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REVIEW ARTICLE

Pharmacological Interventions and Rehabilitation Approach for Enhancing Brain Self-repair and Stroke Recovery

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Abstract: Neuroplasticity is a natural process occurring in the brain for the entire life. Stroke is the leading cause of long term disability and a huge medical and financial problem throughout the world. Research conducted over the past decade focused mainly on neuroprotection in the acute phase of stroke while very little studies target the chronic stage. Recovery after stroke depends on the ability of our brain to reestablish the structural and functional organization of neurovascular networks. Combining adjuvant therapies and drugs may enhance the repair processes and restore impaired brain functions. Currently, there are some drugs and rehabilitative strategies that can facilitate brain repair and improve clinical effect even years after stroke onset. Moreover, some of the compounds such as citicoline, fluoxetine, niacin, levodopa, *etc*. are already in clinical use or are being trialed in clinical issues. Many studies are also testing cell therapies; in our review, we focused on studies where cells have been implemented at the early stage of stroke. Next, we discuss pharmaceutical interventions. In this section, we selected methods of cognitive, behavioral, and physical rehabilitation as well as adjuvant interventions for neuroprotection including noninvasive brain stimulation and extremely low-frequency electromagnetic field. The modern rehabilitation represents a new model of physical interventions with the limited therapeutic window up to six months after stroke. However, previous studies suggest that the time window for stroke recovery is much longer than previously thought. This review attempts to present the progress in neuroprotective strategies, both pharmacological and non-pharmacological that can stimulate the endogenous neuroplasticity in post-stroke patients.

Keywords: Stroke, neuroprotection, recovery, drugs, rehabilitation, rehabilitation, stem cell.

1. INTRODUCTION

1.1. Stroke

Stroke is a medical condition associated with the sudden onset of focal or generalized neurological dysfunction, caused by circulation disorders in the relevant part of the brain, spinal cord, and retina, persisting more than 24 hours [1, 2]. Stroke still remains the main cause of disability among the professionally active people over 40 years of age. However, first of all, stroke is a disease that usually affects older people. In countries where the phenomenon of society aging is observed, there are increasing numbers of stroke diagnosis, despite the growing possibilities of modern medicine, including the development of preventive care. In this way, between 1990 and 2010, the number of first strokes increased by 68% [3].

The consequence of stroke appears suddenly and includes: numbness, sudden unilateral weakness, speech disorders, ataxia, diplopia, and visual loss. All of these symptoms are known to be typical for stroke diagnosis. On the other hand, less commonly occurring, but still present in some patients, are symptoms classified as atypical which include: amnesia, dysarthria, anosognosia, dysphagia, foreign accent, headache, confusion, or alien hand syndrome [1].

1.2. Stroke Recovery

Reducing brain injury and promoting maximum recovery of patients are the major goals of stroke management. The effectiveness of the therapy depends mainly on the early diagnosis of the pre-hospital, rapid, and correct specialist diagnosis, and above all on the early implementation of treatment and rehabilitation. The existing state of knowledge suggests that due to the high plasticity of the brain, immediate and long-term rehabilitation allows reducing the neurological deficit. Neurological deficits caused by stroke are the most harmful at the beginning and they improve over time. The process of recovering of post-stroke patients is extremely heterogeneous, due to the extent of stroke, the degree of spontaneous regeneration, the phenomenon of neuroplasticity, selection of drugs, and appropriate rehabilitation.

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That is why scientists and doctors are trying to find new methods that could improve patients recovery [4-8].

1.3. Neuroplasticity

The term "neuroplasticity" was introduced in the late 1960s and it is associated with the ability of nervous tissue to create new connections, aimed with reorganization, adaptation, and self-healing of the brain, as well as learning and memory processes [9]. Neuroplasticity is a common phenomenon of the nervous system that plays a pivotal role in the spontaneous recovery of post-stroke patients. The compensatory plasticity of a damaged brain is a completely different process than plasticity in a properly functioning brain. This process begins in critical conditions related to edema, inflammation, apoptosis, metabolic disorders, and degeneration of nerve fibers. In the case of stroke, neuroplasticity processes begin immediately after an ischemic event. The phenomenon of brain plasticity in response to damage has been proved in several studies [10, 11]. Present theories on neuroplasticity are based on the Hebb concept created in 1949. Hebb concept says that to change the strength of the connection between neurons, it is necessary to stimulate the postsynaptic neuron by presynaptic neuron effectively and repetitively. Repeated stimulation of the neuron would cause biochemical and anatomic changes that would lead to strengthening the connection between the two neurons. Over time, some improvements were added and explained *i.e*. the phenomenon of weakening of the neuronal connection [12].

In the case of post-stroke patients, neuroplasticity plays a very important role in self-healing. Neuroplasticity is based on strengthening existing synaptic pathways and then creating new connections. Existing but weaker connections between brain centers are activated. As a result, the defective function can be restored partially or completely, because other cortical or subcortical structures assume the function of the damaged area [9]. In studies conducted on animal brains, synaptogenesis was found in the penumbra area (directly adjacent to the damaged tissue), as well as in the contralateral to the damaged hemisphere. The human brain, after damage due to the stroke, has the ability to restore its function, through the use of a distributed neural networks, which are located in the regions that were not be touched by the brain infarction. These functional neural networks can be in the intact hemisphere, reducing lateralization. Changes within the ischemic penumbra, the area that surrounds the damaged ischemic core, start relatively quickly after stroke, giving first symptoms of early recovery. Surviving neurons located on the border of infarction, but with the adequate blood perfusion, undergo structural, and functional remodeling. Neurons compete with each other for available space in the cortex. It happens because neurons are able to take over the functions of nearby neurons. This is the mechanism of how cerebral cortex can rebuild as a result of differentiation or stroke [5]. Sometimes the return of motor function can be spectacular, but improving lost function can be observed for a long time after the onset of stroke. The intensity and speed of changes that lead to the return of motor function are correlated with the onset of stroke. If the time is shorter, the greater will be the intensity of changes and their speed. The recovery of lost functions is associated with the mapping of the brain in the process of synaptogenesis of the adjacent area, with damaged cerebral tissue [12]. It has been shown that neurons which play complex functions, such as memory trace, are distributed throughout the cortex and are not localized in a single brain region [13].

Unfortunately, the mechanism of initiated remapping of lost functions remains unclear. It is suggested that local environment may change after a stroke-injury to simplify neurons to compete more effectively with neurons in intact tissues [14].

1.4. Growth Factors and Other Neuromodulators

There are many different factors that have an impact on neuroplasticity after stroke including: glial-derived thrombospondin 1 and 2, growth-inducing proteins (neuromodulin, CAP23, mArCKS), and growth factors. These factors are able to induce the creation of new axons and support the augmented elaboration of spines and dendrites. The existence of factors promoting neuroplasticity could not exist without factors that inhibit the outgrowth of axons such as RTN4 (NOGO), semaphorin 3A, neuropilin 1, ephrin A5, or chondroitin sulphate proteoglycan that is a result of brain or spinal cord trauma, expression of these negative factors limits the sprouting of axons. Inhibiting the negative factors that limit the reorganization of neurons to promote stroke recovery is a common approach in experimental studies. Regenerative processes within the brain tissue are limited and are regulated by tissue environmental properties, which are affected by changes in the physiology of the organism [15]. Neurotrophic factors affect neurogenesis through the conditionality of the growth of new neurons and the survival of existing ones [16]. The traditional division of neurotrophic factors consists of three protein families: the classic neurotrophins, ligands of Glial cell Derived Neurotrophic Factor (GDNF), and neuropoetic cytokines [15]. Neurotrophins are synthesized and secreted by nerve cells of the brain, spinal cord, and cells of dependent tissue. The classical neurotrophins are: Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT4/5). NGF induces differentiation and regulates the survival of cholinergic neurons of septum, striatum and basal nucleus. Moreover, it promotes differentiation of precursors into the sympathetic neurons in the adrenal glands, acts on fibroblasts and Schwann cells [16]. BDNF as well as NGF effect on neurite growth cones acting as a chemoattractant. The structures dependent on BDNF are hippocampal neurons, the fibers upward mechanoreceptors and the retinal ganglion cells [17]. The action of neurotrophins largely depends on the availability of other neurotrophins because they act synergistically, *e.g*., BDNF and NT3 are involved in synaptogenesis between motoneurons and centripetal fibers Ia in the spinal cord, enhance serotonin turnover, and also affect the function of serotonergic neurons of the CNS [18]. In turn, BDNF may affect the granule cells of the cerebellum and midbrain dopaminergic neurons only in the presence of NT4, while influences the spiral ganglion cells only in the presence of NT3. While GDNF cooperating with Ciliary NeuroTrophic Factor (CNTF), similarly as the

classic neurotrophins, increase the survival of sensory neurons and spinal cord motor neurons [19]. In turn, the factor derived from Pigment Epithelium-Derived Factor (PEDF) has a strong protective and anti-apoptotic effect on neurons, especially in the cerebellum and spinal cord [20], Mesencephalic Astrocyte-derived Neurotrophic Factor (MANF) and Cerebral Dopamine Neurotrophic Factor (CDNF) have the ability to protect and functional regeneration of dopaminergic neurons [21]. The survival, maturation, and functioning of the nervous system also influenced by the cytokines do not belong to neurotrophins, for example: Epidermal Growth Factor (EGF), Insulin-like Growth Factor 1 (IGF-1), basic Fibroblast Growth Factor (bFGF), Hepatocyte Growth Factor (HGF), Stromal Derived Factor-1α (SDF-1α), interleukin 6 (IL-6), erythropoietin (EPO), thrombopoietin (TPO), Granulocyte-Colony Stimulating Factor (G-CSF), Leukemia Inhibitory Factor (LIF), Vascular Endothelial Growth Factor (VEGF), Stem Cell Factor (SCF) [22]. These biomolecules regulate the neuroregeneration and/or neurodegeneration processes and strong impact on stem and progenitor cells [16]. SCF is a cytokine belonging to the control factors of the differentiation of stem cells to neurons and glia, as well it participates in neuron-glia, and neuron-neuron interactions. Due to the capacity of SCF to induction of regeneration of cells lost during brain injury, this cytokine seems particularly essential for the course of compensatory neuroplasticity processes [23]. VEGF is one of the most important proangiogenic agents, critical for blood vessel growth in the nervous system. VEGF-dependent blood vessel growth may be crucial for nervous tissue regeneration during the recovery process. VEGF is essential for cross-talk between the cardiovascular and nervous systems, which is particularly important in the case of brain stroke that damages both blood vessels and nerve cells. Furthermore, a lot of recent studies demonstrate that VEGF possesses significant non-vascular functions in the nervous system, as it promotes neurogenesis, glial growth, and nerve repair [24].

Achieving recovery in post-stroke patients may also be related to the neurogenesis process, which is closely related to neuroplasticity. Neurogenesis is regulated by many factors, including neurotrophins, growth factors, hormones, neurotransmitters, and microenvironmental factors. All of them are synthesized and secreted by nerve cells of the brain, spinal cord, and cells of dependent tissue. Generation of new, fully functioning nerve cells arises during the differentiation of neuronal stem cells (NSC) present in an adult, completely formed brain. NSCs are characterized by the ability to differentiate into the appropriate phenotype, as well as the ability to have an unlimited number of mitotic divisions. In some areas of the brain, the process of neurogenesis occurs throughout life, but the rate of proliferation and the ability of newly emerging neurons to survive decrease with age. Nerve cells arise in areas of the brain responsible for learning, memory, and perception of olfactory sensations, mainly in the subventricular zone (SVZ) and the subgranular zone (SGZ). The augmented proliferation of NSC has been seen in the hippocampus and SVZ after brain-damaged in the first week after injury. Unfortunately, the proliferation of NSC with time return to its previous state [25, 26].

2. STANDARD TREATMENT OF POST-STROKE PATIENTS

The most important factor for determining the most appropriate treatment for stroke patients is to evaluate which type of stroke a patient is undergoing. That is why several tests like physical examination, blood tests, computerized tomography scan, or cerebral angiogram must be done before drug supplementation. Firstly, initial treatment is aimed at securing basic vital function. Connection of a drip (for the medicines, fluids, and nutrients administration) or oxygen (to increase the supply of oxygen to the brain) is aimed at improving the vital functions of the patient [27].

In the case of ischemic stroke, the most effective treatment for saving brain tissue is recanalization of the plugged vessel using thrombolytic therapy. Existing studies and clinical trials have shown that recombinant tissue plasminogen activator (rt-PA - alteplase), administrated in maximal 4.5 hours after stroke onset, can reduce the motor and sensor disability by up to 13% [28, 29]. rt-PA has to be administrated in maximal 4.5 hours after stroke onset because hypoxic brain cells undergo irreversible modifications and die. After this time, treatment with a tissue plasminogen activator is no longer useful [27]. The mechanism of action of rt-PA is to bind to clots rich with fibrin and degrades it by plasminogen-to-plasmin transformation, thereby exerting its thrombolytic action [30]. On the basis of Guidelines for the Early Management of Patients With Acute Ischemic Stroke from 2018, rt-PA combined with antiplatelet drugs is recommended. Data from many studies show that benefits from this combination outweigh the increased possibility of a cerebral haemorrhage. Furthermore, antiplatelet drugs reduce the possibility of secondary ischemic stroke. On the other hand, rt-PA is not recommended in patients who are administrated with heparin, thrombin and Xa inhibitors, and GPIIb/IIIa inhibitors [27].

3. DRUGS TO ENHANCE MOTOR RECOVERY

Drugs that can improve recovery are related to neuroplasticity and neuronal growth. Usually, are not related to reducing infarct volume or in enhancing brain reperfusion. Many studies evaluate the potential role of D-amphetamine, Levodopa, Fluoxetine, Niacin, Inosine, and Citicoline in improving motor recovery in post-stroke patients or in animal models with different results.

3.1. D-amphetamine

Amphetamines in medical practice were introduced in 1935. In the beginning, they were used to treat narcolepsy but over time, amphetamines gain new possible uses: anorexia, ADHD or rehabilitation after brain injuries. Amphetamines stimulate the release of norepinephrine, dopamine, and possibly serotonin. Usually, doctors prescribe d-isomer of amphetamine – D-amphetamine, also known as Dexamphetamine, because of its most potent psychostimulant effect. D-amphetamine is also rapidly absorbed and distributed in high concentration in most tissues, especially the brain and cerebrospinal fluid [31]. Some studies suggest that D-amphetamine enhances motor recovery in post-stroke patients [31]. First reports concerning on the ef-

fectiveness of D-amphetamine in enhancing motor recovery in post-stroke patients comes from 1988 from a study conducted by Crisostomo *et al*. Patients treated with D-amphetamine showed significant improvement in motor function in Fugl-Meyer scale after 3 days of treatment ($p < 0.05$) [32]. Walker-Batson *et al*. also confirmed that D-amphetamine combined with physical therapy increases the motor recovery in post-stroke patients ($p = 0.047$). First results were visible after 1 week after D-amphetamine administration and were still evident after 12 months [33]. On the other hand, there are also studies showing a lack of benefits from D-amphetamine administration in post-stroke patients. In a study conducted by Sonde *et al*. patients receiving D-amphetamine did not differ meaningly from the patients who had been receiving a placebo. After months of D-amphetamine therapy, Fugl-Meyer motor scale showed very similar results for amphetamine-treated patients and for placebo-treated patients (62.5 + 27.8 *vs*. 65.2 + 23.3 respectively) [34]. The most recent randomized clinical trial conducted by Goldstein et al. showed on among 64 patients that administration of D-amphetamine in combination with physical therapy did not enhance the recovery of motor functions ($p = 0.58$) [35]. To evaluate the effectiveness of D-amphetamine in post-stroke patients, it is required to take into consideration the limitations of these works. First of all, the population in all the studies were very small. Patients motor functions were assessed in various scales. Additionally, the dose and time for D-amphetamine administration were also different in those studies. All of these parameters could affect the final result.

3.2. Levodopa

Levodopa (LD) is a major drug used in the treatment of Parkinson's disease (PD), introduced in the 1960s and still remains as a gold standard in reducing the motor symptoms of PD. LD is used to replace losses of dopamine. To work properly, LD must undergo *via* few metabolic pathways in which decarboxylation is the most important to obtain dopamine, and lately, be converted to norepinephrine [36]. Because specific neurotransmitters like norepinephrine are important in neuroplasticity process, LD was evaluated in many studies, to be a potentially motor improvement drug. Klaus Scheidtmann *et al*. conducted a double-blind, randomized and placebo-controlled study in which 100 mg of LD was administrated daily to post-stroke patients, in combination with physical therapy. Motor functions were assessed with the Rivermead Motor Assessment (RMA) scale. After 3 weeks of LD supplementation, patients compared to placebo-controls showed a significant improvement in motor recovery ($p < 0.004$) [37]. Furthermore, Acler *et al*. showed that administration of LD in combination with carbidopa, decarboxylase inhibitor, allowed to improve manual dexterity and speed walking ($p < 0.01$) [38]. On the other hand, double-blind, placebo-controlled trial conducted by Restemeyer *et al*. showed that LD administrated in a single dose has no effect on improving motor functions [39]. Above findings suggests the potential, beneficial role of LD in post-stroke motor recovery. Most of the described trials, unfortunately, had a low population or used crossover design. At this moment, two large clinical trials (SELEIS and DARS) that evaluate the effectiveness of LD and physiotherapy are undergoing and perhaps will be able to deliver new information about LD treatment.

3.3. Fluoxetine

Fluoxetine is a well-known antidepressant medicine belonging to the Selective Serotonin Reuptake Inhibitors (SSRIs). It is used to treat depression, bulimia nervosa, stress, social anxiety, and panic disorders but it is also used in stroke. Fluoxetine's effect is based on augmented concentrations of the serotonin in the synaptic cleft for enhancing postsynaptic neuronal activity. Fluoxetine has also neuroprotective and anti-inflammatory effect. In a study by Lim *et al*., those functions were examined in the rat model. This study showed that intravenously administrated Fluoxetine effectively reduced ischemic volume [40]. In 2009, Berends *et al*. conducted a pilot, crossover, placebo-controlled study on 10 patients after ischemic stroke. To evaluate the effectiveness of Fluoxetine, single dose (20 mg) was administrated and muscle activation was measured. Results showed that after Fluoxetine intake, muscle activation was augmented in agonist and antagonist muscles of the paretic arm ($p < 0.05$). However, the increased activity of muscles was not related to motor functions [41]. An increasing number of scientific reports concerning the positive effect of Fluoxetine on the improvement of motor function has led to the creation of large clinical trials. In 2011, 118 post-stroke patients participated in the FLAME clinical trial. All volunteers were randomly assigned to placebo or fluoxetine. The improvement of motor recovery was evaluated by the Fugl-Meyer scale. All participants start the supplementation within 5 – 10 days after symptoms onset and were aged between 18 and 85 years. The results after 90 days of combined therapy (Fluoxetine + physical therapy) showed significant improvement in motor recovery ($p = 0.003$) [42]. On the other hand, in 2019, second, large, multicenter, double-blind, randomized, placebo-controlled, FOCUS clinical trial that recruited 3127 adult patients were conducted. In contrast to the FLAME trial, patients in the FOCUS trial were diagnosed with ischaemic and haemorrhage stroke. All participants start to administrate 20 mg of Fluoxetine or placebo between 2 – 15 days after stroke onset. Volunteers were evaluated on the basis of the modified Rankin Scale at 6 months. The results demonstrated in the FOCUS trial did not show any beneficial function of Fluoxetine on the improvement of motor functions (OR = 0.951, 95% Cl 0.839 – 1.079) [43].

3.4. Niacin

Niacin, also known as Nicotinic Acid or Vitamin B3 is the main drug used for reducing LDL cholesterol and increasing HDL cholesterol level. Niacin decreases the level of TNF-alpha and TGF-Beta, decreases fibrinogen levels and inhibits lipolysis, increases angiogenesis and expression of endothelial nitric oxide synthase. Binding of Niacin results in inhibition of adenylyl cyclase, resulting in a reduction of intracellular cAMP levels. Reduced cAMP inactivate Protein Kinase A which is necessary for intracellular lipase activation. The final effect causes a reduction in free fatty acids

production from triacylglycerol hydrolysis [44]. Niacin can be a very important medicine for post-stroke patients because of the increase of HDL. In 2004, Paterno *et al*. documented that HDL has a neuroprotective function in the preclinical stroke rat model. A research team showed the reduction of neuronal damage after ischemic stroke onset. The results suggest that HDL has possible antioxidative and anti-inflammatory mechanisms [45]. The animal model was also used in a study by Cui *et al*., in which the level of inducing and/or inhibiting factors of neuroplasticity was measured. Rats were treated with Niacin, 24h after stroke onset for 14 days. Niacin treatment showed a significantly increased level of neuronal growth factors and decreased of Nogo receptor ($p < 0.05$), resulting in augmented neuronal outgrowth [46]. Niacin is not only a good neuroprotective agent but also can significantly improve motor and sensory behavior by reducing infarct volume [47]. Unfortunately, there are no data concerning the effectiveness of Niacin in human stroke treatment.

3.5. Inosine

Inosine is a well-known drug with neuroprotective, cardioprotective, and anti-inflammatory activities. This purine nucleoside is generated by deamination of adenosine [48]. Studies on animal models showed that Inosine can meaningly increase the number of sprout corticospinal tract fibers that arise from the undamaged hemisphere and enter the denervated areas. Photothrombotic injury model used in a study by Zai *et al*. showed that Inosine could significantly improve motor function in rats ($p < 0.01$). This experiment confirmed the role in promoting axon sprouting reported previously by Benowitz *et al* [49]. In the same Zai's study, Inosine was investigated at the molecular level in corticospinal neurons. The results showed that Inosine cause changes in genes involved in protein ubiquitination (downregulation of *ube4A*, *ube2E3*, and *ube2M*), proteasomal proteins (downregulation of *hspA8*, *psmC5*, *psmB4*, *psmB5*, *psmA7*) and downregulation of heat shock protein. The most unexpected effect of Inosine showed highly significant increased expression of proteins in complement cascade (c1qa, c1qB, c1qy, c1, c2, c3, c4B, adipsin) with $p < 10^{-11}$ [50]. In a study conducted by Chen *et al*., Inosine-treated rats showed very strong motor recovery in comparison to saline-treated rats. To explain this phenomenon, Chen *et al*. investigated axonal reorganization after stroke. Results showed that post-stroke niacin-treated rats had an augmented number of crossed corticofugal axons (8 – 10-fold higher than normal rats and 2 – 3-fold higher in post-stroke saline-treated rats) [51].

3.6. Citicoline

Cytidine-5'-diphosphocholine, also known as Citicoline, is phosphocholine donor in phosphatidylcholine synthesis. Because of the phospholipases activation and phospholipid hydrolysis during ischemic stroke, Citicoline has become an interesting substance with potential use as a drug to support the recovery of motor function [52]. Citicoline has been shown to release dopamine and stimulate tyrosine hydroxylase activity and support glucose metabolism and increased the choline level in the brain [53]. There are also several studies proving that Citicoline reduces the infarct volume in stroke animal models [54, 55]. Since 1980 to 2000, there were a few clinical trials concerning the effectiveness of Citicoline in enhancing motor recovery in post-stroke patients. A clinical trial conducted in Europe showed that Citicoline promoted motor recovery and improved neurological functions [56]. The first clinical trial in the USA enrolled 259 patients that were treated with Citicoline within 24h of stroke onset, resulting in the reduction of the neurological deficits and improving the functional outcome [57]. The next clinical trial performed in the USA provided new information about Citicoline impact in post-stroke patients. Citicoline showed significant reduction of lesion volume. Ischemic volume in the placebo group expanded by 180% in comparison to 34% in Citicoline-treated patients [58]. In 2012 Davalos *et al*. conducted a randomized, placebo-controlled, ICTUS clinical trial in which 2298 patients participated. Patients were assigned to Citicoline or placebo in a 1:1 ratio, within 24h after the stroke onset. The results showed no differences between both groups, suggesting that Citicoline is not efficacious for ischemic stroke treatment [59]. The possible explanation of variances in the result from previously described study and ICTUS clinical trial may be related to lack of neuroimaging of ischemic penumbra, which in fact prevent to evaluate stroke evolution. What is more, patients received rt-PA which makes it difficult to assess the effectiveness of Citicoline. Between the first and last clinical trial concerning the positive impact of Citicoline on motor recovery in post-stroke patients, 32 years have passed. Major differences between all described studies are related to stroke treatment. New medicines, which are actually a gold standard in stroke treatment, show much better effect than drugs used a few decades ago, and this phenomenon can influence on the effectiveness of Citicoline in improving motor functions (Table **1**).

4. STEM CELL THERAPY

One of the latest advances in modern medicine, concerning on the treatment of patients suffering from various diseases, including stroke, is the rapidly growing field of stem cell therapy. It involves the use of stem or progenitor cells to regenerate the damaged tissue or organs [60]. In the case of post-stroke patients, stem cell therapy would restore the proper functioning of the central nervous system. In many studies, stem or progenitor cells like neural stem cells, neural precursor cells, embryonic stem cells, mesenchymal stem cells, and induced pluripotent stem cells showed a beneficial effect in restoration of lost neuronal and vascular elements. Transplanted cells survived, proliferated and differentiated [48]. Recently, a clinical trial performed by Moniche *et al*. showed that patients receiving a higher dose of bone marrow mononuclear cells had better restoration of motor function in post-stroke patients [61]. Unfortunately, stem cell therapy is linked with many complications, which traditional pharmaceuticals have not. Achieving the right treatment or dosing is the main limitation that in future may be overcome [48].

5. MODERN REHABILITATION TO MAXIMIZE POSTSTROKE RECOVERY

After a stroke, spontaneous recovery is observed but this recovery is usually not complete. This process can be modulated and amplified by suitably carried rehabilitatio60. Reha-

Table 1. Summary of described drugs with their mechanism of action and application in various disseases.

Drug	Mechanism of Action	Medical Indications for Applying	Refs.
D-amphetamine	Stimulating the release of norepinephrine, dopamine and possibly serotonin	Attention Deficit Hyperactivity Disorder, Narcolepsy	[31]
Levodopa	Use to replace losses of dopamine and norepinephrine	Parkinson's Disease	[36, 37]
Fluoxetine	A selective serotonin-reuptake inhibitor (SSRI) at the reuptake pump of the neuronal membrane, enhancing concentration of the serotonin in the synaptic cleft, thus increasing postsynaptic neuronal activity.	Depression, Bulimia Nervosa, Stress, Social Anxiety, Panic Disorders, Obsessive-compulsive Disorder	[40]
Niacin	Lowering the concentration of free fatty acids from triacylglycerol hydrolysis by inhibiting adenylate cyclase and reducing intracellular cAMP concentration.	Hyperlipidemia	[44]
Inosine	The precise mechanism of action remains unclear.	Cardioprotective, neuroprotective and anti-inflammatory applications	[48]
Citocoline	A donor of choline in phosphoglycerides biosynthesis. Increasing the concentration of choline in the brain by activating tyrosine hydroxylase and supporting metabolism of glucose.	Citocolin is an ingredient in many dietary supplements. Used to support and maintain the proper functioning of the nervous system.	[52, 53]

bilitation is one of the most important parts of care in stroke patients. Consequences of stroke affect many different areas of functioning (motor, speech, and language, cognition, swallowing, sensation, vision, social participation, *etc*.). Therefore, the rehabilitation process should be directed at many various deficits. The framework for programming the most effective rehabilitation should be the International Classification of Functioning, Disability, and Health (ICF) including components such as body functions and structure, activities and participation as well as environmental factors [62]. To reduce mortality, decrease institutionalization needs, enhance recovery, prevent complications, and increase independence, a multi-specialist team should be involved in this process [63].

5.1. Physical Medicine in Post-stroke Patients

Motor impairment refers to a huge number of patients after stroke. Therefore, physical medicine is a key part of the rehabilitation process. To ensure the best possible recovery, physical mobilization should be initiated soon after the incident, after stabilizing the patient's condition [64]. Very early mobilization (within 24 hours of stroke onset) does not give clear benefits in comparison with usual care and may be connected with some hazards at least in some stroke survivors. Further studies in this field are needed [65].

Motor learning is based on repetition [66]. Therefore, intensive, repetitive task-specific training, which involves the active practice of task-specific motor activities, is recommended after stroke [67, 68]. According to the Cochrane review, not one of the physical rehabilitation approaches is more effective than any other. Physical rehabilitation using a mix of components from different available approaches, tailored to the patient's needs, gives beneficial effects on functional recovery and independence after stroke [69].

Despite the participation in rehabilitation programs, a large proportion of patients after stroke remain functionally impaired. Therefore, methods (used as independent therapies or in addition to the conventional treatment) that could improve the recovery process and enhance functional improvement are still being sought. As a rule, to establish clear benefits of these therapies more evidence is needed, but some of them seem to be promising (Table **2**).

5.2. Aerobic Training

An indicator of cardiorespiratory fitness - VO_2 peak, ranged from 8 to 22 ml/kg/min in stroke survivors, which means on average approximately 53% VO_2peak of their healthy peers [94]. The low cardiorespiratory fitness, caused by both pre-stroke factors, post-stroke deconditioning and immobilization, is a risk factor for mortality [95], functional impairment [96] and may limit the patient's ability to participate in effective physical therapy at a level needed to stimulate neuroplasticity processes [72]. That is why improving cardiovascular fitness with aerobic training may bring many benefits for post-stroke survivors. According to Cochrane review, cardiorespiratory training reduces disability during or after usual stroke care [97]. Systematic reviews and meta-analyses indicate the functional effect of this type of exercise both in early [73] and chronic stage after the cerebrovascular incident [70]. Aerobic exercise also reduces risk factors of recurrent stroke and other cardiovascular diseases [98], improves motor learning and cognitive function [99] and is recommended as a basic form of physical activity for the general elderly population [100] as well as for patients after stroke [101]. American Heart Association/American Stroke Association recommend aerobic exercises with moderate intensity (Rating of Perceived Exertion 11-14 in 6–20 scale), 3-5 days per week, 20-60 min/session [101].

Recently, much attention in the literature is devoted to the association of aerobic training with the stimulation of brain plasticity. Systematic review and meta-analysis show that aerobic training after stroke increases brain-derived

Table 2 Systematic reviews regarding the effectiveness of selected therapies used in post-stroke rehabilitation

Therapy	Goal of Therapy	Included Studies/no of Participants	Results	Refs.
Aerobic Exercise (AE)	mobility in long-term stroke survivors	9/680	AE may improve mobility long after a stroke. AE combined with physiotherapy, improves walking capacity and gait speed	[70]
	Brain-Derived Neurotrophic Factor (BDNF)	11/303 2/40 (stroke)	AE may contribute to increased levels of BDNF in neurological populations	[71]
	neuroplasticity outcomes: neurotrophic factors (BDNF, IGF-I, and NGF), neuronal morphology (synaptic and dendritic change), and cortical reorganization	30 (human and animal studies)	Forced AE at moderate to high intensity increases BDNF, IGF-I, NGF, and synaptogenesis in multiple brain regions at least in animal models of stroke	[72]
	aerobic capacity and physical functioning within six months after stroke	11/423	AE early after stroke enhances aerobic capacity by improving VO2peak and walking distance in moderately to mildly affected individuals (robust evidence)	[73]
	indicators of health, functioning and quality of life	25	AE of moderate to high intensity is effective in improving aerobic fitness, maximal walking speed and walking endurance	[74]
	neuroprotection and brain repair	47 (animal models)	Early-initiated (24-48h post-stroke) moderate forced exercise reduce lesion volume and protected perilesional tissue against oxidative damage and inflammation at least for the short term (4 weeks)	[75]
Repetitive task training (RTT)	upper limb function/reach and lower limb function/balance activities of daily living, global motor function, quality of life/health status and adverse events	33/1853	RTT improves arm function, hand function and lower limb functional measures (low-quality evidence) as well as walking and functional ambulation (moderate-quality evidence) up to six months post treatment Insufficient evidence for the risk of adverse events	[68]
Constraint-induced movement therapy (CIMT)	upper limb function	42/ 1453	Limited improvements in motor impairment and motor function, without convincingly reducing disability	[76]
Muscle strengthening	improvement of strength, balance and walking abilities	10/355	Progressive resistance training seemed to be the most effective treatment to improve strength the lower limb, walking distance, fast walking and balance. Training should be intensive and tailored to the patients' needs	[77]
Electromechanical and robot-assisted training	activities of daily living, arm function, and arm muscle strength	45/1619	Therapy might improve activities of daily living, arm function, and arm muscle strength High quality of the evidence, but high heterogeneity of therapies	[78]
	gait	36/1472	Electromechanical-assisted gait training with physiotherapy is more effective in achieving independent walking than training without these devices Training is the most effective in the first three months after stroke and for patients unable to walk	[79]
Mirror therapy	motor function and motor impairment after stroke, activities of daily living, pain, visuospatial neglect	62/1982	Significant positive effect on motor function, motor impairment and improvement in activities of daily living (moderate-quality evidence) Significant positive effect on pain (low-quality evidence) No clear effect for improving visuospatial neglect	[80]

Table. 2 contd….

Therapy	Goal of Therapy	Included Studies/no of Participants	Results	Refs.
	balance, gait, and motor function	17/633	Large effect for gait speed improvement Small positive effect for mobility and lower extremity motor recovery. No effect for balance capacity	[81]
Non-Invasive Brain Stimulation (NIBS) including: transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS	NIBS for hemispatial neglect	10/226	NIBS combined with other therapies has positive effect on hemispatial neglect and performance in ADL (moderate-quality evidence) Both excitatory and inhibitory stimulations are effective.	[82]
	NIBS for gait speed	10/226	NIBS combined with other therapies are effective to improve gait speed (moderate-quality evidence)	[83]
	NIBS for paretic limb force production	23	Improvements in paretic limb force after tDCS and rTMS Positive effects on force production by increasing cortical activity in the ipsilesional hemisphere and decreasing cortical activity in the contralesional hemisphere.	[84]
	tDCS for function and activities of daily living	32/748	Very low to moderate quality evidence of the effectiveness of tDCS (anodal/cathodal/dual) versus control (sham/any other intervention) for improving ADL performance after stroke.	[85]
Virtual reality (VR) Virtual reality	UL function, gait, balance, motor function	72 /2470	VR as an adjunct therapy may be beneficial for in improving UL function and ADL Insufficient evidence for gait speed, balance, participation and quality of life	[86]
	ICF domains (Body Structures, Body Functions, Activity, and Participation)	54/1811	Positive effect in Body Function and Body Structure. Inconclusive effect in the domains Activity and Participation	[87]
Neuromuscular electrical stimulation (NMES)	activities of daily living and motor function of UL	20/431	Statistically significant but very low quality evidence (heterogeneity, low participant numbers and lack of blinding) for benefits from FES applied within 2 months of stroke on primary outcome of ADL	[88]
	shoulder subluxation, shoulder pain, motor function of UL	10	ES in addition to conventional therapy can be used to prevent or reduce shoulder subluxation early after stroke (<6 months). No evidence of pain reduction or an improvement in the arm motor function.	[89]
	lower limb activity, gait speed, Berg Balance Scale, timed Up and Go, 6-minute walk test, Modified Ashworth Scale, and range of motion	21/ 1481	Moderate benefits (especially when with combination with other interventions or treatment time within either 6 or 12 weeks) on gait speed, balance, spasticity, and range of motion. No significant effect for walking endurance	[90]
	spasticity, range of motion	29/940	ES in combination with other intervention is associated with spasticity reductions and improvements in range of motion	[91]
Transcutaneus Electrical Nerve Stimulation (TENS)	spasticity	10/360	TENS as additional treatment to physical interventions can lead to additional reduction in chronic post-stroke spasticity.	[92]
Repetitive peripheral magnetic stimulation (rPMS)	rPMS for activities of daily living and functional ability	3/121	Inadequate evidence to permit any conclusions about routine use of rPMS for people after stroke	[93]

UL – upper limb, ES –electrical stimulation, FES –functional ES.

neurotrophic factor (BDNF) concentration in animal models [72] and in people with neurological disorders [71]. The greatest increase in BDNF following training was observed in the hippocampus, the cortex and the striatum [102, 103]. It is suggested that aerobic exercise may be combined with motor task practice for improving the effectiveness of rehabilitation [104]. It is also reported that aerobic exercise at moderate to high intensity increases others plasticity-promoting factors like insulin-like growth factor-I (IGF-I) or nerve growth factor (NGF), and synaptogenesis in multiple brain regions [72].

5.3. Constraint-Induced Movement Therapy (CIMT)

The concept of CIMT is based on the opinion that the limitation of movement is caused by disuse rather than by an inability to perform. Therefore, intensive therapy of the affected arm is carried out to prevent the stroke-related inability, while limiting the use of an intact limb [105]. This therapy resulted in cortical reorganization connected with an increased cortex area responsible for innervation of affected upper extremity [106]. CIMT may be used only in a selected group of patients with some degree of voluntary movement (at least 20 degrees and 10 degrees of the active wrist and finger extension, respectively), without cognitive deficits and with limited pain and spasticity. Therefore, is not applicable to people with severe paresis after stroke [64, 76]. CIMT is delivered in a relatively long time – even 6 hours per day, which may result in better treatment outcomes. According to Cochrane review, CIMT compared with traditional rehabilitation is associated with limited improvements in motor impairment and motor function, but do not reduce disability [76].

5.4. Strength Training

Muscle function is a very important determinant of functional performance. Meanwhile, stroke survivors are at higher risk of sarcopenia development than the healthy population [107]. Muscle power and contraction velocity may be even more important determinants of functional status than age in stroke survivors [108]. Research indicates that progressive resistance training after stroke improves muscle strength and may be beneficial for some aspect of functional performance [77]. Resistance training with intended high speed of contraction should be also considered because such training may have implications for regaining fast muscle strength in stroke survivors [109].

Resistance training is also recommended as one of the main components of physical activity after stroke by the American Heart Association/American Stroke Association [101].

5.5. Robotics

Robotic-assisted rehabilitation is becoming an increasingly popular form of treatment, also for stroke patients. According to Lin's *et al*. [110] definition, "robotic devices use end-effectors, exoskeletons, or harnesses to guide or assist the planned motions, enabling high training intensity (*e.g.*, high repetitions of movements)". In stroke patients, these devices are used in both the upper limb's rehabilitation [78] and to improve the function of the lower limb - primarily to improve gait [79]. Calabro` *et al*. [111] list three main types of lower-limb rehabilitation robotic systems: stationary systems (exoskeleton-type devices and programmable foot end-effector devices), overground walking systems and wearable robotic walking devices. According to Cochrane review, people undergoing gait training, which included therapy with electromechanical-assisted training (as an additional element of therapy), more easily achieved gait independence than trained without these devices. This therapy is probably more effective for patients in the earlier phase after stroke and for those initially without gait ability [78, 79].

5.6. Mirror Therapy

Mirror therapy is performed by positioning a mirror in the person's midsagittal plane (between limbs), thus reflecting the non-paretic side and giving the impression as if it was the affected side. This may give the visual illusion that affected limb functions normally [80]. The last Cochrane review indicates that mirror therapy may be effective for improving motor function, activities of daily living and pain relieve [80, 112]. Mirror therapy is most often used in upper limb rehabilitation, but may also have a beneficial effect used for improving function in which lower limb are engaged, like gait speed [81].

5.7. Noninvasive Brain Stimulation (NIBS)

Some of the methods like Transcranial Direct Current Stimulation (tDCS) or repetitive Transcranial Magnetic stimulation (rTMS) are aimed at restoring the interhemispheric balance by inhibiting healthy hemisphere or stimulating the lesioned one. These methods noninvasively modulate brain activity, may induce brain plasticity and facilitate stroke recovery. It is assumed that low-frequency rTMS decreases cortical excitability, whereas high-frequency rTMS increases cortical excitability [113]. Anodal stimulation performed during tDCS increases the neuronal excitability of the stimulated area, while cathodal stimulation decreases it [85]. In some systematic reviews and meta-analyses have been shown that NIBS combined with other therapies may be effective to improve gait speed [83], hemispatial neglect and performance in ADL [82], and paretic limb force [84] in patients after stroke.

5.8. Computer-based Training Programs/Virtual Reality

Virtual reality training and interactive video gaming allows patients to interact with the environment and allows them to receive feedback about their activities. Because it is a very attractive and motivating therapy, it can enable stimulated performance of functional tasks at a higher dose than traditional therapies [114]. Those methods are used for improving not only motor function (upper limb, global motor function, gait, balance) but also for cognitive function. The advantage of this therapy is that it can be used without direct supervision of the therapist, *e.g*. in a home environment [86].

5.9. Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) is used for its therapeutic effect (strengthening muscle contraction, improving voluntary motor control, providing sensory stimula-

tion) as well as neuroprosthetic effect (replacing or assisting voluntary muscle contraction during a functional task. This functional electrical stimulation (FES) relates for example, to the stimulation of foot dorsiflexion during gait [115, 116]. NMES may be used as an interesting tool for motor learning, particularly in patients with paresis – this method gives the possibility to participate in goal-oriented repetitive movement therapy [115]. There are some reports that NMES may induce a greater increase in the plasma BDNF level. After 8-week NMES therapy, changes in BDNF plasma level were greater than after the control period in patients with type 2 diabetes [117]. In Kimura's *et al*. study [118], NMES was even more effective for enhancing serum BDNF level than an exercise in healthy males. Research in this topic is needed in stroke patients.

5.10. Magnetic Field

In addition to transcranial brain stimulation (rTMS) magnetic field is also used for peripheral stimulation (repetitive peripheral magnetic stimulation-rPMS). Magnetic field allows the stimulation of deep muscle structures to contraction, which cannot be reached by traditional electrical stimulation. This therapy is painless and does not require the placement of electrodes [93]. However, due to the insufficient evidence of the effectiveness of rPMS based on the recent Cochrane review, there are no clear indications for the routine use of rPMS in stroke patients and additional trials with large sample sizes are needed [93].

Another promising form of magnetic field application in the treatment of patients after stroke is extremely low-frequency electromagnetic field therapy (ELF-EMF). Research shows that the use of EL-EMF may enhance neuroplasticity and functional recovery after stroke by increasing nitric oxide generation and its metabolism, which have both neuroprotective and cytotoxic properties [119], as well as by increasing BDNF concentration [120].

FUTURE PERSPECTIVES AND CONCLUSION

This review focusses on neuroprotective strategies, neural repair and different types of rehabilitation methods that can facilitate brain repair and improve clinical effect even years after stroke onset. The brain plasticity is the hallmark of a synaptic phenomenon that is mainly a stimulus-dependent process. Recovery after stroke is a long and complex process in which certain large brain lesions require not only new anatomical substrate but also renew or creating new network connectivity. However, it is very important to know that stroke is not the regional problem of infarct area but it the distribution of the whole brain networks, resulting in a wide scope of dysfunction and impairments. Complex treatment with pharmacological strategies and rehabilitations interventions with other new therapies such as stem cell transplantation may enhance the repairing power to maximize recovery after stroke. There is the need for creating the next generation of restorative/rehabilitative therapies targeted the entire brain networks not only motor function.

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