# VAGUS NERVE STIMULATION IN TREATMENT-RESISTANT BIPOLAR DEPRESSION

Bernardo Dell'Osso, Alessandro Dario, Mariateresa Ciabatti, Giulia Camuri, Lucio Oldani, Ilaria Balossi, A. Carlo Altamura


## Abstract

Vagus Nerve Stimulation (VNS) is a brain stimulation technique approved as augmentative treatment of drug-resistant depression (TRD). To date, however, the efficacy of VNS has been mostly investigated in unipolar depression and, only to a minor extent, in bipolar depression. However, given that VNS was first introduced in the treatment of refractory epilepsy due to its anticonvulsant properties, it would be of clinical interest to specifically assess the efficacy of this technique in patients with Bipolar Depression, and to evaluate not only its antidepressant effect but also its potential mood-stabilizing properties in the long-term. The present article provides a brief description of the technique and presents the preliminary results at 6 months of 4 patients with Bipolar Disorder and TRD treated with VNS therapy. In addition, hypotheses of potential mechanisms underpinning the efficacy of VNS in Bipolar Disorder are provided and discussed.


**Key Words**: vagus nerve stimulation (VNS), bipolar disorder (BD), treatment resistant depression (TRD)

**Declaration of interest**: Dr. Dell'Osso has received one-year research grant from Cyberonics, Inc.; Prof. Altamura, Drs. Ciabatti, Dario, Oldani, Balossi and Camuri have no financial interest to disclose which might pose a conflict with the present manuscript.

Bernardo Dell'Osso[1], Alessandro Dario[2], Mariateresa Ciabatti[1], Giulia Camuri[1], Lucio Oldani[1], Ilaria Balossi[1], A. Carlo Altamura[1]

[1] Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano, Italy.
[2] Neurosurgical Clinic of Insubria University, Varese, Italy

**Corresponding Author**
Dr. Bernardo Dell'Osso
Department of Psychiatry, University of Milan, Fondazione IRCCS
Ospedale Maggiore Policlinico Mangiagalli e Regina Elena
Via Francesco Sforza 35, 20122 Milano, Italy
Phone: 02-55035994 - Fax: 02-50320310
bernardo.dellosso@policlinico.mi.it

## Introduction

It has been estimated that approximately 1/3 of patients with Major Depression show either partial or no response to standard antidepressant treatments (Nierenberg and DeCecco 2001, Gayetot et al. 2007). In addition, a significant part of depressed patients may develop treatment resistant depression (TRD) (Fava and Davidson 1996), defined as the lack of response to 2 antidepressant trials, given in succession, at therapeutic doses and for an adequate period of time, in compliant subjects (Sackeim 2001). In patients with poor treatment response or with TRD different strategies of intervention may be considered including pharmacological and psychotherapic augmentation as well as brain stimulation techniques (Preskorn and Burke 1992, American Psychiatric Association 2000). The latter include different interventions which share the common feature to provide a selective electric stimulation of specific brain areas. Among these techniques, only electroconvulsive therapy (ECT), vagus nerve stimulation (VNS) and, more recently, transcranial magnetic stimulation (TMS), have received Food and Drug Administration (FDA) approval for resistant Major Depression. VNS, in particular, has been approved as adjunctive treatment in patients with TRD, given that clinical studies with VNS were performed in combination with pharmacological treatments (2005). Since then, several clinical and neurobiological studies on VNS have been conducted providing new insight about the mechanism of action, efficacy and tolerability of the technique.

The aim of the present review is to provide an updated brief overview of VNS therapy, describing the rational of the technique and the procedure, and to present preliminary efficacy and tolerability results of

Submitted March 2009, Accepted June 2009

 

the first 4 patients with TR bipolar depression who completed the 6 months of VNS therapy at the IRCCS Ospedale Maggiore Policlinico of the University Department of Psychiatry of Milan.

## Rational of VNS and description of the technique

Over the last years, different neurobiological studies have provided new insight on the mechanisms through which VNS may operate in Major Depression. The vagus nerve (VN), the longest cranial nerve, is a mixed nerve composed by 80% afferent and 20% efferent fibres and regulates several automatic bodily activities, many of which are important in a variety of emotional tasks (Foley and DuBois 1937). The sensory afferent cell bodies are placed in the nodose and jugular ganglia and project to the nucleus of the solitary tract (NTS). Projections from NTS to the forebrain are widespread and many of these reach regions, such as the Locus Coeruleus, the Amygdala, the Dorsal Raphe, the Hyppocampus etc., which are in turn connected to the Orbitofrontal Cortex, the Insula and the Anterior Cingulate Gyrus (Chae et al. 2003, Kraus et al. 2007), are implicated in the pathophysiology of Major Depression (Drevets 2001, Mayberg 2003). By means of a stimulating electrode attached to the left VN and connected to a pulse generator implanted subcutaneously in the subclavear region of the chest, VNS provides a widespread continuous stimulation of these areas. The VNS implant requires a relatively minor surgical intervention that can be completed under local or general anaesthesia. A first small incision is made below the collarbone in the left upper chest area where the pulse generator is located. A second incision is made in the left side of the neck and a small helicoidal electrode, connected to the pulse generator through a subcutaneous wire, is wrapped around the VN. Once the device is turned on, it delivers chronic, intermittent electrical impulses to the left VN. Classical stimulation parameters include 30 seconds of stimulation followed by 5 minutes of pause with an initial current of 0.25 mA which is progressively increased by 0.25 mA up to 1.50 mA that is considered the optimal stimulation voltage.

## Neurobiological studies and clinical trials with VNS

Neurochemical and neuroimaging studies have investigated the effects of VNS on neurotransmitter metabolism and on cerebral perfusion and metabolism. Carpenter and colleagues investigating the effects of VNS on the dopaminergic system found a significantly elevated level of homovanillic acid in cerebrospinal fluid (CSF) samples of patients with TRD after 24 weeks of VNS therapy whereas no relevant changes were observed in the concentration of other substrates (5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxy-phenylclycol and GABA) (Carpenter et al. 2004).

Dorr and Debonnel investigated 5-HT and NE neuronal firing rates in the Brainstem nuclei - Dorsal Raphe Nucleus (DRN) and Locus Coeruleus (LC) - after VNS therapy in rats and found significantly higher firing rates for LC after short-term VNS therapy, whilst basal firing rates in the DRN and LC were significantly increased after long-term stimulation (Dorr and Debonnel 2006).

Functional imaging investigation and SPECT studies, in particular, have shown regional cerebral blood flow (rCBF) abnormalities of limbic and cortical structures (such as Insula and Temporal Cortex) in depressed patients (Devous et al. 2002). Of clinical interest, a recent SPECT study exploring rCBF changes induced by VNS found decreased rCBF in the Amygdala, left Hippocampus, left Subgenual Cingulate Cortex, left and right Ventral Anterior Cingulum, right Thalamus and Brainstem. These effects are consistent with those reported after the administration of SSRIs (Zobel et al. 2005).

PET studies investigating VNS-induced effects on metabolism have reported mixed results. A previous study found a decreased metabolism in the Substantia Nigra, Ventral Tegmentum, Hypothalamus, Insula/Claustrum and Superior Temporal Gyrus after 1 year of VNS therapy (Hagen et al. 2003). On the other hand, Conway and colleagues reported that VNS therapy caused an increased metabolic activity in the Orbitofrontal Cortex, bilateral Anterior Cingulate Cortex and right Superior and Medial Frontal Cortex, and a decreased rCBF in the bilateral Temporal Cortex and right Parietal Area (Conway et al. 2002). Taken as a whole, neurobiological studies with VNS are still at initial level and require further investigation.

With regard to clinical trials, efficacy studies have been subdivided into acute and long-term investigation. These studies are summarized in table 1 and 2 (Rush et al. 2000, Sackeim et al. 2001, Armitage et al. 2003, Rush et al. 2005a, O'Keane et al. 2005, Neuhaus et al. 2007, Rush et al. 2005b, Nahas et al. 2005, George et al. 2005, Schlaepfer et al. 2008). In general, results have been positive even though, in some cases efficacy was modest if not questionable. Some aspects and potential bias need to be kept into account when considering efficacy studies. VNS has been approved as adjunctive treatment for TRD and the majority of patients recruited in clinical trials had shown proven resistance to different therapies (> 4) frequently including ECT. This means that samples were not always homogeneous and concomitant pharmacological treatment may have influenced the overall clinical picture. In addition, given that VNS is an invasive surgical procedure in which electrodes and pulse generator are implanted, we believe that its effects should not be limited to the acute treatment but, specifically, in the long-term. In other words, it needs to be assessed not only the improvement in depressive symptoms but also relapse rate, duration and severity of eventual recurrences, effects and potential switch in BD and long-term tolerability issues. Actually studies investigating these specific aspects are lacking and we believe that answers in these fields will substantially influence clinicians' confidence in VNS.

## Case Series of patients treated with VNS therapy

Herein are reported the preliminary results of the

**Table 1.** *Summary of short-term efficacy studies with VNS*

| AUTHOR | STUDY DESIGN | FOLLOW-UP | SAMPLE | RESULTS AND CONCLUSIONS |
|---|---|---|---|---|
| Rush et al. 2000 | Multicenter open label study | 10 weeks | 30 adult outpatients (21 with non-psychotic treatment-resistant major depressive disorder 9 with bipolar I or II depressed phase disorders) on concomitant pharmacological treatment | Mean baseline $HDRS_{28}$ scores = 38.0. Response rates were 40% for both the $HDRS_{28}$ and the CGI and 50% for the MADRS. Results suggest that VNS has antidepressant effects in treatment-resistant depression |
| Sackeim et al. 2001 | Open label study | 10 weeks | 60 outpatients with non-psychotic, resistant major depressive or bipolar disorder, on stable medication regimens | Response rate was 30.5% for the primary $HDRS_{28}$, 34.0% for MADRS, and 37.3% for the CGI-I.<br>None of the 13 patients who had not responded to more than 7 adequate antidepressant trials in the current MDE responded.<br>VNS appears to be most effective in patients with low-moderate antidepressant resistance |
| Armitage et al. 2003 | Open label study | 10 weeks | 7 outpatients with resistant-depression on stable medication regimens | 4 out of 7 patients classified as HDRS responders and 2 of these remitters.<br>VNS improved the clinical symptoms of depression and sleep patterns |
| Rush et al. 2005 | Randomized, controlled, masked trial | 10 weeks | 235 outpatients with non-psychotic resistant major depressive disorder or non-psychotic, resistant major depressive episode of bipolar disorder.<br>Medications were kept stable | At 10-weeks, $HDRS_{24}$ response rates were 15.2% for the active and 10.0% for the sham group.<br>This study did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression. |
| O'Keane et al. 2005 | | 12 weeks | 11 patients with resistant depression, 11 test subjects and 11 matched control subjects underwent a CRH challenge | Significant reductions in depression scores. The CRH/ACTH responses in the depressed group before VNS implantation were significantly higher than in the healthy group and were reduced to normal values after VNS. |
| Neuhaus et al. 2007 | Exploratory study | 10 weeks | 13 patients with major depression (mean HAMD scores at baseline = 24.2) | Responders (N=5, mean HAMD post VNS=8.8), non-responders (N=8, mean HAMD post VNS=22.4). Enhancement of P300 distinguished VNS responders from non-responders. |

**Table 2.** *Summary of long-term efficacy studies with VNS*

| AUTHOR | STUDY DESIGN | FOLLOW-UP | SAMPLE | RESULTS AND CONCLUSIONS |
|---|---|---|---|---|
| Rush et al. 2005 | Naturalistic follow-up study | 12 months | 205 outpatients with non-psychotic major depressive or bipolar disorder, depressive episode | Significant reduction in $HDRS_{24}$ scores: response rate was 27.2%; remission rate was 15.8%. Reductions in MADRS of 28.2% and CGI 34%. Potential long-term, growing benefit in TRD. |
| Nahas et al. 2005 | Open label study | 24 months | 59 adult outpatients with chronic or recurrent MD or BD with treatment-resistant, non-psychotic MDE | $HDRS_{28}$ response rates were 31% at 3 months, 44% at 1 year, 42% at 2 years. Remission rates were 15% at 3 months, 27% at 1 year, and 22% at 2 years. Majority of antidepressant effects occurred in the first 3 months. |
| George et al. 2005 | Naturalistic, prospective, open trial | 12 months | 229 treatment-resistant depressed patients. VNS+ treatment as usual (TAU) group vs TAU group | 27% of TAU+VNS group were responders at HDRS at 12 months compared to 13% of TAU group. VNS+TAU was associated with a greater antidepressant benefit over 12 months. |
| Schlaepfer et al. 2008 | Open multicenter study | 12 months | 74 patients with TRD. Treatment unchanged in the first 3 months, then adjusted | $HDRS_{28}$ response and remission rates at 3 months were 37% and 17% of the sample. Response rates increased to 53% after 12 months and remission to 33% of the sample. Median time to response was found to be 9 months. |

first 4 consecutive bipolar patients with TRD involved in a treatment protocol with VNS at the IRCCS Ospedale Maggiore Policlinico of Milan, Italy, who completed 6 months of open-label VNS therapy with periodic monthly clinical evaluations.

The first patient was a 38 year-old single man, part-time employee with positive family history for Bipolar Disorder and comorbid Behcet's disease. He developed the first Major Depressive Episode (MDE) at age 33 and he was treated with clomipramine 150 mg/day achieving full remission. In the following 3 years, the patient had 2 mixed episodes, 2 hypomanic episodes and 3 MDEs that were treated with politherapies of SSRIs (initially sertraline up to 200 mg/day and subsequently paroxetine up to 40 mg/day) plus valproate within therapeutic plasma levels. The patient had been hospitalized during two MDEs and one mixed episode. One hospitalization followed a suicide attempt. At age 36, patient developed a new MDE which was treated with 3 different antidepressants given at subsequent times (venlafaxine up to 300 mg/day, mirtazapine up to 60 mg/day and duloxetine up to 120 mg/day) while maintaining valproate at the same dosage. Patient also completed a 3-week trial of augmentative, low frequency, transcranial magnetic stimulation (TMS) without any significant improvement. When patient came to our observation we administered the structured clinical interview for DSM-IV Axis I (SCID-I) (First et al. 1997) and he was diagnosed as suffering from Bipolar Disorder type I and comorbid Generalized Anxiety Disorder (GAD) with current non-psychotic chronic MDE. He was also evaluated with the following rating scales: HDRS (baseline score 24), Montgomery-Asberg Depression Rating Scale (MADRS; 28) (Montgomery and Asberg 1979), Hamilton Anxiety Rating Scale (HARS; 21) (Hamilton 1959) and Clinical Global Impression Scale, Severity of Illness (CGI-S; 5) (Guy 1976). Patient was selected for VNS therapy and, after providing written informed consent to the procedure, he underwent the surgical implant. Three months later, patient reached the optimal stimulation parameters (1.50 mA) and received a complete psychometric evaluation showing a slight decrease of all outcome measures (HDRS 19, MADRS 24, HARS 19 and CGI 5). Indeed, at six months, rating scales total scores were significantly decreased (HDRS 13, MADRS 18, HARS 9 and CGI 4). With regard to side-effects, patient had moderate voice alteration and cough in the first 3 months which typically occurred during the stimulation periods. These side effects gradually subsided throughout the following 3 months and patient currently shows only a minimal voice alteration. In terms of quality of life, it is noteworthy to highlight that the patient could start working at full-time after 2 years of partial employment.

Two other patients were 45 and 62 year-old women, both married with positive family history for mood disorders and with the same diagnosis of rapid cycling Bipolar Disorder, type II, according to the SCID-I administered when patients came to our observation. They developed their first MDE in the late 20s. In the following years, both patients showed a progressive increase of recurrence index with several MDEs, recurrent brief depressive episodes and few hypomanic episodes. They were treated with several antidepressants of different classes (tricyclics, SSRIs and SNRIs), mood stabilizers (lithium, gabapentin and lamotrigine) and atypical antipsychotics (olanzapine, quetiapine, risperidone and aripiprazole) without achieving a sustained remission. They had also been involved in a TMS trial with initial response but subsequent relapse after few weeks following the end of the stimulation. The younger patient, employee, came to our observation while in treatment with lithium and sertraline (150 mg/day) and showed the following scores during the psychometric evaluation (HDRS 18, MADRS 18, HARS 9 and CGI 4). She also described frequent brief periods (generally a couple of days) during which she could not work due to her illness. The other patient, retired, was on bupropione (150 mg/day), lithium (450 mg/day) and pramipexole (0.72 mg/day) and had the following scores (HDRS 18, MADRS 22, HARS 9 and CGI 5). Both patients had never been hospitalized nor reported suicidal attempts or relevant psychiatric and medical comorbidity. Patients were classified as moderately depressed according to their rating scales scores and SCID-I. Their current MDE had a mean duration of three months. Patients were requested to consider VNS therapy not only on the basis of the severity of their current episode but, overall, in light of their history of chronic and highly recurrent illness. After providing written informed consent to the procedure, they underwent the surgical implant. Compared to the first patient, they could reach the lowest effective voltage of 1 mA in a longer period of time (between the 4th and 6th month after the surgical implant) due to minor tolerability to side-effects (hoarseness and cough). In the third month following surgical implant, the younger patient had a depressive relapse which lasted approximately one month and remitted without any change in the pharmacological regimen (lithium plus sertraline, 150 mg/day). Nevertheless, after the first 6 months of VNS both patients showed a progressive and significant symptom improvement with the following scores (younger patient: HDRS 12, MADRS 15, HARS 7 and CGI 3; older patient: HDRS 15, MADRS 19, HARS 7 and CGI 4). Besides a significant reduction of total scores compared to baseline (between 30% and 40%), it is of greater clinical interest the observation of a significant reduction of the recurrence index with only one episode in the younger patient, though occurred when the voltage of stimulation was below 1 mA, and no further episode in the other patient. Side-effects had gradually subsided being present only a slight hoarseness in both patients at 6 months.

The last patient was a 69 year old retired woman who had been suffering from bipolar II disorder since her late 20's. In approximately 40 years of illness, she had presented numerous Major Depressive Episodes and few hypomanic episodes. During her last two years of illness under our observation patient had 4 major depressive episodes lasting more than 3 months per episode with poor response to pharmacological treatments and residual interepisodic symptoms. Before considering VNS therapy, the patient was experiencing a depressive episode, lasting approximately 4 months (HDRS 18, MADRS 19, HARS 8 and CGI 4), and she was on a pharmacological treatment with venlafaxine (150 mg/day) and quetiapine (300 mg/day), after having shown no response to Duloxetine (120 mg/day) and valproate (1000 mg/day) in the first 8 weeks. Previously, she had been treated with several combinations of antidepressants, mood-stabilizers, typical and atypical antipsychotics without achieving a sustained recovery. The patient was implanted in March 2009 and could reach 1 mA of voltage stimulation after 3 months. During this period her clinical conditions remained unchanged. However, by the 4th month she showed a progressive improvement that was assessed at the 6 month with the following scores (HDRS 7, MADRS 13, HARS 8 and CGI 3). With regard to tolerability, the patient showed hoarseness and cough in the first 3 months which had completely disappeared at 6 months.

In terms of weight changes, taken as a whole, described patients exhibited a weight loss of approximately 1.2 ($\pm$1.2) kilograms after 6 months of VNS therapy.

## Discussion

Present findings are consistent with literature data indicating a progressive symptom reduction for patients treated with VNS, with the most significant improvement in after the first 3 months of treatment (Rush et al. 2005, Nahas et al. 2005, Schlaepfer et al. 2008). In terms of stimulation parameters which are strongly related to tolerability aspects, patients needed a longer period of time to reach what is generally believed to be the lowest effective level of stimulation in terms of voltage (1mA). Even though other parameters such as frequency, duration of stimulation and pulse width, may be varied according to patients' clinical conditions and tolerability, these are generally predefined, whereas voltage stimulation is progressively increased. In order to maintain a favourable profile of tolerability, therefore, we decided to use a slower program of voltage increase allowing patients (2nd and 3rd patient, in particular) to get used to each subsequent change with a minimal interval of 2-4 weeks before increasing to the following step. Of note, 3 out of 4 patients had previously received a cycle of TMS without showing a sustained response. It is also of clinical interest that among them, two patients had treatment-resistant rapid cycling Bipolar Disorder and prevalent depressive episodes. In this perspective, these positive results are consistent with a recent pivotal trial conducted with a small sample of patients with treatment-resistant rapid-cycling Bipolar Disorder (Marangell et al. 2008). Over a 12-month VNS treatment period, authors reported a 38.1% mean improvement in overall illness as compared to baseline. In this perspective, it is noteworthy to highlight that VNS may exert a positive effect not only over depressive symptoms but, also, on the cyclicity that characterizes various forms of mood disorders. This putative effect may also be a *trait d'union* between the anticonvulsant effect of VNS and the clinical use of anticonvulsants as mood stabilizers in different mood disorders.

There are other putative advantages for VNS therapy over standard antidepressant treatments along with clinical issues that should be further investigated in light of potential clinical interest. One of these is represented by compliance that is insured by the continuous stimulation during VNS therapy and does not depend on patient. In addition, VNS has no influence on pregnancy because, differently from pharmacological treatments, it does not pass through the placenta. Nonetheless VNS studies in pregnancy are limited to case-reports and need further investigation (Husain et al. 2005) as for the potential effect of VNS on cognition (Kosel and Schlaepfer 2003).

The reported case series of TRD patients – two of whom with rapid-cycling Bipolar Depression - followed up for one year of VNS therapy showed results that are consistent with literature data in terms of improvement timing, response rates and tolerability issues even though limited by the open design of the study.

## References


American Psychiatric Association (2000). Practice guidelines for the treatment of patients with major depressive disorder. *Am J Psychiatry* 157, 1-45.

Armitage R, Husain M, Hoffmann R, Rush AJ (2003). The effects of vagus nerve stimulation on sleep EEG in depression: a preliminary report. *J Psychosom Res* 54, 475-482.

Carpenter LL, Moreno FA, Kling MA, et al. (2004). Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine and α-aminobutyric acid concentrations in depressed patients. *Biol Psychiatry* 56, 418-426.

Chae JH, Nahas Z, Lomarev M, et al. (2003). A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J Psychiatr Res* 37, 443-455.

Conway CR, Chibnall JT, Fletcher JW, et al. (2002). Three months of vagus nerve stimulation is associated with increased limbic and paralimbic activity (FDG PET) in treatment-resistant depressed subjects. Poster presented at the 57th Annual Scientific Convention of the Society of Biological Psychiatry. Philadelphia, PA, 16-18.

Devous MD, Husain M, Harris TS, Rush AJ (2002). Effects of VNS on regional cerebral blood flow in depressed subjects. Poster presented at the 42nd Annual New Clinical Drug Evaluation Unit Meeting. Boca Raton, FL, 10-13.

Dorr AE, Debonnel G (2006). Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *J Pharmacol Exp Ther* 318, 2, 890-898.

Drevets WC (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurol* 11, 2, 240-9.

Fava M, Davidson KG (1996). Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 19, 179-200.

First First MB, Spitzer RL, Gibbon M, et al. (1997). *Structured Clinical Interview for DSM-IV Axis I (SCID-I) Clinician Version*. American Psychiatric Press, Washington DC.

Foley JO, DuBois F (1937). Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory motor studies. *J Comp Neurol* 67, 49–67.

Gayetot D, Ansseau M, Triffaux JM (2007). When depression does not end. Resistant depression: recent clinical and therapeutic aspects. *Rev Med Liege* 62, 103-11.

George MS, Rush AJ, Marangell LB, et al. (2005). A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 58, 364-373.

Guy W (1976). *ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76–338.* US Department of Health, Education and Welfare, Washington DC, 218-222.

Hagen MC, Sheikh JS, Adson D, et al. (2003). Metabolic changes in treatment-resistant depression responsive to VNS therapy. Poster Presented at the 58th Annual Scientific Convention of the Society of Biological Psychiatry, San Francisco, CA, 5-17.

Hamilton M (1959). The assessment of anxiety states by rating. *Br J Med Psychol* 32, 50-55.

Husain MM, Stegman D, Trevino K (2005). Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. *Ann Gen Psychiatry* 4, 16.

Kosel M, Schlaepfer TE (2003). Beyond the treatment of epilepsy: new applications of vagus nerve stimulation in psychiatry. *CNS Spectr* 8, 7, 515-21.

Kraus T, Hosl K, Kiess O (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *J Neural Transm* 114, 11, 1485-1493.

Marangell LB, Suppes T, Zboyan HA, et al. (2008). A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry* 69, 2, 183-9.

Mayberg HS (2003). Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin N Am* 13, 4, 805-815.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134, 382-9.

Nahas Z, Marangell LB, Husain MM, et al. (2005). Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry* 66, 1097-1104.

Neuhaus AH, Luborzewski A, Rentzsch J, et al. (2007). P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder. *J Affect Disord* 100, 123-128.

Nierenberg AA, DeCecco LM (2001). Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry* 62, 16, 5-9.

O'Keane V, Dinan TG, Scott L, Corcoran C (2005). Changes in hypothalamic-pituitary-adrenal axis measures after vagus nerve stimulation therapy in chronic depression. *Biol Psychiatry* 58, 963-968.

Preskorn SH, Burke M (1992). Somatic therapy for major depressive disorder: selection of an antidepressant. *J Clin Psychiatry* 53, suppl, 5-18.

Rush AJ, George MS, Sackeim HA, et al. (2000). Vagus Nerve Stimulation for treatment resistant depression: a multicenter study. *Biol Psychiatry* 47, 276-286.

Rush AJ, Marangell LB, Sackeim HA, et al. (2005a). Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry* 58, 347-354.

Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM et al. (2005b). Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry* 58, 5, 355-363.

Sackeim HA (2001). The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62, suppl, S16, 10-7.

Sackeim HA, Rush AJ, George MS, et al. (2001). Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 25, 713-728.

Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M et al. (2008). Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med* 4, 1-11.

Zobel A, Joe A, Freymann N, et al. (2005). Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach. *Psychiatry Res* 139, 3, 165-79.