

# Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: a systematic review

Estimulação transcutânea do nervo vago e do nervo trigêmeo para o tratamento de distúrbios neuropsiquiátricos: revisão sistemática

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## ABSTRACT

We reviewed trigeminal nerve stimulation (TNS) and transcutaneous vagus nerve stimulation (tvNS). All techniques have shown preliminary promising results, although the results are mixed. **Method:** We performed a systematic review of the Medline and Embase databases, with no constraint to dates, through June 2013. The keywords were [(1) trigeminal nerve stimulation OR (2) cranial nerve OR (3) trigemin\* OR (4) transcutaneous VNS OR (5) transcutaneous cranial nerve stimulation] and (6) mental disorders. **Results:** We included four preclinical and clinical five studies on TNS. All clinical data were based on open-label studies with small samples, which diminished the external validity of the results, thus reflecting the modest impact of TNS in current clinical practice. Of the tvNS clinical trials, three assessed physiological features in healthy volunteers, and one examined patients with epilepsy. **Conclusion:** TNS and tvNS improve treatment of particular neuropsychiatric disorders such as depression.

**Keywords:** transcutaneous nerve stimulation, trigeminal stimulation, neuropsychiatric disorders.

## RESUMO

O uso de estimulação de nervos cranianos de maneira transcutânea tem sido uma estratégia em desenvolvimento recente. Diferentes estudos apontam para resultados clínicos favoráveis no tratamento de diferentes quadros neuropsiquiátricos. **Método:** Revisão sistemática da literatura com base nas bibliotecas eletrônicas Medline e Embase, sem restrição de data inicial, até agosto de 2013. Os termos de busca utilizados foram [(1) trigeminal nerve stimulation OR (2) cranial nerve OR (3) trigemin\* OR (4) transcutaneous VNS OR (5) transcutaneous cranial nerve stimulation] and (6) mental disorders. **Resultados:** Incluímos quatro estudos pré-clínicos e cinco estudos clínicos abordando estimulação do nervo trigêmeo. Todos os estudos foram abertos, com pequenas amostras, o que reduz a validade externa dos dados, refletindo a ainda incipiente atuação da técnica, apesar de promissora. Considerando-se a estimulação do nervo vago, três artigos avaliaram aspectos fisiológicos em voluntários saudáveis e um artigo estudou pacientes com epilepsia. **Conclusão:** As estratégias de estimulação transcutânea de nervos cranianos, apesar de incipiente, tem demonstrado resultados clínicos favoráveis no tratamento de distúrbios neuropsiquiátricos.

**Palavras-chave:** estimulação transcutânea de nervos cranianos, estimulação do nervo trigêmeo, distúrbios neuropsiquiátricos.

Different nonpharmacological brain stimulation techniques have been used in clinical neurology and psychiatry, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), stereotactic surgery and trigeminal

nerve stimulation (TNS)<sup>1,2,3,4,5</sup>. Theoretically, such techniques present different mechanisms of action. For instance, ECT nonspecifically increases brain activity and excitability through controlled, electrically induced seizures; rTMS through an electromagnetic field induces intracortical electric currents which may modulate neuronal activity focally; and

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tDCS modifies brain excitability through weak, direct electric currents. It is assumed that such techniques are top-down – *i.e.*, they indirectly modulate subcortical activity through primary network changes in cortical activity.

Conversely, both trigeminal and vagus nerve stimulation modulate brain activity through bottom-up mechanisms – that is, by stimulating cranial nerves whose nuclei lie in the brain stem, which, in turn, make extensive connections to the limbic cortex and monoaminergic nuclei. The vagus nerve, for instance, innervates the nucleus tractus solitarius bilaterally, which is connected to regions of the brain that are associated with the regulation of mood, emotion, and seizure activity<sup>6</sup>.

Similarly, the trigeminal nerve has extensive connections to the brainstem and other brain structures. The trigeminal nerve has 3 major sensory branches over the face, all of which are bilateral. The trigeminal ganglion, located in the Meckel cave (cavum trigeminale), projects to the trigeminal nucleus which makes reciprocal projections to the nucleus tractus solitarius, locus coeruleus, and reticular formation<sup>7</sup>.

The aim of this review was to systematically review all clinical and preclinical studies on both transcutaneous trigeminal (TNS) and vagus (tVNS) nerve stimulation as to understand the therapeutic and mechanistic aspects of these interventional techniques in the treatment of neuropsychiatric disorders. This is important because these techniques might modulate brain structures through transcutaneous electric nerve stimulation, although this has not been systematically assessed yet.

We performed a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement<sup>8</sup>. The methodological details are discussed below.

## LITERATURE REVIEW

We searched the Medline and Embase databases for the keywords: [(1) trigeminal nerve stimulation OR (2) cranial nerve OR (3) trigemin\* OR (4) transcutaneous VNS OR (5) transcutaneous cranial nerve stimulation] and (6) mental disorders. These terms were selected even in the absence of specific Mesh terms (items 1, 3, 4 and 5) as to increase sensitivity. The date limits were from the first date available to June 2013. We also looked for potential relevant articles in the study references and contacted experts in the field.

## ELIGIBILITY CRITERIA

We adopted the following inclusion criteria: (a) manuscript written in English, Spanish, or Portuguese; and (b) clinical trials; interventional studies; preclinical studies.

Therefore, other types of articles, such as case reports and editorial letters, studies that assessed conditions other than neuropsychiatric disorders and studies that assessed interventions other than tVNS and TNS were excluded.

## DATA EXTRACTION

The following variables were extracted per a structured checklist that we developed:

(a) Overview – study design, authors, year of publication, technique summary, other relevant data;

(b) Demographics – total sample (number), age (years), gender (percentage females);

(c) Assessment of mental disorder – method of diagnosis (clinical interview, structured checklist); and

(d) Outcomes – description of each study's principal results.

## QUALITY ASSESSMENT

To assess the methodological heterogeneity between studies, each report was evaluated with regard to quality, focusing on 2 critical methodological issues:

(a) Internal validity – for clinical studies, we followed the Cochrane guidelines to determine the risk of bias in randomization/allocation (selection bias), blinding and control comparison (performance bias), and outcome assessment and reporting (attrition, measurement, and reporting biases).

(b) Construct validity – we determined whether the operational criteria for mental disorder, vagus nerve stimulation, and trigeminal nerve stimulation were appropriate – *i.e.*, whether each study fulfilled the following criteria: (i) clinical or preclinical studies that focused on transcutaneous cranial nerve stimulation; (ii) articles on mental disorders.

## QUANTITATIVE ANALYSIS

Anticipating that there would be few studies and that between-study heterogeneity would be important, our initial aim was not to perform a quantitative analysis, such as meta-analysis and meta-regression. Instead, we reviewed the main findings of the studies and addressed their limitations.

## STUDIES OVERVIEW

Our initial search yielded 389 references, 288 of which were initially excluded, based on eligibility criteria, leaving 101 articles. In a subsequent analysis 71 references were excluded after the abstracts were reviewed. Ultimately, 13

studies were included: 9 on TNS (5 clinical trials, n=41 subjects and 4 preclinical studies, *i.e.*, studies evaluating the effects of TNS over animal models) and 4 clinical studies (n=84 subjects) on tVNS.

## TRIGEMINAL NERVE STIMULATION

The initial animal studies of TNS focused on epilepsy. First, experimental models were based on pentylenetetrazole-induced seizure in conscious adult rats. This chemical causes a generalized tonic-clonic seizure with a 4-second period at a frequency of 4 per minute for approximately 2 hours. After the drug was administered, TNS was performed, reducing seizure activity in the thalamus and neocortex. The clinical response of TNS depends on the stimulus frequency and intensity [9]. In humans, TNS is performed through electric stimulation at 120 Hz with a pulse wave duration of 250 microseconds and cycle of 30 seconds. Electrical stimuli creates an asymmetrical biphasic pulse wave, adjustable from 0 to 100 mAs.

In an open-label study (n=07), DeGiorgio et al. evaluated the efficacy of TNS in epilepsy. Fifty-seven percent of the sham experienced a  $\geq 50\%$  reduction in seizures after TNS. This pilot exploratory study indicated that transcutaneous stimulation of the supraorbital and infraorbital divisions of the trigeminal nerve was safe and well tolerated for the 3- and 6-month treatment periods<sup>10</sup>. In a 12-month follow-up open-label trial (n=14), the authors reported a satisfactory result of TNS for epilepsy, which effected a mean reduction in seizure frequency of 66% after 3 months, 66% at 6 months, and 56% at 12 months<sup>11</sup>.

Some years later, this group published another open-label exploratory study on external TNS in 14 subjects, focusing on its side effects. Supraorbital and infraorbital TNS was well tolerated, and there were no significant acute or long-term adverse effects on heart rate or systolic or diastolic blood pressure and no major clinical side effects<sup>12</sup>.

There are few publications on the use of TNS for psychiatric disorders. In a recent analysis, TNS was concluded to be a valuable and promising adjuvant to the current therapeutic management of depressive disorders<sup>7</sup>.

In a recent study, Shraeder et al. described 5 patients (60% female; mean age 49.6 years) with treatment-resistant depression who received TNS over an 8-week follow-up<sup>7</sup>. Subjects had electrodes (Superior Silver 1.25-in. diameter, Tyco) placed on their foreheads to stimulate the V1 branches of the trigeminal nerve bilaterally for approximately 8 hours each night (8 weeks; ~55 nights). Current was adjusted to maintain comfortable but perceptible levels of stimulation (EMS7500 Stimulator, TENS Products, Inc. Granby, CO, USA). As a result, remission rates of depressive symptoms reached 70% in the 2-month follow-up.

TNS has been generally well tolerated in research protocol studies<sup>13</sup>. Side effects are infrequent, transient, and mild and include skin irritation, tingling, forehead pressure, and headache. DeGiorgio et al. reported no effects by electrocardiograph with regard to heart rate or systolic or diastolic blood pressure and conclude that it was safe hemodynamically<sup>11</sup>.

## TRANSCUTANEOUS VAGUS NERVE STIMULATION (TVNS)

Stefan and colleagues verified the efficacy of tVNS in resistant epilepsy in 10 patients. In this open-label trial, 5 of 7 patients experienced a decrease in seizure frequency after a 9-month follow-up<sup>14</sup>. The safety of tVNS has been reported in phase I trials<sup>15,16,17,18,19</sup>.

A recent randomized controlled pilot study<sup>15</sup> showed for the first time an antidepressant effect of a non-invasive auricular electrical nerve stimulation. A total of 37 patients suffering from major depression were included in two randomized sham controlled add-on studies, and the patients were stimulated five times a week on a daily basis for the duration of 2 weeks. The antidepressant effect measured by the Beck Depression Inventory (BDI) was very significant: Patients treated with tVNS gained 12.6 (standard deviation (SD) 6.0) points, compared to 4.4 (SD 9.9) points of the sham-stimulated patients (Tables 1 and 2).

## STUDY ANALYSIS

Our literature review comprised 9 clinical and preclinical studies on TNS and 4 clinical studies on tVNS per the study design. The relative lack of data reflects the recent development of these interventions and the need for consistent interventional studies to determine their clinical value and limitations.

We retrieved 4 preclinical and 5 clinical studies on TNS. All clinical data were based on open-label studies with small samples (total of 44 patients in the clinical studies), which precluded the use of TNS as a tool for clinical practice.

There were 4 clinical studies on tVNS (total of 84 patients – 3 assessed physiological features in healthy volunteers and 1 examined epilepsy patients. One study was a crossover design, and the remaining trials were open-label studies, which also compromised their conclusions and analysis.

## ANATOMICAL CONSIDERATIONS

The basis for using cranial nerve stimulation as an “add-on” therapy for psychiatric disorders underscore the

**Table 1.** Overview of data extraction and quality assessment - Clinical Studies trigeminal enrv stimulation.

Authors	Study design	Subjects	Diagnosis / assessment	Intervention	Main Outcome	Biases Summary
DeGiorgio, 2006	Open Label Study	7	Epilepsy; Clinical assessment	TNS	57% of the sample experienced a $\geq 50\%$ reduction in seizures after TNS intervention.	Small sample size, poor demographical sample description, low impact of results generalizability.
Pop, 2011	Open Label Study	14	Epilepsy; Clinical assessment	TNS	No significant acute or long-term major adverse effects.	Small sample size, poor demographical sample description, low impact of results generalizability.
DeGiorgio, 2009	Open Label Study	13	Epilepsy; Clinical assessment	TNS	Mean seizure frequency reduction: 66% (3 m); 56% (6 m) and 59% (12 m).	Small sample size, poor demographical sample description, low impact of results generalizability.
Schraeder, 2011	Open Label Study	5	TRD / IDC-10; HDRS; BDI	TNS	Significant decreases in symptom severity were observed over 8 weeks.	Small sample size, low impact of results generalizability.
DeGiorgio, 2003	Open Label Study	2	Epilepsy; Clinical assessment	TNS	TNS was well tolerated and patients reported reductions in seizures during stimulation.	Small sample size, low impact of results generalizability.

importance of clearly understanding neuroanatomic pathways related to the stimulated nerve.

The trigeminal nerve is 1 of the 12 pairs of cranial nerves and has motor and sensory function. It originates from a motor nucleus and 3 sensory nuclei that extend throughout most of the length of the brain stem. The vagus nerve comprises motor and sensory fibers. The filaments of this nerve unite and form a flat cord that passes beneath the flocculus to the jugular foramen, through which it leaves the cranium.

The vagus and trigeminal nerves project directly to serotonergic and noradrenergic neurons in the brain, which generate specific neurotransmitters (serotonin and noradrenaline) that are linked to many neuropsychiatric disorders, such as mood and anxiety disorders. Other vagal and trigeminal neuronal projections are directed toward central brain stem structures, such as the nucleus solitarius, locus

coeruleus, and reticular formation, and to other limbic, sensory, cortical, and subcortical areas, such as the locus coeruleus, orbitofrontal cortex, insula, hippocampus, and amygdala. The propagation of electric stimuli through these neuronal projections from peripheral sites to the central nervous system has been proposed to constitute the neurobiological basis of central nervous system (CNS).

## THE “BOTTOM-UP”MECHANISM

In current neuromodulation scenario, clinical results have been working as trully hypothesis driven forces, *i.e.*, empirical observation and data analysis from different studies have been highlighting possible mechanisms related to the neurobiological functioning of neuromodulation

**Table 2.** Overview of data extraction and quality assessment - Clinical Studies trigeminal vagus nerve stimulation.

Authors	Study design	Subjects	Diagnosis / assessment	Intervention	Main Outcome	Biases Summary
Busch, 2012	Crossover	48	Health volunteers; study on pain physiology	tVNS	tVNS was related to an increase in mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity.	Small sample size, poor demographical sample description, low impact of results generalizability.
Stefan, 2012	Open Label Study	10	Pharmacoresistant Epilepsy; Clinical assessment	tVNS	7 patients concluded the trial and presented an overall reduction of 71.4% of seizure frequency after a 9-month follow up.	Small sample size, poor demographical sample description, low impact of results generalizability.
Dietrich, 2008	Open Label Study	4	Health volunteers; neuroimaging study on brain activation patterns	tVNS	A positive fMRI BOLD response was detected during stimulation in different brain areas.	Small sample size, poor demographical sample description, low impact of results generalizability.
Kraus, 2007	Open Label Study	22	Health volunteers; neuroimaging study on brain activation patterns	tVNS	fMRI BOLD-signal decreases in limbic brain areas. Increased activation was seen in the insula, precentral gyrus and the thalamus.	Small sample size, low impact of results generalizability.
Hein, 2013	Double-blinded sham controlled trial	37	Patients with depressive disorder	tVNS	In contrast to sham-treated patients, electrically stimulated persons showed a significantly better outcome in the BDI.	Small sample size, low impact of results generalizability.

strategies. The precise mechanisms by which CNS exerts its effects remain unknown. Empirical evidence has been reported, suggesting that CNS causes long-term neuroplasticity in the brain. Two chief explanations have been hypothesized for the effects of TNS, primarily from preclinical research. First, neuronal firing is suppressed during TNS in rats as soon as nerve stimulation begins<sup>20</sup>. Further, in humans, tVNS and TNS are typically provided on a continuous fixed-duty cycle, and in animal studies, there is a period during which the seizure threshold increases after each “on” cycle terminates<sup>8</sup>. There might also be effects of cranial nerve stimulation that last from tens of seconds to minutes and outlast the period of nerve stimulation. In addition, there appear to be long-term effects of cranial nerve stimulation that tend to decrease in over months to years<sup>15,16,17</sup>.

Electric stimulation provides direct modulatory effects in subcortical sites, *i.e.*, there are changes in cortical excitability. Neuroimaging studies corroborate these effects, showing neuronal activity changes in certain sites of brain, such as the amygdala, insula, precentral gyrus, hippocampus, and thalamus<sup>4,5,16,21</sup>. These neuroanatomical connections have been linked to the “bottom-up” mechanism of modulation by CNS<sup>9</sup>. According to this hypothesis, the propagation of electric stimuli follows an inverse path from peripheral nerves toward the brain stem and central structures, as discussed.

The centrifuges electric propagation throughout neurons contrasts with the well-known “top-down” mechanism of other modulation strategies, such as electroconvulsive therapy and transcranial magnetic stimulation, in which the stimulus acts first on central brain structures, with propagation later to peripheral sites.

## SUMMARY OF CURRENT CLINICAL USE OF TVNS AND TNS

Both TNS and tVNS are performed by the placement of a bipolar electrode transcutaneously over superficial branches of either trigeminal or vagus nerve, which results in further dissemination of a low-frequency electric pulse from the nerve toward the central nervous system. Electric stimulation of the nerve has direct modulatory effects in subcortical sites.

The use of cranial nerve stimulation in current psychiatric practice is sparse and still limited to a few research protocols. TNS and tVNS are recent interventions that causes minor adverse effects. A relevant feature is their transcutaneous-based stimuli, which stands for a non invasive procedure.

## FINAL REMARKS

TNS and tVNS are techniques that, despite their recent development, have elicited satisfactory outcomes in the past decade, which have engendered further research in many clinical situations. Additional controlled studies are needed to overcome the difficulties of standardizing and disseminating the technique. Long-term clinical outcomes and new applications for these techniques in other neuropsychiatric disorders will be invaluable in clinical practice. TNS and tVNS improve treatment of particular neuropsychiatric disorders such as depression, and their development will allow clinicians to intervene in neuroplasticity and neuromodulation.

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