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Review Article

Transcutaneous Auricular Vagus Nerve Stimulation for Major Depressive Disorder: An Updated Systematic Review

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Keywords

- Depression; Major depressive disorder; Trigeminal nerve stimulation; Cranial nerve stimulation; Non-pharmacological therapies; Systematic review

Abstract

Introduction: Major depressive disorder (MDD) is one of the most prevalent of the psychiatric illnesses, with a refractoriness rate up to 30%. Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel neu-romodulation strategy proposed for MDD based on the bottom-up mechanism, which involves the stimulation of the vagus nerve leading to further modulation of impaired brain areas. If effective, tVNS has the potential to increase response and remission rates in patients with psychiatric and neurological disorders.

Objective: We hereby present a systematic review on taVNS for MDD.

Methods: A systematic review was conducted, according to the recommendations of the Cochrane group and to the PRISMA guidelines. Two authors performed independent systematic reviews and data extraction, and any discrepancy was resolved by consensus. Systematic review was performed using MEDLINE and EMBASE from the first article available until April 22, 2016.

Literature Review: We included four studies: one of them was a non-randomized single-blinded controlled trial, one non-randomized controlled study, one open-label study and one sham-controlled randomized double-blinded trial. Most studies had small sample sizes (total of 258, from 12 to 160). Studies reported thrilling posi-tive results for treating MDD with some differences regarding stimulation protocols. taVNS was reported to be safe, with no severe adverse effects reported.

Conclusions: The possibility of using the auricular branch of the vagus nerve enables easier access for pa-tients with psychiatric disorders. However, those results must be analyzed under the strict limitations the study designs have. Most of the trials here described have small sample sizes and only one was a randomized, place-bo-controlled clinical trial. The stimulation parameters varied greatly among the studies and it is conceivable that there may be more ideal stimulation parameters that might result in improved efficacy and/or side effects. Therefore, more rigorous sham-controlled trials are necessary in order to better understand the huge potential involved with this technique.

INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent of the psychiatric illnesses [1] and is the leading cause of disability for people aged between 15 to 44 years in the United States, with levels of refractoriness as high as 30% after the use of three antidepressant medications [2,3]. New therapeutic strategies have been proposed in order to enhance response and remission rates. Vagus nerve stimulation (VNS) involves the direct stimulation of the vagus nerve leading to further modulation of impaired brain areas related to psychiatric disorders [4,5], such as the solitary tract nucleus, dorsal raphe, locus coeruleus, parabrachial area, amygdala, nucleus accumbent, hippocampus and the dorsolateral prefrontal cortex (DLPFC) [6]. Transcutaneous auricular vagus nerve stimulation (taVNS) relies on the fact that the vagus nerve auricular branch is distributed on the surface of the ear and it could be used for stimulation [7]. If effective, tVNS has the potential to increase the use of VNS in patients with psychiatric and neurological diseases. We hereby present a systematic review on taVNS for (MDD).

MATERIAL AND METHODS

A systematic review was conducted, according to the recommendations of the Cochrane group and to the PRISMA guidelines [8]. Two authors performed independent systematic reviews and data extraction, and any discrepancy was resolved by consensus.

We reviewed the MEDLINE and EMBASE databases using the key words: (1) “transcutaneous vagus nerve stimulation”, (2)”transcutaneous vagal nerve stimulation”, (3) “auricular vagus nerve stimulation”, (4) transcutaneous auricular vagus nerve stimulation”, (5) “auricular vagal nerve stimulation”, (6) “ear vagus nerve stimulation”, (7) “tVNS”, (8) “taVNS”, (9) “Major Depressive Disorder”, (10)“Depression”, (11)“Depressive Disorder” and (12)“Treatment-Resistant Depressive Disorder”. The Boolean terms were imputed: [(1) OR (2) OR (3) OR (4) OR (5) OR(6) OR(7) OR (8)] AND [(9) OR (10) OR (11) OR (12)]. We searched for publications listed in MEDLINE and EMBASE up to April 22, 2016.

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 of response and remission rates. We included series of cases and non-controlled trials and randomized controlled trials. We excluded trials assessing conditions other than MDD or interventions other than taVNS and case reports.

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 taVNS 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.

Literature Review

Our systematic review yielded 28 studies after duplicates were removed. Among them, 24 articles did not match eligibility criteria (eleven were not about MDD, five not original, one case report, four not in humans). Four studies were included. One of them was a nonrandomized single-blinded controlled trial, one nonrandomized controlled study, one open-label study and one sham-controlled randomized double-blinded trial. Most studies had small sample sizes (total of 258, from 12 to 160). Studies reported thrilling positive results for treating MDD with some differences regarding stimulation protocols (Table 1).

RESULTS

Hein and colleagues (2013) [9] evaluated a taVNS protocol for MDD using the auricular branch of the vagus nerve in the outer ear in a randomized controlled add-on trial. Patients were stimulated for 15 min once or twice a day, five days per week for two weeks. Active treatment group presented markedly clinical amelioration of symptoms in comparison to sham stimulation as assessed by BDI, with a reduction of 12.6 points in the active group [9].

Fang and colleagues [10] investigated how taVNS can modulate the default mode network (DMN) functional connectivity (FC) in mild or moderate major depressive disorder (MDD) patients through functional Magnetic Resonance Imaging (fMRI) in 49 MDD patients, single-blinded to receive either active or sham tVNS as sole treatments for MDD. Authors reported significant changes in medial prefrontal cortex, anterior cingulate cortex, precuneus, posterior cingulate cortex, bilateral parietal cortex, areas related to depressive symptoms, corroborating the hypothesis of bottom-up stimulation, using the vagus nerve for modulatory effect to cortical and subcortical areas related with functions usually altered in MDD.

Rong and colleagues reported results from studies involving part of the data initially reported by Fang and colleagues (49 patients) [10]. Authors reported their findings in two cohorts. The first one focused on active stimulation enrolling 91 patients that received self-applied taVNS for 12 weeks. The second cohort was composed by 69 patients that performed self-applied sham taVNS for 4 weeks, followed by eight weeks of active stimulation. Authors reported a 80% response rate and 39% remission rate for the active group by the end of the 12 weeks of stimulation and 0% response rate after the 4 weeks of sham stimulation, with a significant difference between sham and active groups.

Trevizol and colleagues (2015) [7] recently proposed a new taVNS assessment, using the auricular branch of the vagus nerve. The authors proposed a stimulation protocol through electrodes placed bilaterally over the mastoid process area, juxtaposed to the ear, near the tympanomastoid fissure. Authors reported their findings in an open-label clinical trial with 12 patients. All of them reported a clinical response defined as a reduction >50% of the HAMD score, and a remission rate of 41.6% [11].

Adverse effects were reported from all studies, however with no severe manifestations. taVNS was reported to be safe and well tolerated, with most common adverse effects being mild to moderate headaches, nauseas, tinnitus an diurnal sleepiness.

Table 1: Study characteristics from four clinical trials included in the systematic review.

Study	Study Design and N	taVNS location	F / Wave width	I (mA)	Duration	Primary outcome
Hein et al. (2013)	randomized controlled trial (37)	outer ear	1.5 Hz / n.a.	0.13	15 min 1 or 2x/d 5 d/w, for 2w	BDI: Active: reduction of 12.6 points Sham: reduction of 4.4 points (p = 0.004)
Fang et al. (2015)	single-blinded clinical trial (49)	concha area	20 hz / <1ms	4–6	30 min 2x/d, 5 d/w, for 4 w	HAMD: Active group: reduction of 13. 5 points. Sham: reduction of 5.56 (p=0.002)
Rong et al. (2016)	nonrandomized, controlled study (160)	concha area	20Hz / 0.2 ms	4–6	30 min 2x/d, for 12w	HAMD-24: Active group: 80% response rate and 39% remission rate Sham: 0% response rate
Trevizol et al. (2016)	Open-label trial (12)	mastoid process area	120 Hz / 0.25 ms	12	30 m, 1 session/d for, 5d/w, for 2 weeks	HAMD: 100% response rate and 41.6% remission rate

Abbreviations: N: Number Of Subjects Included; taVNS: Transcutaneous Auricular Vagus Nerve Stimulation; HAMD: Hamilton Depressive Rating Scale; BDI: Beck Depression Inventory; F: Frequency; I: Intensity; D: Days; W: Weeks; N.A.: Not Available.

Following the enthusiastic results reported with VNS for MDD[12,13-18], studies focused on developing new ways for assessing the vagus nerve transcutaneously have been performed. The idea is to obtain the clinical effects observed with VNS with more feasible and practical technical parameters. The auricular branch of the vagus nerve, also known as Arnold's nerve or Alderman's nerve, originates in the superior ganglia of the vagus nerve and penetrates the mastoid canaliculi, accessing the temporal bone and emerges through the tympanomastoid fissure, between the mastoid process and the tympanic portion of the temporal bone and enervates the skin over the mastoid process in the retroauricular region, the posterior wall of the ear canal and part of the concha area [5]. The positive clinical results from clinical trials here discussed, with the neuroimaging findings reported by Fang and colleagues [10] corroborate the hypothesis that the stimulation of the auricular branch of the vagus nerve could propagate to subcortical and cortical areas.

DISCUSSION AND CONCLUSIONS

The development of an easy access, with an easy-to-use, safe and non-invasive technology, using the auricular branch of the vagus nerve, enables easier access for patients with psychiatric disorders. The studies conducted using taVNS for the treatment of MDD patients have found promising results. However, the results reported in the investigations performed so far must be analyzed under the strict limitations the study designs have. The trials here reported have small sample sizes and only one was a randomized, placebo controlled clinical trial. The stimulation parameter varied greatly among the studies and it is conceivable that there may be more ideal stimulation parameters that might result in improved efficacy and/or side effects. Therefore, more rigorous sham-controlled trials to better understand the huge potential involved with this technique are necessary.

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