Scientific and Educational Eastern European Medical Cluster

MEDICAL ETHICS

SCIENTIFIC INTERDISCIPLINARY JOURNAL OF YAROSLAVL STATE MEDICAL UNIVERSITY
AND PIROGOV RUSSIAN NATIONAL RESEARCH MEDICAL UNIVERSITY

SUBMISSION https://medet.rsmu.press/
CORRESPONDENCE https://medet.rsmu.press/
COLLABORATION editor@rsmu.press
ADDRESS Ostrovityanov Street 1, Moscow, 119997, Russia

Indexed in RSCI

Open access to archive

Issue DOI: 10.24075/medet.2024-04
The mass media registration certificate серия ПИ № ФС77-81021 от 02 июня 2021 г.
Founders: Yaroslavl State Medical University (Yaroslavl, Russia)
Pirogov Russian National Research Medical University (Moscow, Russia).
Publisher: Pirogov Russian National Research Medical University; adress: Ostrovityanov Street 1, Moscow, 117997, Russia

Approved for print 31.12.2024
Circulation: 100 copies. Printed by Print.Formula
www.print-formula.ru

Научно-образовательный медицинский кластер Восточно-Европейский

МЕДИЦИНСКАЯ ЭТИКА

НАУЧНЫЙ МЕЖДИСЦИПЛИНАРНЫЙ ЖУРНАЛ
ЯРОСЛАВСКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА
И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
УНИВЕРСИТЕТА ИМ. Н. И. ПИРОГОВА

ПОДАЧА РУКОПИСЕЙ https://medet.rsmu.press/
ПЕРЕПИСКА С РЕДАКЦИЕЙ https://medet.rsmu.press/
СОТРУДНИЧЕСТВО editor@rsmu.press
АДРЕС РЕДАКЦИИ ул. Островитянова, д.1, г. Москва, 119997

Журнал включен в РИНЦ

Здесь находится открытый архив журнала

DOI выпуска: 10.24075/medet.2024-03
Свидетельство о регистрации средства массовой информации серия ПИ № ФС77-81021 от 02 июня 2021 г.
Учредители: ФГБОУ ВО «Ярославский государственный медицинский университет» Минздрава России (Ярославль, Россия);
ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Минздрава России (Москва, Россия).
Издатель: ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Минздрава России;
адрес: ул. Островитянова, д.1, г. Москва, 117997, Россия, 8(495)434-03-29

Подписано в печать 31.12.2024
Тираж 100 экз. Отпечатано в типографии Print.Formula
www.print-formula.ru

MEDICAL ETHICS **4, 2024**
МЕДИЦИНСКАЯ ЭТИКА

Contents
Содержание

ETHICAL ISSUES OF NEUROTECHNOLOGY

Firsov DE[1] ✉, Ivashkovskaya AV[2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Yaroslavl State University named after PG Demidov, Yaroslavl, Russia

Discussion of the draft of the Recommendations on the Ethics of Neurotechnology proposed by UNESCO reveals the need to develop domestic regulations in this area, taking into account modern challenges of technological development. The purpose of the recommendations in the field of neuroethics is to ensure the human right to protect health, well-being and dignity associated with the risks of technological interference in the brain and mental processes, as well as threats associated with the social and humanitarian consequences of scientific and technological progress in the field of neuroscience and neurotechnology. The draft of domestic recommendations should establish obligations related to the ethical aspects of creation, implementation and use of neurotechnologies, which are currently not regulated by the legislation of the Russian Federation and acts of technical regulation. The objectives of the recommendations are to specify the terminological apparatus in accordance with the current regulatory legal acts, targeted separation of neurotechnologies for medical and non-medical purposes, ensuring safety for the health and well-being of vulnerable persons and social groups. In the socioeconomic aspect, development of domestic recommendations on the use of neurotechnologies shows the relevance of stimulating development of domestic production and socioeconomic growth in accordance with the national development goals of the Russian Federation until 2030.

Keywords: neurotechnology, neuroethics, neurolaw, technological progress, neural interfaces

Author contribution: Firsov DE and Ivashkovskaya AV made an equal contribution to the preparation of the article.

✉ **Correspondence should be addressed:** Denis E. Firsov
Revolyutsionnaya str., 5, Yaroslavl, 150000, Russia; f300670@mail.ru

Received: 02.11.2024 **Accepted:** 27.11.2024 **Published online:** 20.12.2024

DOI: 10.24075/medet.2024.024

РАЗРАБОТКА ЭТИЧЕСКИХ РЕКОМЕНДАЦИЙ В ОБЛАСТИ ВНЕДРЕНИЯ НЕЙРОТЕХНОЛОГИЙ

Д. Е. Фирсов[1] ✉, А. В. Ивашковская[2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославский государственный университет им. П. Г. Демидова, Ярославль, Россия

Обсуждение предложенного ЮНЕСКО проекта Рекомендаций по этике нейротехнологий выявляет необходимость разработки отечественных регламентов в данной области с учетом современных вызовов технологического развития. Целью рекомендаций в сфере нейроэтики является обеспечение права человека на защиту здоровья, благополучия и достоинства, связанных с рисками технологического вмешательства в мозг и ментальные процессы, а также угроз, связанных с социально-гуманитарными следствиями научно-технического прогресса в области нейронаук и нейротехнологий. Проект отечественных рекомендаций должен установить обязательства, связанные с этическими аспектами создания, внедрения и использования нейротехнологий, которые в настоящее время не урегулированы законодательством Российской Федерации и актами технического регулирования. Задачами рекомендаций являются конкретизация терминологического аппарата в соответствии с действующими нормативными правовыми актами, целевое разделение нейротехнологий медицинского и немедицинского назначения, обеспечение безопасности для здоровья и благополучия уязвимых лиц и социальных групп. В социально-экономическом аспекте разработка отечественных рекомендаций применения нейротехнологий отражает актуальность задачи стимулирования развития отечественного производства, социально-экономического роста в соответствии с национальными целями развития Российской Федерации до 2030 г.

Ключевые слова: нейротехнологии, нейроэтика, нейроправо, технологический прогресс, нейроинтерфейсы

Вклад авторов: Д. Е. Фирсов и А. В. Ивашковская внесли равный вклад в подготовку статьи.

✉ **Для корреспонденции:** Денис Евгеньевич Фирсов
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; f300670@mail.ru

Статья поступила: 02.11.2024 **Статья принята к печати:** 27.11.2024 **Опубликована онлайн:** 20.12.2024

DOI: 10.24075/medet.2024.024

In April 2024, UNESCO headquarters in Paris announced the work of an Ad Hoc Expert Group (AHEG) consisting of 24 international experts on development of the first draft of Recommendations on the Ethics of Neurotechnology. Between May and July 2024, global and regional consultations were held “in order to take into account the views of a wide range of key stakeholders and different points of view in order to ensure an open and inclusive process for developing the draft of Recommendations” [1]. Russian experts took part in discussion of the UNESCO project. In particular, consultations held during the All-Russian Conference on Bioethics and Global Social Transformations at Yaroslavl State Medical University on June 28, 2024 were participated by members of the Russian Committee on Bioethics under the Commission of the Russian Federation for UNESCO [2]. Based on the results of the discussions to be held in 2024–2025, the final text of the Recommendations will be submitted for consideration at the 43rd session of the General Conference in November 2025 [1].

The active discussion of the draft of Recommendation on the Ethics of Neurotechnology reflects the Records of the General Conference 42nd session, Paris, November 7–22, 2023, on the need to create a global “ethical framework” to address human rights issues that arise or may arise in connection with the introduction of neurotechnologies into practice. Participation of Russian experts in the discussion of the draft makes it possible to draw attention of the international

community to issues that require additional clarifications, taking into account regional and national interests.

The pressing issues of the use of neurotechnologies in medical practice discussed by Russian experts and the prospects for spread of neurointerfaces in the consumer market reflect the need to develop domestic regulations in the field of neuroethics concerning both the most common topics of global prospects for neurotechnological progress and interests of domestic science.

Preparation of domestic recommendations is one of the solutions to the problems associated with modern challenges of technological development, defined by the Concept of Technological Development for the period up to 2030 as "objectively requiring a response from the state and society, a set of problems, threats and opportunities in the field of technology development and implementation, the complexity and scale of which are such that they cannot be solved, eliminated or implemented without structural changes solely due to increased resources" [3].

The purpose of domestic ethical recommendations on introduction of neurotechnologies can be determined taking into account a wide range of neurointerfaces applied in medical and social practice. The purpose of the recommendations in the field of neuroethics is to ensure the human right to protect health, well-being and dignity associated with the risks of technological interference in the brain and mental processes, as well as to prevent threats associated with the socio-humanitarian consequences of scientific and technological progress in the field of neuroscience and neurotechnology.

When discussing and developing the draft of domestic recommendations in the field of neuroethics, it is necessary to take into account the relevance of previously adopted international agreements, including provisions of the Nuremberg Code (1947), Universal Declaration of Human Rights (December 10, 1948), Helsinki Declaration of the World Medical Association on the Ethical Principles of Medical Research with Human Participation (1964–2013), Convention on the Protection of Human Rights human rights and human dignity in connection with the use of biological and medical preparations: the Convention on Human Rights and Biomedicine of the Council of Europe (April 4, 1997 Oviedo), Montreal Declaration on the Responsible Development of Artificial Intelligence (2017), Ethics Guidelines for Reliable AI of the Council of Europe's High-Level Ad Hoc Expert Group (2018), Global Initiative for Ethics of Autonomous and Intelligent Systems (IEEE, 2016), Recommended Practices for Quality Management of Datasets for Medical Artificial Intelligence (IEEE), Model the Convention on Robotics and Artificial Intelligence (2018), Concept of Development of Regulation of relations in the field of artificial intelligence and robotic technologies until 2024 (2020), Code of Ethics of Artificial Intelligence (2021), taking into account the expert experience of the International Committee on Bioethics (ICD) and Intergovernmental Committee on Bioethics (IPCB), World Commission on Ethics of Scientific Research knowledge and Technology (COMEST), as well as a number of other international documents.

The axiological basis of the dialogue on the prospects of neurotechnology can be the established domestic bioethical discussion, summarizing the ideological value priorities of the scientific community in accordance with the legislation and taking into account historical experience of domestic healthcare, general goal-setting of scientific and technological development, criteria for progress in an actual and promising (prognostic) meaning. Reliance on bioethical thinking makes it possible to consciously apply bioethical axiology to scientific research, practical healthcare and social practice on the basis of a successive and continuous semantic correlation of professional knowledge and its axiological periphery, "knowledge about knowledge".

The draft of domestic neuroethical recommendations should establish obligations related to the ethical aspects of creation, implementation and use of neurotechnologies, which are currently not regulated by the legislation of the Russian Federation and acts of technical regulation. The basis of the recommendations should include general principles, which, if necessary, can be extrapolated in certain areas of neurotechnology application, taking into account the specifics of the goals of application and practical tasks to be solved, both medical and non-medical, as well as predicted risks.

One of the primary tasks of developing domestic recommendations should be specification of the terminological apparatus in accordance with current regulatory legal acts, documents of strategic planning and regulatory and technical regulation in the field of neurotechnology, including the provisions of the Strategy for Scientific and Technological Development of the Russian Federation, Strategy for the Development of the Information Society of the Russian Federation, National Development Goals of the Russian Federation for the period up to 2030 and for the future until 2036, and Roadmap for the development of "end-to-end" Neurotechnology and Artificial Intelligence digital technology [4].

Taking into account the provisions of the above acts, the following definitions can be given to the basic concepts of the recommendations:

- neurotechnologies include technologies that use or help to understand the work of the brain, thought processes, higher nervous activity, including technologies to enhance and improve brain function and mental activity;
- neuroimaging includes structural and/or functional visualization of the brain by computed tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG);
- neuroethics is an interdisciplinary field of research, the subject of which is the impact of neurotechnologies on all areas of human activity. Invasive brain intervention is a direct effect on brain structures, including methods of invasive neurostimulation and neuromodulation through direct stimulation of the nervous system by surgical implantation methods, comprising the therapeutic use of deep brain structure stimulators (DBS), as well as invasive MRI methods;
- noninvasive intervention in the brain includes effects on brain structures without implantation of stimulants, including methods of transcranial magnetic stimulation and transcranial electrical stimulation;
- registration of biometric brain indicators or identification based on unique personal information obtained on the basis of biometric screening of brain indicators.

The recommendations should reflect, at the level of defining clear goals, demarcation of medical neurotechnologies and neurotechnologies for improving the functions of the brain and nervous system of healthy people, including their widespread consumer use in education, sports and for entertainment purposes, taking into account specifics of the computer game industry, designed for the widest audience, including vulnerable groups of persons.

The targeted separation of neurotechnologies for medical and non-medical purposes can be based on the principle of

established necessity. In medical practice, satisfaction with an established objective need is the criterion for the need to use neurotechnologies. The risks assumed in this case should be assessed in comparison with the predicted positive results. The use of neurotechnologies for non-medical purposes as a way to create benefits should be considered from the perspective of ensuring their safety for human physical and mental health.

The basis for assessing the necessity factor may be the procedural bioethical model for implementation of the content of responsibility proposed by Russian researchers [5–7].

The criterion for the expediency of introducing neurotechnologies is their use exclusively in the interests of the consumer or patient and in full accordance with the stated purpose, purpose, objectives and methods of use. In this direction, the recommendations should prevent a discrepancy between the stated goals of the technological direction of neurotechnological developments and the real needs of users. This means that, recognizing the consumer's right to free access to neurotechnologies, it is necessary to ensure it on the basis of effective cooperation of all subjects involved in implementation and application of a neurotechnological project such as researchers, developers of technology (neurointerfaces), software owners, and the recipient of services. At the same time, it is necessary to ensure compliance with the conditions of informed choice, without any discrimination, coercion or violence, based on forecasts, needs and opportunities focused on the interests of the individual and society. In this aspect, the principles of fair competition and effective cooperation among researchers, developers and businesses interested in publishing accessible, reliable and comparable information are of great importance.

Observance of these principles will be consistent with ensuring the safety of people and society in the dissemination of neurotechnological innovations not only by state control bodies, but also by local ethical committees at both the state and interstate levels.

The recommendations should reflect the challenges of the potential capabilities of neurotechnologies to control, monitor and influence brain processes. It is necessary to prevent the use of neurointerfaces to control behavior and personality traits. Neurotechnologies in medicine expand the understanding of how the brain generates certain forms of behavior, but the results should be used exclusively for the purpose of studying the work of the brain, thought processes, and higher nervous activity.

Ensuring safety for human health and well-being is especially relevant for vulnerable individuals and social groups. For people with special rights (disabilities), rehabilitation neurotechnologies and equipment ("smart" things, "connected technologies") are the solution to the problems of socialization. At the same time, there are risks of using individual traits of patients in predicting rehabilitation prospects ("machine ageism").

Patients with polymorbid pathologies, manifestations of combined pathologies seen as changes in the clinical picture and course of the disease are included into a separate category of risk groups. Regardless of the leading pathology, the factors of the course of the disease are the complication of diagnosis, choice of tactics, goals, objectives and means of treatment against the background of a general decrease in quality of life.

The use of neurotechnologies in relation to patients with mental pathologies should take into account the factors of their identity, development of cognitive, communicative and creative abilities, severity of motor coordination problems, behavioral and emotional disorders in order to prevent destructive interference with the mental identity and mental integrity of a person for the patient.

Development and implementation of domestic recommendations, in addition to the main tasks of establishing rules for neurotechnological development, as well as formation of a market for neuroservices, should popularize and build consumer confidence in the positive effects of using neurotechnologies, primarily for medical purposes. In order to form correct user expectations, it is necessary to ensure that user requests correspond to the real capabilities of neurotechnologies. In this context, responsibility of developers and manufacturers includes reliable, complete and user-accessible information about the goals, principles and risks of using neurotechnology, including the possibility of unpredictable, unforeseen consequences associated, in particular, with neural services, with the interaction of neurotechnologies and artificial intelligence (AI). A potential consumer should be aware of the influence of neuropractices on mental and intellectual processes related to the emotional sphere, choice and will of a person. Development of the neuromarket will inevitably be accompanied by advertising offers and consumer product presentations. When making recommendations in this segment, it will be necessary to focus on the compliance of information for the purpose of selling a product with data from randomized scientific studies confirming the principles of operation and effectiveness of the advertised devices.

A consolidated attitude to the problem of the professional medical community, developers, suppliers and recipients of services should be a guarantee of reliable management, ethical control and deontological support for the introduction of neurotechnologies into medical practice and non-medical consumption.

The widespread use of neuroethical recommendations will also reduce the risks of "biohacking" associated with a gradual reduction in price and increased accessibility of technologies for the mass consumer, which carries both immediate risks for the consumer and reputational risks for the professional community.

In the socioeconomic aspect, development of domestic recommendations for the ethical regulation of the introduction of neurotechnologies reflects the urgency of the task stimulating domestic production by establishing and ensuring transparent and stable regulatory rules of behavior and interaction of subjects of technological development, improving scientific directions and putting results into practice by optimizing the scientific and ethical paradigm that reflects real progress. Ethical regulation optimizes the conditions for socioeconomic growth in accordance with the national development goals of the Russian Federation until 2030 and national interests, including the ones used to create its own scientific, personnel and technological base of critical and end-to-end technologies that ensure production of high-tech products.

It is necessary to note the importance of the dialogue on neuroethics in solving the problems of attracting young specialists to the discussion of science development. On November 28–30, 2023, the III Congress of Young Scientists was held at the Sirius federal site, within which a session "Scientific search and ethical and legal issues of research activity" was organized in the format of a meeting of the working group on regulatory legal regulation and bioethics in the field of genetic technologies [8]. The competition of professional achievements of students, residents and postgraduates entitled Start to a Successful Future. Bioethics and Challenges of Technological Development, participated by novice scientists studying under specialist, bachelor, master, residency, postgraduate programs, held by the Yaroslavl regional branch of the All-Russian Public Organization "Russian Professorial Assembly" and Federal State Budgetary Educational Institution of the Ministry of Health of the Russian Federation, is aimed

at forming interest in issues of science ethics. [9]. Educational projects are of great importance, primarily the ones aimed at young scientists, in particular the “School of Ethics of Scientific Research”, as well as comprehensive scientific research at the junction of ethical and legal foundations of a specialist’s activity in various fields of practical healthcare [10–12].

Thus, discussion, development and implementation of domestic recommendations in the field of neurotechnology into medical and social practice are a requirement of the time, an objective need to regulate both the processes of technological progress and the new field of human rights, neurorights.

The specific feature of neurotechnology application is their accelerated development with the rapid transition of projects into the field of wide non-medical application, with the formation of trends in the use of neurointerfaces in various fields of social practice, as well as the convergence of neurotechnologies, biometric and digital technologies, and artificial intelligence. It is necessary to ensure a comprehensive multi-level examination of projects before their introduction into practice and a system for monitoring the biological, socio-humanitarian and economic consequences of the use of medical and non-medical neurotechnologies.

The general provisions of the recommendations on the use of neurotechnologies should relate to all areas of current and potential interest of developers, researchers, and representatives of science in the use of neuroprocedures, including widespread consumer use in education, sports, and leisure. The general principles of ethics and human rights herein should be based on the basic values developed by the scientific community in accordance with social progress experience and recognition that the integrative category of health is determined not only by the level of scientific research and technological achievements, but also by the quality of psychosocial and socio-cultural factors. All aspects of a person’s identity should be taken into account, including biological, psychological, social, cultural and spiritual indicators. It should be borne in mind that decisions based on objective ethical issues of the development of medicine and the “life sciences” in general, as well as related technologies, can have an impact on individuals, families, groups or communities, as well as on humanity as a whole. The widest possible discussion on the ethics of neurotechnology should provide adapted mechanisms for the reasonable regulation of technological development for the benefit of the individual and society.

References

1. YUNESKO. Etika neyrotekhnologiy. Available from URL: https://www.unesco.org/ru/ethics-neurotech#:~:text= (accessed: 14.10.2024). Russian.
2. Plenarnoye zasedaniye konferentsii «Bioetika i global’nyye sotsial’nyye transformatsii». Available from URL: https://ysmu.ru/press-center/news/2024/sostoyalos-plenarnoe-zasedanie-konferentsii-bioetika-i-globalnye-sotsialnye-transformatsii-/ (accessed: 14.10.2024). Russian.
3. Rasporyazheniye Pravitel’stva RF ot 20.05.2023 № 1315-r Ob utverzhdenii Kontseptsii tekhnologicheskogo razvitiya na period do 2030 goda. Ofitsial’nyy internet-portal pravovoy informatsii. Available from URL: http://pravo.gov.ru, 25.05.2023 (accessed: 14.10.2024). Russian.
4. Ukaz Prezidenta RF ot 28.02.2024 № 145 O Strategii nauchno-tekhnologicheskogo razvitiya Rossiyskoy Federatsii. Ofitsial’nyy internet-portal pravovoy informatsii. Available from URL: http://pravo.gov.ru, 28.02.2024 (accessed: 02.11.2024). Russian.
5. Andreyeva IA, Filimonov OV. Etika nauchnogo issledovaniya: kurs. M.: Akademiya upravleniya MVD Rossii. 2018; s. 47–48. Russian.
6. Tomashov VV, Firsov DYe. Protsessual’naya bioeticheskaya model’ realizatsii professional’noy otvetstvennosti. Aktual’nyye problemy sovershenstvovaniya vysshego obrazovaniya: Materialy XIII nauchno-metodicheskoy konferentsii s mezhdunarodnym uchastiyem, Yaroslavl’, 22–23 marta 2018 goda. Yaroslavskiy gosudarstvennyy universitet im. P. G. Demidova. Yaroslavl’: Yaroslavskiy gosudarstvennyy universitet im. P. G. Demidova, 2018; s. 392–394. EDN YWDRES. Russian.
7. Firsov DYe. “Bioethics: Bridge to the Future” (1971 g.) V. R. Pottera kak intellektual’nyy manifest: k 50-letiyu vykhoda knigi. Meditsinskaya etika. 2021; 2: 25–27. DOI: 10.24075/medet.2021.015. Russian.
8. III Kongress molodykh uchenykh. Available from URL: https://sochisirius.ru/obuchenie/graduates-activity/smena1666/7760 (accessed: 14.10.2024). Russian.
9. Konkurs professional’nykh dostizheniy «Start v uspeshnoye budushcheye 2024. bioetika i tekhnologicheskoye razvitiye». Available from URL: https://ysmu.ru/press-center/news/2024/15-marta-nachnetsya-registratsiya-na-konkurs-professionalnykh-dostizheniy-start-v-uspeshnoe-budushch/ (accessed: 14.10.2024). Russian.
10. Shkola etiki nauchnykh issledovaniy. Available from URL: https://ethic.nriph.ru/ (accessed: 14.10.2024). Russian.
11. Firsov DYe. Shkola etiki nauchnykh issledovaniy. Aksiologiya bioetiki i vyzovy tekhnologicheskogo razvitiya. Meditsinskaya etika. 2024; 1: 4–7. DOI: 10.24075/medet.2023.035. Russian.
12. Pleshchev IYe, Shkrebko AN, Ivashkovskaya AV. Meditsinskaya r eabilitatsiya: issledovaniye problem eticheskogo i pravovogo kharaktera., et al. Meditsinskaya etika. 2024: 2: 34–39. DOI: 10.24075/medet.2024.011. EDN AHILFB. Russian.

Литература

1. ЮНЕСКО. Этика нейротехнологий. Режим доступа: [Электронный ресурс] URL: https://www.unesco.org/ru/ethics-neurotech#:~:text= (дата обращения 14.10.2024).
2. Пленарное заседание конференции «Биоэтика и глобальные социальные трансформации». Режим доступа: [Электронный ресурс] URL: https://ysmu.ru/press-center/news/2024/sostoyalos-plenarnoe-zasedanie-konferentsii-bioetika-i-globalnye-sotsialnye-transformatsii-/ (дата обращения 14.10.2024).
3. Распоряжение Правительства РФ от 20.05.2023 № 1315-р «Об утверждении Концепции технологического развития на период до 2030 года. Официальный интернет-портал правовой информации Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru, 25.05.2023 (дата обращения 14.10.2024).
4. Указ Президента РФ от 28.02.2024 № 145 О Стратегии научно-технологического развития Российской Федерации. Официальный интернет-портал правовой информации Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru, 28.02.2024 (дата обращения 02.11.2024).
5. Андреева И. А., Филимонов О. В. Этика научного исследования: курс лекций. М.: Академия управления МВД России. 2018; 47–48 с.
6. Томашов В. В., Фирсов Д. Е. Процессуальная биоэтическая модель реализации профессиональной ответственности. Актуальные проблемы совершенствования высшего образования. Материалы XIII научно-методической конференции с международным участием, Ярославль, 22–23 марта 2018 года. Ярославский государственный

университет им. П. Г. Демидова. Ярославль: Ярославский государственный университет им. П. Г. Демидова. 2018; 392–394 с. EDN YWDRES.
7. Фирсов, Д. Е. “Bioethics: Bridge to the Future” (1971 г.) В. Р. Поттера как интеллектуальный манифест: к 50-летию выхода книги. Медицинская этика. 2021;2; 25–27. DOI: 10.24075/medet.2021.015
8. III Конгресс молодых ученых. Режим доступа: [Электронный ресурс] URL: https://sochisirius.ru/obuchenie/graduates-activity/smena1666/7760 (дата обращения 14.10.2024).
9. Конкурс профессиональных достижений «Старт в успешное будущее 2024. биоэтика и технологическое развитие». Режим доступа: [Электронный ресурс] URL: https://ysmu.ru/press-center/news/2024/15-marta-nachnetsya-registratsiya-na-konkurs-professionalnykh-dostizheniy-start-v-uspeshnoe-budushch/ (дата обращения 14.10.2024).
10. Школа этики научных исследований. Режим доступа: [Электронный ресурс] URL: https://ethic.nriph.ru/ (дата обращения 14.10.2024).
11. Фирсов, Д. Е. Школа этики научных исследований. Аксиология биоэтики и вызовы технологического развития. Медицинская этика. 2024; 1:4–7. DOI: 10.24075/medet.2023.035
12. И. Е. Плещев, А. Н. Шкребко, А. В. Ивашковская [и др.] Медицинская реабилитация: исследование проблем этического и правового характера. Медицинская этика. 2024; 12(2): 34–39. DOI: 10.24075/medet.2024.011. EDN AHILFB.

NEUROETHICS IN MEDICINE. PRESSING ISSUES

Filatova YS ✉, Zolotova IA

Yaroslavl State Medical University, Yaroslavl, Russia

The article focuses on some aspects of neuroethics in medicine. Due to the continuous growth of research, new advances in neuroscience, and use of neurotechnology, ethical issues related to personality, autonomy and confidentiality may arise. The article addresses neuroethical issues of management of patients with various neurological diseases and special psychological conditions. The issue of using neuroethical aspects to solve issues in the field of diagnosis and treatment of disorders of consciousness is also discussed. Another important area of research that uses neuroethics is treatment of drug addiction, namely the ethical aspects of using neurotechnology. The authors conclude that the prospects for using neuroethics in medicine are very diverse. It underlines the importance of its studying at all stages of medical education, including secondary, higher and postgraduate ones.

Keywords: neuroethics, patient management, disorders of consciousness, drug addiction treatment, transcarnial stimulation

Author contribution: Filatova YS and Zolotova IA made an equal contribution to preparation of the article.

✉ **Correspondence should be addressed:** Yulia Sergeevna Filatova
Revolutsionnaya St., 5, Yaroslavl, 150000, Russia; y.s.filatova@mail.ru

Received: 11.11.2024 **Accepted:** 03.12.2024 **Published online:** 31.12.2024

DOI: 10.24075/medet.2024.029

НЕЙРОЭТИКА В МЕДИЦИНЕ. АКТУАЛЬНЫЕ ПРОБЛЕМЫ

Ю. С. Филатова ✉, И. А. Золотова

Ярославский государственный медицинский университет, Ярославль, Россия

В статье обсуждаются некоторые аспекты применения нейроэтики в медицине. Непрерывный рост исследований, активное применение новых достижений нейробиологии, а также использование нейротехнологий могут вызывать этические проблемы, связанные с личностью, автономией и конфиденциальностью. В статье затрагиваются нейроэтические вопросы о ведении пациентов с разнообразными неврологическими заболеваниями и особенными психологическими состояниями. Также обсуждается применение нейроэтических аспектов в решении вопросов, возникающих в области диагностики и лечения расстройств сознания. Другое важное направление исследований, в рамках которых используется нейроэтика, — лечение наркотической зависимости, а именно этические аспекты применения нейротехнологий. В заключение авторы приходят к выводам, что перспективы использования нейроэтики в медицине очень разнообразны, что подчеркивает важность ее изучения на всех этапах медицинского образования, включая среднее, высшее и постдипломное.

Ключевые слова: нейроэтика, ведение пациентов, расстройства сознания, лечение наркотической зависимости, транскарниальная стимуляция

Вклад авторов: Ю. С. Филатова и И. А. Золотова внесли равный вклад в подготовку статьи.

✉ **Для корреспонденции:** Юлия Сергеевна Филатова
ул. Революцинная, д. 5, г. Ярославль, 150000, Россия; y.s.filatova@mail.ru

Статья поступила: 11.11.2024 **Статья принята к печати:** 03.12.2024 **Опубликована онлайн:** 31.12.2024

DOI: 10.24075/medet.2024.029

Neuroscience and neurotechnology are developing rapidly. As a result, brain functions are being discovered in a new way. Neuroscience is an interdisciplinary field of science that studies the nervous system, its structure, functions, and development. It covers a wide range of disciplines, including neuroscience, psychology, molecular biology, medicine, and others. This area can be attributed to a scientific approach that seeks a systematic understanding of the structure and function of the nervous system in humans and animals [1]. Neurotechnologies are a set of methods, systems, and tools that provide direct access to the human brain. They allow to record and analyze brain activity through visualization of the nervous system of the brain, neuromodulation technology, “brain-machine” interface, and also collect, store and process neural or related information.

Such innovative advances in neuroscience and neurotechnology are expected to result in interventions that could not be used previously to treat a number of human diseases and promote health. Using the achievements of neuroscience will allow us to re-examine the relationship between human thoughts, emotions and behavior. Research and development in the field of neuroscience and neurotechnology bring significant benefits to society and individuals, and large-scale investments are being made at the national level for this purpose [2].

Over the past decade, there has been a sharply increased interest in ethical issues arising from the development of neuroscience. A new discipline called “neuroethics” appeared only in 2002. It was conceived as a new field of interdisciplinary discourse on moral dilemmas related to recent advances in neuroscience in a broad sense. Nearly twenty years after its emergence, neuroethics has a wealth of knowledge and an institutional base for further development. However, being a very young discipline, neuroethics is still in its infancy [3].

The discussion of neuroethics requires international cooperation. The most notable global neuroethics event is the Brain Neuroethics Consortium of the Global Neuroethics Working Group of the International Brain Initiative. Discussions in the working group include strengthening integration and collaboration between neuroscience and neuroethics, which is constantly being investigated by experts [4].

Due to the continuous research and use of advances in neuroscience, new challenges may arise related to personality,

autonomy, and protection of confidential information. Existing ethical principles are applicable in solving these problems, but in some situations new ethical, legal and social standards may be required. The above-mentioned problems should be solved in interdisciplinary cooperation with participation of neuroscientists, practicing physicians, ethicists, philosophers, sociologists and lawyers [5].

The use of neurotechnology can lead to significant changes in various fields, from healthcare to human rights. These technologies can help people with paralysis move, improve mental health measures, and boost economic growth. But at the same time, they can also create new threats to security and privacy, challenge human autonomy, and exacerbate inequality. While novel technologies that promise widespread social changes are not new, the connection of neurotechnology to the brain poses unique challenges, whereas scientists and policy makers have identified significant ethical and political issues related to neurotechnology [6,7]

AREAS OF APPLICATION OF NEUROETHICS IN MEDICINE

Neuroethics issues may relate to clinical practice, namely ethical aspects such as a doctor–patient relationship, differences between clinical practice and research, important decision-making issues in treatment of certain diseases, and much more.

Doctors are responsible for following the traditional principles of clinical practice and medical ethics in their field. Clinically oriented documents often provide doctors with a wide degree of opinion independence, but on the other hand limit their actions to algorithms and standards. Thus, there is a number of diseases and conditions in neurology that require intervention of neuroethics.

The case of Phineas Gage, which is probably the first published one, was described by Harlow JM [8]. As a result of an accident at work, the patient suffered a severe traumatic brain injury affecting the medial and orbital areas of the frontal lobe, and became impulsive, violent and rude. Damasio A [8] suggested that damage to the ventromedial prefrontal cortex leads to a loss of ethical and emotional assessments regarding moral consequences of actions, resulting in blurred boundaries between good and evil. Moreover, patients who had damaged the ventromedial prefrontal nucleus were unable to correct or control aggressive behavior and/or unusual reactions, facing negative consequences of their actions. It was morally harmful for the patients and other people [9]. According to Damasio A, the patients are able to speculate, but have impaired emotions that serve as somatic markers and can be used by the brain to quickly and unconsciously filter out options with important positive or negative emotional consequences.

Thus, the Phineas Gage case highlights the importance of the frontal lobe for moral behavior, whereas subsequent studies involving healthy people using neurophysiological techniques such as functional magnetic resonance imaging and non-invasive brain stimulation techniques have revealed a broader and more complex neural network. Among these areas, it is necessary to mention the callosal gyrus of the cerebral cortex, a neural structure that is considered important for resolving the conflict between the emotional and rational components of moral reasoning [10]. Insula, a neural structure, which is essential for development of interoceptive states, appears to be involved in the development of an affective component of a sense of lawlessness (an emotional component associated with perception and experience of the absence of legality, that includes emotions such as fear, anger, anxiety, helplessness and frustration arising in response to a sense of injustice, lack of law and order, or threat to personal rights and freedoms) [11]. And the area of the brain that plays an important role in development of the emotional component of a sense of lawlessness is represented by basal ganglia, as well as the subthalamic nucleus, which is involved in assessing conflict situations related to human behavior, which is determined by a system of norms and values [12].

Returning to the relevance of clinical models in the field of neuroethics, motor disorders such as Parkinson's syndrome, Huntington chorea, and Tourette's syndrome should be mentioned. These diseases are characterized by a low sensitivity to ethical violations when patients do not respond to moral or ethical problems, are not aware of their seriousness, or do not take due care of the consequences of their actions. This is evident in the manifestation of symptoms such as impulsivity in the form of sudden mood swings, outbursts of aggression with shouting, threating others [13–15]. In addition, an important role is played by the study of mental syndromes such as obsessive-compulsive disorder [16] and depression [17], which in turn are characterized by a high sensitivity to ethical violations, when patients are concerned about the consequences of their actions. Although their main manifestations and mechanisms are different, it is interesting to note that all the above-mentioned syndromes are accompanied by similar anatomical and functional changes in neural structures (insular lobe, callosal gyrus, basal ganglia). Thus, the insular part is responsible for integration of sensory information and emotional phenomena, which makes it possible to assess moral dilemmas from the point of view of personal experience and social norms; the cingulate gyrus is associated with processing of emotions and decision-making, which makes it important to assess moral consequences; the basal ganglia are involved in changing habits and automating behavior, which can also affect moral standards, especially in periodic interaction and decision-making. These neural structures interact with each other, creating a complex network that allows people to make ethically informed decisions and respond to moral challenges in a social environment [18].

Other important neuroethical issues relate to recent advances in diagnosis and treatment of disorders of consciousness. This area is rapidly expanding and becoming more relevant. However, it is still insufficiently studied. Modern debates on the boundaries of consciousness are interdisciplinary in nature and affect achievements of such sciences as neurology, ethics, and philosophy [19].

Approaches to determining the level of consciousness have been developed in clinical neurology. Neurologists, especially as consultants, regularly assess patients' level of consciousness, predict the results of loss or decrease in consciousness, identify opportunities for nervous system recovery, and advise families on what to expect and how best to prepare for possible outcomes. In turn, these assessments and recommendations form the dominant axis around which important decisions are made regarding the intensity and duration of care that should be provided to the patient. Assessment of the consciousness level and ability to recover are important in making decisions about limiting or continuing life-sustaining treatment, which strongly indicates that consciousness is a central element of the concept of personality [20].

Prolonged use of limited intensive or supportive care resources for patients who are considered incapable of additional neurological recovery may also raise difficult ethical questions among medical professionals [21]. From this point of view, the ethical importance of a clear understanding of how

to approach decision-making about supportive care becomes obvious.

Treatment of drug addiction is another important clinical area in which achievements of neuroethics can be used. Though some medical treatment methods exist, there is an urgent need in more effective new treatment methods. A promising approach involves electrical neurostimulation as a means of combating addiction or so-called electrotherapeutic methods as an alternative or complement to behavioral and pharmacological interventions [22].

Recently, electrical neurostimulation has been studied as a method of treating addiction. The FDA has approved two non-invasive electrical nerve stimulators for additional treatment of acute opioid withdrawal symptoms. These devices, placed behind the ear, stimulate certain cranial nerves. This nerve stimulation is reported to produce a rapid effect in terms of relieving withdrawal symptoms resulting from abrupt cessation of opioid use. Current experimental evidence indicates that this type of non-invasive neurostimulation can perfectly complement opioid detoxification medications with lower side effects and increased treatment commitment. However, the potential of this method and its possible long-term side effects have not yet been studied [23].

But what areas of the brain, if they are affected, will provide the best result in the treatment of addiction? In this regard, some clues can be found in a number of case reports in humans, which describe complete, permanent, and virtually painless elimination of psychoactive substance use disorders. This elimination was caused by direct effects on certain areas of the brain and neural connections that are known to be involved in the process of addiction formation, such as the insula, nucleus accumbens, dorsolateral prefrontal cortex, and amygdala [24]. For example, smokers spontaneously lost all interest in cigarettes after a stroke that damaged the bilateral anterior insular lobe. More recent studies show that damage to any of the vast areas of the brain that have a functional connection with the anterior insular lobe can also lead to loss of dependence [25].

The possibility of non-invasive stimulation of these brain areas would be of great help, but these types of effects are mainly limited to rather superficial than deep areas of the brain. Existing methods of non-invasive neurostimulation include transcranial direct current stimulation, transcranial alternating current stimulation, transcranial magnetic stimulation, and transcranial focused ultrasound stimulation. These methods have been widely used for decades and involve applying voltage through 2 or more electrodes placed on the scalp, so that the current is usually up to 2 mA. These methods, and especially transcranial direct current stimulation, were used specifically to treat addiction [26]. There are still many unresolved issues regarding potential treatment of addictions using transcranial stimulation. The first question is which area to target and which pulse frequency to use. There are also ethical issues such as interventions that reduce drug cravings, possible side effects that alter the will and ability to make decisions [27]. Side effects can also be worrisome, as invasive deep brain stimulation can lead to mania, disinhibition, and psychosis.

CONCLUSION

Thus, the prospects for using neuroethics in medicine are very diverse. Most of them relate to neurotechnologies, which are important to use for the benefit of the patient. The examples described in the article are only a part of the possible perspectives for condemning ethical aspects in achieving neurobiology, and in most cases, they relate to issues of diagnosis and treatment of a number of neurological diseases and behavioral disorders. This highlights the importance of studying neuroethics at all levels of medical education, including secondary, higher, and postgraduate education.

References

1. Shibkova DZ, Bayguzhin PA. Neyronauka: mezhdistsiplinarnaya integratsiya ili ekspansiya? Psikhologiya. Psikhofiziologiya. 2020;3. Available from URL: https://cyberleninka.ru/article/n/neyronauka-mezhdistsiplinarnaya-integratsiya-ili-ekspansiya (accessed: 11.01.2025).
2. Yoo SH, Choi K, Nam S, Yoon EK, Sohn JW, Oh BM, Shim J, Choi MY. Development of Korea Neuroethics Guidelines. J Korean Med Sci. 2023 Jun 26; 38(25): e193. DOI: 10.3346/jkms.2023.38.e193.
3. Niebrój LT. Neuroetyka: nowa jakość etyki medycznej? (Neuroethics: new quality of medical ethics?). Ann Acad Med Stetin. 2013; 59(1): 130–6. Polish. PMID: 24734347.
4. Zimmer AA. Neuroethics Intergration Landscape Report. Global Neuroethics Summit 2020–2021.
5. O'Shaughnessy MR, Johnson WG, Tournas LN, Rozell CJ, Rommelfanger KS. Neuroethics guidance documents: principles, analysis, and implementation strategies. J Law Biosci. 2023 Oct 26; 10(2): lsad 025. DOI: 10.1093/jlb/lsad025. PMID: 37901886; PMCID: PMC10602660.
6. Larriviere D, Williams MA, Rizzo M, Bonnie RJ & AAN. Ethics, Law and Humanities Committee, Responding to Requests from Adult Patients for Neuroenhancements: Guidance of the Ethics, Law and Humanities Committee. 73 Neurology. 2009; 1406–1412.
7. Nuttin B, Wu H, Mayberg H, Hariz M, Gabriëls L, Galert T, et. al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry. 2014 Sep; 85(9): 1003–8. DOI: 10.1136/jnnp-2013-306580. Epub 2014 Jan 20. Harlow JM. Passage of an Iron Rod through the Head. Northwest Med Surg J. 1849 Feb-Mar; 1(6): 513–518
8. Damasio A. L'errore di Cartesio. Emozione, ragione, cervello umano. Milano: Adelphi; 1994.
9. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994; 50(1–3): 7–15. DOI: 10.1016/0010-0277(94)90018-3.
10. Fumagalli M, Priori A. Functional and clinical neuroanatomy of morality. Brain. 2012; 135(7): 2006–2021. DOI: 10.1093/brain/awr334.
11. Vicario CM. Emotional Appraisal of Moral Dilemmas: What Neuroimaging Can Tell about the Disgust-Morality Link. J Neurosci. 2016;36(2):263–264. DOI: 10.1523/JNEUROSCI.3483-15.2016.
12. Fumagalli M, Giannicola G, Rosa M, et al. Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions. Soc Neurosci. 2011; 6(3): 243–256. DOI: 10.1080/17470919.2010.515148.
13. Vicario CM, Rafal RD, Borgomaneri S, et al. Pictures of disgusting foods and disgusted facial expressions suppress the tongue motor cortex. Soc Cogn Affect Neurosci. 2017; 12(2): 352–362. DOI: 10.1093/scan/nsw129.
14. Vicario CM, Martino D. Social communication in Tourette syndrome: a glimpse at the contribution of the insula and the prefrontal cortex. Brain. 2018; 141(8): e58. DOI: 10.1093/brain/awy140.
15. Vicario CM, Gulisano M, Maugeri N, et al. Moral Decision-Making in Adolescents with Tourette Syndrome. Mov Disord. 2021; 36(9): 2205–2206. DOI: 10.1002/mds.28705.
16. Vicario CM. Morality and disgust: insights from obsessive compulsive disorder. Front Psychiatry. 2013; 3: 113. DOI: 10.3389/fpsyt.2012.00113.
17. Pulcu E, Zahn R, Elliott R. The role of self-blaming moral emotions in major depression and their impact on social-economical decision making. Front Psychol. 2013; 4: 310. DOI: 10.3389/fpsyg.2013.00310.

18. Vicario CM, Lucifora C. Neuroethics: what the study of brain disorders can tell about moral behavior. AIMS Neurosci. 2021 Oct 25; 8(4): 543–547. DOI: 10.3934/Neuroscience.2021029.
19. Young MJ, Bodien YG, Giacino JT, Fins JJ, Truog RD, Hochberg LR, Edlow BL. The neuroethics of disorders of consciousness: a brief history of evolving ideas. Brain. 2021 Dec 16; 144(11): 3291–3310. DOI: 10.1093/brain/awab290. PMID: 34347037; PMCID: PMC8883802.
20. Kriegel U. The value of consciousness. Analysis. 2019; 79(3): 503–520.
21. Hildesheim H, Rogge A, Borzikowsky C, Witt VD, Schäffer E, Berg D. Moral distress among residents in neurology: A pilot study. Neurol Res Pract. 2021; 3(1): 6–9.
22. Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M. Drug discovery: a jump-start for electroceuticals. Nature. 2013; 496: 159–161. DOI: 10.1038/496159a.
23. Qureshi IS, Datta-Chaudhuri T, Tracey KJ, Pavlov VA, Chen ACH. Auricular neural stimulation as a new non-invasive treatment for opioid detoxification. Bioelectron Med. 2020; 6:7. DOI: 10.1186/s42234-020-00044-6.
24. Naqvi NH, Gaznick N, Tranel D, Bechara A. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Ann N Y Acad Sci. 2014; 1316: 53–70. DOI: 10.1111/nyas.12415.
25. Joutsa J, Moussawi K, Siddiqi SH, et al. Brain lesions disrupting addiction map to a common human brain circuit. Nat Med. 2022; 28: 1249–1255. DOI: 10.1038/s41591-022-01834-y.
26. Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. J Ect. 2018; 34: 182–192. DOI: 10.1097/YCT.0000000000000541.
27. Zuk P, Lázaro-Muñoz G. DBS and Autonomy: clarifying the role of theoretical neuroethics. Neuroethics. 2021; 14: 83–93. DOI: 10.1007/s12152-019-09417-4.

Литература

1. Шибкова Д. З., Байгужин П. А. Нейронаука: междисциплинарная интеграция или экспансия? Психология. Психофизиология. 2020;3. Режим доступа: [Электронный ресурс] URL: https://cyberleninka.ru/article/n/neyronauka-mezhdistsiplinarnaya-integratsiya-ili-ekspansiya (дата обращения: 11.01.2025).
2. Yoo SH, Choi K, Nam S, Yoon EK, Sohn JW, Oh BM, Shim J, Choi MY. Development of Korea Neuroethics Guidelines. J Korean Med Sci. 2023 Jun 26; 38(25): e193. DOI: 10.3346/jkms.2023.38.e193.
3. Niebrój LT. Neuroetyka: nowa jakość etyki medycznej? (Neuroethics: new quality of medical ethics?). Ann Acad Med Stetin. 2013; 59(1): 130–6. Polish. PMID: 24734347.
4. Zimmer AA. Neuroethics Intergration Landscape Report. Global Neuroethics Summit 2020–2021.
5. O'Shaughnessy MR, Johnson WG, Tournas LN, Rozell CJ, Rommelfanger KS. Neuroethics guidance documents: principles, analysis, and implementation strategies. J Law Biosci. 2023 Oct 26; 10(2): lsad 025. DOI: 10.1093/jlb/lsad025. PMID: 37901886; PMCID: PMC10602660.
6. Larriviere D, Williams MA, Rizzo M, Bonnie RJ & AAN. Ethics, Law and Humanities Committee, Responding to Requests from Adult Patients for Neuroenhancements: Guidance of the Ethics, Law and Humanities Committee. 73 Neurology. 2009; 1406–1412.
7. Nuttin B, Wu H, Mayberg H, Hariz M, Gabriëls L, Galert T, et. al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry. 2014 Sep; 85(9): 1003–8. DOI: 10.1136/jnnp-2013-306580. Epub 2014 Jan 20. Harlow JM. Passage of an Iron Rod through the Head. Northwest Med Surg J. 1849 Feb-Mar; 1(6): 513–518.
8. Damasio A. L'errore di Cartesio. Emozione, ragione, cervello umano. Milano: Adelphi; 1994.
9. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994; 50(1–3):7–15. DOI: 10.1016/0010-0277(94)90018-3.
10. Fumagalli M, Priori A. Functional and clinical neuroanatomy of morality. Brain. 2012; 135(7): 2006–2021. DOI: 10.1093/brain/awr334.
11. Vicario CM. Emotional Appraisal of Moral Dilemmas: What Neuroimaging Can Tell about the Disgust-Morality Link. J Neurosci. 2016; 36(2): 263–264. DOI: 10.1523/JNEUROSCI.3483-15.2016.
12. Fumagalli M, Giannicola G, Rosa M, et al. Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions. Soc Neurosci. 2011; 6(3): 243–256. DOI: 10.1080/17470919.2010.515148.
13. Vicario CM, Rafal RD, Borgomaneri S, et al. Pictures of disgusting foods and disgusted facial expressions suppress the tongue motor cortex. Soc Cogn Affect Neurosci. 2017; 12(2): 352–362. DOI: 10.1093/scan/nsw129.
14. Vicario CM, Martino D. Social communication in Tourette syndrome: a glimpse at the contribution of the insula and the prefrontal cortex. Brain. 2018; 141(8): e58. DOI: 10.1093/brain/awy140.
15. Vicario CM, Gulisano M, Maugeri N, et al. Moral Decision-Making in Adolescents with Tourette Syndrome. Mov Disord. 2021; 36(9): 2205–2206. DOI: 10.1002/mds.28705
16. Vicario CM. Morality and disgust: insights from obsessive compulsive disorder. Front Psychiatry. 2013; 3: 113. DOI: 10.3389/fpsyt.2012.00113.
17. Pulcu E, Zahn R, Elliott R. The role of self-blaming moral emotions in major depression and their impact on social-economical decision making. Front Psychol. 2013; 4: 310. DOI: 10.3389/fpsyg.2013.00310.
18. Vicario CM, Lucifora C. Neuroethics: what the study of brain disorders can tell about moral behavior. AIMS Neurosci. 2021 Oct 25; 8(4): 543–547. DOI: 10.3934/Neuroscience.2021029.
19. Young MJ, Bodien YG, Giacino JT, Fins JJ, Truog RD, Hochberg LR, Edlow BL. The neuroethics of disorders of consciousness: a brief history of evolving ideas. Brain. 2021 Dec 16; 144(11): 3291–3310. DOI: 10.1093/brain/awab290. PMID: 34347037; PMCID: PMC8883802.
20. Kriegel U. The value of consciousness. Analysis. 2019; 79(3): 503–520.
21. Hildesheim H, Rogge A, Borzikowsky C, Witt VD, Schäffer E, Berg D. Moral distress among residents in neurology: A pilot study. Neurol Res Pract. 2021; 3(1): 6–9.
22. Famm K, Litt B, Tracey KJ, Boyden ES, Slaoui M. Drug discovery: a jump-start for electroceuticals. Nature. 2013; 496: 159–161. DOI: 10.1038/496159a.
23. Qureshi IS, Datta-Chaudhuri T, Tracey KJ, Pavlov VA, Chen ACH. Auricular neural stimulation as a new non-invasive treatment for opioid detoxification. Bioelectron Med. 2020; 6: 7. DOI: 10.1186/s42234-020-00044-6.
24. Naqvi NH, Gaznick N, Tranel D, Bechara A. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Ann N Y Acad Sci. 2014; 1316: 53–70. DOI: 10.1111/nyas.12415.
25. Joutsa J, Moussawi K, Siddiqi SH, et al. Brain lesions disrupting addiction map to a common human brain circuit. Nat Med. 2022; 28: 1249–1255. DOI: 10.1038/s41591-022-01834-y.
26. Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. J Ect. 2018; 34: 182–192. DOI: 10.1097/YCT.0000000000000541.
27. Zuk P, Lázaro-Muñoz G. DBS and Autonomy: clarifying the role of theoretical neuroethics. Neuroethics. 2021; 14: 83–93. DOI: 10.1007/s12152-019-09417-4.

FRAMEWORK OF RISK EVALUATION OF MEDICAL AI SYSTEMS

Volskaya EA[1] ✉, Rogova IV[2]

[1] NA Semashko National Research Institute of Public Health, Moscow, Russia

[2] Russian University of Medicine, Moscow, Russia

Medical technologies using artificial intelligence (AI) systems hold a firm place in real clinical practice as the main providers of important information for making medical decisions in diagnosis and treatment via assisting and auxiliary tools in the process of medical care provision. To obtain valid evidence of quality, effectiveness, and safety, AI software developers conduct clinical trials of these systems in accordance with current regulatory requirements [1], guided by the recommendations of recognized experts in the field of clinical research [2]. Ethical committees have a task to conduct a high-quality ethical review of the planned research, taking into account the specifics of AI technologies used in medicine and risks associated with their use.

Keywords: medical AI-system, ethical evaluation, risk evaluation, ethical postulates

Author contribution: the authors have made an equal contribution to the research and writing of the article.

✉ **Correspondence should be addressed**: Elena Alekseevna Volskaya
Chernyakhovsky St., 4/a, apt. 52, Moscow, 125319, Russia; vols-elena@yandex.ru

Received: 04.11.2024 **Accepted:** 15.12.2024 **Published online:** 31.12.2024

DOI: 10.24075/medet.2024.027

ПОДХОДЫ К ОЦЕНКЕ РИСКОВ МЕДИЦИНСКИХ СИСТЕМ ИСКУССТВЕННОГО ИНТЕЛЛЕКТА

Е. А. Вольская[1] ✉, И. В. Рогова[2]

[1] Национальный НИИ общественного здоровья имени Н. А. Семашко, Москва, Россия

[2] Российский университет медицины, Москва, Россия

Медицинские технологии с использованием систем искусственного интеллекта (ИИ) занимают прочное место в реальной клинической практике в качестве основных поставщиков важной информации для принятия врачебных решений при диагностике и лечении, в формате ассистирующих и вспомогательных инструментов в процессе оказания медицинской помощи. Для получения валидных доказательств качества, эффективности и безопасности разработчики программного обеспечения с использованием ИИ (ПО с ИИ) проводят клинические исследования этих систем в соответствии с действующими нормативными требованиями [1], руководствуясь рекомендациями признанных экспертов в сфере клинических исследований [2]. Перед этическими комитетами стоит задача качественно провести этическую экспертизу планируемых исследований, учитывая специфику технологий ИИ, применяемых в медицине, и риски, связанные с их применением.

Ключевые слова: медицинские системы искусственного интеллекта, этическая экспертиза, оценка рисков, этические постулаты

Вклад авторов: авторы внесли равный вклад в проведение исследования и написание статьи.

✉ **Для корреспонденции**: Елена Алексеевна Вольская
ул. Черняховского, д. 4/а, кв. 52, г. Москва, 125319, Россия; vols-elena@yandex.ru

Статья поступила: 04.11.2024 **Статья принята к печати:** 15.12.2024 **Опубликована онлайн:** 31.12.2024

DOI: 10.24075/medet.2024.027

Artificial intelligence (AI) systems have rapidly entered all spheres of society, including healthcare and medicine. In accordance with current regulatory requirements, AI medical systems are subject to state registration as medical devices (software with artificial intelligence technology or software with AI) [3], which is carried out by Roszdravnadzor. At the beginning of October 2024, 37 medical devices using AI technologies were registered [4].

It should be noted that major clinical trials with AI-based software and, moreover, AI medical systems are associated with many difficulties. Therefore, they are not often conducted in our country and abroad. Thus, in an analysis performed using the US FDA database, only 20% of approved medical AI systems had passed pre-registration clinical trials by 2023, and no randomized trials were recorded among them [5]. And this is despite the fact that the FDA imposes clear requirements on the registration dossier in terms of information about the studies:

- demonstration of the desired medical benefit at set values of certain quality indicators;
- comparison of the evaluated product with classical clinical diagnostic or therapeutic procedures (reference standard);
- demonstration of technical/analytical capabilities;
- a modern prospective randomized multi-center study;
- demonstration of clinical efficacy, etc. [6].

In our country, universities and research institutes are conducting proactive research in the field of using artificial intelligence systems to provide medical care to patients along with major developments by serious manufacturers of medical AI systems, which are submitted to Roszdravnadzor for registration and implementation in medical practice. Such projects, especially if they are carried out as part of dissertation, are usually subject to examination by independent ethics committees (IECs).

Currently, the (IECs) have gained their first experience in ethical evaluation of independent research of medical AI systems. Most often, we are talking about navigation systems that use augmented reality for surgery, software for automatic image analysis for diagnostic purposes, medical decision support systems, etc. Not all systems are original; they include adaptation projects for using a medical device in a new field. Developers consider these studies, including within thesis works, as pilot projects. In case of positive results, they are planning to continue development.

Table 1. Gradation of potential risk levels for the use of medical AI systems proposed by the International Forum of Medical Device Regulators (IMDRF, 2014)

Clinical situation/ condition	The importance of information received from SaMD to take a medical decision		
	For treatment or diagnosis	For clinical management	For patient-management information
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

Table 2. Risk assessment according to the Order of the Ministry of Health of the Russian Federation No. 686n dated July 7, 2020

The type of information provided by the software and its significance for making a medical decision	Categories of software application conditions		
	Category A for emergency cases, surgical intervention	Category B for emergency care without surgery	Category C for planned medical care
Does not require clarification, indicates the need for emergency action	3 — high risk (NB! + AI systems)	2b — increased risk	2a — medium risk
to be clarified	2b — increased risk	2a — medium risk	1 — low risk
3 — no need for immediate medical actions	2a — medium risk	1 — low risk	1 — low risk

The IEC needs to assess the risks of using an AI system in a clinical trial. Of course, IECs mainly follow relevant regulatory acts such as Helsinki Declaration of the WMA, Rules of Good Clinical Practice of the EAEU, and current GOST on clinical trials of medical devices [7], etc. The classification of risks of medical devices, which includes three risk classes (with two subclasses in class 2), should also be taken into account. Despite the fact that the safety degree of patients and subjects of research at the stage of medical device development is the main principle of risk ranking, nevertheless, the specific traits of AI software, including AI medical systems, take into account not only additional parameters [8], but also the entire existing regulatory framework for dealing with AI. Moreover, its detailed and systematic analysis is presented in scientific publications [9].

In 2024, the International Forum of Medical Device Regulators published the final document on the risk categories of software as a medical device (SaMD) [10]. These were the first recommendations on AI-specific software risk classification intended for use in medical technologies, including medical AI systems.

The document provides a matrix (Table 1), based on the clinical situation for which the AI medical system is intended, whereas the second parameter is the importance of medical decision support provided by AI software for a specific clinical situation. According to these criteria, four levels of risk are proposed. They ranged from the first, low level to the fourth, very high and critical risk level.

Three types of a clinical situations were considered:

- critical, when emergency (including surgical) medical care is needed for a patient with life-threatening conditions, including incurable conditions;
- clinical situations requiring serious therapeutic interventions, when a quick decision is required and time constraints can affect the ability of the decision-maker to correctly evaluate the information provided to him by the AI system;
- a clinical situation or patient's condition that does not require serious therapeutic interventions, when there is time to clarify the information received.

Another parameter that determines the risk level is the importance of the information provided by the AI system for making a medical (clinical) decision:

- information provided by SaMD should be used to make an immediate medical decision;
- information important for the diagnosis (detection) of a disease or condition, for clinical decisions on patient management, and for subsequent diagnosis and/or determination of a treatment plan;
- information important for determining the options for planned treatment, diagnosis, prevention, and alleviation of the disease symptoms.

In 2020, the Russian Ministry of Health issued Order No. 686h [11], which introduced very significant substantive changes to Order No. 4h 2012 'On Approval of the Nomenclature Classification of Medical Devices'. Section 'III. Classification of software that is a medical device' of Appendix No. 2 to the order appeared to be the most essential one.

In fact, this classification is based on a concept very close to that proposed in 2014 by the International Forum of Regulators. According to the Order, the structure of risk classes of software that is a medical device (including an AI medical system) fully and verbatim corresponds to that for medical devices. The only difference is that instead of the term 'medical devices' the phrase 'software' (software) is included: class 1 for low-risk software, class 2a for software with medium-risk, class 2b for higher-risk software, class 3 for high-risk software. It is noted that software is given a risk class regardless of the risk class of the medical device in combination with which it is used.

Two criteria are used to determine the level of risk: the type of information provided by the AI system and the clinical conditions of using the AI system.

There are three types of information provided by the AI system:

1) information that does not require clarification in order to make an informed clinical/medical decision and indicates the need for immediate actions;
2) information that needs to be clarified in order to make an informed clinical/medical decision;

3) information that does not show the need for immediate medical actions.

The clinical conditions of the AI medical system are also divided into three categories:

– category A is assigned if the AI system is intended for use in emergency situations, during surgical interventions, as well as in providing care for diseases with a high risk to individual and public health;
– category B is given in case of emergency care or medical care without surgical intervention, with a moderate risk to public health;
– category C is provided in routine medical care, medical care using non-invasive methods, with low risks to public health.

If we structure the paragraphs of rather extensive section III of Appendix 2, we get a table reflecting a very logical risk rating system (Table 2). There is only one exception in the well-structured classification of risks, depending on two criteria such as importance of the information provided by AI and complexity of the clinical situation. It concerns software using artificial intelligence technologies: any AI systems are classified as the ones with the highest risk and belong to Class 3 (clause 15.1.1 of section III of Appendix 2).

Attributing all AI medical systems to the highest risk class without exception might seem excessively rough. Although when it comes to AI systems designed to assist an operator during a surgery, and when the accuracy of the information provided depends on success of the operation, health and life of the patient, such roughness is justified and appropriate. For example, if an AI system performs diagnostic image analysis at the time when a doctor decides on treatment strategy for a patient with an acute stroke, when rapid and accurate differentiation between ischemic and hemorrhagic strokes is crucial for the choice of therapy. However, many AI systems have been introduced into clinical practice and continue to be implemented, providing auxiliary information for medical decision-making in much milder conditions. In fact, they could be classified as 2b or even 2a risk classes.

However, along with risk classification, ethics committees, when examining planned software research for medical technologies, including AI systems, should take into account other risks that the system may be associated with both during the research and in the future. These risks include:

– breach of confidentiality: in the worst case, discrimination in a social environment with consequences for mental health;
– influencing a medical choice, for example, when teaching SaMD using archived data, some of which may be biased;
– loss of a personal contact between the patient and the doctor;
– misleading with low-quality information about the AI system used in the process of providing medical care;
– anxiety, stress, and hypochondria developed due to the constant and frequent use of SaMD;
– errors in interpreting the system's response (incorrect self-treatment);
– technical failures, AI system hacks, cyber-attacks, etc.

To prevent these and other risks, the possibility of which cannot be excluded during the use of medical AI systems, it is necessary not only to minimize their negative effects at the research stages, but also to promote the responsible attitude of developers, control the use of these systems in real clinical practice, and increase patient loyalty to them. Distrust of innovative medical systems by patients can reduce the effectiveness of their use [12]. Therefore, ethics committees should perhaps expand the perspective of prognostic assessment when examining the planned studies, including the likely humanitarian impact of the application of the developed AI system on patients in clinical practice.

To date, it is possible to identify the main ethical postulates that should be followed by both developers of medical AI systems when designing developments, and by ethical committees when evaluating the developments:

– final decision-making authority should always remain with the doctor, since he is responsible for the medical care provided;
– control and storage of confidential medical data should be guaranteed, and periodic independent audits of data protection of subjects should be facilitated;
– patients/consumers should be fully informed about the AI systems used in the applied technologies. Ethics committees should monitor not only information material intended for research subjects, but also information related to the use of the AI system independently or as part of other medical technologies and intended for patients in clinical practice.

CONCLUSION

The system regulating the field of medical AI technologies is being formed and developed both in our country and around the globe (WHO, UNESCO, IMDRF and other organizations). The main provisions, conceptual framework, classification features, etc. are being developed and introduced into the sphere of AI technologies, which lays the foundation for unified approaches to the development of medical AI systems. Thus, in early October 2024 Rosstandart approved two important documents in the field of medical AI technologies such as the main provisions on medical decision support systems [13] and the main provisions on predictive analytics systems based on artificial intelligence [14]. The National Standard of the Russian Federation "Artificial intelligence systems in clinical medicine. Part 1. Clinical assessment" [15] was established as well.

Standardization of the field of medical AI systems is carried out in a very timely manner, since the number of AI systems being introduced into medical practice is constantly increasing. This leads to an increased public interest in both the use of AI software in everyday clinical practice and ethical aspects of development and application of medical AI technologies, which is reflected in the growing number of publications related to this topic.

Ethical issues related to introduction of innovative cognitive technologies capable of imitating thought processes into society are becoming the subject of discussion at representative international forums [16]. They are in the focus of attention of large public associations, such as the Alliance in the Field of Artificial Intelligence, which developed the Code of Ethics of AI [17], and are of scientific interest to serious scientific research teams [18].

However, issues of methodology for the ethical evaluation of clinical trials of medical technologies and systems using AI, as well as ethical aspects related to the introduction of these technologies into clinical practice, their perception by the patient community and variants of sociomental reactions, remain controversial. Obviously, experts in the field of research ethics still have to work together, in discussions and exchange of opinions, to develop criteria for ethical assessment and reference points for ethical committees.

References

1. Decision No.29 of the EEC Council dated February 12, 2016 «On Rules for clinical and laboratory tests (research) of medical products». Russian.
2. Ethical Review of Biomedical Trials. Guidelines for Ethics Committees. Ed. Hohlov AL. M., 2021; 792 p. Russian.
3. Letter of the Russian Federal Ministry of Health dated February 13, 2020 No. 02I-297/20 “On Software”. Russian.
4. Gusev A. Registered medical devices using artificial intelligence technologies. Russian. Available from URL: https://webiomed.ru/blog/zaregistrirovannye-meditsinskie-izdeliia-ai/?ysclid=m2u6g82m51527476645 (accessed: 14.10.2024) Russian.
5. Medical AI Evaluation. Available from URL: https://ericwu09.github.io/medical-ai-evaluation/ (accessed: 14.10.2024)
6. Artificial Intelligence and Machine Learning in Software as a Medical Device. FDA. 2021. Available from URL: https://www.google.com/search?q=Artificial+Intelligence+and+Machine+Learning+in+Software+as+a+Medical+Device&rlz=1C1PRUC_en (accessed: 14.10.2024)
7. GOST R ISO 14155-2022 Clinical Research of medical devices involving Human Participants. Ressian. Available from URL: https://docs.cntd.ru/document/1200194060?ysclid=m2u8wxt2o368417633 (accessed: 14.10.2024) Russian.
8. Gusev AV, Kobyakova OS, Kovshirina YuV, Rebrova OYu. Ethical review of clinical research for AI systems. Guidelines. M.: RIO CNIIOIZ MZ RF, 2024; 32 p. DOI: 10.21045/978-5-94116-182-9-2024. Russian.
9. Hohlov AL, Belousov DYu. Ethical aspects of Sofrware with AI technology. Good clinical Prectice. 2021; 1: 70–84. Russian.
10. Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations. IMDRF. 2014. URL: https://www.imdrf.org/documents/software-medical-device-possible-framework-risk-categorization-and-corresponding-considerations (accessed: 14.10.2024)
11. Order of the Ministry of Health of the Russian Federation of July 7, 2020 No. 686n “On Amendments to Annexes No. 1 and No. 2 to the Order of the Ministry of Health of the Russian Federation of June 6, 2012 No. 4n “On Approval of the Nomenclature Classification of Medical Devices”. Russian.
12. Hohlov AL, Zarubina TV, Kotlovsky Myu, et al. Mechanisms for Introduction of Artificial Intelligence in Healthcare: new ethical Challenges. Russian. Medical Ethics. 2024; 3: 4–10.
13. GOST R 71671-2024 System for supporting medical decision-making using artificial intelligence. Main provisions. Available from URL: https://nd.gostinfo.ru/document/7582986.aspx (accessed: 14.10.2024) Russian.
14. GOST R 71672-2024 “Predictive analytics systems using artificial intelligence in medicine. Main provisions. Available from URL: https://nd.gostinfo.ru/document/7582951.aspx(accessed: 14.10.2024) Russian.
15. GOST R 59921.1-2022. Artificial intelligence systems in clinical medicine. P. 1. Clinical evaluation. Available from URL: https://files.stroyinf.ru/Data/782/78211.pdf (accessed: 14.10.2024) Russian.
16. IV AI Ethics Forum. Moscow. October 9, 2024. Available from URL: https://aiethic.ru/ (accessed: 14.10.2024) Russian.
17. AI Ethics Code. Available from URL: https://ethics.a-ai.ru/ (accessed: 14.10.2024) Russian.
18. Ethical review in the field of AI. Project of HSE AI Research Centre. Available from URL: https://cs.hse.ru/aicenter/ethical_review (accessed: 14.10.2024) Russian.

Литература

1. Решение Совета Евразийской экономической комиссии от 12.02.2016 № 29 «О правилах проведения клинических и клинико-лабораторных испытаний (исследований) медицинских изделий».
2. Этическая экспертиза биомедицинских исследований. Руководство для комитетов по этике. Под общей ред. А. Л. Хохлова. 3-е изд., перераб. и доп. М. ОКИ, 2021; 792 с.
3. Письмо Федеральной службы по надзору в сфере здравоохранения от 13 февраля 2020 г. № 02И-297/20 «О программном обеспечении».
4. Гусев А. Зарегистрированные медицинские изделия, использующие технологии искусственного интеллекта. Режим доступа: [Электронный ресурс] URL: https://webiomed.ru/blog/zaregistrirovannye-meditsinskie-izdeliia-ai/?ysclid=m2u6g82m51527476645 (дата обращения 14.10.2024).
5. Medical AI Evaluation. Available from URL: https://ericwu09.github.io/medical-ai-evaluation/ (accessed: 14.10.2024).
6. Artificial Intelligence and Machine Learning in Software as a Medical Device. FDA. 2021. Available from URL: https://www.google.com/search?q=Artificial+Intelligence+and+Machine+Learning+in+Software+as+a+Medical+Device&rlz=1C1PRUC_en (accessed: 14.10.2024).
7. ГОСТ Р ИСО 14155-2022. Клинические исследования медицинских изделий, проводимые с участием человека в качестве субъекта. Надлежащая клиническая практика. Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/1200194060?ysclid=m2u8wxt2o368417633 (дата обращения 14.10.2024).
8. Гусев А. В., Кобякова О. С., Ковширина Ю. В., Реброва О. Ю. Этическая экспертиза клинических испытаний систем искусственного интеллекта. Методические рекомендации. М.: РИО ЦНИИОИЗ МЗ РФ, 2024; 32 с. DOI: 10.21045/978-5-94116-182-9-2024.
9. Хохлов А. Л., Белоусов Д. Ю. Этические аспекты применения программного обеспечения с технологией искусственного интеллекта. Качественная клиническая практика. 2021; 1: 70–84.
10. Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations. IMDRF. 2014. Available from URL: https://www.imdrf.org/documents/software-medical-device-possible-framework-risk-categorization-and-corresponding-considerations (accessed: 14.10.2024).
11. Приказ Министерства здравоохранения Российской Федерации от 7 июля 2020 г. № 686н «О внесении изменений в приложения № 1 и № 2 к приказу Министерства здравоохранения Российской Федерации от 6 июня 2012 г. № 4н “Об утверждении номенклатурной классификации медицинских изделий”».
12. Хохлов А. Л., Зарубина Т. В., Котловский М. Ю. и др. Механизмы внедрения технологий искусственного интеллекта в здравоохранение: новые этические вызовы. Медицинская этика. 2024; 3: 4–10.
13. ГОСТ Р 71671-2024 «Система поддержки принятия врачебных решений с применением искусственного интеллекта. Основные положения. Режим доступа: [Электронный ресурс] URL: https://nd.gostinfo.ru/document/7582986.aspx (дата обращения 14.10.2024).
14. ГОСТ Р 71672-2024 «Системы прогнозной аналитики на основе искусственного интеллекта в клинической медицине. Основные положения». Режим доступа: [Электронный ресурс] URL: https://nd.gostinfo.ru/document/7582951.aspx (дата обращения 14.10.2024).
15. ГОСТ Р 59921.1-2022. Системы искусственного интеллекта в клинической медицине. Ч. 1. Клиническая оценка. Режим доступа: [Электронный ресурс] URL: https://files.stroyinf.ru/Data/782/78211.pdf (дата обращения 14.10.2024).
16. IV Форум этики в сфере искусственного интеллекта. Москва. 9 октября 2024. Режим доступа: [Электронный ресурс] URL: https://aiethic.ru/ (дата обращения 14.10.2024).
17. Кодекс этики в сфере ИИ. Режим доступа: [Электронный ресурс] URL: https://ethics.a-ai.ru/ (дата обращения 14.10.2024).
18. «Этическая экспертиза в сфере искусственного интеллекта». Проект Центра ИИ НИУ ВШЭ. Режим доступа: [Электронный ресурс] URL: https://cs.hse.ru/aicenter/ethical_review (дата обращения 14.10.2024).

THE ROLE OF CHRISTIAN ETHICS IN SHAPING MEDICAL PRACTICE

Filkin AN[1] ✉, Kudrina SA[2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Yaroslavl State University named after Demidov PG, Yaroslavl, Russia

Religion, ethics and medicine are recognized to be related since antiquity. This article discusses the ethical aspect of medicine and focuses on the moral qualities of a doctor in the face of modern challenges. The main focus is on returning to traditional values based on Christian morality. The Bible changed the relationship between humanity and the Divine, when a man is viewed as an image of the Creator and the need for divine intervention in healing is emphasized. Unlike ancient rationalism, Christian faith is aware of the cognition limits and understands the importance of the spiritual aspect of health. The article analyzes how the Hippocratic oath has changed under the influence of Christian values. The importance of cooperation between doctors and priests who healed patients is considered, and the need for compassion in medical practice is emphasized. The synthesis of faith and medical science makes us understand that healing involves achieving both physical and mental, as well as spiritual well-being.

Keywords: religion, ethics, medicine, Christian morality, compassion, traditional values, Divine intervention, Hippocratic oath, spiritual health, collaboration between doctors and priests, eternal life

✉ **Correspondence should be addressed:** Andrey N. Filkin
Revolyutsionnaya Str., 5, Yaroslavl, 150000, Russia; filkin1964@mail.ru

Received: 28.10.2024 **Accepted:** 20.11.2024 **Published online:** 31.12.2024

DOI: 10.24075/medet.2024.026

РОЛЬ ХРИСТИАНСКОЙ ЭТИКИ В ФОРМИРОВАНИИ МЕДИЦИНСКОЙ ПРАКТИКИ

А. Н. Филькин[1] ✉, С. А. Кудрина[2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославский государственный университет им. П. Г. Демидова, Ярославль, Россия

Связь между религией, этикой и медициной признана с древних времен. В данной статье обсуждается этический аспект медицины, акцентируется внимание на нравственных качествах врача в условиях современных вызовов. Основное внимание уделяется возвращению к традиционным ценностям, основанным на христианской морали. Библейское послание изменило понимание отношения между человеком и Богом, рассматривая человека как образ Творца и подчеркивая необходимость божественного вмешательства в исцеление. В отличие от античного рационализма, христианская вера предполагает осознание границ познания и понимание важности духовного аспекта здоровья. В статье анализируются изменения, которые претерпел текст клятвы Гиппократа под влиянием христианских ценностей. Рассматривается важность сотрудничества врачей и священников в деле исцеления пациентов, подчеркивается необходимость сострадания в медицинской практике. Синтез веры и медицинской науки подвигает к осознанию того факта, что исцеление предполагает достижение как физического и душевного, так и духовного благополучия.

Ключевые слова: религия, этика, медицина, христианская мораль, милосердие, традиционные ценности, Божественное вмешательство, клятва Гиппократа, духовное здоровье, сотрудничество врачей и священников, вечная жизнь

✉ **Для корреспонденции:** Андрей Николаевич Филькин
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; filkin1964@mail.ru

Статья поступила: 28.10.2024 **Статья принята к печати:** 20.11.2024 **Опубликована онлайн:** 31.12.2024

DOI: 10.24075/medet.2024.026

The connection between religion, ethics and medicine has existed and been recognized since ancient times. Mercy, one of the most important Christian virtues, is largely manifested and implemented in the field of healing. In this regard, the ethical state of a doctor is one of the most important issues in modern Russian medicine. A modern man faces many challenges which are manifested through man-made, social and bioethical risks and threats. It is possible to respond to these challenges based on traditional Christian moral values. That is why it is especially important to turn to the spiritual heritage these days.

The Biblical message radically changed understanding of the reality and a man: “the word of Christ contained in the New Testament … turned over all the concepts and problems posed by philosophy in the past, determining their formulation in the future” [1]. First of all, a new understanding of the “divine” and “transcendent” has emerged. Now, God cannot be compared with anything created. And if an ancient Greek thought was cosmocentric and understood a man as a kind of microcosm repeating all the laws of the greater cosmos and never going beyond the laws of the outer space, in the Bible a man appears as an image and likeness of God the Creator and, therefore, becomes higher than any creation, higher than nature, higher than the cosmos. Man’s ability to accept the will of God makes him superior to the created world. For the ancient Greek, the law is the law of the cosmos, which is the same for both gods and people, whereas in the Bible, virtue means to follow God’s commandments, which God himself reveals to man directly. Now the moral law is given from above, and its essence is the coincidence of the will of man with the will of God. If virtue means to follow the will of God, then sin means to ignore that will, rebel against it, and strive to act according to one’s own mind. By committing a sin, a person perhaps seeks to take the place of God without realizing it. With Adam, sin entered a man and brought diseases, suffering and death. The ancient Greek mind saw that a man can independently get rid of the consequences of sin, for example, through self-knowledge and moral improvement. The Christian world view does not abolish these great human abilities, but, at the same time, asserts that

a person can be freed from the consequences of sin only with God's help, when God himself comes to meet a person through the sacrifice of Jesus Christ on the cross. Only by patiently accepting his cross and becoming like Christ, a person can overcome the consequences of sin such as illness, suffering, and death.

According to the Christian anthropology, a man is understood not as a contradictory unity of soul and body, but as a tri-partite unity of body, soul and spirit. The spiritual hypostasis is understood as the communion of the soul with God, as a godlike principle in the human soul, determining his ability to distinguish good from evil, truth from falsehood, beauty from ugliness, that is, saving the soul from destructive elements. To live in the spirit means to live by "the main noble forces and aspirations" [2]. Humility becomes the highest virtue of Christianity, "for whoever wants to save his life will lose it, but whoever loses his life because of me and the gospel will save it" (Mark 8:35) [3]. The great example of true humility and love is the sacrifice of Jesus Christ.

A Christian does not rely on transmigration of the soul after death, as many ancients did, he believes in resurrection and union of the soul with the body after the Last Judgment, because, according to the Christian view, a full-fledged person is the unity of soul and body.

Returning to the ancient Greek medical ethics, which found its expression in the Hippocratic oath, we cannot help noticing its connection with religion. Doctors of antiquity understood the limitations of rational knowledge differently. It is known that in severe cases, when rational medicine was powerless, patients turned to the sanctuary of the Asclepius the God.

The need to rely on God the Creator in all cases of medical practice was intensified during the Christian era. A Christianized medieval version of the Hippocratic Oath appeared. It sounded as follows: "From the Hippocratic oath, how suitable is it for a Christian. Blessed be God, the Father of our Lord Jesus Christ, who is blessed forever and ever; I am not lying. I will not tarnish the study of the medical art. Nor shall any man's entreaty prevail upon me to administer poison to anyone; neither will I counsel any man to do so. Moreover, I will give no sort of medicine to any pregnant woman, with a view to destroy the child. I will teach this art to those who need it, without claims and without a contract. I use treatment to help the suffering according to my abilities and my understanding. I will maintain my life and my art in purity and holiness. Whatsoever house I may enter, my visit shall be for the convenience and advantage of the patient; and I will willingly refrain from doing any injury or wrong from falsehood, and from acts of an amorous nature, whatever may be the rank of those who it may be my duty to cure, whether mistress or servant, bond or free. Whatever, in the course of my practice, I may see or hear (even when not invited), whatever I may happen to obtain knowledge of, if it be not proper to repeat it, I will keep sacred and secret within my own breast. If I faithfully observe this oath, may I thrive and prosper in my fortune and profession, and live in the estimation of posterity; or on breach thereof, may the reverse be my fate!" [4].

We see that in the Hippocratic oath much was in tune with the ideas of the Christian doctor. It included the willingness to teach those in need to master the medical art, inadmissibility of using lethal means and performing abortions, a promise to lead a virtuous life, abstinence from unethical behavior towards patients, and a promise not to disclose what they saw and heard during treatment. According to the French philosopher and theologian Jean-Claude Larchet, the distinctive feature of a Christian doctor is "the conviction that they can achieve nothing if acting independently and relying on their art alone". Therefore, "before making a diagnosis, they pray to God for guidance and before prescribing treatment, they ask the Lord that it be appropriate and effective" [5].

Christians excluded the part of the Hippocratic oath devoted to loyalty to the mentor and medical community, which most likely show that Christian doctors distrust pagan associations. "Put not your trust in princes, in mortal man, who cannot save" (Psalm 145:3) [3]. But the trust in God the Father and Christ, God the Son, has been noticeably strengthened.

In the light of a holistic approach to man as a unity of body, soul and spirit, a distinction has emerged between bodily, mental and spiritual diseases. Bodily diseases are associated with a violation of the normal functioning of organs and body systems, but even their real causes may be hidden in the spiritual life of a person. Bodily illnesses can be sent as a kind of admonition to a person from God. It is very important for the patient to understand what part of his life contradicts the Divine commandments, what kind of mental disharmony causes the body to suffer. In the book of Jesus, the son of Sirach, it is said: "Honor the physician with the honor due him, according to your need of him, for the Lord created him; for healing comes from the Most High…The Lord created medicines from the earth, and a sensible man will not despise them… And he gave skill to men that he might be glorified in his marvelous works. By them he heals and takes away pain…My son, when you are sick do not be negligent, but pray to the Lord, and he will heal you… Give up your faults and direct your hands aright, and cleanse your heart from all sin…And give the physician his place, for the Lord created him; let him not leave you, for there is need of him…" (Sirach 38: 1–14) [3].

It is important to note that although the physicality of man makes it related to the animal world by composition, nevertheless, man has a high vocation to stand above the whole world, above nature. Since man, having fallen into sin, infected the whole world, it is through man, through his purification, that the environment is cleansed. Christ was the first person who cleansed the material composition of the human body and indeed the entire material composition of the universe from corruption and death.

If bodily diseases are associated with disharmony of the body, mental illnesses are reflected in a change in the human psyche. In the New Testament, Christ speaks of the high status of the soul: "Be not afraid of those who kill the body, but are not able to kill the soul" (Matthew 10:28) [3]. The soul is a symbol of life, God is its source. The soul needs a body, and the body needs a soul. The soul uses the brain, but if the brain is sick, the soul cannot reason sensibly. Illness shows a person the power of death over him, and this is already a religious problem related to the fall of man, the consequences of which are illness and death.

If the soul is "God's breath", as St. Gregory the Theologian claimed, the spirit is fullness of divine grace, "a particle of Divinity" [6]. A person has a healthy spirit when he lives in a Christian way, in accordance with the commandments given by God. Accordingly, a damaged sick spirit lives a sinful life, violating the commandments. That is why the concept of "healing" is more often used in Christian literature, since, escaping from sin, a person is not just "treated". He restores himself as a complete image.

A doctor is needed to treat physical and mental illnesses. And the priest provides assistance in spiritual healing and preparation for eternal life. In the New Testament, there is a canonical justification for the priest to perform the sacrament of unction: "If any of you is sick, let him call the elders of the church, and let them pray over him, anointing him with oil in the name of the

Lord" (James 5:14) [3]. Here, the union of a priest and a doctor is very important in accordance with such principles of bioethics as the principle of patient autonomy, principle of benevolence, principle of non-harm and principle of justice. Both the doctor and the priest, each in his own way, contribute to the healing of a sick person. The priest helps a person to find inner peace and spiritual strength both for the continuation of earthly life and for the transition to eternity. The participation of the priesthood in helping people under post-traumatic conditions and in the rehabilitation of addicts, along with doctors and psychologists, is an important component of the manifestation of spiritual care. According to the New Testament, helping the sick was an important part of the apostles' ministry: "Heal the sick… cleanse the lepers…" (Matthew 10:8) [3]. As for terminal patients, priests help them overcome the fear of death. They confess, receive communion and administer unction to hospice patients, while doctors alleviate their physical suffering.

Metropolitan Anthony of Sourozh, a doctor of secular education, draws attention to the fact that preparation of terminal patients for death must be carried out throughout the development of their disease, but, he urges, "prepare the dying not for death, but for eternal life" [7]. Moreover, Metropolitan Anthony speaks of a "willingness to let a person die," meaning that a doctor's attitude towards a patient cannot be simply "scientific," it must include compassion and pity. And this implies, in some cases, giving a person the opportunity to die peacefully, no matter how paradoxical it may sound. The task of a doctor, as Metropolitan Anthony precisely formulated it, is to "protect life." "God created both medicine and a doctor, and sometimes our healing is in his hand." St. Theophan the Recluse says that "there is no sin to turn to medicines, for the healer, and the medicines, and the recipes belong to God… As God has given these means to us, we should use them. God was pleased to surround us with supernatural means apart from natural ones. Access to these sources is available to everyone. Faith is the key. When God wants to heal this way, He absorbs the power of faith and takes it where He is pleased to give healing" [8].

References

1. Reale D, Antiseri D. Zapadnaya filosofiya ot istokov do nashikh dney. Srednevekov'e (Ot Bibliyskogo poslaniya do Makkiavelli). SPb. Petropolis. 1997; 2: 368 s. Russian.
2. Ilyin IA. Religioznaya filosofiya. Moskva: Medium. 1994; 2: 574 s.
3. Bibliya. Knigi Svyashchennogo Pisaniya Vetkhogo i Novogo Zaveta. M.: Danilov stavropigial'nyy muzhskoy monastyr'. 2015; 1408 s. Russian.
4. Pravoslavnaya tserkov' i sovremennaya meditsina. Sbornik. Pod red.k.m.n. svyashchennika Sergeya Filimonova. SPb. Obshchestvo svyatitelia Vasiliya Velikogo. 2000; 432 s. Russian.
5. Larshe Zhan-Klod. Bolezn' v svete pravoslavnogo veroucheniya. Moskva. Izd-vo Sretenskogo monastyria. 2016; 176 s. Russian.
6. Svyatitel Grigoriy Bogoslov, arkhiep. Konstantinopol'skiy. Stikhotvoreniya. Pis'ma. Zaveshchanie. Moskva: Sibirskaia blagozvonnitsa. 2007; 2: 943 s. Available from URL: https://azbyka.ru/otechnik/Grigorij_Bogoslov/stihotvorenija-bogoslovskie/#sel=1309:7,1309:51 (accessed: 28.10.2024). Russian.
7. Mitropolit Antoniy Surzhskiy. Iscelenie tela i spaseniye dushi. Chelovek. 1995; 5: 113 s. Russian.
8. Feofan Zatvornik, Svyatitel'. Nastavleniya v dukhovnoi zhizni. Moskva: Otchiy dom. 2009; 333 s. Available from URL: https://azbyka.ru/otechnik/Feofan_Zatvornik/nastavlenija-v-duhovnoj-zhizni/14_2#source (accessed: 28.10.2024). Russian.

Литература

1. Реале Д., Антисери Д. Западная философия от истоков до наших дней. Средневековье (От Библейского послания до Макиавелли). СПб. Петрополис. 1997; 2: 368 с.
2. Ильин И. А. Религиозная философия. Москва: Медиум, 1994; 2: 574 с.
3. Библия. Книги Священного Писания Ветхого и Нового Завета. М.: Данилов ставропигиальный мужской монастырь. 2015; 1408 с.
4. Православная церковь и современная медицина. Сборник. Под ред.к.м.н. священника Сергея Филимонова. СПб. Общество святителя Василия Великого. 2000; 432 с.
5. Ларше Жан-Клод. Болезнь в свете православного вероучения. Москва. Изд-во Сретенского монастыря. 2016; 176 с.
6. Святитель Григорий Богослов, архиеп. Константинопольский. Стихотворения. Письма. Завещание. Москва: Сибирская благозвонница, 2007; 2: 943 с. Режим доступа: [Электронный ресурс] URL: https://azbyka.ru/otechnik/Grigorij_Bogoslov/stihotvorenija-bogoslovskie/#sel=1309:7,1309:51 (дата обращения: 28.10.2024).
7. Митрополит Антоний Сурожский. Исцеление тела и спасение души. Человек. 1995; 5: 113 с.
8. Святитель Феофан Затворник. Наставления в духовной жизни. Москва: Отчий дом. 2009; 333 с. Режим доступа: [Электронный ресурс] URL: https://azbyka.ru/otechnik/Feofan_Zatvornik/nastavlenija-v-duhovnoj-zhizni/14_2#source (дата обращения: 28.10.2024).

THE ATTITUDE OF YOUNG DOCTORS TOWARD PATIENT-CENTRED MEDICAL CARE

Mylnikova IS[1] ✉, Mylnikova MA[2], Shkolnikova EA[2]

[1] Pirogov Russian National Research Medical University

[2] Institute of Additional Professional Education of Social Workers of the Department of Labor and Social Protection of the Population of Moscow, Moscow, Russia

Patient-centredness is a relatively new proof-of-concept setting associated with the concept of quality of medical care, which gradually becomes a new moral standard of medical practice. We conducted a study of the attitude of the younger generation of doctors (graduate students and residents of the Pirogov Russian National Research Medical University and RUDN, 2024) towards patient-centredness. They were offered a questionnaire consisting of 21 questions on different aspects of patient-centred communication. 155 completed questionnaires were received. The answers indicated that many young doctors are familiar with the concept of patient-centred approach and practice patient-centred communication skills. At the same time, many people feel a lack of training in this area and realize their vulnerability in communicating with the patient. At the same time, the survey revealed paternalistic attitudes in more than half of the respondents. It can be concluded that young doctors need not only mastering the skills of patient-centred communication, but also a deeper study of the moral foundations of patient-centredness, which can be implemented within the training courses in bioethics, as well as while teaching clinical disciplines.

Keywords: patient-centredness, patient-centred communication, patient-centred communication skills, therapeutic alliance

Author contribution: Mylnikova IS wrote the article; Shkolnikova EA and Mylnikova MA conducted the study and processed the results.

✉ **Correspondence should be addressed**: Irina S Mylnikova
Ostrovityanova str., 1, Moscow, 117997, Russia; expert.med@mail.ru

Received: 22.10.2024 **Accepted:** 17.11.2024 **Published online:** 16.12.2024

DOI: 10.24075/medet.2024.023

ОТНОШЕНИЕ МОЛОДЫХ ВРАЧЕЙ К ПАЦИЕНТООРИЕНТИРОВАННОСТИ ПРИ ОКАЗАНИИ МЕДИЦИНСКОЙ ПОМОЩИ

И. С. Мыльникова[1] ✉, М. А. Мыльникова[2], Е. Э. Школьникова[1]

[1] Российский национальный исследовательский медицинский университет имени Н. И. Пирогова

[2] Институт дополнительного профессионального образования работников социальной сферы Департамента труда и социальной защиты населения г. Москвы, Москва, Россия

Пациентоориентированность — относительно новая концептуальная установка, ассоциируемая с понятием качества медицинской помощи, которая постепенно приобретает характер новой моральной нормы врачебной практики. Нами было проведено исследование отношения молодого поколения врачей (аспирантов и ординаторов РНИМУ им. Н. И. Пирогова и РУДН, 2024 г.) к пациентоориентированности. Им была предложена анкета из 21 вопроса, касающегося разных сторон пациентоориентированного общения. Получено 155 заполненных анкет. Полученные ответы указали на то, что многие молодые врачи знакомы с концепцией пациентоориентированности, практикуют навыки пациентоориентированного общения. Одновременно многие ощущают недостаток подготовки в этой области, осознают свою уязвимость в общении с пациентом. Вместе с тем опрос выявил патерналистические установки более чем у половины опрошенных. Можно сделать вывод, что молодые врачи нуждаются не только в освоении навыков пациентоориентированного общения, но и в более глубоком изучении моральных основ пациентоориентированности, что может быть реализовано в рамках учебных курсов биоэтики, а также в ходе преподавания клинических дисциплин.

Ключевые слова: пациентоцентрированность, пациентоцентрированная коммуникация, навыки пациентоцентрированной коммуникации, терапевтический альянс

Вклад авторов: И. С. Мыльникова — написание статьи; Е. Э. Школьникова и М. А. Мыльникова — проведение исследования, обработка результатов.

✉ **Для корреспонденции:** Ирина Сергеевна Мыльникова
ул. Островитянова, д. 1, г. Москва, 117997, Россия; expert.med@mail.ru

Статья поступила: 22.10.2024 **Статья принята к печати:** 17.11.2024

Опубликована онлайн: 16.12.2024

DOI: 10.24075/medet.2024.023

DEFINITION OF PATIENT-CENTREDNESS

In recent decades, patient-centredness has become firmly established as an important component within practical healthcare. It denotes a certain ideal doctor/healthcare system-patient relationship with its primary focus on the individual patient. Its implementation is an essential element of high-quality medical care [1, 2].

To date, many clinical, organizational and research initiatives have been initiated and implemented around the world to promote and provide patient-centred care. There are thousands of publications devoted to the topic. However, despite the impressive extent of these initiatives, there is still no clearly formulated and unified opinion on what patient-centred care is [3].

So, Olson et al. recognize that 'patient-centredness' is a complex theoretical structure consisting of a combination of various concepts and practices that have been developed by representatives of various professional groups in the field of healthcare such as doctors, psychotherapists, care professionals, health care organizers, and specialists in the field of medical ethics. They all share a common ideal, though every person looks at the problem from different perspectives [4].

Psychologist Rogers and psychotherapist Balint were the first to propose the idea of person-centred therapy. In 1951, Rogers formulated the idea that people are able to solve their problems independently using their own resources, provided that they have necessary supportive conditions [5]. In turn, Balint proposed to consider person-centredness' as a way

of medical thinking, when a doctor perceives his patient as a unique human being, and this vision should precede the clinical diagnosis [6].

Later, the idea of patient-centredness applies to other sectors of medicine and healthcare, with different experts defining it in different ways. In 2000, Mead and Bauer conducted a review of the published literature on patient-centredness [7]. They concluded that patient-centredness is a multidimensional concept with five dimensions that includes as follows:

1) a biopsychosocial approach that expanded the view on the patient's disease from a strictly biomedical framework to a biopsychosocial perspective;
2) considering the patient as a multifaceted personality who may have a variety of experiences about his illness. Mead and Bauer described it as follows: "A compound leg fracture will not be perceived equally by two different patients; it can cause much less suffering to an office worker than to a professional athlete" [p. 1089];
3) separation of power and responsibility, depending on proper patient information and participation in medical decision-making. An obvious obstacle to complete egalitarianism in the doctor-patient relationship is the "competence gap", asymmetry of knowledge between the patient and the doctor, which nevertheless should not interfere with the transition from the paternalistic model of "leadership-subordination" to the model of mutual participation and division of responsibility (p. 1989 onwards);
4) therapeutic alliance in the doctor-patient relationship. Mutual benevolent relationships can improve treatment outcomes, whereas negative relationships, on the contrary, can reduce the chances of successful treatment;
5) perception of a doctor as a person. As in any relationship, both sides influence each other through interaction. This dimension highlights the importance of realizing that the doctor's personality, way of thinking, mood and well-being affect the current relationship with the patient and choices made during the consultation.

The presented definition of Mead and Bauer, according to Langberg et al, is still one of the most cited ones [8].

An interesting approach to the definition of patient-centred care was used by Duggan et al. They suggested going from the opposite, describing what it is not. So, it is not a doctor-centred help. Patient-centredness can be opposed to medical paternalism, when a patient's needs and opinions are ignored by a doctor. Being patient-centred, it can be opposed to disease-centred medicine. Finally, patient-centred approach differs from the technical or biomedical model of rendering aid, when a doctor is considered as a technician who makes interventions and performs procedures. According to Dagan et al., patient-centredness can be considered as a strategy that allows simultaneous correction of all these negative trends in medicine [9].

In 2019, Langberg et al. have prepared a scientific review on patient-centredness, in which the definitions given by various authors since 2010 were provided. According to them, there is still no uniformity in defining the concept, but the authors identify the same components of patient-centredness. Separation of powers and responsibilities, including informed consent and joint decision-making, as well as a therapeutic alliance are mentioned in articles devoted to patient-centredness. Less often, but quite often, there are references to the biosocial perspective when looking at the patients and the topic "the doctor as a person" is covered in some articles only. According to the analysis of Langberg et al., one more aspect represented by coordinated care that meets the patient's needs has appeared in the literature on patient-centredness [8].

PATIENT-CENTREDNESS AS A MORAL STANDARD

Despite the absence of a single strict definition, patient-centredness is considered as a form of doctor-patient relationship, which is the standard of high-quality interaction between a doctor and a patient while providing medical care and is recommended for widespread implementation in medical practice. [2]. Its proponents believe that it should be pursued as an ideal, and in its absence, the relationship between the doctor and the patient should be assessed as not entirely satisfactory. Thus, patient-centredness becomes prescriptive or normative [9]. It can be said that it is becoming a new moral norm for medical practice. In this regard, moral justification of patient-centredness, which was given by Duggan et al., is of interest. They examined patient-centredness from the perspective of three groups of ethical theories.

Thus, from the point of view of utilitarianism, patient-centred medical care will be recognized as ethical, since it can be proved that it provides better results compared to the doctor-centred model of care. In the review by Duggan et al, a number of studies have been presented in which a positive relationship between the patient-centred model, treatment outcomes and quality of medical care, assessed by a variety of indicators, has been found. For example, Safran et al. have shown that elements of patient-centred care have a positive effect on patient satisfaction [10]. Kaplan et al. found a positive relationship between the nature of doctor-patient interaction and functional parameters in chronic diseases [11]. Hall et al. found a connection between patient-centredness and commitment to treatment: rejected dominance in communication with the patient, nonviolent communication on the part of the doctor is associated with increased adherence to therapy [12], etc.

Substantiating the morality of patient-centredness from the point of view of deontological ethical theories, Duggan et al. ask whether patient-centredness has some internal feature of "correctness", which should be sought as a due. And answering it, the authors refer to Balint's definition of patient-centredness when each person is taken as a unique human being. It coincides with Kant's categorical imperative who recognized that every person has an unconditional moral value and dignity [13].

The third group of ethical theories requires an answer to the question of whether patient-centredness is a virtue. Unlike utilitarian ethical theories, the theory of virtue does not consider the consequences of actions as an important characteristic for distinguishing between good and evil. It does not insist on following pre-existing rules out of a sense of duty, as in deontological theories. The theory of virtue rather focuses on the education of correct attitudes and character traits that determine further moral actions. A person learns to act correctly by following the example of a teacher or mentor. Duggan et al. note that considering patient-centredness we understand that it is impossible to be truly attentive to the patient if there are no attitudes and beliefs that form the basis of patient-centricity. In the absence of these attitudes, it is impossible to act in a patient-centred way. These attitudes of respect and interest in the patient's personality are virtuous in themselves. They constitute a moral standard. A person acts in accordance with them willingly, with joy and enthusiasm, because he knows that being virtuous is the best thing he can do for himself as well. Virtues promote beneficial relationships with others, make it possible to avoid judicial and social conflicts, and enhance self-esteem.

A STUDY OF THE ATTITUDE OF YOUNG DOCTORS TOPATIENT-CENTREDNESS

The conclusion that patient-centredness can be considered as a new moral norm of medical practice, allows us to raise the question of the attitude of the younger generation of doctors towards it, which will determine our medicine for years to come. To answer this question, we conducted a study participated by postgraduate doctors (Pirogov Russian National Research Medical University) and medical residents (RUDN). They were offered a questionnaire consisting of 21 questions on different aspects of patient-centred communication. 155 completed questionnaires were received from 24 surgeons, 90 therapists, and 41 representatives of other specialties. There were 48 men and 107 women among the respondents. 125, 19 and 11 respondents had employment history of up to 3 years, from 3 to 5 years, and more than 5 years respectively. The questionnaire consisted of several blocks and contained questions about the doctor-patient relationship, communication skills, attitude to informed voluntary consent, and caring skills used.

Study outcomes

The question *"Have you ever encountered ethical problems when communicating with patients?"* was addressed to young doctors in order to find out how sensitive they are to ethical issues while dealing with patients. The answer "yes" was provided by 67% of the respondents. We believed that a group of young surgeons would show less sensitivity to ethical issues than a group of therapists, as numerous surveys indicate a relatively lower level of empathy among surgical professionals. The hypothesis was not confirmed: no surgeon provided a negative response. On the contrary, in the group of therapists, the proportion of those who faced ethical problems reached 31% (23% and 48% for female and male therapists respectively). However, in this survey, the unexpected difference in the sensitivity level can be explained by the fact that a group of surgeons were interviewed at the end of a one-year postgraduate course in bioethics. The majority of therapists (70% of the respondents) were residents with less than three years of medical experience, who had not studied bioethics in residency. This allows us to draw a cautious conclusion that bioethics training increases sensitivity of young doctors to ethical issues.

The majority of respondent provided positive replies (82.6%, 67%, 67.8% respectively) to the following questions *"Have you ever been dissatisfied with unsuccessful communication with a patient?", "Have you ever felt that you did not want to go to the ward because it was difficult for you to communicate with a patient or consult such a patient on an outpatient basis?"* and *"Has it happened that after communicating with a patient you felt unusual fatigue, emptiness, anxiety, etc.?"*. It indicates that young doctors are aware of the intersubjective nature of their communication with a patient and their vulnerability during this communication. The answers of young doctors allow us to raise a question whether they need training of their communication skills in difficult situations, and psychological support to prevent emotional burnout.

Asking the questions about communication skills, researchers wanted to know how important patient-centred communication skills are for young doctors, how they assess their mastery of the skills and the communication training they received during the training process.

74.8% of the patients gave a negative answer to the question *"Do you agree with the statement that if a doctor is good at diagnosis and treatment, his/her communication skills do not matter while interacting with a patient?"*, indicating that the ability to communicate is very important for the respondents. Nevertheless, it should be noted that almost a quarter of doctors gave a positive answer to the question, which means that the ability to communicate is not important in the presence of good clinical skills and abilities. It should be noted that 28% of those who agree with the proposed statement nevertheless believe that their training in the field of communication is insufficient, which indirectly indicates that they do not take such skills as superfluous.

58.3% and 36.5% rated their communications skills as "good" and "satisfactory" respectively. Only a few considered their communication skills to be poor. It is obvious that awareness of insufficiency of one's communication skills can play a positive motivational role in learning effective communication.

The answers to the questions *"Are you familiar with the term "patient-centred consultation?"* and *"Have you seen examples of patient-centred communication in your practice?"* showed that the majority of respondents are familiar with the term (80.9%) and have seen such examples in their practice (76.5%), i.e. they imagine what it should look like. It can be assumed that this knowledge is the result of university education, when teachers of clinical disciplines passed on to students not only medical knowledge, but also cultural norms of communication with patients [14].

Probably, this can also explain the paternalistic attitudes of the respondents, which were revealed while answering the questions about how young doctors imagine an ideal patient and a relationship with him. 67% of respondents agreed that the ideal patient is laconic, ready to discuss the topic set by the doctor, and complies to treatment. This indicates that already during university studies, paternalism has penetrated into their ideas about what is proper in relationships with patients, and this will certainly hamper transition to patient-centred communication as a new norm.

Since an important aspect of patient-centred interaction includes rejection of gross paternalism, respect for patient autonomy and desire for joint decision-making, some of the questions were devoted to this topic. 83.5% of respondents i.e. the vast majority, gave a positive answer to the question *"Does discussion with the patient help to choose the best option for an examination and treatment plan?"*. Interestingly, that this percentage almost coincides with the proportion of doctors who, when asked what they would have spent extra time on during medical consultations, replied that they would have spent it on communicating with the patient. Based on the answers, it becomes clear that young doctors are aware of the lack of communication with the patient and consider it useful to increase the time that should be spent on it.

A patient-centred attitude includes caring for the patient, and therefore questions related to this aspect are included in the questionnaire. They allow us to judge whether young doctors practice patient care skills. So, in response to a question whether they touch patients while establishing contact, 79% of respondents provided a positive reply. However, in the male group, the proportion of practitioners with trusting touching is much lower and constitutes 22%. 64.3% gave a positive answer to the question *"Have you ever sought the help of family, nurse, colleagues in situations where a patient is experiencing stress or anxiety?"*. The proportion of men who answered "yes" was lower (32%) in this case as well.

CONCLUSIONS

A survey of young doctors showed that most of them are familiar with the concept of patient-centredness, have an idea of patient-centred relationships, respect their autonomy,

and practice such communication, including the use of patient-centred communication and caring skills. At the same time, many people feel vulnerable while communicating with the patient and unprepared for communication. Thus, it can be concluded that they are motivated to learn patient-centred communication skills.

At the same time, the answers to the questions revealed the presence of paternalistic attitudes among young doctors towards patients, most likely formed at the stage of university education, which may interfere with the spread of patient-centred practice. The introduction of patient centredness will require not only technical training in communication skills, but also the study of the moral foundations of patient-centred care in the framework of bioethics courses, as well as in the form of "hidden" curricula of clinical disciplines, when studying clinical issues, teachers form ideas among students and residents/graduate students about a proper, patient-centred attitude to the patient, which is considered as a new the moral norm.

Authors of the study realize that in order to get a better understanding of the attitude of young doctors towards patient-centredness, the group of respondents should be expanded. Also, in the upcoming study, it is necessary to determine the dynamics of formation of patient-centred attitudes among students in the process of university and postgraduate studies. This will make it possible to clarify approaches to the formation of training programs for future doctors.

Reference

1. Institute of Medicine (US) Committee on Quality of Health Care in America. Corporate Author. Crossing the Quality Chasm: A New Health System for the 21st Century M. Washington (DC): National Academies Press (US), 2001.
2. Epstein RM, Street RL. The values and value of patient-centered care. Ann Fam Med. 2011; 9 (2): 100–103.
3. McCormack LA, Treiman K, Rupert D, Williams-Piehota P, Nadler E, Arora NK, Lawrence William, Street RL. Measuring patient-centered communication in cancer care. A literature review and the development of a systematic approach. Social Science & Medicine. 2011: 72 (7): 1085–95. ISSN 0277-9536. DOI: 10.1016/j.socscimed.2011.01.020. Available from URL: https://www.sciencedirect.com/science/article/pii/S0277953611000633. (accessed: 07.10. 2024)
4. Olson AW, Stratton TP, Isetts BJ, Vaidyanathan R, Van Hooser JC, Schommer JC. Seeing the Elephant: A Systematic Scoping Review and Comparison of Patient-Centeredness Conceptualizations from Three Seminal Perspectives. Journal of Multidisciplinary Healthcare. 2021; 14:1297–1298. Available from URL: https://www.dovepress.com/journal-of-multidisciplinary-healthcare-journal (accessed: 01.06. 2021)
5. Rogers CR, Carl R. Client-Centered Therapy: Its Current Practice, Implications and Theory. Houghton Mifflin, 1951.
6. Balint E. The possibilities of patient-centred medicine. J R Coll Gen Pract. 1969; 17: 269–76.
7. Mead N, Bower P. Patient-centredness: A conceptual framework and review of the empirical literature. Social Science and Medicine. 2000; 51: 1087–1110.
8. Langberg EM, Dyhr L, & Davidsen AS. Development of the concept of patient-centredness — A systematic review. Patient Education and Counseling. 2019. DOI: 10.1016/j.pec.2019.02.023.
9. Duggan PS, Geller G, Cooper LA & Beach MC. The moral nature of patient-centeredness: Is it "just the right thing to do"? Patient Education and Counseling. 2006; 62(2): 271–76. DOI: 10.1016/j.pec.2005.08.001.
10. Safran DG, Taira DA, Rogers WH, Kosinski M, Ware JE, Tarlov AR. Linking primary care performance to outcomes of care. J Fam Pract. 1998; 47: 213–20.
11. Kaplan SH, Greenfield S, Ware Jr JE. Assessing the effects of physician–patient interactions on the outcomes of chronic disease. Med Care. 1989; 27: S110–27.
12. Hall JA, Roter DL, Katz NR. Meta-analysis of correlates of provider behavior in medical encounters. Med Care. 1988; 26: 657–75.
13. Kant I. Ethical philosophy: the complete texts of grounding for the metaphysics of morals, and metaphysical principles of virtue. Indianapolis: Hackett Publishing Company, 1983.
14. Hafferty FW. Beyond curriculum reform: confronting medicine's hidden curriculum. Acad Med. 1998; 73: 403–407.

Литература

1. Institute of Medicine (US) Committee on Quality of Health Care in America. Corporate Author. Crossing the Quality Chasm: A New Health System for the 21st Century M. Washington (DC): National Academies Press (US). 2001.
2. Epstein RM, Street RL. The values and value of patient-centered care. Ann Fam Med. 2011; 9 (2): 100–103.
3. McCormack LA, Treiman K, Rupert D, Williams-Piehota P, Nadler E, Arora NK, Lawrence William, Street RL. Measuring patient-centered communication in cancer care. A literature review and the development of a systematic approach. Social Science & Medicine. 2011: 72 (7): 1085–95. ISSN 0277-9536. DOI: 10.1016/j.socscimed.2011.01.020. Available from URL: https://www.sciencedirect.com/science/article/pii/S0277953611000633). (accessed: 07.10. 2024)
4. Olson AW, Stratton TP, Isetts BJ, Vaidyanathan R, Van Hooser JC, Schommer JC. Seeing the Elephant: A Systematic Scoping Review and Comparison of Patient-Centeredness Conceptualizations from Three Seminal Perspectives. Journal of Multidisciplinary Healthcare. 2021; 14: 1297–1298. Available from URL: https://www.dovepress.com/journal-of-multidisciplinary-healthcare-journal (accessed: 01.06. 2021)
5. Rogers CR, Carl R. Client-Centered Therapy: Its Current Practice, Implications and Theory. Houghton Mifflin, 1951.
6. Balint E. The possibilities of patient-centred medicine. J R Coll Gen Pract. 1969; 17: 269–76.
7. Mead N, Bower P. Patient-centredness: A conceptual framework and review of the empirical literature. Social Science and Medicine. 2000; 51: 1087–1110.
8. Langberg EM, Dyhr L & Davidsen AS. Development of the concept of patient-centredness — A systematic review. Patient Education and Counseling. 2019. DOI: 10.1016/j.pec.2019.02.023
9. Duggan PS, Geller G, Cooper LA & Beach MC. The moral nature of patient-centeredness: Is it "just the right thing to do"? Patient Education and Counseling. 2006; 62(2): 271–76. DOI: 10.1016/j.pec.2005.08.001.
10. Safran DG, Taira DA, Rogers WH, Kosinski M, Ware JE, Tarlov AR. Linking primary care performance to outcomes of care. J Fam Pract. 1998; 47: 213–20.
11. Kaplan SH, Greenfield S, Ware Jr JE. Assessing the effects of physician–patient interactions on the outcomes of chronic disease. Med Care. 1989; 27: S110–27.
12. Hall JA, Roter DL, Katz NR. Meta-analysis of correlates of provider behavior in medical encounters. Med Care. 1988; 26: 657–75.
13. Kant I. Ethical philosophy: the complete texts of grounding for the metaphysics of morals, and metaphysical principles of virtue. Indianapolis: Hackett Publishing Company, 1983.
14. Hafferty FW. Beyond curriculum reform: confronting medicine's hidden curriculum. Acad Med. 1998; 73: 403–407.

ETHICAL ASPECTS OF COUNSELING PEOPLE WITH MENTAL DISORDERS WHO ARE PLANNING THEIR PREGNANCY

Lobanova IV, Sataev AE, Manaeva TA ✉

Yaroslavl State Medical University, Yaroslavl, Russia

This article highlights the ethical aspects that arise when the attending psychiatrist communicates with patients and their family members on the issues of planning a pregnancy. While counseling people with mental disorders about their reproductive plans, it is difficult from an ethical point of view to discuss some issues such as the risks of pathology in an unborn child and a possibility of reducing the risks, in particular the probability of genetic inheritance of a mental disorder; the expediency of discontinuing psychotropic drugs used by the expectant mother and/or father to treat or prevent a mental disorder exacerbations, given that drugs can affect the quality of reproductive biological material, whereas cancellation of therapy is associated with risks to the mental health of expectant parents; the need to inform the patient's family members about his/her mental disorder, the treatment used and all available personal risks to offspring. Different literature sources, including domestic and foreign ones, were reviewed. The keywords used in literature were "genetics", "psychiatry", "ethical aspects of genetic counseling", "psychopharmacotherapy during pregnancy", "the effect of psychotropic drugs on spermatogenesis" with filtering by language (Russian and English) and document type. Two own clinical observations are presented. The purpose of the article is a comprehensive analysis of ethical aspects of counseling people with mental disorders on pregnancy planning by a psychiatrist.

Keywords: genetic counseling, ethical aspects of counseling, pregnancy planning, psychotropic drugs

✉ **Correspondence should be addressed:** Tatyana A. Manaeva

Yakovlevsky passage, 1, b. 25, Yaroslavl, 152280, Russia; manaeva002@gmail.com

Received: 13.11.2024 **Accepted:** 05.12.2024 **Published online:** 23.12.2024

DOI: 10.24075/medet.2024.025

ЭТИЧЕСКИЕ АСПЕКТЫ КОНСУЛЬТИРОВАНИЯ ЛИЦ С ПСИХИЧЕСКИМИ РАССТРОЙСТВАМИ ПРИ ПЛАНИРОВАНИИ ДЕТОРОЖДЕНИЯ

И. В. Лобанова, А. Е. Сатаев, Т. А. Манаева ✉

Ярославский государственный медицинский университет, Ярославль, Россия

В данной статье освещаются этические аспекты, возникающие при общении лечащего врача-психиатра с пациентами и членами их семей по вопросам планирования деторождения. В ходе консультирования лиц с психическими расстройствами по поводу их репродуктивных планов сложным с этической точки зрения оказывается обсуждение следующих вопросов: риски возникновения патологии у будущего ребенка и возможности их снижения, в частности вероятность генетического наследования психического расстройства; целесообразность отмены психотропных препаратов, применяемых будущими матерью *и/или* отцом для лечения психического расстройства или профилактики его обострения, учитывая, что лекарственные средства могут влиять на качество репродуктивного биологического материала, а отмена терапии сопряжена с рисками для психического здоровья будущих родителей; необходимость информирования членов семьи пациента об имеющемся у него/нее психическом расстройстве, применяемом лечении и всех имеющихся персональных рисках для потомства. Проведен обзор литературы, включая отечественные и иностранные источники. Поиск литературы осуществлялся по ключевым словам, таким как «генетика», «психиатрия», «этические аспекты генетического консультирования», «психофармакотерапия при беременности», «влияние психотропных препаратов на сперматогенез» с фильтрацией по языку (русский и английский) и типу документа. Представлены два собственных клинических наблюдения. Целью статьи является разносторонний анализ этических аспектов консультирования психиатром лиц с психическими расстройствами по вопросам планирования беременности.

Ключевые слова: генетическое консультирование, этические аспекты консультирования, планирование деторождения, психотропные препараты

✉ **Для корреспонденции:** Татьяна Алексеевна Манаева

Яковлевский проезд, д. 1, к. 25, г. Ярославль, 152280, Россия; manaeva002@gmail.com

Статья поступила: 13.11.2024 **Статья принята к печати:** 05.12.2024 **Опубликована онлайн:** 23.12.2024

DOI: 10.24075/medet.2024.025

Modern possibilities of psychopharmacology, medical and psychological support, rehabilitation of people with mental disorders reach the level with a desire for a high quality of life, including such aspects as maintaining working capacity, a possibility of full-fledged independent functioning, and building personal and intra-family relationships. The issue of childbearing potential becomes relevant as well.

In recent years, more and more patients with various mental disorders have turned to a psychiatrist for advice, planning to conceive a child, wanting to know the existing risks for themselves and for their future children and the possibilities of reducing the risks. In this article, the issues of counseling by a psychiatrist of patients with preserved critical abilities, including those treating their existing mental disorder critically, are discussed.

It is well known that most mental disorders have a hereditary component in their etiology. Despite the fact that a significant number of mental health professionals believe that mental disorders are genetic in nature, most patients report that psychiatrists have never discussed ethical issues of psychiatric genetics with them. This contrasts with the data that in the families of a large number of patients there were questions related to genetics of mental disorders, and that almost half of the patients were worried about transmission of a mental disorder to their offspring [1]. Consultation of patients on the issues of psychiatric genetics should be aimed at providing accessible information about the genetic

risk of mental disorders, at communicating theses about their multifactorial polygenic nature, and eliminating misconceptions about the causes of their occurrence [2]. The same variations in the number of copies of genes can occur in different mental disorders, i.e. variations in a number of copies of genes predispose to a number of neuropsychiatric disorders [3]. Multiple single nucleotide polymorphisms rather emphasize the tendency to neuropsychiatric diseases than being a marker of a specific disease [4]. The phenotypic consequences of single nucleotide polymorphisms depend on the genetic background of the individual. Since mental illnesses are multifactorial and polygenetic, it is impossible to talk about a high risk of mental disorders in a patient based only on the data of genetic testing. The circumstance should be stressed while communicating with patients and their families. It is necessary to show incompleteness of genetic knowledge to date, as well as make it clear to patients that quantitative data on the risk of developing mental disorders obtained in epidemiological studies cannot be extrapolated to the personal risk of developing psychopathology in the patient, his relatives and planned children [5]. After all, individually, the most common genetic variants have an extremely insignificant effect size for development of mental disorders [6].

The European Psychiatric Association's policy document on ethical aspects of communication with patients and their families (Carpiniello B, Wasserman D, 2020) postulates the following key rules for psychiatrists in genetic counseling.

- Take special care while communicating with patients and families about genetic risks and provide updated information on the current state of affairs in this area.
- Make it clear that modern genetic knowledge is still incomplete, as it is an evolving scientific field and future results may change our existing ideas.
- Remember that disclosure of the results can cause negative and destructive effects not only in patients, but also in other family members.
- Discuss with the patient the possibility of sharing genetic information with family members and obtain explicit consent to disclosure of this information.
- Counselors should consider ethical implications of disclosing genetic information and complexity of the psychological consequences and be prepared to offer psychotherapeutic support as part of the counseling process.
- Genetic counseling on the issues of planning of family and abortions should include all the information necessary to help patients make decisions; in these cases, psychiatrists should treat values and decisions of patients with special respect [7].

In addition to genetic predisposition, factors associated with adverse environmental influences are definitely essential in the development of mental disorders, which must be taken into account and discussed when advising patients on childbearing planning, since some of these risks are modifiable. Epigenetic mechanisms imply that certain genes can either manifest under the influence of external causes, or be suppressed in the process of ontogenesis. It depends on many factors whether the alleged inherited genetic disorders of offspring will manifest or not. An important role is played by living conditions, environmental problems, poor nutrition, physical inactivity, stress, and disharmonious upbringing. Thus, the social status and psychological microclimate of the family are important. The latter is vulnerable in the presence of a mental disorder in one or both parents, possibility of financial and other support from relatives and other surroundings.

An increased likelihood of developing a mental disorder may also be due to medical and biological influences, the effect of damaging factors on gamete, embryo, and fetus. For example, the use of alcohol, cannabinoids and other psychoactive substances by future parents and smoking will significantly increase the risk of psychopathology in offspring. It is necessary to discuss the unequivocal exclusion of these harmful effects with patients. However, drugs can produce a damaging effect as well. It is difficult for a doctor to decide on withdrawal of a drug by a woman while planning pregnancy in order to prevent a risk to the health of the fetus or newborn (the danger of the formation of congenital malformations, pre- and neonatal complications, etc.). Psychotropic drugs can penetrate through placenta and have an adverse effect on the fetus. The constant use of drugs by a pregnant woman can lead to drug dependence of the fetus and ultimately to withdrawal syndrome in a newborn [8].

There are three classes of teratogenicity of psychotropic drugs: class A — teratogenicity in animals is absent, there are no studies of the risk of teratogenicity in humans or teratogenicity in animals has been established, but is absent in humans; class B — teratogenicity in animals has been established, there are no studies of the risk of teratogenicity in humans or there are no studies of the risk of teratogenicity in both animals and humans; class B — teratogenicity has been proven, but the benefits associated with prescribing drugs sometimes exceed the risk (for example, in a life-threatening situation) [8].

Obviously, psychotropic drugs taken during conception and pregnancy would increase potential prenatal risks to the fetus. Thus, withdrawal of the medications is desirable. However, when choosing such an alternative (the proportion of benefit to the mother and potential risk to the child), it is necessary to take into account a number of other circumstances, including the influence of the mother's mental state on her quality of life, the ability to carry out pregnancy and take further care of the newborn, as well as the possibility of a negative impact of severe mental state of the mother during pregnancy on the fetus development. The issue of the use of psychotropic drugs during gestation should be solved individually after careful consideration of the benefit/risk of pharmacotherapy and its absence. When choosing therapy for pregnant women with chronic mental disorders in stable remission, it is recommended to take into account, in particular, the frequency of previous episodes, age, family situation, and the possibility of providing care to a newborn in case of relapse in the mother [9].

Another aspect that requires discussion and an informed decision is the use of psychotropic drugs by the future father. Many psychotropic drugs produce undesirable effects on sexual function, spermatogenesis and ejaculate quality. In January 2024, the safety committee of the European Medicines Agency (EMA) recommended precautionary measures regarding the potential risk of neurodevelopmental disorders in children born to men who took valproate. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has introduced stricter precautions, warning against prescribing valproate to people under 55 years of age [10]. The use of selective serotonin reuptake inhibitors (SSRIs) is common among men of reproductive age. There are studies indicating a decrease in sperm parameters among men taking SSRIs: an increase in the number of single-strand and double-strand breaks in the DNA molecule. There is also a drop in sperm concentration and motility [11]. Other antidepressants that regulate serotonin, norepinephrine and/or dopamine levels in synapses may have toxic effects similar to SSRIs, but most

of them have not been studied as far as this subject goes. Most antipsychotic drugs contribute to an increase in prolactin levels, a decrease in testosterone levels and cause side effects related to sexual function [12]. For some drugs, the effect of their administration on sperm quality has not been sufficiently investigated. In order to avoid an increase in risk factors for the fetus, it is advisable for the future father to stop taking drugs for about three months before the planned conception, since during this period the ejaculate indicators practically return to their initial values. In the studies of Tanrikut S, improvement in sperm quality was observed 1–2 months after drug withdrawal [13]. However, when making such a decision, it should be borne in mind that in many cases the risk of deterioration of a man's mental state increases, exacerbation of symptoms in chronic mental disorder, which will certainly negatively affect his health and quality of life, may entail a more or less significant change in social status and working capacity, cause financial problems and generally worsen the psychological climate in the family.

When consultation is looked for by one of the spouses, the issue of informing the partner is difficult from an ethical point of view. The right of patients to confidentiality of data concerning their health in general and mental health in particular is recognized by law. However, in case of pregnancy planning, there is the following opinion: the patient's family members should be informed about genetic and other risks (for example, those associated with taking psychotropic drugs), in possible development of a disease in relatives, and burdening relatives with caring for a family member at risk of developing a mental illness [14]. However, it is worth considering that within the family, this information can provoke conflicts, which in turn is an epigenetic risk.

The patient's right to receive personal information about his diagnosis is generally recognized [15]. At the same time, patients have the right not to know about their diagnosis if they do not wish to do so.

The "right not to know" should be applied ethically to stigmatization-related disorders [16]. However, when the patient/patient seeks advice on planning the conception of a child, it becomes necessary to more clearly identify his/her mental health problems and estimated prognosis of his/her further development. If the patient is ready to discuss all these issues, the specialist should competently approach their disclosure. It is necessary to assess whether the patient feels comfortable enough, whether he is in an acute condition or experiencing serious worries at the moment. It is important to take into account the cultural aspect, which also plays an important role. The specialist should find out how well the patient is familiar with the nature of mental disorders, their determinants, the contribution of genetics to the disease [17], based on the data obtained, provide information and hold discussions, respond sensitively to patients' emotions in connection with the news they receive, respond to individual needs, providing additional opportunities to discuss the problem and related issues [18].

Here are some clinical observations.

CLINICAL EXAMPLES

Observation 1

Male, 36 years old. Diagnosis: bipolar affective disorder type II, drug-induced remission.

Higher education. He works as a programmer, has a good income, but changes jobs every year.

He neither smokes nor drinks alcohol.

He has been married for 10 years, and has been raising a 9-year-old daughter. Family relations are currently stable and trusting.

There is a history of psychopathology hereditary burden, recurrent depressive disorder in his sister.

The patient has been under supervision of a psychiatrist for five years (since the age of 31), episodes of moderate depression are noted annually, mainly in autumn and winter, lasting about a month, phase inversion was recorded twice, hypomanic episodes lasting for about two weeks. During the last year, pharmacological remission has been observed, two weeks ago he canceled treatment independently as he was planning conception of the second child.

His wife does not have chronic mental disorders, she previously contacted a psychotherapist about an anxiety-depressive state associated with an adaptation disorder, currently has no complaints, does not take psychotropic drugs. He works in the civil service, has a stable income. The spouse is aware of her husband's existing mental disorder and the treatment he is receiving.

The 9-year-old daughter is studying in the 3rd grade of secondary school. She had no mental health problems at preschool age. While studying in the 1–2 grade, she needed psychological support due to emotional and behavioral disorders, including problems of interaction with her father, partly due to his unstable mental state.

They required a consultation to discuss reproductive plans. The patient and his spouse wanted to ask if it was possible to inherit the father's mental disorder, and discuss the benefits and risks of canceling supportive treatment.

During the conversation with the patient and his wife, the attending physician identified existing genetic risk factors, given that BAR refers to endogenous mental disorders and there is a hereditary burden in the patient. However, the impossibility of unambiguous prediction of risks for a particular child was emphasized, the multifactorial polygenic nature of mental disorders and the importance of epigenetic factors were explained. When deciding on the birth of the second child in this family, it is necessary to keep in mind the uncertain prognosis regarding further development of a mental disorder in the father, possible difficulties associated with raising a child, given the psychological problems that have already arisen in the eldest daughter. Financial and economic difficulties may also arise due to the unstable labor potential of the patient. The main issue discussed at the consultation concerned modifiable risk factors related to the use of psychotropic drugs by the father. Considering that the patient had independently stopped maintenance therapy before the consultation, a joint decision was made not to resume taking drugs for three months. The attending physician explained the high probability of deterioration of the patient's mental state, and made an observation plan with an increased frequency of visits. The patient's condition destabilized after a month, and it was necessary to resume psychopharmacotherapy. The final decision on the conception of a child is made by the family independently, taking into account all the risks and a variety of personal motivations (cultural, social, etc.).

Observation 2

Female, 28 years old. Diagnosis: recurrent depressive disorder.

Higher education. She works as a self-employed math tutor.

She doesn't smoke. She does not drink alcohol.

Married for three years, no children. She has a friendly relationship with her husband, but there is not enough trust.

Heredity is not psychopathologically burdened.

He has been observed by a psychiatrist for four years, there were two depressive episodes with a pronounced anxiety component that required observation in a day hospital of a psychiatric clinic. During the year, the condition is stable, remission is of good quality, and supportive treatment is provided.

She applied for a consultation in connection with pregnancy planning. She is observed by a gynecologist and endocrinologist for pituitary microadenoma, hyperprolactinemia. Hormonal therapy is being provided, including that aimed at preparing for pregnancy.

It is known that her husband has a higher education and is stably employed. The family is financially secure.

The patient categorically refuses to tell her husband about her mental health problems and that she is taking psychotropic drugs, believing that he will not be able to understand her problems and intra-family conflicts will arise. From an ethical point of view, the issue of whether it is necessary and possible for the attending physician to inform the father of the unborn child about all the risks identified in this article is difficult and debatable. The patient's reproductive plans are clearly outlined, preparations for pregnancy are being carried out under the supervision of a gynecologist, the only relevant question for her sent to a psychiatrist concerned the assessment of the benefits/risk of withdrawal/continuation of psychopharmacotherapy. Despite the assumed high risk of relapse of depression, taking into account all the circumstances, a joint decision was made to gradually cancel medications and increase the frequency of visits to the attending psychiatrist. The pregnancy occurred two months later. Remission persisted until 22 weeks of gestation. In the future, anxiety and depression were developed. Taking into account the ratio of benefit to the mother and risk to the fetus, treatment with a SSRIs antidepressant is prescribed, which can be used during pregnancy. Gradually, a drug-induced remission was achieved. The issue of prolongation of psychopharmacotherapy was raised repeatedly during the further management of the patient, a joint decision was made to continue taking an antidepressant drug, informing the obstetrician-gynecologist hereof, and additional psychological support was provided. Childbirth and the postpartum period proceeded without complications in the mother and the newborn. Further, it became necessary to solve the dilemma with continuation/cancellation of supportive treatment during the lactation period. The patient decided to artificially feed the newborn. During catamnestic observation, the patient has been into remission for two years, successfully taking care of and upbringing the child.

CONCLUSIONS

Despite the ethical complexity, treating psychiatrists need to discuss reproductive plans with their patients. The data of fundamental science should be reasonably translated into understandable theses on the genetics of mental disorders. The expectant mother or father should take a joint and balanced decision on the issue of prolongation/ cancellation of psychopharmacotherapy, taking into account all possible risks and benefits. While counseling patients with mental disorders who are planning a pregnancy, the doctor is required to exercise a delicate approach and choose correct wording, taking into account the individual characteristics of the patient's personality, mental state, intra-family relationships, and readiness to discuss certain issues at the present moment.

References

1. Martorell L, Sanfeliu A, Blázquez A, Lojo E, Cortés MJ, de Pablo J, Vilella E. Genetics and genetic counseling in psychiatry: Results from an opinion survey of professionals and users. Mol Genet Genomic Med. 2019 Aug; 7(8): e830. DOI: 10.1002/mgg3.830. Epub 2019 Jun 29. PMID: 31254460; PMCID: PMC6687663.
2. Torrey EF, Yolken RH. Toxoplasma gondii and schizophrenia. Emerg Infect Dis. Date cited Nov 2003. Available from: URL: http://www.cdc.gov/ncidod/EID/ vol9no11/03-0143.htm (accessed: 24.10.2024)
3. Gudmundsson OO. Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. Translation Psychiatre 9(1). DOI:10.1038/s41398-019-0599-y.
4. Bosia M, Pigoni A, Cavallaro R. Genomics and epigenomics in novel schizophrenia drug discovery: translating animal models to clinical research and back. Expert Opin. Drug Disc. 2015; 10 (2): 125–139. DOI: 10.1517/17460441.2015.976552.
5. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet. 2003; 123: 48–58.
6. Schmitt A, Malchow B, Hasan A, Fallkai P. The impact of environmental factors in severe psychiatric disorders. Frontiers in Neuroscience. February 2014. DOI: 10.3389/fnins.2014.00019
7. Carpiniello B, Wasserman. European Psychiatric Association policy paper on ethical aspects in communication with patients and their families. European Psychiatry. 2020; 63(1): e36, 1–7. DOI: 10.1192/j.eurpsy.2020.33
8. Smulevich AB. Depressii v obshchey meditsine: Rukovodstvo dlya vrachey. Meditsinskoye informatsionnoye agentstvo, 2007; 256 s. ISBN: 5-89481-103-1. Russian.
9. Neznanova NG, Mazo GE. Taktika vracha-psikhiatra: prakticheskoye rukovodstvo. GEOTAR-Media. 2022; 232 s. ISBN: 978-5-9704-6570-7. Russian.
10. Garey JD,Damkier P Scialli AR, et al. Paternal Valproate Treatment and Risk of Childhood Neurodevelopmental Disorders: Precautionary Regulatory Measures Are Insufficiently Substantiated. Birth Defects Res. Aug 2024; 116(8): e2392. DOI: 10.1002/bdr2.2392.
11. Safarneiad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis andsperm chromatin structure assay. J Urol. 2008; 180(5): 2124–2128.
12. Drobnis EZ, Nangia AK. Psikhotropnyye preparaty i muzhskaya reproduktsiya. 2017; 1034: 63–101. Russian.
13. Tanrekut C, Schlegel P. Antidepressant-associated changes in semen parameters. J Urol. 2007; 69(1): 185–187.
14. Doukas DJ, Berg JW, The Family Covenant and Genetic Testing. American Journal of Bioethics. 2001; 1(3): 2–10.
15. Milton AC, Mullan BA. Communication of a mental health diagnosis: a systematic synthesis and narrative review. Journal of Mental Health. 2014; 23(5): 261–270. DOI:10.3109/09638237.2014.951474.
16. Bortolotti L, Widdows H. The right not to know: the case of psychiatric disorders. J Med Ethics. 2011; 37: 673–6.
17. Milton AC, Mullan BA, Hunt C. Information giving challenges and support strategies at the time of a mental health diagnosis: qualitative views from Australian health professionals. Soc Psychiatry Psychiatr Epidemiol. 2016; 51: 735–46.
18. Milton AC, Mullan B. Views and experience of communication when receiving a serious mental health diagnosis: satisfaction levels, communication preferences and acceptability of the SPIKES protocol. J Ment Health. 2017; 26: 395–404.

Литература

1. Martorell L, Sanfeliu A, Blázquez A, Lojo E, Cortés MJ, de Pablo J, Vilella E. Genetics and genetic counseling in psychiatry: Results from an opinion survey of professionals and users. Mol Genet Genomic Med. 2019 Aug; 7(8): e830. DOI: 10.1002/mgg3.830. Epub 2019 Jun 29. PMID: 31254460; PMCID: PMC6687663.
2. Torrey EF, Yolken RH. Toxoplasma gondii and schizophrenia. Emerg Infect Dis. Date cited Nov 2003. Available from: URL: http://www.cdc.gov/ncidod/EID/ vol9no11/03-0143.htm (accessed: 24.10.2024)
3. Gudmundsson OO. Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. Translation Psychiatre 9(1). DOI:10.1038/s41398-019-0599-y.
4. Bosia M, Pigoni A, Cavallaro R. Genomics and epigenomics in novel schizophrenia drug discovery: translating animal models to clinical research and back. Expert Opin. Drug Disc. 2015; 10 (2):125–139. DOI: 10.1517/17460441.2015.976552.
5. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet. 2003; 123: 48–58.
6. Schmitt A, Malchow B, Hasan A, Fallkai P. The impact of environmental factors in severe psychiatric disorders. Frontiers in Neuroscience. February 2014. DOI: 10.3389/fnins.2014.00019
7. Carpiniello B, Wasserman. European Psychiatric Association policy paper on ethical aspects in communication with patients and their families. European Psychiatry. 2020; 63(1): e36, 1–7 DOI: 10.1192/j.eurpsy.2020.33.
8. Смулевич А. Б. Депрессии в общей медицине: Руководство для врачей. Медицинское информационное агентство. 2007; 256 с. ISBN: 5-89481-103-1.
9. Незнанова Н. Г., Мазо Г. Э. Тактика врача-психиатра: практическое руководство. ГЭОТАР-Медиа. 2022; 232 с. ISBN: 978-5-9704-6570-7.
10. Garey JD,Damkier P Scialli AR, et al. Paternal Valproate Treatment and Risk of Childhood Neurodevelopmental Disorders: Precautionary Regulatory Measures Are Insufficiently Substantiated. Birth Defects Res. Aug 2024; 116(8): e2392. DOI: 10.1002/bdr2.2392.
11. Safarneiad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis andsperm chromatin structure assay. J Urol. 2008;180(5): 2124–2128.
12. Дробнис Э. З., Нангиа А. К. Психотропные препараты и мужская репродукция. 2017; 1034: 63–101.
13. Tanrekut C, Schlegel P. Antidepressant-associated changes in semen parameters. J Urol. 2007; 69(1): 185–187.
14. Doukas DJ, Berg JW, The Family Covenant and Genetic Testing. American Journal of Bioethics. 2001; 1(3): 2–10.
15. Milton AC, Mullan BA. Communication of a mental health diagnosis: a systematic synthesis and narrative review. Journal of Mental Health. 2014; 23(5): 261–270. DOI:10.3109/09638237.2014.951474.
16. Bortolotti L, Widdows H. The right not to know: the case of psychiatric disorders. J Med Ethics. 2011; 37: 673–6.
17. Milton AC, Mullan BA, Hunt C. Information giving challenges and support strategies at the time of a mental health diagnosis: qualitative views from Australian health professionals. Soc Psychiatry Psychiatr Epidemiol. 2016; 51: 735–46.
18. Milton AC, Mullan B. Views and experience of communication when receiving a serious mental health diagnosis: satisfaction levels, communication preferences and acceptability of the SPIKES protocol. J Ment Health. 2017; 26: 395–404.

ANTIRHEUMATIC ACTIVITY OF 3-IMIDAZOLE-SUBSTITUTED-4,5-DIARYLOISOXAZOL-3-CARBOXYLIC ACID AMIDE DERIVATIVE, A PROTEINASE INHIBITOR-ACTIVATED TYPE II RECEPTOR

Fedorov VN[1,2], Korsakov MK[1], Shetnev AA[1,2], Grechischeva OV[1,2], Vdovichenko VP[3], Volkhin NN[1,2] ✉, Smirnov NA[2], Khokhlova AA[4], Arshinov AV[3]

[1] Yaroslavl State Pedagogical University named after KD Ushinsky, Yaroslavl, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

[3] Grodno State Medical University, Grodno, Belarus

[4] Russian University of Medicine, Moscow, Russia

Treatment of rheumatoid arthritis is a complex and time-consuming process that does not always lead to significant results both due to poor effectiveness of drugs and drug toxicity. It means we need to search for new pharmacological targets to influence the pathological process, one of which is inhibition of proteinase-activated receptors 2 (PAR2 receptors) activity. In 2016–2019, synthesis of low-molecular-weight antagonists of PAR2 receptors belonging to 4,5-dihydroisoxazole-5-carboxamide derivatives was carried out, and in 2023 their anti-inflammatory efficacy was examined using the formaldehyde edema model. The most effective laboratory R004 compound was tested on a model of autoimmune pristane-induced inflammation in rats. During treatment of chronic inflammation in rats, R004 inhibited significant development of edema of feet, damage to small joints, and specific changes in the formula of white blood, and according to biochemical blood test led to normalization of liver and kidney functions and energy metabolism. R004 turned out to be more effective and safer than the comparator drugs such as diclofenac sodium and dexamethasone.

Keywords: rheumatoid arthritis, PAR2-receptors, pristane, autoimmune inflammation, 4,5-dihydroisoxazole-5-carboxamide amide derivative

Compliance with ethical standards: the study was carried out in compliance with all ethical standards recommended in the Russian Federation. Rats were selected as a test system, as animals with a minimum set of characteristics that make it possible to conduct an experiment: a sufficient size of paws for convenient measurements and possibility of taking the volume of blood necessary for the study. The animals were kept in cages of sufficient area and with timely bedding change (2 times a week). Animals are provided with free access to water and food, a 12-hour lighting cycle, optimal temperature and humidity, and supervision by a licensed veterinarian. Although the research protocol did not allow to use painkillers that could distort the results of experiments, all procedures were carried out by qualified and experienced personnel, which ensured minimization of stress and pain. The animal study was preceded by *in vitro* studies of the drug. The power of the statistical tests used was evaluated, which made it possible to form samples of an optimal size. The animal study was approved by the Independent Ethical Committee of the Federal State Budgetary Educational Institution of Higher Education Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 6 dated 09/14/2023.

Funding: this study was supported by the Ministry of Health of the Russian Federation (state assignment 1022051600008-9-3.1.5;3.2.22) “Development of a drug for the treatment of rheumatoid arthritis and other inflammatory diseases”.

Author contribution: Fedorov VN — idea development, analysis and layout of the collected material; Korsakov MK — writing the text; Shetnev AA — a general idea and planning of the article, synthesis of the compound under study; Grechishcheva OV — conducting an experiment; Vdovichenko VP — collection and primary analysis of material, working with literature; Volkhin NN — conducting an experiment; Smirnov NA — primary analysis of the collected material; Khokhlova AA — collection of primary material, design of the list of references; Arshinov AV — text editing.

Acknowledgement: the work was carried out in collaboration with the Scientific Department of the Institute of Pharmacy of Yaroslavl State Medical University, Yaroslavl.

✉ **Correspondence should be addressed**: Nikita N Volkhin
Technopark str., 11/2, Yaroslavl, 150030, Russia; nnvolkhin@ysmu.ru

Received: 29.10.2024 **Accepted:** 15.11.2024 **Published online:** 13.12.2024

DOI: 10.24075/medet.2024.022

ПРОТИВОРЕВМАТИЧЕСКАЯ АКТИВНОСТЬ ПРОИЗВОДНОГО АМИДА 3-ИМИДАЗОЛ-ЗАМЕЩЕННОЙ-4,5-ДИГИДРОИЗОКСАЗОЛКАРБОНОВОЙ КИСЛОТЫ — ИНГИБИТОРА ПРОТЕИНАЗА-АКТИВИРОВАННОГО РЕЦЕПТОРА II ТИПА

В. Н. Федоров[1,2], М. К. Корсаков[1], А. А. Шетнев[1,2], О. В. Гречищева[1,2], В. П. Вдовиченко[3], Н. Н. Вольхин[1,2] ✉, Н. А. Смирнов[2], А. А. Хохлова[4], А. В. Аршинов[3]

[1] Ярославский государственный педагогический университет им. К. Д. Ушинского, Ярославль, Россия

[2] Ярославский государственный медицинский университет, Ярославль, Россия

[3] Гродненский государственный медицинский университет, Гродно, Беларусь

[4] Российский университет медицины, Москва, Россия

Лечение ревматоидного артрита является сложным и длительным процессом, не всегда приводящим к значимым результатам как в следствие недостаточной эффективности препаратов, так и их лекарственной токсичности для человека. Это диктует поиск новых фармакологических мишеней воздействия на патологический процесс, одной из которых является блокада активности протеиназа-активированных рецепторов 2 типа (proteinase-activated receptors, II) — PAR2-рецепторов. В течение 2016–2019 гг. был осуществлен синтез низкомолекулярных антагонистов PAR2-рецепторов, относящихся к производным 4,5-дигидроизоксазол-5-карбоксамида, а в 2023 г. была доказана их противовоспалительная эффективность на модели формалинового отека. Наиболее эффективное соединение с лабораторным шифром R004 было испытано на модели аутоиммунного воспаления у крыс, вызванного пристаном. Применение соединения R004 в терапии хронического воспаления у крыс препятствовало значимому развитию отека стоп и поражению мелких суставов, предупреждало специфические изменения формулы белой крови, а по данным биохимического исследования крови приводило к нормализации функций печени и почек и энергетического обмена организма. Соединение R004 оказалось более эффективно и безопасно, чем препараты сравнения диклофенак натрия и дексаметазон.

Ключевые слова: ревматоидный артрит, PAR2-рецепторы, пристан, аутоиммунное воспаление, производное 4,5-дигидроизоксазол-5-карбоксамида

Соблюдение этических стандартов: исследование выполнено с соблюдением всех этических стандартов, рекомендованных в Российской Федерации. В качестве тест-системы были выбраны крысы, как минимально удовлетворяющие по своим характеристикам животные для возможности проведения эксперимента: достаточный размер лап для удобства измерений и возможность забора необходимого для исследования объема крови. Животные содержались в клетках достаточной площади и с своевременной сменой подстила (2 раза в неделю). Животным обеспечен свободный

доступ к воде и пище, 12-часовой цикл смены освещения, оптимальные температура и влажность, наблюдение лицензированного ветеринара. Хотя протокол исследования не позволял применения обезболивающих препаратов, способных исказить результаты экспериментов, все процедуры проводились квалифицированным и опытным персоналом, что обеспечило минимизацию стресса и болезненных ощущений. Настоящему исследованию на животных предшествовали исследования препарата *in vitro.* Проведена оценка мощности используемых статистических тестов, что позволило сформировать оптимальные по размеру выборки. Исследование на животных одобрено независимым этическим комитетом Федерального государственного бюджетного образовательного учреждения высшего образования «Ярославский государственный медицинский университет» Министерства здравоохранения Российской Федерации, протокол от 14.09.2023 № 6.

Финансирование: данное исследование было поддержано Министерством здравоохранения Российской Федерации (государственное задание 1022051600008-9-3.1.5;3.2.22) «Разработка лекарственного препарата для лечения ревматоидного артрита и других воспалительных заболеваний».

Вклад авторов: В. Н. Федоров — разработка идеи, анализ и компоновка собранного материала; М. К. Корсаков — написание текста; А. А. Шетнев — общая идея и планирование статьи, синтез исследуемого соединения; О. В. Гречищева — проведение эксперимента; В. П. Вдовиченко — сбор и первичный анализ материала, работа с литературой; Н. Н. Вольхин — проведение эксперимента; Н. А. Смирнов — первичный анализ собранного материала; А. А. Хохлова — сбор первичного материала, оформление списка литературы; А. В. Аршинов — редактирование текста.

Благодарности: работа выполнена в содружестве с научным отделом Института фармации Ярославского государственного медицинского университета, Ярославль.

✉ **Для корреспонденции:** Никита Николаевич Вольхин
ул. Технопарковая, д. 11/2, г. Ярославль, 150030, Россия; nnvolkhin@ysmu.ru

Статья поступила: 29.10.2024 **Статья принята к печати:** 15.11.2024

Опубликована онлайн: 13.12.2024

DOI: 10.24075/medet.2024.022

Rheumatoid arthritis (RA) is an incurable immune-mediated inflammatory disease with a multifactorial etiology, which affects up to 1.0% of the world's population [1], with its prevalence being increased with age. According to official statistics, more than 300 thousand patients with RA were registered in Russia in 2017 [2]. Its progression leads to joint deformities, destruction of cartilage and bone tissue and subsequent disability.

Currently, treat-to-target (T2T) has been established as a guiding principle for the treatment of RA [2, 3]. It does not recommend any specific drugs, but only gives general treatment recommendations. The primary therapeutic goal for RA is to achieve remission [2]. For this purpose, several classes of drugs are used such as disease-modifying anti-rheumatic drug (DMARDs), which constitute an extensive group of synthetic and biological drugs that have a common ability to influence the pathogenetic mechanisms of RA; glucocorticoids, which are recommended to be used in combination with DMARDs, and nonsteroidal anti-inflammatory drugs used to relieve acute and chronic pain [4].

Treatment of rheumatoid arthritis is a long process, and the drugs used to treat it are far from being safe and significantly effective. In average, 20–50% of patients are forced to discontinue therapy due to lack of efficacy or intolerance to prescribed medications [5]. Therefore, there is an urgent need to develop new pharmacological targets, which would increase the effectiveness and reduce the toxicity of the drugs used.

One of the promising therapeutic targets includes proteinase-activated receptors (PARs). They belong to the class of G-protein-coupled receptors (GPCRs). Irreversible activation by proteases is the specific feature of these receptors. Discovered in the 1990s, 4 forms of PARs (PAR1, PAR2, PAR3 and PAR4) are expressed on the cell membrane of almost all organs and systems and regulate numerous physiological functions, including contraction of smooth muscle cells, sensitivity to pain, release of lipid mediators, cytokines, and neuropeptides. Activation of PAR2 is associated with clinical manifestations in the form of inflammation, swelling, and pain. They are expressed in immune cells of both the innate and adaptive immune systems and play an important role in the development of a wide range of diseases [6]. Their activation contributes to the occurrence of inflammation, fibrosis and proliferation of connective tissue. Experiments have demonstrated that inhibition of PAR2 activity prevents the development of RA pathogenesis and positively modifies the course of the disease [6]. The drugs that inhibit PAR2 are searched in the following directions: indirect blockade of PAR2 activity; creation of monoclonal antibodies; search for PAR2 inhibitors among peptide compounds; and synthesis of low molecular weight inhibitory compounds. The last direction is the most perspective one [7].

During 2016–2019, synthesis of low molecular weight PAR-2 antagonists related to 4,5-dihydroisoxazole-5-carboxamide amide derivatives was done. The work was based on preliminary mathematical prediction of pharmacologically significant properties of a large number of multinucleated derivatives of imidazole, isoxazole and oxazole with a wide structural diversity. The antagonistic activity of the compounds with respect to PAR-2 was evaluated in *vitro* using the CHO cell line with high expression of human PAR-2 [8]. Five most active P AR-2 antagonists, derivatives of 4.5- dihydroisoxazol-5-carboxamide, the structure of which is shown in the figure, were investigated in *vivo* on a formaldehyde edema model in various dosages. It would allow to select the most active compound for testing on a model of chronic autoimmune inflammation [9].

The aim of the study was to determine the potential therapeutic efficacy of a promising compound from a number of 3-imidazole-substituted-4,5-dihydroisoxazole carboxylic acid amide derivatives on a model of autoimmune inflammation in rats.

MATERIALS AND METHODS

A single subcutaneous injection of pristane into the base of the rat tail in a volume of 0.1 ml [10], caused chronic inflammation followed by pathological changes seen in white rats at early stages of RA: a chronic recurrent process, typical histological signs of joint damage, as well as development of specific serological immune abnormalities can be observed [10].

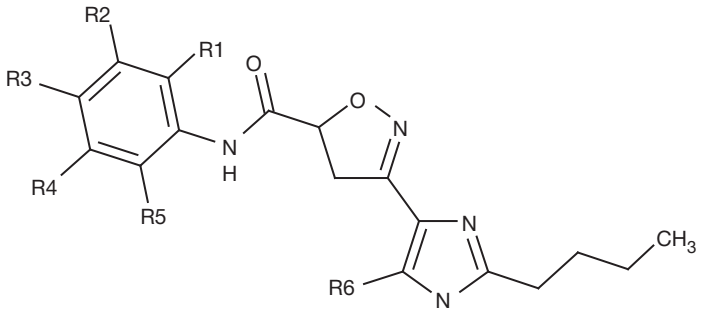

Fig. The general formula of synthesized derivatives of 4,5-dihydroisoxazole-5-carboxamide

Table 1. Changes in paw volume in rats with pristane inflammation

Intervals	Paws	Intact animals	Control animals	Diclofenac sodium	Dexamethasone	R004
Initially	Right	193.6±9.9	194.3±8.3	203.2±13.0	196.7±7.9	188.0±8.1
	Left	196.5±9.7	198.6±9.9	201.7±9.2	201.0±5.9	194.8±7,.9
	Average value	195.1±5.9	197.4±6.7	202.4±7.7	198.8±4.9	191.4±5.8
At 7 days	Right	194.1±8.7	202.0±7.2	196.4±11.9	174.3±5.9*/***	185.0±9.1
	Left	196.0±8.0	203.1±5.8	207.0±11.5	186.7±5.4***	189.8±6.1
	Average value	195.0±5.1	202.7±4.6	201.7±9.1	180.5±4.8*/**/***	187.4±5.2***
At 14 days	Right	184.3±7.0	205.0±4.1*/**	202.8±13.7	170.2±5.2*/***	168.0±6.0***
	Left	193.3±7.3	204.8±7.5	205.0±14.0	180.2±5.6*/***	178.2±7.7***
	Average value	188.8±4.8	204.9±5.1*/**	203.9±8.1	175.1±4.5*/**/***	173.6±6.0***
At 21 days	Right	191.3±5.0	209.0±4.6*/**	214.5±9.1*	177.4±5.0*/***	170.0±7.0***
	Left	195.1±6.6	207.8±5.5*	209.3±11.0	189.4±4.4*/***	182.8±7.7***
	Average value	193.2±4.3	208.5±4.4*/**	211.9±8.0**	183.4±4.2*/***	176.4±6.0***
At 28 days	Right	186.3±5.5	204.4±4.5*/**	208.6±8.8**	184.5±6.2*/***	175.0±6.0***
	Left	190.3±5.3	200.6±6.5	203.8±8.8	194.1±5.4	185.2±7.0
	Average value	188.3±4.7	202.7±4.8*/**	206.2±7.2	189.5±4.6***	180.1±5.6***

*) significant difference from baseline (in dynamics)
**) significant difference from intact ones
***) significant difference from control one

The experiment was carried out on 50 white mongrel rats with a mean weight of 180–220 g, kept at a temperature of 22 ± 2 °C, humidity of 55 ± 5%, in a 12/12-hour light cycle, with unlimited access to food and water. All animals were divided into 5 groups with 10 rats in every group: intact animals in the first group; control animals (rats were injected with pristane and saline solution) in the second group; rats of the third group were injected pristane + diclofenac sodium at a dose of 5 mg/kg [11]; rats of the fourth group were injected with pristane + dexamethasone 1 mg/kg [10]; animals of the fifth group were injected with pristane + R004 10 mg/kg. The duration of the experiment was 28 days; on a daily basis, dexamethasone and physiological solution, diclofenac sodium and R004 were administered s/c and intragastrically respectively. Dynamic examination of the animals was carried out 5 times: at baseline and on the 7th, 14th, 21st and 28th days of the experiment. The following parameters were studied: the volume of the affected foot using digital anhydrous plethysmometer PH1901 (Russia), the width of the articular slits using digital X-ray of the lower extremities (on day 28 only) [12], rectal temperature, general blood test, biochemical values (total protein, albumins, globulins, glucose, triglycerides, total cholesterol, AlAT, AsAT, total bilirubin, GGT, alkaline phosphatase, creatinine, urea).

The results were statistically processed using the Biostat program. Every value determined in various experiments was 6–10. The Student's t-test (in the presence of a normal distribution) and the Mann-Whitney U-test was applied to the comparison of the values between groups, whereas the Student's T-test with a Bonferroni adjustment was used in case of multiple testing. Reliability of intra-group differences was determined by the Student's paired *t*-test. The differences were considered significant at $p < 0.05$ [13].

THE RESULTS OF THE SURVEY AND THEIR DISCUSSION

Changes of rectal temperature and paw volume of animals, as well as the width of the interarticular gap of their feet are the investigated values that most specifically reflect the process of inflammation in rats.

In the intact group, there was an unreliable change in the volume of feet throughout the experiment (Tab. 1). At 14 days after pristane injection to white rats, the volume of the right foot and the average value of both feet were significantly increased from baseline by 5.5% and 3.8% respectively. On the 21st day of the experiment, the volume of both feet significantly increased from baseline: by 7.6% for the right one, by 3.1% for the left one; on the 28th day, the volume of the right foot and both feet remained significantly increased by 5.2% and 2.7%, respectively. In relation to healthy animals, foot volume in rats was significantly increased by 6.5–11.2% on days 14–28 of pristane inflammation.

When treating rats with diclofenac sodium, a significant increase in foot volume (right and average) by 5.6% and 4.7% from baseline occurred only on the 21st day of the experiment.

Table 2. Width of the interarticular foot slits in rats with pristane inflammation

Group	Tarsometatarsal	Metatarsal-phalangeal	Interphalangeal
Intact animals	0.266±0.008	0.283±0.011	0.228±0.018
Control animals	0.236±0.004*	0.251±0.007*	0.204±0.008
R004	0.240±0.004*/***	0.256±0.011	0.226±0.007**/****
Diclofenac	0.213±0.010*/**	0.247±0.006*	0.198±0.014
Dexamethasone	0.223±0.010*	0.230±0.014*	0.202±0.09

*) significant difference with the intact ones
**) significant difference with the control one
***) significant difference with Diclofenac
****) significant difference with Dexamethasone

On day 28, the volume of feet in rats became normal from baseline, but the right foot became significantly more voluminous (+12%) than in intact animals. No increased foot volume was seen in rats treated with dexamethasone. Starting from the 7th day of the experiment and until the end, there was a significant decrease in foot volume by 9.4–13.4% from baseline and by 9.3–16.6% in relation to the control group. No significant increase in foot volume was seen when R004 was administered to animals, and, moreover, the paw volume of treated rats was significantly lower by 7.5–18.7% than in the control group and, at the same time, did not differ from those in the intact group (Tab. 2).

The experiment showed that when administered to animals, chronic inflammation is developed, which is accompanied by swelling of paws. Diclofenac sodium reduced (but did not completely prevent) severity of the inflammatory process; its therapeutic effect was more pronounced in the first three weeks of the developing process, and then slightly decreased (against the background of its administration, there was a significant increase in the volume of the rat's right paw on day 21 and a significant increase in its volume relative to intact animals on day 28). Dexamethasone completely blocked the inflammatory edema significantly reducing the volume of rat paws both in comparison with the baseline and in relation to intact control on days 4 and 14 of the experiment. This may be evidence of dexamethasone myopathy due to impaired synthesis of muscle proteins. Treatment of rates with R004 was optimal: in animals, there was no significant increase of foot edema, both when compared with baseline and in relation to healthy rats.

Modeling of autoimmune inflammation with pristane caused damage to the joint tissue of white rats, one of the manifestations of which was an X-ray change in the width of the articular gap (Tab. 2). It significantly decreased by 11.1% in the prematarsal-metatarsal joints and by 11.3% in the metatarsal-phalangeal joints; in the interphalangeal joint, the narrowing was observed as a trend (–11.5%). In this case, diclofenac sodium did not exert any therapeutic activity: the width of the articular gap in the metatarsal-phalangeal and metatarsal-phalangeal joints changed almost to the same extent as in the control group (–12.7% and –13.2%), and in the premaxillary-metatarsal joint, there was even a deterioration: the width of the interarticular gap was significantly decreased not only in relation to intact animals (–20%), but also in relation to control ones as well (–9.7%). Dexamethasone also had no therapeutic activity: the width of the articular gap significantly decreased by 16.4% in the prematarsal-metatarsal joint and by 18.7% in the metatarsal-phalangeal joints, and in the interphalangeal joint, narrowing of the articular gap was observed as a trend

(–11.4%). Administration of R004 reduced the degree of narrowing of the articular gap significantly by 9.8% in relation to healthy animals, this occurred in the pre-metatarsal joint only. At the same time, changes in the width of the articular gap in the metatarsophalangeal joint did not reach the level of reliability (–9.5%), and they were absent in the interphalangeal joint. It was significantly wider by 10.8% in relation to the control group and by 11.9% in relation to the dexamethasone group.

Thus, experience has shown that with pristane inflammation, damage to the articular surfaces occurs. Diclofenac sodium and dexamethasone proved to be ineffective; R004 partially prevented the damaging effect of pristane on articular tissue.

Measurement of rectal temperature in white rats turned out to be a less informative indicator: its changes in all the studied groups did not actually differ from those of intact animals.

Blood test in animals allowed measurement in dynamics: before the initial injection of pristane and on the 28th day of the experiment. In the intact control group, an elevation in the white blood cell count was observed during the experiment, but only eosinophils and monocytes were significantly increased by 51% and 80% respectively. After administration of pristane, the qualitative picture did not change for most of the studied values, only two values significantly differed from those in the intact control group: there was a 2.5-fold increase in neutrophil count from baseline (p 0.05), and lymphocyte count decreased by 35% (Tab. 3).

While using diclofenac sodium, there was an even greater increase in neutrophil count (4 times compared to baseline, p 0.05), whereas lymphocyte count in blood decreased almost twice (p 0.05). Additionally, basophils were no longer detected in blood. When using dexamethasone, there was a tendency to a low number of neutrophils (their content increased in other groups), the content of neutrophils increased 4 times, but the level of lymphocytes dropped 20 times. Basophils and eosinophils were not detected in blood any longer. R004 leveled drug-induced blood changes: none of the investigated values was changed in a reliable way. Qualitative differences between animals of this group and intact rats consisted in a tendency to a decreased number of basophils and lymphocytes, and significant quantitative differences were determined for lymphocytes only: WBC content in R004 group in relation to intact animals was 36.2% lower though the baseline content was almost the same (Tab. 3).

Thus, a significantly high neutrophils and low lymphocytes in the control group of rats indicate that the immune system was affected. Unlike with reference drugs, therapeutic use of R004 neutralizes these processes to some extent. With diclofenac sodium, these changes were aggravated (monocytes and basophils were added to the drop in lymphocyte content), and dexamethasone itself had a significant immunosuppressive and lymphotoxic activity, contributing to an even greater change in the investigated parameters.

Analyzing the data obtained with respect to red blood, it can be noted that the administration of pristane produced practically no negative effect on its values.

Metabolism of proteins, fats and carbohydrates. Pristane causes a disturbed balance of protein metabolism.

Table 3. Changes in white blood values (x10^9/l) against the background of pristane inflammation

Values	Intervals	Intact animals	Control animals	Diclofenac sodium	Dexamethasone	R004
WBC	initially	7.40±0.71	8.08±0.77	7.41±1.52	8.51±0.91	8.29±1.01
	28 days	9.32±1.12	9.20±1.67	9.80±1.82	7.88±1.92	9.01±1.12
Basophils	initially	0.008±0.001	0.015±0.007	0.018±0.006	0.017±0.008	0.024±0.010
	28 days	0.032±0.014	0.022±0.008	0*/**/***	0*/**/***	0.006±0.006
Eosinophils	initially	0.098±0.016	0.137±0.046	0.114±0.036	0.067±0.031	0.144±0.048
	28 days	0.148±0.016*	0.152±0.031	0.178±0.038	0*/**/***	0.188±0.042
Neutrophils	initially	1.62±0.45	1.95±0.45	1.63±0.25	1.76±0.21	2.34±0.55
	28 days	2.12±0.43	4.80±1.02*/**	6.48±1.75*/**	7.05±1.57*/**	3.96±0.81
Lymphocytes	initially	5.32±0.85	5.48±0.89	5.30±1.49	6.05±1.19	5.30±0.56
	28 days	6.22±0.88	3.55±0.36**	2.88±0.56*/**	0.33±0.02 */**/***	3.97±0.69**
Monocytes	initially	0.368±0.105	0.493±0.135	0.348±0.088	0.620±0.105	0.486±0.125
	28 days	0.663±0.110*	0.610±0.216	0.260±0.84**/***	0.500±0.146	0.590±0.136

*) significant difference from baseline
**) significant difference from intact ones
***) significant difference from control one

Table 4. Effect of pristane inflammation on blood biochemical parameters

Values	Intact animals	Control animals	Diclofenac sodium	Dexamethasone	R004
Total protein g/l	70.63±1.05	70.50±0.45	57.90±2.64*	66.67±2.16	70.20±0.71
Albumins g/l	36.25±0.31	34.00±0.90	30.20±0.31*	31.33±2.31	35.40±0.90
Globulins g/l	34.38±0.81	36.50±0.55	27.00±0.81*	35.34±2.01	34.80±0.78
Albumins/globulins	1.08±0.04	0.93±0.04*	1.19±0.06**	0.87±0.07*	1.02±0.04
Glucose mmol/l	9.10±0.09	8.22±0.15*	8.81±0.13**	9.73±0.61**	9.05±0.30**
Triglycerides	0.44±0.05	0.57±0.07	0.68±0.17	2.30±0.25*/**	0.51±0.06
Glucose/triglycerides	20.70±1.41	14.42±1.12*	12.96±1.56*	4.23±1.02*/**	17.75±1.18**
Total cholesterol	2.86±0.09	2.19±0.08*	2.57±0.12**	2.50±0.29	2.39±0.26
AlAT	43.25±5.30	43.08±3.32	64.30±10.30	80.50±15.30*/**	47.75±2.80
AsAt	93.25±5.07	126.58±8.03*	117.50±11.07	150.17±18.96*	105.12±1.64**
Total bilirubin	1.93±0.07	1.88±0.06	2.07±0.09	1.95±0.04	2.14±0.09
GGT	4.00±0.00	4.00±0.00	4.00±0.00	7.33±1.20*	4.00±0.00
Creatinine	30.75±0.30	34.83±0.80*	33.80±1.00*	26.00±2.30**	33.75±0.60*
Urea	3.43±0.18	3.46±0.11	4.30±0.16*	4.45±0.18*	3.81±0.08
Alkaline phosphatase	74.75±17.65	73.17±8.62	103.40±16.60	225.00±76.85	97.40±3.67

*) significant difference with the intact ones
**) significant difference with the control one

Despite the fact that the change in blood albumin and globulin is trending, a significant decrease in the albumin/globulin index (AHI) by 13.9% indicates a shift in protein synthesis towards globulins, which structurally include antibodies that are essential in autoimmune inflammation. A significant decrease in glucose by 9.7% and cholesterol by 23.6% (decrease in the rate of synthesis of steroid hormones and repair of cell membranes) was observed as well. Against the background of a decrease in glucose concentration and a tendency to increase the TG content, the carbohydrate-fat index (CFI) significantly decreased by 30% (the ratio of glucose and triglycerides). It shows the body's shift to "fatty" energy, which is more consumable in terms of oxygen and energy substrates (Tab. 4).

Diclofenac sodium caused a uniform decrease in the synthesis of both albumins and globulins, which may be associated with the impaired liver function. A further decrease in the CFI by 37.4% compared to intact animals occurred, demonstrating an increase in the lipid component of energy balance. With dexamethasone, dissonance increased in favor of globulin synthesis (a significant decrease in AHI by 19.5% in relation to healthy animals) and a sharp decrease in CFI by almost 5 times, showing the body's shift to "lipid" energy (the effect of high doses of glucocorticoids). The therapeutic administration of R004 stops changes in metabolism of proteins, fats and carbohydrates that occur against the background of pristane inflammation.

Functional biochemistry of the liver and kidneys. When pristane was administered, there was a significant increase of AsAT activity by 35.7% and creatinine content by 14% (Tab. 4). It means that the liver and kidneys display an interest in developing inflammatory process. There was only a significant increase in blood creatinine (+9.8%) with R004, but to a lesser extent than for the control group. When using diclofenac sodium in sick animals, only blood creatinine (+9.9%) and urea (+25.4%) significantly increased, indicating at a possible kidney damage. The tendency to an increased activity of blood transaminases and alkaline phosphatase, as well as to an increased concentration of bilirubin, demonstrates liver function strain. Dexamethasone showed a significant increase in the activity of AlAT by almost

2 times, AsAT by 1.6 times, GGT by 1.8 times and alkaline phosphatase by 3.1 times (the latter $p > 0.05$), demonstrating cytolysis of hepatocytes and developing cholestasis. A significant increase of blood levels of urea shows a decrease in the reabsorption function of the kidneys.

Thus, the experiment showed that with pristane inflammation, liver and kidney damage is possible. R004 weakens this process, whereas diclofenac sodium and dexamethasone enhance it.

CONCLUSIONS

1. R004 in the treatment of chronic inflammation in rats prevented significant development of edema of feet, damage to small joints, and specific changes in white blood count, and according to biochemical blood test led to normalization of liver and kidney functions and energy metabolism.

2. R004 turned out to be more effective and safer than the comparator drugs such as diclofenac sodium and dexamethasone.

References

1. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023; 5 (10): e594-e610. DOI: 10.1016/S2665-9913(23)00211-4. PMID: 37795020; PMCID: PMC10546867.
2. Klinicheskie rekomendatsii. Revmatoidnyy artrit. 2021–2022–2023 (24.08.2021). Utverzhdeny Minzdravom RF. Russian.
3. Tanaka Y. Current concepts in the management of rheumatoid arthritis. Korean J Intern Med. 2016; 31 (2): 210–218. DOI: 10.3904/kjim.2015.137. Epub 2016 Feb 26. PMID: 26932398; PMCID: PMC4773729.
4. Nasonov EL. Lechenie revmatoidnogo artrita. Klinicheskaya farmakologiya i farmakoterapiya. 2017; 26 (1): 4–10. Russian.
5. Prasad P, Verma S, Surbhi, Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. Mol Cell Biochem. 2023; 478 (1): 69–88. DOI: 10.1007/s11010-022-04492-3. PMID: 35725992.
6. McCulloch K, McGrath S, Huesa C, Dunning L, Litherland G, Crilly A, et al. Rheumatic Disease: Protease-Activated Receptor-2 in Synovial Joint Pathobiology. Front Endocrinol (Lausanne). 2018; 9: 257. DOI: 10.3389/fendo.2018.00257. PMID: 29875735; PMCID: PMC5974038.
7. Cho NC, Seo SH, Kim D, Shin JS, Ju J, Seong J, et al. Pharmacophore-based virtual screening, biological evaluation and binding mode analysis of a novel protease-activated receptor 2 antagonist. J Comput Aided Mol Des. 2016; 30 (8): 625–37. DOI: 10.1007/s10822-016-9937-9. PMID: 27600555.
8. Abassi YA, Xi B, Zhang W, Ye P, Kirstein SL, Gaylord MR, et al. Kinetic cell-based morphological screening: prediction of mechanism of compound action and off-target effects. Chem Biol. 2009; 16 (7): 712–23. DOI: 10.1016/j.chembiol.2009.05.011. PMID: 19635408; PMCID: PMC2836189.
9. Korsakov MK, Fedorov VN, Smirnov NA, Shetnev AA, Leonova OV, Volkhin NN, et al. Screening of anti-inflammatory activity of 4.5-dihydroisoxazol-5-carboxamide (PAR-2 inhibitors) based on formaldehyde oedema model among white lab rats. Research Results in Pharmacology. 2023; 9 (4): 105–111. DOI: 10.18413/rrpharmacology.9.10061.
10. Tuncel J, Haag S, Hoffmann MH, Yau AC, Hultqvist M, Olofsson P, et al. Animal Models of Rheumatoid Arthritis (I): Pristane-Induced Arthritis in the Rat. PLoS One. 2016 May 26; 11 (5): e0155936. DOI: 10.1371/journal.pone.0155936. PMID: 27227821; PMCID: PMC4881957.
11. Bibik EYu, Yaroshevskaya OG, Devdera AV, Demenko AV, Zakharov VV, Frolov KA, et al. Poisk sredstv s protivovospalitel'noy aktivnost'yu sredi proizvodnykh tetragidropiridо [2,1] [1,3,5] tiadiazina. Khimiko-farmatsevticheskiy zhurnal. 2017; 51 (8): 16–19. Russian.
12. Skupnevskiy SV, Pukhaeva EG, Badtiev AK, Rurua FK, Batagova FE, Farnieva Zh G. Metod neinvazivnoy otsenki razvitiya revmatoidnogo artrita u laboratornykh gryzunov. Vestnik novykh meditsinskikh tekhnologiy. 2022; (4): 69–72. DOI: 10.24412/1609-2163-2022-4-69-72. Russian.
13. Glants S. Mediko-biologicheskaya statistika. M.: Praktika, 1998; 459 p. Russian.

Литература

1. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023; 5 (10): e594-e610. DOI: 10.1016/S2665-9913(23)00211-4. PMID: 37795020; PMCID: PMC10546867.
2. Клинические рекомендации. Ревматоидный артрит. 2021–2022–2023 (24.08.2021). Утверждены Минздравом РФ.
3. Tanaka Y. Current concepts in the management of rheumatoid arthritis. Korean J Intern Med. 2016; 31(2): 210–218. DOI: 10.3904/kjim.2015.137. Epub 2016 Feb 26. PMID: 26932398; PMCID: PMC4773729.
4. Насонов Е. Л. Лечение ревматоидного артрита. Клиническая фармакология и фармакотерапия. 2017; 26 (1): 4–10.
5. Prasad P, Verma S, Surbhi, Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. Mol Cell Biochem. 2023; 478 (1): 69–88. DOI: 10.1007/s11010-022-04492-3. PMID: 35725992.
6. McCulloch K, McGrath S, Huesa C, Dunning L, Litherland G, Crilly A, et al. Rheumatic Disease: Protease-Activated Receptor-2 in Synovial Joint Pathobiology. Front Endocrinol (Lausanne). 2018; 9: 257. DOI: 10.3389/fendo.2018.00257. PMID: 29875735; PMCID: PMC5974038.
7. Cho NC, Seo SH, Kim D, Shin JS, Ju J, Seong J, et al. Pharmacophore-based virtual screening, biological evaluation and binding mode analysis of a novel protease-activated receptor 2 antagonist. J Comput Aided Mol Des. 2016; 30 (8): 625–37. DOI: 10.1007/s10822-016-9937-9. PMID: 27600555.
8. Abassi YA, Xi B, Zhang W, Ye P, Kirstein SL, Gaylord MR, et al. Kinetic cell-based morphological screening: prediction of mechanism of compound action and off-target effects. Chem Biol. 2009; 16 (7): 712–23. DOI: 10.1016/j.chembiol.2009.05.011. PMID: 19635408; PMCID: PMC2836189.
9. Korsakov MK, Fedorov VN, Smirnov NA, Shetnev AA, Leonova OV, Volkhin NN, et al. Screening of anti-inflammatory activity of 4.5-dihydroisoxazol-5-carboxamide (PAR-2 inhibitors) based on formaldehyde oedema model among white lab rats. Research Results in Pharmacology. 2023; 9 (4): 105–111. DOI: 10.18413/rrpharmacology.9.10061.
10. Tuncel J, Haag S, Hoffmann MH, Yau AC, Hultqvist M, Olofsson P, et al. Animal Models of Rheumatoid Arthritis (I): Pristane-Induced Arthritis in the Rat. PLoS One. 2016 May 26; 11 (5): e0155936. DOI: 10.1371/journal.pone.0155936. PMID: 27227821; PMCID: PMC4881957.
11. Бибик Е. Ю., Ярошевская О. Г., Девдера А. В., Деменко А. В., Захаров В. В., Фролов К. А. и др. Поиск средств с противовоспалительной активностью среди производных тетрагидропиридо [2,1] [1,3,5] тиадиазина. Химико-фармацевтический журнал. 2017; 51 (8): 16–19.
12. Скупневский С. В., Пухаева Е. Г., Бадтиев А. К., Руруа Ф. К., Батагова Ф. Э., Фарниева Ж. Г. Метод неинвазивной оценки развития ревматоидного артрита у лабораторных грызунов. Вестник новых медицинских технологий. 2022; (4): 69–72. DOI: 10.24412/1609-2163-2022-4-69-72.
13. Гланц С. Медико-биологическая статистика. М.: Практика, 1998; 459 с.

EVIDENCE OBTAINED DURING REAL WORLD DATA ANALYSIS: WHAT IT IS AND HOW WE FORM IT

Verbitskaya EV ✉, Kolbin AC

IP Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia

The article is devoted to the pressing issue of using real world data (RWD) to prove effectiveness and safety of medical technologies. The authors consider the advantages and limitations of this approach compared to traditional randomized clinical trials. According to the main provisions of the article, RWD complement the results of clinical trials and make it possible to evaluate the effectiveness of drugs in everyday practice. Key stages of conducting RWD-based research are described such as research design, selection and evaluation of data source quality, analytical methods, ensuring transparency and reproducibility. Modern tools for planning and conducting RWD research are presented, for example, the HARPER protocol template, structured SPACE approach, and SPIFD data assessment tool. The features and limitations of RWD are discussed, including their unstructured nature, omissions, and inconsistency. The importance of observing the principles of transparency, integrity, and minimizing systematic errors when working with RWD is emphasized. There is a growing recognition of RWD by regulatory authorities and a need to develop standardized approaches to obtain it. In conclusion, the authors emphasize that with proper application of the research methodology, RWD can provide valuable information for decision-making in healthcare, complementing traditional clinical trials.

Keywords: real world evidence, real world research, databases, electronic health records (EHR), real world research design, reliability, reproducibility

Author contribution: Verbitskaya EV and Kolbin AS made an equal contribution to the preparation of the article.

✉ **Correspondence shall be addressed:** Elena Vladimirovna Verbitskaya
L'va Tolstogo Str., 6–8/1, Saint Petersburg, 197022, Russia; everbitskaya@internet.ru

Received: 19.11.2024 **Accepted:** 16.12.2024 **Published online:** 31.12.2024

DOI: 10.24075/medet.2024.028

ДОКАЗАТЕЛЬСТВА, ПОЛУЧЕННЫЕ НА ОСНОВЕ АНАЛИЗА ДАННЫХ РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ: ЧТО ЭТО И КАК ФОРМИРУЕМ

Е. В. Вербицкая ✉, А. С. Колбин

Первый Санкт-Петербургский государственный медицинский университет имени академика И. П. Павлова, Санкт-Петербург, Россия

Статья посвящена актуальной теме использования данных реальной клинической практики (РКП) для получения доказательств эффективности и безопасности медицинских технологий. Авторы рассматривают преимущества и ограничения этого подхода по сравнению с традиционными рандомизированными клиническими испытаниями. Основные положения статьи: данные РКП дополняют результаты клинических испытаний и позволяют оценить эффективность препаратов в условиях повседневной практики. Описаны ключевые этапы проведения исследований на основе РКП: дизайн исследования, выбор и оценка качества источников данных, аналитические методы, обеспечение прозрачности и воспроизводимости. Представлены современные инструменты для планирования и проведения исследований РКП, такие как шаблон протокола HARPER, структурированный подход SPACE, инструмент оценки данных SPIFD. Обсуждаются особенности и ограничения данных РКП, включая их неструктурированность, пропуски, несогласованность. Подчеркивается важность соблюдения принципов прозрачности, целостности и минимизации систематических ошибок при работе с данными РКП. Отмечается растущее признание ценности доказательств РКП регуляторными органами и необходимость разработки стандартизированных подходов к их получению. В заключение авторы подчеркивают, что при правильном применении методологии исследования РКП могут предоставить ценную информацию для принятия решений в здравоохранении, дополняя традиционные клинические испытания.

Ключевые слова: доказательства реальной клинической практики, исследования реальной клинической практики, базы данных, электронные медицинские карты (ЭМК), дизайн исследований реальной клинической практики, достоверность, воспроизводимость

Вклад авторов: Е. В. Вербицкая, А. С. Колбин внесли равный вклад в подготовку статьи.

✉ **Для корреспонденции:** Елена Владимировна Вербицкая
ул. Льва Толстого, д. 6–8/1, г. Санкт-Петербург, 197022, Россия; everbitskaya@internet.ru

Статья поступила: 02.11.2024 **Статья принята к печати:** 16.12.2024 **Опубликована онлайн:** 31.12.2024

DOI: 10.24075/medet.2024.028

Randomized controlled clinical trials (RCTs) are considered the gold standard for obtaining pre-marketing evidence of drug safety and efficacy. However, the life cycle of a medicinal product certainly does not end after registration. Real world data (RWD) expand and add to the knowledge [1–3]. When making regulatory decisions, real world evidence (RWE) is increasingly being taken into account. Real world evidence is clinical evidence of the use, potential benefits, or risks of medical technology application obtained from the analysis of real world data [4]. The reasons why RWE is actively gaining supporters are that classical clinical trials, especially RCTs, have a number of following significant limitations and disadvantages:

1. Limited external validity. RCTs are often performed under strictly controlled conditions that may not correspond to real clinical practice, and the careful selection of study participants based on strict inclusion and non-inclusion criteria does not reflect the diversity of real patients;
2. Insufficient representativeness. Many groups of patients (e.g., the elderly, those with concomitant diseases, etc.) are often excluded from RCTs, limiting applicability of the results to broader patient populations;
3. Limited duration of observation. RCTs usually have a relatively short follow-up period, making it difficult to identify long-term effects and adverse events;
4. High cost and complexity. Conducting RCTs requires significant financial and time costs, and complexity of design and strict protocols can make it difficult to recruit participants and complete the study.

In addition to the above, evidence based on traditional clinical studies can also be significantly influenced by ethical issues, conflicts of interest, and publication bias.

In this regard, there is a growing need in the medical community for information about the effectiveness of medicinal products (MPs) in the context of RWD. This approach allows us to assess to what extent the results obtained under controlled conditions of RCTs correspond to the effects of MPs when used in everyday medical practice. The real world evidence can be used:

- in drug development and registration;
- in studying post-registration safety and efficacy;
- in formulating clinical guidelines;
- in health economics, reimbursement systems, and pharmaceutical provision.

At the same time, RWD complements but does not replace RCT data; they are especially important for evaluation of innovative drugs and treatment of rare diseases.

In this way, RWE provides valuable information about the application of medical technologies in real clinical practice, which helps to take more informed decisions in healthcare.

There have been significant changes in RWE regulation over the past ten years. Thus, there are significant positive developments in the documents of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) [5, 6].

Despite the growing recognition of RWE potential, an analysis published in 2021, revealed a significant gap in this area represented by the lack of comprehensive guidelines on best practices for conducting such research [7]. The authors of this analysis developed a set of criteria to assess credibility of evidence in recommendations and conducted a classification of 41 published methodological guidelines from various organizations, including regulatory authorities, health technology assessment (HTA) agencies and professional communities.

In the absence of a single standardized guideline, researchers working with the RWD are forced to rely on a disparate set of recommendations from various sources. These sources include regulatory authorities (e.g., the FDA), UK HTS agencies (such as NICE (National Institute for Health and Care Excellence)), professional organizations (e.g., ISPOR (International Society For Pharmacoeconomics and Outcomes Research)), and academic groups.

To overcome this fragmentation, it is proposed to consider the possibility of creating a systematic structure of RWE recommendations. This “organized structure” should cover all the key aspects necessary for conducting high-quality RWE research (Fig. 1).

Such an approach could provide more consistent and comprehensive guidance for researchers working in the RWE field, thereby improving quality and reliability of the results obtained.

The blocks focus on the fact that high-quality RWEs are based on a fundamental scientific process that involves as follows:

- “research design” building block 1 includes a research plan that meets the goal and protocol development;
- “data quality” building block 2 implies the overall quality of RWD sources and identification of suitable sources for the purpose;
- “analytical methods” building block 3 includes data sources and selection of appropriate analytical methods;
- “transparency and reproducibility” building block 4 pays special attention to transparency and reproducibility when developing a research report;
- building block 5 is the final stage of the fundamental scientific process in RWD research. It gives rise to a clear understanding of how decision makers will evaluate the quality of the results obtained. This stage, known as the “final report assessment”, plays a key role in ensuring practical applicability of the study [7].
- building block 6. The main components of the RWE process are supported by two additional elements: “RWE use cases” and “demonstration projects”. “RWE use cases” define the types of hypotheses relevant to RWE studies, such as post-marketing safety assessment or expansion of drug indications.

RESEARCH DESIGN

Research planning based on data from real clinical practice is a complex process that requires a careful approach and consideration of multiple factors. A key aspect of RWE research planning is the definition of research goals and objectives. A clear formulation of the specific research tasks that need to be solved is based on what kind of evidence you want to obtain (effectiveness, safety, economic feasibility, etc.).

Figure 2 presents the optimal algorithm for constructing a research design, the main initial factor of which is the purpose of the study. “Strategic/scientific considerations” are based on the purpose of the research; they determine who will use the information and how. Depending on the objectives of the study, it will be necessary to collect specific information about outcomes, ranging clinical results to patient-reported outcomes and economic results. Categories of outcomes and instruments, in turn, influence data collection needs and, ultimately, design of the study.

The “operational aspects” relate to availability of data sources and overall feasibility (what data is available, what can be easily collected, and who should be involved) and degrees of quality (what level of administrative quality and data reliability is expected by the study stakeholders). In the field of RWE, the feasibility of a study largely depends on central and local

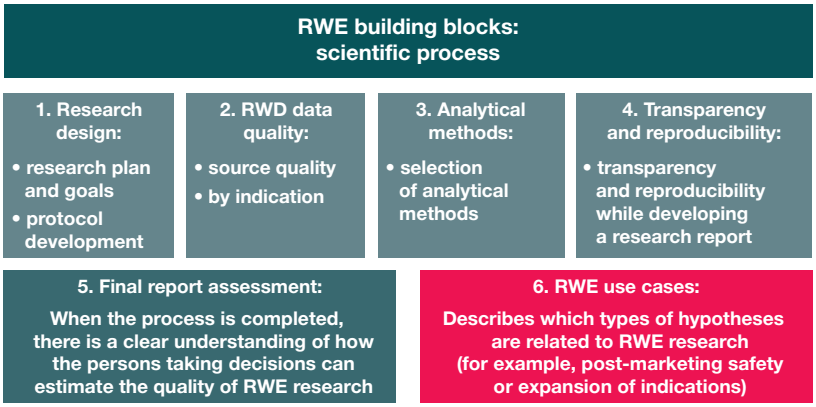

Fig. 1. RWE building blocks (adapted from [7])

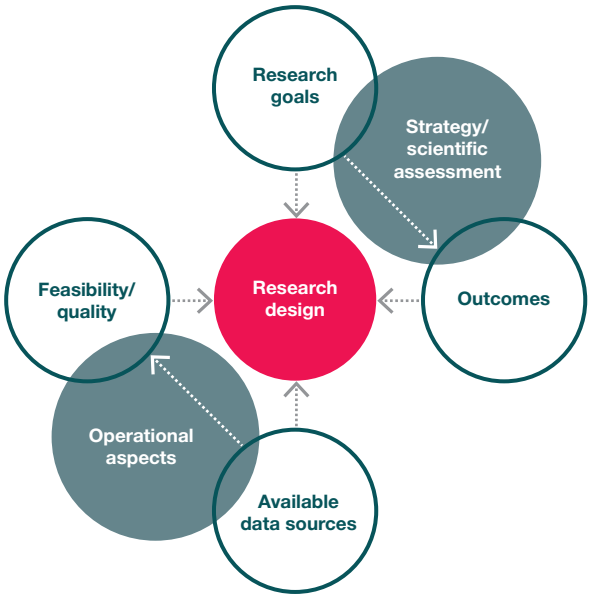

Fig. 2. The optimal algorithm for building a research design

regulations, ethical and legal requirements, and the associated quality requirements of the research.

From an operational point of view, there is also a hierarchy or sequence of approaches, starting with easily accessible data from existing sources and ending with complex, long-term interventional or observational prospective approaches to research.

If secondary data, such as claims or electronic medical records (EHR) databases, is available to achieve the purpose of the study and meet the relevant needs for results, a retrospective database study often provides a cost-effective and timely solution. To some extent, this is also true for primary research and retrospective design of medical records analysis. However, database or diagram-based retrospective approaches are limited in the possibility of follow-up or reconciliation, for example, for AE safety reports, whereas availability of information about patient-Reported Outcomes (PROs) is usually minimal.

In 2022, NICE presented generalized aspects of conducting research to collect data from real clinical practice.

By 2022, several protocol templates for RWE have been developed, most of which are based on the principles of simulating a "targeted study", namely, the idea that first you need to write a protocol for RCT that would answer the question posed, and then translate it into an observational study protocol, taking into account possible biases that appear as randomization is lacking [8]. In 2023, an agreed HARmonized Protocol Template to Enhance Reproducibility (HARPER) of RWE research was introduced [9, 10].

The HARPER template helps understand proposed scientific solutions through a common textual, tabular, and visual structure. It contains a set of basic guidelines for clear and reproducible RWE research protocols and is intended to be used as a framework throughout the entire research process from development of a valid research protocol to registration, implementation, and reporting based on the results of this implementation [1].

In 2019, a structured tool was proposed to design pre- and post-registration comparative studies and obtain reliable and transparent real evidence (SPACE) [11].

Starting with a clear research question and following a targeted trial approach, SPACE provides a step-by-step process to identify RW research design elements and minimum criteria for feasibility and data validity issues, as well as to document research design decisions, including planned analysis. At the same time, SPACE supports the first steps in the study design necessary to identify data or compile protocol documents.

IDENTIFICATION OF SUITABLE SOURCES, HIGH-QUALITY RWD SOURCES AND SELECTION OF APPROPRIATE ANALYTICAL METHODS

Data collection and processing are key steps in research aimed at generating evidence based on real clinical practice. These processes require careful planning and organization to ensure reliability and representativeness of the data obtained.

The first step in data collection is to identify information sources. In the context of real clinical practice, such sources can include electronic medical records, patient registers, databases of medical institutions, as well as results of clinical trials and observational studies. It is important to keep in mind that data must be collected from a variety of sources to ensure their diversity and completeness. It allows to avoid systematic errors and improve reliability of conclusions.

Trust in RWD research. Data from real clinical practice are often heterogeneous and require careful preparation before analysis. In addition, for some purposes, such as calculating comparative effects, the analysis methods need to be improved. By using the data already collected, researchers can access the data before drawing up a final Statistical Analysis Plan. Data preparation and analytical decisions can have a significant impact on the final calculation results. Thus, it is necessary to eliminate the factors that can affect integrity and reliability of the evidence obtained (for example, by data dredging or a selective approach).

The data from actual clinical practice differ significantly from the data obtained during clinical trials. These differences play a key role in research planning and directly affect the quality and reliability of the RWE.

Main characteristics of RWD. The primary purpose of RWD is not originally intended for scientific purposes. They are collected to support the functioning of the healthcare system. This leads to such consequences as insufficient data ordering and possible lack of important information (for example, indications for the use of the drug or key patient characteristics in electronic medical records) [12].

Data structure. RWD can be divided into two categories:

– Structured data: ready for analysis without preprocessing;
– Unstructured data: requires identifying the structure and encoding of information. This data can be processed manually or using big data analysis and artificial intelligence technologies.

In some cases, the same information can be presented in both structured and unstructured form.

Missing data. The problem of missing data is a characteristic feature of RWD and requires special attention during analysis. Understanding these features of RWD is critically important for proper research planning, ensuring quality and reliability of the evidence obtained, and correct interpretation of the analysis results. Taking these factors into account allows researchers to develop more effective strategies of working with RWD and increase the value of evidence obtained on their basis for clinical and managerial decisions in healthcare.

Data inconsistency. Despite the existence of external controls (inspections of medical facilities by insurance companies, regulatory supervision, routine laboratory inspections), the problem of data inconsistency remains relevant. This applies both to contradictions between different sources and within the same source, especially the EMC.

Key aspects:
– External control is not a substitute for the data validation process;
– The need to identify contradictions (for example, the presence of a diagnosis in the absence of therapy or changes in laboratory parameters).

The principle of non-interference. It is important to minimize interference in the process of creating the RWD in order to avoid distortions.

Recommended approaches: implementation of checks for completeness and quality of data in source input systems, use of validation checks during data extraction, transparent documentation of all changes made and variability of data quality. The quality of RWD varies significantly depending on the source and can be unstable even within a single source.

The influencing factors are differences in how optional fields are filled in by different employees.

Recommendations for working with the RWD.
– Clearly define the prospects and volume of RWE received based on the available RWD;
– Carefully evaluate compliance of the RWD with the study objectives;
– Understand the process of creating a specific data source: who enters the information, under what conditions, based on what data, and for what purpose;
– Take into account the specifics of various sources (for example, a large number of unstructured elements and subjective assessments in the EMC);
– Use specialized guidelines for selecting RWD databases for various types of research.

Thus, working with RWD requires an integrated approach that takes into account their characteristics and limitations in order to obtain reliable and valid research results [12].

In 2021, the FDA published, as an extension of SPACE, guidelines for assessing the appropriateness of data sources for their intended purpose (Structured Process to Identify Fit-For-Purpose Data (SPIFD) [11–13], which is a step-by-step process of conducting and documenting the results of a systematic feasibility assessment to ensure the suitability of data for a research question of interest. When used together, SPACE and SPIFD facilitate informed and transparent research design, planned analysis, and data selection to meet regulatory decision-making standards.

TRANSPARENCY AND REPRODUCIBILITY

The final stage of the fundamental scientific process in RWD research is formation of a clear understanding of how decision makers will evaluate the quality of the results obtained. This stage, known as the “final report assessment”, plays a key role in ensuring practical applicability of the study [7].

Compared to clinical trials and non-experimental studies that prospectively collect data, studies using routinely collected electronic medical data have greater variability in design and analysis options.

Existing guidelines and checklists have a strong consensus as to what key elements are important to communicate, but they can lead to ambiguity, assumptions, and misinterpretation when planning and implementing RWE research.

More stakeholders are moving towards routine registration of RWD studies with fully defined research implementation protocols to support regulatory and reimbursement decisions.

To increase transparency and reproducibility of the results, Wang et al. (2021) developed the structured STaRT-RWE (Structured template and reporting tool for real world evidence) template [14].

STaRT-RWE is intended for use as a didactic tool for designing and conducting qualitative RWE research; setting clear expectations for communication of RWE methods; reducing misinterpretation of insufficiently specific descriptions; enabling reviewers to quickly find key information; and facilitating reproducibility, validity assessment, and synthesis of evidence.

The template was approved by the International Society of Pharmacoepidemiology (ISPE) and the Transparency Initiative, led by the International Society for Pharmacoeconomics and Outcomes Research in partnership with ISPE, the Duke Margolis Center for Health Policy, and the National Pharmaceutical Council.

STaRT-RWE advantages:
– Improving interdisciplinary collaboration;
– Improving the quality of working with data from multiple sources;
– Optimizing the joint development and research of RWE;
– Clearer documentation of critical research details;
– Improving the effectiveness of communication between research groups;
– Improving the decision-making process based on research results.

Regulators and other decision makers encourage researchers to use standards agreed upon by the professional community when conducting and reporting on RWE research. This is necessary to obtain timely, high-quality evidence and to create a basis for evaluating and distinguishing carefully planned studies from studies with validity problems.

Thus, a structured approach such as STaRT-RWE can significantly improve the quality and reliability of real world clinical practice research, contributing to a more effective use of their results in the decision-making process in healthcare.

Adherence to essential scientific processes increases trust in research results, which can expand the range of RWE applications.

When conducting research using RWD data, it is necessary to adhere to the following key principles:
– Use of up-to-date data of appropriate quality and established origin;
– Ensuring transparency and integrity at all stages of research, from planning to reporting;
– Use of analytical methods that minimize the risk of systematic errors.

Compliance with these principles improves reliability and validity of RWE research results, which in turn increases their value for decision-making in healthcare.

References

1. Kolbin AS, et al. Issledovaniya, predstavlyayushchiye klinicheskuyu praktiku. M.: Izdatel'stvo OKI: Buki Ved, 2020. Available from URL: https://izdat-oki.ru/issledovaniya-realnoj-klinicheskoj-praktiki (accessed 10.05.2022). Russian.
2. Eskola SM, Leufkens HG M, Bate A, De Bruin ML, and Gardarsdottir H, Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019. Clin. Pharmacol. Ther. Jan. 2022; 111(1): 310–320. DOI: 10.1002/CPT.2462.
3. Rudnicki M. Use of Real World Data (RWD) to generate Real World Evidence (RWE) in gynecologic surgery. Acta Obstetricia et Gynecologica Scandinavica. 2021; 100(12): 2133–2134. DOI: 10.1111/aogs.14292.
4. Yevraziyskiy ekonomicheskiy soyuz. Ob obshchikh podkhodakh k razvitiyu regulirovaniya obrashcheniya lekarstvennykh sredstv v ramkakh Yevraziyskogo ekonomicheskogo soyuza v chasti sbora, analiza i ispol'zovaniya dannykh real'noy klinicheskoy praktiki. Rekomendatsiya Soveta Yevraziyskoy ekonomicheskoy komissii ot 18.10.2024. 2024; 1(1) Available from URL: https://www.consultant.ru/cons/cgi/online.cgi?req=doc&base=LAW&n=488573&dst=100001#lv8sBTUQZwxAADEo (accessed 04.11.2024). Russian.
5. US Food & Drug Administration. Advancing Real-World Evidence Program. Available from URL: https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program (accessed 04.11. 2024).
6. Prilla S, et al. Real-World Evidence to Support EU Regulatory Decision Making-Results from a Pilot of Regulatory Use Cases. Clin Pharmacol Ther. Nov. 2024; 116(5). DOI: 10.1002/CPT.3355
7. Jaksa A, Wu J, Jónsson P, Eichler HG, Vititoe S, and Gatto NM. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. J Comp Eff Res. Jun. 2021; 10(9): 711–731. DOI: 10.2217/CER-2020-0228
8. Hernán MA, Wang W, and Leaf DE. Target Trial Emulation: A Framework for Causal Inference from Observational Data. JAMA. Dec. 2022; 328(24): 2446–2447 DOI: 10.1001/jama.2022.21383
9. Mukhina SM, Baranova MI, Balykina YuYe. HARPER — shablon protokola po issledovaniyam real'noy klinicheskoy praktiki dlya otsenki effektivnosti lecheniya. Real'naya klinicheskaya praktika dannyye i dokazatel'stva. Dec. 2022; 2(4): 17–25. DOI: 10.37489/2782-3784-MYRWD-23 Russian.
10. Wang SV, et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. Pharmacoepidemiol Drug Saf. Jan. 2023; 32(1): 44–55. DOI: 10.1002/PDS.5507.
11. Gatto NM, Vititoe SE, Rubinstein E, Reynolds RF and Campbell UB. A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses. Clin Pharmacol Ther. Jun. 2023; 113(6): 1235–1239. DOI: 10.1002/cpt.2883.
12. Solodovnikov AG, Sorokina YeYu., Gol'dina TA. Dannyye rutinnoy praktiki (real-world data): ot planirovaniya k analizu. Meditsinskiye tekhnologii. Otsenka i vybor. 2020; 41(3): 9. DOI: 10.17116/medtech2020410319 Russian.
13. Gatto NM, et al. The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clin Pharmacol Ther. Jan 2022; 111(1): 122–134 DOI: 10.1002/CPT.2466.
14. Wang SV, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. BMJ. Jan. 2021; 372 s. DOI: 10.1136/BMJ.M4856.

Литература

1. Колбин А. С. и др. Исследования реальной клинической практики. М.: Издательство ОКИ: Буки Вед, 2020. Режим доступа: [Электронный ресурс] URL: https://izdat-oki.ru/issledovaniya-realnoj-klinicheskoj-praktiki (дата обращения 10.05.2022).
2. Eskola SM, Leufkens HG M, Bate A, De Bruin ML, and Gardarsdottir H, Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019. Clin Pharmacol Ther. Jan. 2022; 111(1): 310–320. DOI: 10.1002/CPT.2462.
3. Rudnicki M. Use of Real World Data (RWD) to generate Real World Evidence (RWE) in gynecologic surgery. Acta Obstetricia et Gynecologica Scandinavica. 2021; 100(12): 2133–2134. DOI: 10.1111/aogs.14292.
4. Евразийский экономический союз. Об общих подходах к развитию регулирования обращения лекарственных средств в рамках Евразийского экономического союза в части сбора, анализа и использования данных реальной клинической практики. Рекомендация Совета Евразийской экономической комиссии от 18.10.2024. 2024; 1(1) Режим доступа: [Электронный ресурс] URL: https://www.consultant.ru/cons/cgi/online.cgi?req=doc&base=LAW&n=488573&dst=100001#lv8sBTUQZwxAADEo (дата обращения 04.11.2024).
5. US Food & Drug Administration. Advancing Real-World Evidence Program. Available from URL: https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program (accessed 04.11. 2024).
6. Prilla S, et al. Real-World Evidence to Support EU Regulatory Decision Making-Results from a Pilot of Regulatory Use Cases. Clin Pharmacol Ther. Nov. 2024; 116(5). DOI: 10.1002/CPT.3355.
7. Jaksa A, Wu J, Jónsson P, Eichler HG, Vititoe S, and Gatto NM. Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance. J Comp Eff Res. Jun. 2021;10(9): 711–731. DOI: 10.2217/CER-2020-0228
8. Hernán MA, Wang W, and Leaf DE. Target Trial Emulation: A Framework for Causal Inference from Observational Data. JAMA. Dec. 2022; 328(24): 2446–2447 DOI: 10.1001/jama.2022.21383.
9. Мухина С. М., Баранова М. И., Балыкина Ю. Е. HARPER — шаблон протокола по исследованиям реальной клинической практики для оценки эффективности лечения. Реальная клиническая практика данные и доказательства. Dec. 2022; 2(4): 17–25. DOI: 10.37489/2782-3784-MYRWD-23.
10. Wang SV, et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: a good practices report of a joint ISPE/ISPOR task force. Pharmacoepidemiol Drug Saf. Jan. 2023; 32(1): 44–55. DOI: 10.1002/PDS.5507.
11. Gatto NM, Vititoe SE, Rubinstein E, Reynolds RF and Campbell UB. A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses. Clin Pharmacol Ther. Jun. 2023; 113(6): 1235–1239. DOI: 10.1002/cpt.2883.
12. Солодовников А. Г., Сорокина Е. Ю., Гольдина Т. А. Данные рутинной практики (real-world data): от планирования к анализу. Медицинские технологии. Оценка и выбор. 2020; 41(3): 9. DOI: 10.17116/medtech2020410319.
13. Gatto NM et al. The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clin Pharmacol Ther. Jan 2022; 111(1): 122–134 DOI: 10.1002/CPT.2466.
14. Wang SV, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. BMJ. Jan. 2021;372 s. DOI: 10.1136/BMJ.M4856.