Burdenko's Journal of Neurosurgery
2024, №3, pp. 74–80
https://doi.org/10.17116/neiro20248803174

Neuromodulatory pharmacotherapy individualization in prolonged and chronic consciousness disorders after severe traumatic brain injury

© E.V. ALEKSANDROVA, O.S. ZAITSEV, A.A. POTAPOV

Burdenko Neurosurgical Center, Moscow, Russia

ABSTRACT

One of the most probable causes of effective therapy for post-comatose disorders of consciousness is the lack of individualization of drug prescriptions. In this observational study, we analyzed 48 courses of neuromodulatory therapy in 28 patients with prolonged and chronic disorders of consciousness following severe traumatic brain injury. Comparison of 24 effective and 24 ineffective courses demonstrated higher effectiveness of pharmacotherapy through its individualization, i.e. the choice of a drug whose neuromodulatory spectrum would correspond to neurological syndromes of neurotransmitter dysfunction. In this approach, 74% of therapy courses were effective while opposite management resulted only 34% of effective courses.

Keywords: *traumatic brain injury, unconsciousness, disorder of consciousness, vegetative state, minimal consciousness state, neuromodulatory pharmacological therapy.*

INFORMATION ABOUT THE AUTHORS:
Alexandrova E.V. — https://orcid.org/0000-0001-5327-314X
Zaitsev O.S. — https://orcid.org/0000-0003-0767-879X
Potapov A.A. — https://orcid.org/0000-0001-8343-3511
Corresponding author: Alexandrova E.V. — ealexandrova.nsi@gmail.com

TO CITE THIS ARTICLE:
Aleksandrova EV, Zaitsev OS, Potapov AA. Neuromodulatory pharmacotherapy individualization in prolonged and chronic consciousness disorders after severe traumatic brain injury. *Burdenko's Journal of Neurosurgery*. 2024;88(3):74–80. (In Russ.).
https://doi.org/10.17116/neiro20248803174

Introduction

An important issue of the last 10 years is searching for effective methods for accelerating recovery of patients with impaired consciousness after traumatic brain injury.

Pharmacological treatment of these patients is important as evidenced by multiple studies devoted to this issue [1—5]. This is not surprising in view of direct correlation of duration of coma and post-comatose disturbances of consciousness with the outcome of brain damage [6, 7].

Neuromodulatory pharmacotherapy looks perspective for this problem. Appropriate drugs modulate activity of the main low-molecular neurotransmitter systems which are essential in maintaining consciousness [8], processes of adaptive behavior and decision-making in response to changed external conditions [9].

The effect of neuromodulatory agents on restoration of consciousness after brain injury was first described in the 80s of the last century. Nevertheless, only a few randomized controlled trials (RCTs) devoted to these drugs have been carried out [10, 11]. This situation is largely due to difficult selection of clinical cases because of numerous factors influencing the course of traumatic brain disease and diverse clinical manifestations of this trauma. This complicates interpretation of results.

To date, only amantadine has been relatively studied and included in the clinical guidelines for the treatment of chronic disorders of consciousness [12—14]. There are data to effectiveness of GABA-ergic (gamma-aminobutyric acid) drug zolpidem [15, 16], but feasibility of this drug was not confirmed in RCTs [17].

According to empirical data and ideas developed at the Burdenko Neurosurgery Center [18—21], effectiveness of a particular neurotransmitter drug depends on specific «neurotransmitter landscape» occurring after «neurotransmitter storm» in acute period of brain damage. It is almost always possible to determine predominance of a particular dysfunction («weak neurotransmitter link») with advisable correction by appropriate neurotransmitter drug.

We have previously studied post-traumatic unconscious states and identified the main neurotransmitter disorders. These are syndromes of cholinergic deficiency, glutamatergic deficiency and redundancy, dopaminergic deficiency and redundancy [21, 22]. These syndromes differ from each other by clinical signs. Thus, cholinergic deficiency is characterized by muscle hypotonia

with normal or low tendon reflexes and pathological reflexes, hypotonia of masticatory muscles, bilateral mydriasis with decreased photoreactions, tachycardia, hyperthermia, dry skin, hypotonia of the gastrointestinal tract. Glutamatergic deficiency includes paresis with increased extensor tone and decreased tendon reflexes, no clonus, or paresis with decreased muscle tone and increased tendon reflexes +/– pathological foot signs, as well as trismus with oral automatisms, pseudobulbar syndrome, paresis of upward gaze reflex, suppression of corneal reflexes and oculocephalic reflex, disconjugate gaze palsies. Glutamatergic redundancy is characterized by paresis with hypertonicity of flexors and hyperreflexia, or paresis with hypertonicity of extensors and hyperreflexia, or hyperreflexia, pathological signs and normotonia, as well as decerebration and decortication rigidity. Dopaminergic deficiency includes parkinsonian disorders, dystonia, fetal position, greasiness of skin and hypersalivation. Dopaminergic redundancy includes hyperkinesis and dyskinesia, psychomotor agitation.

The purpose of the study was to evaluate whether the effectiveness of therapy is affected by correspondence of neuromodulatory actions of the drug to neurological syndromes of neurotransmitter dysfunction in the treatment of patients with prolonged and chronic impairment of consciousness following severe traumatic brain injury (TBI).

Material and methods

A prospective observational single-center study included 94 patients (68 men and 26 women) aged 32.5±13.6 years with severe TBI (GCS score ⩽8) with recovery from coma into vegetative state (VS) or minimally conscious state (MCS–).

In 66 (70.4%) cases, recovery occurred spontaneously without addition of any neuromodulatory drugs to basic and symptomatic therapy. In other 28 (29.6%) patients, duration of unconsciousness at inclusion in the study was more than two weeks (15—457 days) that corresponded to prolonged [23] or chronic [24] impairment of consciousness. In this group, we routinely prescribed certain neuromodulatory drugs approved in Russia for the treatment of severe brain damage. Four groups of drugs were used: 1) cholinergic — ipidacrine or choline alfoscerate; 2) dopaminergic — L-dopa + carbidopa; 3) antiglutamatergic — amantadine sulfate; 4) GABAergic — aminophenylbutyric acid hydrochloride or calcium hopantenate.

Effective therapy implied new significant manifestations of consciousness — gaze fixation and/or emotional reactions (typical for recovery to MCS– from VS) or signs of speech understanding (typical for MCS+ and further restoration of mental activity). Finally, we compared two groups of prescriptions where neurotransmitter therapy corresponded or did not correspond to clinical syndromes of neurotransmitter dysfunction [22].

Statistical analysis was carried out using the Statistica 8.0 software and non-parametric Fisher's exact test.

Results

In the main group (n=28), chronic impairment of consciousness persisted in 7 (25%) patients despite neurotransmitter therapy. Twenty-one (75%) patients recovered from chronic impairment of consciousness for subsequent stages of mental recovery. Mean duration of impaired consciousness in this group was 46.7±19.6 days vs. 12±7.6 days among 66 patients without neurotransmitter therapy. This is due earlier spontaneous recovery of consciousness without the need for neurotransmitter therapy (up to 2—3 weeks). The indication for neurotransmitter therapy was the tendency to prolonged period of impaired consciousness (duration of one of the variants of unconsciousness was more than 15 days).

Various neuromodulatory drugs were effective **(fig. 1)**. Seven (25%) patients recovered consciousness under cholinergic drugs (ipidacrine 40—60 mg/day, choline alfoscerate 1000—2000 mg/day), 5 (18%) patients — under GABAergic drugs (aminophenylbutyric acid 2000—2250 mg/day, calcium hopantenate 500—750 mg/day). In 4 (14%) patients, impaired consciousness regressed under dopaminergic therapy (L-dopa + carbidopa 750 mg), 4 (14%) patients — under glutamate receptor blocker with concomitant dopaminergic effect (amantadine sulfate 100—400 mg/day). One (4%) patient recovered consciousness under combination of cholinergic drug (choline alfoscerate 1000 mg) and glutamate receptor blocker (amantadine sulfate 100 mg/day).

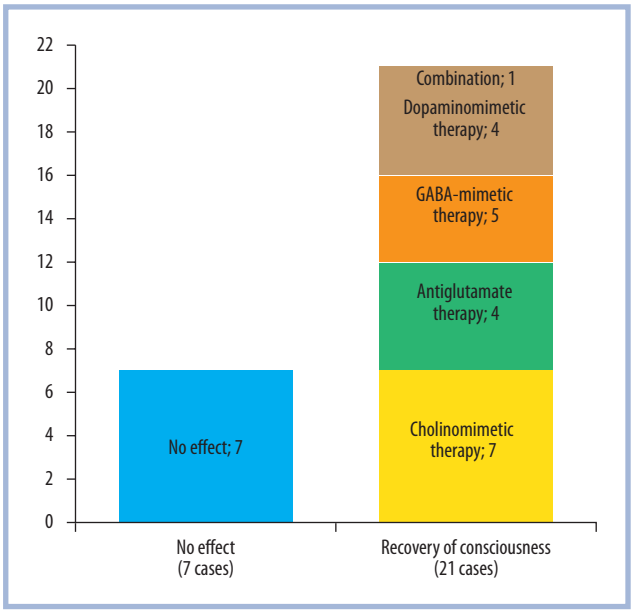

Fig. 1. **Distribution of 28 patients with impaired consciousness depending on effectiveness (signs of recovery) and type of successful neurotransmitter therapy.**

Table 1. **Characteristics of patients with recovery of consciousness under various neuromodulatory therapies**

Factor	Therapy			
	Cholinomimetic (*n*=7)	Dopaminomimetic (*n*=4)	Antiglutamate (*n*=4)	GABA-mimetic (*n*=5)
Age, years	34.7±17.8	22.2±4.7	26.2±11.5	43±16.6
Men, %	100	25	25	20
Women, %	0	75	75	80
Duration of impaired consciousness, days	20.3±6.1	104.2±43.2	32±12.8	30.4±16.6
Minimum GCS score	5.6±1.7	4.0±0	4.5±0.6	5.2±0.8

Table 2. **Efficacy of targeted and non-targeted neuromodulator therapy for various syndromes of neurotransmitter dysfunction**

Syndrome	Therapy	N_{ef}/N_{inef}	Efficacy, %
Targeted therapy	All groups of drugs according to syndrome	14/5	74
Cholinergic deficiency syndrome	Cholinomimetics (ipidacrine, choline alfoscerate)	4/1	80
Glutamatergic redundancy syndrome	Glutamate blockers (amantadine sulfate) or GABAergic agents (aminophenylbutyric acid, calcium hopantenate)	6/3	66.7
Dopaminergic deficiency syndrome	Dopaminomimetics (levodopa + carbidopa)	4/1	80
Non-targeted therapy for all syndromes, including glutamatergic deficiency syndrome	All groups of drugs without correspondence to neurotransmitter dysfunction syndrome	10/19 2/4	34 33
Total	All courses	24/24	50

Note. N_{ef}/N_{inef} — ratio of effective and ineffective courses.

Characteristics of patients depending on various neuromodulatory therapies are presented in **table 1**.

The shortest period of impaired consciousness was observed in patients with effective cholinomimetic therapy, the longest period — in case of effective dopaminergic drugs.

Importantly, there were 12 out of 21 patients with recovery of consciousness, and neuromodulatory therapy was not immediately selected in these cases (effective courses were preceded by 12 ineffective ones). In 3 patients, two courses were effective. The first course recovered MCS- after VS, and the second therapy contributed to MCS+ and subsequent stages of mental restoration. We also analyzed 12 ineffective courses of neurotransmitter therapy in 7 patients with stable impairment of consciousness. Thus, final analysis included 24 effective and 24 ineffective courses of neurotransmitter therapy.

In 19 courses, effectiveness of neuromodulatory therapy corresponded to clinical syndrome (cholinomimetics for cholinergic deficiency, glutamate receptor blockers or GABAergic drugs for glutamatergic redundancy, dopaminomimetics for dopaminergic deficiency). In 29 courses, therapy was non-targeted and did not correspond to neurotransmitter dysfunction **(table 2)**.

Importantly, treatment of patients with glutamatergic deficiency syndrome was classified as non-targeted neurotransmitter therapy because the drugs increasing glutamatergic transmission were unavailable (for example, glutamic acid). Effectiveness of therapy was low for this syndrome (2 out of 6, 33.3%), and mainly cholinergic (but less often than in cholinergic deficiency syndrome) and dopaminergic drugs (in concomitant signs of dopaminergic deficiency syndrome) were effective.

Overall effectiveness of targeted neurotransmitter therapy was 40% higher than non-targeted therapy (p=0.02) **(fig. 2)**.

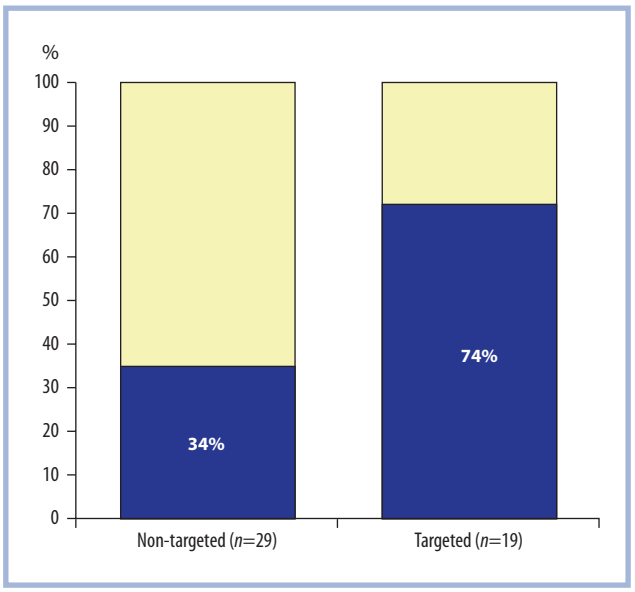

Fig. 2. **Effectiveness of 29 courses of non-targeted and 19 courses of targeted neurotransmitter therapy in 28 patients with prolonged post-traumatic impairment of consciousness.**
Effective prescriptions — dark bars, ineffective prescriptions — light bars.

Discussion

Neurotransmitter dysfunction is one of the mechanisms of impaired consciousness. These disorders occur within a few hours after injury and can persist for weeks and even months. Neuromodulatory pharmacotherapy may be effective for correction of these disorders [20]. Complex and multifactorial problem of restoration of consciousness complicates multiple-center RCTs and formulation of clear recommendations for specific neuromodulatory drugs.

There were no previous studies devoted to individual selection of pharmacological therapy in patients with chronic impairment of consciousness due to no individualization criteria. We proposed clinical syndromes of neurotransmitter cerebral dysfunction as such criteria. Selection of neuromodulatory drugs may be based on these syndromes until high quality RCTs will be available.

According to our data, cholinomimetic drugs (ipidacrine, choline alfoscerate, citicoline) are preferable for cholinergic deficiency syndrome, glutamate receptor blockers (amantadine sulfate or chloride) or GABAergic agents (aminophenylbutyric acid, calcium hopanthenate) — for glutamatergic redundancy syndrome. The drugs increasing glutamatergic transmission may be preferable for glutamatergic deficiency syndrome. However, glutamic acid poorly penetrates the blood-brain barrier, and D-cycloserine as an activator of glutamatergic system has so far been studied only for post-traumatic stress disorders [25—27].

Dopaminergic deficiency syndrome necessitates levodopa or dopamine receptor agonists. Amantadine sulfate is also possible, since it combines antiglutamate and dopaminomimetic effects through enhanced synthesis of dopamine receptors. W. Matsuda et al. [28] also found that effectiveness of treatment with this drug depends on concomitant symptoms of Parkinsonism and MR signs of damage to dopaminergic structures. The exact mechanism of beneficial effects of dopaminergic agents on recovery of consciousness is still unclear. It is likely due to enhanced neurotransmission in dopaminergic (nigrostriatal, mesolimbic, mesocortical and thalamic) pathways [29]. Specific effect of these drugs on striatum and frontal cortex prevents dysfunction of anterior cerebral parts that are most vulnerable to injury [30].

Most studies devoted to effectiveness of a particular drug for restoring consciousness do not consider mechanism of brain damage (traumatic, hypoxic, toxic or other), localization of structural brain damage and, most importantly, heterogeneity of clinical manifestations. This is probably the reason why many drugs have not proven their effectiveness in clinical trials.

The limitations of this study are small sample size, no blinding of investigators and comparison of therapeutic effects with placebo.

Conclusion

Specific neuromodulatory therapy may be used in patients with post-traumatic disturbances of consciousness lasting more than two weeks without signs of spontaneous recovery of consciousness. Individual selection of neurotransmitter therapy in accordance with clinical syndrome can increase effectiveness. This approach is described in the modern clinical guidelines for chronic disorders of consciousness of the All-Russian public organization "Federation of Anesthesiologists and Reanimatologists" [31], but not accepted by other professional communities.

A large-scale multiple-center RCT comparing effectiveness of therapy in the following groups is needed to increase significance of statements: 1) compliance of drug properties with clinical syndromes of neurotransmitter dysfunction; 2) without this compliance; 3) placebo.

Author contribution:
Concept and design of the study — Aleksandrova E.V., Zaitsev O.S., Potapova A.A.
Collection and analysis of data — Aleksandrova E.V.
Statistical analysis — Aleksandrova E.V.
Writing the text — Aleksandrova E.V.
Editing — Zaitsev O.S.

No conflict of interests to declare.

REFERENCES

1. Meyer MJ, Megyesi J, Meythaler J, Murie-Fernandez M, Aubut JA, Foley N, Salter K, Bayley M, Marshall S, Teasell R. Acute management of acquired brain injury Part III: an evidence-based review of interventions used to promote arousal from coma. *Brain injury*. 2010;24(5):722-729. https://doi.org/10.3109/02699051003692134
2. McAllister TW. Neurobehavioral sequelae of traumatic brain injury: evaluation and management. *World Psychiatry*. 2008;7(1):3-10. https://doi.org/10.1002/j.2051-5545.2008.tb00139.x
3. Gosseries O, Charland-Verville V, Thonnard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. *Current Pharmaceutical Design*. 2014;20(26):4167-4184.
4. Sanz LRD, Lejeune N, Blandiaux S, Bonin E, Thibaut A, Stender J, Farber NM, Zafonte RD, Schiff ND, Laureys S, Gosseries O Treating Disorders of Consciousness With Apomorphine: Protocol for a Double-Blind Randomized Controlled Trial Using Multimodal Assessments. *Frontiers in Neurology*. 2019;10:248. https://doi.org/10.3389/fneur.2019.00248
5. Houston AL, Wilson NS, Morrall MC, Lodh R, Oddy JR. Interventions to improve outcomes in children and young people with unresponsive wakefulness syndrome following acquired brain injury: A systematic review. *European Journal of Paediatric Neurology*. 2020;25:40-51. https://doi.org/10.1016/j.ejpn.2020.01.015
6. Potapov AA, Zakharova NE, Kornienko VN, Pronin IN, Aleksandrova EV, Zaĭtsev OS, Likhterman LB, Gavrilov AG, Danilov GV, Oshorov AV, Sychev AA, Polupan AA. Neuroanatomical basis for traumatic coma: clinical and magnetic resonance correlates. *Burdenko's Journal of Neurosurgery*. 2014;78(1):4-13. (In Russ.).

7. Potapov AA, Danilov GV, Sychev AA, Zakharova NE, Pronin IN, Savin IA, Oshorov AV, Polupan AA, Aleksandrova EV, Strunina YuV, Likhterman LB, Ohlopkov VA, Latyshev YaA, Chelushkin DM, Baranich AI, Kravchuk AD. Clinical and MRI predictors of coma duration, critical care intensity and outcomes in traumatic brain injury. *Burdenko's Journal of Neurosurgery*. 2020;84(4):5-16. (In Russ.). https://doi.org/10.17116/neiro2020840415
8. Aleksandrova EV, Zaĭtsev OS, Potapov AA. Neurotransmitter basis of consciousness and uncosciousness states. *Burdenko's Journal of Neurosurgery*. 2014;78(1):26-32. (In Russ.).
9. Krichmar J. The Neuromodulatory System: A Framework for Survival and Adaptive Behavior in a Challenging World. *Adaptive behavior*. 2008;16:385-399. https://doi.org/10.1177/1059712308095775
10. Whyte J, Katz D, Long D, DiPasquale MC, Polansky M, Kalmar K, Giacino J, Childs N, Mercer W, Novak P, Maurer P, Eifert B. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Archives of Physical Medicine and Rehabilitation*. 2005;86(3):453-462. https://doi.org/10.1016/j.apmr.2004.05.016
11. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, Yablon SA, Luther M, Hammond FM, Nordenbo A, Novak P, Mercer W, Maurer-Karattup P, Sherer M. Placebo-controlled trial of amantadine for severe traumatic brain injury. *The New England Journal of Medicine*. 2012;366(9):819-826. https://doi.org/10.1056/NEJMoa1102609
12. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GSF, Nakase-Richardson R, Seel RT, Yablon S, Getchius TSD, Gronseth GS, Armstrong MJ. Comprehensive Systematic Review Update Summary: Disorders of Consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Archives of Physical Medicine and Rehabilitation*. 2018;99(9):1710-1719. https://doi.org/10.1016/j.apmr.2018.07.002
13. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GSF, Nakase-Richardson R, Seel RT, Yablon S, Getchius TSD, Gronseth GS, Armstrong MJ. Practice Guideline Update Recommendations Summary: Disorders of Consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Archives of Physical Medicine and Rehabilitation*. 2018;99(9):1699-1709. https://doi.org/10.1016/j.apmr.2018.07.001
14. Kondziella D, Bender A, Diserens K, van Erp W, Estraneo A, Formisano R, Laureys S, Naccache L, Ozturk S, Rohaut B, Sitt JD, Stender J, Tiainen M, Rossetti AO, Gosseries O, Chatelle C. EAN Panel on Coma, Disorders of Consciousness. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *European Journal of Neurology*. 2020;27(5):741-756. https://doi.org/10.1111/ene.14151
15. Kondratyeva EA, Sinkin MV, Sharova EV, Laureys S, Kondratyev AN. Zolpidem Action During Prolonged Disorders of Consciousness (Case Report). *General Reanimatology*. 2019;15(5):44-60. https://doi.org/10.15360/1813-9779-2019-5-44-60
16. Clauss RP, Güldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem. A case report. *South African Medical Journal*. 2000;90(1):68-72.
17. Thonnard M, Gosseries O, Demertzi A, Lugo Z, Vanhaudenhuyse A, Bruno MA, Chatelle C, Thibaut A, Charland-Verville V, Habbal D, Schnakers C, Laureys S. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. *Functional Neurology*. 2013;28(4):259-264. https://doi.org/10.11138/FNeur/2013.28.4.259
18. Zaitsev OS. Selection of neuromethabolic drug in severe brain injury. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2010;110(9):66-69. (In Russ.).
19. Zaitsev OS, Tsarenko SV. *Neuroresuscitation. Coming out of a coma (therapy for post-comatose states)*. OS Zaitsev, SV Tsarenko, eds. M.: Litass; 2012. (In Russ.).
20. Zaitsev OS, Tsarenko SV, Chelyapina MV, Sharova EV, Alexandrova EV. Issues of the accounting of a weak neurotransmitter component in the pharmacotherapy of postcomatose states. *Neurology, Neuropsychiatry, Psychosomatics*. 2016;8(4):87-90. (In Russ.). https://doi.org/10.14412/2074-2711-2016-4-87-90
21. Alexandrova EV. *Syndromes of dysfunction of neurotransmitter systems in the process of restoration of consciousness after traumatic brain injury*: Dis. ... kand. med. nauk. 2013. (In Russ.).
22. Aleksandrova EV, Zaitsev OS, Potapov AA. Clinical syndromes of neurotransmitter system dysfunction in severe brain injury. *S.S. Korsakov Journal of Neurology and Psychiatry*. 2015;115(7):40-46. (In Russ.). https://doi.org/10.17116/jnevro20151157140-46
23. Belkin AA, Suponeva NA, Voznyuk IA, Zaitsev OS, Zampolini M, Ivanova NE, Ivanova GE, Kondratieva EA, Lubnin AYu, Petrova MV, Petrikov SS, Piradov MA, Popugaev KA, Pryanikov IV, Ryabinkina YuV, Savin IA, Sergeev DV, Shchegolev AV, Zabolotskikh IB. Prolonged Disorder of Consciousness — a New Concept in the Evaluation of Chronical Disorders of Consciousness in ICU Patients. A Multi-Disciplinary Concensus. *Vestnik intensivnoi terapii imeni A.I. Saltanova*. 2021;2:7-16. (In Russ.). https://doi.org/10.21320/1818-474X-2021-2-7-16
24. Piradov MA, Suponeva NA, Voznyuk IA, Kondratyev AN, Shchegolev AV, Belkin AA, Zaytsev OS, Pryanikov IV, Petrova MV, Ivanova NE, Gnedovskaya EV, Ryabinkina YuV, Sergeev DV, Yazeva EG, Legostaeva LA, Fufaeva EV, Petrikov SS. Rossiiskaya rabochaya gruppa po problemam khronicheskikh narushenii soznaniya. Khronicheskie narusheniya soznaniya: terminologiya i diagnosticheskie kriterii. Rezul'taty pervogo zasedaniya Rossiiskoi rabochei gruppy po problemam khronicheskikh narushenii soznaniya. *Annaly klinicheskoi i eksperimental'noi nevrologii*. 2020;14(1):5-16. (In Russ.).
25. de Kleine RA, Hendriks GJ, Kusters WJ, Broekman TG, van Minnen A. A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biological Psychiatry*. 2012;71(11):962-968. https://doi.org/10.1016/j.biopsych.2012.02.033
26. Litz BT, Salters-Pedneault K, Steenkamp MM, Hermos JA, Bryant RA, Otto MW, Hofmann SG. A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. *Journal of Psychiatric Research*. 2012;46(9):1184-1190. https://doi.org/10.1016/j.jpsychires.2012.05.006
27. Krystal JH. Enhancing prolonged exposure therapy for posttraumatic stress disorder with D-cycloserine: further support for treatments that promote experience-dependent neuroplasticity. *Biological Psychiatry*. 2012;71(11):932-934. https://doi.org/10.1016/j.biopsych.2012.03.031
28. Matsuda W, Komatsu Y, Yanaka K, Matsumura A. Levodopa treatment for patients in persistent vegetative or minimally conscious states. *Neuropsychol Rehabil*. 2005;15(3-4):414-427. https://doi.org/10.1080/09602010443000588
29. Stahl S. *Essential psychopharmacology: neuroscientific basis and practical applications*. New York: Press CU; 2000.
30. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends in Neurosciences*. 2010;33(1):1-9. https://doi.org/10.1016/j.tins.2009.11.002
31. Belkin AA, Aleksandrova EV, Akhutina TV, Belkin VA, Berdnikovich ES, Bykova VI, Varako NA, Vozniuk IA, Hnedovskaya EV, Grigorieva VN, Zaitsev OS, Zinchenko YuP, Ivanova GE, Ivanova NE, Kovyazina MS, Kondratiev AN, Kondratieva EA, Kondratiev SA, Krylov VV, Latyshev YaA, Lebedinsky KM, Legostaeva LA, Maksakova OA, Martynov MYu, Mikadze YuV, Petrikov SS, Petrova MV, Piradov MA, Popugaev KA, Pryanikov IV, Ryabinkina YuV, Savin IA, Sergeev DV, Sinkin MV, Skvortsov AA, Skripai EYu, Suvorov AYu, Suponeva NA, Usachev DYu, Fufaeva EV, Shamalov NA, Shchegolev AV, Yazeva EG, Zabolotskikh IB. Chronic Disorders of Consciousness: guidelines of the All-Russian public organization «Federation of Anesthesiologists and Reanimatologists». *Vestnik intensivnoi terapii imeni A.I. Saltanova*. 2023;3:7-42. (In Russ.). https://doi.org/10.21320/1818-474X-2023-3-7-42

Received 20.08.2023
Accepted 22.03.2024

COMMENT

We have an excellent report devoted to important, but, alas, usually not going beyond intentions and speculative declarations, personalized approach to treatment.

Instead of unfounded arguments about the benefits of genomics, proteomics, metobolomics and other "omics", the authors proposed a real alternative to faceless randomized clinical trials. The last ones led the issue of personalization and individualization of treatment to methodological dead end. This impasse is especially clear in the treatment of long-term unconscious states with polymorphic symptoms and etiopathogenetic basis. These features make evidence-based medicine methods meaningless, as evidenced by almost complete absence of international and national guidelines for the treatment of such patients.

The proposed treatment methods are based on classical heuristic approach followed by clinical evaluation of effectiveness. The medications are prescribed differentially depending on baseline neurological symptoms and continuous clinical assessment of effectiveness (or ineffectiveness).

I welcome this direction and consider this report extremely important.

S.V. Tsarenko (Moscow)