



BRIEF REVIEW

Neurology

The Role of Non-Drug Treatment Methods in the Management of Epilepsy

Ekaterina A. Narodova, PhD*; Natalia A. Shnayder, PhD, ScD; Valeria V. Narodova, PhD, ScD; Diana V. Dmitrenko, PhD, ScD; Ivan P. Artyukhov, PhD, ScD

*Krasnoyarsk State Medical University named after Prof. V.F. Voino-Yasenetsky
Krasnoyarsk, the Russian Federation*

Abstract

This review is dedicated to the issue of non-pharmacological treatment of epilepsy in the adult population in Russia and other countries. A literature review was conducted using international databases for the period between 2010 and 2017. A total of 64 full-text editions were included in this review, which allowed us to reveal the basic non-pharmacological epilepsy treatment options. However, not all of these options have a sufficient evidence base, and some of them are not always safe. Particularly, methods with a low level of evidence include acupuncture and aromatherapy. Further studies are needed to explore the methods aimed at eliminating the dominant epileptic system through the development of a new, more powerful dominant system. One of the methods that can influence the pathogenesis of epilepsy is physical activity for patients with epilepsy, since epileptiform activity is reported to disappear from the EEG during exercises. The positive results of the application of music therapy are also described in the modern literature. Specifically, according to the results of some studies, the positive effect of reducing the frequency of seizures was achieved in epileptic patients who listened to music during sleep over a year. However, these studies are not numerous, so they cannot constitute a high level of evidence. Therefore, care should be exercised in applying these methods in epileptic patients. (**International Journal of Biomedicine. 2018;8(1):9-14.**)

Key Words: epilepsy • adults • non-pharmacological treatment • music therapy

Introduction

According to the world statistics, epilepsy takes the third place for overall morbidity after cardiovascular diseases and diabetes mellitus, and the third place in neurological morbidity.⁽¹⁾ Therefore, epilepsy is a relevant public health problem in Russia and other countries.⁽²⁾ In recent years, considerable attention has been paid to the development and implementation of medicinal and alternative (non-pharmacological) methods for epilepsy treatment. However, current epilepsy treatment options allow achieving remission or reducing the number of seizures in only 60%-70% of patients.⁽³⁾ An important problem of epileptology is ensuring the safety and acceptability of the treatment as well as preventing adverse side effects (ASEs) of antiepileptic drugs (AEDs). ASEs can often

decrease patients' quality of life, thereby offsetting the positive effect of the treatment. Moreover, such ASEs as depression and anxiety (the fear of the coming seizure) may aggravate epileptic seizures.⁽⁴⁾ Some ASEs are associated with the effects of AEDs on the liver enzymes. These effects cause induction or inhibition of the liver enzymes, displacing other AEDs from protein linkages. These reactions increase the rate of metabolism and cause a reduction of the plasma concentration of AEDs, which may lead to difficulties in the choice of AED dosage. On average, the frequency of ASEs and complications of antiepileptic therapy remains high and varies, according to different authors, from 7% to 25%.⁽⁵⁻⁷⁾

Therefore, the presence of ASEs requires the immediate withdrawal of AEDs, even if drug-induced epilepsy remission is achieved. It should be noted that 40% of epileptic patients need polytherapy. This leads to an increase in the frequency of ASEs, adverse drug-drug interactions, and teratogenicity.⁽⁸⁾ In addition, there are difficulties in assessing the effectiveness of ASEs of a single drug. Drug-drug interactions often decrease the efficiency of antiepileptic treatment and contribute to the

*Corresponding author: Ekaterina A. Narodova, PhD.
Krasnoyarsk State Medical University named after Prof. V.F. Voino-Yasenetsky, Krasnoyarsk, the Russian Federation. E-mail: nataliashnayder@gmail.com

development of ASEs.^(2,9,10) Consequently, non-drug methods of epilepsy treatment should also be used, both as an additional therapy and (in some cases) as the basic therapy (for example, vagus nerve stimulation) (Table 1).

Table 1.

Non-drug methods of epilepsy treatment

Non-invasive Methods	Invasive Methods
Physical Activity	Vagus Nerve Stimulation
Transcranial Magnetic Stimulation	Deep Brain Stimulation
Psychotherapy	Percutaneous Stimulation of the Trigeminal Nerve
Music Therapy	Surgery
Aromatherapy	
Acupuncture	
Referential Bioadaptation	

The aim of this review is to analyze studies dedicated to non-pharmacological treatment of epilepsy in adults.

Materials and Methods

We have analyzed recent full-text publications in such Russian and international databases as E-Library, PubMed, Scopus, Oxford University Press, Springer, Web of Science Core Collection. The analyzed period comprised 8 years (from 2010 to 2017). The search for publications was conducted using the following keywords: “structural epilepsy”, “drug-resistance”, “epilepsy”, “refractory epilepsy”, “focal epilepsy”, “intractable epilepsy”, “drug-resistant focal epilepsy”, and “non-drug therapy”.

Results and Discussion

Patients with epilepsy experience a range of social restrictions, leading to their external and internal stigmatization. These limitations include employment problems, driving prohibition, and restriction of physical activity. However, it is a well-known fact that physical exercises lead to better functional adaptation.⁽¹¹⁾

Patients with epilepsy who are involved in sport can receive the same benefits from physical activity as healthy people, including an increase in performance efficiency and tolerance, weight loss, and normalization of cardiovascular system functioning. Physical activity is also a critical factor in reducing the risks of diabetes, hypertension, coronary heart disease, obesity, and osteoarthritis. As for psychological advantages, the research in this field found that physically active patients have better mental health than those leading a sedentary lifestyle.⁽¹²⁻¹⁴⁾

Physical activity in early age can cause formation of a neuronal reserve, which then will be used during the life course. Consequently, physically active patients have a lower risk of developing the cognitive impairments associated with epilepsy.⁽¹⁵⁻¹⁷⁾

The preventive and curative effects of physical activity in cases of epilepsy can be achieved in accordance with several principles, including the principles of consistency, regularity, duration, monitoring, and personalization of the training load. Despite this, it is believed that enhanced muscular activity is accompanied with tachypnea (hyperventilation), which can initiate the seizures.

However, some authors claim that physical activity can reduce the likelihood of seizures. Usually, seizures do not occur while running, swimming, ice-skating, skiing, crossing a crowded street, or during sporting events, although this issue is disputable. On the other side, it is reported that seizures often start when patients are relaxed or sleeping. The described data accounts for the development of new dominant excitation areas in the CNS during vigorous exercises. Due to the negative induction, these areas slow down or inhibit activity in the epileptic area, thereby preventing the occurrence of seizures. It is reported that during physical exercises, seizures occur much more rarely than during relaxation.⁽¹¹⁾ The disappearance of epileptiform activity in many patients' EEG during physical activity supports this theory.⁽¹⁸⁻²¹⁾

Neurostimulation

Vagus nerve stimulation (VNS) is one of the non-drug epileptic treatment methods. The principle of this method is in the chronic electrical stimulation of the left vagus nerve, using an implantable stimulator.⁽²²⁾ The primary candidates for the application of this method are patients with drug-refractory epilepsy (DRE) who cannot get resection surgery. The main contraindications for this method are pregnancy and lactation, cardiac arrhythmia, bronchial asthma, chronic obstructive pulmonary disease, acute peptic and duodenal ulcer, vasovagal syncope and the type 1 diabetes.⁽²³⁾ Against the background of VNS therapy during the period from 3 months to 3 years, a complete cessation of seizures was revealed in 4.8%-17.6% of patients. A decrease in the number of seizures by 50% or more was detected in 27.3%-47% of patients, while a decrease in the number of seizures by less than 50% was detected in 23.5% of patients.⁽²⁴⁻²⁶⁾

Deep Brain Stimulation

Deep brain stimulation is an effective therapeutic method for DRE treatment, especially for temporal lobe epilepsy. Thus, according to a randomized study, assessing the effectiveness of hippocampal stimulation in patients with temporal lobe DRE, a positive effect in the form of complete disappearance of seizures was found in 50% of patients.⁽²⁷⁾ Other studies have shown that after 11 years of deep brain stimulation, the attacks were not registered for at least 12 months in only 13.8% of the patients.⁽²⁸⁾

The principle of this method lies in electrode implantation into certain brain structures (target-structures); these electrodes are supplied with low voltage and high frequency electric current. Due to the impulses generated by the neurostimulator, the selected brain structures change their functions. Thus, this high frequency stimulation of the target-structures reduces the severity of the symptoms and allows reducing the amount of AEDs taken by the patients as well as bringing the patient back into society.⁽²³⁾

Transcranial Magnetic Stimulation

Low-frequency repetitive transcranial magnetic stimulation (rTMS) leads to a decrease in cerebral cortex neuronal excitability, while high-frequency rTMS increases the excitability.⁽²⁾ The mechanisms of rTMS are related to its ability to cause long-term effects of postsynaptic inhibition in excitatory neurotransmitter systems, and a reduction in neuronal excitability through inactivation of the voltage-dependent ion channels.⁽²⁹⁾

Based on the data published till now and taking all restrictions into account, a group of European experts assigned evidentiary class C (probably effective) to the low-frequency mode of epileptic focus stimulation in cases where its location is in the cortex or in proximity to cortex dysplasia.⁽³⁰⁾

Percutaneous trigeminal nerve stimulation

Percutaneous trigeminal nerve stimulation is a minimally invasive method in which the branches of the first trigeminal nerve are exposed to electricity. To implement this method in practice, a special system is used which consists of an external electric impulse generator and electro-conductive plasters. There are few studies that report the use of this method, but most of those that do consider this method to have a positive clinical effect. During preliminary clinical trials, 57% of patients noticed a 50% or more reduction in the number of seizures.

Psychotherapeutic options

Currently, it is the practice to distinguish three fundamental categories of psychotherapeutic techniques used in epileptology: rewards/sanctions, self-control, and neurofeedback. The rewards/sanctions and self-control categories are used for self-induced seizures and for so-called "reflective attacks" as well as for epileptic seizures that are amplified under the influence of emotional factors. Neurofeedback is a non-pharmacological method of epilepsy treatment with objective registration, amplification and feedback of physiological information to the patient. This method is based on the principle of self-identification of one's own EEG data.

According to information from different authors, neurofeedback can lead to a great reduction in the number of seizures in 50% of cases of patients with epileptic risk factors. From this 50%, in 10% of cases, it is possible to completely discontinue AEDs without the reappearance of epileptic seizures for 2-3 years and more, and in the remaining 40%-50% of cases, after the use of the neurofeedback method, it is possible to halve pharmacological treatment.⁽³¹⁾

There are also art-therapy options for epilepsy treatment. For example, there is an actively developing method, based on the creation of therapeutic music, to reduce the number of epileptic seizures. This method is based on the theory that epileptic seizures occur because of abnormal synchronization of the brain's electrical activity, and that the majority of them stop spontaneously. The effect of structured auditory stimuli provides non-invasive galvanic cortex stimulation, which can reduce epileptiform activity.⁽³²⁾ To prove this hypothesis, researchers conducted a randomized study, which explored the effectiveness of music therapy for patients diagnosed with

epilepsy.⁽³³⁾ Patients were exposed to Mozart's music every night for one year. This research resulted in a 17% reduction in the number of epileptic seizures. The achieved effect remained stable during the next year.^(34,35)

In another randomized study, which studied both children and adult patients with epilepsy, 85% of patients had a positive response to music therapy with an average reduction of the epileptiform activity index by 31% during listening to the music and by 24% afterwards.⁽³⁶⁻⁴⁴⁾

The methodology of audiogenic stimuli, proposed by Alfred Tomatis, is another art-therapy method, which is close to music therapy.⁽⁴⁵⁾ However, in clinical practice, we meet with an increase in the number of epileptic seizures by 50%-60% after the use of this method. As a result, currently, the effectiveness of this method remains debatable.

Aromatherapy can be useful (for achieving a state of relaxation) as a component of epilepsy behavioral treatment. However, its use is more justified for the treatment of conditions accompanying epilepsy, such as anxiety and depression. In the application of aromatherapy for patients with epilepsy, camphora, sage, and rosemary should be avoided because these substances are known to aggravate patients' condition and increase the number of epileptic seizures.⁽¹⁰⁾

In the Asian-Pacific region, acupuncture is actively used as a non-pharmacological method of epilepsy treatment. There are data on the use of acupuncture for patients with strokes in order to avoid post-stroke epilepsy. S.Weng and colleagues showed that patients with strokes who received acupuncture had significantly less probability of post-stroke epilepsy, compared to those who did not receive such treatment ($P < 0.0001$). However, defensive effects associated with acupuncture need further exploration.⁽⁴⁶⁾

Some authors report neuroprotective, anti-inflammatory and neurotrophic effects of acupuncture and electroacupuncture. These effects are explained by the amplification of recurrent inhibition of the brain cortex and hippocampus with the liberation of different neurotransmitters, including gamma-aminobutyric acid and serotonin. However, due to the lack of controlled clinical trials, those methods cannot be recommended as reliably effective and safe in epileptology.⁽⁴⁷⁾

Conclusion

Based on the results of our literature review, it can be stated that an adequate number of studies of the analyzed period are dedicated to non-pharmacological epilepsy treatment. Methods with both proved clinical effectiveness and low reliable treatment options were found in the studied literature. Most of the authors emphasize a positive influence of physical activity on epileptic patients, including prevention of epileptic seizures. Besides, physical activity is reported to have a positive influence on patients' psychic function, preventing cognitive disorders. However, up until now, physical exercises as an additional therapy are not included in any treatment program for patients with epilepsy. The analysis of the literature showed that this lack of inclusion is due to a current concern among neurologists and epileptologists about the

occurrence of epileptic seizures in a state of hyperventilation. Those concerns are not unfounded, because hyperventilation can provoke epileptic seizures in a certain group of patients with epilepsy. As a result, it is reasonable not to ban physical activity for all epileptic patients, but to limit its intensity for the group of patients in whom hyperventilation can provoke epileptic seizures. Meanwhile, the fact is reported that during physical exercising, epileptic patients' EEGs show reduced epileptiform activity. Finally, regarding music therapy, there are studies that suggest it has a positive effect, but the issue is still under-investigated.

All the options for non-pharmacological epilepsy treatment represented in the present review are based on the classical theory of G.N.Kryzhanivsky about the creation and destruction of pathological systems.⁽⁴⁸⁾ The author noted that in early stages of the disease, the elimination of the pathological determinant leads to liquidation of the pathological system.

In late stages, the fixation of a pathological system leads to chronization of the pathological process and corresponding neural disorders. The battle with pathological systems, especially with those with complicated and matured forms, is hard and is not always effective. It requires a complex pathogenetic therapy, focused on elimination of the pathological determinant (for example, the elimination of epileptic focus) and normalization of other links of the pathological system. Activation of the anti-epileptic system, amplification of overall control and other genetic mechanisms are important as well. It is also known that there is a constant countdown in living systems, on which homeostasis is based.⁽⁴⁹⁾

According to the theory of V.A.Rudnev,⁽⁵⁰⁾ so-called "internal time" is a genetic core of any motor activity, having characteristics of both populations and individuals. Internal time is expressed as an individual rhythm. Many studies explore individual rhythm, its "maturation" in late ontogenesis, as well as its breaking in different cases of neural disorders.⁽⁵¹⁾ Individual rhythm is a reflection of the harmony of the brain's work, and its breaking is a sign of disintegration in the brain's work. Since it is an established fact that in cases of epilepsy a pathological activation of the brain's neurons occurs, which is a stress for the central neural system, it is possible that the occurrence of an epileptic system can change a patient's individual rhythm.

Consequently, research on individual rhythm changes in patients with symptomatic post-surgery epilepsy, and comparison of these changes with the individual rhythm indicators of healthy persons, can help to create a new dominant in the absence of pathological focus and reset the remaining epileptic system links, imposing the mode of operation closest to the physiological one, and activate the anti-epileptic system. There is also a concept that states "seizures lead to seizures." First proposed by doctor William Gowers (1881) and reflecting the concept of epilepsy as a progressing disease,⁽⁵²⁾ this concept remains relevant. Therefore, taking into account the prevalence rate of epilepsy and lack of desired effects of pharmacological therapy, the development of new non-pharmacological treatment options, dedicated to creation of a new dominant in the human brain to suppress the formation and activity of a pathological epileptic system, becomes relevant.

Competing interests

The authors declare that they have no competing interests.

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