatment as usual; VNS, vagus nerve stimulation.

Study 6 Aaronson ST (2013) [included in study 1]

Details

Study type	**Randomised controlled trial**
Country	USA (multiple centres; 29 sites)
Recruitment period	2006 to 2010
Study population and number	**n=331 (102 low stimulation, 101 medium stimulation, and 107 high stimulation)** Patient with treatment-resistant depression
Age and sex	Mean 47.9 years; 67.7% female
Patient selection criteria	Inclusion criteria: i) 18 years of age or older with a diagnosis of chronic (>2 years) or recurrent (≥2 prior episodes) MDD or bipolar disorder (BP), and a current diagnosis of major depressive episode (MDE) as defined by the Diagnostic and Statistical Manual of Mental Disorders, and determined using the Mini-International Neuropsychiatric Interview; ii) a history of failure to respond to >4 adequate does/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories, as documented through medical history and record review; iii) a minimum pre-study and baseline score of 24 on the MADRS, with no greater than a 25% decrease in the MADRS score between the pre-study and baseline visits required for randomisation; iv) currently receiving at least 1 antidepressant treatment in the form of medication or electroconvulsive therapy (ECT); and v) a stable regimen of all current antidepressant treatments for a minimum of 4 weeks before the baseline visit. Patients with BP had to be receiving a mood stabiliser at baseline, and all patients had to be able to complete the necessary evaluations, provide written informed consent, and provide the Health Insurance Portability and Accountability Act of 1996 authorisation. Exclusion criteria: i) a history of any psychotic disorder; ii) a history of rapid cycling BP, iii) clinically significant suicidal intent at the time of screening; iv) a history of drug or alcohol dependence in the last 12 months; v) a current diagnosis of BP mixed phase; vi) a history of borderline personality disorder; vii) a history of previous VNS system implant; viii) if considered at high risk for surgery; and ix) if currently enrolled in another investigational treatment study.
Technique	The procedure was performed using a VNS Therapy system. After a postoperative recovery period (generally 2 weeks in duration following implantation), each patient began VNS dose titration according protocol specified guidelines.
Follow-up	**50 weeks**
Conflict of interest/source of funding	Statistical analyses were performed by Cyberonics, Inc. and reviewed by the senior author.

Analysis

Follow-up issues: Patients were evaluated at baseline, and then at weeks 10, 14, 18 and 22 (during the acute phase) and at weeks 26, 32, 38, 44 and 50 (during the long-term phase). Of the 331 enrolled patients, 330 completed the dose titration, of whom 96% (316/330) completed the 22-week acute phase while 94% (298/316) finished the 50-week long-term phase.

Study design issues: This multicentre, double blind study compared the safety and effectiveness of different stimulation levels of adjunctive VNS therapy for the treatment of treatment-resistant depression. Efficacy evaluations were made using the Inventory of Depressive Symptomatology Clinician Administered Version (IDS-C), the Quick Inventory of Depressive Symptoms Clinician Administered (QIDS-C) data extrapolated from the IDS-C, MADRS, IDS-SR, and CGI-I, while safety evaluation used the adverse events records. The ITT population was defined as all implanted patients who had a baseline and at least 1 post-stimulation assessment on the IDS-C and who were not excluded by an IDS-C baseline score <35 or by a baseline IDS-C score in the lower 5th percentile, whichever number was less. The operator's training and experience of the procedure were not detailed.

Following the implantation, but prior to the initiation of stimulation, patients were randomised to 1 of 3 treatment groups based on target settings: low stimulation (LOW; output current of 0.25 mA, pulse width of 130 μs), medium stimulation (MEDIUM; 0.5 to 1.0 mA, 250 μs), or high stimulation (HIGH; 1.25 to 1.5 mA, 250 μs). All treatment groups employed the same duty cycles (30 s ON and 5 min OFF) and pulse frequencies (20 Hz). All implanted patients were consecutively randomised based on the date of implantation. The only study personnel unblinded to treatment group assignment were study programmers at each site and clinical engineers who were employed by the sponsor to monitor the programmers. All other study site and sponsor personnel and the patients were blinded to treatment group assignment.

Study population issues: The ITT population was 310 (LOW, n=102; MEDIUM, n=101, and HIGH, n=107). Of the ITT population, >97% had failed to respond to ≥6 previous treatments. On average, patients had experienced 3 to 4 prior hospital admissions for mood disorders, 45.6% of the patients had attempted suicide at least once prior to enrolment, and 56.8% had received ECT. The treatment groups were similar with respect to age, gender, race, demographic features, psychiatric history, and antidepressant treatment modalities being used prior to study enrolment. The proportions of patients in the safety population who reached their assigned stimulation were: HIGH (74.3% at week 10 and 72.6% at week 18), MEDIUM (85% at week 10 and 87.9% at week 18), and LOW (88.3% at week 10 and 85.6% at week 18). The primary reasons for not attaining the assigned stimulations were general discomfort, increased cough, voice alteration, hoarseness and other non-specified reasons.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **331**

Acute phase:

Mean (SD) change in IDS-C score relative to baseline, acute phase (ITT population)

IDS-C score	LOW	MEDIUM	HIGH	Total
Baseline	46.2 (8.0) n=102	45.8(7.5) n=101	45.7 (8.0) n=107	46.0 (7.9) n=310
Week 10	-9.0 (10.4) n=101	-9.8 (10.3) n=100	-8.3 (11.0) n=106	-9.0 (10.6) n=307
Week 14	-10.2 (11.4) n=101	-10.7 (12.3) n=96	-9.9 (11.6) n=105	-10.3 (11.7) n=302
Week 18	-10.7 (10.2) n=97	-10.3 (12.7) n=97	-12.3 (11.2) n=101	-11.1 (11.4) n=295
Week 22	-10.2 (11.4) n=97	-11.5 (12.9) n=97	-11.5 (13.4) n=105	-11.1 (12.6) n=299

Statistically significant improvement in mean scores during the acute phase after the initiation of stimulation for all treatment groups (data not shown):

- IDS-C: p=0.0023
- QICS-C: p=0.0005
- MADRS: p<0.0001

Safety

Implantation-related adverse events at ≥1% incidence

Adverse events, n (%)	LOW n=111	MEDIUM n=107	HIGH n=113	Total n=331
Incision pain	20 (18.0)	23 (21.5)	19 (16.8)	62 (18.7)
Incision site reaction	15 (13.5)	6 (5.6)	10 (8.8)	31 (9.4)
Voice alteration	7 (6.3)	13 (12.1)	5 (4.4)	25 (7.6)
Pain	5 (4.5)	5 (4.7)	10 (8.8)	20 (6.0)
Device site reaction	5 (4.5)	3 (2.8)	3 (2.7)	11 (3.3)
Paraesthesia	2 (1.8)	2 (1.9)	4 (3.5)	8 (2.4)
Pharyngitis	2 (1.8)	2 (1.9)	2 (1.8)	6 (1.8)
Neck pain	1 (0.9)	0	4 (3.5)	5 (1.5)
Device site pain	4 (3.6)	0	0	4 (1.2)

Post-implant adverse events at ≥10% incidence

Adverse events, n (%)	LOW n=111	MEDIUM n=107	HIGH n=113	Total n=331
Voice alteration	71 (64.0)	82 (76.6)	86 (76.1)	239 (72.2)
Dyspnoea	33 (29.7)	36 (33.6)	38 (33.6)	107 (32.3)
Pain	28 (25.2)	30 (28.0)	47 (41.6)	105 (31.7)

- CGI-I: p<0.0001
- IDS-SR: p=0.0003

There were no statistically significant differences noted between the 3 stimulation groups.

No statistically significant differences for any of the between-stimulation group comparisons over time for IDS-C:

- LOW versus MEDIUM, p=0.8131
- LOW versus HIGH, p=8027
- MEDIUM versus HIGH, p=0.9921

IDS-C scores for those patients in each stimulation group who attended their assigned stimulation at week 22: the combined MEDIUM and HIGH stimulation groups average about 2 points more improvement than the LOW stimulation group (p=0.089)

Response and remission rates for IDS-C, QIDS-C, MADRS, IDS-SR and CGI-I at week 22:

- Remission rates in both MEDIUM and HIGH group: 9% to 11% for each rating scale,
- Remission rates in the LOW group: 5% to 6% for each rating scale

No statistically significant results were noted for any of the between-group comparisons (exact data were not reported).

Response and remissions rates across IDS-C, QIDS-C, MADRS, IDS-SR and/or CGI-I at week 50:

	Response rates	Remission rates
LOW	27% to 42%	15% to 23%
MEDIUM	36% to 53%	
HIGH	27% to 48%	

Regression analyses showed **a higher stimulation of electrical stimulation was associated with decreased depression symptomatology in IDS-C score** (r=-0.21, p<0.001).

Responders at week 22 with a sustained IDS-C or MADRS response at week 50

	LOW n=111	MEDIUM n=107	HIGH n=113	Total n=331
IDS-C				
Patients with ≥50% improvement at week 22	16	17	22	55
Patients with ≥50% improvement at week 50	7	15	18	40
Responders at week 22 with sustained	43.8%	88.2%	81.8%	72.7%

Paraesthesia	31 (27.9)	35 (32.7)	39 (34.5)	105 (31.7)
Incision pain	24 (21.6)	33 (30.8)	27 (23.9)	84 (25.4)
Increased cough	27 (24.3)	28 (26.2)	28 (24.8)	83 (25.1)
Headache	19 (17.1)	21 (19.6)	21 (18.6)	61 (18.4)
Depression	25 (22.5)	14 (13.1)	21 (18.6)	60 (18.1)
Pharyngitis	19 (17.1)	19 (17.8)	19 (16.8)	57 (17.2)
Hypertonia	22 (19.8)	17 (15.9)	17 (15.0)	56 (16.9)
Neck pain	12 (10.8)	14 (13.1)	20 (17.7)	46 (13.9)
Dysphagia	10 (9.0)	17 (15.9)	18 (15.9)	45 (13.6)
Nasopharyngitis	16 (14.4)	17 (15.9)	12 (10.6)	45 (13.6)
Incision site reaction	18 (16.2)	11 (10.3)	13 (11.5)	42 (12.7)
Nausea	15 (13.5)	15 (14.0)	9 (8.0)	39 (11.8)
Anxiety	13 (11.7)	12 (11.2)	13 (11.5)	38 (11.5)
Insomnia	12 (10.8)	12 (11.2)	12 (10.6)	36 (10.9)
Device site reaction	16 (14.4)	8 (7.5)	9 (8.0)	33 (10.0)

Serious adverse event:

- **Depression**: LOW (7.2%), MEDIUM (5.6%), and HIGH (3.5%)

response at week 50				
MADRS				
Patients with ≥50% improvement at week 22	16	25	30	71
Patients with ≥50% improvement at week 50	11	23	23	57
Responders at week 22 with sustained response at week 50	68.8%	92.0%	76.7%	80.3%

Pairwise comparisons detected statistically significant differences on the IDS-C (LOW versus MEDIUM, p=0.0186; LOW versus HIGH, p=0.0166), but not the MADRS.

Suicide attempts: LOW (6.3%) compared with MEDIUM (0.9%) and HIGH (3.5%), p=0.065

Death: n=6, but the VNS-related death occurred in 1 patient who was from the LOW stimulation group with a history of 2 lifetime suicide attempts.

Abbreviations used: CGI-I, clinical global impressions-improvement; IDS-C, inventory of depressive symptomatology clinician administered version; IDS-SR, inventory of depressive symptomology-self-report; QIDS-C, quick inventory of depressive symptoms clinician administered version; MADRS, Montgomery - Åsberg depression rating scale.

Study 7 Trottier-Duclos F (2018)

Details

Study type	**Case series**
Country	Canada (single centre)
Recruitment period	2007 to 2010
Study population and number	n=**10 (7 unipolar depression and 3 bipolar depression)** Patients with treatment-resistant depression
Age and sex	Mean 50 years; 60% (6/10) female
Patient selection criteria	Inclusion criteria: Patients had treatment-resistant depression which was defined as a major depressive episode, confirmed with Mini-International Neuropsychiatric Interview, including bipolar depression, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria despite 3 antidepressant trials and at least 1 pharmacological potentiation. Exclusion criteria: patients had active neurological disorder, acute medical disorder, severe Axis II disorder, or another major Axis I disorder.
Technique	The VNS device (Cyberonics Inc, Houston, Tex) was implanted. It was activated 10 days after the implantation. Initial parameters were initiated at 0.25 mA output current and 30 Hz with 250 μs impulse duration. The stimulation duration was 30 seconds (on) with 5 minutes between stimulation (off). These parameters were modified during follow-up based on clinical response and tolerability to adverse effects. TAU was continued, yet no change was permitted for the first year of VNS.
Follow-up	**6 years**
Conflict of interest/source of funding	One author received an unrestricted grant from Xycorp Medical Inc, Missisauga, ON, Canada (former Canadian distributor of Cyberonics, Inc, Houston, Tex). One author received a student grant from the Centre Hospitalier Universitaire de Montréal foundation.

Analysis

Follow-up issues: Patients were followed up at 1, 3, 6, 12, 24, 36, 48, 60 and 72 months. None of the patients enrolled left the study or was lost to follow up.

Study design issues: This pilot study evaluated the long-term effects of VNS on both clinical symptoms and QOL for patients with treatment-resistant depression, through a 6-year naturalistic follow-up. QoL was assessed with SF-36, complied using the standard method and Canadian normative data, which gives a mental health summary score and a physical health summary score. Depression symptoms were evaluated with $HDRS_{28}$, and anxiety symptoms were evaluated using the Hamilton Anxiety Rating Scale (HAM-A).

Study population issues: Of the 10 patients, 7 had a diagnosis of unipolar depression and 3 had a diagnosis of bipolar depression. The mean number of depressive episodes was 4.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **10**

Mean (95% CI) of rating scales through follow-up

		QoL (SF-36)		Symptom rating scales	
		MCS	**PCS**	**HDRS**	**HAM-A**
Baseline		19.4 (11.7 to 27.0)	43.5 (35.8 to 51.2)	27.3 (23.2 to 31.4)	16.2 (11.0 to 21.4)
1 month		28.0 (17.3 to 38.7)	42.35 (36.3 to 48.42)	16.0 (9.8 to 22.2)	9.7 (5.9 to 13.5)
3 months		36.0 (24.7 to 47.4)	40.5 (30.0 to 51.1)	12.4 (6.4 to 18.4)	7.7 (5.2 to 10.2)
6 months		33.5 (25.1 to 41.9)	45.3 (34.5 to 56.1)	10.1 (7.5 to 12.7)	7.5 (5.2 to 9.8)
12 months		31.6 (20.5 to 42.7)	47.4 (39.4 to 54.2)	11.6 (4.3 to 18.9)	7.0 (3.6 to 10.4)
24 months		36.0 (25.2 to 46.7)	47.4 (37.4 to 57.4)	10.1 (4.7 to 15.5)	7.0 (3.2 to 10.8)
36 months		34.2 (23.6 to 44.8)	52.1 (45.3 to 58.8)	9.5 95.0 to 14.0)	5.2 (2.8 to 7.6)
48 months		36.0 (24.8 to 47.3)	49.9 (42.9 to 57.0)	9.1 (4.8 to 13.4)	6.3 (2.5 to 10.0)
60 months		35.8 (25.0 to 46.5)	52.1 (47.3 to 56.9)	7.2 (3.7 to 10.7)	4.7 (2.4 to 7.0)
72 months		38.7 (28.1 to 49.3)	50.9 (45.2 to 56.5)	7.9 (3.7 to 12.1)	6.2 (2.7 to 9.7)
Repeated measure MANOVA	F	3.479	14.745	7.211	3.479
	P	0.012	<0.002	<0.001	<0.001

Statistically significant improvements through the follow-up:

- $HDRS_{28}$ score: $F_{9,81}=14.745$, $p<0.001$
- HAM-A score: $F_{9,81}=7.211$, $p<0.001$
- MCA score: $F_{9,81}=2.566$, $p=0.012$
- PCS score: $F_{9,81}=3.479$, $p<0.002$

Negative linear trend in depressive symptoms:

- $HDRS_{28}$ scores: $F_{1,9}=60.593$, $p<0.001$, a statistically significant difference between baseline and 1st month evaluation ($F_{1,9}=26.352$, $p=0.001$)
- HAM-A scores: $F_{1,9}=36.761$, $p<0.001$

Positive linear trend in QoL:

- MCA score: $F_{1,9}=5.973$, $p=0.037$, a statistically significant difference between months 1 and 3 ($F_{1,9}=5.839$, $p=0.039$)
- PCA scores: $F_{1,9}=15.410$, $p=0.003$

$HDRS_{28}$ response and remission rates:

	Response	**Remission**
1 month	30%	30%
12 months	70%	50%
72 months	80%	50%

80% of patients are currently working, seeking employment or volunteering.

Abbreviations used: CI, confidence interval; HAM-A, Hamilton anxiety rating scale; $HDRS_{28}$, 28-item Hamilton depression rating scale; MCS, mental component score; PCS, physical component score; QoL, quality of life; SF-36, 36-item short form questionnaire.

Study 8 Jodoin VD (2018)

Details

Study type	**Case series**
Country	Canada (single centre)
Recruitment period	2007 to 2015
Study population and number	n=14 (8 major depression disorder and 6 bipolar disorder) Patients with treatment-resistant depression
Age and sex	Mean 50 years; 64% (9/14) female
Patient selection criteria	Inclusion criteria: Patients met the selection criterion of treatment resistance, defined as a partial response or no response to at least 4 antidepressant medications, either as a monotherapy or in combination, at minimum adequate dose and duration. All patients had received at least 6 weeks of cognitive behavioural therapy psychotherapy. Exclusion criteria: Patients had psychiatric conditions, medical contraindication, and spontaneous remission of the major depressive episode before the surgery.
Technique	The VNS device (Cyberonics, Inc, Houston, Tex [now LivaNova PLC, London, UK]) was implanted. VNS activation was initiated at a 0.25 mA current and gradually increased in increments of 0.25 mA, depending on tolerability. Intensity was set to the highest comfortable setting at which a clinical response was observed. At 12 months, the output currents of the VNS ranged from 0.75 to 1.75 mA. Most patients were stimulated at a 30 Hz frequency and at a 250-microsecond pulse width. The frequency of stimulation was generally 30 seconds on and 5 minutes off, except for 1 patient who was stimulated 30 seconds on every 3 minutes because higher VNS work cycle was better tolerated than high current output.
Follow-up	**2 years**
Conflict of interest/source of funding	One author received an unrestricted grant from Xycorp Medicla Inc, Mississauga, Ontario, Canada.

Analysis

Follow-up issues: Patients were followed up at 1, 3, 6, 12 and 12 months after the onset of stimulation.

Study design issues: This study assessed the long-term cognitive effects of VNS in patients with treatment-resistant depression and its relationship to changes in mood. Data for mood and cognition were collected using a short neuropsychological battery, cognitive battery (included measures of verbal and visuospatial memory, attention/executive functions, and psychomotor speed), alternate forms of the cognitive tasks, and MADRS.

Study population issues: In terms of unipolar and bipolar patients, they were similar in terms of age (p=0.6), number of depressive episodes (p=0.3), age at the current episode (p=0.13), length of the current depressive episode (p=0.58) and severity of the current depressive episode (p=0.51). For their current episode, unipolar and bipolar patients were also similar in terms of use of selective serotonin reuptake inhibitors (p=0.76), serotonin-norepinephrine reuptake inhibitors (p=0.57), tricyclic antidepressants (p=0.89) and atypical antipsychotics (p=0.67); 2 patients had received previous ECT.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **14**

Percentage changes in MADRS score compared to baseline, mean (range):

- MADRS % change 1 month: 46% (-11% to 92%)
- MADRS % change at 3 months: 62% (26% to 93%)
- MADRS % change at 12 months: 63% (23% to 93%) (unipolar patients, 48%; bipolar patients: 82%)
- MADRS % change at 24 months: 70% (22% to 90%)

The improvement was clinically significant at 12 month (RCI=2.14) and at 24 months (RCI=3.25).

Response rate (>50% improvement in MADRS) at 3, 12 and 24 months: 71% (10/14)

Remission rate (MADRS score ≤10):

- 1 month: 29% (4/14)
- 3 months: 50% (7/14)
- 12 months: 57% (8/14)
- 24 months: 64% (9/14)

Analysis on the entire sample showed a **statistically significant improvement in MADRS score** over time ($F_{4,48}$=30.4, p<0.001, η^2=0.72), with planned contrasts showing a significant improvement at 1 month (p<0.001) and no significant change from 1 month to the following evaluations.

VNS results on cognitive measures, mean±SD (range):

Measure	Baseline	1 month	3 months	12 months	24 months	RCI	P	Partial η^2
Memory[a]							<0.001	0.78
RAVLT learning (total 5 trials)[b]	45.5±10.2 (29 to 64)	57±8 (48 to 73)	57.2±7.9 (45 to 70)	58.5±5.6 (51 to 71)	58.3±8.4 (42 to 71)	1.78	<0.001	0.5
RAVLT delayed recall[c]	10.5±3.3 (6 to 15)	12.7±1.7 (9 to 15)	12.4±2.5 (9 to 15)	13±2.2 (8 to 15)	12.8±2 (10 to 15)	0.80	0.001	0.35
ROCF delayed recall[d]	18.7±5.8 (9 to 29)	25.5±4 (19.5 to 32)	28.4±5.1 (15 to 35)	22.9±3.7 (15.5 to 33)	29.3±5 (16 to 35)	1.38	<0.001	0.62
Information-processing speed[e]							0.001	0.33
SDMT score[f]	46±10.7 (18 to 60)	47.6±8.1 (33 to 60)	48.4±11.5 (30 to 61)	52.4±7.9 (38 to 65)	52.3±8.9 (34 to 64)	0.69	0.009	.022
Stroop colour[g]	76.3±18.1 (28 to 96)	77.4±18.7 (44 to 107)	81.6±17.2 (54 to 106)	87.7±14.9 (57 to 112)	88.6±12.8 (61 to 110)	0.95	0.002	0.28
Attention/executive functions[h]							.001	0.43
Phonemic fluency (total 3 letters)[i]	36.6±9.6 (18 to 50)	39.6±8.7 (20 to 51)	43.9±12.1 (22 to 59)	43.9±8.9 (22 to 55)	44.07±11.2 (24 to 64)	0.66	0.011	0.22
Stroop interference[j]	39.7±12.3 (8 to 60)	40.4±11.5 (14 to 60)	43.6±10.7 (36 to 65)	47.6±8.4 (40 to 72)	50.2±8.6 (31 to 64)	1.01	<0.001	0.36

[a]Results of the MANOVA for memory tests show a significant difference among the testing sessions across the 4 memory measures (Λ=0.218, $F_{16,125.895}$=5.081, p<0.001, η^2 partial=0.78).

[b]Univariate tests revealed that verbal learning scores showed a statistically significant effect of evaluation time ($F_{4,44}$=10.933, p<0.001, $\eta^2_{partial}$=0.50) with a significant improvement between the baseline and 1-month evaluation (p<0.001, t_{11}=25.9) and maintenance of the response until 24 months of stimulation.

[c]There was a statistically significant effect of evaluation time ($F_{4,44}$=5.892, p=0.001, $\eta^2_{partial}$=0.35), with a statistically significant improvement between the baseline and the 1-month evaluation (p=0.007, t_{11}=10.735) and a maintenance of the response until 24 months.

[d]There was a statistically significant effect of evaluation time ($F_{4,44}$=17.737, p<0.001, $\eta^2_{partial}$=0.62), and a statistically significant difference between the baseline and 1-month evaluation (p=0.001, t_{11}=18.184), as well as a statistically significant difference between the 3-month and the 12-month evaluation (p=0.014, t_{11}=8.539), and between the 12- and 24-month evaluation (p<0.001, t_{11}=41.605).

[e]The MANOVA on measures of information-processing speed showed a significant effect of evaluation time (Λ=0.672, $F_{8,102}$=2.808, p=0.007, η^2=0.33).

[f]There was a statistically significant effect of evaluation time ($F_{4,52}$=3.758, p=0.009, $\eta^2_{partial}$=0.22).

[g]There was a statistically significant effect of evaluation time ($F_{4,52}$=5.102, p=0.002, $\eta^2_{partial}$=0.28).

[h]The MANOVA on attention and executive functions tests showed a significant effect of evaluation time across the 2 tests (Λ=0.572, $F_{8,104}$=4.108, p<0.001, η^2=0.43).

[i]Verbal fluency scores showed a statistically significant effect of evaluation time ($F_{4,52}$=3.661, p=0.011, $\eta^2_{partial}$=0.22).

[j]The interference score of the Stroop interference test showed a statistically significant improvement over time ($F_{4,52}$=7.214, p<0.001, $\eta^2_{partial}$=0.36)

Associations between cognitive and clinical improvement:

- At 1 month, the improvement in MADRS scores was not significantly correlated with changes in any of the cognitive scores: (all r's<-0.443, all p's<0.15).
- At 12 months, the change in MADRS score was significant correlated with several measures: Stroop interference: r=-0.65, p=0.01; verbal fluency: r=-0.63, p=0.01; ROCF: r=-0.58, p=0.05.

Abbreviations used: MADRS, Montgomery - Åsberg depression rating scale; RAVLT, rey auditory verbal learning test; RCI, reliable change indices; ROCF, rey-osterrieth complex figure; SDMT, symbol digit modalities test.

Study 9 Singleton AH (2009)

Details

Study type	**Case report**
Country	USA
Recruitment period	2006
Study population and number	n=1 Patients with long-term history of treatment-resistant depression
Age and sex	52 years; female
Patient selection criteria	The patient had a long-standing history of treatment-resistant depression.
Technique	The VNS device (Cyberonics Inc, Houston, Tex) was implanted and activated 2 weeks after the procedure.
Follow-up	**2 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: The patient was followed up from May 2006 to July 2008.

Study design issues: This case report presented a patient who was using VNS for treatment-resistant depression subsequently developed second- and third-degree heart block with ventricular standstill 1 year and 7 months after the implantation.

Study population issues: The patient had a medical history of significant hypertension, obesity, hypercholesterolemia, hypothyroidism, hypokalemia, noninsulin-dependent diabetes mellitus, and mild obstructive sleep apnoea, a history of fainting episodes and a nonspecific complaint of fast heart rate, as well as a significant psychiatric history of long-standing treatment-resistant depression. The patient also reported a history of multiple suicide attempts including overdose on tricyclic antidepressants and had repeated voluntary and involuntary psychiatric admissions. Although the patient gained short-term benefits from ECT, her symptoms failed to respond afterwards.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1** Gradual improvement in mood and ability for self-case (data were not reported). **Psychiatric hospitalisation for suicidal ideation**: n=1 at month 2 after the VNS implantation.	**Heart block and ventricular standstill**: caused by VNS stimulation at month 7. The patient experienced falls 7 months after the implantation. At the time of these falls, her VNS parameters were at the maximum settings (output current of 1.00mA, signal frequency of 20 Hz, pulse width of 500 microseconds, signal on time of 30 seconds, a signal off time of 5 minutes, with magnet set to 0 mA and magnet on time of 60 seconds). The patient had periods of **nausea and light headedness** and noted that the VNS had fired just before these symptoms. The King of Hearts monitor recorded intermittent episodes of **second- and third-degree AV heart block with 5 to 6 seconds of ventricular standstill** that correlated with her symptoms. After the VNS was deactivated with a magnet by cardiology, the patient reported no further pre-syncopal or syncopal episodes, and no further ventricular pauses or AV blocks were recorded for the remaining 1.5 years.
Abbreviations used: AV, atrioventricular; VNS, vagus nerve stimulation.	

Validity and generalisability of the studies

- Studies 1, 3 to 9 were conducted in the USA, Canada and/or Europe, and study 2 did not report the country.
- Studies 1, 3 to 6 were done in multiple centres.
- There were several publications including the same population; there was likely to be some patient overlap between them.
- Patient populations were heterogenous, including different definitions of treatment-resistant depression, among the studies; so, significant remaining uncertainty about the efficacy of VNS in treating patients with truly treatment-resistant depression.
- The mean age was >46 years among the studies apart from 1 of the systematic reviews, where the mean ages of the individual studies ranged from 11 to 48 years.[2]
- The longest follow-up period was 6 years in study 7, with most remaining studies having a follow-up of 2 years or 5 years.
- Losses to follow-up were high (>25%) in 3 studies[3-5].
- There was a variation in the techniques relating to current intensity, pulse frequency, pulse width, and stimulation duration.
- Cyberonics, Inc (Houston, TX, USA) is the manufacturer of VNS Therapy and 6 studies were supported by, or some authors had financial relationships with, the manufacturer.

Existing assessments of this procedure

The Royal College of Psychiatrists position statement on neurosurgery for mental disorder, also known as psychiatric neurosurgery, was published in 2017. The statement described that there had been several open case series reporting encouraging results of the use of VNS in patients with chronic and refractory depression, the literature was generally of low quality and a pivotal blinded controlled comparison of active vagus nerve stimulation (VNS) with sham stimulation failed to demonstrate efficacy (Ruth et al. 2000, the mainly cited

paper relating to VNS). RCP considered that VNS for all psychiatric indications, including depression, should continue to be viewed as investigational and therefore should not be performed unless as part of an ethically approved research protocol.

The American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder was published in 2010. The efficacy and safety of VNS for treating patients with treatment-resistant depression were based on 1 systematic review, 1 randomised controlled trial and 2 case series. APA recommended that VNS might be an additional option for individuals who have not responded to at least 4 adequate trials of antidepressant treatment, including electroconvulsive therapy. This recommendation is 1 of the strategies to address nonresponse and is under category III, “may be recommended on the basis of individual circumstances”.

The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on Brain Stimulation Treatment in Psychiatry were published in 2010. The efficacy and safety of VNS for treating patients with treatment-resistant depression were based on 2 randomised controlled trials, 3 case series and 1 case report. WFSBP recommended that psychiatrists considered using VNS along with other options in highly treatment-resistant patients with a chronic course who had tried and failed more than 3 other antidepressants. Prior response to electroconvulsive therapy seemed to be a predictor of response to VNS.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. NICE interventional procedures guidance 552 (2016). Available from https://www.nice.org.uk/guidance/ipg552

- Repetitive transcranial magnetic stimulation for depression. NICE interventional procedures guidance 542 (2015). Available from https://www.nice.org.uk/guidance/ipg542

- Transcranial direct current stimulation (tDCS) for depression. NICE interventional procedures guidance 530 (2015). Available from https://www.nice.org.uk/guidance/ipg530

- Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004). Available from https://www.nice.org.uk/guidance/ipg50

NICE guidelines

- Bipolar disorder: assessment and management. NICE clinical guideline 185 (2018). Available from https://www.nice.org.uk/guidance/cg185
- Depression in adults: recognition and management. NICE clinical guideline 90 (2018). Available from https://www.nice.org.uk/guidance/cg90
- Depression in children and young people: identification and management. NICE clinical guideline 28 (2017). Available from https://www.nice.org.uk/guidance/cg28

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two professional expert questionnaires for implanted vagus nerve stimulation for treatment-resistant depression were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE received 1 completed questionnaire. The patient's commentator's views on the procedure were consistent with the published evidence and the opinions of the professional experts.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed

submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trial

A Study to Assess Effectiveness and Efficiency of VNS Therapy in Patients with Difficult to Treat Depression. (RESTORE-LIFE). NCT03320304. Active. Patient registry. Estimated study completion date: December 2025. Estimated enrollment: 500 patients. Belgium, Germany, United Kingdom.

A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy® System as Adjunctive Therapy Versus a No Stimulation Control in Subjects with Treatment-Resistant Depression (RECOVER). NCT03887715. Active. RCT. Estimated study completion date: December 2030. Estimated enrollment: 6800 patients. United States.

References

1. Berry SM, Broglio K, Bunker M et al. (2013) A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Medical devices: Evidence and research 6: 17-35
2. Martin JLR and Martín-Sánchez E (2012) Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study design. European psychiatry 27: 147-155
3. Rush AJ, Marangell LB, Sackeim HA et al. (2005) Vagus nerve stimulation for treatment-resistant depression: A randomised, controlled acute phase trial. Biologicla psychiatry 58(5): 347-354

   Rush AJ, Sackeim HA, Marangell LB et al. (2005) Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: A naturalistic study. Biological psychiatry 58(5): 355-363
4. Aaronson AT, Sears P, Ruvuna F et al. (2017) A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: Comparison of response, remission, and suicidality. The American journal of psychiatry 174(7): 640-648
5. Conway CR, Kumar A, Xiong W et al. (2018) Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. Journal of clinical psychiatry 79(5): 52-59
6. Aaronson ST, Carpenter LL, Conway CR et al. (2013) Vagus nerve stimulation therapy randomised to different amounts of electrical charge for treatment-resistant depression: Acute and chronic effects. Brain stimulation 6: 631-640
7. Trottier-Duclos, F, Jodoin VD, Fournier-Gosselin MP et al. (2018) A 6-year follow-up study of vagus nerve stimulation effect on quality of life in treatment-resistant depression: A pilot study. The journal of ECT 34: e58-e60.
8. Jodoin VD, Richer F, Miron JP et al. (2018) Long-term sustained cognitive benefits of vagus nerve stimulation in refractory depression. The journal of ECT 34: 283-290
9. Singleton AH, Rosenquist PB, Kimball J et al. (2009) Cardiac rhythm disturbance in a depressed patient after implantation with a vagus nerve stimulator. The journal of ECT 25(3): 195-197
10. Royal College of Psychiatrists (2017) Statement on neurosurgery for mental disorder (NMD), also known as psychiatric neurosurgery. Available from: https://www.rcpsych.ac.uk/docs/default-source/about-us/who-we-

are/ectcommittee-vns-dbs-ablative-neurosurgery-statement-feb17.pdf?sfvrsn=eba0287a_2

11. American Psychiatric Association (2010) Practice guideline for the treatment of patients with major depressive disorder. Available from: https://psychiatryonline.org/guidelines
12. Schlaepfer TE, George MS and Mayberg H (2010) WFSBP guidelines on brain stimulation treatments in psychiatry. The world journal of biological psychiatry 11: 2-18

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	31/07/2019	Issue 7 of 12, July 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	31/07/2019	Issue 7 of 12, July 2019
HTA database (Cochrane)	31/07/2019	Last updated March 2018
MEDLINE (Ovid)	31/07/2019	1946 to July 30, 2019
MEDLINE In-Process (Ovid) & MEDLINE Epubs ahead of print (Ovid)	31/07/2019	1946 to July 30, 2019
EMBASE (Ovid)	31/07/2019	1974 to 2019 Week 30
BLIC (British Library)	31/07/2019	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Depression/
2	exp Depressive Disorder/
3	Mood Disorders/ or cyclothymic disorder/
4	Bipolar Disorder/
5	((Depress* or Mood* or Bipolar* or Bi-polar* or Manic* or Neurotic* or Neuros* or Seasonal* or SAD or Dysthymic* or dysphori* or mourning) adj4 (Disorder* or Episode* or Syndrome* or Postpartum* or Post-partum* or Postnatal or Post-natal)).tw.
6	(depression or depressed or dysphori* or dysthym* or melanchol* or pseudodementia or sadness).tw.

7	or/1-6
8	Vagus Nerve Stimulation/
9	VNS.tw.
10	(Vagus* adj4 Nerve* Stimulat*).tw.
11	((implant* or electrod*) adj4 vagus*).tw.
12	exp Vagus Nerve/
13	cranial* nerv* stimulat*.tw.
14	livanova.tw.
15	cyberonics.tw.
16	or/8-15
17	7 and 16
18	Animals/ not Humans/
19	17 not 18
20	limit 19 to ed=20090506-20190731

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Albert U, Maina G, Aguglia A et al. (2015) Vagus nerve stimulation for treatment-resistant mood disorders: a long-term naturalistic study. BMC Psychiatry, 15(64)	Case series n=5 Follow-up: 5 years	Response and remission rates were both 40% (2/5) after 1 year, and 60% (3/5) at 5 years. Two patients withdrew from the study because of side effects or inefficacy of stimulation	Studies with a larger sample were included in table 2.
Bajbouj M, Merkl A, Schlaepfer TE et al. (2010). Two-year outcome of vagus nerve stimulation (VNS) in treatment-resistant depression. Journal of clinical psychopharmacology, 30(3): 273-281	Case series n=74 Follow-up: 2 years	Mixed-model repeated-measures analysis of variance revealed a significant reduction ($p \leq 0.05$) at months 3, 12 and 24 in $HDRS_{28}$ score. After 2 years, 53.1% (26/49) of the patients fulfilled the response criteria and 38.9% (19/49) fulfilled the remission criteria. The proportion of patients who fulfilled the remission criteria remained constant as the duration of VNS treatment increased. Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study.	Studies with a larger sample and/or longer follow-up were included in table 2.
Christmas D, Douglas Steele J, Tolomeo S et al. (2013) Vagus nerve stimulation for chronic major depressive disorder: 12-month outcomes in highly treatment-refractory patients. Journal of affective disorders, 150(3): 1221-1225	Case series n=41 Follow-up: 12 months	In the D-03 cohort (n=28), the response rate at 12 months was 35.7%. in the Dundee VNS case series (n=13), the equivalent response rate was 30.8%.	Studies with a larger sample and/or longer follow-up were included in table 2.
Cristancho P, Cristancho MA, Baltuch GH et al. (2011) Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDS approval: outcomes at 1 year. Journal of clinical	Case series n=15 (mean 49 years; 60% female) Follow-up: 12 months	The BDI score decreased significantly compared to baseline at 6 months ($p<0.05$) and 12 months ($p<0.01$), from a mean o f37.8 (SD=7.8) before VNS activation to a mean of 24.6 (SD=11.4) at 12 months. By 1 year, 28.6% (n=4) of patients responded to VNS and 7.12% (n=1)	Studies with a larger sample and/or longer follow-up were included in table 2.

psychiatry, 72(10): 1376-1389		remitted according to the BDI. $HDRS_{24}$ showed similar improvement at 1 year, with a 43% response rate (n=6) and 14.3% remission rate (n=2). Side effects of VNS included hoarseness (73%), dyspnoea (47%), nausea (40%), pain (33%), and anxiety (20%); no patient terminated treatment due to intolerable side effects.	
Corcoran CD, Thomas P, Phillips J et al. (2006) Vagus nerve stimulation in chronic treatment-resistant depression: preliminary findings of an open-label study. The British journal of psychiatry: the journal of mental science, 189: 282-283	Case series n=11 Follow-up: 1 year	The findings indicated that all measures of depression, including the HDRS reduced significantly. The response and remission rates were 55% and 27% respectively at 1 year. Side-effects were common, and some were severe.	The open-label study this article referred to was included in table 2.
Delll'Osso b, Oldani L, Grancini B et al. (2018) Ten-year outcome of vagus nerve stimulation-implanted patients with treatment-resistant depression: two Italian cases. Neuropsychiatric disease and treatment, 14: 915-918	Case series n=2 (mean 58.5 years; 50% female) Follow-up: 10 years	Both patients were found to benefit from augmentative VNS, and the latency of their stimulation response, tolerability, associated pharmacological treatment, number and duration of recurrences, and overall level of functioning are described and discussed.	Studies with a larger sample were included in table 2.
Franzini A, Messina G, Marras C et al. (2008) Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment of treatment-resistant depression: series report. Journal of the international neuromodulation society, 11(4): 267-271	Case series n=9 (mean 57 years; 36% [4/9] female) Follow-up: 1 year	Five out of 9 patients, having at least 1-year follow-up, were responders (≥50% reduction of HDRS scoring) and 4 of these also were remitters (HDRS<10). One patient with bipolar II disorder and 1 patient with melancholic depression did not significantly benefit from the procedure; the latter 3 patients have follow-ups shorter than 3 months and1 of them meets the remittance criteria; nonetheless, for the other 2, $HDRS_{21}$ score is gradually decreasing with time.	Studies with a larger sample and/or longer follow-up were included in table 2.
Mu Q, Bohning DE, Nahas Z et al. (2004) Acute vagus nerve stimulation using different pulse widths produces varying brain effects. Biological psychiatry, 55(8): 816-825	Case series n=9 (mean 47.4 years; 22% [2/9] female)	The data confirmed that VNS at PW 500 globally produces no more activation than dose PW 250, and PW 130 is insufficient for activation of some regions. These data suggest that PW is an	Lack of clinical outcomes.

		important variable in producing VNS brain effects.	
Perini GI, Toffanin T, Pigato G et al. (2017) Hippocampal gray volumes increase in treatment-resistant depression responding to vagus nerve stimulation. Journal of ECT, 33(3): 160-166	Case series n=6 (mean 51.3 years; 33% [2/6] female) Follow-up: 12 months	Six patients with unipolar treatment-resistant depression were implanted with a VNS device, showing a significant improvement on Hamilton Depression Rating Scale and Beck Depression Inventory scores ($p<0.05$). further studies across a larger sample of patients with treatment-resistant depression are warranted.	Studies with a large sample and/or longer follow-up were included in table 2.
Sackeim HA, Brannam SK, John Rush A et al. (2007) Durability of antidepressant response to vagus nerve stimulation (VNS™). International journal of neuropsychopharmacology, 10: 817-826.	Case series n=264 (age 46 years; 64% [169/264] female) Follow-up= 24 months	In the pilot study, 30.5%, 23.7% and 45.8% were early responders, later responders and non-responders, respectively. These rates were 14.6%, 19.5% and 65.9% in the pivotal trial. In the pilot study, 72.2% and 61.1% of early responders (n=18) were responders at 12 and 24 months respectively; 78.8% of late responders (n=14) were responders at 24 months. In the pivotal trial, of early responders (n=30), 63.3% and 76.7% maintained response at 12 and 24 months respectively; of late responders (n=40), 65.0% maintained response at 24 months. Early and late responders had fewer changes in medication than non-responders across the pivotal study period.	This study was included in the previous overview
Schlaepfer TE, Frick C, Zobel A et al. (2008) Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychological medicine, 38: 651-661	Case series n=74 (age 47 years; 68% female) Follow-up: 12 months	The baseline HAMD-28 score averaged 34. After 3 months of VNS, response rates reached 37% and remission rates 17%. Response rates increased to 53% after 1 year of VNS, and remission rates reached 33%. 44% of patients showed a sustained response. Median time to response was 9 months. Most frequent side-effects were voice alteration (63% at 3 months of stimulation) and coughing (23%).	This study was included in study 1 (Berry et al. 2013) which was in table 2 and was included in the previous overview.
Sharma A, Chaturvedi R, Sharma A et al. (2009) Electroconvulsive therapy	Case series	Two cases demonstrated the success of combining ECT with VNS, suggesting ECT	Studies with a large sample were included in table 2.

in patients with vagus nerve stimulation. The journal of ECT, 25(2): 141-143	n=2 (mean 61.5 years; 100 female)	and VNS could be used safety either sequentially or concurrently where VNS would work for maintenance therapy for chronic depression and ECT for emergently worsening depression. Further trials and research are warranted to assess the safety of the combined treatment.	
Spuck S, Tronnier V, Orosz I et al. (2010) Operative and technical complications of vagus nerve stimulator implantation. Operative neurosurgery, 67: ons489-ons494	Case series n=105 (mean 10.5 years)	Twenty (19%) patients had technical problems or complications. In 6 (5.7%) patients these problems were caused by the operation. The device was removed in 8 cases. The range of surgically and technically induced complications included electrode fractures, early and late onset of deep wound infections, transient vocal cord palsy, cardiac arrhythmia under test stimulation, electrode malfunction, and posttraumatic dysfunction of the stimulator.	Studies with a larger sample and/or longer follow-up were included in table 2.
Salloum NC, Walker MC, Gangwani S et al. (2016) Emergence of mania in two middle-aged patients with a history of unipolar treatment-refractory depression receiving vagus nerve stimulation. Bipolar disorders, 19: 60-64	Case series n=2 (mean 50.5 years; 50% female) Follow-up: 5 years	The 2 patients had emergence of full manic symptoms after 8 and 9 months of VNS, respectively. Manic symptoms were adequately managed with standard treatments (mood stabilizer and electroconvulsive therapy) and VNS was continued in the 2 subjects for up to 5 years without any further occurrences of manic/hypomanic episodes.	Studies with a larger and/or longer follow-up were included in table 2.
Tisi G, Franzini A, Messina G et al. (2014) Vagus nerve stimulation therapy in treatment-resistant depression: a series report. Psychiatry and clinical neurosciences, 68: 606-611	Case series n=27 (mean 57.5 years; 33.3 [9/27] female) Follow-up: 5 years	Of the 27 patients, 22 were evaluated after 1 year of treatment, and the mean improvement of the HAM-D score was of 10.3. Five patients (20%) went into complete remission (HAM-D < 7) after 1 year, 6 (22.3%) were considered responders (50% reduction of HAM-D scoring) and 8 had score reduction of less than 20%. Nineteen patients were evaluated after 24 to 36 months: the average improvement on the HAM-D score was of 12.1 points (47.2%). One patient went into complete remission and 8	Studies with a larger sample were included in table 2.

		(42.1%) were responders. Up to the present date, 7 patients have undergone re-evaluation at 48 to 60 months from surgery showing an average score reduction of 14.2. Two more patients obtained complete remission, while 4 of them did not have any improvement since their last follow-up control visit.	
Conway CR, Gebretsadik MD and Bucholz RD (2011) Marked response to VNS in a post-cingulotomy patient: implications for the mechanism of action of VNS in TRD. CNS Spectrums, 16: 135-141	Case report n=1 (53 years; female) Follow-up: 3.5 years	This case study showed that VNS and ECT could be safely administered at the same time and may have synergistic effects. This study also highlighted the potential efficacy of VNS in very treatment resistant clinical depression and emphasised the need for further studies to determine the mechanism of action of VNS in TRMD.	Studies with a larger sample and/or longer follow-up were included in table 2.
Husain MM, Stegman D and Trevino K (2005) Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. Annals of general psychiatry, 4(16)	Case report n=1 (28 years; female) Follow-up: 4 years	VNS therapy provided effective treatment for treatment-resistant depression during pregnancy and delivery. VNS was safe for the patient and her child.	Studies with a larger sample and/or longer follow-up were included in table 2.
Richieri R, Cermolacce M, Spatola G et al. (2019) Vagal nerve stimulation (VNS): a practical option to discountinue rTMS in treatment-resistant depression? Neurology, psychiatry and brain research, 31: 29-31	Case report n=1 (43 years; female) Follow-up: 18 months	This case report illustrated that VNS could provide an effective minimally invasive chronic neurostimulation treatment for difficult-to-treat depression that could be considered before resorting to more invasive options. VNS may be regarded as an adjunctive treatment for maintenance rTMS responders with the potential goal of prolonging the intervals between rTMS treatments without relapse.	Studies with a large sample and/or longer follow-up were included in table 2.
Tang JE and Hyman JB (2019) Syncope after administration of epidural analgesia in an obstetric patient with a vagus nerve stimulator. International journal of obstetric anaesthesia, 38: 134-137	Case report n=1 (34 years; female)	This case report illustrated an obstetric patient who received epidural analgesia and subsequently experienced 2 episodes of syncope synchronous with stimulation from her VNS device. These resolved after deactivating the device. This study reported a suspected arrhythmia during	Studies with a larger and/or longer follow-up were included in table 2.

		VNS in the setting of epidural analgesia.	
Nierenberg AA, Alpert JE, Gardner-Schuster EE et al. (2008) Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biological Psychiatry 64: 455−60	Randomised controlled trial n=235 (46.3 years; 64% female) Follow-up: 3 months RCT and 2 years open label therapy	At baseline, bipolar treatment-resistant depression was as severe as unipolar treatment-resistant depression but with depressive episodes of shorter duration and more failed antidepressant trials/year. Acute, 1-year, and 2-year outcomes were similar for both groups, even when the definition of response for bipolar treatment-resistant depression was expanded to include lack of manic symptoms.	The study was included in the previous review, and studies with a larger sample and/or longer follow-up were included in table 2.
Burke MJ and Husain MM (2006) Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. The journal of ECT, 22(3): 218-222	Non-randomised comparative study n=205 (191 VNS [mean 46.6 years] versus 14 VNS+ECT [mean 42.4 years]; 64% [131/205] female) Follow-up: 12 months	VNS and ECT can be used safely and effectively either sequentially or concurrently. Each can be prescribed as the depressive condition warrants – VNS for chronic, long-term therapy and ECT for emergently worsening depressive symptoms and maintenance therapy.	Studies with a larger sample and longer follow-up were included in table 2. Also, this study explored the use of ECT in the pivotal study of VNS for treatment-resistant depression (ECT was the primary phenomenon of interest).
Christmas D and Matthews K (2016) Neurosurgicla treatmetns for patients with chronic, treatment refractory depression: a retrospective, consecutive, case series comparison of anterior capsulotomy, anterior cingulotomy, and vagus nerve stimulation. Stereotactic and functional neurosurgery, 93(6): 387-392	Non-randomised comparative study n=15 (VNS, n=5; ACAPS, n=5; ACING, n=5; Follow-up: 12 months	With clinical response defined as ≥50% reduction from baseline MADRS score, response rates were: VNS (20%); ACAPS (40%); and ACING (60%). Adverse effects from all three procedures were relatively mild. Adverse effects from VNS were related to active stimulation, modifiable and diminished in severity over time.	Studies with a larger sample and/or longer follow-up were included in table 2.
Feldman RL, Dunner DL, Muller JS et al. (2013) Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. Journal of medical economics, 16(1): 62-74	Non-randomised comparative study n=690 Follow-up: 2 years	VNSBs achieving positive health outcomes (measured by lack of negative events post-implantation) tend to have fewer psychiatric co-occurring conditions.	Studies with a longer follow-up were included in table 2.
George MS, John Rush A, Marangell LB et al. (2005) A one-year comparison of	Non-randomised comparative study	VNS+TAU was associated with greater improvement per month in IDS-SR_{30} than TAU	This study was included in study 1

vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biological psychiatry, 58(5): 364-373	n=329 (205 VNS+TAU: mean 46.3 years, 64% female; 124 TAU: mean 45.5 years, 69% female) Follow-up: 12 months	across 12 months (p<0.001). response rates according to $HRSC_{24}$ at 12 months were 27% for VNS+TAU and 13% for TAU (p<0.011). both groups received similar TAU during follow-up.	(Berry et al. 2013) which was table 2.
Kumar A, Bunker MT, Aaronson ST et al. (2019) Durability of symptomatic responses obtained with adjunctive vagus nerve stimulation in treatment-resistant depression. Neuropsychiatric disease and treatment, 15: 457-468	Non-randomised comparative study n=599 Follow-up: 5 years	In the VNS + TAU arm, 62.5% (205/328) of participants had a first response over 5 years compared with 39.9% (108/271) in TAU. The time to first response was significantly shorter for VNS+TAU than for TAU (p<0.01). For responders in the 1st year, median time to relapse from first response was 10.1 months (Q1=4.2, Q3=31.5) for VNS+TAU vs 7.3 months (Q1=3.1, Q3=17.6) for TAU (p<0.01). HR=0.6 (95% CI: 0.4, 0.9) revealed a significantly lower chance for relapse in VNS+TAU. Probability of retaining first response for a year was 0.39 (0.27, 0.51) for TAU and 0.47 (0.38, 0.56) for VNS+TAU. Timing of the onset of the response did not impact the durability of the response.	The population was part of Aaronson et al. (2017) which was included in table 2.
Sperling W, Reulback U and Kornhuber J (2009) Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. Pharmacopsychiatry, 42: 85-88	Non-randomised controlled trial n=18 (mean 50 years; 56% female) Follow-up: 12 months	Compared with baseline values in the HAMD scale (mean 23.7; SD=2.4), there was a statistically significant (t=14.5; df=8; p<0.001) improvement in symptoms after 12 months stimulation (mean 10.2; SD=2.4). the duration of hospitalisation dropped on average by 20 days in the first post-implantation year, the treatment frequency from 33 to 14 visits, and drug treatment from 4 to an average of 3 psychotropic drugs.	This study was included in the previous overview.
Andrade P, Noblesse LMH, Temel Y et al. (2010) Neurostimulatory and ablative treatment options in major depressive disorder: a systematic	Systematic review	Evidence has proven the efficacy of VNS for treatment-resistant depression and MDD while VNS is well tolerated. Further research is required to elucidate the specific action of	The mainly cited papers relating to VNS were included in table 2 and appendix.

review. Acta neurochir, 152: 565-577		VNS, considering the anatomy of the vagus nerve with its projections.	
Cimpianu CL, Strube W, Falkai P et al. (2017) Vagus nerve stimulation in psychiatry: a systematic review of the available evidence. Journal of neural transmission, 124(1): 145-158	Systematic review	The efficacy data of VNS in affective disorders is promising, whereas more in controlled and naturalistic studies are needed.	The mainly cited papers relating to VNS and treatment-resistant depression were included in table 2 and appendix.
Lv H, Zhao YH, Chen JG et al. (2019) Vagus nerve stimulation for depression: a systematic review. Frontiers in psychology, 10:64	Systematic review	The efficacy and safety of VNS for depression is still unclear, so further RCTs are needed to confirm its efficacy and safety.	The mainly cited paper relating to the implanted VNS was included in table 2.
Cimpianu CL, Strube W, Falkai P et al. (2017) Vagus nerve stimulation in psychiatry: a systematic review of the available evidence. Journal of neural transmission, 124(1), 145-158	Systematic review	The efficacy data of VNS in affective disorders is promising, whereas more in controlled and naturalistic studies are needed.	The mainly cited studies relating to VNS for treatment-resistant depression were included in table 2 and appendix.
McGirr A and Berlim MT (2018) Clinical usefulness of therapeutic neuromodulation for major depression: a systematic meta-review of recent meta-analyses. The psychiatric clinics of North America, 41(3): 485-503	Meta-review	Evidence demonstrated the preliminary effectiveness of VNS for (treatment-resistant) MD.	The cited 2 meta-analyses relating to VSN were included in table 2.
Aaronson ST and Conway CR (2018) Vagus nerve stimulation: changing the paradigm for chronic severe depression? The psychiatric clinics of North America, 41(3): 409-418	Review	Although 2 large RCTs failed to reach their primary outcome measure, an open-label, naturalistic study of 795 treatment-resistant depression patients followed over 5 years showed a much great likelihood of achieving response and remission of implanted with VNS than TAU.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Al-Harbbi KS (2012) Treatment-resistant depression: therapeutic trends, challenges, and further directions. Patient preference and adherence, 6: 369-388	Review	VNS has been approved for treatment-resistant depression, but long-term effects and tolerability are needed.	The mainly cited paper relating to VNS was included in the appendix.
Akhtar H, Bukhari F, Nazir M et al. (2016) Therapeutic efficacy of neurostimulation for depression: Techniques, current	Review	VNS has been approved for treatment-resistant depression. It interferes with the memory for negative information by modifying the	The mainly cited papers relating to VNS were included in table 2 and appendix.

modalities, and future challenges. Neurosci, 32(1): 115-126		concentrations of monoamines within the CNS. The therapy requires minor surgery which affects the patients' quality of life and makes the procedure a bit complicated and less favourable than the non-invasive therapies (tDCS, rTMS).	
Alexopoulos GS and Kelly RE (2009) Research advances in geriatric depression. World Psychiatry, 8: 140-149	Review	The effects of VNS on treatment-resistant depression did not significantly differ from sham treatment in a 10-week RCT. However, treatment response was significantly greater for VNS+TAU than for TAU in a 12-month open continuation phase of the study.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Beekwilder JP and Beems T (2010) Overview of the clinical applications of vagus nerve stimulation. Journal of clinical neurophysiology	Review	Although much evidence is available, showing the efficacy of VNS for treatment-resistant depression, long-term RCTs that demonstrate unequivocally a benefit for these patients is lacking.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Ben-Menachem E, Revesz D, Simon J et al. (2015) Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. European journal of neurology, 22: 1260-1268	Review	Evidence suggested the long-term effects of VNS on treatment-resistant depression and safety and tolerability were associated with device implantation (e.g. infection, bradycardia, asystole, vocal cord paresis) and VNS stimulation (voice alteration, paraesthesia, cough, headache, dyspnoea, pharyngitis and pain).	The mainly cited papers relating to VNS for treatment-resistant depression were included in table 2 and appendix.
Bewernick B and Schlaepfer TE (2015) Update on neuromodulation for treatment-resistant depression. F1000Research 2015, 4 (F1000 Faculty Rev):1389	Review	For treating chronic or recurrent depression, long-term effects were significantly superior by outcomes in comparison to patients receiving treatment as usual. However, VNS therapy is more effective in patients with moderate but not extreme level of resistance. Possible side-effects of VNS therapy are: an infection at the device, a hoarse voice, cough, and shortness of breath, as well as difficulties in swallowing.	The 2 cited studies relating to VNS were included in the appendix.
Blumberger DM, Mulsant BM and Daskalakis ZJ (2013) What is the role of brain stimulation therapies	Review	Evidence supported the use of VNS in patients with treatment-resistant depression, however, the lack	The mainly cited papers relating to VNS were included

in the treatment of depression? Curretn psychiatry reports, 15: 368		of difference from placebo in controlled studies led to limited adoption of VNS.	in table 2 and appendix.
Brunoni AR, Teng, CT, Correa C et al. (2010) Neuromodulation approaches for the treatment of major depression. Arq neuropsiquiatr, 68(3): 433-451	Review	VNS may be seen as a new promising form of treatment for chronic or refractory depression, however, the present evidence supporting its use is still limited.	The mainly cited papers relating to VNS were included in the previous overview.
Carpenter.LL, Megna JL, Herrera-Rojas M et al. (2011) When medication fails: Neurostimulation therapies for depression. Clinical neuropsychiatry, 8(1): 61-80	Review	Evidence supported the antidepressant efficacy of VNS (long-term effects) and the side effects were generally mild.	The mainly cited papers relating to VNS for depression were included in table 2 and appendix.
Carreno FR and Frazer A (2017) Vagal nerve stimulation for treatment-resistant depression. Neurotherapeutics, 14: 716-727	Review	Evidence showed that VNS was much more efficacy when compared with results from treatment as usual studies. However, more RCTs of VNS need to be carried out before a definitive conclusion can be reached about its efficacy.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Cusin C and Dougherty DD (2012) Somatic therapies for treatment-resistant depression: ECT, TMS, VNS, DBS. Biology of mood & anxiety disorders, 2(14): 1-9	Review	VNS appears to be effective in patients with MDD and can safely be combined with ECT in case of an acute relapse. Although its effects take much longer to appear compared to antidepressants or ECT, VNS cannot be considered a treatment for acute treatment-resistant depression.	The mainly cited papers relating to VNS were included in table 2 and appendix.
De Leon VC, Drysdale AT, Conway CR et al. (in press) Predictors of response for vagus nerve stimulation in treatment-resistant depression. Personalised medicine in psychiatry.	Review	Existing data supported that VNS was effective: equally for bipolar versus unipolar treatment-resistant depression, in highly resistant patients, as well as for patients suffering from prolonged depression. Clinical trial data also supported that higher electrical current/charge delivered over time likely contributed to sustained antidepressant response. Additional studies are needed to assess predictors of response of VNS in treatment-resistant depression.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Eljamel S (2016) Vagus nerve stimulation for major depressive episodes.	Review	Evidence suggested the modest efficacy of VNS for major depression, with better	The mainly cited papers relating to VNS for depression

Progress in neurological surgery, 29: 53-63		long-term outcomes. VNS has also been approved to be safe and well-tolerated treatment.	were included in table 2 and appendix.
Findling RL, Feeny NC, Stansbrey RJ et al. (2002) Somatic treatment for depressive illnesses in children and adolescents. Child adolescent psychiatric clinics of North America, 11(3): 555-578	Review	Evidence from an open clinical trial indicates that VNS may be useful in the treatment of adults with treatment-resistant depression. What role, if any, vagal nerve stimulation will have in the treatment of paediatric depression has not been determined.	The only cited paper relating to VNS was included in the previous overview.
Fitzgerald PB (2013) Non-pharmacological biological treatment approaches to difficult-to-treat depression. The medical journal of Australia, 199:S48-S51	Review	Limited research suggested that VNS had potentially long-lasting antidepressant effects in a small group of patients.	The mainly cited papers relating to VNS were included in the appendix.
Gersner R, Rosenberg O and Dannon PN (2012) Major depressive disorder: treatment and future perspective. Clin Pract, 9(3): 269-278	Review	Evidence showed the efficacy of VNS for treating patients with treatment-resistant depression, with a gradual onset, though there was a lack of favourable response in the short term. Long-term VNS was generally well tolerated.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Grimm S and Bajbouj M (2010) Efficacy of vagus nerve stimulation in the treatment of depression. Expert Rev. Neurother, 10(1): 87-92	Review	The review indicated that the acute and long-term efficacy of vagus nerve stimulation were still under debate, further studies are required, especially relating to the exact mode of action of vagus nerve stimulation.	The mainly cited studies were included in table 2 and appendix.
Holtzheimer PE and Mayberg HS (2010) Deep brain stimulation for treatment-resistant depression. Am J Psychiatry, 167(12): 1437-1444	Review	Evidence showed that the risks of VNS surgery were relatively minor, and long-term treatment was generally well tolerated.	The mainly cited studies were included in table 2 and appendix.
Holtzheimer PE and Mayberg HS (2012) Neuromodulation for treatment-resistant depression. F1000 Medicine reports, 4 (22)	Review	Evidence suggested the efficacy of VNS for treating patient with treatment-resistant depression. Evidence also highlighted the surgery was relatively minor with few significant risks and stimulation-related side effects presented during active stimulation.	The mainly cited studies were included in table 2 and appendix.
Howland RH (2014) Vagus nerve stimulation. Curr behave neuroscie rep, 1(2): 64-73	Review	Left cervical VNS is an approved therapy for treatment resistant depression. The efficacy of	The mainly cited papers relating to VNS were included in table 2 and appendix.

		VNS has been illustrated by the existing studies.	
Johnson RL and Wilson CG (2018) A review of vagus nerve stimulation as a therapeutic intervention. Journal of inflammation research, 11: 203-213	Review	VNS has been proven to be a useful treatment across a number of domains and has been used effectively to treat depression in adults.	The mainly cited papers relating to VNS for treatment-resistant depression were included in the appendix.
Haddad PM, Talbot PS, Anderson IM et al. (2015) Managing inadequate antidepressant response in depressive illness. British medical bulletin, 115: 183-201	Review	The limited evidence suggested that the efficacy of vagus nerve stimulation was unclear.	The mainly cited papers relating to VNS were included in table 2.
Kamath MV, Thomson MS, Gaitonde S et al. (2010). Journal of long-term effects of medical implants, 20(3): 251-267	Review	Long-term VNS therapy has become an accepted promising therapy for refractive depression, with a high safety profile. Further research will determine the place of VNS in the armament of therapeutic modalities available for major depression.	The mainly cited papers relating to VNS for depression were included in the appendix
Little A (2009) Treatment-resistant depression. American family physician, 80(2): 167-172	Review	evidence showed the limited efficacy of VNS. Serious adverse events were infection requiring removal of the device and suicide. Side effects included hoarseness, headache, neck pain and cough.	The mainly cited RCT was included in table 2.
Macritchie KAN and Young AH (2001) Emerging targets for the treatment of depressive disorder. Expert opinion on therapeutic targets, 5(5): 601-612	Review	Evidence suggested that VNS has antidepressant effects in treatment-resistant depression but there appears to be a latent period prior to treatment response.	The mainly cited paper relating to VNS was included in the previous overview.
Manepalli J and Sapkota N (2014) Neuromodulation therapies in the elderly depressed patient. Current geriatrics reports, 3: 229-236	Review	VNS remains controversial as evidence shows mixed results in terms of the efficacy. There is also scarcity of literature about the use of VNS in elderly patients and its cognitive side effects.	The mainly cited papers relating to VNS were included in table 2 and appendix.
Mohr P, Rodriguz M, Slavickova A et al. (2011) The application of vagus nerve stimulation and deep brain stimulation in depression. Neuropsychobiology, 64: 170-181	Review	VNS demonstrated steadily increasing improvement with full benefit after 6 to12 months, sustained up to 2 years. Patients who responded best had a low-to-moderate antidepressant resistance. However, the primary results of the only controlled trial were negative.	The mainly cited studies were included in table 2 and appendix.

Moreines JL, McClintock SM and Holtzheimer PE (2011) Neuropsychological effects of neuromodulation techniques for treatment-resistant depression: a review. Brain stimul, 4(1): 17-27	Review	Evidence indicated better long-term efficacy outcomes of VNS for treating patients with treatment-resistant depression, with mild side effects. However, cognitive safety data on VNS are limited.	The mainly cited studies were included in table 2 and appendix.
Müller HH, Moeller S, Lücke C et al. (2018) Vagus nerve stimulation (VNS) and other augmentation strategies for therapy-resistant depression (TRD): review of the evidence and clinical advice for use. Frontiers in neuroscience, 12(239)	Review	VNS has the advantages of more solid scientific evidence for efficacy compared to MST, tDCS and CES and, after initial implantation, a comparably small burden of time and effort for maintenance treatment compared to ECT and rTMS. Compared to maintenance ECT, VNS is also less invasive in the long term. However, VNS has the delay of effects after implantation, with substantial treatment effects often only occurring after 3 to 12 months of treatment.	The mainly cited papers relating to vagus nerve stimulation were included in table 2 and appendix.
Pandurangi AK, Fernicola-Bledowski C and Bledowski J (2012) Brain stimulation therapies for psychiatric disorders: the first decade of the new millennium – a review. Asian journal of psychiatry, 5: 3-10	Review	Evidence suggested that VNS was efficacious in treating depression in patients with moderate treatment-resistant depression and that the sustained antidepressant effect of VNS held promise. However, further studies are needed.	The mainly cited papers relating to vagus nerve stimulation were included in table 2 and appendix.
Rakofsky JJ, Holtzheimer PE and Nemeroff CB (2015) Emerging targets for antidepressant therapies. Curr opin chem boil, 13(3): 291-302	Review	Evidence showed the efficacy of VNS for treating patients with treatment-resistant depression, however, further research is required.	The mainly cited papers relating to vagus nerve stimulation were included in table 2 and appendix.
Rizvi SK, Donovan M, Giacobbe P et al. (2011) Neurostimulation therapies for treatment resistant depression: A focus on vagus nerve stimulation and deep brain stimulation. International review of psychiatry, 23(5): 424-436	Review	Evidence indicated that the antidepressant effects of VNS required a longer trajectory and VNS had minimal side effects.	The mainly cited papers relating to VNS for treatment-resistant depression were included in table 2 and appendix.
Rosenberg O, Shoenfeld N, Kotler M et al. (2009) Mood disorders in elderly population: Neurostimulative treatment possibilities. Recent	Review	Evidence showed modest response rates when using VNS for (treatment-resistant) depression, with a safe and feasible profile, but the greater output current was associated with increased side effects	The mainly cited papers relating to VNS were included in the table 2 and appendix.

patients on CNS drug discovery, 4(2): 149-159			
Rush AJ and Siefert SE (2009) Clinical issues in considering vagus nerve stimulation for treatment-resistant depression. Experimental Neurology, 219: 36-43	Review	A range of studies have shown that VNS was clearly well tolerated, it seemed to provide substantial longer-term benefit for a meaningful proportion of patients with treatment-resistant depression. However, there was no appropriate methodology for patient selection and for optimal dosing for VNS.	The mainly cited studies were included in table 2 and appendix.
Shelton RC, Osuntokun O, Heinloth AN and et al. (2010) Therapeutic options for treatment-resistant depression. CNS Drugs, 24(2): 131-161	Review	Evidence showed a mixture of results relating to the short- and long-term efficacy of VNS in treating patients with treatment-resistant depression.	The mainly cited studies were included in table 2 and appendix.
Shah A, Carreno FR and Frazer A (2014) Therapeutic modalities for treatment resistant depression: focus on vagal nerve stimulation and ketamine. Clinical psychopharmacology and neuroscience, 12(2): 83-93	Review	Evidence showed the efficacy of VNS in treating patients with treatment-resistant depression, further research is needed to address concerns relating to side-effects.	The mainly cited studies were included in table 2 and appendix.
Tracy DK and David AS (2015) Clinical neuromodulation in psychiatry: the state of the art or an art in a state? BJPsych Advances, 21: 396-401	Review	Although limited evidence illustrated the efficacy of VNS in treating patients with treatment-resistant depression and that VNS has generally been a well-tolerated intervention, further studies are needed.	The mainly cited studies were included in table 2.
Temel Y, Hescham SA, Jahanshahi A et al. (2012) International review of neurobiology, 107: 283-314	Review	Studies with long-term follow-up have shown that VNS can be beneficial in patients with major depression, while the therapeutic effect at short term can be less pronounced.	The mainly cited studies were included in table 2 and appendix.
Vonck K, Raedt R, Naulaerts J et al. (2014) Vagus nerve stimulation…25 years later! What do we know about the effects on cognition? Neuroscience and biobehavioral reviews, 45: 63-71	Review	Evidence suggested that VNS in treatment-resistant depression might result in cognitive enhancement, primarily in patients who had clinical improvement.	The mainly cited paper relating to VNS was included in the appendix.
Ward MP and Irazoqui PP (2010) Evolving refractory major depressive disorder diagnostic and treatment	Review	VNS is a promising treatment for patients with refractory major depressive disorder, but it is plagued with inconsistent	The mainly cited papers relating to VNS were included in the appendix.

paradigms: toward closed-loop therapeutics. Frontiers in neuroengineering, 3(7): 1-15		reports of efficacy and variable side effects.	
Yan H, Li A, Sun X et al. (2016) Vagus nerve stimulation in treating depression: a tale of two stories. Current molecular medicine, 16: 33-39	Review	Evidence suggested that VNS-enhanced adult hippocampal neurogenesis may contribute to its antidepressive effects, in addition to its regulation on monoamine neurotransmitters. Nevertheless, more efforts are needed to elucidate uncertainties in this antidepressive process before extensively conducting VNS in clinical practice.	The mainly cited papers relating to VNS were included in table 2 and appendix.