**УДК616.74-009**

**R. A. Belyaev[1], A.V. Miroshnichenko[2*]**

## SPASTICITY: MODERN THERAPEUTIC SOLUTIONS THROUGH THE PRISM OF PATHOGENESIS

[1]Department of Neurology, Psychiatry and Rehabilitation, Non-Commercial Joint-Stock Company «Medical University of Karaganda» (Karaganda, Kazakhstan)
[2]School of Medicine, Non-Commercial Joint-Stock Company «Medical University of Karaganda» (Karaganda, Kazakhstan)

*Анна Викторовна Мирошниченко – интерн Школы медицины Некоммерческого акционерного общества «Медицинский университет Караганды» (Караганда, Казахстан); e-mail: ctnsuguda@mail.ru, тел.: +7 747 493 8798.

The study of the pathophysiological mechanisms of spasticity continues, but its heterogeneity, combination and mutual influence of various mechanisms in its development is already quite clear. Optimal management of patients depends on understanding the underlying physiology of spasticity, understanding its natural course, assessing the impact on the patient, and an integrated approach to minimizing this impact.

*Key words:* spasticity; upper motor neuron syndrome; pathophysiology; spasticity scales; treatment

Spasticity is one of the most common syndromes in neurology, occupying a significant share among the causes of disability, leading to a significant limitation of not only labor, but also daily activity, the ability to self-service, and as a result, significantly affects the quality of life of patients and their families. Spasticity is not an independent problem of increased muscle tone, but part of the problem of loss of motor control. This disorder is detected in 40-80% of patients who have had a stroke, and in more than 15% of cases leads to severe disabling consequences [2,55,54]. Spasticity prevails in the picture of cerebral palsy - 78-88% of cases are associated with this pathology [14]. Spinal cord injury is associated with spasticity in 65% of cases, and muscle relaxant therapy is required in 35% [15].

Up now, lots of the theoretical and experimental studies, results of clinical researches have been accumulated, which make it possible to judge the causes and mechanisms of the development of spasticity. There are also quite a lot of recommendations on the diagnostic and treatment decisions according to the patients with this pathology management. In this regard, there is a need to analyze and generalize the accumulated information, which is reflected in this review.

Lance (1980) has defined spasticity as a movement disorder characterized by a rate-dependent increase in tonic stretch reflexes and an increase in tendon reflexes resulting from hyperexcitability of the stretch reflex, as one of the components of the upper motor neuron syndrome [24]. However, this definition has a number of disadvantages, in the form of an exclusion of the influence of the sensory component. In this connection, within the framework of the SPASM project (2005), spasticity was presented as "a violation of sensory-motor control resulting from damage to the upper motor neuron, manifested as intermittent or sustained involuntary muscle activation" [5]. In 2018, spasticity was broadly defined as "involuntary muscle hyperactivity in the presence of central paresis" [7].

Spasticity is not specific syndrome for any disease, while it has nosological, pathophysiological and clinical heterogeneity, and it's observed in a variety of organic lesions of the brain and spinal cord.

Spasticity is more commonly found in the flexor muscles of the upper limb (flexors of the fingers, wrist, and elbow) and in the extensor muscles of the lower limb (extensors of the knee and ankle joints) [51].

### *Pathophysiological basis of spasticity*

The formation of spasticity is due to 2 levels of influence: the spinal (areas of the brain and spinal cord that control motor function) and the supraspinal level. The cerebral motor cortex, as well as the posterior parietal cortex and the primary somatosensory cortex, provide the initial processing and formation of command motor signals. At the same time, spasticity does not develop in case of an isolated lesion of these structures [9,31].

At the spinal level, pathological changes can manifest themselves in the motor unit (a motoneuron and its innervated muscules) and in the structure of spinal cord reflexes (withdrawal and stretch reflexes). In this case, a violation of the activating and inhibitory mechanisms of influence takes its place.

Activating spinal mechanisms of spasticity are:

1. Primary increased excitability of alpha motor neurons based on the active properties of membranes. Voltage-dependent constant internal currents of Ca 2+ and Na + ions increase and lengthen the response of motoneurons to synaptic excitation. These internal currents are capable of leading to prolonged depolarization (plateau potentials).

2. Strengthening the flexion reflex, which is due to disturbances in the work of the descending reticulospinal tract and spinothalamic tract reasoning the occure pathological pain reactions to minor stimulies.[9,31]

Spinal inhibitory mechanisms of spasticity place a more significant clinical role.

Monosynaptic excitation Ia, which underlies the dynamic and tonic components of the stretch reflex, can be inhibited by various reflex pathways, both at the supraspinal level and due to secondary intracellular changes in the spinal cord below the level of the lesion. Presynaptic inhibition of afferent type Ia-endings, through axo-axon GABAergic synapses, can cause spasticity in multiple sclerosis, with spinal cord injury, thou in the pathogenesis of stroke it`s role is quiet small. In the case of a stroke, damage to the descending tract results in a decrease in the control of inhibition in the spinal cord, causing an increase in the stretch reflex, which indicates the development of spasticity as a facilitating adaptive mechanism. [13,28]. Type Ia disynaptic reciprocal inhibition, the imbalance of which causes reflex-induced joint contraction of antagonist muscle groups, is another spinal mechanism of spasticity. Clinically, it manifests as spastic weakness, usually observed via amyotrophic lateral sclerosis [9,31].

When the differential control of spinal neurons is disturbed by a descending monoaminergic impulse from the brain stem, the change of effect on the anterior and posterior horns of the spinal cord takes place. It causes next effects: In the acute phase of traumatic myelopathy, inhibitions of monoaminergic excitation don`t activate long-term reflexes. In the chronic stages of damage, motor neurons become highly sensitive to residual monoamines available below the level of the lesion, leading to the development of spasticity.

The effect on these mechanisms underlies the action of the «baclofen», which partially acts on motor neurons and suppresses their excitability by reducing Ca 2+ and shortens the duration of monosynaptic excitatory postsynaptic potentials. [8]

Spinal cord neuroplasticity in the form of receptor hypersensitivity against the background of axonal outgrowth or morphological changes in denervated receptors can also play a role in the development of motor spastic symptoms [8,9,31].

Disorders of the corticospinal, reticulospinal and vestibulospinal pathways are recognized as the most important in the pathophysiology of the development of spasticity. It has been established that an isolated pyramidal lesion does not affect the pathology of tone, since the ipsilateral accessory motor and premotor areas and the contralateral motor cortex can take over part of the pyramidal tract functions and prevent the development of spasticity.

Muscle tone is maintained by a balance of the inhibitory influence of the corticospinal and dorsal reticulospinal tracts, and the activating influence of the medial reticulospinal and vestibulospinal tracts. In partial myelopathy involving the lateral cord (like while early phase of the multiple sclerosis), spasticity may occur predominantly in the extensor muscles, but spasticity may also occur in the flexors. Severe myelopathy extending to all four descending pathways results less spasticity compared to the isolated involvement of the lateral funiculus. At the same time, an isolated dorsal lesion of the reticulospinal tract with preservation of the corticospinal tract causes significant spasticity and spasms against a background of shallow paresis. With an isolated lesion of the anterior spinal cord, only hyperreflexia with normal tone can be observed. [8,9,31]

Variations in the severity of spasticity that occur in practice are most often associated with the degree of involvement of the dynamic and static components of the stretch reflex ("phase" and "tonic" spasticity).

"The Jackknife Phenomenon"

This phenomenon is manifested in a sudden decrease in tone after primary hypertonicity. The reverse stretch reflex mediated by the Golgi tendon organ is activated when the muscle is stretched sustainably, resulting in a sudden relaxation of the muscle. This speed-dependent increase in stretch reflexes is associated with increased muscle spindle excitability and velocity sensitivity of spindle type-Ia afferents, resulting in over-activation of spinal cord alpha motor neurons. [9,31,38]

Rigidity

Unlike spasticity, it does not depend on the speed of the movement, is detected both in the flexor and extensor muscles, and the phenomenon of "lead pipe" or "gear wheel" is typical during the examination [9]. Rigidity is pathognomonic for such pathologies as Parkinson's disease, progressive supranuclear palsy, neuroleptic malignant syndrome, and others [3,9].

Chart 1 – Modified Ashworth Spasticity Scale

| Instructions for Using the Modified Ashworth Scale (MAS) | |
|---|---|
| - The patient should lie on his back;<br>- for examining the flexor muscle, give the limb the position of maximum flexion and extend it as much as possible in 1 second;<br>- for examining the extensor muscle, give the limb the position of maximum extension and bend it as much as possible in 1 second;<br>- determine points using the rules below. | |
| Determination of points (according to R.W.Bohannon, M.B.Smith, 1987): | |
| 0 | Muscle tone is not increased. |
| 1 | A slight increase of tone in the form of short-term tension and rapid relaxation of the muscle or minimal resistance at the end of passive flexion or extension. |
| 1+ | A slight increase of tone in the form of short-term muscle tension with minimal resistance while continuing passive movement (less than half the amplitude). |
| 2 | A more pronounced increase of muscle tone, felt during almost the entire passive movement; while the affected(e) segment(s) of the limb is easily amenable to movement. |
| 3 | A significant increase of muscle tone, passive movements are difficult. |
| 4 | The affected segment(s) are immobile when flexed or extended. |

*Diagnostic Spasticity Scales*

The following scales are mainly used to assess the state of the muscles: modified Ashworth scale (MAS) and its validated Russian version - spasticity scale of the Scientific Center of Neurology (2015) [46], as well as the modified Tardieu Scale (MTS), which brings the possibility of both scoring the degree of muscle response and using the Tardieu index [22].

Chart 2 – Spasticity Scale of the Scientific Center of Neurology of the Russian Academy of Medical Sciences (Kadykov A.S., Manvelov L.S., 2015)

| Score | Movement characteristic |
|---|---|
| 0 | The tone is normal |
| 1 | Slight increasinge (minor resistance) |
| 2 | Moderate increase (although the tone is increased, but the resistance is not difficult to overcome) |
| 3 | Pronounced increase (during the study, it is difficult to overcome muscle resistance) |
| 4 | Rapid increasing (dynamic contracture, passive movement limited) |
| 5 | Highly severe increasing (passive movements are almost impossible) |

Chart 3 – Assessment of muscle response according to the modified Tardieu scale

| Score | Interpretation |
|---|---|
| 0 | Does not resist during passive movements |
| 1 | Slight resistance when moving passively, absence of a clear at a certain angle |
| 2 | An accurate interrupting passive movement stop at a certain angle, followed by continuation of movement |
| 3 | Decaying clonus less than 10 s, provoked by stretching of the tendon and occurring at a certain angle |
| 4 | Continuous clonus for more than 10 seconds, provoked by stretching of the tendon and occurring at a certain angle |
| 5 | Fixed joint |

**Treatment methods of spasticity**

Methods for the treatment of spasticity have been developed and dynamically changed over decades, and therefore there is a fairly rich experience in the field of tactics for correcting muscle tone disorders, depending on its etiology, time of occurrence, concomitant diseases, and treatment goals. A stepwise approach is needed in clinical management, starting with more conservative methods and progressing to more invasive surgical procedures [16,39].

*Correction of spasticity-provoking factors.* Spasticity is often the result of hypersensitivity to pain stimuli, therefore, at the first stage, it is necessary to identify obvious and possible provoking factors. In patients with the development of spasticity after spinal cord injury, the following factors are considered: pregnancy, uncomfortable posture, low temperature, circadian rhythms, skin lesions, bowel and bladder function problems, a phase of the menstrual cycle, psychological stress, deep vein thrombosis, systemic infection [34].

*Systemic pharmacotherapy with muscle relaxants.* Baclofen is a central-acting muscle relaxant, an agonist of gamma-aminobutyric acid receptors (GABAB receptors), which inhibits the transmission of excitation at the level of mono- and polysynaptic reflexes in the spinal cord [40]. Baclofen is the only FDA-approved gamma-aminobutyric acid agonist [19]. Currently, there is a lot of research on the use of baclofen not to treat spasticity, but to achieve and maintain abstinence or reduce alcohol consumption in alcohol dependent individuals [10,30].

Sudden withdrawal of baclofen, regardless of the route of ingestion, can cause an activation of the autonomic system due to the loss of inhibition of the monoamine pathway, and is accompanied by various neuropsychiatric manifestations [25]. The clinical picture of the withdrawal syndrome can mimic various pathologies, such as delirium, severe sepsis, meningitis, neuroleptic malignant syndrome, convulsive disorder, or alcohol withdrawal syndrome [20]. On average, continuous 5 months of using baclofen can lead to delirium on withdrawal [40].

An alternative to oral baclofen is intrathecal applying of baclofen through a spinal catheter and an implanted pump. This method has been used since the 80s of the 20th century, and is currently widely used in the treatment of severe disabling spasticity via cerebral palsy, stroke, spinal cord and brain injuries. The main advantages of this form of applying are a reduction in the effective dose of the drug, and a decrease in cognitive side effects [12,44,53].

Tizanidine hydrochloride is an imidazoline alpha-2-adrenergic agonist with activity both at the spinal and supraspinal levels [6,18]. The drug is effective for the treatment of spasticity caused by multiple sclerosis, acquired brain injury or spinal cord injury [18]. The monotherapy with tizanidine is as effective as baclofen or diazepam, while being better tolerated. In some cases, combination therapy of tizanidine + baclofen can be used to increase the management of spasticity [1].

An overdose of tizanidine can lead to mental status disorders, nephropathy, bradycardia and arterial hypotension [4,27,42]. The drug can be used in various dosage forms: solid oral, liquid dosage form for parenteral, intranasal and oral administration, buccal and transdermal [17,41].

Tolperisone hydrochloride is a central-acting muscle relaxant that inhibits voltage-gated Na+ and, to a lesser extent, N-type Ca2+ ions channels. The drug inhibits spinal reflexes, and weakens the conduction of excitation along the descending reticulo-spinal pathways. The development and research of tolperisone has been carried out since 1956, but its full pharmacodynamics is not completely clear [35,49].

Compared with baclofen, tolperisone is slightly less effective or has an equal muscle relaxant effect, but provides a greater improvement of daily

activity, causes fewer side effects associated with muscle weakness and drowsiness [1,26,29,43].

Dantrolene is a peripherally-acting muscle relaxant, a peripherally acting ryanodine receptor-1 antagonist that inhibits the release of calcium from the sarcoplasmic reticulum of skeletal muscles, which leads to muscle relaxation [48]. It is indicated for the treatment of spasticity, malignant hyperthermia, and has a neuroprotective effect [21,32,45,52]. It is possible to take dantrolene orally, intravenously and intranasally [45,52]. Side effects are manifested mainly in the form of weakness of the skeletal and respiratory muscles, in rare cases, respiratory arrest is possible, as well as neuropsychiatric disorders (drowsiness and confusion), liver dysfunction [23].

Other drugs. Gabapentin is an anticonvulsant drug which can also be used in the treatment of neuropathic pain. Gabapentin reduces spasticity in patients with spinal cord injury, but the mechanism of action is still not all clear. This effect may be due to the inhibition of presynaptic release of glutamate [36,37].

Diazepam is a drug from the group of benzodiazepines with sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant effects. The mechanism of its action in spasticity is mainly associated with interaction with BNZ2 receptors and an increase in the affinity of GABA for GABA-receptors, increasing the total inhibition of neuronal excitation, thus inhibiting monosynaptic and polysynaptic pathways, and directly inhibiting the functions of motor nerves, enhancing their function to relax skeletal muscle spasticity [33]. Diazepam is considered one of the first-line drugs for the treatment of spasticity in patients with cerebral palsy, however, due to the many side effects, its short-term use is currently preferred [11,33,50].

In addition to systemic drugs in the treatment of spasticity, targeted impact is possible - neurolysis, chemodenervation, blockade of nerves and motor points (by using lidocaine, naropine), cryoablation, chemiodenervation with botulinum toxin, and the intrathecal applying of baclofen. These procedures are predominantly used to treat focal spasticity or when the systemic effects of drugs are unacceptable at the required therapeutic doses [16,39,47].

In the management of spasticity, the need of abandoning passive expectant tactics becomes clear.

Up to the moment, despite the advances made in the pathophysiology of spasticity, there are still many unclear points. Researches into the medical treatment of spasticity still do not include a high-level evidence base. Well-designed and sufficiently powerful studies with using functional outcome measures are needed to test interventions used in clinical practice.

**REFERENCES**

1 Agarwal S., Patel T., Shah N., Patel B.M. Comparative study of therapeutic response to baclofen vs tolperisone in spasticity [Text] / Agarwal S. Patel T., Shah N., Patel B.M. // Biomed Pharmacother. — 2017. — V. 87. — P.628-635.

2 Bavikatte G., Subramanian G., Ashford S., et al. Early Identification, Intervention and Management of Post-stroke Spasticity: Expert Consensus Recommendations [Text] / Bavikatte G., Subramanian G., Ashford S., Allison R., Hicklin D // J Cent Nerv Syst Dis. — 2021. — V. 13. — P. 117. doi: 10.1177/11795735211036576.

3 Bhidayasiri R., Sringean J., Reich S.G., et al. Red flags phenotyping: A systematic review on clinical features in atypical parkinsonian disorders [Text] / Bhidayasiri R., Sringean J., Reich S.G., et al. // Parkinsonism Relat Disord. — 2019. — V. 59. — P.82-92.

4 Brucculeri M.J., Garcia J. Potassium wasting nephropathy in the setting of tizanidine overdose: a case report [Text] / Brucculeri M.J., Garcia J. // J Med Case Rep. — 2021. — V. 15(1). — P.250.

5 Burridge J.H., Wood D.E., Hermens H.J. et al. Theoretical and methodological considerations in the measurement of spasticity [Text] / Burridge J.H., Wood D.E., Hermens H.J., Voerman G.E., Johnson G.R., van Wijck F., Platz T., Gregoric M., Hitchcock R., Pandyan A.D. // Disabil Rehabil. . — 2005. — V. 27(1-2). — P.69-80.

6 Danilov A.B. The use of tizanidine (Sirdalud) in the treatment of pain and spasm [Text] / Danilov A.B. // RMZh= «RMJ» (Russian Medical Journal). . — 2012. — V. 31. — P.1543.

7 Dressler D., Bhidayasiri R., Bohlega S., et al. Defining spasticity: a new approach considering current movement disorders terminology and botulinum toxin therapy [Text] / Dressler D., Bhidayasiri R., Bohlega S., Chana P., Chien H.F., Chung T.M., Colosimo C., Ebke M., Fedoroff K., Frank B., Kaji R., Kanovsky P., Koçer S., Micheli F., Orlova O., Paus S., Pirtosek Z., Relja M., Rosales R.L., Sagástegui-Rodríguez J.A., Schoenle P.W., Shahidi G.A., Timerbaeva S., Walter U., Saberi F.A. // J Neurol. — 2018. — V. 265(4). — P.856-862.

8 Elbasiouny S.M., Moroz D., Bakr M.M., et al. Management of spasticity after spinal cord injury: current techniques and future directions [Text] / Elbasiouny S.M., Moroz D., Bakr M.M., Mushahwar V.K. // Neurorehabil Neural Repair. . — 2010. — V. 24(1). — P.23-33.

9 Ganguly J., Kulshreshtha D., Almotiri M., et al. Muscle Tone Physiology and Abnormalities [Text] / Ganguly J., Kulshreshtha D., Almotiri M., Jog M. // Toxins (Basel). — 2021. — V. 13(4). — P.282.

10 Garbutt J.C., Kampov-Polevoy A.B., Pedersen C., et al. Efficacy and tolerability of baclofen in a U.S. community population with alcohol use disorder: a dose-response, randomized, controlled trial [Text] / Garbutt J.C., Kampov-Polevoy A.B., Pedersen C., Stansbury M., Jordan R., Willing L., Gallop R.J. // Neuropsychopharmacology. — 2021. — V. 46(13). — P.2250-2256.

11 Goyal V., Laisram N., Wadhwa R.K., et al. Prospective Randomized Study of Oral Diazepam and Baclofen on Spasticity in Cerebral Palsy [Text] / Goyal V., Laisram N., Wadhwa R.K., Kothari S.Y. // J Clin Diagn Res. — 2016. — V. 10(6). — RC01-5. doi: 10.7860/JCDR/2016/17067.7975.

12 Gunnarsson S., Lemming D., Alehagen S., et al. Dosing Patterns In Treatment of Disabling Spasticity With Intrathecal Baclofen [Text] / Gunnarsson S., Lemming D., Alehagen S., Berntsson S., Ertzgaard P., Samuelsson K. // Rehabil Nurs. — 2021. — V. 46(6): — P.315-322.

13 Hiersemenzel L.P., Curt A., Dietz V. From spinal shock to spasticity: Neuronal adaptations to a spinal cord injury [Text] / Hiersemenzel L.P., Curt A., Dietz V. // Neurology. — 2000. — V. 54 (8). — P.1574-1582.

14 Hollung S.J., Hägglund G., Gaston M.S., et al. Point prevalence and motor function of children and adolescents with cerebral palsy in Scandinavia and Scotland: a CP-North study [Text] / Hollung S.J., Hägglund G., Gaston M.S., Seid A.K., Lydersen S., Alriksson-Schmidt A.I., Andersen G.L. // Dev Med Child Neurol. — 2021. — V. 63(6). — P.721-728.

15 Holtz K.A., Lipson R., Noonan V.K., et al. Prevalence and Effect of Problematic Spasticity After Traumatic Spinal Cord Injury [Text] / Holtz K.A., Lipson R., Noonan V.K., Kwon B.K., Mills P.B. // Arch Phys Med Rehabil. . — 2017. — V. 98(6). — P.1132-1138.

16 Iskra D.A., Kovalenko A.P., Koshkarev M.A., et al. Spasticity: from pathophysiology to treatment [Text] / Iskra D.A., Kovalenko A.P., Koshkarev M.A., Dyskin D.E. // Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova. — 2018. — V. 118(10). — P.108-114. (In Russ.)

17 Jagdale S., Brahmane S., Chabukswar A. Optimization of Microemulgel for Tizanidine Hydrochloride [Text] / Jagdale S., Brahmane S., Chabukswar A. // Antiinflamm Antiallergy Agents Med Chem. . — 2020. —V. 19(2). — P.158-179.

18 Kamen L., Henney H.R. 3rd, Runyan J.D. A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury [Text] / Kamen L., Henney H.R. 3rd, Runyan J.D. // Curr Med Res Opin. — 2008. — V. 24(2). — P.425-439.

19 Kent C.N., Park C., Lindsley C.W. Classics in Chemical Neuroscience: Baclofen [Text] / Kent CN, Park C, Lindsley CW // ACS Chem Neurosci. — 2020. — V. 11(12). — P.1740-1755.

20 Khanal R., Oli S., Chan Gomez J., et al. Severe Case of Oral Baclofen Withdrawal Resulting in Mechanical Ventilation [Text] / Khanal R., Oli S., Chan Gomez J., Tahir S., Bhandari B., Komanduri S. // J Investig Med High Impact Case Rep. — 2022. — V. 10. — P.23247096211060584.

21 Kocogullari C.U., Emmiler M., Cemek M., et al. Can dantrolene protect spinal cord against ischemia/reperfusion injury? An experimental study [Text] / Kocogullari C.U., Emmiler M., Cemek M., Sahin O., Aslan A., Ayva E., Tur L., Buyukokuroglu M.E., Demirkan I., Cekirdekci A. // Thorac Cardiovasc Surg. — 2008. — V. 56(7). — P.406-411.

22 Kovalenko A.P., Misikov V.K., Iskra D.A., et al. Tardieu scale in the diagnosis of spasticity [Text] / Kovalenko A.P., Misikov V.K., Iskra D.A. Koshkarev M.A., Sinelnikov K.A. // Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova= S.S. Korsakov Journal of Neurology and Psychiatry. — 2019. — V. 119(9). — P.83-90. (In Russ.)

23 Krause T., Gerbershagen M.U., Fiege M., et al. Dantrolene--a review of its pharmacology, therapeutic use and new developments [Text] / Krause T., Gerbershagen M.U., Fiege M., Weisshorn R., Wappler F. // Anaesthesia — 2004. — V. 59(4). — P.364-373.

24 Lance J.W., Feldman R.G., Young P.R., et al. Spasticity: Disordered Motor Control / Lance J.W., Feldman R.G., Young P.R., Koella W.P. [Text] // Symposium synopsis. — Chicago, IL: USA: Year Book Medical Publishers, 1980. — P.485-494.

25 Leo R.J., Baer D. Delirium associated with baclofen withdrawal: a review of common presentations and management strategies [Text] / Leo R.J., Baer D. // Psychosomatics. — 2005. — V. 46(6). — P.503-507.

26 Li M., Huang Y., Chen R., et al. Efficacy and safety of tolperisone versus baclofen among Chinese patients with spasticity associated with spinal cord injury: a non-randomized retrospective study [Text] / Li M., Huang Y., Chen R., Liu N., Fang S. // Braz J Med Biol Res. — 2021. — V. 54(11). — 293. doi: 10.1590/1414-431X2021e11293.

27 Li X., Jin Y. Irreversible profound symptomatic bradycardia requiring pacemaker after tizanidine/loxoprofen combination therapy: a case report [Text] / Li X., Jin Y. // J Int Med Res. — 2018. — V. 46(6). — P.2466-2469.

28 Lundstrom E., Smits A., Borg J., et al. Four-fold increase in direct costs of stroke survivors with spasticity compared with stroke survivors without spasticity: the first year after the event [Text] / Erik Lundström., Anja Smits, Jörgen Borg., Andreas Terént // Stroke. — 2010. — V. 41(2). — P.319-324.

29 Luo D., Wu G., Ji Y., et al. The comparative study of clinical efficacy and safety of baclofen vs tolperisone in spasticity caused by spinal cord injury [Text] / Luo D., Wu G., Ji Y., Zhang Z., He F., Mou X., Zhu Q., Yang B. // Saudi Pharm J. — 2020. — V. 25(4). — P.639.

30 Minozzi S., Saulle R., Rösner S. Baclofen for alcohol use disorder [Text] / Minozzi S., Saulle R., Rösner S. // Cochrane Database Syst Rev. — 2018. — V. 11(11). — P.125. doi: 10.1002/14651858.CD012557.pub2.

31 Mukherjee A., Chakravarty A. Spasticity mechanisms - for the clinician. [Text] / Mukherjee A., Chakravarty A. // Front Neurol. — 2010. — V. 1. — P.149. doi: 10.3389/fneur.2010.00149

32 Nakamura-Maruyama E., Miyamoto O., Okabe N., et al. Ryanodine receptors contribute to the induction of ischemic tolerance [Text] / Nakamura-Maruyama E., Miyamoto O., Okabe N., Himi N., Feng L., Narita K., Keep R.F., Yamamoto T., Nakamura T. // Brain Res Bull. — 2016. — V. 122. — P.45-53.

33 Peck J., Urits I., Crane J., et al. Oral Muscle Relaxants for the Treatment of Chronic Pain Associated with Cerebral Palsy [Text] / Peck J., Urits I., Crane J., McNally A., Noor N., Patel M., Berger A.A., Cornett E.M., Kassem H., Kaye A.D., Viswanath O. // Psychopharmacol Bull. . — 2020. — V. 50(4 Suppl 1). — P.142-162.

34 Phadke C.P., Balasubramanian C.K., Ismail F., et al. Revisiting physiologic and psychologic

triggers that increase spasticity [Text] / Phadke C.P., Balasubramanian C.K., Ismail F., Boulias C. // Am J Phys Med Rehabil. — 2013. — V. 92(4). — P.357-369.

35 Quasthoff S., Möckel C., Zieglgänsberger W., et al. Tolperisone: a typical representative of a class of centrally acting muscle relaxants with less sedative side effects [Text] / Quasthoff S., Möckel C., Zieglgänsberger W., Schreibmayer W. // CNS Neurosci Ther. — 2008. — V. 14(2). — P.107-119.

36 Rabchevsky A.G., Patel S.P., Duale H., et al. Gabapentin for spasticity and autonomic dysreflexia after severe spinal cord injury [Text] / Rabchevsky A.G., Patel .SP., Duale H., Lyttle T.S., O'Dell C.R., Kitzman P.H. // Spinal Cord. — 2011. — V. 49(1). — P.99-105.

37 Rabchevsky A.G., Patel S.P., Lyttle T.S., et al. Effects of gabapentin on muscle spasticity and both induced as well as spontaneous autonomic dysreflexia after complete spinal cord injury [Text] / Rabchevsky A.G., Patel S.P., Lyttle T.S., Eldahan K.C., O'Dell C.R., Zhang Y., Popovich P.G., Kitzman P.H., Donohue K.D. // Front Physiol. — 2012. — V. 3. — P.329.

38 Ramanathan V., Baskar D., Pari H. 'Seatbelt Effect' of Spasticity: Contrasting Velocity Dependence from the Clasp Knife Phenomenon [Text] / Ramanathan V., Baskar D., Pari H. // Ann Indian Acad Neurol. — 2022. — V. 25(3). — P.517-519.

39 Rivelis Y., Zafar N., Morice K. Spasticity. / Rivelis Y., Zafar N., Morice K [Text] // StatPearls. — Treasure Island (FL): StatPearls Publishing, 2022. — PMID: 29939646.

40 Romito J.W., Turner E.R, Rosener JA, et al. Baclofen therapeutics, toxicity, and withdrawal: A narrative review [Text] / Romito J.W., Turner E.R., Rosener J.A., Coldiron L., Udipi A., Nohrn L., Tausiani J., Romito B.T. // SAGE Open Med. — 2021. — V. 9. — P.205. doi: 10.1177/20503121211022197

41 Shanker G., Kumar C.K., Gonugunta C.S., et al. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets [Text] / Shanker G., Kumar C.K., Gonugunta C.S., Kumar B.V., Veerareddy P.R. // AAPS PharmSciTech. — 2009. — V. 10(2). — P.530-539.

42 Spiller H.A., Bosse G.M., Adamson L.A. Retrospective review of Tizanidine (Zanaflex) overdose [Text] / Spiller H.A., Bosse G.M., Adamson L.A. // Toxicol Clin Toxicol. — 2004. — V. 42(5). — P.593-596.

43 Stamenova P., Koytchev R., Kuhn K., et al. A randomized, double blind, placebo-controlled study of the efficacy and safety of tolperisone in spasticity following cerebral stroke [Text] / Stamenova P., Koytchev R., Kuhn K., Hanasen C., Horvath F., Ramm S., Pongratz D. // Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova= S.S. Korsakov Journal of Neurology and Psychiatry. — 2006. — V. 106(1). — P.34-42.

44 Stetkarova I., Brabec K., Vasko P., et al. Intrathecal Baclofen in Spinal Spasticity: Frequency and Severity of Withdrawal Syndrome [Text] / Stetkarova I., Brabec K., Vasko P., Mencl L. // Pain Physician. — 2015. — V. 18(4). — E633-41. PMID: 26218954

45 Sturgill E.L., Wittwer R.L. Novel Treatment Using Intravenous Dantrolene Sodium for Postoperative Exacerbated Spasticity in Multiple Sclerosis: A Case Report [Text] / Sturgill E.L., Wittwer R.L. // A A Pract. — 2018. — V. 11(1). — P. 25-27.

46 Suponeva N.A., Yusupova D.G., Il'ina K.A., et al. Validation of the Modified Ashworth Scale (Modified Ashworth Scale) in Russia [Text] / Suponeva N.A., Yusupova D.G., Il'ina K.A., Mel'chenko D.A., Butkovskaya A.A., Zhirova E.S., Taratukhina A.S., Zimin A.A., Zaitsev A.B., Klochkov A.S., Lyukmanov R.Kh., Kotovsmolenskii A.M., Khizhnikova A.E., Gatina G.A., Kutlubaev M.A., Piradov M.A. // Annaly klinicheskoi i eksperimental'noinevrologii = Annals of Clinical and Experimental Neurology. — 2020. — V. 14(1). — P.89-96. (InRuss.)

47 Synnot A., Chau M., Pitt V., et al. Interventions for managing skeletal muscle spasticity following traumatic brain injury [Text] / Synnot A., Chau M., Pitt V., O'Connor D., Gruen R.L., Wasiak J., Clavisi O., Pattuwage L., Phillips K. // Cochrane Database Syst Rev. — 2017. — V. 11(11). — CD008929. doi: 10.1002/14651858.

48 Szentesi P., Collet C., Sárközi S., et al. Effects of dantrolene on steps of excitation-contraction coupling in mammalian skeletal muscle fibers [Text] / Szentesi P., Collet C., Sárközi S., Szegedi C., Jona I., Jacquemond V., Kovács L., Csernoch L. // Gen Physiol. — 2001. — V. 118(4). — P.355-375.

49 Tekes K. Basic aspects of the pharmacodynamics of tolperisone, a widely applicable centrally acting muscle relaxant [Text] / Tekes K. // Open Med Chem J. — 2001. — V. 8. — P.17-22.

50 Tilton A. Management of spasticity in children with cerebral palsy [Text] / Tilton A. // Semin Pediatr Neurol. — 2009. — V. 16(2). — P.82-89.

51 Trompetto C., Marinelli L., Mori L., et al. Pathophysiology of spasticity: implications for neurorehabilitation [Text] / Trompetto C., Marinelli L., Mori L., Pelosin E., Currà A., Molfetta L., Abbruzzese G. // Biomed Res Int. — 2014. — V. 3. — P.549-556.

52 Wang J., Shi Y., Yu S., et al. Intranasal administration of dantrolene increased brain concentration and duration [Text] / Wang J., Shi Y., Yu S., Wang Y., Meng Q., Liang G., Eckenhoff M.F., Wei H. // PLoS One. — 2020. — V. 15(3) — doi: 10.1371/journal.pone.0229156

53 Wang Z.M., Law J.H., King N.K., et al. Treatment of severe, disabling spasticity with continuous intrathecal baclofen therapy following acquired brain injury: the experience of a tertiary institution in Singapore [Text] / Wang Z.M., Law J.H., King N.K., Rajeswaran D.K., Soh S., Rao J.P., Ng W.H., Chua K.S. // Singapore Med J. — 2016. — V. 57(1). — P.8-12.

54 Wissel J., Manack A., Brainin M. Toward an epidemiology of poststroke spasticity [Text] / Wissel J, Manack A, Brainin M. // Neurology. — 2013. — V. 80(3 Suppl 2). — P.13-9.

55 Zorowitz R.D., Gillard P.J., Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers [Text] / Zorowitz R.D., Gillard P.J., Brainin M. // Neurology. — 2013. — V. 80(3 Suppl 2). — P.45-52.

Поступила 24.06.2022

*Р. А. Беляев[1], А. В. Мирошниченко[2*]*

*СПАСТИЧНОСТЬ: СОВРЕМЕННЫЕ ТЕРАПЕВТИЧЕСКИЕ РЕШЕНИЯ ЧЕРЕЗ ПРИЗМУ ПАТОГЕНЕЗА*

*[1]Кафедра неврологии, психиатрии и реабилитации Некоммерческого акционерного общества «Карагандинский медицинский университет» (Караганда, Казахстан)*
*[2]Школа медицины Некоммерческого акционерного общества «Карагандинский медицинский университет» (Караганда, Казахстан)*

Изучение патофизиологических механизмов спастичности продолжается, однако уже вполне ясна ее гетерогенность, комбинация и взаимовлияние различных механизмов в ее развитии. Оптимальное ведение пациентов зависит от понимания лежащей в основе спастичности физиологии, понимания ее естественного течения, оценки воздействия на пациента и комплексного подхода к минимизации этого воздействия.

*Ключевые слова:* спастичность; синдром верхнего мотонейрона; патофизиология; шкалы оценки спастичности; лечение

*Р. А. Беляев[1], А. В. Мирошниченко[2*]*

*СПАСТИКА: ПАТОГЕНЕЗ ПРИЗМАСЫ АРҚЫЛЫ ЗАМАНАУИ ТЕРАПЕВТІК ШЕШІМДЕР*

*[1]«Қарағанды медициналық университеті» коммерциялық емес акционерлік қоғамының неврология, психиатрия және оңалту кафедрасы (Қарағанды, Қазақстан)*
*[2]Медицина мектебі, «Қарағанды медициналық университеті» коммерциялық емес акционерлік қоғамы (Қарағанды, Қазақстан)*

Спастиканың патофизиологиялық механизмдерін зерттеу жалғасуда, бірақ оның гетерогенділігі, оның дамуындағы әртүрлі механизмдердің тіркесімі мен өзара әсері қазірдің өзінде айқын. Пациенттерді оңтайлы басқару физиологияның негізгі спастикасын түсінуге, оның табиғи ағымын түсінуге, пациенттің әсерін бағалауға және осы әсерді барынша азайтуға кешенді көзқарасқа байланысты.

*Кілт сөздер:* спастика; жоғарғы моторлы нейрон синдромы; патофизиология; спастиканы бағалау шкаласы; емдеу