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THE ROLE OF MOLECULAR BIOMARKERS IN PREDICTING THE EFFECTIVENESS OF PSYCHOTHERAPY IN ANXIETY AND DEPRESSIVE DISORDERS

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ABSTRACT

The review analyzes the role of molecular biomarkers in predicting the effectiveness of psychotherapy in anxiety and depressive disorders, with an emphasis on neurotrophic, inflammatory, neurotransmitter, and genetic-epigenetic predictors. The presented data demonstrate that the variability of biological systems, from neuroplasticity to immune activity, determines individual differences in therapeutic response and can serve as the basis for a personalized choice of psychotherapeutic strategies. Special attention is paid to multiomic approaches and extracellular vesicles as promising sources of highly informative biomarkers capable of improving the accuracy of clinical prognosis. The systematization of the results of modern research makes it possible to form a conceptual model of precision psychotherapy that combines data from various biological levels. The generalizations obtained can be useful to specialists focused on the introduction of biomarkers into the practice of mental health, as well as to researchers engaged in the development of new tools for personalized treatment.

KEYWORDS: molecular biomarkers; precision psychotherapy; anxiety and depressive disorders; neurotrophic factors; inflammatory markers; genetic and epigenetic predictors; extracellular vesicles.

INTRODUCTION

Anxiety disorders are considered today as one of the most common mental disorders that accompany a person throughout life, and are formed mainly in childhood or adolescence, which is confirmed by data from foreign epidemiological studies [1]. Their high prevalence is reflected in the lifelong risk, which reaches about a third of the population, as well as in a significant level of functional disorders and a decrease in the quality of life in both adults and children. According to estimates of the global burden of disease, anxiety disorders are among the leading causes of disability, and in Russia there is a steady increase in the incidence of anxiety-depressive symptoms, which indicates an increased socio-psychological significance of this group of conditions [2-6]. Despite the variety of available treatments, including pharmacotherapy and psychotherapy, approximately half of adults and a significant proportion of children do not show clinically significant improvement, which turns the selection of an effective intervention into a trial-and-error process. The lack of tools for predicting the response to psychotherapy makes treatment lengthy, insufficiently predictable, and costly, which underscores the need to find objective indicators of the effectiveness of the intervention even before it begins.

In this regard, the study of molecular biomarkers - inflammatory, neurotrophic, neurotransmitter and endocrine parameters - is of particular relevance, which are potentially able to reflect the individual reactivity of the patient and predict the likelihood of a response to psychotherapeutic strategies, including cognitive behavioral therapy [7-10]. The development of precision psychiatry involves a transition from universal treatment regimens to personalized models where the choice of psychotherapy can be based on objective biological signatures [8-15]. Given the variety of potential biomarkers and the significant variability in patient response, the purpose of this review is to systematize current data on molecular predictors of the effectiveness of psychotherapy in anxiety and depressive disorders and assess their potential for improving clinical decisions. Thus, the research is aimed at identifying those biological indicators that can become the basis for the development of accurate, reproducible and clinically significant models for predicting therapeutic response.

Biological basis of anxiety and depressive disorders: dysfunctions of neural and neuroendocrine systems

The modern understanding of anxiety and depressive disorders requires an analysis of their biological foundations, since it is neural and neuroendocrine disorders that form the foundation of these conditions. Beckman et al. [14] have shown

that dysregulation of monoaminergic systems can trigger depressive-like behavior, emphasizing the primacy of neurochemical imbalance. The work of Brennan and colleagues [16] revealed that changes in GABA levels in the anterior cingulate cortex determine the effectiveness of the antidepressant response, demonstrating the importance of inhibitory neural circuits. Research by Burkhouse et al. [17] indicate that atypical activation of cortical structures during threat perception is a key link in the pathogenesis of anxiety disorders. Since these processes affect the fundamental mechanisms of neuroplasticity, stress response, and regulation of neurotransmitters, it is their dysfunction that forms the basis for the search for molecular and neuroimaging biomarkers. Such a pathophysiological analysis makes it possible to identify specific signaling pathways through which early detection of disorders is possible even before clinical manifestation. Taken together, these data confirm the need to develop biomarkers that can improve diagnostic accuracy and provide personalized treatment choices.

Molecular biomarkers as tools of precision psychotherapy: conceptual approaches and classification

Modern research demonstrates that precision psychotherapy is made possible by the systematic use of molecular biomarkers that reflect the dysfunctions of key neurobiological networks and make it possible to differentiate the mechanisms of depressive and anxiety disorders at the level of individual patterns [1, 7]. Among the most informative markers are neurotransmitter indicators (serotonergic and dopaminergic activity), which, according to S.O. Ovchinnikov and D.S. Kasatkina [3], correlate with the severity of clinical symptoms and the patient's ability to respond to psychotherapeutic interventions. Equally important are neurotrophic factors, primarily BDNF, the variability of which, as noted by T.I. Vazagaeva et al. [6], is closely related to the plasticity of neural networks and determines the potential of psychotherapy to influence the processes of restructuring emotional and cognitive circuits. An important contribution to the typology of biomarkers is made by inflammatory and hormonal parameters — interleukins, cytokines, cortisol, markers of endothelial dysfunction - which, as Vorobyeva and Fateeva point out [4], serve as indicators of an unfavorable prognosis and a decrease in the likelihood of a sustained therapeutic response. Finally, the genetic and epigenetic biomarkers described by Zobin [2] form the basis for the classification of biological subtypes of depressive disorders, which opens the way to the development of algorithms for stratified psychotherapy and allows the integration of data from all five systems into a comprehensive biomarker panel (Table 1).

Table 1: Molecular biomarkers in precision psychotherapy

Type of biomarkers	Basic mechanisms	Key sources	Clinical significance
Neurotransmitters (serotonin, dopamine, norepinephrine, GABA)	Regulation of emotional reactivity, motivation, and cognitive processes	Ovchinnikov & Kasatkin [3]; Beckman et al. [14]	Prognosis of the response to psychotherapy; identification of the risk of therapeutic resistance
Neurotrophic (BDNF, NGF, GDNF)	Neuroplasticity and the formation of stable changes in neural networks	Vazagaeva et al. [6]	Assessment of the potential of psychotherapeutic effects; monitoring of treatment dynamics
Inflammatory (IL 6, CRP, TNF α)	Systemic inflammation, effects on mood and cognitive functions	Bradley et al. [18]	Determination of depression subtypes; prognosis of therapy effectiveness
Hormonal (cortisol, ACTH, DHEA, TSH)	Stress reactivity, regulation of the HPA axis	Gratch [19]	Predicting the effectiveness of psychotherapy and the risk of chronicling
Genetic and epigenetic markers	Polymorphisms, DNA methylation, gene expression	Zobin [2]; Dunn et al. [20]	Stratification of patients; selection of personalized psychotherapy

Note: IL — interleukin; CRP — C-reactive protein; TNFa — tumor necrosis factor alpha; GF — growth factors; BDNF — neurotrophic factor derived from the brain; VEGF — vascular endothelial growth factor; NGF — nerve growth factor; GDNF — neurotrophic factor derived from glial cells; IGF-1 — insulin-like growth factor-1; 5—HT - serotonin (5—hydroxytryptamine); NA — norepinephrine; DA — dopamine; GABA - γ—aminobutyric acid; ACTH — adrenocorticotropic hormone; CRH - corticotropin-releasing hormone; TSH — thyroid—stimulating hormone; GWAS - genome-wide association study; PET — positron emission tomography; HPA — hypothalamic-pituitary-adrenal axis.

Thus, the molecular biomarkers presented in the table demonstrate that predictors of response to psychotherapy are formed at the intersection of neurochemical, immune, hormonal, and genetic processes, which enhances the importance of a comprehensive biomarker assessment. Turning to the analysis of individual subsystems, inflammatory markers deserve special attention, since they are the ones most consistently associated with variations in therapeutic response and the stability of clinical outcomes.

Inflammatory markers (IL-6, TNF-α, CRP) as predictors of the effectiveness of psychotherapy

In recent years, research has increasingly shown that inflammatory markers, primarily IL-6, TNF-α, and CRP, play an essential role in the pathophysiology of depression and can serve as indicators of individual differences in the course of the disease [19]. The accumulated data demonstrate that elevated levels of these cytokines are associated with more severe symptoms, decreased neuroplasticity, and impaired emotional regulation. At the same time, there is a growing number of

studies indicating the prognostic value of inflammatory markers for the effectiveness of psychotherapy, since their increased concentration often predicts a weak or delayed therapeutic response [21-25]. A dynamic decrease in IL-6 and CRP during treatment, on the contrary, correlates with an improvement in mental state, which highlights their potential as objective response indicators [26-28]. These observations form the basis for the transition to the consideration of neurotrophic factors such as BDNF and GDNF, which reflect the plasticity of the brain and have their own predictive value for the psychotherapeutic response.

Neurotrophic factors (BDNF, GDNF) and their prognostic significance for the psychotherapeutic response

Neurotrophic factors, primarily BDNF and GDNF, are considered as key biomarkers reflecting the brain's ability to plasticity, the mechanism underlying successful psychotherapeutic change [29-32]. Studies consistently demonstrate that higher or increasing levels of BDNF during treatment are associated with a better response to cognitive behavioral therapy, as enhanced neuroplasticity facilitates the formation of new cognitive and emotional patterns [33-36]. Similarly, changes in GDNF expression are associated with the restoration of neural networks involved in mood regulation, which allows us to consider this factor as an additional indicator of therapeutic susceptibility [37]. Therefore, the dynamics of neurotrophic markers can serve as a predictive tool for assessing the likelihood of effective psychotherapy and choosing personalized intervention strategies [39]. Given the growing evidence base, neurotrophic factors are becoming an important link in understanding why some patients show marked therapeutic progress, while others remain resistant [40]. This logic naturally leads to the consideration of genetic and epigenetic predictors of psychotherapeutic response, which allow us to further explain the interindividual differences in response to treatment.

Genetic and epigenetic predictors of response to psychotherapy: current achievements and limitations

Current research demonstrates that variations in genes regulating neuroplasticity and serotonergic transmission can significantly affect the degree of clinical improvement when using cognitive behavioral therapy and other psychotherapeutic methods. Data on polymorphisms SLC6A4, BDNF, and HTR2A, summarized in the works of Kashchenko et al. [1], Zobin [2], and Dunn et al. [20] indicate that genetic features form individual sensitivity to psychotherapeutic effects, although the reproducibility of such effects remains incomplete. Epigenetic changes, including the levels of methylation of the BDNF and SLC6A4 promoter zones described by Ovchinnikov and Kasatkin [3], confirm that psychotherapy is able to modify the expression of key genes associated with the regulation of emotions and stress reactivity, which makes the patient's molecular profile a potential predictor of a sustained therapeutic response. Despite the growing body of data on the association of SNPs and the dynamics of epigenetic markers with clinical outcomes, numerous limitations — variability of samples, heterogeneity of psychotherapeutic protocols, lack of standardized biomolecular panels — prevent the introduction of these findings into routine practice [41-45]. Thus, the analysis of genetic and epigenetic predictors is a promising area of precision psychotherapy, and the SNP variants studied in the studies and their potential predictive value are systematized in Table 2.

Table 2: Genetic and epigenetic predictors of response to psychotherapy in depressive disorders

The gene / marker	SNP / epigenetic modification	Biological function	Predictive value	Sources
BDNF	of RS6265 (Val66Met)	Regulation of neuroplasticity and synaptic growth	The Met allele is associated with a reduced response to CBT and lower plasticity	Vazagaeva et al., 2019; Dunn et al., [20]
SLC6A4	5 HTTLPR / RS25531	Serotonin transporter, regulation of serotonergic transmission	. The s allele reduces the response to psychotherapy and increases stress reactivity	Kashchenko et al., [1]; Ovchinnikov & Kasatkin [3]
HTR2A	RS6311 / RS6313 / RS7997012	Serotonin 5 HT2A receptors, regulation of emotions and cognitive flexibility	Associations with the CBT response are confirmed, but differ between samples.	Jaggar & Vaidya, [32]; Ilchibaeva et al., [33]
Epigenetic modifications of BDNF	Methylation of the BDNF promoter zone	Changes in BDNF expression, effects on stress resistance	A decrease in methylation after CBT predicts stable remission	Zobin [2]
Epigenetic changes in SLC6A4	Methylation of CpG islands of SLC6A4	Regulation of serotonin transport	High methylation is associated with a worse response to therapy	Brennan et al., [16]

Note: SNP is a single nucleotide polymorphism; BDNF is a neurotrophic factor derived from the brain; GDNF is a neurotrophic factor derived from glial cells; SLC6A4 is a serotonin transporter gene; HTR2A is a serotonin type 2A receptor gene; 5-HTTLPR - serotonin-transporter-linked polymorphic region, a polymorphic region associated with the transporter gene serotonin; rs25531 is a single nucleotide polymorphism in the promoter region of the SLC6A4 gene that modifies the functional variants of 5-HTTLPR; rs6265 (Val66Met) is a functional polymorphism of the BDNF gene that causes the amino acid valine → methionine to be replaced in the encoded protein; rs6311 / rs6313 / rs7997012 is a SNP

of the HTR2A gene encoding type 2A serotonin receptor; 5-HT2A — 5-hydroxytryptamine receptor 2A, serotonin receptor 2A.

The presented data demonstrate that genetic and epigenetic markers can serve as important components of prognostic models, making it possible to more accurately determine the likelihood of successful psychotherapeutic intervention. This creates the basis for the transition to the analysis of promising areas, including the role of extracellular vesicles, multiomics and integrative predictive models that can bring personalized psychotherapy to a new level.

Promising areas: extracellular vesicles (EV), multimics, and integrative models for predicting treatment response

A promising direction in the development of precision psychotherapy is the use of extracellular vesicles (EV) as carriers of informative molecular signals capable of reflecting the dynamics of neuroinflammation, neuroplasticity, and metabolic disorders in depressive and anxiety disorders, which is confirmed by data on the diagnostic value of EV-associated RNAs and proteins [1, 7]. Their molecular "cargo" — microRNAs, mRNAs, proteins, lipids, and metabolites — is characterized by high sensitivity to psychopathological processes and can serve as a basis for creating noninvasive biomarker panels that complement traditional laboratory parameters [2]. The inclusion of EV in multi-genomic platforms combining transcriptomic, epigenetic, proteomic, and metabolomic profiles makes it possible to form more accurate models of patient stratification and identify biological subtypes of affective disorders, which is consistent with the trend towards the systemic biology of mental illness [46-50].

The development of integrative bioinformatic approaches makes it possible to create predictive models combining EV signatures with genetic and epigenetic markers, including polymorphisms SLC6A4, BDNF and HTR2A, thereby increasing the accuracy of predicting an individual response to psychotherapy [5, 51-55]. These models can potentially be integrated into clinical decision support systems, allowing optimal therapeutic strategies to be selected based on the individual biological profile of the patient. In parallel, the direction of using EV as therapeutic carriers is developing, which creates prerequisites for future interventions aimed at modulating neuroinflammatory cascades and restoring neuroplasticity in affective disorders [56-64].

Thus, the combination of EV biomarkers, multiomic methods, and integrative forecasting models forms the basis for the next generation of bioinformatic and clinical tools capable of enabling the transition to truly personalized psychotherapy.

CONCLUSION

The review demonstrates that molecular biomarkers, ranging from neurotrophic and inflammatory to genetic and epigenetic, have significant potential for predicting the effectiveness of psychotherapeutic interventions in anxiety and depressive disorders. Analysis of neurobiological mechanisms confirms that it is the interaction of neuroplasticity, stress reactivity, and systemic inflammation that forms the basis for individual differences in therapeutic response. The summarized data show the promise of complex multiomic approaches and the use of extracellular vesicles as new sources of biomarkers that can improve the accuracy of predictive models. The presented directions create prerequisites for the formation of personalized psychotherapy algorithms focused on the biological profile of the patient. Thus, the review forms the theoretical basis necessary for the development of clinically applicable tools for precision psychotherapy and further research in the field of biomarkers of psychiatric disorders.

REFERENCES

1. Kashchenko S.A., Kormachenko K.A., Musaelyan M.G., Galenko D.V., Salakhova A.N. Identification of biomarkers of depression: prospects of use in clinical practice. S.S. Korsakov Journal of Neurology and Psychiatry. 2025; 125 (5): 51-55.
2. Zobin Ya.S. On the use of biomarkers in the diagnosis of depression of various etiologies. Proceedings of the Russian Military Medical Academy. 2022; 41 (2S).
3. Ovchinnikov S.O., Kasatkin D.S. Laboratory markers of depression: literature review. Patient-oriented medicine and pharmacy. 2024; 2 (1): 61–66. doi: 10.37489/2949-1924-0043.
4. Vorobyeva O.V., Fateeva V.V. The relationship of markers of endothelial dysfunction with the severity of depression in middle-aged patients with cerebral microangiopathy. S.S. Korsakov Journal of Neurology and Psychiatry. 2021; 121 (4): 7–11. doi: 10.17116/jnevro20211210417.
5. Shamrey V.K., Kurasov E.S., Zobin Ya.S., Tsygan N.V. The possibilities of using laboratory biomarkers for the objective diagnosis of depressive disorders. Neurology, neuropsychiatry, psychosomatics. 2021; 13 (2): 34–39. doi: 10.14412/2074-2711-2021-2-34-39.
6. Vazagaeva T.I., Akhapkin R.V., Alexandrovsky Yu.A. The role of the brain neurotrophic factor in the effects of antidepressants in the treatment of depression. Bulletin of the Russian Academy of Medical Sciences. 2019; 74 (1): 20-28.
7. Uzbekov M.G., Gurovich I.Ya., Ivanova S.A. Potential biomarkers of mental illness in the aspect of a systemic approach. Social and clinical psychiatry. 2016; 26 (1): 77–94.
8. Huang S., Li Y., Shen J., Liang W., Li C. Identification of a diagnostic model and molecular subtypes of major depressive disorder based on endoplasmic reticulum stress-related genes. Front Psychiatry. 2023; 14: 1168516. doi: 10.3389/fpsyt.2023.1168516.

9. Malujlo-Balcerska E., Pietras T. Adipocytokines levels as potential biomarkers for discriminating patients with a diagnosis of depressive disorder from healthy controls. J Psychiatr Res. 2024; 171: 163–170. doi: 10.1016/j.jpsychires.2024.01.026.
10. Bhikram T., Sandor P. Neutrophil-lymphocyte ratios as inflammatory biomarkers in psychiatric patients. Brain Behav Immun. 2022; 105: 237–246. doi: 10.1016/j.bbi.2022.07.006.
11. Brinn A., Stone J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. BMJ Open. 2020; 10 (7): e036859. doi: 10.1136/bmjopen-2020-036859.
12. Klaus F., Guetter K., Schlegel R., et al. Common and disorder-specific upregulation of the inflammatory markers TRAIL and CCL20 in depression and schizophrenia. Sci Rep. 2021; 11 (1): 19204. doi: 10.1038/s41598-021-98769-0.
13. Mazza M.G., Lucchi S., Tringali A.G.M., et al. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018; 84 (Pt A): 229–236. doi: 10.1016/j.pnpbp.2018.03.012.
14. Beckman D., Santos L.E., Americo T.A., Ledo J.H., De Mello F.G., Linden R. Prion protein modulates monoaminergic systems and depressive-like behavior in mice. J Biol Chem. 2015; 290: 20488–20498. doi: 10.1074/jbc.M115.666156.
15. Bousman C.A., Dunlop B.W. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. Pharmacogenomics J. 2018. doi: 10.1038/s41397-018-0027-3.
16. Bradley P., Shiekh M., Mehra V., Vrbicky K., Layle S., Olson M.C., Maciel A., Cullors A., Garces J.A., Lukowiak A.A. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018; 96: 100–107. doi: 10.1016/j.jpsychires.2017.09.024.
17. Brennan B.P., Admon R., Perriello C., LaFlamme E.M., Athey A.J., Pizzagalli D.A., Hudson J.I., Pope H.G., Jensen J.E. Acute change in anterior cingulate cortex GABA, but not glutamine/glutamate, mediates antidepressant response to citalopram. Psychiatry Res Neuroimaging. 2017. doi: 10.1016/j.pscychresns.2017.08.009.
18. Burkhouse K.L., Kujawa A., Hosseini B., Klumpp H., Fitzgerald K.D., Langenecker S.A., Monk C.S., Phan K.L. Anterior cingulate activation to implicit threat before and after treatment for pediatric anxiety disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018. doi: 10.1016/j.pnpbp.2018.03.013.
19. Gratch I., Choo T.H., Galfalvy H., Keilp J.G., Itzhaky L., Mann J.J., Oquendo M.A., Stanley B. Detecting suicidal thoughts: the power of ecological momentary assessment. Depress Anxiety. 2020. doi: 10.1002/da.23043.
20. Gyorkos A., Baker M.H., Miutz L.N., Lown D.A., Jones M.A., Houghton-Rahrig L.D. Carbohydrate-restricted diet and exercise increase brain-derived neurotrophic factor and cognitive function: a randomized crossover trial. Cureus. 2019; 11 (6): e5604. doi: 10.7759/cureus.5604.
21. Suire C.N., Eitan E., Shaffer N.C., Tian Q., Studenski S., Mattson M.P., Kapogiannis D. Walking speed decline in older adults is associated with elevated pro-BDNF in plasma extracellular vesicles. Exp Gerontol. 2017. doi: 10.1016/j.exger.2017.08.024.
22. Taylor J.H., Landeros-Weisenberger A., Coughlin C., Mulqueen J., Johnson J.A., Gabriel D., Reed M.O., Jakubovski E., Bloch M.H. Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. Neuropsychopharmacology. 2018; 43: 325–333. doi: 10.1038/npp.2017.194.
23. Kim S.H., Weiss C., Hoffmann U., Borggrefe M., Akin I., Behnes M. Advantages and limitations of current biomarker research: from experimental research to clinical application. Curr Pharm Biotechnol. 2017; 18 (6): 445–455. doi: 10.2174/1389201018666170601091205.
24. Lippolis J.D., Powell E.J., Reinhardt T.A., Thacker T.C., Casas E. Symposium review: omics in dairy and animal science—promise, potential, and pitfalls. J Dairy Sci. 2019; 102 (5): 4741–4754. doi: 10.3168/jds.2018-15267.
25. Jazvinšćak Jembrek M., Oršolić N., Karlović D., Peitl V. Flavonols in action: targeting oxidative stress and neuroinflammation in major depressive disorder. Int J Mol Sci. 2023; 24: 6888. doi: 10.3390/ijms24086888.
26. Haroon E., Miller A.H., Sanacora G. Inflammation, glutamate, and glia: a trio of trouble in mood disorders. Neuropsychopharmacology. 2017; 42: 193–215. doi: 10.1038/npp.2016.199.
27. Wang H., Jin M., Xie M., Yang Y., Xue F., Li W., Zhang M., Li Z., Li X., Jia N., et al. Protective role of antioxidant supplementation for depression and anxiety: a meta-analysis of randomized clinical trials. J Affect Disord. 2023; 323: 264–279. doi: 10.1016/j.jad.2022.11.072.
28. Moncrieff J., Cooper R.E., Stockmann T., Amendola S., Hengartner M.P., Horowitz M.A. The serotonin theory of depression: a systematic umbrella review of the evidence. Mol Psychiatry. 2022; 27: 2403–2414. doi: 10.1038/s41380-022-01661-0.
29. Cowen P.J., Browning M. What has serotonin to do with depression? World Psychiatry. 2015; 14: 158–160. doi: 10.1002/wps.20229.
30. Baudat M., Kort A.R., Hove D.L.A., Joosten E.A. Early-life exposure to selective serotonin reuptake inhibitors: long-term effects on pain and affective comorbidities. Eur J Neurosci. 2022; 55: 295–317. doi: 10.1111/ejn.15544.
31. Jaggar M., Vaidya V.A. 5-HT2A receptors in the central nervous system. In: Jaggar M., Vaidya V.A., editors. 5-HT2A receptors and BDNF regulation: implications for psychopathology. Berlin–Heidelberg: Springer; 2018. p. 395–438.

32. Ilchibaeva T., Tsybko A., Zeug A., Müller F.E., Guseva D., Bischoff S., Ponimaskin E., Naumenko V. Serotonin receptor 5-HT2A regulates TrkB receptor function in heteroreceptor complexes. Cells. 2022; 11: 2384. doi: 10.3390/cells11152384.
33. Moliner R., Girych M., Brunello C.A., Kovaleva V., Biojone C., Enkavi G., Antenucci L., Kot E.F., Goncharuk S.A., Kaurinkoski K., et al. Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. Nat Neurosci. 2023; 26: 1032–1041. doi: 10.1038/s41593-023-01316-5.
34. Fukumoto K., Fogaça M.V., Liu R.-J., Duman C.H., Li X.-Y., Chaki S., Duman R.S. Medial PFC AMPA receptor and BDNF signaling are required for the rapid and sustained antidepressant-like effects of 5-HT1A receptor stimulation. Neuropsychopharmacology. 2020; 45: 1725–1734. doi: 10.1038/s41386-020-0705-0.
35. Pierscionek T., Adekunte O., Watson S., Ferrier N., Alabi A. Role of corticosteroids in the antidepressant response. ChronoPhys Ther. 2014; 4: 87–98.
36. Hage M.P., Azar S.T. The link between thyroid function and depression. J Thyroid Res. 2012; 2012: 590648. doi: 10.1155/2012/590648.
37. Dunn E.C., Brown R.C., Dai Y., et al. Genetic determinants of depression: recent findings and future directions. Harv Rev Psychiatry. 2015; 23 (1): 1–18. doi: 10.1097/HRP.0000000000000054.
38. Woods A.J., Antal A., Bikson M., Boggio P.S., Brunoni A.R., Celnik P., et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016; 127: 1031–1048. doi: 10.1016/j.clinph.2015.11.012.
39. Bikson M., Brunoni A.R., Charvet L.E., Clark V.P., Cohen L.G., Deng Z.D., et al. Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul. 2018; 11: 465–480. doi: 10.1016/j.brs.2017.12.008.
40. Brunoni A.R., Sampaio-Junior B., Moffa A.H., Aparício L.V., Gordon P., Klein I., et al. Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry. 2019; 41: 70–81. doi: 10.1590/1516-4446-2017-0018.
41. Kaiser R.H., Andrews-Hanna J.R., Wager T.D., Pizzagalli D.A. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry. 2015; 72: 603–611. doi: 10.1001/jamapsychiatry.2015.0071.
42. Baeken C., De Raedt R. Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuitry in unipolar depression. Dialogues Clin Neurosci. 2011; 13: 139–145. doi: 10.31887/DCNS.2011.13.1/cbaeken.
43. Aparicio L.V., Guarienti F., Razza L.B., Carvalho A.F., Fregni F., Brunoni A.R. A systematic review on the acceptability and tolerability of transcranial direct current stimulation treatment in neuropsychiatry trials. Brain Stimul. 2016; 9: 671–681. doi: 10.1016/j.brs.2016.05.004.
44. Lin J.Y., Jiang M.Y., Kan Z.M., Chu Y. Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: a meta-analysis. J Affect Disord. 2014; 168: 430–438. doi: 10.1016/j.jad.2014.06.012.
45. Brunoni A.R., Moffa A.H., Fregni F., Palm U., Padberg F., Blumberger D.M., et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016; 208: 522–531. doi: 10.1192/bjp.bp.115.164715.
46. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022; 9: 137–150.
47. Martínez-Torres A.M., Morán J. CB1 receptor activation provides neuroprotection in an animal model of glutamate-induced excitotoxicity through a reduction of NOX-2 activity and oxidative stress. CNS Neurosci Ther. 2024; 30: e70099.
48. Zou M., Li D., Li L., Wu L., Sun C. Role of the endocannabinoid system in neurological disorders. Int J Dev Neurosci. 2019; 76: 95–102.
49. Navarrete F., García-Gutiérrez M.S., Jurado-Barba R., Rubio G., Gasparyan A., Austrich-Olivares A., Manzanares J. Endocannabinoid system components as potential biomarkers in psychiatry. Front Psychiatry. 2020; 11: 315.
50. Colangeli R., Pierucci M., Benigno A., Campiani G., Butini S., Di Giovanni G. The FAAH inhibitor URB597 suppresses hippocampal maximal dentate afterdischarges and restores seizure-induced impairment of short and long-term synaptic plasticity. Sci Rep. 2017; 7: 11152.
51. Post J.M., Loch S., Lerner R., Remmers F., Lomazzo E., Lutz B., Bindila L. Antiepileptogenic effect of subchronic palmitoylethanolamide treatment in a mouse model of acute epilepsy. Front Mol Neurosci. 2018; 11: 67.
52. Khan H., Ghori F.K., Ghani U., Javed A., Zahid S. Cannabinoid and endocannabinoid system: a promising therapeutic intervention for multiple sclerosis. Mol Biol Rep. 2022; 49: 5117–5131.
53. Sobue A., Komine O., Endo F., Kakimi C., Miyoshi Y., Kawade N., Watanabe S., Saito Y., Murayama S., Saido T.C. Microglial cannabinoid receptor type II stimulation improves cognitive impairment and neuroinflammation in Alzheimer's disease mice by controlling astrocyte activation. Cell Death Dis. 2024; 15: 858.
54. Mazurka R., Harkness K.L., Hassel S., Stensson N., Nogovitsyn N., Poppenk J., Foster J.A., Squires S.D., Rowe J., Milev R.V., et al. Endocannabinoid concentrations in major depression: effects of childhood maltreatment and relation to hippocampal volume. Transl Psychiatry. 2024; 14: 431.

55. Bluett R.J., Báldi R., Haymer A., Gaulden A.D., Hartley N.D., Parrish W.P., Baechle J., Marcus D.J., Mardam-Bey R., Shonesy B.C., et al. Endocannabinoid signalling modulates susceptibility to traumatic stress exposure. Nat Commun. 2017; 8: 14782.
56. Morena M., Patel S., Bains J.S., Hill M.N. Neurobiological interactions between stress and the endocannabinoid system. Neuropsychopharmacology. 2016; 41: 80–102.
57. Cristino L., Bisogno T., Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nat Rev Neurol. 2020; 16: 9–29.
58. Bernal-Chico A., Tepavcevic V., Manterola A., Utrilla C., Matute C., Mato S. Endocannabinoid signaling in brain diseases: emerging relevance of glial cells. Glia. 2023; 71: 103–126.
59. Ali N., Sayeed U., Shahid S.M.A., Akhtar S., Khan M.K.A. Molecular mechanisms and biomarkers in neurodegenerative disorders: a comprehensive review. Mol Biol Rep. 2025; 52: 337.
60. Amoah S.K., Rodriguez B.A., Logothetis C.N., Chander P., Sellgren C.M., Weick J.P., et al. Exosomal secretion of a psychosis-altered miRNA that regulates glutamate receptor expression is affected by antipsychotics. Neuropsychopharmacology. 2020; 45: 656–665. doi: 10.1038/s41386-019-0579-1.
61. Tsivion-Visbord H., Perets N., Sofer T., Bikovski L., Goldshmit Y., Ruban A., et al. Mesenchymal stem cells derived extracellular vesicles improve behavioral and biochemical deficits in a phencyclidine model of schizophrenia. Transl Psychiatry. 2020; 10: 305. doi: 10.1038/s41398-020-00988-y.
62. Woelfer M., Kasties V., Kahlfuss S., Walter M. The role of depressive subtypes within the neuroinflammation hypothesis of major depressive disorder. Neuroscience. 2019; 403: 93–110. doi: 10.1016/j.neuroscience.2018.03.034.
63. Fries G.R., Lima C.N.C., Valvassori S.S., Zunta-Soares G., Soares J.C., Quevedo J. Preliminary investigation of peripheral extracellular vesicles' microRNAs in bipolar disorder. J Affect Disord. 2019; 255: 10–14. doi: 10.1016/j.jad.2019.05.020.
64. Ceylan D., Tufekci K.U., Keskinoglu P., Genc S., Ozerdem A. Circulating exosomal microRNAs in bipolar disorder. J Affect Disord. 2020; 262: 99–107. doi: 10.1016/j.jad.2019.10.038.

Contribution of the authors

The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

Conflict of interests. The authors declare that there is no conflict of interest