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Use of transcutaneous auricular vagus nerve stimulation (taVNS) in the treatment of drug-resistant depression – a pilot study, presentation of five clinical cases

Mateusz Kaczmarczyk[1], Anna Antosik-Wójcińska[1], Monika Dominiak[2], Łukasz Święcicki[1]

[1] Institute of Psychiatry and Neurology in Warsaw, Second Department of Psychiatry, Department of Affective Disorders

[2] Institute of Psychiatry and Neurology in Warsaw, Department of Pharmacology

Summary

Aim. The aim of the study was to assess safety and efficacy of transcutaneous vagus nerve stimulation (taVNS) as the method added to standard pharmacotherapy in the group of patients with treatment-resistant depression.

Methods. We present results of pilot study involving the use of commercially available transcutaneous vagus nerve stimulators. With external, non-invasive nature of new solution, the patient is avoiding possible side effects of surgical operation. taVNS is a relatively new, noninvasive VNS method based on the location of afferent vagus nerve distribution on the surface of the ear. The pilot study group consisted of 5 patients with treatment-resistant depression. All patients suffered from severe depression with no response to appropriate courses of at least two different antidepressants. The assumed observation time was 12 weeks. The duration of stimulation was 4 hours/day, divided in 2 sessions. Mental state was assessed by clinician with the use of the Hamilton Depression Rating Scale (HAMD-17) and the Clinical Global Impression Scale (CGI).

Results. In 2 cases substantial improvement of mental state was observed (significant improvement in scoring scales, improvement of mood and drive, decrease of anxiety). 3 patients resigned from the study because of difficulties in handling devices.

Conclusions. Vagus nerve stimulation may represent major advance in management of chronic and treatment-resistant depression. taVNS could represent safer alternative to previously used invasive methods. The results can be observed after few weeks or even few months of therapy. Because of the possible long-term benefits and side-effects of taVNS, further clinical trials are required to assess its effectiveness.

Key words: vagus nerve stimulation, taVNS, transcutaneous vagus nerve stimulation

Introduction

Depression is a common mental disorder worldwide, with more than 300 million people affected, and constitutes a leading cause of disability, negatively impacts the quality of life and increases the risk of suicide [1, 2].

Pharmacotherapy with the use of antidepressants and psychotherapy are the most common treatment for depression. Although there are various antidepressants available, approximately 35% of patients still cannot achieve remission. Treatment-resistant depression (TRD) develops in a certain group of patients [3]. The STAR-D study showed that approximately 30% of patients with recurrent depression experience remission after using the first antidepressant in a given episode, and that remission rates decrease and subsequent relapse rates increase with the number of failed antidepressant therapies [4]. Up to 15% of patients with depression suffer from drug-resistant depression defined as a lack of response to treatment with two consecutive antidepressants belonging to different groups, at the right dose and for the appropriate time [5, 6]. Such patients are proposed various pharmacological methods of treatment potentiation that may be associated with systemic side effects (e.g., metabolic abnormalities and sexual dysfunction) and limited efficacy. Considering the response rates, it seems that in the group of patients whose pharmacotherapy modifications did not cause the improvement of mental state, physical, non-pharmacological methods of depression treatment give a greater chance to obtain remission.

Among the non-pharmacological methods of treating depression, we distinguish between direct and indirect (involving peripheral nerve fibers) methods of brain stimulation. Deep brain stimulation and electroconvulsive therapy are direct methods. The effectiveness of electroconvulsive therapy in drug-resistant depression has been proven, while deep brain stimulation remains an experimental method.

The best known method of indirect neurostimulation is vagus nerve stimulation (VNS). The vagus nerve is the longest cranial nerve, reaching all the way to the abdominal cavity. The therapeutic mechanism of vagus nerve stimulation, both anti-epileptic and antidepressant one, is not well known. Within the brain, the vagus nerve is known to form connections within many structures. It is presumed that the most important from the point of view of therapeutic action may be the vagus nerve pathways that lead to key centers of the noradrenergic system such as the nucleus coeruleus. These centers exert an important influence on the functioning of the amygdala, hypothalamus, thalamus, and prefrontal cortex, i.e., structures associated with the regulation of mood, emotions, drive, and biological rhythms [7].

So far, two methods of vagus nerve stimulation have been developed. The first, invasive VNS (iVNS), requires the surgical implantation of a small pulse generator. The vagus nerve stimulator is placed during surgery under the skin in the upper part of the chest. The connecting wire is tunneled under the skin from the impulse generator to the electrode connected to the vagus nerve. The stimulation starts a few weeks

after implantation, the pulse generator is programmed to send electrical impulses at regular intervals, while the parameters of stimulation are adjusted individually to the patient, gradually increased to the limit which is acceptable to the patients "without ailments" [8].

Invasive vagus nerve stimulation was approved in 1997 by the FDA as a treatment for drug-resistant epilepsy. In 2005, this method was approved for long-term treatment of recurrent and drug-resistant depression. It is estimated that the antidepressant effectiveness of VNS in patients with drug-resistant depression is 20–50% [9, 10]. Despite the observed effectiveness, the method carries a relatively high risk of complications during the perioperative period and of undesirable effects associated with stimulation. Almost half of patients undergoing VNS have a change in timbre, often hoarseness, sometimes there is hiccups, nausea or tremors in the neck, that is why it was necessary to find a safer and at least equally effective method of combating severe depression. This led to the development of another method of transcutaneous stimulation of the vagus branch in the auricle or the lower half of the posterior surface of the outer ear.

According to the 'bottom-up' mechanism of the central nervous system (CNS), electrical stimulation of these areas can cause changes in activity in the vagus nerve pathway in the brainstem and central structures, producing an iVNS-like modulation effect. The effectiveness of taVNS has so far been studied in the treatment of disorders such as epilepsy, depression and chronic tinnitus.

Some authors have proved that the effectiveness of taVNS in the form of a modulation effect is similar to that observed with the use of invasive stimulation methods [11]. Previous studies suggest that taVNS, as a non-invasive method, has good efficacy in the treatment of neuropsychiatric disorders [12]. To date, the results of one randomized sham controlled trial evaluating the efficacy of taVNS in the treatment of depression have been published [13]. The authors studied the effect of bilateral taVNS treatment in the MDD patient population as an add-on therapy (antidepressant treatment with real or sham taVNS). Compared with the sham stimulation group, the true taVNS stimulation group showed a significant reduction in the Beck Depression Inventory (BDI) score after two weeks of treatment (five times weekly stimulation). At the same time, there was no significant difference between the groups in the Hamilton Depression Rating Scale (HAMD). The results of the cited study were inconclusive: in the study group there was a subjective clinical improvement on the BDI scale, however, there was no improvement in the assessment by a specialist in the HAMD. The authors of the publication indicate that during the study period no significant adverse effects occurred in the study group. Other published research [14] also confirmed the safety of this method. Only one study showed that 2 patients in the taVNS group and 3 patients in the sham stimulation group had adverse effects in the form of tinnitus that fully resolved after the end of the study.

The studies mentioned above used a combination of VNS and antidepressants to treat TRD. This was partly due to bioethical reasons and the belief that abrupt discontinuation of current treatment may worsen symptoms [15] and, moreover, due to the insufficient effectiveness of VNS in monotherapy. The basic assumption of the VNS method was therefore the use of stimulation as a method added to pharmacological treatment, which was supposed not only to increase the antidepressant effect, but also to reduce the dose of drugs. Unfortunately, data from previous studies do not confirm that the use of VNS leads to a reduction in drug doses [9, 10]. According to *Standards for the treatment of some mental disorders* edited by Marek Jarema, the use of VNS is recommended for patients with recurrent or chronic depression in whom numerous previous pharmacological treatments have not resulted in clinical improvement [16]. This method is not recommended for the treatment of the acute phase of depression. There is still insufficient evidence confirming the efficacy and safety of transcutaneous VNS. Determining the potential benefits and clinical role of taVNS in the treatment of depressive disorders requires further research on this topic.

We present the results of a pilot study which assess the safety and efficacy of transcutaneous vagus nerve stimulation (taVNS) as the method added to the standard pharmacotherapy in the group of patients with treatment-resistant depression.

Material

The pilot study group consisted of 5 subjects recruited from both inpatients and outpatients suffering from drug-resistant depression. All patients showed no response to at least two properly managed antidepressant courses.

The inclusion criteria included: 1) the patient meets the diagnostic criteria for a severe major depressive episode according to ICD-10; 2) age over 18 years; 3) pharmacological treatment was not changed 2 weeks before the intervention and during the study; 4) depressive symptoms occur in a patient for at least the last two months, but not for more than 7 years.

Table 1 shows the detailed characteristics of the patient population participating in the study.

Table 1. **Population data**

Number of patients	5
Age (years)	53.6
Women	3
Mean time since the diagnosis of mental disorders (years)	17
Number of depressive episodes	4.7
Duration of the last depressive episode until the use of taVNS (years)	3.7
Period of use of taVNS (months)	2.7

table continued on the next page

Inpatients	2
Outpatients	3

Methods

In the study we used commercially available transcutaneous vagus nerve stimulators, which are successfully used in the treatment of epilepsy. In the presented pilot study, it was the NEMOS stimulator produced by CERBOMED GmbH. The transcutaneous vagus nerve stimulator consists of a pulse generator and ear electrode. The stimulator, which is similar in size to a mobile phone, sends electrical impulses. It is connected via a wire to an ear electrode, which patients wear just like a music earphone. The impulses are transmitted through the ear electrode and through the skin to the branches of the vagus nerve.

Patients control the treatment themselves using the device. The recommended duration of daily stimulation to be sought each day is four hours. Users regulate and adjust the intensity of stimulation depending on their own sensitivity, which can change from day to day or even throughout the course of treatment. To ensure optimal stimulation, users should adjust the intensity to feel a stinging or tingling sensation. Stimulation should be perceptible but it should not be painful or uncomfortable.

Thanks to the external, non-invasive nature of the new solution, the patient avoids the possible side effects of surgery. taVNS is a relatively new, non-invasive VNS method which uses in its action the fact that an afferent branch of the vagus nerve appears on the surface of the ear. This branch f the vagus nerve supplies the skin of the auricle in the human ear and can be stimulated by using an ear electrode. The intensity, pulse duration and frequency of taVNS stimulation have been optimized to induce signals in thick myelinated Aβ fibres of the auricular branch of the vagus nerve.

The stimulation parameters used in the study were as follows: current of 0.5 mA–5 mA, frequency 25 Hz, on time (ON) 30 s, off time (OFF) 30 s.

The assumed observation time was 12 weeks. The duration of stimulation was 4 hours daily and was divided into 2 sessions a day.

The mental state was assessed during a clinical mental state examination with the use of 17-point Hamilton Depression Rating Scale (HAMD-17) and the Clinical Global Impression Scale (CGI).

The study was conducted from September 2016 to May 2017. The study was not sponsored. The study was reported to and considered by the competent Bioethics Committee (at the Institute of Psychiatry and Neurology). At the meeting of the IPIN Bioethics Committee (25.08.2016) the project and the methodology of the study was presented and a question was formulated as to whether the study is subject to the obligation to submit a study protocol and request for the approval of Bioethics Committee.

Bioethics Committee, having read the description of the study, decided that it is not necessary in this case to obtain the above-mentioned approval. Patient consent for the participation in the study was obtained in both oral and written form.

Results

Case descriptions

Case 1

A 55-year-old man diagnosed with bipolar disorder has been treated psychiatrically for 17 years; in the past he was treated with amitriptyline for a long time with good effect.

In the last two years preceding the use of taVNS, in the course of the disease severe and drug-resistant depressive episodes occurred. During this time the patient was repeatedly hospitalized (5 times), multiple modifications of pharmacotherapy with antidepressants and mood stabilizers (therapy with venlafaxine, clomipramine, olanzapine, valproate, carbamazepine, lithium carbonate) and non-pharmacological treatment – electroconvulsive therapy (ECT) – were performed without a satisfactory effect. TaVNS was used for 2 months (1 month in the hospital and 1 month at home). Patient reported a gradual improvement of mental state in the form of reduction of the severity of depressive symptoms during the second month of use of taVNS (CGI initially 5 – markedly ill, CGI at the end of the study 3 – mildly ill). The patient tolerated treatment well – no side effects were reported.

Case 2

An 83-year-old woman has been treated psychiatrically for 25 years with the diagnosis of recurrent depression (unipolar affective disorder). Long-term remission was observed during the treatment with mianserin. So far she was hospitalized psychiatrically 3 times. The last depressive episode has lasted for 3 years without improvement despite repeated attempts to modify pharmacological treatment (e.g., venlafaxine, duloxetine, clomipramine, citalopram, fluvoxamine, olanzapine) and biological therapy via rTMS – without good effect. Patient disqualified from electroconvulsive therapy (ECT) due to arrhythmia.

The patient used taVNS for 4 weeks in hospital conditions. No significant clinical improvement was observed during the use of the device (CGI at baseline 5 – markedly ill, at the end of the study 4/5). The patient tolerated taVNS well, reported only problems with the device in the form of non-durable electrode adhesion to the auricle.

Case 3

A 47-year-old woman has been treated psychiatrically for 15 years, initially diagnosed with anxiety disorders, then bipolar disorders (at the age of 24.). In the course of the disease depressive and hypomanic episodes with poor response to pharmacological treatment have been reported. Multiple attempts of modification of pharmacological treatment (e.g., amitriptyline, opipramol, clomipramine, fluoxetine, citalopram, escitalopram, sertraline, venlafaxine, duloxetine, bupropion, moclobemide, mirtazapine, lamotrigine, carbamazepine, vortioxetine, pregabalin) were performed – with no satisfactory effect. Moreover, the rTMS treatment was initiated but it was discontinued after first procedure due to poor tolerance of this method (patient reported headache and neuralgia of the trigeminal nerve).

The patient used taVNS for 6 months. A gradual improvement in mood, activity and anxiety was observed (CGI at baseline 5 – markedly ill, at the end of taVNS treatment 3 – mildly ill). The patient tolerated VNS well – reported no side effects. However, she reported on the non-durable adhesion of the electrode to the auricle. In the patient's opinion, you cannot walk during therapeutic sessions because then the electrode protrudes from the ear. Immediately after cessation of the use of taVNS, deterioration of mental state in the form of irritability and decrease of mood was observed.

Case 4

A 32-year-old man has been treated psychiatrically for 13 years with the diagnosis of recurrent depression. In the current course of the disease, 3 episodes of depression have occurred. The last episode has been ongoing for 7 years. Despite of repeated attempts to modify pharmacological treatment (including ketamine infusions) and ECT treatment, the remission was not observed.

The patient used taVNS at home for 1.5 months. There was no significant clinical improvement in reducing the severity of depressive symptoms (CGI at baseline 5 – markedly ill, at the end CGI 4/5). However, the patient reported a decrease in the severity of involuntary movements of the neck and torso. The patient also reported on the non-durable adhesion of the electrode to the auricle. Despite this, he tolerated taVNS well.

Case 5

A 51-year-old woman has been treated psychiatrically for 6 years with the diagnosis of recurrent depression. The last depressive episode lasted for 1.5 years before applying taVNS. During this period several attempts to modify pharmacological treatment (amon others: paroxetine, fluvoxamine, escitalopram, venlafaxine, duloxetine, tianeptine, clomipramine, mirtazapine, mianserin, reboxetine, bupropion, moclobemide,

lamotrigine, lithium carbonate) were made and non-pharmacological methods (rTMS) were performed – without good effect.

The patient used taVNS for 3 months at home. No significant clinical improvement in reducing the severity of depressive symptoms was observed (CGI at baseline 4, at the end of the study 4). The patient tolerated this treatment well, did not report any side effects or difficulties with the operation of the device.

Conclusions

Based on these few cases of using taVNS in a population of patients with drug-resistant depression, several conclusions can be made. The tolerance of this method is good, most complaints were related to the quality of the equipment and not the side effects occurring during or after treatment. However, it is difficult to refer to the effectiveness of the method itself (due to the small sample size, heterogeneity of the group and technical problems in the use of the device). Certainly, the method requires further multicenter, randomized trials evaluating the efficacy and tolerability of the taVNS method in the population of patients with drug-resistant depression

Limitations

The limitations of the study included:

- small study population;
- the study group included only patients with high severity of the illness – depression resistant to other commonly used treatment methods;
- the observation period was short;
- observed service difficulties or possible technological deficiencies resulting in the lack of electrode adhesion to the ear during stimulation.

It is also worth mentioning that the medical staff did not have the possibility to control the compliance regarding the correct time and technique of taVNS use during outpatient treatment, which could have an impact on the observed effectiveness and the frequency of difficulties with operating the device.

Recapitulation

The small sample size makes it impossible to formulate general conclusions. The good tolerance of the treatment method is worth noticing. The only problems the patients complained about were technical difficulties – the placement of the electrode in the auricle is quite difficult, the electrode easily loosens and falls out. It seems that these problems should be relatively easy to solve (e.g., by modifying the shape of the electrode or changing the material from which it is made to be more adhesive). Due

to the long duration of therapeutic sessions (4 hours a day), it is important for patients to be able to maintain normal physical activity during treatment without a fear of problems with the equipment.

We have observed a marked improvement in the mental state of two subjects with significant drug resistance, which undoubtedly encourages us to further studies in this field. It is necessary to conduct a large randomized trial to assess the effectiveness of taVNS and the possibilities of its wider use in the future.

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Address: Anna Antosik-Wójcińska
Department of Affective Disorders
Institute of Psychiatry and Neurology
02-947 Warszawa, Sobieskiego Street 9
e-mail: aantosik@ipin.edu.pl