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# Neuromodulation in the treatment of symptoms of spinal cord injury

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## ABSTRACT

**Introduction and purpose:** Spinal cord injury may be associated with loss of motor and sensory functions, autonomic system functions and chronic pain. The development of technology has enabled the emergence of invasive and non-invasive methods of electrical and magnetic stimulation of the nervous system, which show a growing potential in the treatment of these symptoms in human and animal studies.

The purpose of the study is a presentation of the most current studies about the selected methods of neuromodulation of the nervous system in the treatment of symptoms of spinal cord injury.

**Description of the state of knowledge:** Neuromodulatory methods improve the functioning of patients affected by spinal cord injury. Studies on epidural stimulation of the spinal cord, transcranial magnetic stimulation, transcranial direct current stimulation transcutaneous spinal cord, and use of neuromodulation methods in combination with brain-machine interfaces stimulation show a reduction of chronic pain resistant to pharmacotherapy, improvement of motor limb function, respiratory function and bladder function. However, there are few large randomized studies with higher evidence strength.

**Conclusions:** Neuromodulation is effective in the treatment of symptoms of spinal cord injury. Promising results should lead to further research to increase the strength of evidence for the effectiveness of these therapies, improve technology and a deeper understanding of the mechanisms behind their effectiveness.

**Key words:** neuromodulation, spinal cord injury

## 1. INTRODUCTION AND PURPOSE

Spinal cord injury (SCI) is one of the most common causes of death and disability in the world [1]. It results not only in motor, sensory and autonomic dysfunctions, but also in deterioration of mental health. Spinal cord injury results from mechanical trauma to neurons, glial cells and adjacent blood vessels, and secondary degeneration of the tissues surrounding the spinal cord. Due to the multifactorial pathogenesis of injury, many therapeutic strategies are used to treat it. In order to prevent the occurrence of neurological deficits after SCI, it is necessary to start treatment early - control vital parameters, use surgical decompression of the spinal cord, use methylprednisolone to reduce inflammation and improve blood flow in the spinal cord, and maintain an average blood pressure> 85 mmHg for 7 days after acute stage of SCI. [2]. In the later stages, neurorehabilitation training and supportive treatment are commonly used [3], but the effectiveness of these methods is limited, therefore, new methods of therapy with a lower number of potential complications are sought.

One of the newest therapeutic strategies for treating complications of SCI is the use of endogenous stem cells, which enable replacement of lost cells with new neurons, as well as glial cells in order to create functional synapses and provide an appropriate environment for axonal regeneration [4].

Neuroprotective methods with the use of riluzole, minocycline, magnesium or therapeutic hypothermia are aimed at preventing secondary damage to neurons as a result of, for example, action of proinflammatory cytokines.

Another method of therapy - neuromodulation - may be beneficial in the case of spinal cord injury, from supporting basic functions, such as respiratory stimulation and bladder control, to restoring voluntary movements [5]. One of the most recognized forms of neuromodulation in spinal cord injury is direct stimulation of the peripheral nervous system. Also, increasing the excitability of the spinal cord with epidural or transcutaneous stimulation can restore some voluntary motor function, even in people with limb paralysis

[6]. Stimulation of the brain itself may also be important in treating the spinal cord injury.

**Purpose of the work**

Presentation of the current state of knowledge on selected methods of neuromodulation of the nervous system in the treatment of symptoms of spinal cord injury, including indications and contraindications for individual forms of therapeutic treatment and potential mechanisms of neuromodulation (Table 1).

**Material and methodology**

The search for clinical trials was based on a detailed protocol developed prior to the commencement of the systematic review work. It took into account the criteria for including studies in the review, the search strategy, the method of selecting studies and the planned methodology for conducting data analysis. The following inclusion criteria were used: 1) studies published in English or Polish, 2) available in full text, 3) published in the last 5 years. An analysis of scientific publications available on the PubMed and Google Scholar platform was performed using the keywords linked by logical operators: "spinal cord injury" and "neuromodulation". As a result, 55 scientific publications were used after selection by two independent analysts. The verification at the level of abstracts and titles was carried out in such a way that all reports considered useful by at least one of the analysts were included in the next stage.

## 2. DESCRIPTION OF THE CURRENT STATE OF KNOWLEDGE

**Current indications for the use of neuromodulation**

Neuromodulation is used in the treatment of chronic pain when pharmacological therapies are not effective enough or the side effects become too severe, preventing long-term use of pharmacotherapy [7]. It is also used after an unsuccessful spine surgery, in complex regional pain syndrome, diabetic neuropathy, angina pectoris and chronic migraine. Transcutaneous Electrical Nerve Stimulation - TENS has been shown to reduce headaches and the use of pain medications, serving as a good therapeutic alternative for migraine patients. Transcutaneous supraorbital nerve stimulation is currently FDA approved for migraine prevention and transcranial magnetic stimulation is approved for the treatment of migraine with aura. [8]. Neurostimulation is also used in pelvic floor disorders - urinary retention and incontinence, as well as in gastrointestinal dysfunctions - stimulation of the sacral plexus brings benefits in IBS (irritable bowel syndrome), especially with constipation [9].

In addition, gastric electrostimulation has been shown to be effective in the treatment of nausea and vomiting in patients with gastroparesis. Vagus nerve stimulation has also found clinical application in the treatment of obesity.

Due to the frequent drug resistance of epilepsy in children, attempts were made to treat epilepsy with the use of neurostimulation in order to reduce the severity and frequency of seizures [10]. The most studied method of neurostimulation and at the same time approved by the FDA in the treatment of epilepsy in children is vagal nerve stimulation (VNS). It is well tolerated, but caution should be exercised in people with central and obstructive sleep apnea.

tDCS - transcranial direct current stimulation is considered an effective method not only in the treatment of epilepsy, but also fibromyalgia, depression and addiction. It is also used in the treatment of stroke, Parkinson's disease, multiple sclerosis, bipolar disorder or obsessive-compulsive disorder, among others.

**Contraindications to the use of neuromodulation**

In the case of an implanted neurostimulation system, one should refrain from performing MRI imaging tests, diathermy therapy and the use of monopolar electrosurgical devices. The safety and efficacy of neurostimulation in children and women during pregnancy or breastfeeding have not yet been fully described, however, peripheral stimulation in pregnant women and people with uncontrolled epilepsy is contraindicated. The use of rTMS high-frequency – transcranial stimulation in patients with a history of seizures is also considered illegal. For therapeutic rTMS, metal devices (e.g., cochlear implants, brain stimulators, or aneurysm clips) anywhere in the head, except in the oral cavity, are strictly contraindicated. Relative contraindications include the presence of a pacemaker, implantable defibrillator, a history of epilepsy, or the presence of brain damage (vascular, traumatic, cancerous, infectious or metabolic) [11].

**Mechanisms of neuromodulation action**

Regeneration of the central nervous system of adult mammals, including the spinal cord, is difficult due to the limited plasticity of neurons, the inhibitory effect of myelin, the hypertrophy of astrocytes, as well as chemicals secreted by them, limiting the growth of nerve cells [2]. Research suggests that plastic changes in the preserved ascending and descending connections are possible [12].

According to James et al., among the probable mechanisms of neuroplasticity enabling the operation of neurostimulatory methods, there is a change in the myelination pattern of certain nerve pathways [5]. Another case is tDCS - transcranial DC stimulation. This type of stimulation does not induce action potentials, however, partial depolarization of cortical neurons leads to increased excitability of disabled neural circuits, which gives the effect of increased cortical drive through the surviving / present intact nerve pathways [13]. Lower values of the current intensity resulted in a higher degree of excitability of the motor cortex. The only side effects of the method used are a short-term tingling sensation, burning sensation and reddening of the skin at the electrode site [12].

Another mechanism of action concerns the stimulation of the spinal cord. A study in rats has shown that epidural stimulation of the spinal cord increases the survival and differentiation of oligodendrocytes, protects myelin, and promotes motor regeneration by inhibiting the BMP4-Smad1 / 5/9 signaling pathway [14]. Another mechanism, described by Lee et al., assumes the inhibition of the same pathway, which in turn is expected to lead to axonal remyelination after SCI and the recovery of motor function [15]. Moreover, it is suspected that modulation of proprioceptive ascending pathways may cooperate with the natural feedback response in the control of motor response [5].

Table 1. Probable mechanisms of action of neuromodulation methods

| Type of stimulation | Mechanism |
|---|---|
| Brain stimulation | ● changes in the connections of the stimulated pathways due to neuroplasticity, altered patterns of myelination and compensatory sprouting;<br>● sub-threshold depolarization or hyperpolarisation increases or decreases the excitability of neurons |
| Spinal cord stimulation | ● modulation of proprioceptive afferent fibers interacts with the natural sensory feedback by participating in the control of motor functions;<br>● increase oligodendrocyte survival and differentiation along with the protection of myelin;<br>● increased neuronal activity leads to increased neuronal growth and neuroplasticity;<br>● denervation and synaptic silencing lead to synaptic scaling |
| Peripheral stimulation | ● increased levels of neurotrophic factors lead to plastic changes in the CNS;<br>● increased activation of muscle tissue prevents muscle atrophy and can change muscle composition |

Source: Own study based on the source [1] and [9]

## Epidural spinal cord stimulation

Epidural stimulation is based on the delivery of electric current by means of electrodes surgically placed on the dura mater of the dorsal spinal cord and was initially used as a treatment for chronic pain [15]. There is distinguished stimulation with the use of low (10-100 Hz) and high (1-10 kHz) frequencies [5]. In a large (198 patients) randomized comparative study of these two methods, conducted by Kapural et al., high-frequency stimulation proved to be more effective in the long-term treatment of back and upper limb pain [16]. Epidural stimulation can also be used to restore spinal cord motor and autonomic functions. In some cases, the degree of recovery of the normal motor function of the lower limbs and the stability of the torso allowed even standing and walking [17]. There was a significant improvement in defecation control, urination, and recovery of sexual function in the studies of Darrow et al. and Walter et al. [18, 19]. Positive results were also obtained in the treatment of symptoms of the loss of the ability to self-regulate arterial pressure - chronic hypotension and orthostatic hypotension [20, 21, 22].

Attention should be paid to developing stimulation methods that preserve deep sensation. In humans, it is significantly blocked in the case of continuous stimulation, while in the case of spatio-temporal and serial stimulation, proprioception is not limited [23].

## Transcutaneous spinal cord stimulation

This method involves electrically activating the spinal neural circuits with electrodes placed on the skin overlying the vertebrae of the lower thoracic spine and/or the lumbosacral vertebrae. The described therapeutic approach uses pulses lasting from 0.3 to 1.0 ms with a carrier frequency of 10 kHz, used at frequencies from 5 to 40 Hz [24, 25]. One of its innovative features is the use of a specific course of stimulation that does not cause pain, even when using the energy level required to transcutaneously reach the spinal neural networks [24].

The advantage of transcutaneous spinal cord stimulation over epidural stimulation is the non-invasive method of electrode implantation, lower price and wide availability, but the greater distance separating the electrodes from the nervous tissue does not allow for such precise stimulation of selected nerve pathways as in the case of epidural stimulation of the spinal cord [5]. The results obtained by Hofstoetter et al. suggest that regardless of specific mechanisms, a 50 Hz tSCS applied for 30 minutes leads to a reduction in spasticity and an improvement in physiological voluntary motor control [26]. If transcutaneous spinal stimulation becomes widespread, it is possible that this therapeutic approach will find application, replacing the systematic drugs and ablation procedures that have been used to date and have a high incidence of side effects.

A recent study by Barss et al. emphasize the significant impact of percutaneous stimulation on the improvement of cervical-lumbar connectivity of the spinal cord, which is one of the goals of rehabilitation procedures in patients with spinal cord injury. It is reported that both the rhythmic activation of the cervical spinal cord by cyclic arm movements, with the use of specially adapted ergometers, and the tonic activation of the cervical spinal cord by tSCS significantly modulate the activity of the lumbar neural networks [27]. This action may also lead to the improvement of locomotor functions, mainly walking [5, 27].

Table 2. A comparison of the advantages and disadvantages of epidural spinal cord stimulation and percutaneous spinal cord stimulation

| Compared feature | Epidural spinal cord stimulation | Transcutaneous spinal cord stimulation |
|---|---|---|
| Electrode implantation method | invasive | non-invasive |
| Availability | lower | higher |
| The cost of therapy | higher | lower |
| Precision of stimulation | higher | lower |

Source: Own study based on the source [1]

**Transcranial direct current stimulation**

Transcranial direct current stimulation (tDCS) is a non-invasive method of neuromodulation of the cerebral cortex. Its advantages include low cost, easy application and good tolerance [28]. During a tDCS session, which typically lasts 10 to 30 minutes, a DC stimulus is delivered with values in the range of 1-2 mA, which causes depolarization or hyperpolarization of the neurolemma with a consequent increase or decrease in the level of excitation of the cerebral cortex. The flow of direct current is forced by the power source, usually it is a battery, and its direction is two electrodes: active (also called polarizing) and reference. The effect of anodic polarization is the accumulation of negative charge at the anode, depolarization and an increase in the neuronal activity of the cortex. The opposite situation occurs when the active electrode is a cathode - a positive charge accumulates at the cathode, causing hyperpolarization of the cell membrane of neurons, resulting in a lower cortical excitation threshold [29]. Studies with the use of neuroimaging showed changes in blood flow after the initiation of the session, which may be associated with an increase in oxygen supply in the cortical areas, and, as a result, an increase in neuronal excitability [28].

This method, already used in the treatment of stroke, Parkinson's disease, multiple sclerosis, depression, bipolar disorder or obsessive-compulsive disorder, among others, has also been investigated as a method of treating symptoms of incomplete damage to the spinal cord.

Most recent studies on improving motor function have combined transcranial DC stimulation with other forms of rehabilitation. In a study by Potter-Baker et al. in patients treated with tDCS combined with training, an increase in the strength of the wrist muscles (22% to 10%) and hand muscles (39% to 16%) was observed immediately and three months after the end of stimulation compared to the group receiving sham stimulation [30]. Patients in another study tended to perform better on the Jebsen-Taylor hand function test and the AOU-MAL scale when tDCS was combined with robotic-assisted arm training (R-AAT).

The group subjected to active stimulation, both immediately after treatment and after two months of observation, showed better efficiency of the work of arms and hands compared to the group of sham stimulation [31]. As reported by Cortes et al., who compared tDSC of 1 mA, 2 mA and sham stimulation over three separate sessions, there was a significant improvement in the ratio of mean grip to peak velocity in the 2 mA group. There was no statistically significant difference in the results of the BBT (Box and Block Test) manual dexterity test, but a positive trend of improvement was shown [32]. In a case series of four right-handed adults with a cervical injury reported by Yozbatiran et al., after 10 treatment sessions, greater improvements in hand function and hand utilization were found in patients who received active tDCS compared to sham treatment. There was also an overall positive change in the fractional anisotropy of the cortical-spinal tract in all patients [33]. In one study, the efficacy of 20-day daily 20-minute anode tDCS sessions did not differ significantly from sham stimulation. During observation, in both groups, 5 out of 12 patients could walk without significant differences in walking speed, cadence, stride length and WISCI-II scores between the two groups [34].

The 2020 meta-analysis of studies evaluating the effect of tDCS on motor functions in patients with incomplete spinal cord injury, developed by de Araújo et al., published in 2020, showed that motor function may be significantly improved, but no statistically significant increase in muscle strength was found compared to sham stimulation [ 35].

Based on the assessment of heart rate variability in 19 patients, after a single 12-minute session of active tDCS (anodal, 2 mA) and a control session of sham tDCS of the motor cortex, it was estimated that this type of stimulation can at least partially restore the activity of the autonomic system, regardless of gender , type and time of damage [36].

The above-mentioned results mostly indicate the ability of tDCS to improve motor and autonomic functions in patients with incomplete SCI, however, due to the lack of studies on numerous groups of patients, it becomes impossible to unequivocally confirm the noticeable therapeutic results - further studies are recommended.

**Transcranial magnetic stimulation**

Transcranial magnetic stimulation (TMS) is based on the activation of neuronal axons in the cortex and subcortical white matter as a result of the induction of an electric field in the area under the coil through an easily and painlessly penetrating magnetic field of the scalp and skull. The most commonly used is rTMS - repetitive transcranial magnetic stimulation, which at low frequency (1 Hz or less) reduces the excitability of the cortex, while at high frequency (5 Hz or more) it increases excitability, although these are not absolute rules, because prolonged use of rTMS with high frequency also lowers excitability. Continuous stimulation (cTMS), delivered for 20 or 40 seconds, reduces cortical excitability, while intermittent theta stimulation (iTBS) for 3 minutes increases it [37].

TMS has been shown to be effective in treating spasticity following spinal cord injury - in a study by Nardone et al. patients receiving iTBS showed a significant increase in the amplitude of the motor-induced potentials. In these patients, the Modified Ashworth Scale (MAS) and Spinal Cord Injury Rating Scale for Spasticity (SCAT) scores were also significantly reduced after treatment.

These changes persisted up to 1 week after the end of treatment and were not observed after sham stimulation [38]. Also, the 2018 meta-analysis confirms the statistically significant effect of reducing spasticity in spinal cord injuries after using TMS [39].

According to a meta-analysis on the treatment of neuropathic pain associated with spinal cord injury, by Gao et al. from 2017, patients who received rTMS obtained greater pain reduction than those who received sham rTMS intervention (placebo), although the results did not reach statistical significance [40]. The result of a more recent meta-analysis based on 11 randomized clinical trials on this subject shows no significant effect of rTMS on neuropathic pain compared to placebo [41].

**Peripheral stimulation**

Peripheral stimulation is divided into functional electrostimulation - FES and somatosensory stimulation - TENS/SES. Both methods allow to improve the functions of paralyzed muscles, including the improvement of grasping, reaching, walking and function of the urinary bladder [5, 42, 43]. FES electrically activates several muscles in a coordinated and sequenced manner through the nerve fibers to achieve a specific function. The FES system generates a series of electrical stimuli that evoke action potentials in intact peripheral nerves, which additionally activate muscle contractions. Intensity of the stimulus determines the number of activated nerve fibers, and thus the strength of muscle contraction [42]. This action is used to treat spasticity and improve locomotor and manual functions. Comparing the effect of FES to TENS Garcia et al. did not show a statistically significant difference – both treatments significantly reduced the spasticity of the hip adductors and knee extensors [43]. TENS is also an established non-pharmacological method of pain control in which electric current is applied through electrodes placed on the skin [44,45,46]. After the use of somatosensory stimulation - TENS/SES in patients with neuropathic pains resulting from incomplete spinal cord injury, a reduction in the intensity of pain was observed as compared to the state before treatment [45]. The most effective effect of TENS in the treatment of neuropathic pain was observed when electrodes were placed around the pain area [46, 47]. However, according to Zeb et al., this method cannot be used in pregnant women, people with uncontrolled epilepsy, in case of indications for stimulation over carotid bifurcation, and in diagnosed allodynia - in the region of the damaged nerve [44].

The mechanism of changes resulting from the application of peripheral stimulation is unknown [5, 48]. Among the potential mechanisms, there is an increase in the level of neurotrophic factors affecting the high plasticity of the neural circuits of the central nervous system [5]. Other studies indicate a reduction in the amount of activated microglia [48].

**Brain-machine interface**

Brain-machine interfaces (BMI), also known as brain-computer interfaces (BCIs), are neural prostheses that allow devices to communicate directly with different parts of the brain, usually the cerebral cortex, and thus enable control of prosthetic limb functions or controlled movement of paralyzed muscles. Thus, they have the potential to help patients with spinal cord injury [49].

Among the recent advances in the creation of interfaces enabling the control of prostheses or exoskeletons, replacing lost motor functions or supporting their rehabilitation, one can mention the development and use of a system based on signals from EEG and EEA for moving the exoskeleton of the hand in paraplegic patients, enabling them to eat and drink on their own in non-laboratory conditions [50]. In 2019, the first report on the successful long-term use of wireless epidural multichannel recorders for the activation of a neuroprosthetic exoskeleton in a patient with tetraplegia was published [51].

There have also been developed devices that, through the FES stimulation (functional electrical stimulation) coordinated with BMI, allowed the restoration of the reaching and grasping functions in a person with tetraplegia [52]. In another patient with tetraplegia, a return of isolated finger movements was observed with continuous cortical control of six different wrist and hand movements [53]. In another study by Selfslagh et al., two patients with paraplegia restored the ability to walk safely with the support of 65-70% of body weight, and at the same time improved the function of the cardiovascular system and gradually decreased dependence on walking aid, as well as partial neurological regeneration, indicating a significant rate of motor improvement in one of the patients [54].

The limitation of the use of this technology is currently, among other things, a high price. The importance of ethical issues regarding safety, autonomy, responsibility, psychosocial identity, consent, privacy and data security of patients assisted by such devices is also raised [55].

## 3. CONCLUSIONS

Restoring motor, sensory and autonomic functions is a priority in the treatment of patients with spinal cord injury. For this purpose, an interdisciplinary approach is required, involving a team consisting of a physiotherapist, psychologist, dietician, speech therapist and the support of the patient's family. Apart from pharmacological treatment and rehabilitation, neuromodulation may be a helpful form of therapy. According to recent studies, the recovery of motor, sensory and autonomic functions by patients is possible to a degree that exceeds the current therapeutic possibilities, but with a small size of the test groups, which prompts us to conduct further clinical trials with a higher strength of evidence, as well as research on improving technology and a deeper understanding of the mechanisms which stand behind the effectiveness of neuromodulation methods.

A developing topic of research is the use of neuromodulation in other diseases - diabetic neuropathy, angina, chronic migraine, epilepsy, depression, Parkinson's disease and many others. Also in this area, there is a need for randomized trials to be carried out on more numerous research groups.

A modern therapeutic tool – brain-machine interfaces, starting to more and more widely demonstrate their clinical potential, can cooperate with neuromodulation methods, increasing their effectiveness. A great challenge is to reduce the price of these devices so that they can be widely available to patients in need.

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