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Trigeminal Nerve Stimulation for Major Depressive Disorder: An Updated Systematic Review

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Abstract

Context: Trigeminal nerve stimulation (TNS) is a promising non-invasive brain stimulation intervention. The TNS has been proposed for major depressive disorder (MDD) with auspicious results. The aim of this study was to review the literature on TNS for MDD.
Evidence Acquisition: Systematic review, using MEDLINE and EMBASE, of first articles available until 22nd of April 2016.
Results: We included seven studies; six of them were open-label studies and one sham-controlled randomized double-blinded trial. Most studies had small sample sizes. Two studies were on MDD with comorbid posttraumatic stress disorder and one study focused on the elderly population. Two different protocols of stimulation were reported. Studies had interesting positive results for treating MDD.
Conclusions: The TNS was reported to be well tolerated, with no severe adverse effect reported, and had impressive results for MDD. This promising, safe and easy-to-use new neuromodulation technique could be a useful tool for MDD treatment. However, the results reported in the studies performed so far must be analyzed under the strict limitations of the study design. Most of the studies on TNS are case studies or open-label trials with very small sample sizes. We acknowledge that it is the time to initiate more rigorous sham-controlled trials to better understand the huge potential involved with this technique, which could lead to the development of more accessible, easy-to-use, safe and non-invasive technology.

Keywords: Depression, Major Depressive Disorder, Trigeminal Nerve Stimulation, Cranial Nerve Stimulation, Non-Pharmacological Therapies, Systematic Review

1. Context

Trigeminal nerve stimulation (TNS) is a novel neuromodulation technology, recently described for neurological and psychiatric disorders such as epilepsy and major depressive disorder (MDD). It is hypothesized that the use of electrical stimulation over cranial nerves could neuromodulate cortical and subcortical areas related to neuropsychiatric disorders, such as the amygdala, insular cortex, prefrontal cortex, hippocampus, thalamus, locus coeruleus, nucleus of the solitary tract, and the anterior cingulate cortex (1, 2), called the bottom-up mechanism, in which the stimuli propagates from the cranial nerve in the direction of the brainstem and central areas (3). The neuromodulatory effect of TNS over these areas has been evaluated for MDD in different protocols with interesting positive results. We hereby present a short-review on TNS for MDD.

2. Evidence Acquisition

A systematic review according to the recommendations of the Cochrane group and to the PRISMA guidelines was conducted (4). Two authors performed independent systematic reviews and data extraction, and discrepancies were resolved by consensus.

We reviewed the MEDLINE and EMBASE databases using the key words: 1) "trigeminal nerve stimulation", 2) "TNS", 3) "trigeminal stimulation", 4) "eTNS", 6) "major depressive disorder", 7) "depression", 8) "depressive disorder" and 9) "treatment-resistant depressive disorder". The Boolean terms were imputed: [(1) OR (2) OR (3) OR (4)] AND [(6) OR (7) OR (8) OR (9)]. We searched for publications listed in MEDLINE up to 22nd of April 2016.

2.1. Eligibility Criteria

We adopted the following inclusion criteria: 1) Manuscript written in English 2) Randomized, sham-controlled trials; 3) Provided data (on the manuscript or upon request) for the estimation of the main outcomes, i.e., mean (SD) values and response and remission rates. We included series of cases, non-controlled trials and randomized controlled trials. We excluded trials assessing conditions other than MDD or interventions other than TNS and case reports.

2.2. Data Extraction

The following variables were extracted according to a structured checklist previously elaborated by the authors: 1) metadata (i.e., authorship, publication date, etc.); 2) demographics (i.e., sample size in each group, age, gender); 3)

characteristics of the TNS technique (i.e., frequency; intensity; pulse duration; time period of stimulation; number of sessions;); 4) study design (i.e. open-label study or randomized sham-controlled study); 5) response and remission rates; 6) adverse effects and dropout rates.

3. Literature Review

Our systematic review yielded 35 studies after duplicates were removed. Among them, 28 articles did not match the eligibility criteria. Seven studies were included (Table 1).

Stimulation protocols were divided into protocols I and II. Both protocols had the following stimulation parameters: frequency of 120 Hz, asymmetrical alternate current, pulse duration of 0.25 ms and intensity established based on individual sensitivity and pain threshold. Stimulation was delivered in order to achieve the sensitivity threshold without causing pain. The first protocol was performed during an eight-hour session, during sleep, for eight weeks, with a 30 seconds on/30 seconds off cycle. The second protocol was performed in 30-minute sessions, for 10 weekday sessions for two weeks, of continuous stimulation.

The stimulation of the supraorbital branch of the trigeminal nerve was at first described for treatment-resistant epilepsy disorder patients by DeGiorgio and collaborators (5), with interesting results, and later evaluated in a randomized controlled trial (6). The TNS was performed at home, in an eight-hour session, during sleep and for eight weeks, with improvements observed for refractory epilepsy. Following the studies on epilepsy, Schrader (7) and colleagues (8) reported their findings firstly from a pilot study with five patients with a mean age of 49.6 years and later from an open-label trial with 12 patients that underwent TNS by the nocturnal protocol for 55 sessions during eight weeks with impressive positive results (response rates of 75% and 54.5% in the HDRS-17, respectively). Following these studies, Shiozawa and collaborators (9) investigated the use of TNS for MDD with changes to the stimulation protocol. The TNS was performed in 30-minute sessions for ten sessions during two weeks. The on/off cycle used in the previous studies was changed for a continuous stimulation for 30 minutes. Firstly, an open-label trial was performed (9) with 11 patients (mean age of 50.36 year) in order to observe the effect of the reduced session of TNS and the authors reported great results with the technique, with a mean reduction of 5.72 points in HDRS-17, with all patients presenting a reduction of at least 50% of the depressive symptoms and ten patients (90.9%) presenting remission of depressive symptoms as defined by less than eight points in HDRS-17. In sequence, the same group conducted a randomized, sham-controlled double-blinded study with 40 patients (mean age of 47.15) with 20 patients in each group, performing the same 10-session protocol. The authors reported that despite a great placebo effect, a difference of 6.36 points in HDRS-17 between the sham and the active group was obtained ($F = 6.38, df = 2, P = 0.0033$) with a maintenance of the clinical effect for one month after the last day of stimulation.

Trevizol and colleagues later evaluated the safety and efficacy for the elderly in an open-label trial with ten patients (mean age 73 years), reproducing the results observed in younger patients, with 80% response rate and 40% of remission rate by the HDRS-17. The TNS was well tolerated with no severe adverse effects reported even for this population. Due to common pathways involved in anxiety symptoms, depressive symptoms and trauma-related disorders, Cook et al. (10) and Trevizol et al. (11, 12) performed studies on TNS for comorbid MDD and Posttraumatic Stress Disorder with twelve and five patients, respectively. Both groups reported their positive findings on depressive, anxiety and the core symptoms of Posttraumatic Stress Disorder (PTSD), enhancing the possibilities of uses in neuropsychiatric disorders.

Following the hypothesis that subcortical and cortical areas such as the amygdala, hippocampus, brainstem, locus coeruleus and nucleus of solitary tract could be stimulated trough the trigeminal nerve transcutaneously, the technique was used for the treatment of other neuropsychiatric disorders such as panic disorder (13), generalized anxiety disorder (14), irritable bowel syndrome (15), fibromyalgia (16, 17), attention-deficit/hyperactivity disorder (18) and social anxiety disorder (19). The impact on quantitative electroencephalography was reported in one patient with MDD treated with TNS, with changes that correlated to the improvements in depressive symptoms (20). The authors also reported one case of MDD during pregnancy with complete remission of depressive symptoms without any pharmacological intervention, with no unwanted consequences for childbirth or newborns (21). The TNS was reported to be a well-tolerated technique, with no severe adverse effect reported, and to have impressive results for MDD. Previous studies on the impact of TNS on cognition reported no changes at cognitive evaluations pre and post stimulation (22) and unlike what can be observed with continuous current techniques such as transcranial direct current stimulation, no skin lesions were reported (23). This promising, safe and easy-to-use new neuromodulation technique could be a useful tool for psychiatric disorders treatment, given the positive results reported so far on a variety of disorders.

However, the results reported in the studies performed so far must be analyzed under the strict limitations of the

Table 1. Study Characteristics from the Seven Trials Included in the Systematic Review

Study	Study Design and (No.)	Mean Age (SD)	Percentage of Females	Psychiatric Comorbidities	TNS Protocol	Results for MDD Symptoms
Schrader, 2011	Open-Label Trial (5)	49.6 (10.9)	60%	None	I	HDRS-28: response 75% BDI: response 100%
Cook, 2013	Open-Label Trial (11)	48.1 (8.3)	63%	None	I	HDRS-17: response 54,5% and remission 36.4% BDI: response 63.6%
Shiozawa, 2014	Open-Label Trial (11)	50.36 (11.8)	90.9%	None	II	HDRS-17: response 100% and remission 90.9%
Shiozawa, 2015	RCT (40)	47.15 (12.05)	65%	None	II	Mean difference between groups of -6.36 (F = 6.38,df = 2, p=0.0033)
Trevizol, 2016	Open-Label Trial (10)	73 (7.4)	70%	None	II	HDRS-17: 80% response and 40% remission
Cook, 2016	Open-Label Trial (12)	52.8 (13.7)	66.6%	PTSD	I	HDRS-17: 42% response and 25%remission
Trevizol, 2016	Open-Label Trial (5)	41.6 (6.02)	80%	PTSD	II	HDRS-17: 80% response and 40% remission

Abbreviations: df, degrees of freedom; HDRS-17, 17-item hamilton depressive rating scale; MDD, major depressive disorder; No.,number of subjects included; PTSD, post-traumatic stress disorder; RCT, randomized clinical trial; SD, standard deviation; TNS, trigeminal nerve stimulation.

study designs. Most of the studies on TNS are case studies or open-label trials with very small sample sizes and although they evaluate TNS for many psychiatric disorders, most of them have very similar symptoms, such as PTSD, panic disorder, fibromyalgia, MDD and GAD. Regarding the limitations here and the potential benefits of TNS, we acknowledge that it is time to initiate more rigorous sham-controlled trials to better understand the huge potential involved with this technique, which could lead to the development of accessible, easy-to-use, safe, and non-invasive technology.

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Footnote

Authors' Contribution: All authors participated in the literature review and manuscript elaboration and approved the manuscript and agreed with its submission.

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