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Deep brain stimulation *versus* vagus nerve stimulation in the treatment of therapy-resistant depression: A systematic review and meta-analysis

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Resumen

Introducción: "Depresión" representa un grupo de condiciones clínicas heterogéneas que impone un grave problema de salud pública. La OMS estima que la depresión será la tercera causa principal de enfermedades debilitantes en 2030. El tratamiento establecido incluye antidepresivos, psicoterapia, terapia electroconvulsiva y estimulación magnética transcraneal. 10 a 20% de los pacientes son depresores resistentes a los tratamientos convencionales (TRD) y para estos, la psicocirugía moderna se está convirtiendo en parte del arsenal terapéutico. Este artículo analiza la evidencia actual y el potencial para la aplicación de la estimulación del nervio vagal (VNS) y la estimulación cerebral profunda (DBS) en la corteza cingulada subgenual (SCC) en el tratamiento de la depresión. **Material y Métodos:** Una revisión sistemática de los ensayos clínicos prospectivos realizados en centros americanos y europeos por Medline / Pubmed entre 2000 y 2016, con $p < 0,05$ $n > 10$, con una revisión de las referencias citadas por todos los estudios localizados relevantes. Se obtuvieron 66 referencias para VNS y 137 para DBS, diez estudios de VNS y tres de DBS fueron seleccionados de acuerdo a los criterios de elegibilidad. Se realizó un meta-análisis exploratorio a través de las tasas de eventos encontradas. **Resultados:** Se obtuvo una muestra de 643 pacientes con TRD en los estudios VNS y 58 DBS. La tasa de respuesta a VNS después de 12 meses fue del 42,0% (IC del 95% = 31,2% al 56,7%) y la tasa de remisión fue del 22,3% (IC del 95%: 16,5% a 30,0%). Las tasas de DBS fueron 37,0% (IC del 95%: 22,9% a 59,6%) y 26,2% (IC del 95%: 15,4% a 44,5%), respectivamente. **Conclusión:** El análisis individual de los ensayos clínicos demuestra que tanto VNS como DBS son recursos prometedores en el tratamiento de TRD, especialmente a corto y medio plazo, sin embargo la mayoría de los estudios no son aleatorizados. El metanálisis reveló una alta heterogeneidad debido al reducido número de ensayos clínicos, diferencias técnicas y sesgo de selección.

Palabras clave: Depresión, Estimulacion del nervio vagal, Estimulacion cerebral profunda, terapia eletrocolvulsiva.

Abstract

Introduction: "Depression" represents a group of heterogeneous clinical conditions that imposes a serious public health problem. The WHO estimates that depression will be the third leading cause of debilitating diseases by 2030. The established treatment involves antidepressants, psychotherapy, electroconvulsive therapy and transcranial magnetic stimulation. 10 to 20% of patients are depressants resistant to conventional treatments (TRD) and for these, modern psychosurgery is becoming

part of the therapeutic arsenal. This paper analyzes the current evidence and the potential for the application of vagal nerve stimulation (VNS) and deep brain stimulation (DBS) in the subgenual cingulate cortex (SCC) in the treatment of depression. **Material and Methods:** A systematic review of the prospective clinical trials conducted in American and European centers by Medline / Pubmed between 2000 and 2016, with p <0.05 n> 10, with a review of the references cited by all relevant localized studies. We obtained 66 references for VNS and 137 for DBS, ten studies of VNS and three of DBS were selected according to eligibility criteria. An exploratory meta-analysis was performed through the event rates found. **Results:** A sample of 643 patients with TRD was obtained in the VNS and 58 DBS studies. The VNS response rate after 12 months was 42.0% (95% CI = 31.2% to 56.7%) and the remission rate was 22.3% (95% CI = 16.5% to 30.0%). DBS rates were 37.0% (95% CI = 22.9% to 59.6%) and 26.2% (95% CI = 15.4% to 44.5%) respectively. **Conclusion:** Individual analysis of clinical trials demonstrates that both VNS and DBS are promising resources in the treatment of TRD, especially in the short and medium term, however most studies are not randomized. The meta-analysis revealed high heterogeneity due to the reduced number of clinical trials, technical differences and selection bias.

Key words: Depression, Vagal nerve stimulation, Deep brain stimulation, electroconvulsive therapy.

Introduction

"Depression" represents a group of heterogeneous clinical conditions that imposes a serious public health problem. In the USA, the prevalence of Major Unipolar Depressive Disorder is estimated between 2.6-5.5% in men and 6.0-11.8% in women[1]. Most of patients (50-85%) have recurrent episodes. Depression can cause profound disability, as well as severe suffering, which can be reflected in marital, parental, social, professional and academic impairments[2]. Among the complications, the main one is the suicide[3]; the coexistence between cardiovascular diseases or câncer with depression, increase mortality[4,5]. The WHO estimates that depression Will become the third of the top ten causes of disablin illnesses by 2030. The financial costs of depression in 2000 were $ 83,1 billion in the US[6].

The initial therapeutic approach to depression comprises the use of antidepressants, associated or not with psychotherapy. In patients who remain with clinical condition, the alternatives established are the combination of antidepressants of the same or different classes and, eventually, the electroconvulsive therapy (ECT) and the transcranical magnetic stimulation (TMS). The main goals of treatment are remission of symptoms, restoration of daily functionality and prevention of relapses and recurrences. Although most patients respond favorably to treatment, 10-20% will present chronic forms that are resistant to treatment. For these patients, classified as Therapy-resistant depression (TRD), surgical treatments has been used as part of the therapeutic arsenal[7].

Modern techniques of neurosurgery for depression are mainly based on three methods: ablative procedures to deactivate pathologically active circuits, deep brain stimulation (DBS) and vagus nerve stimulation (VNS); procedures such as cortical stimulation are also being investigated[7].

This paper will analyze the current state of clinical evidence and the potential of VNS and DBS application in the subgenual cingulate cortex (SCC) in the treatment of depression through a systematic review and meta-analysis.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an invasive technique consisting of inserting a pulse generator under the skin of the upper chest, which sends signals through the electrodes of the lead to the brain by way of the left vagus nerve[8,9]. In 1997, it was approved by the United States Food and Drug Administration (FDA) as an adjunctive therapy for reducing the frequency of seizures in adults and adolescents who were refractory to antiepileptic medications[10]. Clinical studies conducted on such patients indicated that the technique might possibly affect their mood[11]. This finding, together with the technique's apparent biological plausibility -inasmuch as the vagus nerve affords access to encephalic structures traditionally linked to neuropsychiatric disorders[12,13]- led to studies being undertaken on the technique's indication for use in the treatment of depression. In 2005, the FDA approved the use of VNS for treatment of major depressive disorder (MDD) in patients over the age of 18 years, refractory to other treatments, defined as patients who have not shown an satisfactory response to two or more adequate antidepressant treatments. To date, however, the only evidence of the technique's efficacy and safety when used on this type of patient comes from individual uncontrolled studies[14,15,16,17,18,19,20] of varying duration which have reported initially positive results. This is in contrast to the negative results reported by one, controlled, 10-week study that used a placebo[21]. The study conducted by George et al., in 2005[22] compared two non-randomised groups of patients with refractory depression, and reported greater antidepressive efficacy for the group that received VNS along with treatment as usual than for the group that only received treatment as usual, after 12 months of intervention.

In view of the high prevalence of depression, coupled with the high rates of subjects refractory to pharmacological treatments[23,24], the consequences in terms of patients' health and quality of life[25,26], and the ensuing cost for health care systems[27,28], a coadjuvant non-pharmacological intervention for the treatment of such patients would appear to be a promising tool for clinical practice.

Deep Brain Stimulation

The successful replacement of ablative neurosurgical procedures in movement disorder patients by deep brain stimulation (DBS) has laid the foundation for such a transition in psychiatric neurosurgery. Indeed, deep brain stimulation (DBS) has emerged as a potential treatment for unremitting TRD[29,30], and has displaced ablative techniques as the focus of empirical trials. Briefly, DBS involves the bilateral stereotactic

implantation of electrodes into specific brain structures where continuous stimulation of variable parameters is applied via neurostimulator devices placed subcutaneously in the infraclavicular region[31]. The programming of these devices is carried out by an external transmitter, and systematic out patient adjustment of stimulation parameters (e.g., active contacts, amplitude or voltage, pulsewidth, frequency) is necessary, especially during the initial months after implantation[32]. DBS is a relatively safe technique with potential adverse effects commonly including headache, agitation, and pain at the incision site, although cerebral hemorrhage, suicide and infection have also been reported[29,33].

Brain target selection for DBS in TRD has been guided tractography of older ablative techniques and by neuroimaging studies identifying neuroanatomical structures with inputatively dysfunctional neural circuits modulating different aspects of MD via connections to limbic, cortical, and subcortical áreas[33,34]. While the precise mechanisms through which DBS exert sits therapeutic effects are still unclear, preliminary data suggest that chronic electrical stimulation of the brain exerts both immediate and long-term effects on complex neuronal firing rates and patterns[35].

A series of putative DBS targets for MD are being investigated, such as the ventral anterior limb of the internal capsule and ventral striatum[36,37], the medial forebrain bundle[38] and the nucleus accumbens[39]. The small number of studies for each approach do not lend themselves well to meta-analytical techniques. We have chosen to focus on studies of SCC as these have been most numerous. The rationale for targeting the SCC is mainly derived from functional neuroimaging studies that have shown MD to be associated with overactivity in this brain region[40,41,42], and the finding that disparate interventions including pharmacotherapy[43,44], repetitive transcranial magnetic stimulation[45,46], anterio cingulotomy[47] and electroconvulsive therapy[48] ameliorate the clinical features of MD and alter the activity of the SCC.

Material and Methods

Search Strategy

We performed a systematic review of the scientific literature available since january 2000 until october 2016, with a search of the Medline/Pubmed database, and reviewed the references cited by all the pertinent studies located. For search purposes, the relevant search terms are “depression”, “vagus nerve stimulation”, “VNS”, “deep brain stimulation”, “DBS”. The systematic review was performed by four reviewers that after applying the exclusion criteria on the abstracts selected, made a complete reading of the potentially eligible papers, extracted and recorded the necessary data for the development of the meta-analysis in individual tables. Corrected the divergences, a table with the data of the VNS and one of the DBS were elaborated.

Study Selection

Candidate studies had to meet the following criteria:

- Prospective studies - randomised controlled Trial (RCT) and clinical trial (before-after analytical studies), and inclusion of $\geq$ 10 subjects with MDD;
- Follow-up of at least one year;
- Studies with 95% CI, $p < 0.05$, from january 2000 to october 2016;
- Subjects aged 18-75 years with a diagnosis primary major depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical Manual of Mental Disorders – 4th edition or later[49] or the International Classification of Diseases criteria[50];
- DBS applied to the SCC and VNS as a treatment for TRD;
- Articles written in english.

Sudies were excluded if:

- Duplicated samples;
- Did not report depression scores, and/or rates of response/remission.

Data extraction

The following data were extracted and recorded in a structured fashion in the tables:

- Sample size, follow-up, mean age, gender, baseline depression intensity;
- Characteristics of the intervention: current intensity, pulse frequency, pulse width;
- Number of responders to treatment based on the studies’ primary efficacy measures (defined as a $\geq$ 50% reduction in post-treatment scores on the Hamilton Depression Rating Scale [HAM-D][51], Montgomery-Asberg Depression Rating Scale [MADRS][52] or Inventory of Depressive Symptomatology - Clinician [IDS-C][53] at follow-up;
- Number of remmiters based on the studies’ primary efficacy measure (21-item, 24-item or 28-item HAM-D scores $\leq$ 7, $\leq$8 or $\leq$9 respectively, or MADRS scores $\leq$ 6 at follow-up.

Data synthesis and analyses

Analyses were performed using STATA® Statistics/Data Analysis Version 13.0 (StataCorp, Lakeway Drive College Station, Texas, USA). We used intention-to-treat data from the VNS and DBS studies - particularly the response and remission rates for TRD. For these binary outcomes, we calculated the respective event rates (the proportion of patients in whom the event was observed at a specific time point, in case after 12 months of tretament). Weighting was stablished according to the level of study precision, through the inverse variance method.

Heterogeneity was assessed using Q statistics and the I^2 index. Values of $p < 0.10$ for the resultant and or >45% for the latter suggests study heterogeneity. Funnel Plots were made to summarize the meta-analysis. The other studies included in this systematic review, but which were not inserted in the meta-analysis due to incompatibility in the follow-up studied, are reported descriptively only.

Literature search

We found a total of 66 references on VNS and 137 from DBS, through the MEDLINE / Pubmed database. Of these, ten VNS and three DBS studies met our eligibility criteria for the systematic review. Of these, four VNS studies were excluded from the meta-analysis because they had follow-up shorter than one year, to avoid time-related bias. (Figure 1).

Results

Included trials: main characteristics

From the VNS studies included in the meta-analysis, there is a total sample of 643 subjects with TRD (mean age = 46.8 ± 1.63 years, 60.96% female). And of the DBS studies, a total of 58 subjects (mean age = 45.5 ± 3.08 years, 58.6% woman). Aspects related

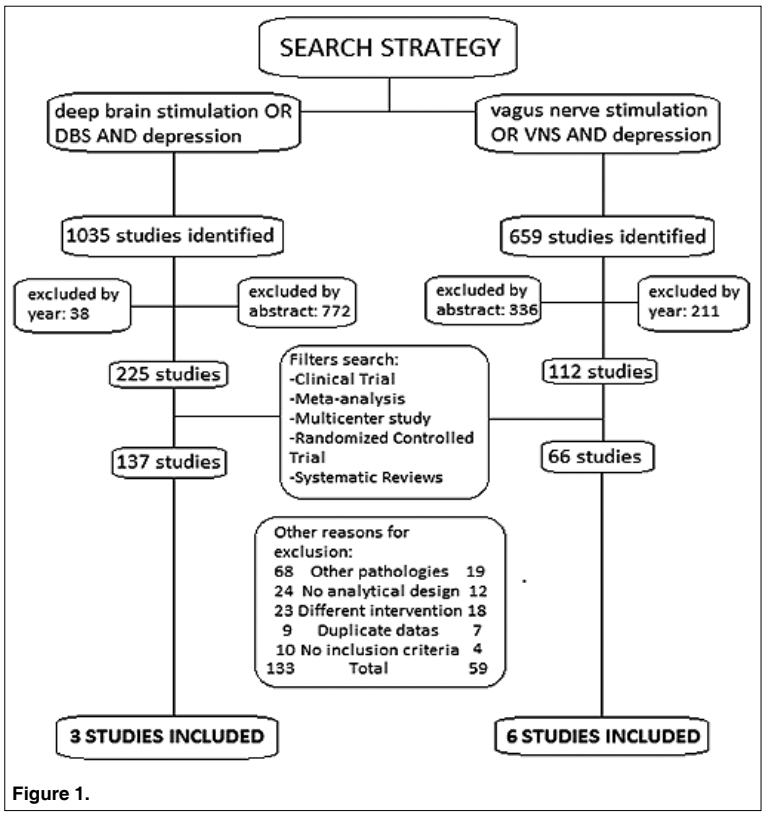

Figure 1.

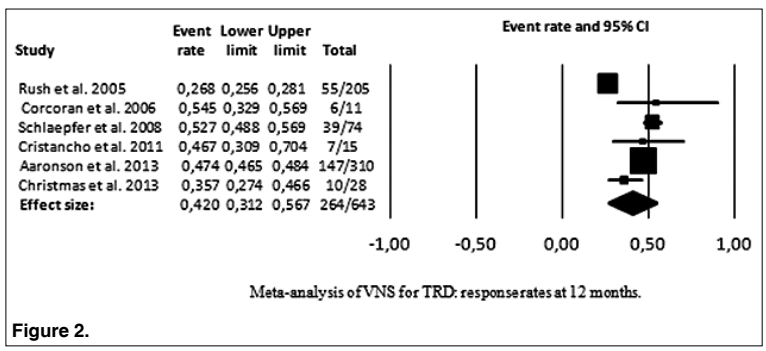

Figure 2.

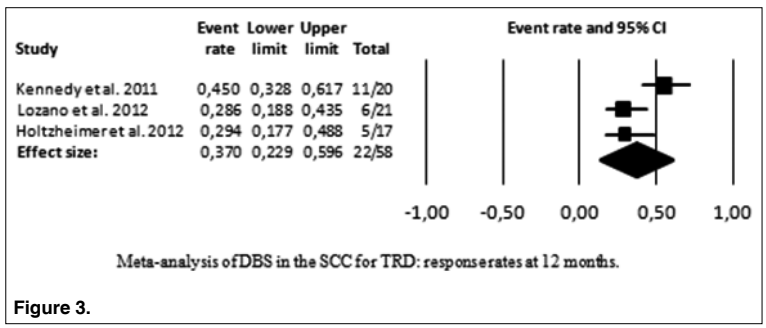

Figure 3.

to the baseline depression intensity of the patients, follow-up, and stimulation parameters of the devices are listed in Tables 1 and 2.

Response rates

In the VNS meta-analysis, pooled response rate at 12 months of treatment was 42.0% (95% CI= 31.2% to 56.7%), p= 0.000 for a random effects model, and indicated high heterogeneity (I^2= 99.1%), due to the differences between the patology of individuals in each study (there are studies in which there are cases of unipolar depression and bipolar disorder in the same sample), which reflects on the basal level of the scales used to assess the severity of the disease; year of publication and the size of the study. Most of the studies used similar stimulation patterns, which would not justify the observed heterogeneity. In a meta-analysis carried out in 2012, a meta-regression was performed, using subjects' mean baseline severity of depression to estimate this variable in the study's effect size, evidenced that for every one-point increased in baseline level, there was a 0.07 point increase in the magnitude of the observed effect. Adjusted coefficient of determination (R^2_{adj}) was 0.84, which mean that an 84% variation in the effect size in the studies was explained by baseline severity of depression ($p < 0.0001$)[54]. (Figure 2).

Pooled response rates in DBS 12 - months was 37.0% (95% CI = 22.9% to 59.6%), p= 0.012 for a random effects model, I^2 index = 77.2%, a elevated heterogeneity response analysis, but lower than that of VNS. Heterogeneity between studies exceed that expected, implying that the variance among the effect sizes was greater than expected by sampling error. The DBS funnel plots were reasonably more symmetrical than the VNS funnel plots. (Figure 3).

Although there is a smaller number of DBS studies, it is possible to see that there is a tendency to present more homogeneous results, which in the long term with the establishment of new studies can be achieved.

Remission rates

The VNS studies has presented pooled remission rate of 22.3% (95% CI= 16.5% to 30.0%) at 12 months follow-up, p= 0.000 and I^2= 97.3%, a evident heterogeneity, probably attributed by the great difference between studies sample weight. (Figure 4).

Pooled remission rate in 12 months follow-up DBS sudies was 26.2% (95% CI = 15.4% to 44.5%) p = 0.081 and I^2= 60.3% that represents a moderate

Table 1.
Characteristics of VNS selected studies

Authors	Demographics		DBS intervention		Results
	n (follow up) ♀/♂ (n) Baseline depression	Age ± SD	Current (mA) (μs)	Frequency Widht (Hz)	
Rush et al. (2005)	205 (12 months) 131/74	46.3 ± 8.9 28.0 ± 5.7	0.75-2.25 500	20	Response rates $HRSD_{24}$: 27.2% Remission rates $HRSD_{24}$: 15.8%
Corcoran et al. (2006)	11 (12 months) 83	43.0 ± 8.7 36.3 ± 3.4	0.75-1.0 500	20	Response rates $HRSD_{24}$: 54.5% Remission rates $HRSD_{24}$: 27.2%
Schlaepfer et al. (2008)	74 (12 months) 50/24	47.4 ± 11.7 34.0 ± 5.8	0.25-2.0 500	20	Response rates $HRSD_{28}$: 53% Remission rates $HRSD_{28}$: 33%
Cristancho et al. (2011)	15 (12 months)		Not reported		Response rates $HRSD_{28}$: 43% Remission rates $HRSD_{28}$: 14.3%
Aaronson et al. (2013)	310 (12 months) 207/103	47.9 ± 10.8 34.1 ± 4.7	0.25-1.5 130-250	20	Response rates MADRS: 47.4% Remission rates MADRS: 23%
Christmas et al. (2013)	28 (12 months) 19/9	47.9 ± 11.7 not reported	1.0 500	20	Response rates $HRSD_{28}$: 35,7% Remission rates Not reported

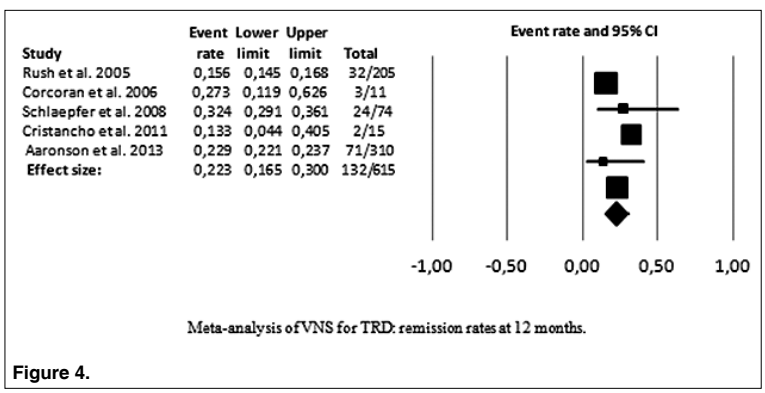

Figure 4.

heterogeneity, attributed by the study Lozano et al. 2012. (Figure 5).

Adverse effects

Among the VNS studies, the most common adverse effects are related to the respiratory system (voice alterations, pharyngitis, dyspnea, coughing) and digestive system (dysphagia, dyspepsia, nausea) at rates ranging from 2% to 23%. Serious adverse events included suicide (0,9%), suicide attempt (3.6%), worsening of depression (7.2%) and mania (0.9%).

The principal adverse effects found in the DBS studies were pain at incision site, nausea and vomit (rates between 3.5% to 10%). Serious adverse events related are suicide (5.0%), suicide attempt (5.0%), and worsening of depression (5.0%).

Although studies of VNS have a relatively lower rate of serious adverse effects, there is clear evidence that their most common adverse effects are related to device placement, which still not been related to the DBS in works. Bias of samples (difference in sample size between studies, disease severity prior to intervention, selection of subjects - if they already had a previous history of suicide attempts) and of treatment (the majority of patients continued to use their antidepressant medications prescribed prior to surgical intervention - which does not rule out the improvement of depression by the usual treatment) need to be corrected in order to have a better conclusion about the serious adverse effects.

Table 2.
Characteristics of DBS selected studies

Authors	Demographics			DBS intervention		
	n (follow up) (n) Baseline depression	Age ± SD ♀/♂		Current Amplitude (mA) (V) (μs)	Frequency Widht (Hz)	Results
Kennedy et al. (2011)	20 (36 - 72 months) 24.4 ± 3.5	47.4 ± 10.4	11/9 - 90	- 3.5-5	130	Response rates $HRSD_{17}$: 3 years: 75% Last follow-up: 64.3% Remission rates $HRSD_{17}$: 3 years: 50% Last follow-up: 42.9%
Lozano et al. (2012)	21 (12 months) 27.6 ± 4.5	47.3 ± 6.1	13/8 2.5-7 140	4.2-5.2 65-182	110-	Response rates $HRSD_{17}$: 6 months: 48% 12 months: 29% Remission rates Not reported
Holtzheimer et al. (2012)	17 (24 months) 23.9 ± 3.1	42.0 ± 8.9	10/7 4-10 91	-	130	Response rates MADRS: 6 months: 41% 1 year: 36% 2 years: 92% Remission rates 6 months: 18% 1 year: 36% 2 years: 58%

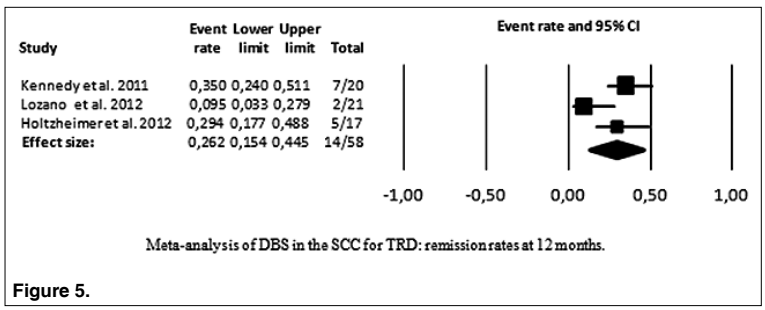

Figure 5.

Discussion

With a mean prevalence of 10%, MDD tends to remain one of the most cases of disability in years to come[1,2]. With a remission rate of only 30% and a response to conventional antidepressants between 45 to 55%, efforts should be made in prevention, screening, research and interventions in order to seek improvement in the quality of life and treatment of these patients. Among the neurosurgical interventions, VNS studies were selected to the systematic review because it has been FDA approved since 2005 as a long-term adjuvant therapy among patients with chronic or recurrent depression who did not respond adequately to conventional antidepressants. From the DBS studies, those that are implanted in the SCC region have been selected because present more studies, and for being one of the most eloquent areas in the pathophysiology of depression[42]. The studies analyzed presented heterogeneities related to the variability of depression scales used, differences in epidemiological profiles (age, gender ratio, predominance of women in all studies) and pathological characteristics of the patients (studies do not clarify whether or not there are comorbidities psychiatric disorders such as personality disorders, psychosis, the overlapping of a mixed-mood disorders such as bipolar disorder, all of which may aggravate the patient's treatment process.

Regarding the study designs, only one randomized clinical trial of VNS was found, the others were characterized as before-after study, not able to compare the effectiveness of the intervention *versus* placebo, which does not constitute the best model to estimate

The potential for causality. The lack of randomization, the rigorous selection of the participants and the intense follow-up, favors the occurrence of the Hawthorne effect. The effectiveness between VNS and DBS for the treatment of TRD presented a relative similarity of results between the methods (response of 42% of VNS x 37% DBS; remission of 22.3% VNS x 26.2 DBS), although the mechanism and the sites of action are different.

Of the adverse effects reported, we observed that those related to DBS presented higher severity, due to the greater invasion of the method. Suicide was present in both methods. In the DBS, it corresponded to 5% (2 cases), while in the VNS, 0.9% (6 cases).

With regard to cost, it is known that the implementation of DBS is above 100,000 dollars, because in addition to the technological refinement of the device, a more sophisticated contribution of neuroimaging, such as MRIfunctional, can be used to ascertain the location More eloquent for placement of the implant. It is also possible to establish the location of the implant by the frequencies and neuronal sound transmissions obtained through the capture of the implant electrodes during the procedure. The VNS implantation exceeds $ 25,000, is less invasive, and the surgery time is shorter, approximately 2 hours.

Conclusion

Individual analysis of clinical trials demonstrate that both VNS and DBS are promising features of TRD treatment, especially in the short and medium term, however most clinical trials are not controlled and randomized. The meta-analysis revealed a high heterogeneity, due to the reduced number of clinical trials, technical differences and selection bias, situations that could be solved from controlled and randomized multicenter studies.

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