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Electric Vagus Nerve Stimulation: Anew Neuromodulation in Medicine (Overview)

Pop-Jordanova Nada and Pop-Jordanov Jordan
Macedonian Academy of Sciences and Arts
Skopje, Bul. Krste Misirkov 2
E-mail: popjordanova.nadica@gmail.com

Abstract: *This article is anoverview of electrical vagal nerve stimulation used as neuromodulationin medicalpractice. The workshop of COST EMF-MED BM 1309 organized in Vienna this autumn was devoted to this topic as an additional tool in treating different disorders. In this paper some of the applications discussed in the workshop are presented. Additionally, we analyzed some of over 10.000 different publications in Medline. Additionally, we present our own experience with a similar method published recently.*
Vagal nerve stimulation (VNS) has a long history in medicine having different modes and names (acupuncture, acupressure, eastern healthy modes of gymnastics like yoga etc.). VNS is practically non-invasive, cheap and easy for application method. Future research is needed for evidence base.
Key words:*vagal nerve stimulation, medicine, disorders.*

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I. Introduction

The homeostasis, the balances of all bodily functions, depends mainly on the interplay between sympathetic and parasympathetic autonomous nerve systems.

The vagus nerve (veɪgəs), historically cited as the pneumogastric nerve, is the tenth cranial nerve. It is the longest nerve and belong to the autonomic nervous system in the human body. The vagus nerve has a main parasympathetic function but it also has a sympathetic function via the peripheral chemoreceptors.This nerve controls involuntary bodily functions, like motor functions in the diaphragm and stomach, heart functions and ear and tongue sensory functions.This means that the vagus nerve is responsible for varied tasks as heart rate, gastrointestinal peristalsis, sweating, and quite a few muscle movements in the mouth, including speech (via the recurrent laryngeal nerve). It also has some afferent fibers that innervate the inner (canal) portion of the outer ear and part of the meninges.

The vagus nerve is largely responsible for the mind-body connection since it goes to all the major organs (except adrenal and thyroid glands). It reaches the brain, gut (intestines, stomach), heart, liver, pancreas, gallbladder, kidney, ureter, spleen, lungs, fertility organs (female), neck (pharynx, larynx, and esophagus), ears, and tongue. When vagus nerve is not working properly, many digestive disorders could appear such as: dyspepsia, gastroparesis, esophageal reflux, ulcerative colitis, anorexia or bulimia.

Stimulating the vagus nerve the release of histamine by stomach cells is obtained, which helps release stomach acid. As a consequence, low stomach acidity is usually, in part, a vagus nerve problem. By releasing intrinsic factor, the vagus nerve also help the absorption of vitamin B12, which is important factor in erythropoiesis.

During emotional stress beside sympathetic system, excessive activation of the vagal nerve appeared too. Excessive nervus vagus stimulation can cause vasovagal syncope due to a sudden drop in cardiac output, causing cerebral hypoperfusion. Vasovagal syncope affects especially young children and women more than other people. It can also lead to temporary loss of bladder control under moments of extreme fear.

Vagus nerve stimulation

Vagal nerve stimulation (VNS) has a long history in medicine having different modes and names (acupuncture, acupressure, eastern healthy modes of gymnastics like yoga etc.).Since the vagus nerve is associated with many different functions and brain regions, research shows positive effects of vagal stimulation on a variety of conditions:Anxiety Disorders, Heart disease, OCD, Alzheimer's, Migraines, Fibromyalgia, Obesity, Tinnitus, Alcohol addiction, Autism, Bulimia, Multiple sclerosis, Chronic heart failure, Memory disorders, Mood disorders, Cancer,Bad blood circulation,Leaky gut, Severe mental diseases etc**.**However, not all of these conditions have an evidence-based medical aprouvement for benefit of stimulation therapy. The workshop of COST EMF-MED BM 1309 organized in Vienna this autumn was devoted to vagus nerve

stimulation as an additional tool in treating different disorders. In this paper some of the applications will be presented.

Vagus nerve stimulation (VNS) is a procedure that involves implantation of a device that stimulates the vagus nerve with electrical impulses.In conventional vagus nerve stimulation, a device is surgically implanted under the skin on the chest, and a wire is connecting the device to the left vagus nerve. The right vagus nerve is not used because it carries fibers that supply nerves to the heart.However, there is another, less invasive procedure using skin application of tools for vagus nerve stimulation, without surgical implantation.

Twenty years ago, the United States Food and Drug Administration (FDA) approved the use of VNS as a treatment for **epileptic seizures**. This approach is usedfor patients unsuccessfully treated with anti-epileptic drugs. In this context recently many authors [1, 2, 3, 4]published results obtained with this methodology in the treatment of refractory epileptic seizures, even in children.

Generally, the patient is placed under local anesthesia, and the 1.5-inch diameter device is implanted in the chest. The device is similar in size and function to a pacemaker; in fact, VNS devices have been referred to as the "pacemaker for the brain".

The pulse generator is implanted on the upper left side of the chest (Figure 1). The stimulator contains a battery, which can last from one to 15 years. When the battery is low, the stimulator is replaced with a less invasive procedure which requires only opening the chest wall incision.

Fig. 1 Pulse Generator

Fig.2 Lead

A second incision is made horizontally on the left side of the lower neck, along a crease of skin. This is where the thin, flexible wires that connect the pulse generator to the vagus nerve are inserted (Figure 2).The treating neurologist programs the stimulator with a small hand-held computer, programming software and a programming wand (Figure3).

Fig. 3 Programming Wand

Fig. 4 Magnet Bracelet

Additionally, patients are provided with a handheld magnet (Figure 4) to control the stimulator at home (which must be activated by the physician to magnet mode).

The goal of VNS is to reduce the number, length and severity of seizures. However, VNS is not successful in all patients. Recently, Bayasgalan B. et al. (2017) [5] published paper in which they explained how they could predict good responders to vagus nerve stimulation through slow cortical potentials in EEG records. This procedure mainly is safe, but minimal side effects are possible, such as: throat or neck pain, hoarseness, voice changes and coughing, headache, insomnia or muscle twitches.

Because the vagus nerve is associated with many different functions and brain regions, clinical research has been done to determine its usefulness in treating other illnesses, including various anxiety disorders[6], Alzheimer's disease, [7]obesity [8], alcohol addiction [9], chronic heart failure [10], asthmatic attacks [11], etc.

VNS has also been studied in small trials of people with neurodevelopmental disorders, generally who also have had epilepsy, including Landau-Kleffner syndrome, Rett syndrome, Asperger syndrome, autism spectrum disordersetc. [12].

It was proven that in people with fatigue, food sensitivities, anxiety, gut problems, brain fog, and depersonalization, the vagus nerve is almost always at play. These people have lower vagal tone, which means a lower ability to perform its functions. In all this condition, VNS could be applied.

Like electroconvulsive therapy**,** VNS works by using electricity to influence the production of brain chemicals called neurotransmitters. Because **depression** has been supposed to be the result of an imbalance in those chemicals, the VNS is used to treat severe depression [13]. Research showed that after one year of application20-30 percent of patients reported significant improvements, and half of these patients reported that their symptoms had nearly resolved completely. However, some other patients did not improve or their symptoms worsened. In patients with suicidal attempt, schizophrenia or bipolar disorder this kind of therapy is not applicable.

The fact that the vagus nerve is known to prevents **inflammation**, the VNS is used for treatment of severe inflammations, especially sepsis or rheumatoid arthritis. It is supposed that vagus alerts the brain and elicits anti-inflammatory neurotransmitters via the cholinergic anti-inflammatory pathway. Some implants are createdto stimulate the vagus nerve via electronic implants and showed a drastic reduction, and even remission, in rheumatoid arthritis, hemorrhagic shock, and other equally serious inflammatory syndromes [14, 15, 16, 17].

A study performed at the University of Virginia showed success in strengthening memory in rats by stimulating the vagus nerve, consolidating memories. Related studies were done on humans, opening promising treatments for conditions like **Alzheimer's disease**[18].

Chronic diseases such as diabetes mellitus are usually associated with a dysregulation of autonomic state, i.e., an imbalanced sympathovagal activity. A reduced vagal tone promotes autonomic neuropathy, impaired microcirculatory perfusion and upregulated pro-inflammatory pathways. In case of peripheral tissue trauma this may lead to **chronic leg ulcerations**. VNS is very promising in the treatment of wounds caused by diabetic neuropathy [19]. The same modality for vagus nerve stimulation the team from Vienna Technical University used in the treatment of dystonia [20]. Additionally, modulation of total heart rate variability (HRV), when corrected for changes in mean heart rate,could be obtained by VNS. It is especially needed in the treatment of diabetic patients.

It is known from physiology that vagus nerve is a chain component in**hormone's regulation.** Vagus Nerve Stimulation normalizes an elevated HPA axis (CRH, ACTH, and cortisol).The vagus nerve can help reduce pain [21], and this is the mechanism by which estradiol reduces pain in certain circumstances.Insulin activates the vagus nerve through a domino of steps leading to decreased glucose production by the liver.

In rats, the thyroid hormone (T3) increases appetite by activation of the vagus nerve, which also increases ghrelin.Besides influencing the release of oxytocin the vagus nerve is important for releasing testosterone. Testosterone can make people more aggressive, but this is not the case when the vagus nerve is functioning right.Proper functioning of the vagus nerve is important for the production ofGHRH (growth hormone releasing hormone) and IGF-1.

The vagus nerve can stimulate other hormones such as parathyroid hormone, which is important for the conversion of vitamin D3 to active vitamin D (1,25).

Newest approach to non-invasive vagus nerve stimulation is the auricular application. There are several types of tools using peripheral branches of vagus nerve ending in auricular (Fig. 5, 6).

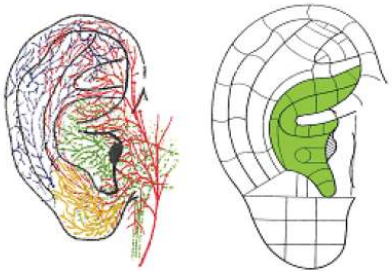

Fig. 5 Auricular braches of n. vagus (green color indicates placement of stimulator)

Fig. 6 Auricular vagus nerve stimulator

In the context of VNS, the tool we used is named CES (cranial electric stimulator- Alpha Stim^{R}) which has similar effects- to stimulate auricular branches of vagal nerve. Our results obtained for patients with moderate depression, anxiety, sleep problems as well as moderate hypertension are very positive [22, 23]. In addition, we will present some specific results (changes in arterial tension, changes in pulse as well as changes in scores for depression and anxiety) obtained with our method (Table 1, Fig 7). The study was performed at the University Center, Skopje, number of patients was 100, both gender included and mean age 38, 7± 3,5 years. Children with anxiety and depression were N= 35, mean age 12, 5 ± 1, 5 years.

Table 1. Student t- test for changes of arterial tension and pulse

TA before	*TA after*	*t- value*	*p value*
126.3333 ± 13.18	113.0952 ± 6.46	4.3	0.000047*
Pulse before	*Pulse after*	*t- value*	*p value*
69.16± 8.4	63.85± 8.8	8.2	0.0011*

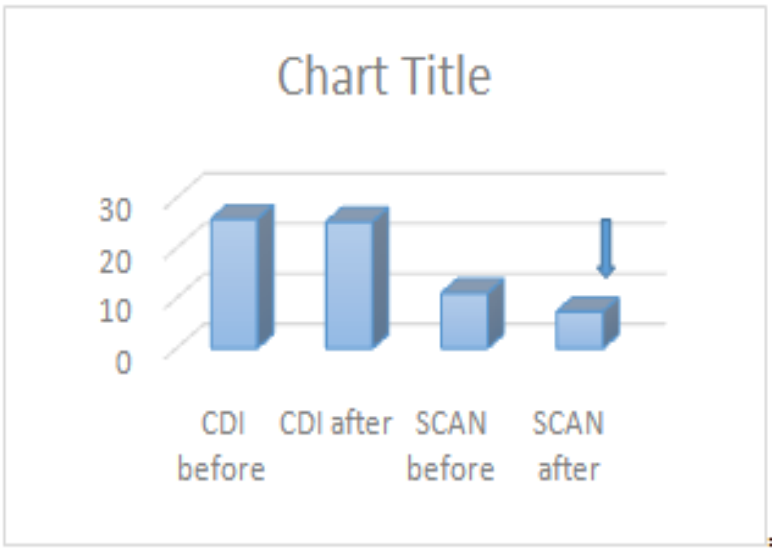

Fig. 7 Changes in scores for depression obtained with Child depression inventory (CDI) and Child anxiety inventory (SCAN)

Obtained results with this kind of peripheral vagus stimulation were very positive. Anxiety dropped, depression was reduced, and arterial tension and pulse have been stabilized.

VNS is used in regulation heart rate regulation [24], restoring consciousness [25], in the treatment of Parkinson's disease [26] etc.

In this occasion we must mentioned that VNS is used broadly in many other medical conditions, but scientific aprouvement for this topics are not sure and further research is needed.

II. Conclusions

As can be seen from presented review, electrical nervus vagus stimulationis non-pharmacological, easy for application and practically non-invasive method and it is used broadly for different medical problems. The future research will confirm or reject the effectiveness. Our own results confirmed positive influence of VNS in the treatment of moderate depression, hypertension, sleep problems and anxiety.

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