REVIEW ARTICLE

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Vagus nerve stimulation in epilepsy – literature review

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Abstract

Introduction and Objective. Epilepsy is a brain disorder characterized by a predisposition to induce epileptic seizures. Neurostimulation is one of the therapeutic methods for drug-resistant epilepsy. The choice of therapeutic method is determined by the patient's condition and an assessment of the benefits and risks of possible side-effects during the use of a particular treatment method. The aim of this review is to provide information on vagus nerve stimulation (VNS) as a therapeutic method for epilepsy.

Review methods. The review is based on scientific publications in PubMed, Google Scholar, and NCBI databases. The articles were published in English. After the initial evaluation of articles, meta-analyses, case series studies and reviews considering VNS were chosen.

Brief description of the state of knowledge. VNS is usually considered as a palliative procedure for patients who have unsuccessfully used multiple antiepileptic drugs, and have contraindications to surgical resection of the epileptogenic focus. The device used to stimulate the vagus nerve consists of a pulse generator and a wire with electrodes that are wrapped around the left vagus nerve. About 45–65% of patients respond positively to VNS implantation. However, side-effects include post-operative infection, vocal cord paresis, cough and neck pain, among the others. In addition to VNS, neuromodulation techniques include deep brain stimulation (DBS) and responsive neurostimulation (RNS).

Summary. The therapeutic process of epilepsy is a major challenge for doctors. The emergence of new therapeutic methods obliges doctors to update their knowledge of the available methods. The authors of the review emphasize the importance of VNS in the treatment of patients with epileptic seizures. When administered and used correctly, the VNS can be an effective therapeutic solution.

Key words

epilepsy, drug resistant epilepsy, drug resistant epilepsy treatment, vagus nerve stimulation, neurostimulation therapy

INTRODUCTION

Epilepsy is a brain disorder characterized by a persistent predisposition to induce seizures. Thus, it is not a disease unit but a set of symptoms that may occur against the background of various morphological and metabolic changes in the brain. Depending on the area of the brain where the discharge occurs, two types of seizures are distinguished: generalized and partial (focal) seizures [1, 2].

According to the International League Against Epilepsy definition, at least one of the following conditions must be met to recognize epilepsy:

1) at least two unprovoked (or reflex) seizures with an interval of at least 24 hours;
2) one unprovoked (or reflex) seizure and risk of another seizure is at least 60%;
3) epileptic syndrome diagnosed [3].

Epilepsy can be considered drug-resistant if seizures have not been controlled despite the use of at least two appropriately selected and correctly administered antiepileptic drugs [4, 5].

Neurostimulation is one of the available therapeutic methods for epilepsy. The implantable device was first approved for the treatment of epilepsy in Europe in 1994 and in the United States in 1997 [6, 7]. Stimulation of the vagus nerve is effective for both focal and generalized epilepsy. It is now safely used in both paediatric and adult patients. The effectiveness of the vagus nerve stimulation (VNS) becomes optimal by about the sixth month of treatment, and approximately 45–65% of patients achieve a 50–100% reduction in seizure frequency [8–11].

The choice of treatment is determined by the patient's condition and assessment of the benefits and risks of possible adverse reactions during the treatment. The aim of this review is to present the therapeutic possibility VNS in epilepsy.

Methodology. This review is based on scientific publications in PubMed, Google Scholar, and NCBI databases. The articles were published in English. After initial evaluation of the articles, case series studies, meta-analyses and reviews considering: epilepsy, drug-resistant epilepsy, drug-resistant epilepsy treatment, vagus nerve stimulation, and neurostimulation therapy were chosen. Publications were analyzed by abstract which was the main criteria for exclusion. Finally, 68 articles were selected.

BRIEF DESCRIPTION OF THE STATE OF KNOWLEDGE

Indications for use of VNS in the treatment of drug-resistant epilepsy. According to the the National Institute

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for Health and Care Excellence's (NICE) committee, implantation of a VNS device is usually considered a palliative procedure for patients who have been unsuccessfully treated with multiple anti-epileptic drugs, and for whom there are contraindications to resection an epilepsy focal point [12]. In the absence of seizure control after the use of two different anticonvulsant regimens (used alone or in combination), drug-resistant epilepsy is diagnosed [13]. In 1997, the Food and Drug Administration (FDA) in the USA approved vagus nerve stimulation as an adjunctive treatment for drug-resistant epilepsy for people with partial seizures >12 years of age [14]. Currently, the FDA allows the use of this method in patients >4 years of age with partial seizures [15], while European guidelines do not provide an age threshold for the use of VNS [12].

There is evidence of the efficacy of this method in younger children with different types of epilepsy [6, 16], including those with observed epilepsy states [17]. According to the American Academy of Neurology, VNS is applicable in both partial and generalized seizures in children, as well as in patients with Lennox-Gastaut syndrome [14]. Resection surgery and callostomy appear to be more effective in Lennox-Gastaut syndrome than VNS, but VNS has also been shown to reduce the incidence of seizures [18, 19]. Temporal lobe epilepsy may also be an indication for VNS therapy if the patient is not eligible for primary lesion resection due to bilateral epilepsy foci in the temporal lobe, or other factors [20]. Positive results have also been obtained in studies on the use of VNS in patients with brain tumor-related epilepsy (BTRE).

VNS should only be used in patients for whom other oncological treatments have been excluded, as the use of this method limits the ability to perform magnetic resonance imaging (MRI) for oncological control, and involves a specialized procedure to remove the conduits prior to scanning [21].

Stimulation of the malignant nerve also reduces the incidence of epileptic seizures in Dravet syndrome (DS) [22]. Publications on DS and Tuberous Sclerosis Complex (TSC) agree that VNS is a third-line method for these conditions [23–25]. According to some reports, DS and TSC are the only genetically-conditioned cases in which the use of VNS has shown anti-epileptic efficacy [26, 27]. However, there have been reports of beneficial effects of VNS on the reduction of seizures associated with Angelman syndrome [28] and Lafora disease [29, 30]. Earlier studies have also reported the benefits of VNS in patients with hypothalamic hamartoma [31, 32], epileptic encephalopathies [33], and Rett syndrome [34]. There is a case in which the use of VNS allowed to achieve seizure-free status in a 29-month-old child with super-refractory status epilepticus during Febrile Infection-Related Epilepsy Syndrome, after combined pharmacological methods did not help [35]. A small number of studies have also shown significant benefits of the use of vagus nerve stimulation in patients with post-traumatic epilepsy [36].

Methods of implantation of VNS. The device used to stimulate the vagus nerve consists of a pulse generator and lead with three electrodes (cathode, anode, anchor tether) that are wrapped around the left vagus nerve. The battery-powered generator is implanted below the left clavicle, while the lead connects to the vagus nerve in the carotid sheath [37]. The battery life span is 5–10 years, after which it needs to be replaced [6]. Implantation of the device requires surgery under general anesthesia, and the pulse generator itself has to be turned-off during the procedure [38]. Electrodes are connected to the left vagus nerve since the right vagus nerve innervates the sinoatrial node. Additional impulses from the generator might produce arrhythmias if implanted on the right side [39].

During the procedure, the patient lies in the horizontal position with the head elevated above the level of the heart, and turned slightly to the right. The surgeon makes the transverse incision in the skin on the left side of the neck to gain access to the carotid sheath. After localizing the left vagus nerve, electrodes are connected below the branching of the cardiac branches of the vagus nerve in subsequent order (Tab. 1) [39].

Table 1. Implantation of electrodes [39]

Order of attachment	Position on the nerve	Electrode
1	Inferior	Anchor tether
2	Middle	Positive
3	Upper	Negative

A second incision is made in order to create a subcutaneous pocket five centimeters below the left clavicle, where the pulse generator is to be placed [40]. Another possible localization for the device is the axillary area [6]. The pulse generator is programmed to meet the needs of the patient, who is able to initiate an impulse or interrupt it using a magnet placed above the device [38]. Guidelines from the Association of Anaesthetists published in 2023, indicate safety measures regarding the management of VNS therapy in the peri-operative period [41]. Two weeks after implantation of the pulse generator, the stimulation procedures begin. Initial intensity (1.0–2.0 mA) is increased with every week of the therapy [39].

An alternative, non-invasive method which aims to achieve the same effect is the transcutaneous VNS (tVNS). A number of devices have been produced, such as the transcutaneous cervical VNS (tcVNS), percutaneous auricular VNS (paVNS), and transcutaneous auricular VNS (taVNS) [42]. During taVNS, the electrode is connected to the left auricle, and the impulse passes through the auricular branch of the vagus nerve [43]. TaVNS stimulates only the sensory fibres, whereas VNS stimulates sensory along with the motor fibers of the vagus nerve, which can lead to side-effects, such as hoarseness, dysphagia, and cough [44]. Comparison between invasive VNS (iVNS) and transcutaneous auricular VNS (taVNS) is been shown in Table 2.

Table 2. Comparison of invasive VNS (iVNS) and transcutaneous auricular VNS (taVNS) [6, 37–44]

Attribute	iVNS	taVNS
Stimulated division of vagus nerve	Cervical vagus nerve	Auricular branch of vagus nerve
Point of entry for electrodes	Carotid sheath	Auricle
Stimulated fibres	Sensory, motor	Sensory

VNS Efficiency. Approximately 45–65% of patients respond positively to a VNS implant. Interestingly, the effectiveness of VNS increases with time since implantation. On average, the

full effect is obtained about three months after implantation of the electrode at high intensities of stimulation [6, 45–47]. Regarding magnetic activation of VNS by patients' caregivers or eyewitnesses, in clinical studies, a decrease in seizures was observed in approximately 31.2% of patients, compared to those without magnetic activation – 28.8% [6, 46]. Activation of VNS by automatic discharge involves the seizure-related VNS pulses being activated, with a corresponding increase in the value of ictal tachycardia. Clinical studies have determined that tachycardia occurs in temporal lobe seizures, orbito-frontal seizures, and hippocampal seizures. Unfortunately, the problem with this activation method is that it often activates VNS at inappropriate times. An observational study by Hampel et al., s showed that seizure-related VNS-pulses had a sensitivity of 92%, and a specificity of 13.5% [6, 46, 48, 49].

Also of importance in the effectiveness of VNS, are the parameters of the device settings, with the intensity of stimulation being increased slowly. According to the meta-analysis carried out by Panebianco et al., higher intensities (average 1.61–1.91 mA) are much more effective compared to smaller stimulation in stopping seizures. Side-effects of too high intensities were withdrawals and voice alteration or hoarseness. At lower values, side-effects were cough, dyspnea, pain, paresthesias, nausea, and headache [6, 45, 46, 50].

Other diseases that can occur with epilepsy are depression, generalized anxiety disorder, and psychoses. Studies have shown that VNS reduces the severity of anxiety and depression symptoms. In addition, there is an improvement in the quality of life in patients with VNS, which is associated with improved alertness, improved postictal status, changes in mood, better performance at work or school, and memory [6, 46].

Unfortunately, there is no accurate information confirming that VNS reduces mortality in patients with drug-resistant epilepsy [6]. In addition, the earlier the electrode is implanted, in newly-formed epilepsy the results are better. VNS efficacy is higher in children up to six years of age – 62%, compared to older children – 55.3% and adults – 49.5%. In focal epilepsy, there is a poorer response to the effects of VNS, while better in generalized and mixed-seizure conditions [6, 46].

VNS adverse effects. In a cohort study by Alshehri et al., 67.4% of patients using VNS experienced side-effects. Serious adverse reactions included dysphagia (39.5%), dyspnoea (23.3%), aspiration pneumonia (9,3%), increased secretions (7%), snoring (7%), and increased seizure frequency (2 3%). Mild side-effects included cough (23.3%), hoarseness (18.6%), vomiting, and fatigue [51].

According to the meta-analysis by Toff et al., the side-effects of VNS include post-operative infection, vocal cord paresis, cough, neck pain, hoarseness, dysphonia, cough, and snoring. Side-effects of too high intensities of stimulation were withdrawals and voice alteration or hoarseness. At lower values, cough, dyspnea, pain, paresthesias, nausea, and headache were observed as side-effects [6].

Because the electrode is an electrical device, there may be side-effects associated with it, including electrode breakage, disconnection, extinction and pacemaker failure. In addition, surgical complications after electrode insertion surgery, such as infection, hematoma, vocal cord palsy and cable discomfort, should be taken into account [6, 37].

Comparison of VNS with other neurostimulation methods. Neuromodulation techniques include deep brain stimulation (DBS) and responsive neurostimulation (RNS). Both techniques use electrical stimulators and are palliative treatments for drug-resistant epilepsy [52]. An important difference between the use of these techniques is their availability to paediatric patients. VNS can be used in children over four years of age, and in younger off-label children, while the other DBS and RNS are used off-label, regardless of the age of the child [53].

The DBS system comprises a pulse generator implanted in the left subclavian region and electrodes placed intracranially [54]. In DBS practice, stimulation of the thalamus (mainly anterior and centromedian nucleus), hypothalamus, cerebellum, and hippocampus, is used [55–57], among which the anterior and centromedian nuclei of the thalamus are the most prominent [53]. DBS of the anterior nucleus of the thalamus was shown to be more efficient among patients with the origin of seizures located in the temporal lobes [58]. The exact mechanism of action of DBS remains unclear, although it is known that rhythmically stimulating the thalamus or other structures helps prevent the development of seizures, although there is no single template for the exact parameters of stimulation, such as its frequency and intensity. The effects using the same configuration of stimulation may vary depending on which structure is stimulated at the moment [59]. After implanting bilateral electrodes used in DBS, their location is verified via MRI [60]. RNS is designed as a closed-loop stimulation system, unlike VNS and DBS, which belong to open-loop (continuous stimulation) systems [46, 53]. The RNS system consists of a neurostimulator implanted in the skull, which is connected to two four-contact strips or depth electrodes, placed intracranially in the seizure onset zone(s) [61]. Patients receive a laptop and interrogation wand with their devices, and are advised to upload data from their devices every day or every few days [46]. RNS includes patients with two seizure foci, patients with a single but inoperable seizure foci, and patients with regional neocortex seizures [61]. Indications for treatments such as DBS include drug-resistant epilepsy, characterized by partial seizures that may be generalized [62]. In turn, indications for the use of VNS are varied and include drug-resistant epilepsy with partial and generalized seizures [14], numerous bilateral independent outbreaks, and seizures with multiple epileptic disorders [62]. These methods are fairly well tolerated and are characterized by different adverse reactions, which are generally infrequent [47, 63, 64]. Side-effects that may occur with RNS include superficial infections and intracranial haemorrhages, muscle tremors, dizziness and paraesthesia, and onset of epilepsy. There was no evidence of mood changes or cognitive impairment. [61]. With DBS, the side-effects associated with the stimulation itself are usually mild and transient, such as tingling or muscle spasms. Serious complications are rare, but may include infection, electrode migration, or equipment problems [64]. Cognitive impairment is also observed [47].

Many randomized controlled trials have explored the efficiency and safety of DSB among DRE patients. Regarding efficiency, most sources claim VNS presents a 50% decrease in the number of seizures in patients, while DBS and RNS still lack significant data to determine superiority over any other DRE treatment [53, 65–68]. Comparison of various attributes of neurostimulation methods are shown in Table 3.

Table 3. Comparison of neurostimulation methods [6, 14, 15, 37, 40, 46, 47, 51–55, 58, 61–64]

Attribute	VNS	DBS	RNS
Location of pulse generator	Subclavicular area	Subclavicural area	Cranial area
Location of electrodes	Attached to left vagus nerve	Intracranial	Intracranial
Type of system	Open-loop	Open-loop	Closed-loop
Applicability in adults	Applicable	Applicable	Applicable
Applicability in children	Applicable in children > 4 years old Applicable off-label in younger children	Applicable off-label in children	Applicable off-label in children
Indication	DRE - with multiple and a bilateral independent foci, symptomatic generalized epilepsy with diffuse epileptogenic abnormalities	DRE - partial-onset seizures with or without secondary generalization	DRE, but no more than 2 epileptogenic foci
Side-effects	Superficial infections, cough, hoarseness, paresthesia, dysphagia, dyspnea, neck pain, aspiration pneumonia, increase secretions, snoring, increase seizure frequency, vomiting and fatique	Superficial infections, intracranial haemorrhages, muscle tremors, dizziness and paresthesia, occurrence of status epilepticus	Superficial infection, muscle cramps, tingling sensation, cognitive decline

CONCLUSIONS

The therapeutic process of epilepsy is a major challenge for doctors. The emergence of new therapeutic methods obliges doctors to update their knowledge of the available methods. For many patients suffering from drug-resistant epilepsy, VNS can be an effective therapeutic solution. The authors of this review emphasize the importance of VNS in the treatment of epileptic seizures. When administered and used correctly, the therapy can improve the quality of life of epileptic patients.

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