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MODERN METHODS OF BRAIN STIMULATION: ACHIEVEMENTS AND PROSPECTS OF APPLICATION

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This is a review article that offers an analysis of non-pharmacological treatment possibilities in psychiatry, and speci fi cally, the up-to-date methods of brain stimulation. The author pays special attention to current principles of using ECT and transcranial magnetic stimulation (TMS). The author also presents the data of his own research on this subject.Besides, the article contains an analysis of publications concerning new treatment methods, such as the vagus nerve stimulation and deep brain stimulation.

Key words: Parkinson's disease, dystonia, dyskinesia, deep brain stimulation, basal ganglia, subthalamic nucleus, neuromodulation, synaptic plasticity

Progress in neuropsychiatry in the last two decades has determined a kind of leap in the development of brain stimulation techniques, the emergence of new methods and the improvement of old ones. Based on the idea of the functioning brain as a kind of electrochemical organ, its stimulation can indirectly affect therapeutically, correcting pathologically altered functional activity. Traditionally, the "therapeutic niche" of non-drug methods was located where the use of pharmacotherapy is limited by inefficiency or its poor tolerability. At the same time, scientific achievements of the recent period concerning the neurobiology of mental disorders, as well as the improvement of the technology of devices for brain stimulation can change the principles of treatment, expanding the clinical indications for the use of brain stimulation methods.

Brain stimulation methods include electroconvulsive therapy and a whole range of new techniques, the development and implementation of which is taking place in two fundamentally different directions. The first direction includes methods that are safer than ECT and provide local stimulation (TMS, alpha stimulation, direct brain stimulation). The second direction includes high-tech invasive methods (vagal stimulation, deep brain stimulation), developed by neurosurgeons and psychiatrists.

Electroconvulsive therapy has a rather turbulent 75-year history of use in psychiatry. Having survived periods of bright ups and rapid falls, it is currently a universal and highly effective method of treating extremely severe mental disorders and, at the same time, perhaps the most stigmatized method of existing in medicine. Another paradox is the urgent need for ECT for many patients, while at the same time it is inaccessible.

The main indications for ECT were identified more than half a century ago, confirmed by numerous controlled studies, two systematic reviews and implemented in clinical practice for a long time [1, 8, 9, 11, 13, 14, 59, etc.]. At the same time, this topic remains a subject of discussion to this day. The current situation in domestic psychiatry, when ECT is used in a limited number of clinics, leads to a certain polarization of assessments of the place of this method in the system of biological therapy. On the one hand, existing prejudices, excessive conservatism with an attitude to ECT as a therapy of "despair", "last chance", narrow its indications to febrile schizophrenia and catatonia. On the other hand, the existing enthusiasm and unjustified optimism with the assessment of ECT as a first-line therapy of choice for a number of psychopathological conditions. It is clear that publications of data from small pilot studies and even individual clinical observations cannot serve as a basis for generating new indications for ECT.

Currently, ECT is used only as a method for achieving rapid relief of severe psychopathological symptoms after adequate psychopharmacotherapy has been proven ineffective, or as a first-line method of choice in a number of urgent, life-threatening conditions [59]. The main clinical indications are three groups of disorders: severe depression, catatonia, and prolonged severe mania.

In general, depression is one of the first and main indications for ECT, and in severe, life-threatening clinical manifestations it becomes the method of choice [1, 14, 21, 30]. The main markers of “urgency” are: attempted suicide, persistent suicidal ideation or suicide planning, as well as a life-threatening somatic condition due to depression.

In addition, ECT may be prescribed as a first-line treatment for depression in the presence of: stupor/severe psychomotor retardation or psychotic symptoms. Additional indications for ECT as a first-line treatment include severe depression in the first trimester of pregnancy and breastfeeding [14].

Other indications for electroconvulsive therapy in depression include ineffectiveness/resistance to previous treatment with antidepressants [1, 2, 7, 14, 21]. ECT is usually prescribed as a third or even fourth course, but a number of guidelines indicate that it can be a second line of therapy. Another controversial issue is the criteria for the effectiveness of thymoanaleptic therapy, which in turn determines some discrepancies in the indications for ECT: from refractoriness of depression to the lack of restoration of the pre-morbid level of social functioning [14, 21]. It should also be noted that to date, cautious assessments of the possibility of prescribing ECT as a preventive therapy for recurrent depression remain [14, 59].

Manic states are less often an indication for ECT. Longer courses with a greater number of sessions are required to achieve the effect. The main target in mania is resistance to pharmacotherapy, as well as the life-threatening physical condition of the patient [7, 8, 21].

The initially assumed effectiveness of ECT in schizophrenia was not confirmed in studies where it was used as monotherapy. The effect of ECT in schizophrenia is characterized by instability (the “6-week effect”), can manifest itself in both primary and chronic patients and, in general, is clinically difficult to predict [21, 39]. Recent years have seen the appearance of a number of studies devoted to the use of this method in combination with antipsychotics in resistant schizophrenia. In general, the data obtained can be regarded as ambiguous and in need of further study. Interestingly, two systematic reviews analyzing the use of ECT in schizophrenia and published almost simultaneously obtained fundamentally different data [54, 59]. However, it seems important that a number of studies have consistently demonstrated the effectiveness of ECT in so-called ultraresistant schizophrenia, when it was added to previously ineffective treatment with clozapine. In a study conducted in our clinic, ECT was used in combination with clozapine and olanzapine in comparison with monotherapy with these drugs in patients with resistant schizophrenia [10]. The results showed that when ECT was added: the number of responders remained approximately the same. The main differences concerned the speed and depth of the effect, which was higher with combination therapy. In addition, ECT showed a clear effect on negative symptoms.

In conclusion of a brief review of the use of ECT in schizophrenia, it should be noted that this area is currently the subject of intense research and debate. Today, views on the place of ECT in the treatment of schizophrenia in various guidelines and standards of therapy vary significantly from "the absence of an evidence base for use in schizophrenia in general..." to considering it as the 4th step in the algorithm for treating schizophrenia (after clozapine therapy).

Finally, the last main indication for ECT is catatonic symptoms. Here, ECT should be prescribed after benzodiazepines have failed as a second-line treatment.

In general, the choice of this method of therapy is based on a carefully conducted analysis of the expected risk-benefit ratio of ECT in a particular patient [21]. First of all, these are the following assessment parameters: risks of anesthesia, current somatic state, expected side effects, primarily from the cognitive sphere, and, finally, the risks associated with the refusal to use this method of treatment.

The choice of dose and other physical parameters of electric current for ECT have recently received priority attention in research and, as a result, in therapy standards [9, 14, 21, 54]. The optimal task is stimulation in the parameters of the "therapeutic window", in the range that ensures the optimal efficiency/safety ratio. Accordingly, these requirements apply to both ECT devices and the technique of the procedures. The well-known disappointments from the use of ECT in the 40-50s of the last century are associated with severe cognitive impairment after the procedures. It is clear that severe memory disorders are associated with the use of wide sinusoidal and even continuous electric currents in the first ECT devices. Short-pulse (1.5 ms) rectangular currents are quite safe and most widely used at present. The latest ECT devices are capable of producing ultrashort (0.3 ms) currents, providing faster depolarization of the neuron. When performing ECT with ultrashort currents, the seizure threshold is reduced by 3-4 times [13, 54]. The large individual variability in the seizure threshold level, determined by both demographic indicators (age and gender) and the influence of the psychopharmacotherapy, is a requirement for the ability to produce current in a large range of strength (from 25-50 to 1,000 mC).

The concept of electrical dose is consistent with the idea of ECT as a highly potent method of brain stimulation within the framework of biological therapy.

pts in psychiatry. The problem of dosing electrical impulses is closely related to the lateralization of stimulation, i.e., to the ECT technique. There are two well-known types of ECT: unilateral and bilateral techniques. The assessments of each of them have undergone significant dynamics over 50 years, and during this time, clinical preferences have changed twice. To date, the question of the advantage of each of them for individual psychopathological conditions remains ambiguous. Unilateral ECT was developed as a significantly safer stimulation method with comparable high efficiency. Subsequent comparative studies, as well as accumulated clinical experience, have shown the advantage of bilateral ECT in psychoses and especially in the presence of catatonia with comparable efficiency in depression. In addition, when using unilateral ECT, a critical "break" in symptoms is observed much less often after the first 1-2 procedures, and a large number of sessions are required to achieve the course effect. As is known, this fact is of no small importance in the treatment of urgent , life-threatening conditions. Technical progress and the emergence of new ECT devices have for a certain time leveled the advantages of the unilateral technique as safer in terms of cognitive functions and significantly better subjectively perceived by patients. A modified bilateral technique was also developed, in which the electrodes are applied not bitemporally, but bifrontally. According to the first studies, bifrontal ECT, with comparable effectiveness, caused less cognitive impairment. At the same time, a relatively recent meta-analysis of the comparative effectiveness and safety of both bilateral ECT techniques did not reveal reliable differences [54]. The authors, however, point to the small study groups and the associated vulnerability of the evidence.

As noted above, the introduction of the concept of ECT dose and its gradation were an extremely important achievement, allowing for the optimization of therapeutic approaches. Currently, low doses (up to 1.5-2 seizure thresholds - SP), medium (2.5 SP) and high (six times exceeding the SP) are distinguished. In addition, in some cases, very high doses of

ECT are used, corresponding to 8-12 SP. High and very high doses of ECT are used only with the unilateral technique. The explanation for this is a significant increase in efficiency with an increase in the electrical dose from 3 SP to 6 SP. Moreover, this pattern is not observed with bilateral ECT, where an increase in the dose above 1.5-2.5 SP does not lead to an increase in responders. A study on the ratio of methods used over a certain period was conducted

conducted in the 1990s revealed that bilateral ECT was chosen by doctors more than 10 times more often [21]. In recent years, there has been a rapid reorientation of psychiatrists' preferences; it is associated with the introduction of unilateral ECT in high doses. The first two comparative controlled studies of bi- (2.5 and 1.5 SP) and unilateral (6 SP) methods showed their, at least, comparable effectiveness in depression (with a slight advantage of unilateral) [54]. In a recent similar study, the methods were compared in two groups: in treatment-resistant depression and schizophrenia. The effectiveness of unilateral ECT was higher in depression and comparable in patients with schizophrenia, with better tolerability in both groups. Cognitive impairments developing during ECT, after the introduction of mandatory anesthesia into the technique of its use, are, in fact, the main undesirable phenomenon. At the same time, there is data on a certain neuroprotective effect of ECT, manifested in the growth of new dendrites, glia, and a quantitative increase in the level of other neuroprotective factors. In addition, a positive effect on cognitive functions is reported when using subthreshold stimulation [54]. A study conducted in our clinic also revealed a multidirectional effect of ECT on cognitive functions: with a general tendency to temporary impairment of attention, visual and secondary verbal memory, some patients showed an improvement in these indicators [3, 12]. Analysis of the obtained data did not reveal what this positive effect in some patients is associated with: the action of ECT or due to the reduction of depression.

A number of studies have shown a fairly demonstrative dependence of side effects on the technique and dose. First of all, this is a high level of retrograde and anterograde amnesia and, in general, cognitive impairment when using bilateral ECT, especially in high doses [54]. Another study assessed the duration of post-ictal disorientation, which, according to the authors, is a possible predictor of cognitive side effects (30). When using unilateral ECT in a low dose, it was 20 minutes, and in a high dose - 30 minutes. Whereas with bilateral ECT in low doses, disorientation lasted at least 45 minutes [54]. A higher level of cognitive impairment when prescribing bilateral ECT in low doses compared to high doses of unilateral ECT has also been shown in recent studies [13, 54].

Thus, modern approaches to the use of electroconvulsive therapy consider the unilateral technique in high doses as the most optimal for clinical use.

with a rational balance of efficacy and safety. Bilateral ECT is considered the method of choice for life-threatening psychopathological conditions. It should be noted that there is great interest in the use of ultrashort stimulation in ECT. Recent studies have shown high safety and superior efficacy of unilateral ultrashort ECT in high doses compared to bilateral ECT [54]. At the same time, an extremely low level of cognitive impairment is indicated, especially in non-resistant depressive patients. The use of ECT with ultrashort pulses and lower stimulation frequencies close to the biological rhythm of the brain may also be promising [21, 54]. In this case, new clinical effects and, accordingly, possible new indications for its use can be expected.

Transcranial Magnetic Stimulation (TMS)

— a method of influencing the brain with magnetic pulses of various frequencies. Magnetic pulses in brain tissue form local electric inductance currents, which in turn cause depolarization of neurons. The high ability of the magnetic field to penetrate the skin and bone tissue compared to electric current allows for more precise intensity dosing. Another advantage of the technique is the relatively narrow focus of the effect, which provides stimulation of local brain structures. Focal stimulation is achieved using an inductance coil of a special configuration (in the shape of the number "8") [46]. For more precise guidance of TMS, including in accordance with the results of EEG, MRI, PET or MEEG, neuronavigation compatible with a magnetic stimulator is used. In recent years, several studies have been conducted using coils that provide an effect on deep brain structures ('DBS') [30]. In addition, TMS devices are used to conduct magnetoconvulsive therapy (MST) [19]. In this case, magnetic pulses of higher frequency and intensity are used. Two small comparative studies did not reveal any specific differences in the clinical effects of MST and ECT, with a significantly better safety profile for magnetoconvulsive therapy [30].

Finally, TMS is a well-known diagnostic and research tool. It is primarily used to determine the conductivity of motor pathways, as well as in studies of brain function when combining TMS with PET and functional MRI.

There are two fundamentally different methods of magnetic stimulation: cyclic (cTMS) and low-frequency or pulse TMS. With the cyclic method, stimulation is carried out

are performed in cycles or trains, with a frequency of 5-20 Hz, while low-frequency TMS is performed at a frequency of 1 Hz. It is assumed that cTMS has a local stimulating effect on neuronal activity, while low-frequency TMS, suppressing ipsilateral neuronal activity, stimulates the contralateral one. These hypothetical mechanisms, caused by different methods of magnetic stimulation, determine the choice of lateralization of the effect of the pulsed magnetic field. With cTMS, stimulation is performed on the projection of the left prefrontal cortex, and low-frequency TMS is performed on the projection of the right prefrontal cortex [24, 28, 31]. Comparative analysis of the two TMS methods indicates a more powerful antidepressant effect of cyclic stimulation, while low-frequency TMS has a clearly expressed anti-anxiety effect [3, 4]. Interestingly, when using TMS with a high frequency (over 20 Hz), a temporary block of the functioning of a part of the brain can be observed (for example, a block of the speech center) [49].

Over the past 15 years, an impressive number of studies have been conducted on the use of TMS for various mental and neurological disorders. Most of them were conducted on small groups of patients at one clinical site. The main target for TMS is depression. The first studies developed the technique: intensity, stimulation frequency, course duration and area of impact [22, 23, 32, 36]. Interestingly, the methodological principles of TMS have not changed significantly until recently, with the exception of a tendency to increase stimulation intensity. To date, about 30 randomized controlled studies of TMS for depression and 6 meta-analyses of these studies have been conducted [29, 33, 38, 45, etc.] . In 5 of the 6 meta-analyses, the antidepressant effect of TMS and a reliable advantage over placebo were confirmed. Young age and the absence of psychotic symptoms are considered to be predictors of effectiveness. One meta-analysis conducted according to strict Cochrane criteria found that the effect of TMS is not clinically significant [44]. Two first multicenter studies conducted in the USA and Germany also yielded conflicting results. The American study (300 patients with resistant recurrent depression without antidepressant therapy) confirmed the antidepressant effect of TMS with reliable differences from placebo [20]. The German study did not reveal any differences between active therapy and placebo TMS [56]. It should be noted that the majority of the cohort consisted of patients with moderate depression. In addition, the study used a new

placebo-TMS method, the so-called "active pseudo-TMS". In the subsequent discussion, it was noted that "active pseudo-TMS" may also be able to cause a biological effect. Thus, the results of using TMS in depression are not so clear-cut, and the technique needs to be improved. Another consensus concerns the "cognitive" safety of TMS, which is significantly superior to ECT and does not depend on the duration of the magnetic stimulation course [15]. Moreover, data are accumulating on the improvement of a number of cognitive indicators after a TMS course [12, 16, etc.]. Other potential therapeutic targets for TMS include its use in OCD, PTSD and other anxiety disorders, as well as in neurological pathology (epilepsy, chronic pain syndrome, vestibulopathy). Perhaps the most interesting is the use of TMS in patients with schizophrenia. In particular, low-frequency TMS is used to treat verbal hallucinosis on the projection of the speech center [31]. To date, several controlled studies have been conducted with a total of over 200 patients. A published meta-analysis has shown the reliable effectiveness of TMS in drug-resistant verbal hallucinosis [30]. Unfortunately, TMS is not effective against other psychotic symptoms. Our studies in stable patients with schizophrenia have shown the effect of TMS on negative symptoms and depression, as well as on individual indicators of cognitive deficit [6].

Vagal stimulation (VS) is a method of cyclic intermittent stimulation of the vagus nerve with a low electric current. It is assumed that the vagus nerve is a modulator of brain activity, regulating to the greatest extent the reticular formation, anterior ganglia, as well as the nucleus of the solitary tract (nucleus solitarius) and the ambiguous nucleus (nucleus ambigius) [25]. Vagal stimulation is performed through 2 electrodes implanted in the cervical region on the left locally with the location of the vagus nerve bundle. The generator is controlled by a portable computer, which can change the therapy mode, as well as temporarily stop stimulation, including by the patient himself [37, 51]. VS was initially used to treat resistant epilepsy, with some patients reporting a gradual significant improvement in mood and a decrease in anxiety [17]. The first two open studies on 59 and 74 patients, conducted in the USA and Europe, showed comparable and quite convincing results [43, 47, 57]. The number of responders by the 10th week of therapy in resistant depressive patients reached 30% and continued to gradually increase by the 12th month of therapy.

therapy. However, in a double-blind 10-week study, the number of responders did not exceed 15% and did not differ from the placebo group [52]. One of the latest long-term studies of BS was open and revealed a higher efficacy of BS compared to "usual" therapy in patients with resistant depression (27% and 13%) [25]. These data served as the basis for the FDA approval of BS for the treatment of "chronic depression" as a 4th-line therapy. It should be noted that repeated data show that the effectiveness of ECT in the past is a predictor of the effect of BS [18, 53]. In recent years, the psychiatric community has taken a more cautious position in assessing this method, justifying the need for additional research due to the lack of evidence [53].

Deep brain stimulation (DBS) is a stereotactic neurosurgical technique and represents a long-term (constant) high-frequency electrical stimulation of deep brain structures, mainly the subthalamic nuclei. Initially, it was used to treat severe forms of Parkinson's disease. At present, in neurology, DBS is an effective and registered method for treating essential tremor, dystonia and resistant epilepsy. MRI and neurophysiological navigation during electrode implantation, as well as the use of individual stimulation parameters, increase the therapeutic effect.

In psychiatry, DBS is used primarily in the treatment of resistant OCD and resistant depression. In OCD, electrodes are implanted uni-, less often bilaterally, into the anterior sections of the internal capsule. A whole series of publications of clinical observations on the effective use of high-frequency DBS, primarily in the USA and Belgium, in severe forms of OCD resistant to pharmacotherapy have now determined its preliminary clinical niche [48, etc.]. We are talking about chronic severe compulsions in adults, where DBS can be used in combination with pharmacotherapy. Evidence of the effectiveness of DBS in OCD is indirectly regulated by ethical aspects, limiting the conduct of controlled studies.

A kind of impetus for research on the use of DMS in depression was provided by repeated cases of mood improvement in patients with OCD after stimulation, regardless of the dynamics of obsessive-compulsive symptoms. Accordingly, in the first studies, electrodes were also implanted in the internal capsule. In a study on 15 patients conducted at Brown University, 40% of patients achieved remission by the 6th month of stimulation [27].

The next strategy implemented at the University of Toronto Clinic was stimulation of the subcallosal space adjacent to the ringulate gyrus. In 60% of 20 patients with resistant recurrent depression, a clinical effect was registered, which was maintained during a follow-up assessment after one year [41, 42]. A remote 3-6-year follow-up showed that the initially achieved therapeutic effect at least persists, and in some patients it tends to increase with good tolerability of the procedure [35]. The only confounding factor in the results is that 2 patients out of 20 died during this period due to suicide. It should be noted that GMS was administered to rather severe patients as a 4th-line therapy with the ineffectiveness of the previous 3 courses of antidepressants, ECT and psychotherapy.

The application of neuropsychological and neurophysiological research data served as the basis for the development of the third GMS technique. Direct stimulation of the lenticular nucleus (nucleus accumbens) can presumably influence the manifestations of anhedonia in depression. In a recent

In an open study of GMS using this method, a critical disappearance of anhedonia was indeed recorded in the first days of stimulation, followed by a rapid reduction in depression in 50% of patients [57].

Of course, the data on the clinical use of GMS are limited and cannot be interpreted as conclusive. Long-term placebo-controlled studies are currently being conducted, the results of which should clarify the prospects for using this method in psychiatry.

The effectiveness of brain stimulation methods and probable mechanisms of therapeutic action remain unexplored, while the stimulation methods and techniques themselves continue to be developed and improved. Advances in neurobiology determine the development and improvement of brain stimulation techniques. At the same time, modern research on the use of ECT, TMS, GMS and vagal stimulation contribute to a greater understanding of individual clinical phenomena and, in general, the nature of some mental disorders.

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